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: P 66
10th European Meeting on HIV & Hepatitis
Treatment Strategies and Antiviral Drug Resistance
28-30 March 2012; Barcelona, Spain

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], Nelson[5], M, Perez-Elias[6], MJ, Lane HC[7], Montaner JSG[8], 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: 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

- The optimum selection and sequencing of combination therapy (cART) to maintain viral suppression can be challenging particularly in settings where access to drugs, diagnostics or expertise may be limited but also due to the complexity of HIV drug resistance and the number of potential drug combinations.
- The HIV Resistance Response Database Initiative (RDI) pioneered the development of computational models that predict the virological response to cART.
- The RDI makes these models available, free, online as the HIV Treatment Response Prediction System (HIV-TRePS).
- Accurate models have been developed using a range of input variables, including different categories of treatment history information.
- Here we describe the development and testing of new random forest models to power HIV-TRePS.
- We compared models that used limited or comprehensive treatment history information and we included predictions of response to raltegravir for the first time.

Methods

- Data for model development were extracted from the RDI database of 83,871 patients
- Data filters were applied to exclude, for example, data involving drugs that are no longer in use and cases of probable non-adherence
- 7,263 treatment change episodes (TCEs) were extracted that met all entry criteria with no missing data points
- 2,550 were treatment responses (defined as a follow-up plasma viral load <50 copies HIV RNA/ml)
- The essential data for a TCE are summarised in Figure 1 and the characteristics of the database summarised in Table 1
- The TCEs were used to train two committees of 5 random forest models to predict the probability of virological response to the new regimen, using a 5 x cross-validation scheme
- The input variables were baseline CD4 cell count, viral load and genotype (62 mutations in protease and reverse transcriptase), drugs in the new regimen and time from treatment change to follow-up
- Committee 1 also included six binary treatment history variables coding for any previous exposure to: zidovudine, lamivudine/emtracitabine, enfuvirtide, raltegravir. These simple variables were selected on the basis of previous research showing them to be the most influential in terms of predictive accuracy
- Committee 2 included instead 18 binary treatment variables for exposure to individual drugs
- The accuracy of the models was assessed during cross validation by plotting receiver–operator characteristic (ROC) curves – the primary metric being the under the curve (AUC)

Figure 1: The treatment change episode

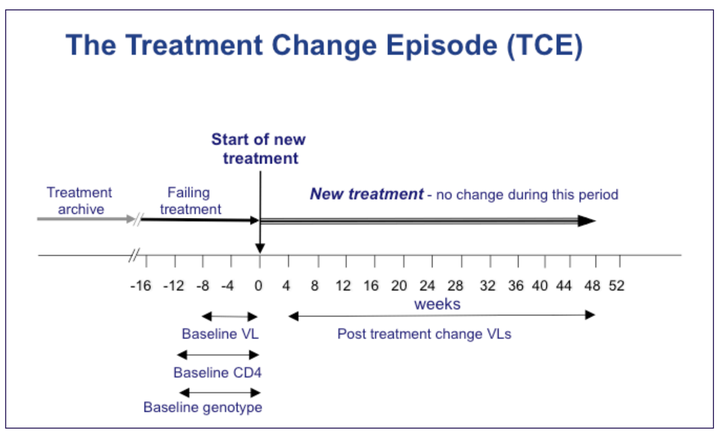


Table 1: Descriptive statistics for the training data

	Mean	Median	SD
Baseline plasma viral load (log_{10} copies HIV RNA/ml)	4.11	4.2	1
Baseline CD4 count	269	230	209
Number of previous drugs	5.82	5	2.98
Number of protease mutations	4.47	3	3.82
Number of RT mutations	4.01	3	3.33
Time to follow-up (days)	111	88	77
Follow-up viral load (log10 copies/ml)	2.71	2.22	1.18

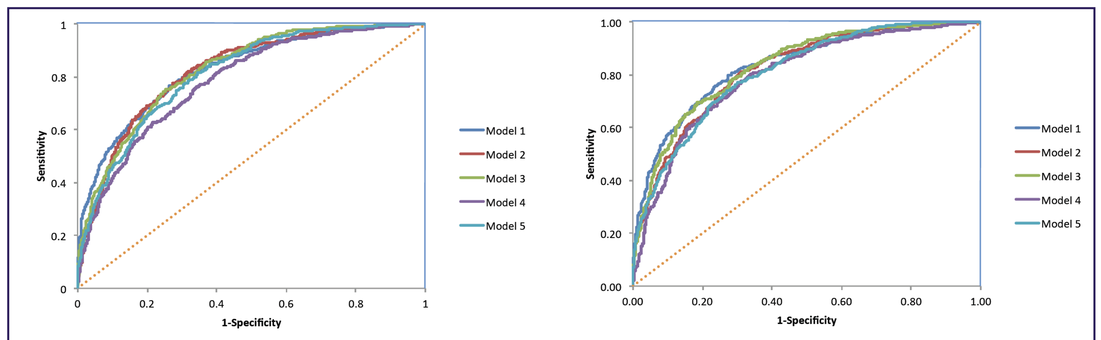
Results

- The models in Committee 1 achieved AUC values during cross-validation of 0.78–0.83 (mean = 0.815).
- Overall accuracy was 73% - 77% (mean = 75%); sensitivity was 61–68% (mean = 64%); and specificity 80–84% (mean = 81%).
- The models in Committee 2 achieved an AUC of 0.80–0.84 (mean = 0.820)
- Overall accuracy was 75% - 78% (mean = 76%); sensitivity was 60–65% (mean = 62%); and specificity was 81–87% (mean = 84%). The difference in AUC between the two committees was not statistically significant (p=0.21), using a paired t-test.
- The AUC values for the 243 TCEs containing raltegravir ranged from 0.66-0.76 (mean=0.71) for Committee 1 and 0.63 to 0.78 (mean=0.71) for Committee 2.

Table 2: Summary of results

Treatment History (simple)					Treatment History (18 individual drugs)				
Model	AUC	Overall accuracy	Sensitivity	Specificity	Model	AUC	Overall accuracy	Sensitivity	Specificity
1	**0.829**	76.56	63.64	84.23	**1**	**0.837**	77.54	64.86	85.06
2	**0.824**	76.97	67.51	81.68	**2**	**0.821**	76.69	61.18	84.42
3	**0.827**	75.02	65.24	80.43	**3**	**0.834**	77.99	62.52	86.56
4	**0.784**	73.16	61.21	79.6	**4**	**0.798**	75.41	60.43	83.49
5	**0.813**	75.04	64.08	80.72	**5**	**0.811**	74.53	61.55	81.26
Mean	0.815	75.35	64.34	81.33	Mean	0.82	76.43	62.11	84.16
SD	0.018	1.51	2.3	1.78	SD	0.016	1.45	1.71	1.97

Figure 2: ROC curves for the two sets of RF models



Conclusions

- **Overall, the models achieved a consistently high level of accuracy in predicting treatment responses.**
- **The differences between the models using the restricted set of treatment history variables and those using 18 individual drug history variables were minimal and not statistically significant.**
- **The accuracy of the models for raltegravir TCEs was somewhat reduced compared with the overall performance, reflecting perhaps the relatively small number of raltegravir TCEs and/or the absence of genotype information relating to this inhibitor**
- **The models are being used to power HIV-TRePS, the online aid to treatment selection, at: www.hivrdi.org/treps.**

Acknowledgements

- 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
- US Military HIV Research Program: Scott Wegner & Brian Agan
- Tibotec Pharmaceuticals: Gaston Picchio and Marie-Pierre deBethune.