Poster: MOPE744

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

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

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

Predicting response to antiretroviral therapy without a genotype: a clinical tool for resource-limited settings

BA Larder[1], AD Revell[1], D Wang[1], R Hamers[2], H Tempelman[3], R Barth[4], AMJ Wensing[4], C Morrow[5], R Wood[5], F DeWolf[6], B Gazzard[7], HC Lane[8], JM Montaner[9] *on behalf of the global RDI study group*

1 HIV Resistance Response Database Initiative (RDI), London, UK; 2 PharmAccess Foundation, Academic Medical Centre, Amsterdam, The Netherlands; 3 Ndlovu Care Group, Elandsdoorn, South Africa; 4 University Medical Centre, Utrecht, The Netherlands; 5 Desmond Tutu HIV Centre, Cape Town, South Africa; 6 Netherlands HIV Monitoring Foundation, Amsterdam, The Netherlands; 7 Chelsea and Westminster Hospital, London, UK; 8 National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA; 9 BC Centre for Excellence in HIV/AIDS, Vancouver, Canada.

Background

- In resource-limited settings (RLS), optimising therapy following treatment failure is particularly challenging due to limited treatment options and the general unavailability of resistance testing.
- In resource-rich settings (RRS), computational models can predict virological response accurately from a range of laboratory data including a genotype, and are useful web-based clinical tools[1-3].
- In this study we developed models that do not require a genotype to predict virological response to antiretroviral therapy and assess their potential clinical utility using data from RLS.

Methods

- Random forest (RF) models were trained to predict the probability of virological response (viral load <400 copies/ml) following a treatment change, using baseline viral load and CD4 count (while on the failing regimen), treatment history, drugs in the new regimen and time to follow-up.
- Approximately 16,000 treatment change episodes (TCEs) meeting the entry criteria were extracted from our database of 85,000 patients (largely from RRS) and randomised into a training set of 14,891 and a test set of 800 TCEs.
- The models were assessed in three ways: during cross-validation, with the 800 test set and with 231 cases from a range of clinics and cohorts in sub-Saharan Africa. The area under the ROC curve (AUC) was the main outcome measure.
- The models were used to identify alternative regimens, using only those drugs available in the local setting, that were predicted to be effective for those cases in the test set where the new treatment regimen failed.

Results

- The characteristics of the data sets are summarised in Table 1.
- The data from RLS had somewhat higher baseline viral loads than the training data, consistent with patients in RLS switching after a greater degree of virological failure, often based on clinical symptoms or CD4 counts.
- Almost all of the cases from Africa had received NRTIs and NNRTIs in their history and most had been switched onto 2 NRTIS + PI.
- The training data covered a range of new regimens with 35% moving to 2 NRTIs + PI, 24% to 2 NRTIs + NNRTI and 41% to another type of regimen altogether.

Table 1: Characteristics of training and test data sets

	Training set	RDI Test set	Ndlovu	Gugulethu	PASER-M	South Africa
TCEs	14,891	800	39	114	78	164
Patients	4,878	800	38	104	78	153
Male	68%	75%	31%	25%	56%	30%
Median Baseline VL (log10 c/mL)	3·77	3·79	4·31	3·95	4·64	4·04
Mean Baseline VL (log10 c/mL)	3·74	3·74	4·23	4·02	4·59	4·08
Median Baseline CD4 (cells/µL)	260	260	214	239	84	228
Mean Baseline CD4 (cells/µL)	310	294	302	276	111	275
Treatment History						
Number of previous drugs (median)	5	5	4	4	4	4
NRTI experience (%)	100%	100%	100%	100%	100%	100%
NNRTI experience (%)	68%	67%	100%	99%	100%	99%
PI experience (%)	83%	81%	0%	4%	6%	4%
Failures (>2·6 log10 c/mL follow-up VL)	6,501	309	14	41	8	57
Percent	44%	39%	36%	36%	10%	35%
Responses	8,390	491	25	73	70	107
Percent	56%	61%	64%	64%	90%	65%
New Regimens						
2 NRTI + PI (%)	35%	35%	92%	88%	91%	87%
2 NRTI + NNRTI (%)	24%	22%	8%	12%	1%	10%
Other (%)	41%	43%	0	0	8%	3%

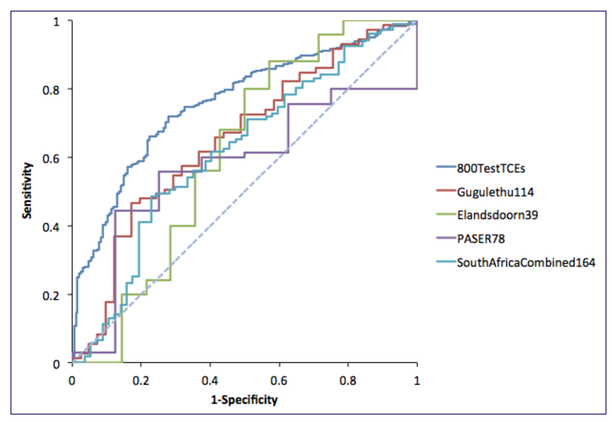
TCEs= treatment change episodes. VL= viral load. NRTI=nucleoside reverse transcriptase inhibitor. NNRT= non-nucleoside reverse transcriptase inhibitor. PI=protease inhibitor

Results (continued)

Table 2: Performance of the models during independent testing

Data set	AUC	Overall accuracy	Sensitivity	Specificity
800 RDI subset	0·77	71%	71%	70%
95%CI	(0·73, 0·80)	(68%, 74%)	(67%, 75%)	(64%, 75%)
Ndlovu clinic	0·61	64%	68%	57%
95%CI	(0·40, 0·73)	(47%, 79%)	(46%, 85%)	(29%, 82%)
Gugulethu clinic	0·65	62%	62%	63%
95%CI	(0·55, 0·76)	(57%, 75%)	(50%, 73%)	(47%, 78%)
PASER-M cohort	0·58	60%	60%	63%
95%CI	(0·38, 0·77)	(49%, 71%)	(48%, 72%)	(24%, 91%)
South Africa combined	0·62	61%	62%	60%
95%CI	(0·53, 0·71)	(53%, 68%)	(52%, 71%)	(46%, 72%)

Figure 1: ROC curves for the RLS test data sets



- The models achieved a mean AUC of 0.77 (95%CI 0.76,0.78) during cross validation and 0.77 (95%CI 0.73,0.80) with the 800 test set.
- For the RLS test sets, AUC ranged from 0.58-0.65 (Table 2, Figure 1).
- For the combined South African data, AUC= 0.62 (95%CI 0.53,0.71).
- The models correctly predicted approximately 60% of the RLS treatment failures and identified alternative 3-drug regimens comprising locally available drugs with higher probabilities of response for all clinical failures (Table 3).

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

	Ndlovu	Gugulethu	PASER-M	South Africa
No (%) of cases that failed	14 (36%)	41 (36%)	8 (10%)	57 (35%)
Number of cases overall for which the models were unable to identify a regimen that was predicted to be effective	0 (0%)	3 (3%)	3 (4%)	2 (4%)
No. (%) of actual failures for which alternative regimens were found that were predicted to be effective	14 (100%)	20 (77%)	2 (40%)	27 (79%)
No. (%) for which alternative regimens were found with higher predictions of response	14 (100%)	26 (100%)	5 (100%)	34 (100%)

Conclusions

- **Models trained with large data sets from resource-rich countries can predict virological response without a genotype for cases in RLS with an accuracy that is comparable to that of genotyping with rules-based interpretation.**
- **The models can predict and potentially avoid treatment failure by identifying effective, alternative, practical regimens.**
- **This approach may have substantial clinical utility for managing cases of treatment failure in RLS.**
- **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.

References

1. Larder BA, Wang D, Revell A, Montaner J, Harrigan R, De Wolf F et al. The development of artificial neural networks to predict virological response to combination HIV therapy. *Antivir Ther* 2007; **12**:15-24.
2. Revell AD, Wang D, Boyd MA, Emery S, Pozniak A, De Wolf F, et al. The development of an expert system to predict virological response to HIV therapy as part of an online treatment support tool. *AIDS* 2011;**25**:1855-1863.
3. 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