The HIV Treatment Response Prediction System – using the experience of treating tens of thousands of patients to guide optimal drug selection

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Background

- Optimising the selection of antiretroviral drugs for patients experiencing virological failure remains a challenge
- This is particularly true in resource-limited settings where the latest drugs may not be accessible and/or genotyping may not be affordable to guide drug selection
- The RDI was set up in 2002 to develop computational models that predict virological response to different combinations of drugs, and to make those models freely available to assist optimal, individualised drug selection.

Methods

- In order to collect sufficient data to develop such models, HIV cohorts and clinics around the world were approached for a range of longitudinal clinical, virological and treatment data for their patients
- These data have been used to train a range of neural network, support vector machine, linear regression and random forest models
- The models provide quantitative predictions of viral load response to any HIV drug combination, from baseline viral load, CD4 count genotype if available (not essential), HIV treatment history, the drugs in the new regimen and the time to follow-up
- The models are tested during cross validation and with independent validation sets and their accuracy compared with that of genotyping using rules-based interpretation.

Results - 1

- Data from approximately 150,000 patients with >1million viral load values have been collected
- The best performing models (random forests) routinely predict virological response/failure to a change of therapy with an accuracy of 80% or more, even without the use of a genotype1-3
- They are able to identify simple, alternative drug combinations that are predicted to be effective for the majority of cases that failed following a treatment change in the clinic
- The latest models that did not use a genotype in their predictions achieved accuracy of 0.82 during cross validation and 0.80 in independent testing - significantly superior to 0.56-0.57 for genotyping (p<0.001) (Table 1 and Figure 1)4
- In clinical prospective testing by HIV experts use of HIV-TRePS led to one third of treatment decisions being revised5
- In a study of an Indian cohort the system identified alternative regimens using locally available drugs that were less costly and predicted to be more effective than the salvage regimen actually prescribed in the clinic (Table 3)

Table 1: Performance of the models vs genotyping with rules-based interpretation

<table>
<thead>
<tr>
<th>Prediction System</th>
<th>AUC</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Accuracy (%)</th>
<th>Statistical comparison vs models</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF models</td>
<td>0.80</td>
<td>65</td>
<td>80</td>
<td>75</td>
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<tr>
<td>GSS (genotyping + rules interpretation)</td>
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<td></td>
<td></td>
<td></td>
<td>p&lt;0.0001</td>
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<tr>
<td>ANRS</td>
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<tr>
<td>HIVdb</td>
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<td>57</td>
<td>66</td>
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<tr>
<td>Riegel</td>
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<td>52</td>
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<tr>
<td>Genotyping average</td>
<td>0.57</td>
<td>52</td>
<td>56</td>
<td>55</td>
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</tr>
</tbody>
</table>

Conclusions

- Computational models can be accurate predictors of virological response, even without a genotype
- They are significantly more accurate than genotyping
- The models have the potential to avoid treatment failure by identifying effective, alternative, practical regimens
- The system has the potential to save money by identifying less costly but effective alternative ART
- The models are used to power the free, online HIV Treatment Response Prediction System (HIV-TRePS)
- HIV-TrePS has the potential to help optimise therapy in settings with limited resources where certain drugs and/or genotyping may not be available

References