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Computational models can accurately predict response to antiretroviral therapy without a genotype

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hiv resistance response database initiative
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Introduction

- Combination antiretroviral therapy (cART) is being rolled out in resource-limited 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 compare the performance of models developed to predict response to cART with and without genotype data to assess the potential of the latter for use as a treatment decision-making aid in resource-poor countries.

Methods

Data selection and partition

- 3,288 treatment change episodes (TCEs) from > 20 centres in North America, Europe, Asia and Australia were selected from the RDI database
- The TCEs included treatment with zidovudine, lamivudine, emtracitabine didanosine, stavudine, abacavir, nevirapine, efavirenz, indinavir, nelfinavir, saquinavir, amprenavir, fos-amprenavir, atazanavir, darunavir, ritonavir (as a booster) and enfuvirtide
- The data were partitioned at random by patient into 3,188 training and 100 independent test TCEs (Table 1).

Table 1: Descriptive statistics for the training and test datasets

	Training (3,118 TCEs)	Test (100 TCEs)
Median baseline viral load (log copies HIV RNA/ml)	4.27	4.32
Median baseline CD4 count (cells/ml)	254	241
Number of treatment failures	2,193 (70%)	63 (63%)

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.

Methods (continued)

Model 1 was trained using the following 88 input variables:

- Baseline viral load
- Baseline CD4 count
- Baseline HIV genotype coded as 58 mutations (reverse transcriptase mutations: M41L, E44D, A62V, K65R, D67N, 69 insert, T69D/N, K70R, L74V, V75I, F77L, A98G, L100I, L101I/E, K103N, V106A, V108I, Y115F, F116Y, V118I, Q151M, V179D, Y181C, M184V, Y188C/L/H, G190S/A, L210W, T215Y, T215F, K219Q/E, P236L; protease mutations: L10F/I/R/V, V11I, K20M/R, L24I, D30N, V32I, L33F, M36I, M46I/L, I47V, G48V, I50V, I50L, F53L, I54V/L, L63P, A71V/T, G73S/A, L76V, V77I, V82A/F/S, V82T, I84V, I84A, N88S, L89V & L90M)
- Treatment history (4 variables: previous AZT, 3TC, any protease inhibitor and any non-nucleoside reverse transcriptase inhibitor, NNRTI)
- The drugs in the new regimen
- Time to follow-up.

Model 2 was trained using the same input variables as Model 1 without the genotype - a total of 30 variables.

Testing the models

- The RF models analysed the baseline data from the 100 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 the models' predictions vs actual responses
- Genotypic Sensitivity Scores (GSS) were calculated for the test set using the Rega, ANRS, Stanford HIVdb and Stanford mutation score rules-based interpretation systems
- These GSS scores were used as predictors of virological response and an ROC curve plotted for each for comparison with the RF models
- The performance of the two RF models and the GSS scores as predictors of virological reponse were compared in terms of the area under the curve (AUC) using the *Z*-test

Results

- RF Model 1 achieved accuracy of 82%, AUC of 0.88, sensitivity of 76% and specificity of 86%
- Model 2 achieved accuracy of 78%, AUC of 0.86, sensitivity of 89% and specificity of 71%
- The AUC values for the two RF models were not statistically significantly different

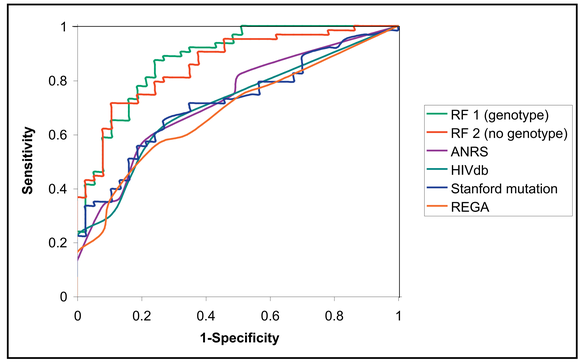
Results (continued)

- The optimal operating points (cut-offs for virological response defined as viral load <50 copies) were 0.59 and 0.69 for models 1 and 2
- The most important variable in the RF modelling was baseline viral load
- The accuracy of the ANRS, REGA, Stanford HIVdb and Stanford mutation score was 66%, 63%, 67% and 68% respectively, with AUC of 0.72, 0.68, 0.71 and 0.72
- Both RF models performed significantly better in terms of AUC than each rules-based system (p<0.01)
- There were no significant differences between the AUC values for the GSS scores generated by the different rules-based systems.

Table 2: Summary of main results

	Model 1	Model 2	Mean of rules based GSS scores
AUC	0.88	0.86	0.71
Accuracy	82%	78%	66%
Sensitivity	76%	89%	62%
Specificity	86%	71%	74%

Figure 1: ROC curves for Models 1 & 2 and GSS from four rules based systems



Conclusions

- **RF models that do not use a genotype can accurately predict virological response to cART with only a small loss of accuracy compared with models that use a genotype**
- **RF models that do not require a genotype can predict virological response with significantly more accuracy than GSS scores derived from rules-based genotype interpretation systems**
- **This approach has potential clinical application as a treatment selection aid in resource-limited settings.**

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