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HIV TRePS
HIV Treatment Response Prediction System

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The development of computer models that accurately predict response to HIV therapy without a genotype: a potential tool for therapy optimisation in resource-limited settings

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Background

- Optimisation of antiretroviral therapy in resource-limited settings (RLS) can be challenging without access to the newest drugs, or genotyping to help tailor therapy against resistance.
- Computational models have been developed to predict virological response to therapy as an aid to optimal drug selection
- However, most require a genotype, have been developed using western data and are less accurate for patients from RLS.
- Here we describe the development of models that do not require a genotype, using substantial data from RLS.

Methods

- Random forest (RF) models were trained to predict the probability of virological response (VL<50 copies/ml) using 22,567 treatment change episodes (TCEs) in which a new regimen was introduced following virological failure, including 1,090 cases from southern Africa and 328 from Eastern Europe
- The input variables from which the models made their predictions were: baseline viral load, CD4 count, treatment history, new drug regimen and time to follow-up
- The models were assessed during cross-validation, with an independent test set (n=1,000) including 582 from Europe, 23 from Eastern Europe and 100 from southern Africa
- The area under the ROC curve (AUC) was the main outcome, with secondary measures of sensitivity, specificity and overall accuracy
- The predictive accuracy of the models was compared to genotyping using three rules-based interpretation systems (ANRS, REGA & Stanford) to produce genotypic sensitivity scores (GSS) for the 346 test cases with genotypes
- The 100 test cases from southern Africa were used for *in silico* modelling whereby the models were used to identify alternative 3-drug regimens using only the drugs available in that setting at the time that might be more effective than those used in the clinic.

Results

Table 1: Characteristics of the TCEs in the training and test sets

	Training set	Global test set
TCEs	**22,567**	**1,000**
Patients	7,568	1,000
Male	5,055	661
Female	1,584	218
Not known	929	121
Median age	40	39
Baseline data		
Median (IQR) baseline VL (log10 copies/mL)	3.83 (2.83-4.84)	3.97 (2.98-4.97)
Median (IQR) baseline CD4 (cells/mm3)	268 (128-407)	260 (123-387)
Treatment History		
Median no.(IQR) previous drugs	4 (3-7)	4 (3-6)
N(t)RTI experience (%)	22,478 (100%)	998 (100%)
NNRTI experience (%)	13,998 (62%)	634 (63%)
PI experience (%)	15,532 (69%)	630 (63%)
New Regimens		
2 N(t)RTIs + PI (%)	7,114 (32%)	335 (34%)
2 N(t)RTIs + NNRTI (%)	4,801 (21%)	228 (23%)
3N(t)RTIs + PI (%)	1,587 (7%)	74 (7%)
3N(t)RTIs (%)	1,472 (7%)	59 (6%)
3 N(t)RTIs + NNRTI (%)	1,031 (5%)	40 (4%)
Other	6,562 (29%)	264 (26%)

Abbreviations: TCEs (treatment change episodes); IQR (interquartile range); VL (viral load); N(t)RTI (nucleoside or nucleotide reverse transcriptase inhibitor); NNRTI (non-nucleoside reverse transcriptase inhibitor); PI (protease inhibitor)

- The models achieved a mean AUC of 0.82 during cross validation, 0.80 with the 1,000 test set, 0.81 for the European, 0.82 for the Eastern European and 0.78 for the southern African test cases (Table 2).
- Of the 1,000 test TCEs, 346 had genotypes and the AUC for the GSS ranged between 0.56 and 0.57 - significantly inferior to the accuracy of the models (p<0.0001)
- The models identified regimens that were predicted to be effective in 76 of the southern African cases and in 65% of the 48 cases where the new regimen introduced in the clinic failed (Table 3)

Results (continued)

- Alternative regimens with a higher predicted probability of virological response than the regimen used in the clinic were identified in 85% of cases and 96% of the failures (Table 3)

Table 2: Results of the modeling

Model testing		AUC	Sensitivity (%)	Specificity (%)	Overall accuracy (%)
Cross validation (22,567)	**Mean**	**0.82**	**66**	**79**	74
10x cross validation scheme	95% CI	[0.78, 0.85]	[58, 74]	[74, 88]	[73, 80]
Global test set (1,000)	**Model average**	**0.80**	**66**	**79**	**74**
Average predictions of 10 models	95% CI	[0.77, 0.82]	[61, 71]	[76, 82]	[71, 77]
Southern African subset (100)	**Model average**	**0.78**	**81**	**60**	**71**
Average predictions of 10 models	95% CI	[0.69, 0.87]	[67, 90]	[45, 74]	[61, 80]
European subset (n=582)	**Model average**	**0.81**	**66**	**81**	**75**
Average predictions of 10 models	95% CI	[0.77, 0.84]	[59, 72]	[77, 85]	[71, 79]

Figure 1: ROC curves for the RF models (tested with the 1,000 global test set and 100 southern African cases) and for GSS (for those cases with genotypes)

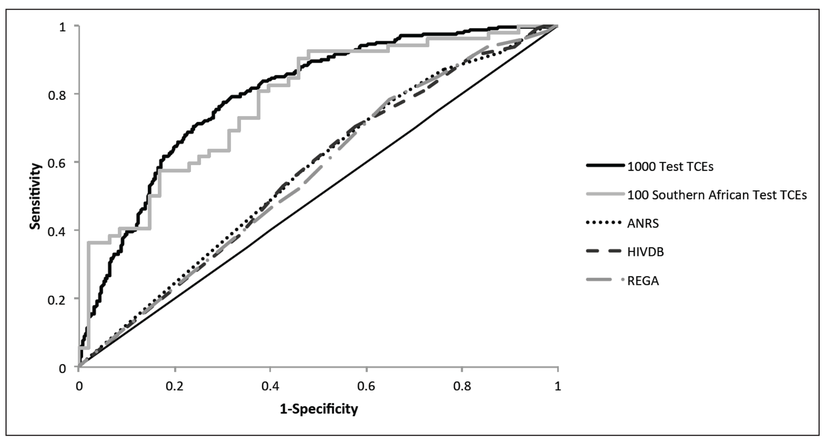

Table 3: In silico modelling to identify potentially effective alternative regimens for the Southern African cases

	All cases (100)	Failures (48)
Percentage of cases for which alternative 3-drug regimens were predicted to be effective	76	65
Median number of alternatives	17.5	13.5
Percentage of cases for which alternative 3-drug regimens were predicted to be more effective than the regimen selected	85	96
Median number of alternatives	10.75	12.75

Conclusions

- These models, trained with the largest dataset so far, were able to predict response to HIV therapy *without a genotype* significantly more accurately than genotyping with rules-based interpretation.
- The models were accurate for cases from different RLS.
- The models identified potentially effective alternative regimens for the great majority of cases evaluated
- The models are freely available online as part of the HIV Treatment Response Prediction System (HIV-TRePS).
- This system has significant potential utility as a treatment support tool, particularly in settings where genotyping is unavailable

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