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

Revell AD, Wang D, Alvarez-Uria G, *Streinu-Cercel A,* Ene L, Wensing AMJ, Hamers RL, Morrow C, Wood R, Tempelman H, DeWolf F, Nelson M, Montaner JS, Lane HC, Larder BA ***on behalf of the RDI study group***

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rdi hiv resistance response database initiative

State of the ART

Key features of HIV treatment	Well-resourced settings	Resource-limited settings
Strategy	**Individualised**	**Public health**
Antiretroviral drugs	Approx. 25 from 6 classes	Limited availability / affordability
Diagnostic & monitoring tools	CD4, viral loads, resistance testing	CD4 (Viral load?)
Detection of failure	Early – using regular viral loads	Later – using CD4 counts or clinical symptoms
Salvage	Individualised – using genotype	Standard protocol – genotypes unaffordable
Expertise available	High and multidisciplinary	Mixed and thinly spread

Consequences of the public health strategy for resource-limited settings

- Rapid roll-out of ART[1]
- Short-term cost-savings = more patients on therapy[1]
- Extended the lives of millions
- Unnecessary treatment switching[2]
- Delayed detection of failure and deferred treatment switching[3]
- Increased accumulation of resistance mutations[2,4]
- Loss of therapeutic options[5]
- Increased morbidity/mortality[4]

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A big ?

What can we do to maximise the long-term effectiveness of ART in RLS?

How do we get the best out of a limited range of drugs?

Could the individualization of salvage ART using computational models be beneficial?

Predicting response using computational models

- Models can predict the response to ART with approx. 80% accuracy:
  - Trained using data from many thousands of patients
  - Input variables including genotype, viral load, CD4 count and treatment history[1,2]
- Models can predict response <u>without a genotype</u> with a circa 70-75% accuracy[3,4]
- At least comparable to the predictive accuracy of genotyping with rules based interpretation (62-69%)[5]
- Models now freely available via online HIV Treatment Response Prediction System (HIV-TRePS)

1. Revell AD, Wang D, Boyd MA, et al. The development of an expert system to predict virological response to HIV therapy. *AIDS* 2011;**25**:1855-1863.
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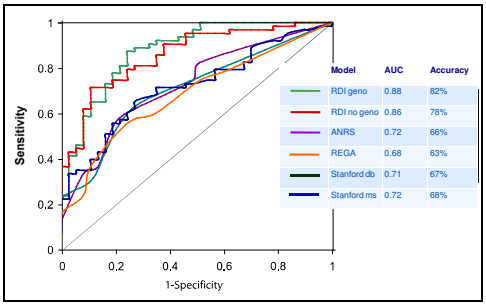
3. Revell AD, Wang D, Harrigan R, et al. Modelling response to HIV therapy without a genotype. *J Antimicrob Chemother* 2010; **65**(4):605-607
4. Prosperi MCF, Rosen-Zvi M, Altman A, et al. Antiretroviral therapy optimisation without genotype resistance testing. *PLoS One* 2010; **5**(10):e13753
5. Frentz et al. Comparison of HIV-1 Genotypic Resistance Test Interpretation Systems in Predicting Virological Outcomes Over Time. *PLoS One.* 2010; **5**(7): e11505

RDI models with and without genotype and GSS from common rules systems



Larder BA *et al.* 49th ICAAC, 2009; H-894

The issue of generalisability

- Previous studies have shown that models are more accurate for patients from 'familiar' settings (with data in the training set) than from unfamiliar settings
- Our models are therefore evaluated not only during cross validation but with independent test sets and data from other settings

Current study objectives

1. To compare the accuracy of HIV-TRePS for patients from 'familiar' settings to those from 'unfamiliar' resource-limited settings (RLS)
2. To investigate if the system could identify alternative regimens for cases that failed in the clinic with a higher predicted probability of success and without additional cost

Methods 1: HIV-TRePS models

- 10 random forest models
- 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)**

Methods 2: Assessment of model accuracy

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

Unfamiliar RLS test sets

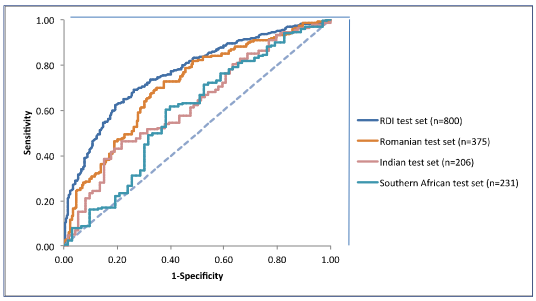
- 231 cases from sub-Saharan Africa (5 countries)
- 375 cases from Romania
- 206 cases from India
- Main outcome measure: The area under the ROC curve (AUC)

Results 1: Accuracy: familiar vs unfamiliar settings

DATA SET	AUC
Familiar	
RDI (n=800)	**0·77**
95%CI	(0·73, 0·80)
Unfamiliar from RLS	
Southern Africa (n=231)	**0·60****
95%CI	(0·52, 0·69)
Romania (n=375)	**0.71**
95%CI	(0.66, 0.76)
India (n=206)	**0.63***
95%CI	(0.55, 0.71)

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

Results 2: ROC curves



Methods 3: Modelling of alternative regimens

- Baseline data input to models
- Predictions of the probability of virological response obtained for alternative 3-drug regimens comprising only those drugs available in the clinic
- Is the regimen predicted to produce a virological response (using the optimum 'cut off' for classifying predictions as response or failure established with the 800 RDI test set)?
- Is the estimated probability of response higher than for the regimen actually used in the clinic?
- Annual therapy costs used to determine the potential cost effectiveness of this strategy for the Indian cases

Results 3: Modelling of alternative regimens

	Southern Africa (n=231)	Romania (n=375)	India (n=206)
Alternative regimens identified that were predicted to produce a response	217 (94%)	362 (97%)	206 (100%)
No (%) of cases that failed in the clinic	63 (27%)	176 (47%)	74 (36%)
No. (%) of failures for which alternative regimens were identified that were predicted to produce a response	59 (94%)	164 (93%)	73(99%)

Results 4: Modelling cost & effectiveness for India

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

Conclusions 1

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

- Showed comparable accuracy to genotyping with rules-based interpretation for patients in unfamiliar RLS
- Were more accurate for patients from familiar than unfamiliar settings suggesting further improvement in accuracy is possible with more data from RLS
- Identified alternative regimens that were predicted to be effective for the great majority of cases where the new regimen used in the clinic failed

Conclusions 2

- Identified cost-saving alternatives for most cases of failure in India
- Savings were substantial and could potentially fund additional patients' treatment and/or viral load monitoring

Conclusions 3

- **The system has the potential to help optimise antiretroviral therapy in countries with limited resources where genotyping is not generally available**
- **Viral load monitoring and use of computer modelling to individualise therapy could be a potentially cost effective alternative strategy**

Limitations of the study

- Retrospective so difficult to quantify the potential impact when used prospectively as a management tool
- Relatively small test sets from RLS because of shortage of data including viral load that conform to our stringent criteria

Quotes

- "The number one benefit of information technology is that it empowers people to do what they want to do"

  Steve Ballmer, CEO of Microsoft

- "This approach literally puts the experience of treating thousands of different patients at the individual doctor's fingertips."

  Dr. Julio Montaner, Director of the BC Centre for Excellence in HIV & AIDS, Vancouver, Canada.

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Acknowledgments 2

RDI

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