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HIV TRePS
HIV Treatment Response Prediction System

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The use of data from multiple cohorts to develop an on-line HIV treatment selection tool

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Introduction

- Selection of the optimum HIV drug combination for cases of virological failure can be challenging given the number of combinations possible, the variety of patients' treatment experience, the complexity of viral resistance and other factors
- The RDI was established in 2002 to collect sufficient data to develop systems to predict virological response to combination antiretroviral therapy (cART), quantitatively and accurately as an aid to treatment decision-making
- Here we describe the use of data from multiple cohorts to train computational models to predict virological response to cART and the assessment of the online treatment support system that uses them.

Methods

Model development

- The RDI database has data from approximately 75,000 patients from 10 clinics, 7 cohorts and 10 clinical trials across approximately 20 countries
- 5,752 complete treatment change episodes (TCEs) were extracted that met all criteria for modelling
- 85 input variables were used: baseline viral load, CD4 count and genotype (59 mutations) collected while on failing therapy, treatment history, the drugs in the new regimen and time to follow-up
- 10 Random Forest (RF) models were developed to predict the probability of a follow-up viral load <50 copies/ml after a change to cART
- The models were evaluated during 10 x cross validation and also using an independent test set of 50 TCEs from a single clinic in Australia
- Receiver-operator characteristic (ROC) curves were plotted and accuracy assessed in terms of the area under the curve (AUC), overall accuracy (OA) sensitivity and specificity.

System evaluation

- An online system was developed through which physicians could enter their patients' data and their initial treatment decision
- Within seconds they received a report listing the RDI models' predictions of response to the physician's selection and to possible alternative regimens
- They entered their final treatment decision having reviewed the report
- The system was evaluated in two clinical pilot studies in which 114 cases of treatment failure were entered by 23 physicians who were also required to complete online evaluation
- Minor improvements were made to the interface prior to launch in October 2010
- Since launch, users of the live system are invited to complete the same online evaluation.

Results

Model development

- During cross-validation the models performed with an overall accuracy of 77% (72-81%) and an area under the ROC curve of 0.82 (0.77-0.87) (Figure1)
- 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%, and an AUC of 0.83 (Figure 2).

Clinical pilot studies

- The evaluation of the system by physicians is summarised in Table 1
- There was a change of treatment decision in 33% of cases and an average saving in the number of drugs in the final regimen of approximately 10%
- The final treatment decisions and the best of the RDI alternatives were predicted to produce greater virological responses than the physician's original selections (Table 2).

Evaluations of the live system

- From launch in October 2010 to the end of February 2011, 322 users from 54 countries had registered and were using
- 14 evaluations have been completed and submitted
- The results are summarised in Table 1

Overall evaluations

- Evaluations of the live system were more positive than those of the prototype
- Overall 78% of physicians found the system easy or very easy to use and 95% intend to use it in clincial practice
- Physicians indicated that they would use the system primarily for highly treatment-experienced patients and those with complex resistance patterns.

Results (continued)

Figure 1: ROC curve for the best RF model during cross validation

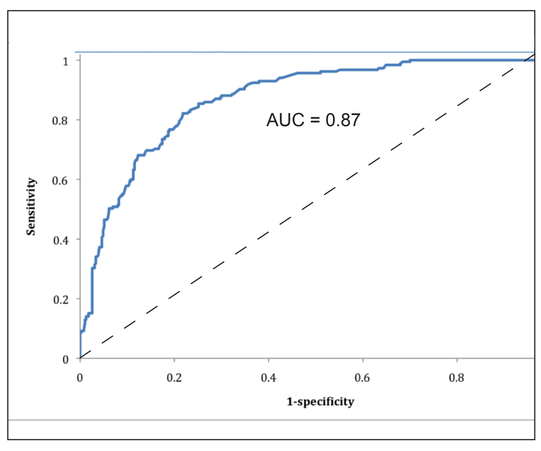

Figure 2: ROC curve for the independent test set of 50 TCEs

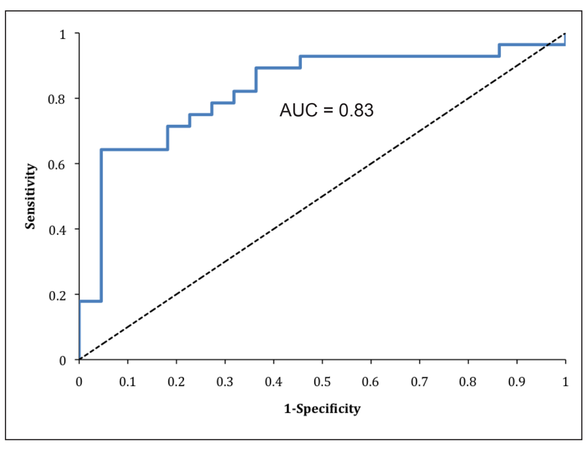

Table 1: Summary of physician's evaluations of the system (most popular responses highlighted)

Question	Study	Response options with number (%) of respondents				
How easy was it to enter the baseline data?		Very easy	Quite easy	Satisfactory	Quite difficult	Very difficult
	Pilot	6 (26%)	**14 (61%)**	2 (9%)	1 (4%)	0 (0%)
	Live	**9 (64%)**	4 (29%)	1 (7%)	0 (0%)	0 (0%)
	Combined	15 (38%)	**18 (49%)**	3 (16%)	1 (3%)	0 (0%)
How easy to use was the web-based interface overall?		Very easy	Quite easy	Satisfactory	Quite difficult	Very difficult
	Pilot	6 (26%)	**9 (39%)**	5 (22%)	1 (4%)	2 (9%)
	Live	**10 (71%)**	4 (29%)	0 (0%)	0 (0%)	0 (0%)
	Combined	**16 (43%)**	13 (35%)	5 (14%)	1 (3%)	2 (5%)
How easy was it to understand the RDI report?		Very easy	Quite easy	Satisfactory	Quite difficult	Very difficult
	Pilot	6 (26%)	**11 (48%)**	6 (26%)	0 (0%)	0 (0%)
	Live	**9 (64%)**	5 (36%)	0 (0%)	0 (0%)	0 (0%)
	Combined	15 (38%)	**16 (43%)**	6 (16%)	0 (0%)	0 (0%)
How useful was the system in making treatment decisions?		Very useful	Quite	Satisfactory	Not very	Not at all
	Pilot	0 (0%)	5 (22%)	**11 (48%)**	7 (30%)	0 (0%)
	Live	2 (14%)	**4 (29%)**	3 (21%)	3 (21%)	0 (0%)
	Combined	2 (5%)	9 (24%)	**14 (38%)**	10 27%)	0 (0%)
How frequently would you use it?		Very	Quite	Sometimes	Infrequent	Never
	Pilot	1 (4%)	7 (30%)	**11 (48%)**	3 (13%)	1 (4%)
	Live	3 (21%)	**5 (36%)**	2 (14%)	3 (21%)	1 (7%)
	Combined	4 (11%)	12 (32%)	**13 (35%)**	6 (16%)	2 (5%)

Table 2: Comparison of predicted changes in viral load from baseline

	Physician's selection		RDI system	
A: All cases (n=114)	**Initial**	**Final**	**A***	**B***
Mean predicted change in viral load from baseline	-1.88	-1.90	-2.03	-2.03
Median	-1.85	-1.85	-1.98	-1.98
Proportion with >2 log reduction	39%	41%	50%	50%
Statistical significance (vs physician's initial selection)**		p=0.06	p<0.0001	p<0.0001
B: Cases where the treatment decision was changed (n=38)				
Mean	-1.92	-1.99	-2.12	-2.13
Median	-1.91	-1.99	-2.06	-2.07
Proportion with >2 log reduction	39%	50%	58%	58%
Statistical significance (vs physician's initial selection)**		p<0.05	p<0.0001	p<0.0001

* A: Alternative regimens with no more drugs than the physician's initial selection
B: Alternative regimens with no more than six drugs
** One tailed t-tests

Conclusions

- The RF models were accurate predictors of response to cART
- Use of the system was associated with a change in treatment decision in one-third of cases
- The system was rated as being easy to use, potentially helpful and likely to be used in practice
- Use of the system may result in a reduction in the number of drugs prescribed and potentially lower treatment costs
- The results suggest that use of the system could improve virological responses in treatment-experienced patients.
- An updated version of the system is available as a free on-line experimental tool at www.hivrdi.org
- **The application of powerful computational methodologies to large datasets from multiple cohorts can be of clinical benefit by predicting how patients will respond to treatment of complex diseases enabling therapy to be optimised.**

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