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Computational models that predict response to HIV therapy may reduce virological failure and therapy costs in resource-limited settings

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Background

- The long-term effectiveness of antiretroviral therapy (ART) in resource-limited settings (RLS) is challenged by limited access to drugs, diagnostics and expertise
- The adoption of a public health strategy involving simple treatment protocols and the use of clinical or immunological monitoring to detect therapy failure can be associated with deferred/inappropriate treatment switching, accumulation of resistance and increased morbidity and mortality[1-4]
- Computational models have been developed that can predict response to ART from a range of variables including a genotype with circa 80% accuracy[5,6]
- Models can predict response to ART without a genotype with circa 70-75% accuracy, at least comparable to the accuracy of genotyping with rules-based interpretation[7-9]
- Models have proved more accurate for patients from familiar settings (with data in the training set) than unfamiliar settings[10]

Objectives

1. **To compare the accuracy of models for patients from 'familiar' settings to those from 'unfamiliar' resource-limited settings (RLS)**
2. **To investigate if the models can identify alternative regimens for cases of failure that have a higher predicted probability of success without additional cost**

Methods

- Random forest models used to power the HIV Treatment Response Prediction system (HIV-TRePS)
- Trained with data from 14,891 cases of ART change following virological failure in well-resourced countries
- Input variables: viral load and CD4 count prior to treatment change, treatment history, drugs in the new regimen, time to follow-up and follow-up viral load.
- *Output: prediction of the probability of response to ART (<400 copies HIV RNA/ml)*

Assessment of models
- Cross-validation
- Independent set of 800 cases from familiar settings

Unfamiliar test sets from RLS
- 231 cases from RLS in Southern Africa
- 375 cases from Romania
- 206 cases from India

Main outcome measure: The area under the ROC curve (AUC)

Modelling alternative regimens
- Baseline data input to models
- Predictions of response obtained for alternative 3-drug regimens comprising only those drugs available in the clinic
- Annual therapy costs used to determine the potential cost effectiveness of this strategy for the Indian cases

Results - 1

Table 1: Accuracy of the models for familiar vs unfamiliar settings

DATA SET	AUC	Overall accuracy	Sensitivity	Specificity
Familiar				
RDI (n=800)	**0·77**	71%	71%	70%
95%CI	(0·73, 0·80)	(68, 74)	(67, 75)	(64, 75)
Unfamiliar				
Southern Africa (n=231)	**0·60****	61%	60%	62%
95%CI	(0·52, 0·69)	(53%, 67%)	(52%, 68%)	(49%, 74%)
Romania (n=375)	**0.71**	67%	67%	68%
95%CI	(0.66, 0.76)	(62%, 72%)	(60%, 74%)	(60%, 74%)
India (n=206)	**0.63***	57%	55%	61%
95%CI	(0.55, 0.71)	(50%, 64%)	(47%, 63%)	(49%, 72%)

*p<0.01 vs RDI 800 **p<0.001 vs RDI 800 (De Long's test)

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Results - 2

Figure 1: ROC curves for the different test sets

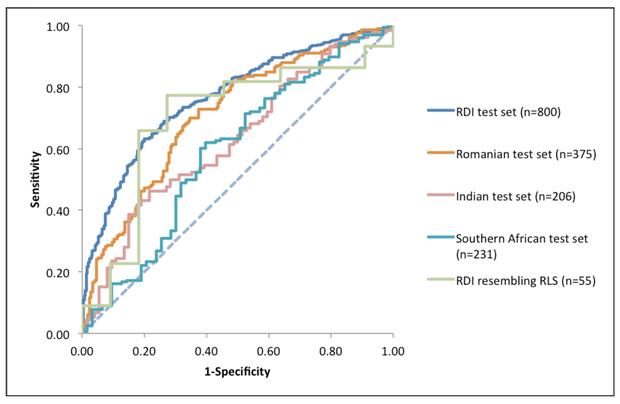

Table 2: Modelling of alternative regimens

	Southern Africa (n=231)	Romania (n=375)	India (n=206)
Number (proportion) of all cases for which the models were able to identify a regimen that was predicted to be effective	217 (94%)	362 (97%)	206 (100%)
No. (%) of cases that failed in the clinic	63 (27%)	176 (47%)	74 (36%)
No. (%) of actual failures for which alternative regimens were found that were predicted to be effective	59 (94%)	164 (93%)	73(99%)
No. (%) for which alternative regimens were found with higher predictions of response	63(100%)	176 (100%)	74 (100%)

Table 3: Modelling cost and effectiveness for cases from India

Analysis	All (n=206)	Failures (n=74)
No (%) of cases for which the models were able to identify alternative regimens predicted to be effective	206 (100%	74 (100%)
No (%) of category 1 alternatives with a higher estimated probability of response than the regimen used in the clinic	175 (85%)	65 (88%)
No (%) of category 2 alternatives where one or more of the alternatives was less costly than the regimen used in the clinic	175 (100%)	65 (100%)
Mean number of alternatives in category 3	10	8
The mean annual cost saving of the least costly regimens in category 3	$638	$555

Conclusions

The HIV-TRePS models that predict virological response to ART without a genotype:

1. **Showed comparable accuracy to genotyping with rules-based interpretation for patients from unfamiliar RLS**
2. **Were more accurate for patients from familiar settings suggesting further improvement is possible with more data from RLS**
3. **Identified alternative regimens that were predicted to be effective for the great majority of cases where the new regimen prescribed in the clinic failed**
4. **Identified cost-saving alternatives for most cases of failure in India that could fund additional patients' treatment and/or viral load monitoring**
5. **Have the potential to help optimise antiretroviral therapy in countries with limited resources where genotyping is not generally available.**

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... and most of all their patients.