Previous Drug Exposure Data Significantly Increase the Accuracy of Artificial Neural Networks in Predicting Virological Response to Combination Therapy

BA Larder[1], D Wang[1], A Revell[2], R Harrigan[3], J Montaner[3] and C Lane[4]

1: The HIV Resistance Response Database Initiative (RDI), Cambridge, UK; 2: RDI Ltd, London, UK; 3: The BC Centre for Excellence in HIV/AIDS Vancouver, Canada; 4: National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, USA.

Poster 109

13th International Drug Resistance Workshop
Costa Adeje - Tenerife Sur, Canary Islands, Spain; June 8-12, 2004

Introduction

The RDI has previously demonstrated that Artificial Neural Networks (ANN) trained using genotype, viral load and drug treatment data, can successfully predict virological response to combination therapy.

However, the accuracy of these models may be limited by pre-existing minority populations of resistant virus, not detected by standard genotyping technologies. These minority populations may accelerate treatment failure. For example, AZT-related mutations have been shown to reduce response to d4T, abacavir (ABC) and tenofovir (TDF).

This study was designed to address whether inclusion of previous AZT exposure data, as a 'surrogate' for minority mutant populations, can increase the accuracy of ANN in predicting response to combination therapy involving these drugs.

Methods

716 'treatment change episodes' (TCEs) were used from five clinical cohorts. 349 had historical (but not immediately prior) AZT exposure. All had d4T, ABC, or TDF introduced at TCE.

An independent 'test set' of 76 TCE's was removed at random.

20 ANN models were developed with the remaining data.

INPUT VARIABLES: 49 mutations, 15 drugs, baseline viral load (VL)
OUTPUT VARIABLE: on treatment VL.

10 'AZT history' models had previous AZT exposure (yes or no) as additional binary input variable.

1800 candidate models were trained for each model using different ANN parameters (e.g. learning rate, number of hidden units).

Sub-validation sets were applied to 1800 trained models and the best performing model selected to join each committee of 10.

This was repeated for all 20 models - a total of 36,000 models trained.

Each model was then tested with the independent test set of 76 TCEs.

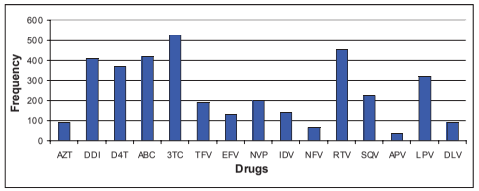
Performance of basic and 'historical AZT' models was compared:

- Correlation between predicted and actual ΔVL
- Percentage correct VL trajectory prediction
- Percentage correct prediction of response (≥0.5 log VL decline in VL) & failure (<0.5 log decline in VL).

Methods (continued)

The frequencies of individual drugs involved in the TCEs are summarised in Figure 1.

Figure 1: Single drug frequencies



Results

Correlations between predicted and actual VL change for the committee of 10 basic ANN models produced r^2 values ranging from 0.57 to 0.73, with a mean of 0.64 (Table 1).

The 'AZT history' models produced r^2 values ranging from 0.69 to 0.76 with a mean of 0.73 (Table 1, Figure 2).

The basic and 'AZT history' models produced mean correct trajectory prediction rates of 87% and 89% respectively.

The difference in accuracy between the two ANN committees, as measured by the differences between predicted and actual viral load changes, was statistically significant ($p<0.05$).

VL response as ≥0.5 log decline: mean correct prediction of response was 90% for basic models and 93% for 'AZT history' models (Figure 3).

VL failure as <0.5 log decline: mean correct prediction of VL failure was 69% for basic models and 79% for 'AZT history' models (Figure 3).

12 TCEs in the 76 test cases with historical AZT but no AZT mutations had virological failure (<0.5 log reduction in VL) and were predicted to respond by the basic ANN model but correctly predicted to fail by the 'AZT history' model (Table 2).

Results (continued)

Model number	With historical AZT data	Basic ANN models
1	0.74	0.67
2	0.76	0.63
3	0.73	0.65
4	0.74	0.63
5	0.74	0.65
6	0.73	0.62
7	0.69	0.63
8	0.70	0.57
9	0.73	0.73
10	0.71	0.63
Mean	**0.73**	**0.64**

Table 1: Correlations between predicted and actual viral load changes

Figure 2: Predicted vs actual change in VL for ANN 'AZT history' Model 5

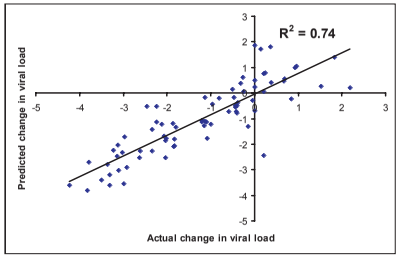
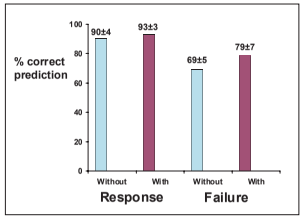


Figure 3: Prediction of response or failure by ANN models with and without historical AZT data



Results (continued)

Table 2: 12 cases of virological failure predicted by the basic model to respond but correctly predicted by the AZT history model to fail

Drug combination	Number of cases
D4T+3TC+ IDV	4
D4T+3TC+SQV	2
D4T+3TC+NFV	1
AZT+ABC+RTV	1
DDI+D4T+NFV	1
D4T+ABC+NVP+RTV+LPV	1
ABC+3TC+EFV+IDV+RTV	1
AZT+ABC+3TC+DDI+RTV+APV+LPV	1

Conclusions

- The addition of historical AZT exposure data significantly improved the accuracy of ANN in predicting response to combination therapy including d4T, ABC or TDF
- This confirms that historical exposure to antiretroviral drugs can influence response to a new regimen
- ANN models with and without historical AZT data were highly sensitive in terms of predicting virological response
- The models showed lower specificity (predicting virological failure) but models with previous AZT exposure data were superior to those without
- 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 procedures.

Acknowledgments

The RDI gratefully acknowledges the support of the BC Centre for Excellence in HIV/AIDS for their support as a Founding Academic Member of the RDI.