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Computational models developed without a genotype for resource-poor countries predict response to HIV treatment with 82% accuracy

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hiv resistance response database initiative

A global non-profit initiative against HIV drug resistance

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Introduction

- Combination antiretroviral therapy (cART) is being urgently rolled out in resource-poor countries
- Treatments are failing at a comparable rate to other countries with resistance a significant factor
- Selecting the optimum drug combination after failure in these settings is a major challenge because:
  - Resistance testing is not widely available
  - Treatment options are limited
  - Healthcare provider experience may be limited
- The RDI has developed computational models that accurately predict the absolute virological response and the probability of the viral load being reduced to <50 copies from a range of baseline data, including genotype
- Here we model response to cart without genotype for potential use in resource-poor countries.

Objectives

1. To train RF models to predict virological response to ART without the use of genotype and test their accuracy
2. To use a large dataset representative of clinical practice in resource-poor countries
3. To use the models to identify potentially effective alternative regimens for cases of virological failure

Methods

Data selection and partition

- 8,514 treatment change episodes (TCEs) from > 20 centres were selected from the RDI database
- TCEs were selected with no previous exposure to protease inhibitors (PIs), no T-20, raltegravir or maraviroc but PIs were allowed in the new regimen (to represent typical clinical practice in resource-poor countries)
- The data were partitioned at random by patient into 8,114 training and 400 independent test TCEs (Table 1).

Table 1: Descriptive statistics for the training and test datasets

	Training (8,114 TCEs)	Test (400 TCEs)
Male	6,410 (79%)	308 (77%)
Median baseline viral load (log copies HIV RNA/ml)	2.27	3.04
Median baseline CD4 count (cells/ml)	316	287
Number of different treatment regimens started	248	51
Number of failures	3,215 (40%)	205 (51%)

Methods (continued)

Model development

Two Random Forest models were trained to predict the probability of the follow-up viral load being <50 copies/ml after a treatment change.

Model 1 was trained using the following 24 input variables:

- Baseline viral load
- CD4 count
- Treatment history (3 variables previous AZT, 3TC, any NNRTI)
- The drugs in the new regimen
- Time to follow-up.

Model 2 was as Model 1 except 11 individual drug treatment history variables were used.

Testing the models

- The RF models analysed the baseline data from the test TCEs
- They produced estimates of the probability of the follow-up VL being <50 copies (between 0 and 1)
- Receiver-operator characteristic (ROC) curves were plotted for models' predictions vs actual responses
- The models were also programmed to predict responses to multiple alternative 3-drug regimens using baseline data from the cases where the new treatment failed (VL > 50 copies at follow-up), using two drug lists:
  - Old PIs only (IDV, SQV, LPV/r, NFV)
  - Including 'new' PIs (APV, ATZ, DRV)

Results

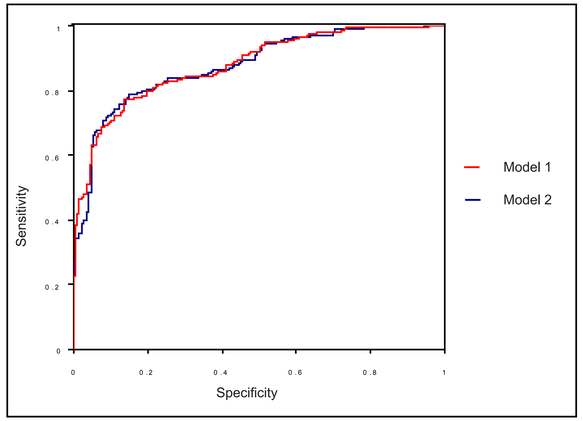
- Both models achieved an accuracy of 82% and an area under the curve (AUC) of 0.88 (Figure 1).
- Sensitivity was 77% and 79% and specificity 86% and 85% for Models 1 and 2 respectively.
- The optimal operating points (cut-offs for virological response defined as viral load <50 copies) were 0.44 and 0.47 (Table 2 for a summary of the results).

Table 2: Summary of results

	Model 1	Model 2
Accuracy	82%	82%
AUC	88%	88%
Sensitivity	77%	79%
Specificity	86%	85%
Optimal Operating Point	0.44	0.47
% failures for which potentially effective	46%	48%
% failures for which potentially effective alternatives were found (new PIS added)	49%	52%

Results (continued)

Figure 1: ROC curves for Models 1 & 2



The most important variable in the modelling was baseline viral load (Table 3).

Table 3: The 10 most important input variables for Model 2

Input variable	Importance rank	Importance score
Baseline viral load	1	150.67
Time to follow-up	2	42.58
Baseline CD4 count	3	33.56
Historical EFV	4	29.98
TDF	5	25.17
ddI	6	20.04
Historical AZT	7	18.32
d4T	8	18.20
AZT	9	17.87
Historical 3TC	10	17.45

In silico modelling

- Models 1 and 2 identified alternative 3-drug regimens that were predicted to be fully suppressive for 94 (46%) and 98 (48%) of the failures respectively.
- When all currently licensed protease inhibitors were included, these figures rose to 100 (49%) and 106 (52%).

Conclusions

- **Models trained with large, representative datasets can predict virological response to cART accurately without a genotype**
- **The results highlight viral load as the most important predictor of response**
- **Models are able to identify potentially effective regimens comprising older drugs in a substantial proportion of failures**
- **This approach has potential for optimising antiretroviral therapy in resource-poor countries**

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