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The application of artificial intelligence to predict response to different HIV therapies, without a genotype: new models for therapy optimisation in resource-limited settings

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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 (RLS), without access to the newest drugs, or genotyping to help tailor therapy for the individual
- Many computational models developed to predict virological response to therapy require a genotype, have been developed using western data and have stringent data requirements making them impractical for use in RLS.
- Here we describe the development of new models that do not require a genotype, using a large data set that includes substantial data from RLS
- These models included, for the first time, tipranavir, maraviroc and elvitegravir.

Methods

- Treatment and outcome data have been collected from approximately 200,000 patients from more than 50 HIV cohorts and clinics around the world
- Packages of data termed 'treatment change episodes' (TCEs) were identified where antiretroviral therapy was changed following virological failure (plasma HIV RNA >50 copies/ml)
- Random forest (RF) models were trained to predict the probability of virological response (viral load <50 copies/ml) to a new regimen following virological failure, using data from 52,270 TCEs including 5,329 from RLS (4,190 from South Africa)
- The 44 input variables from which the models made their predictions included: baseline viral load, CD4 count, treatment history (each individual drug), the drugs in the new regimen and the time to follow-up
- The length of time before the treatment change from which baseline data were accepted was extended compared to previous studies, from 8 to 16 weeks for viral loads and 12 to 24 weeks for CD4 counts, to make the models more practical for use in RLS
- The models were assessed during cross-validation, with an independent test set (n=3,000 including 461 TCEs from South Africa)
- The area under the receiver operator characteristic (ROC) curve (AUROC) was the main outcome, with sensitivity, specificity and overall accuracy as secondary measure
- For those cases that had genotypes on file, the predictive accuracy of the models was compared to genotyping using three rules-based interpretation systems to derive genotypic sensitivity scores (GSS)
- The models were used to identify alternative regimens that are in common clinical use that were predicted to be effective for those cases that failed the new regimen introduced in the clinic.

Results - 1

- The models achieved a mean AUROC of 0.83 during cross validation and 0.81 with the independent 3,000 TCE test set
- Sensitivity was 73%, specificity 76% and overall accuracy 75%
- Performance of the models was not inferior to that of control models developed using the more stringent baseline data windows, which produced an AUROC of 0.82
- For the South African test cases the models achieved an AUROC of 0.76, sensitivity of 72%, specificity of 69% and overall accuracy of 70%
- The AUROC values for cases involving tipranavir, maraviroc and elvitegravir, ranged from 0.75 to 0.85.

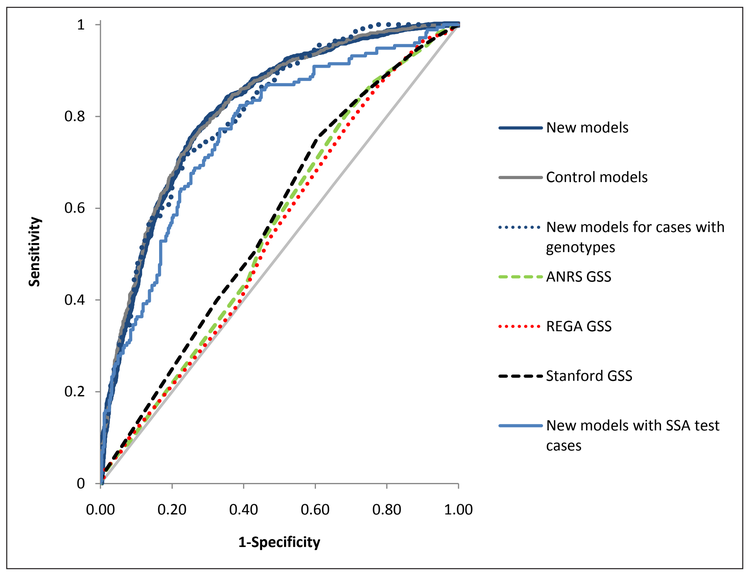
Table 1: Accuracy of the models models

	AUROC	Overall accuracy	Sensitivity	Specificity
CROSS VALIDATION				
Mean of the five models	**0·83**	76%	71%	80%
INDEPENDENT TESTING				
All test cases (n=3,000)	**0·81**	75%	73%	76%
Control models with standard baseline data windows	0.82	75%	72%	77%
Southern African cases (n=461)	**0.76**	70%	72%	69%
Elvitegravir* (n=50)	0.75	76%	74%	79%
Maraviroc* (n=50)	0.83	74%	74%	74%
Tipranavir (n=50)	0.85	80%	70%	82%
Genotyping (n=634)				
ANRS	0.56	54%	53%	55%
REGA	0.55	53%	53%	53%
Stanford HIVdb	0.58	56%	40%	68%

* Overall accuracy, sensitivity and specificity reported using drug-specific optimum operating point

Results - 2

Figure 1: ROC curves



- Of the 3,000 test TCEs, 634 had genotypes and the AUROC for the GSS ranged between 0.55 and 0.58 - significantly inferior to the accuracy of the models (p<0.0001)
- The models were able to identify one or more alternative regimens that were predicted to be effective for 96% of the 1,716 test cases that failed the new regimen introduced in the clinic.

Table 2: Modelling of alternative regimens

	Number of cases identified	Percent
Test cases for which the models were able to identify an alternative regimen that was predicted to be effective (out of total of 2,783 cases)	2,714	98%
Cases that failed their new regimen in the clinic for which alternative regimens were predicted to be effective	1,652	96%
Cases that failed their new regimen in the clinic for which alternative regimens were predicted to have a higher probability of response	1,716	100%

Conclusions

- **These new models, trained with our largest dataset so far, were able to predict response to HIV therapy significantly more accurately than genotyping with rules-based interpretation**
- **The models were accurate for cases from South Africa and cases involving new drugs**
- **The models have the potential to predict and avoid treatment failure by identifying potentially effective, alternative regimens**
- **The models are practical for use in RLS in that they do not require a genotype and have less stringent data requirements than is customary**
- **The models are freely accessible online via the HIV Treatment Response Prediction System, HIV-TRePS, at www.hivrdi.org/treps**

Data contributors

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