hiv resistance
response database initiative
A global non-profit initiative against HIV drug resistance
www.hivrdi.org email: info@hivrdi.org

HIV TRePS
HIV Treatment Response
Prediction System
www.hivrdi.org/treps

Poster: O131
HIV Drug Therapy in the Americas
8-10 May 2014
Rio de Janeiro, Brazil

The HIV Treatment Response Prediction System – using the experience of treating tens of thousands of patients to guide optimal drug selection

Revell AD[1], Wang D[1], Reiss P,[2] van Sighem A [2], Hamers R [3], Morrow C [4], Gazzard B [5], Montaner JS[6], Lane HC[7], Larder BA[1] *on behalf of the global RDI study group*

1: HIV Resistance Response Database Initiative (RDI), London, UK; 2: Netherlands HIV Monitoring Foundation, Amsterdam, The Netherlands; 3: PharmAccess Foundation, Academic Medical Centre of the University of Amsterdam, Amsterdam, The Netherlands; 4: Desmond Tutu HIV Centre, Cape Town, South Africa; 5: Chelsea and Westminster Hospital, London, UK; 6: BC Centre for Excellence in HIV/AIDS, Vancouver, Canada; 7: National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA

Background

- Optimising the selection of antiretroviral drugs for patients experiencing virological failure remains a challenge
- This is particularly true in resource-limited settings where the latest drugs may not be accessible and/or genotyping may not be affordable to guide drug selection
- The RDI was set up in 2002 to develop computational models that predict virological response to different combinations of drugs, and to make those models freely available to assist optimal, individualised drug selection.

Methods

- In order to collect sufficient data to develop such models, HIV cohorts and clinics around the world were approached for a range of longitudinal clinical, virological and treatment data for their patients
- These data have been used to train a range of neural network, support vector machine, linear regression and random forest models[1]
- The models provide quantitative predictions of viral load response to any HIV drug combination, from baseline viral load, CD4 count genotype if available (not essential), HIV treatment history, the drugs in the new regimen and the time to follow-up
- The models are tested during cross validation and with independent validation sets and their accuracy compared with that of genotyping with rules-based interpretation.

Results - 1

- Data from approximately 150,000 patients with >1million viral load values have been collected
- The best performing models (random forests) routinely predict virological response/ failure to a change of therapy with an accuracy of 80% or more, even without the use of a genotype[2,3]
- Moreover, they are significantly more accurate than genotyping itself[2-3]
- They are able to identify simple, alternative drug combinations that are predicted to be effective for the majority of cases that failed following a treatment change in the clinic[3]
- The latest models that did not use a genotype in their predictions achieved accuracy of 0.82 during cross validation and 0.80 in independent testing - significantly superior to 0.56-0.57 for genotyping ($p<0.001$) (Table 1 and Figure 1)[3]
- In clinical prospective testing by HIV experts use of HIV-TRePS led to one third of treatment decisions being revised[4]
- In a study of an Indian cohort the system identified alternative regimens using locally available drugs that were less costly and predicted to be more effective than the salvage regimen actually prescribed in the clinic (Table 3)[5]

Table 1: Performance of the models *vs* genotyping with rules-based interpretation

Prediction System	AUC	Sensitivity (%)	Specificity (%)	Accuracy (%)	Statistical comparison vs models
RF models	**0.80**	**65**	**80**	**75**	
GSS (genotyping + rules interpretation)					
ANRS	0.57	51	58	55	p<0.0001
HIVdb	0.57	53	57	56	p<0.0001
Rega	0.56	52	54	53	p<0.0001
Genotypng average	0.57	52	56	55	

References

1. Wang D, Larder BA, Revell AD, Montaner J, Harrigan R, De Wolf, F et al. A comparison of three computational modelling methods for the prediction of virological response to combination HIV therapy. Artificial Intelligence in Medicine 2009; 47: 63-74.
2. Revell, A., Boyd, M., Wang, D., Emery, S., Gazzard, B., Reiss, P., van Sighem, A., Montaner, J., Lane, H. and Larder, B. (2014), A comparison of computational models with and without genotyping for prediction of response to second-line HIV therapy. HIV Medicine. doi: 10.1111/hiv.12156.
3. Revell AD, Wang D, Wood R et al. An update to the HIV-TRePS system: The development of new computational models that do not require a genotype to predict HIV treatment outcomes. J Antimicrob Chemother 2014: 69:1104-1110
4. Larder, BA, Revell, AD, Mican J, Agan BK, Harris M, Torti C, et al. Clinical Evaluation of the Potential Utility of Computational Modeling as an HIV Treatment Selection Tool by Physicians with Considerable HIV Experience. AIDS Patient Care and STDs 2011; 25(1):29-36
5. Revell AD, Alvarez-Uria G, Wang D, Pozniak A, Montaner JSG, Lane HC, Larder BA. Potential Impact of a Free Online HIV Treatment Response Prediction System for Reducing Virological Failures and Drug Costs after Antiretroviral Therapy Failure in a Resource-Limited Setting. BioMed Res Int 2013; doi 10.1155/2013/579741

Results - 2

Figure 1: ROC curves for the models and genotyping with different interpretation systems as predictors of virological response to ART

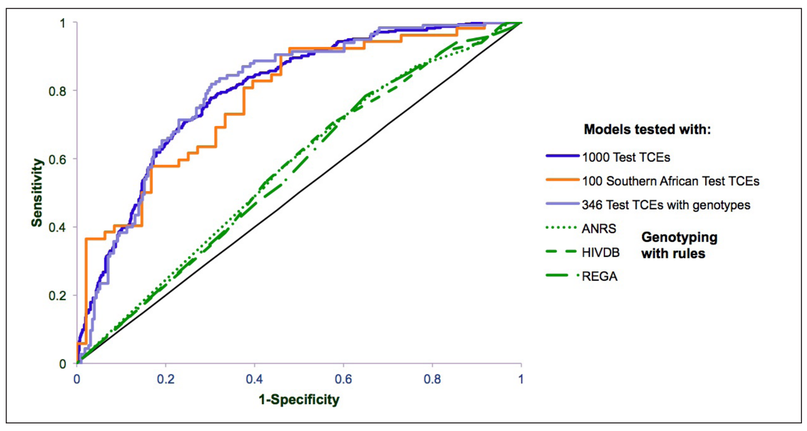

Table 2: In silico modelling of alternative, available regimens for Southern African cases

	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	14.5	14
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	7	9

Table 3: In silico modelling of alternative, availble less costly regimens for cases of first line failure in India

Analysis	All (n=206)	Failures (n=74)
No (%) of cases for which the models were able to identify alternative second-line regimens predicted to be effective	206 (100%)	74 (100%)
No (%) where one or more of the alternatives was less costly than the second line regimen used in the clinic	175 (100%)	65 (100%)
Mean number of alternatives in category 3	10	8
The mean cost saving from the median costing alternative for each patient (95% CI)	$364 ($332, $395)	$421 ($361, $481)

Conclusions

- Computational models can be accurate predictors of virological response, even without a genotype
- They are significantly more accurate than genotyping
- The models have the potential to avoid treatment failure by identifying effective, alternative, practical regimens
- The system has the potential to save money by identifying less costly but effective alternative ART
- The models are used to power the free, online HIV Treatment Response Prediction System (HIV-TRePS)
- **HIV-TRePS has the potential to help optimise therapy in settings with limited resources where certain drugs and/or genotyping may not be available**

Acknowledgements

AREVIR database, c/o the University of Cologne, Germany: Rolf Kaiser
ATHENA database c/o Netherlands HIV Monitoring Foundation, Amsterdam, The Netherlands: Frank DeWolf & Joep Lange
BC Centre for Excellence in HIV/AIDS: Richard Harrigan & Julio Montaner
Chelsea and Westminster Hospital, London: Brian Gazzard, Anton Pozniak & Mark Nelson
CPCRA: John Bartlett, Mike Kozal, Jody Lawrence
Desmond Tutu HIV Centre, Cape town, South Africa: Carl Morrow and Robin Wood
"Dr. Victor Babes" Hospital for Infectious and Tropical Diseases, Bucharest, Romania: Luminita Ene
Federal University of Sao Paulo, Sao Paulo, Brazil: Ricardo Diaz & Cecilia Sucupira
Fundacion IrsiCaixa, Badelona: Bonaventura Clotet & Lidia Ruiz
Gilead Sciences: Michael Miller and Jim Rooney
Hôpital Timone, Marseilles, France: Catherine Tamalet
Hospital Clinic Barcelona: Jose Gatell & Elisa Lazzari
Hospital of the JW Goethe University, Frankfurt: Schlomo Staszewski
ICONA: Antonella Monforte & Alessandro Cozzi-Lepri
Istituto Superiore di Sanità, Rome, Italy: Stefano Vella and Raffaella Bucciardini
Italian MASTER Cohort (c/o University of Brescia, Italy): Carlo Torti
Italian ARCA database, University of Siena, Siena, Italy: Maurizio Zazzi
The Kirby Institute, University of New South Wales, Sydney, Australia: Sean Emery and Mark Boyd
National Institutes of Allergy and Infectious Diseases: Cliff Lane, Julie Metcalf, Robin Dewar
National Institute of Infectious Diseases, Bucharest, Romania: Adrian Streinu-Cercel and Oana Streinu-Cercel
National Institute of Infectious Diseases, Tokyo: Wataru Sugiura
Ndlovu Medical Centre, Elandsdoorn, South Africa: Roos Barth & Hugo Tempelman
PASER-M Cohort, Kenya, Nigeria, South Africa, Uganda, Zambia and Zimbabwe: Raph Hamers
PhenGen study, Italy: Laura Monno
PHIDISA study, c/o National Institutes of Allergy and Infectious Diseases, Bethesda, USA: Julie Metcalf
Ramon y Cajal Hospital, Madrid, Spain: Maria-Jesus Perez-Elias
Royal Free Hospital, London, UK: Anna Maria Geretti
Rural Development Trust (RDT) Hospital, Bathalapalli, AP, India: Gerardo Alvarez-Uria
Sapienza University, Rome, Italy: Gabriella d'Ettorre
SATuRN Netowrk in Southern Africa: Tulio de Oliveira
Tibotec Pharmaceuticals: Gaston Picchio and Marie-Pierre deBethune
US Military HIV Research Program: Scott Wegner & Brian Agan
University of Belgrade, Belgrade, Serbia: Gordana Dragovic

... and all their patients.