hiv resistance
response database initiative

# RDI e-News

15th July 2004 Issue #3

## Treatment history improves accuracy of neural networks' predictions

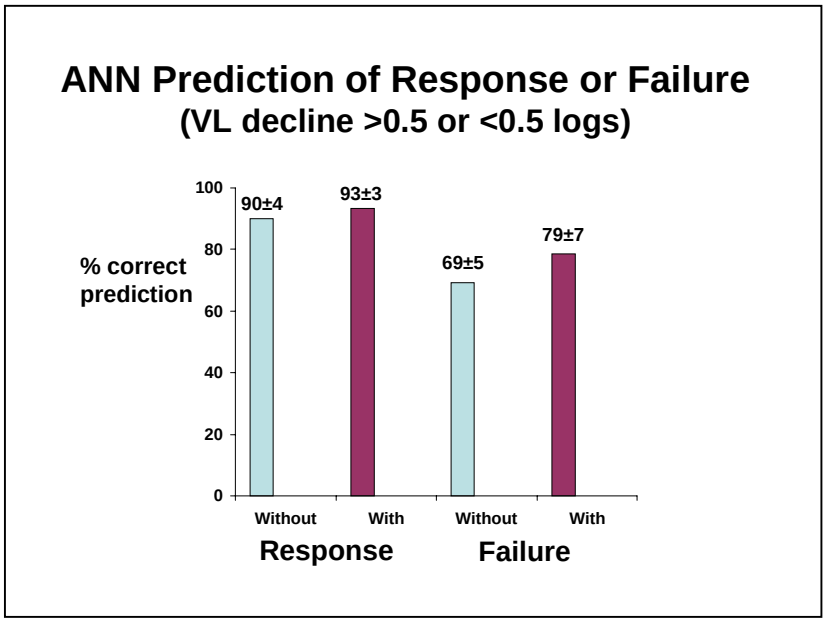
*Historical AZT exposure affects response to d4T, ABC and TDF*

The addition of historical AZT exposure data to neural network models significantly improved their accuracy in predicting virological response to combination therapy involving d4T, abacavir and tenofovir. This was the main finding of a new study conducted by the RDI and presented at the 13th International HIV Drug Resistance Workshop in Tenerife, in June.

The RDI has already demonstrated that Artificial Neural Networks (ANN) trained using genotype, viral load and drug treatment data, can successfully predict virological response to combination therapy. However, as with genotyping as a whole, the accuracy of these models may at times be limited by pre-existing minority populations of resistant virus, not detected by standard genotyping technologies. This study was designed to address whether inclusion of historical AZT exposure data, as a 'surrogate' for minority mutant populations, can increase the accuracy of ANN in predicting response to combination therapy involving d4T, abacavir (ABC) and tenofovir (TDF).

716 'treatment change episodes' (TCEs) were selected from five clinical cohorts. These all involved the introduction of d4T, ABC, or TDF and 349 had historical (not immediately prior) AZT exposure. 20 ANN models were developed using mutations, drugs and viral load as input variables, 10 of which also included previous AZT exposure (yes or no) as a binary input variable. Each model was trained using 640 TCE's and tested with the remaining 76. All the training and testing sub-datasets were independent, randomly partitioned and normalised.

Correlations between predicted and actual VL change for the 10 basic models gave a mean $r^2$ value of 0.64 and mean correct trajectory prediction rate of 87%. However, the 'AZT history' models gave a mean $r^2$ value of 0.73 and mean correct trajectory prediction rate of 89%. The difference in accuracy between the two groups, as measured by the differences between predicted and actual viral loads, was statistically significant ($p<0.05$).




**Graph of the sensitivity and specificity of ANN models trained with and without historical AZT exposure data in predicting virological response to combination therapy**

There were 12 cases with historical AZT but no AZT mutations who experienced virologic failure (<0.5 log reduction) and who were predicted by the basic ANN model to respond but correctly predicted to fail by the 'AZT history' model.

This study suggests that historical treatment information may act as a surrogate for the presence of minority mutant populations and can enable ANN to overcome this potential shortcoming of current genotyping.

# HIV opinion leaders support RDI

*Meeting at Retrovirus conference is heavily over-subscribed*

Fifty of the world's foremost HIV clinicians and researchers showed their interest and support for the RDI by attending the initiative's first external update meeting, hold on Monday 9th February in association with the 11th Conference on Retroviruses in San Francisco. Participants at the meeting pledged to donate data to the initiative from more than 2,600 patients, with many more open-ended pledges of data and support.

"We were delighted with the level of support shown by everyone who gave up their first evening at one of the busiest HIV conferences of the year to participate", commented Andrew Revell, Executive Director of the RDI. "The participation of so many leading figures shows that the initiative is gaining momentum and we were particularly grateful to all those who committed to donate their data".

Participants at the meeting were given an update on the status of the initiative, the results of recent research and its plans for the next two years. Some of the highlights were:

- Neural network models trained using genotype, drug therapy and viral load data have proved able to predict the direction of virologic response to different combination of drug for the great majority of patients.
- Correlations between the models' quantitative predictions of the extent of virologic response and the actual virologic response recorded by the clinic have been very good, (r2 values typically 0.6 to 0.75.
- When the most accurate models were asked to identify potentially effective salvage regimens for actual cases of treatment failure (where physicians with the benefit of a genotype test instigated a treatment change which was followed by virologic failure), the models have been able to do so in every case, with average predicted reductions in viral load of 2.6 logs.
- The RDI plans to develop and launch a Research Query Function (RQF) during 2004 that will enable researchers to query the RDI database via the web site
- The ultimate goal is an on-line resistance interpretation service
- Institutions and companies are invited to join the RDI by contributing data and/or financial support
- Institutional members of the RDI have input into RDI strategy, opportunities for collaborative research using RDI database, co-authorship of results, and trial and first access to research tools and resistance interpretation services

The presentations were followed by lengthy discussions and the RDI's plans to address a wide range of issues including the challenge of minority populations of resistant virus that evade genotyping, the use of adherence data in modelling, the effects of the diversity and size of datasets on modelling and the intention to obtain more data from non-clade B virus.

A full report, Executive Summary and meeting slides are all available from the RDI website: www.hivrdi.org.

# New research contract

The RDI has signed a substantial research contract with the US Department of Defense to import data from approximately 700 patients and perform a range of analyses comparing the performance of neural network models developed using data from a single clinic, a cohort and the entire RDI database. The results of this study could have important implications for future research, the development of the RDI and ultimately for the clinical application of neural network models as treatment decision-making tool.

***If you have any suggestions for how this newsletter could be improved or if you have any questions about the RDI please contact us at info@hivrdi.org.***

***And don't forget: the latest information on the RDI can be found on our website: www.hivrdi.org***

# Data update

Data have recently been provided to the RDI by the following institutions

- BC Centre for Excellence in HIV/AIDS, Vancouver, Canada
- Fundacion IrsiCaixa, Badelona, Spain
- Hospital Clinic of Barcelona, Spain
- Gilead Sciences, Foster City, USA
- ICONA, Italy
- National Institute of Allergy and infectious Diseases, Bethesda, USA
- Northwestern University Hospital, Chicago, USA
- US Military AIDS Research Program

The RDI database now contains data from approximately 8,000 patients from around 250 clinic. B**ut we need more so please…**

## …send us your data!