

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

Larder BA¹, Revell AD¹, Wang D¹, Ene L², Tempelman H³, Barth RE⁴, Wensing AM⁴, Gazzard B⁵, DeWolf F⁶, Lane HC⁷, Montaner JSS⁸

1: RDI, London UK; 2: "Dr. Victor Babes" Hospital for Infectious and Tropical Diseases, Bucharest, Romania; 3: Ndlovu Care Group, Elandsdoorn, South Africa; 4: UMC Utrecht, Netherlands; 5: Chelsea and Westminster Hospital, London, UK; 6: Netherlands HIV Monitoring Foundation, Amsterdam, The Netherlands; 7: NIAID, Bethesda, USA; 8: BC Centre for Excellence in HIV/AIDS, Vancouver, Canada

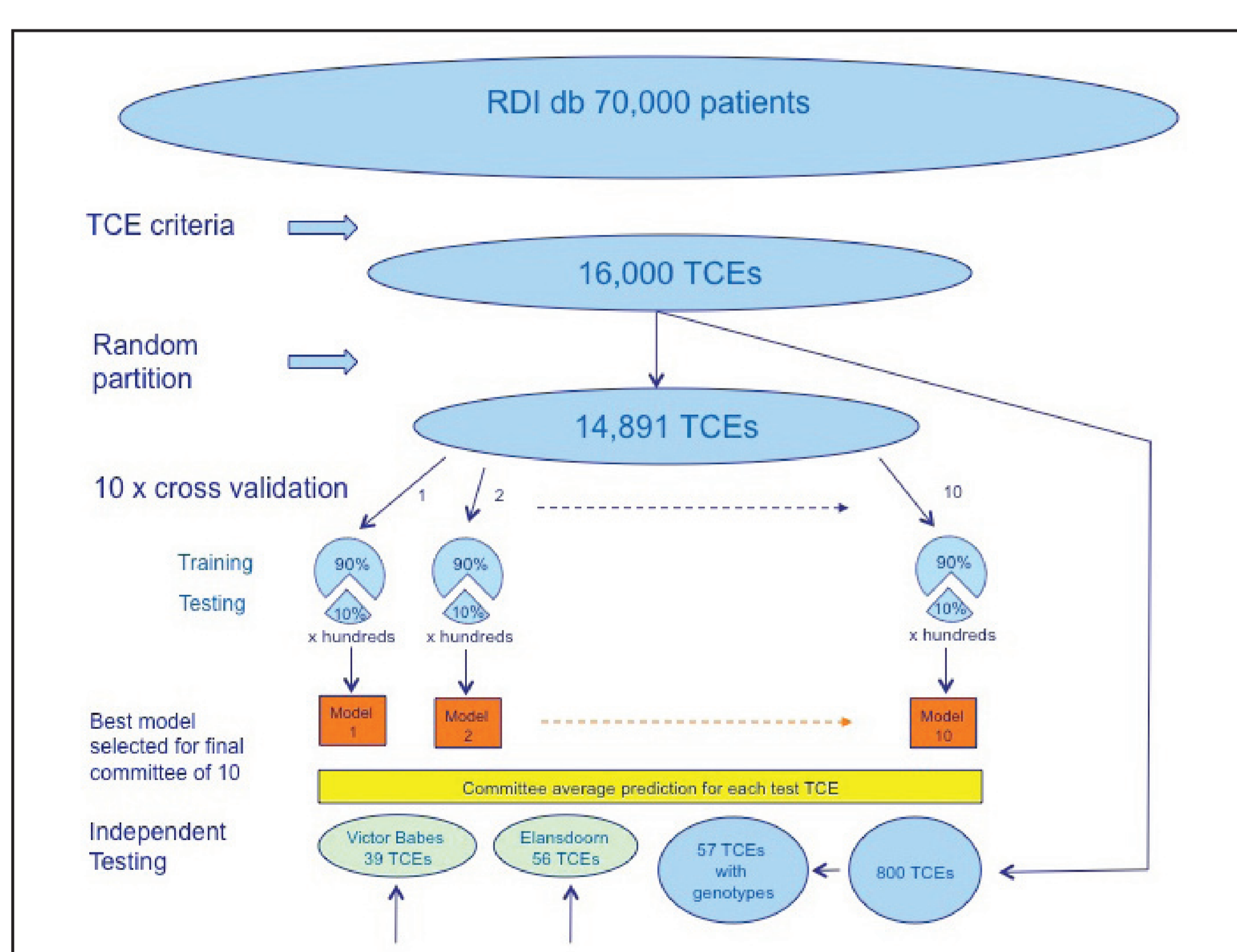
Background

- Optimising therapy following treatment failure in resource-limited settings (RLS) is challenging due to limited treatment options and the general unavailability of resistance testing
- We have developed computational models that can predict virological response from genotype, viral load, CD4 count and treatment history with accuracy of approximately 80% compared to 60-65% for genotypic sensitivity scores (GSS) (1)
- In clinical studies, a web-based system using our computational models was assessed as being a useful clinical tool (2)
- Here we use a large dataset to develop new models that do not require a genotype and 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/ml following a change in therapy
- 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
- Additional test sets were provided by clinics in Romania ("Dr. Victor Babes" Hospital for Infectious and Tropical Diseases, Bucharest; 39 TCEs) and South Africa (Ndlovu Care Group, Elandsdoorn; 56 TCEs)
- A subset of 57 TCEs from the 800 RDI test set that had genotypes available were also tested with the RDI's models that use a genotype in their predictions
- Model performance was assessed using ROC curves, in terms of area under the curve (AUC) and overall accuracy
- Baseline data from cases in the RLS test sets where the new regimen failed (and this failure was correctly predicted by the models) were used by the models to identify potentially effective alternative 3-drug regimens using drugs that are currently available in that setting
- Different optimum operating points (OOPs) for classifying predictions as responses or failures were used: one derived from the 800 RDI test set (OOP-1) and one optimised for the local RLS test data (OOP-2 and OOP-3).

Figure 1: Dataset development



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 1)
- The models achieved an AUC of 0.68 (95%CI 0.51,0.85) and accuracy of 67% for the Romanian test set and 0.69 (95%CI 0.54,0.84) and 68% with the South African test set
- The RDI models that use a genotype for their predictions achieved an AUC of 0.77 (95%CI 0.61,0.92) and accuracy of 74% with the 57 subset, compared to 0.76 (95%CI 0.62,0.90) and 68% for the 'no-genotype' models
- Using locally optimised OOPs, the models correctly predicted 11 of 14 (79%) and 16 of 22 (73%) of actual failures in the Romanian and South African data sets and identified alternative 3-drug regimens, using locally available drugs, which were predicted to be effective for 100% and 38% of these (Table 2).

Results

Table 1: Accuracy of the models

	Cross validation (n=14,891)	Test (n=800)	Victor Babes (n=56)	Elandsdoorn (n=39)	RDI test subset (n=57)
ROC AUC without genotype	0.77	0.77	0.68	0.69	0.77
Overall accuracy without genotype	72%	71%	67%	68%	74%
ROC AUC with genotype					0.76
Overall accuracy with genotype					68%

Figure 1: ROC curves for the models with the three main test sets

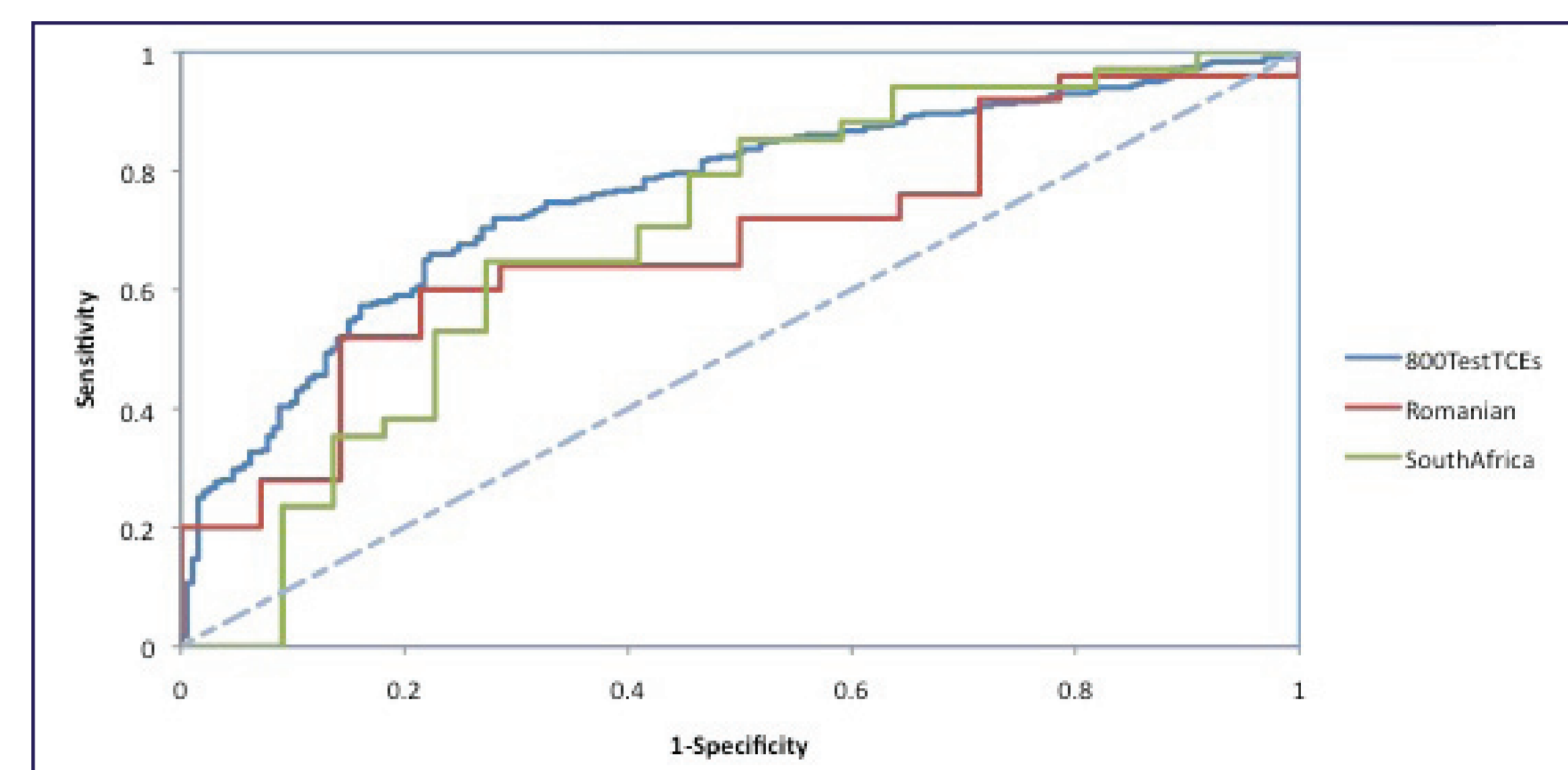


Table 2: in silico analysis

	Victor Babes (n=39)		Elandsdoorn (n=56)	
	OOP-1	OOP-2	OOP-1	OOP-3
No. of correctly predicted failures (total no. of failures)	11 (14)	11 (14)	8 (22)	16 (22)
No. (%) for which alternatives were found that were predicted to be effective	9 (82%)	11 (100%)	4 (50%)	6 (38%)

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 and only slightly less accurate than models including a genotype
- The models are less accurate for cases from Romania and South 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 for managing cases of treatment failure 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 in order to develop region-specific models.

References

- 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.
- 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.

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