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# Treatment history improves the accuracy of neural networks predicting virological response to HIV therapy

D. Wang[1], B.A. Larder1, A. Revell[1], R. Harrigan[2], J. Montaner[2], S. Wegner[3], and C. Lane[4].

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

## Introduction

- Standard HIV genotyping tests have limited sensitivity (≥20%) for detecting minority resistant virus
- Artificial Neural Networks (ANN) can successfully predict virological response to combination therapy from genotype but undetected minority resistant species might limit their accuracy
- This study addresses whether inclusion of treatment history data improves the accuracy of ANN.

## Methods

### ANN training and testing

- Two committees of 10 ANN models were trained to predict virological response (ΔVL) to combination therapy using 2,559 treatment change episodes (TCEs)
- The 'basic' committee models were trained using the following input variables: baseline viral load, drugs in new regimen, genotype (55 resistance mutations) and time to follow-up
- The 'treatment history models' were trained with the above input variables plus four additional treatment history variables, coded as '0' or '1' for any previous AZT, 3TC, NNRTIs, or PIs (selected because of the well-characterised effects of mutations associated with these drugs).
- Training was performed as follows:

1. TCEs partitioned 10 times into 90% for training and 10% for validation with each TCE appearing in a validation set once
2. For each training partition, 1800 ANN models developed using different parameters (learning rate, error thresholds, number of nodes in hidden layer, maximum iteration number).
3. These models were provided the input variables from the validation set and produced predictions of the output variable - ΔVL. The most accurate model was selected from the 1800 for each partition.
4. By repeating 10 times a 'committee' of 10 ANN models was derived.

- The ANN committees were tested by being given the input variables from 51 independent TCEs, selected at random from different patients within the RDI database, and predicting ΔVL
- The 'committee average prediction' was used (the average prediction of all 10 models in the committee for each test TCE)
- The models' performance was assessed by comparing these predictions to the actual ΔVL from the test TCEs in terms of:

1. Correlations between the ANN models' predictions and the actual ΔVL
2. Mean absolute differences between the models' predictions and actual ΔVL
3. The percentage of the models' predictions that had the correct trajectory, positive or negative

### ANOVA

The importance of the 75 input variables, including previous treatment, was estimated as follows:

1. Whole data set divided into 12 different groups based on the viral load changes using intervals of 0.5 $\log_{10}$ copies/ml.
2. ANOVA performed to test the mean differences across groups.
3. p-values for the input variables were obtained and ranked.
4. Statistical significance was accepted if the p-value was <0.05.

## Results

- Correlations between predicted and actual ΔVL produced $r^2$ values of 0.30 ($p<0.0001$) for the basic models and 0.45 ($p<0.00001$) for the treatment history models. The difference in performance was statistically significant ($p<0.05$)
- The mean absolute difference between predicted and actual ΔVL was 0.88 for the basic models and 0.78 for the treatment history models ($p=0.05$)
- The mean percentage of correct trajectory predictions was 76% for the basic models and 78% for the treatment history models ($p<0.05$).

These results are summarised in Table 1 and the scatterplots of the correlations between the predicted and actual ΔVL values are presented in Figures 1 and 2.

**Table 1: Summary of results**

| | Correlation ($r^2$) | Mean absolute difference score | Percentage correct trajectory predictions |
|---|---|---|---|
| Basic models | 0.30 | 0.88 | 76% |
| Treatment history models | 0.45 | 0.78 | 78% |
| Statistical significance* | $p<0.01$ | $p=0.05$ | $p<0.05$ |

* For correlations and mean percentage correct trajectory predictions, the scores for the ten individual ANN models within each committee were compared using a two-tailed t-test for unrelated samples. For the absolute difference scores the committee average predictions for each TCE were compared using a two-tailed t-test for paired samples.

The results of the ANOVA demonstrated that each of the four new historical drug exposure input variables had a significant impact on virological response. The rank positions (out of a total of 75 input variables) and p-values are presented in Table 2.

**Table 2: Results of ANOVA for historical drug exposure variables**

| | Historical drug exposure variable | | | |
|---|---|---|---|---|
| | AZT | 3TC | NNRTI | PI |
| Rank Position (out of 75 input variables) | 39 | 41 | 40 | 38 |
| p-value | 0.0091 | 0.0215 | 0.0096 | 0.00001 |

**Figure 1: Predicted vs actual ΔVL for basic ANN models**

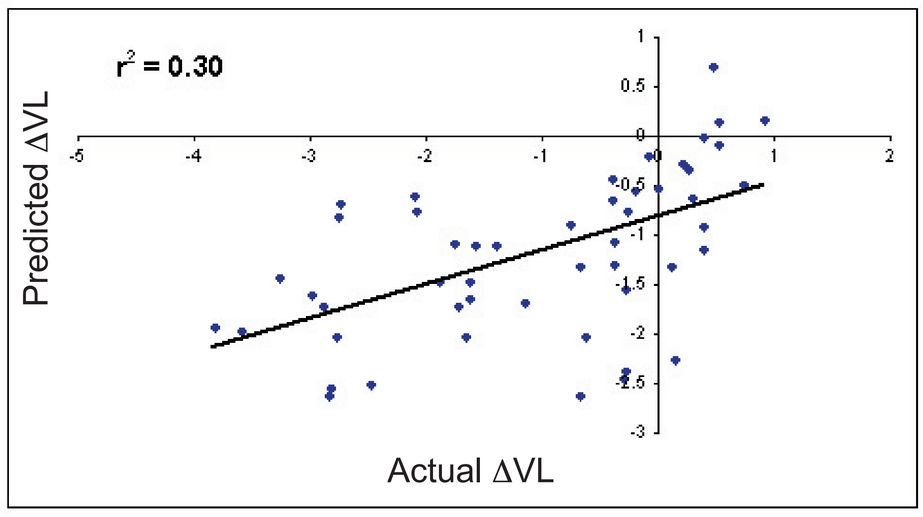
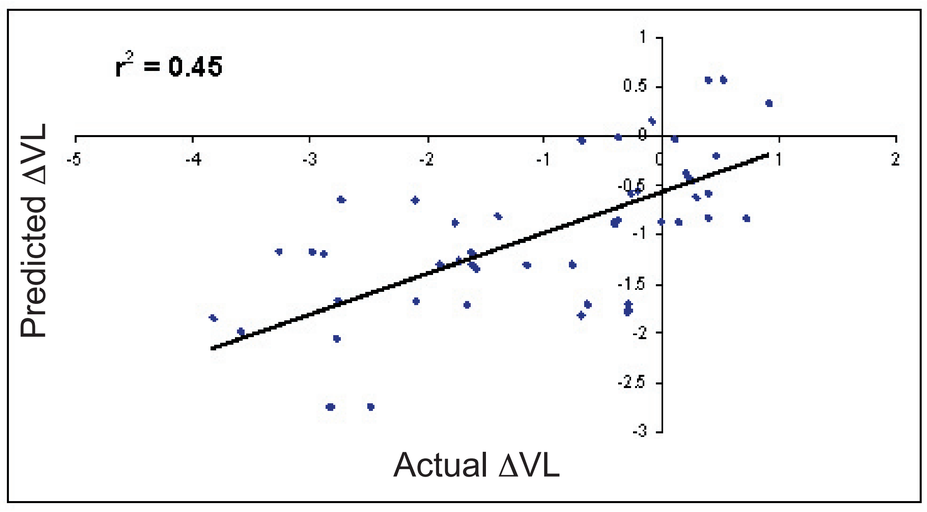



**Figure 2: Predicted vs actual ΔVL for treatment history models**




## Conclusions

- **Treatment history data significantly improved the accuracy of ANN in predicting virological response to combination antiretroviral therapy**
- **Visual inspection of the scatterplots indicates this was largely due to a reduction in the number of cases where the models predicted a greater virological reponse than actually achieved**
- **The treatment history data may have acted as a surrogate for minority populations of resistant virus that undermined subsequent therapy**

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