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
The clinical issue

• Combination antiretroviral therapy (cART) is being 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:
  – Resistance testing is not widely available
  – Treatment options are limited
  – Healthcare provider experience may be limited

• Could the RDI’s approach be of help?
What is the RDI’s approach?

To develop computational models using data from many ‘000s patients to predict response to cART:

- Initially: the change in viral load from baseline following a treatment change
  - Correlation of predicted vs actual virological response typically gave $r^2 \geq 0.70$ and mean difference of $<0.5$ log copies/ml

- Recently: the probability that the viral load will go ‘undetectable’ ($<50$ copies/ml)
RF model developed to predict probability of VL<50 copies

- 3,188 training treatment change episodes (TCEs) & 100 test TCEs used
- The RDI’s ‘standard’ set of 82 input variables, including 58 mutations plus BL VL, CD4, treatment history, drugs in new regimen and time to follow-up
- Predictive accuracy compared with performance of genotypic sensitivity scores (GSS) derived from current ‘rules’ systems for interpretation of genotype
ROC curve for RF model & GSS from common rules systems predicting VL<50 copies

RDI RF: AUC = 0.88
Accuracy = 82%

GSS: AUC = 0.68-0.72
Accuracy = 63-68%
Current study objectives

1. To develop RF models to predict virological response to cART (VL<50 copies) without the use of genotype
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 actual virological failure
Data selection/partition

- 8,514 TCEs from > 20 centres in ‘rich countries’ selected from RDI database
- No historical exposure to PIs, T-20, raltegravir or maraviroc but PIs allowed in the new regimen (to represent typical clinical practice in resource-poor countries)
- Data partitioned at random by patient into 8,114 training and 400 test TCEs
## Datasets - Descriptive Statistics

<table>
<thead>
<tr>
<th></th>
<th>Training (8,114 TCEs)</th>
<th>Test (400 TCEs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>6,410 (79%)</td>
<td>308 (77%)</td>
</tr>
<tr>
<td>Median BL viral load</td>
<td>2.27</td>
<td>3.04</td>
</tr>
<tr>
<td>(log copies HIV RNA/ml)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median BL CD4 (cells/ml)</td>
<td>316</td>
<td>287</td>
</tr>
<tr>
<td>Number of different regimens (new treatment)</td>
<td>248</td>
<td>51</td>
</tr>
<tr>
<td>Number (percent) failures</td>
<td>3,215 (40%)</td>
<td>205 (51%)</td>
</tr>
</tbody>
</table>
Developing the models

Two RF models were trained to predict the probability of the follow-up viral load being <50 copies:

**Model 1**
24 Input variables:
- Baseline viral load
- Baseline CD4 count
- Treatment history (AZT, 3TC, any NNRTI)
- Drugs in the new regimen
- Time to follow-up

**Model 2**
32 Input variables:
- As Model 1 except 11 individual drug treatment history variables were used.
Testing the models

- RF models analysed baseline data from test TCEs
- Produced estimate of probability of the follow-up VL being <50 copies
- ROC curves plotted for models’ predictions vs actual responses
ROC curve

Model 1
AUC = 0.879
Accuracy = 82%
Sensitivity = 77%
Specificity = 86%

Model 2
AUC = 0.878
Accuracy = 82%
Sensitivity = 79%
Specificity = 85%
Relative importance of input variables for modelling virological response (Model 2)

<table>
<thead>
<tr>
<th>Input variable</th>
<th>Importance rank</th>
<th>Importance score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline viral load</td>
<td>1</td>
<td>150.67</td>
</tr>
<tr>
<td>Time to follow-up</td>
<td>2</td>
<td>42.58</td>
</tr>
<tr>
<td>Baseline CD4 count</td>
<td>3</td>
<td>33.56</td>
</tr>
<tr>
<td>EFV - historical</td>
<td>4</td>
<td>29.98</td>
</tr>
<tr>
<td>TDF - current</td>
<td>5</td>
<td>25.17</td>
</tr>
<tr>
<td>ddl - current</td>
<td>6</td>
<td>20.04</td>
</tr>
<tr>
<td>AZT - historical</td>
<td>7</td>
<td>18.32</td>
</tr>
<tr>
<td>d4T - current</td>
<td>8</td>
<td>18.20</td>
</tr>
<tr>
<td>AZT - current</td>
<td>9</td>
<td>17.87</td>
</tr>
<tr>
<td>3TC - historical</td>
<td>10</td>
<td>17.45</td>
</tr>
</tbody>
</table>
In silico analysis

- Models were programmed to predict responses to multiple alternative 3-drug regimens using baseline data from the cases where the new treatment failed using two drug lists:
  - ‘Old’ PIs only (IDV/r, SQV/r, LPV/r, NFV)
  - Including ‘newer’ PIs ((fos-)APV/r, ATZ/r, DRV/r)
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<table>
<thead>
<tr>
<th></th>
<th>Model 1 (3 TH)</th>
<th>Model 2 (11 TH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>% failures for which effective</td>
<td>46%</td>
<td>48%</td>
</tr>
<tr>
<td>alternatives found (old drugs only)</td>
<td>49%</td>
<td>52%</td>
</tr>
<tr>
<td>% failures for which effective</td>
<td></td>
<td></td>
</tr>
<tr>
<td>alternatives found (new PIs added)</td>
<td></td>
<td></td>
</tr>
</tbody>
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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 variable in modelling response.
- Models are able to identify potentially effective 3-drug regimens comprising older drugs in a substantial proportion of failures.
- This approach has potential for optimising antiretroviral therapy in resource-poor countries.
Thanks to our data contributors

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The RDI ...

Brendan Larder

Dechao Wang          Daniel Coe