

# Neural networks are more accurate predictors of virological response to HAART than rules-based genotype interpretation systems

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## Introduction

- HIV drug resistance is a major cause of failure of highly active antiretroviral therapy (HAART).
- Genotyping with rules-based interpretation is commonly used to predict the virological responses available from alternative antiretroviral combinations and help select the optimum HAART regimen for the individual.
- Our previous studies demonstrated that artificial neural networks (ANN) can predict virological response to combination therapy from genotype.
- Here we compare directly the accuracy and utility of these approaches by comparing ANN predictions with genotypic sensitivity scores (GSS) from rules-based systems in terms of correlations with actual virological responses ( $\Delta$ VL).

## Methods

- A committee of 5 ANN models was trained using back propagation to predict  $\Delta$ VL with data from 2,983 treatment change episodes (TCEs)
- The following input variables were used in the training: 55 resistance mutations, drugs in new regimen, baseline viral load and time to follow-up.
- The accuracy of the ANN was tested by providing the models with input variables from 27 randomly-selected independent TCEs and correlating their predictions (the average of the predictions of the committee of 5 ANN models for each TCE) with the actual  $\Delta$ VL values.
- Total and normalized GSS were derived for the 27 test TCEs using Stanford (HIVdb 4.1.2), ANRS (v2004.09) and Rega (v6.2) rules-based interpretation systems.
- Stanford also awards points for each mutation according to the impact on susceptibility to each drug and these scores were used as an additional resistance measure for each test regimen.
- The GSS and 'Stanford mutation' scores were correlated with actual  $\Delta$ VL for the test TCEs.

## Results

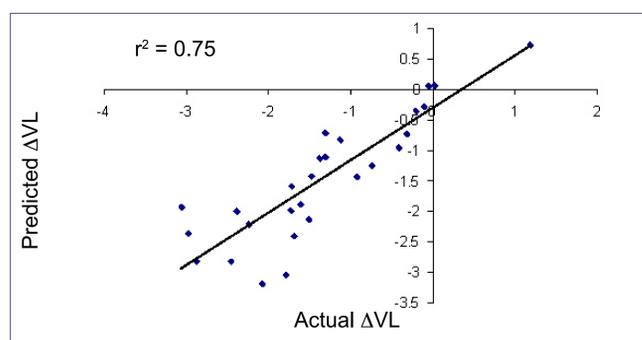
- Correlations with actual  $\Delta$ VL data for the test TCEs gave  $r^2$  values of 0.75 for the ANN predictions, 0.22 for Stanford mutation scores and between 0.13 (Rega) and 0.29 (ANRS) for GSS scores.
- Correlations between the GSS from the different rules systems gave  $r^2$  values between 0.83 and 0.91.
- The  $r^2$  values and levels of statistical significance for the ANN and the different interpretation systems are summarised in Table 1.

**Table 1: Correlations ( $r^2$ ) and statistical significance for ANN and different genotype interpretation systems**

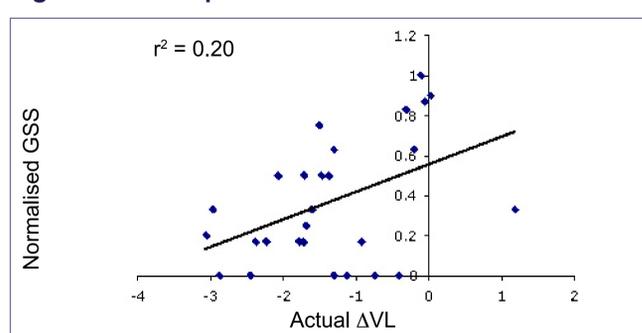
Interpretation method	$r^2$	Statistical significance
RDI ANN	0.75	$p < 0.000001$
Stanford mutation scores	0.22	$p < 0.05$
Stanford total GSS	0.21	$p < 0.05$
ANRS total GSS	0.27	$p < 0.01$
REGA total GSS	0.13	ns
Stanford normalised GSS	0.20	$p < 0.05$
ANRS normalised GSS	0.29	$p < 0.01$
REGA normalised GSS	0.15	$p = 0.05$

- The scatterplot of predicted vs actual  $\Delta$ VL for the ANN is presented in Figure 1.
- The scatterplots of the normalised GSS scores vs  $\Delta$ VL are presented in Figures 2, 3 and 4.

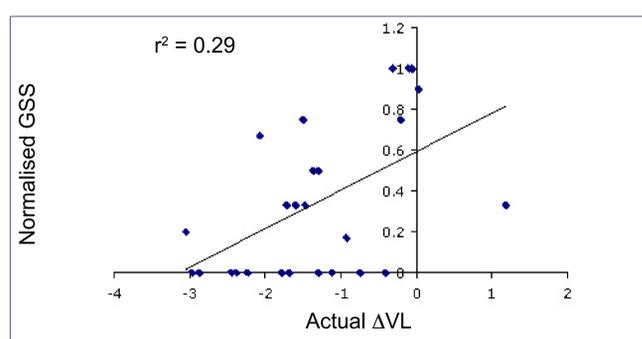
**Figure 1: Scatterplot of predicted vs actual  $\Delta$ VL for ANN**



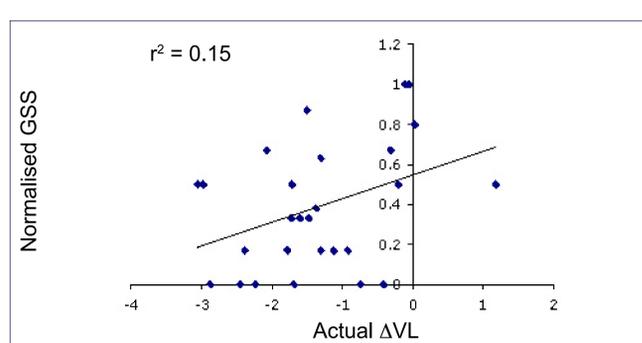
**Figure 2: Scatterplot of Stanford normalised GSS vs actual  $\Delta$ VL**



**Figure 3: Scatterplot of ANRS normalised GSS vs actual  $\Delta$ VL**



**Figure 4: Scatterplot of REGA normalised GSS vs actual  $\Delta$ VL**



## Discussion

- ANN were considerably more accurate predictors of virological response to combination therapy than rules-based GSS, explaining 75% of the variance in  $\Delta$ VL vs 13 to 29%.
- Scatterplots indicated that ANN were able to differentiate between regimens that GSS scores indicated would be equally effective.
- These data suggest that ANN may have significant utility as treatment decision-making tools.

## Acknowledgments

The RDI thanks:

- NIAID and the US Military HIV Research Program and the BC Centre for Excellence in HIV/AIDS for their support and collaboration with this research
- All the centres around the world that have contributed the data used in this study, including:
  - National Institute of Allergy and Infectious Disease, Bethesda, MD, USA
  - BC Center for Excellence in HIV/AIDS, Vancouver, BC, Canada
  - US Military HIV Research Program, Rockville, MD, USA
  - ICONA cohort
  - The Italian ARCA database, University of Siena, Siena, Italy
  - Hospital Clinic of Barcelona, Spain
  - Fundacion IrsiCaixa, Badelona, Spain
  - Northwestern University Hospital, Chicago, IL, USA
  - National Centre in HIV Epidemiology and Clinical Research, Sydney, Australia
  - Ramon y Cajal Hospital, Madrid, Spain
  - Italian MASTER Cohort (coordinated by the University of Brescia, Italy)
  - Community Programs for Clinical Research on AIDS (CPCRA).
- The patients.