Poster: TUPE091

XIX International AIDS Conference
22-27 July 2012; Washington DC, USA

HIV TRePS
HIV Treatment Response Prediction System
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The development of new computational models for the HIV-TRePS online treatment selection tool

Revell AD[1], Wang D[1], DeWolf F[2], Gatell J[3], Ruiz L[4], Pozniak A[5], Perez-Elias MJ[6], Lane HC[7], Montaner JSG[8], Larder, BA[1]
on behalf of the global RDI study group

1: The HIV Resistance Response Database Initiative (RDI), London, UK; 2: Netherlands HIV Monitoring Foundation, Amsterdam, The Netherlands; 3: Hospital Clinic of Barcelona, Barcelona, Spain; 4: Fundació irsiCaixa, Badalona, Spain; 5: Chelsea and Westminster Hospital, London, UK; 6: Ramón y Cajal Hospital, Madrid, Spain; 7: NIAID, Bethesda, USA; 8: BC Centre for Excellence in HIV/AIDS, Vancouver, Canada.

Background

- Selecting the optimal combination of antiretroviral drugs for an individual patient can be challenging, particularly in the face of extensive treatment history and viral drug resistance.
- Computational models that predict accurately virological response to combination antiretroviral therapy (ART) have been developed and can help treatment decisions[1-3].
- Here we developed and compared random forest (RF) models that use different levels of treatment history information to predict virological response to combinations of drugs including, for the first time, raltegravir.

Methods

- 7,263 treatment change episodes (TCEs) (instances where the treatment was changed following virological failure) were used to train two committees of 5 RF models to predict the probability of virological response to a new ART regimen.
- The input variables were baseline CD4 cell count, viral load and genotype (protease and RT), drugs in the new regimen and time to follow-up.
- Committee 1 also included six treatment history variables (zidovudine, lamivudine/emtracitabine, any PI, any NNRTI, enfuvirtide, raltegravir),
- Committee 2 included separate treatment history variables for previous exposure to each of 18 individual drugs.
- The accuracy of the models' predictions was assessed during cross-validation and with 375 independent TCEs from clinics the models have not been exposed to before (obtained from: http://hivdb.stanford.edu) by plotting receiver–operator characteristic (ROC) curves and compared to the use of genotypic sensitivity scores as a predictor of response or failure in the test cases.
- The models were used to identify alternative regimens that were predicted to be effective for those cases in the test set where the new treatment regimen failed.

Results

- The training and test sets were comparable except only 5% of the test set responded to the new treatment initiated in the clinic vs 35% of those in the training set (Table 1).
- The AUC for Committee 1 during cross-validation was 0.78–0.83 (mean=0.815) and for Committee 2, 0.80–0.84 (mean=0.820) (Table 2).
- The mean sensitivity was 64% and 62% and specificity was 81% and 84% for committees 1 and 2 respectively.
- The AUC for the 243 TCEs containing raltegravir ranged from 0.66-0.76 (mean=0.71) and 0.63-0.78 (mean=0.71) for the two committees.
- When tested with the 375 independent TCEs, Committee 1 achieved an AUC of 0.87 and Committee 2, 0.86.
- This compares with AUC values of 0.57-0.59 for genotypic sensitivity scores.

Table 1: Characteristics of training and test sets

	Training set	Test set
TCEs	7,263	375
Mean (median) baseline VL (log10 c/mL)	4.20 (4.11)	4.34 (4.30)
Mean (median) baseline CD4 (cells/µL)	269 (230)	277 (235)
Treatment History		
Mean (median) number of previous drugs	5.82 (5)	5.56 (5)
NRTI experience	99%	100%
NNRTI experience	65%	54%
PI experience	75%	79%
Enfuvirtide experience	6%	0%
Raltegravir experience	1%	1%
Mean (median) resistance mutations	8.48 (6)	8.34 (8)
Responders (<1.7 log10 c/mL follow-up VL)	2,550 (35%)	18 (5%)
Failures (≥1.7 log10 c/mL follow-up VL)	4,713 (65%)	357 (95%)

TCEs= treatment change episodes. VL= viral load. NRTI=nucleoside reverse transcriptase inhibitor. NNRT=non-nucleoside reverse transcriptase inhibitor. PI=protease inhibitor

Results (continued)

Table 2: Performance of the models during cross validation and independent testing

Models	AUC*	Sensitivity (%)	Specificity (%)
Simple treatment history models	0.870	66.67	90.48
95% CI	0.87-0.97	41-87	87-93
Individual treatment history models	0.855	61.11	87.47
95% CI	0.76-0.95	36-83	85-92
Genotype interpretation systems**			
Stanford HIVdb	0.591	47.06	41.26
95% CI	[0.49, 0.69]	[23, 72]	[36, 47]
ANRS v2011.05	0.573	23.53	61.03
95% CI	[0.45, 0.69]	[7,50]	[56,66]
REGA v8.0.2	0.566	35.29	54.44
95% CI	[0.44, 0.69]	[14, 62]	[49, 60]

*AUC = area under the (receiver-operator characteristic) curve.
** Based on 366 TCEs after those containing maraviroc or raltegravir were removed

- The models correctly predicted 330 (92%) of the virological failures that occurred in the test set and were able to identify alternative regimens that were predicted to be effective in 75% of the failures, using no more drugs that were used in the clinic and 40% using only those drugs approved at the time of the treatment decision (Table 3).

Figure 1: ROC curves

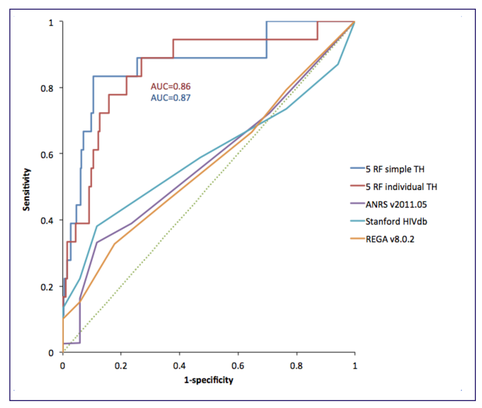

Table 3: Modelling effective alternative regimens for cases of virological failure

	18 drugs available (excl. tipranavir & maraviroc)	Only drugs available at the time of each TCE
Number (%) of actual failures for which the models identified alternative regimens predicted to be effective*	267 (75%)	143 (40%)
Number (%) of actual failures for which the models identified alternative regimens with a higher probability of success	357 (100%)	356 (100%)

* The estimated probability of virological response was above the optimum operating point established during cross-validation of the models

Conclusions

- **The models achieved a consistent, high level of accuracy in predicting treatment responses for independent test cases**
- **This performance was significantly superior to that of GSS**
- **The difference between models with restricted or comprehensive treatment history variables were minimal and not statistically significant**
- **The models are able to predict the great majority of failures and identify alternatives that are predicted to be effective for a substantial proportion of these**
- **The models are being used to power HIV-TRePS, the free online treatment selection tool at www.hivrdi.org/treps.**

Acknowledgements

This project has been funded in whole or in part with federal funds from the National Cancer Institute, National Institutes of Health, under Contract No. HHSN261200800001E. This research was supported by the National Institute of Allergy and Infectious Diseases. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

The RDI would like to thank the following individuals, institutions and their patients for providing the data used in the development of the models.

- AREVIR database, c/o the University of Cologne, Germany: Rolf Kaiser
- 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
- 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 "Prof.Dr. Matei Balş, 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
- Netherlands HIV Monitoring Foundation, Amsterdam, The Netherlands : Frank DeWolf & Joep Lange
- PharmAccess Foundation, AMC, Amsterdam, The Netherlands: Raph Hamers, Rob Schuurman & Joep Lange
- Ramon y Cajal Hospital, Madrid, Spain: Maria-Jesus Perez-Elias
- Royal Free Hospital, London, UK: Anna Maria Geretti
- Sapienza University, Rome, Italy: Gabriella d'Ettorre
- Stanford HIV TCE Repository: Bob Shafer
- US Military HIV Research Program: Scott Wegner & Brian Agan
- Tibotec Pharmaceuticals: Gaston Picchio and Marie-Pierre deBethune.

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