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The Development of Computational Models That Accurately Predict Virological Response to HIV Therapy to Power an Online Treatment Selection Tool

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Introduction

- Optimizing antiretroviral drug therapy on an individual basis to maximise response and overcome/prevent viral drug resistance can be challenging.
- Genotyping with rules-based interpretation is routinely used to support such decisions. However, current rules systems have a number of limitations and are not highly predictive of virological response.
- Here we describe the development and testing of novel mathematical models designed to predict the probability of virological response as the potential engine for a treatment selection tool.

Methods

- Random Forest (RF) models (n=10) were developed, using data from clinical cohorts in several countries, to predict the probability of a follow-up viral load <50 copies/ml after a change to antiretroviral treatment (ART).
- 5,752 treatment change episodes (TCEs) were used comprising baseline viral load, CD4 count and genotype (collected while on failing therapy), treatment history, the drugs in the new regimen and time to follow-up.
- The accuracy of the models in predicting the virological responses observed in the TCEs was evaluated after 10 x cross validation by plotting ROC curves for the individual models and for their combined outputs.
- A second evaluation of the accuracy of their combined predictions was performed using an independent test set of 50 TCEs from a single clinic.
- The models were compared with genotypic sensitivity scores (GSS) derived using three interpretation systems in common use (Stanford HIVDB, REGA V8.0.2 and ANRS V2009.07, accessed 16/03/10) in terms of the accuracy of their predictions for the 50 independent test TCEs.

Results

- The models performed with a mean overall accuracy of 77% (72-81%) and an area under the ROC curve of 0.82 (0.77-0.87) during cross validation.
- Sensitivity was 67% (62-80%) and specificity was 81% (75-89%).
- When tested with the independent test set, the models performed with an overall accuracy of 76% (71-80%), the AUC was 0.83 (0.70-0.88).
- Sensitivity was 71% (65-81%) and specificity 82% (76-87%).
- The RF models were significantly more accurate as predictors of response than the GSS for the test TCEs (mean overall accuracy of 54% and an AUC of 0.51, p<0.01).

Figure 1: ROC curve for best performing RF model

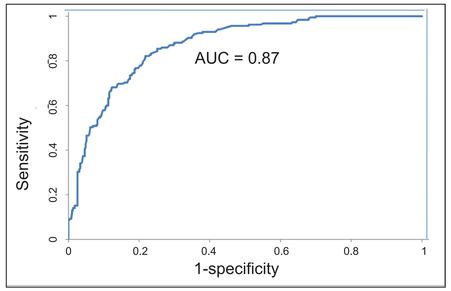


Table 1: Performance of the RF models and GSS systems

Performance during cross validation

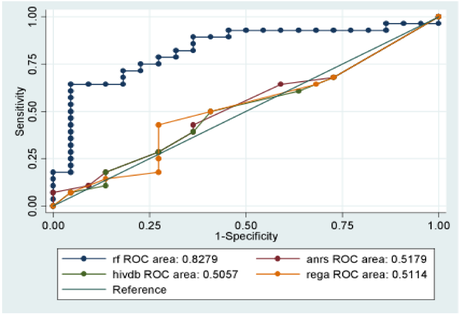
	RF1	RF2	RF3	RF4	RF5	RF6	RF7	RF8	RF9	RF10	**Mean**
AUC	0.82	0.80	0.82	0.80	0.85	0.83	0.81	0.87	0.85	0.77	**0.82**
Accuracy (%)	76	75	76	74	77	79	74	81	81	72	**77**
Sensitivity (%)	65	69	62	63	80	70	71	66	62	63	**67**
Specificity (%)	82	78	81	79	75	84	76	88	89	75	**81**

Performance with independent test set (n=50)

	RF Committee	Stanford HIVdb	ANRS	REGA
AUC	0.83	0.51	0.52	0.51
Accuracy (%)	76	54	54	56
Sensitivity (%)	71	50	64	43
Specificity (%)	82	59	41	73

Results

Figure 2: ROC curves for RF committee and GSS systems



Conclusions

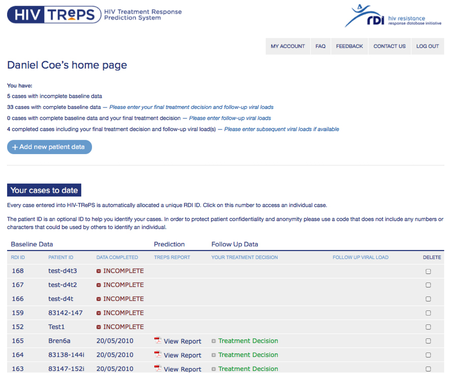
- **The RF models were accurate predictors of virological response to HAART**
- **The models were more accurate in their predictions than were GSS derived from genotype interpretation systems in common use as an aid to treatment decision-making.**
- **The combination of RF models is being taken forward to power an experimental treatment-decision support tool.**

HIV-TRePS

- The RDI is in the final stages of development of its HIV Treatment Response Prediction System, HIV-TRePS, which will be launched during 2010
- HIV-TRePS is an experimental system to support HIV treatment decision-making and will be available free online
- The system will include the following feature options:
  - Model regimens defined by the user and/or alternatives identified by the system
  - Exclude unavailable drugs from modeling as a user-setting
  - Model regimens with 3, 4, or 5 drugs
  - Save results in the user's archive for future reference

HIV-TRePS

Figure 3: Screen shot of HIV-TRePS user home page



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