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Models that accurately predict response to HIV therapy are generalisable to unfamiliar data sets and settings

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Background

- The optimal selection of antiretroviral drugs following treatment failure is challenging, for example due to:
  - The complexity of resistance and range of treatment options in well-resourced settings or
  - The unaffordability of genotyping and some drugs in resource-limited settings
- Computer models have been developed that accurately predict response to therapy to aid decision-making[1-3]
- Clinical evaluation has indicated this could be a useful clinical tool[4]
- However, previous studies suggest that model performance may not be generalisable to data from 'unfamiliar' settings not represented in the training data[1]
- Here we test recent models with independent data from unfamiliar settings.

Methods

Two sets of random forest models, developed using data from USA, Canada, Europe and Australia, were evaluated:

- All predicted the probability of response from a range of variables, including: baseline viral load and CD4 count, (sampled while on the previous, failing therapy and no more than 8 and 12 weeks before the new treatment was introduced); ≤18 treatment history variables; time to follow-up and the drugs in the new regimen.
- The models' unique characteristics were:
  - **Set 1:** Do not require a genotype, predict follow-up viral load ≤400 copies, trained using 14,891 treatment change episodes (TCEs) and achieved an AUC of 0.77 and 72% accuracy during development.
  - **Set 2:** Require a genotype (62 mutations) predict follow-up viral load ≤50 copies, trained using 7,263 TCEs and achieved an AUC of 0.82 and 76% accuracy during development.
- The generalisability of Set 1 (no genotype) was assessed using 375 TCEs without genotypes from two sources in Romania
- Set 2 (including genotype) was assessed using 375 TCEs with genotypes obtained from the Stanford TCE repository (www. hivdb.stanford.edu) from clinics in North America and Europe not represented in the training data.
- The key characteristics of the data sets are summarised in Table 1.

Table 1: Characteristics of training and test sets

	Set 1 (no genotype) Training data	Set 2 (incl. genotype) Training data	No genotype test TCEs (Romania)	With genotype test TCEs (Stanford)
TCEs	14,891	7,263	375	375
Date range	1993-2009	1996-2010	2000-2011	1997-2010
Mean (median) baseline VL (log10 c/mL)	3.74 (3.77)	4.34 (4.30)	3.95 (4.07)	4.20 (4.11)
Mean (median) baseline CD4 (cells/µL)	310 (260)	277 (235)	360 (285)	269 (230)
Mean (median) no. of previous drugs	6.88 (6)	5.56 (5)	4.95 (4)	5.82 (5)
Mean (median) drug resistance mutations	N/A	8.34 (8)	N/A	8.48 (6)
Responders (<1.7 (Set 1) or <2.6 (Set 2) log10 c/mL follow-up VL)	6,966 (47%)	2,550 (35%)	176 (47%)	18 (5%)

The potential utility of the models in identifying alternative regimens that were more likely to result in a virological response than teh regimens that failed in the clinic was evaluated as follows:

- The baseline data from the virological failures in the test sets were provided to the models and their predictions of response obtained for a range of alternative regimens using only those drugs that were represented in the test sets and no more drugs than were in the failed regimen
- The following metrics were obtained:
  - The number (proportion) of failures that were correctly predicted by the models
  - The number (proportion) for which the models were able to identify alternative regimens that were predicted to give a response (the estimated probability of virological response was greater than the optimum cut-off for the system)
  - The proportion for which the models were able to identify alternative regimens with a higher predicted probability of success than the regimen that failed
- The analysis was repeated excluding drugs that were not yet approved by both the FDA or EMEA at the time for each case (contemporised analysis).

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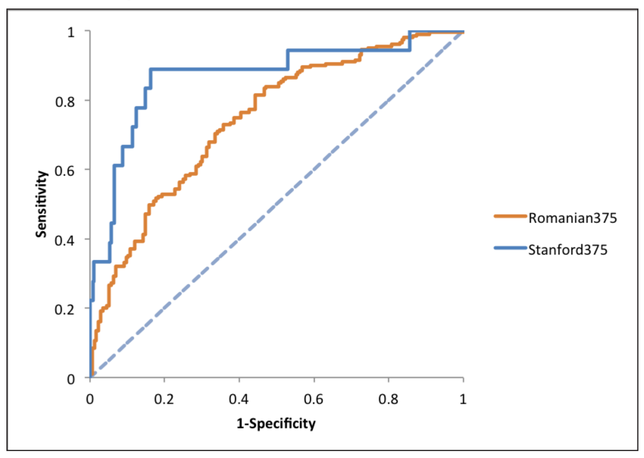
Results

- Set 1 (no genotype) achieved a mean AUC of 0.73 (95% CI 0.69, 0.79), sensitivity of 65% (38, 71%), specificity of 70% (63, 77%) and overall accuracy of 67% (62, 72%) when tested with the 375 independent test cases from Romania
- Set 2 (including genotype) achieved a mean AUC value of 0.87 (95% CI 0.77, 0.97) sensitivity of 61% (36, 83%), specificity of 92% (89, 95%) and overall accuracy of 91% (88, 94%), when tested with the 375 independent test cases.

Figure 1: ROC curves for the two sets of models with independent test cases



- Set 1 correctly predicted 70% of the virological failures and Set 2 92% (Table 2)
- Set 1 identified alternative regimens that were predicted to be effective in 94% and Set 2 97% of those cases where the new regimen used in the clinic had failed
- In the contemporised analysis the figures were 88% for Set 1 (no genotype) and 143 (40%) for Set 2 (genotype)
- Both sets of models identified alternative regimens with a higher probability of success than the regimen selected in the clinic for all failures.

Table 2: Using the models to identify effective alternative treatments for cases where the new treatment failed in the clinic

	Set 1 (no genotype) models with 375 test cases		Set 2 (genotype) models with 375 test cases	
No of virological failures	176		357	
No (%) correctly predicted	123 (70%)		330 (92%)	
Drugs included in the in silico analysis	**All drugs from test data**	**Contemporised by case**	**All drugs from test data**	**Contemporised by case**
No (%) of failures for which effective* alternative regimens were found	165 (94%)	154 (88%)	346 (97%)	143 (40%)
No (%) for which alternative regimens more likely to be effective were found**	176 (100%)	176 (100%)	357 (100%)	356 (100%)

* the estimated probability of virological response was above the optimum cut-off
** the estimated probability of response was higher than that for the regimen that failed in the clinic

Conclusions

- **The models were accurate predictors of virological response for patients from unfamiliar settings**
- **They were able to identify potentially effective regimens for a substantial proportion of cases where the new treatment introduced in the clinic failed**
- **While the models that use a genotype performed significantly better than those that do not, the performance of the 'no-genotype' models for patients from an unfamiliar setting (Romania) was encouraging**
- **These results suggest that this system has the potential to reduce virological failures in settings that have not contributed data to the system's development, particuarlry where a genotype is not available**
- **The models were made available through the RDI's online treatment support tool HIV-TRePS (www.hivrdi.org)**

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