Poster 39

International Workshop on HIV & Hepatitis Drug Resistance
and Curative Strategies; 7-10 June 2011; Los Cabos, Mexico

HIV TRePS
HIV Treatment Response Prediction System

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

Modelling response to antiretroviral therapy without a genotype as 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], R Kaiser[7], A Pozniak[8], HC Lane[9], JM Montaner[10]

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: AREVIR cohort, University of Cologne, Cologne, Germany; 8: Chelsea and Westminster Hospital, London, UK; 9: National Institute of Allergy and Infectious Diseases, Bethesda, MD, USA; 10: BC Centre for Excellence in HIV/AIDS, Vancouver, Canada

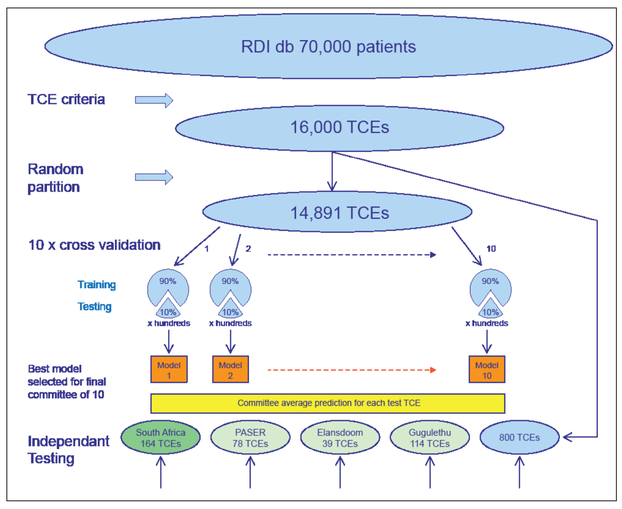
Background

- Optimising therapy following treatment failure in resource-limited settings (RLS) is challenging due to limited treatment options and the general unavailability of resistance testing
- In previous studies we have demonstrated that computational models can predict virological response from genotype, viral load, CD4 count and treatment history and are a useful clinical tool
- Prototype models developed to predict virological response without the need for a genotype showed promise when tested with data from the well-resourced clinics that provided the training data
- Here we develop new models that do not require a genotype using a large dataset and, for the first time, assess their potential clinical utility using data from RLS.

Methods

- 10 random forest (RF) models were trained to predict the probability of a follow-up viral load being <400 copies HIV RNA/ml
- The input variables were baseline viral load, CD4 count, treatment history, drugs in the new regimen and time to follow-up
- 14,891 treatment change episodes (TCEs), predominantly from Europe and North America, were used for training with 800 set aside at random as an independent test set (no patient could have TCEs in both the training and test sets, see Figure 1 for dataset development in full)

Figure 1: Dataset development



- Additional test sets were provided by two South African clinics, Gugulethu (114 TCEs) and Elandsdoorn (39 TCEs) and the PASER-M cohort in six sub-Saharan African countries (78 TCEs). Relevant TCEs were extracted from PASER and added to Elandsdoorn and Gugulethu to give a South African test set (164 TCEs) (see Table 1 for dataset statistics)
- A sub-set of the 800 RDI test TCEs that closely resemble the TCEs from Africa (no PI history, drugs limited to those used in the African clinics, one PI in the new regimen) was used as an additional test set (55 TCEs)
- Model performance was assessed using receiver-operator characteristic (ROC) curves, in terms of area under the curve (AUC) and overall accuracy.
- Cases from the RLS were identified where the new treatment failed and this failure was correctly predicted by the models
- Models used the baseline data from these cases to predict responses to multiple alternative 3-drug regimens involving only those drugs in use in the centre(s), in order to identify potentially effective alternatives.

Table 1: Patient disposition and dataset statistics

	Training set	Test set	ELA	GUG	PAS	South Africa
TCEs	14,891	800	39	114	78	164
Patients	4878	800	38	104	78	153
Gender						
Male	11,006	601	12	29	44	49
Female	2,341	137	27	85	34	115
Median Baseline VL	3.77	3.79	4.31	3.95	4.64	4.04
Mean Baseline VL	3.74	3.74	4.23	4.02	4.59	4.08
Range of Baseline VL	1.71-7.0	1.71-6.01	2.83-5.7	2.82-5.52	2.89-6.49	2.82-5.7
Median Baseline CD4	260	260	214	256	84	228
Treatment History						
Number of previous drugs (median)	5	5	4	4	4	4
NNRTI	10,127	533	39	113	78	163
NRTI	12,342	648	39	114	78	16
PI	736	61	0	5	5	1
Failures (>2.6 fu 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	5,240	282	36	100	71	142
2 NRTI + NNRTI	3,522	176	3	14	1	17
Other	6,129	342	0	0	6	5

Results

- The models achieved a mean AUC of 0.77 (95%CI 0.76,0.78) and accuracy of 72% during cross validation and 0.77 (95%CI 0.73,0.80) and 71% with the 800 test set (Table 2, Figure 2)
- For the three RLS test sets, AUC ranged from 0.58-0.65 and accuracy from 67-72%. For South African TCEs, AUC= 0.62 and accuracy = 65%.
- For the 55 RDI TCEs that resembled those from RLS, AUC was 0.70 and accuracy was 75%.

Figure 2: ROC curves

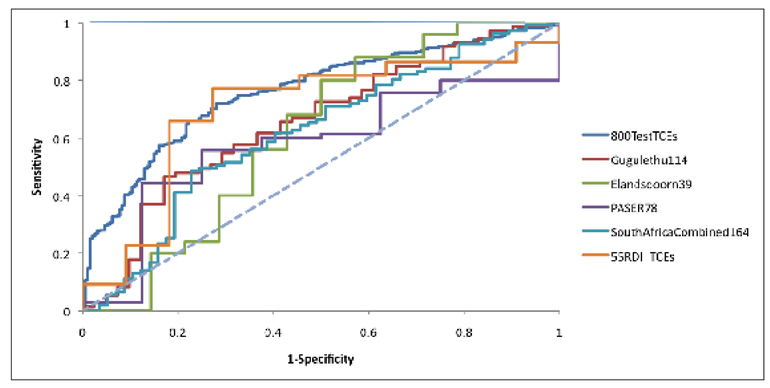


Table 2: Accuracy of the models

	CV (n=14,891)	Test	GUG (n=114)	ELA (n=39)	PASER (n=78)	South Africa (n=164)	Comparable RDI cases (n=55
ROC AUC (95% CI)	0.77 (0.76, 0.78)	0.77 (0.73, 0.80)	0.65* (0.55, 0.76)	0.61 (0.40, 0.73)	0.58 * (0.38.0.77)	0.62 ** (0.53, 0.71)	0.70 (0.51, 0.88)
Overall accuracy (95% CI)	72% (71%, 73%	71% (68%, 74%)	67% (57%, 75%)	72% (55%, 85%)	71% (59%, 80%)	65% (57%, 72%)	75% (61%, 85%)

Comparison *vs* 800 test set using Delong's test for comparing ROC curves: * Statistical trend (p<0.1) ** Statistical difference (p<0.01)

- The models correctly predicted 60% of actual failures and identified alternative 3-drug regimens, using locally available drugs, which were predicted to be effective for 79% of these cases (Table 3).

Table 3: Results of *in silico* analysis

	GUG	ELA	PASER	South Africa
No. of correctly predicted failures (total no. of failures)	26 (41)	7 (14)	6 (8)	34 (57)
No. (%) for which alternatives were found that were predicted to be effective	20 (77%)	6 (86%)	2 (33%)	27 (79%)

Conclusions

- RF models that do not require a genotype, trained with large datasets from resource-rich countries are accurate predictors of virological response for cases from those countries but approximately 5% less accurate than typical for models including a genotype
- The models are less accurate for cases from southern Africa but comparable to genotypic sensitivity scores from genotyping with rules-based interpretation
- The models have the potential to predict and avoid treatment failure by identifying effective, alternative, practical regimens.
- This approach has potential clinical utility as an aid to the management of treatment failures in RLS
- A version of the RDI on-line treatment tool, HIV-TRePS that does not require a genotype is being made available
- Data are being collected from RLS and sub-Saharan Africa in particular in order to develop region-specific models with maximum accuracy.

Acknowledgements

The RDI thanks the follwoing centres and their patientss for providing data to the RDI:

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