

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

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The clinical need

The development of an accurate and reliable method to predict quantitative virological response to combination therapy directly from genotype

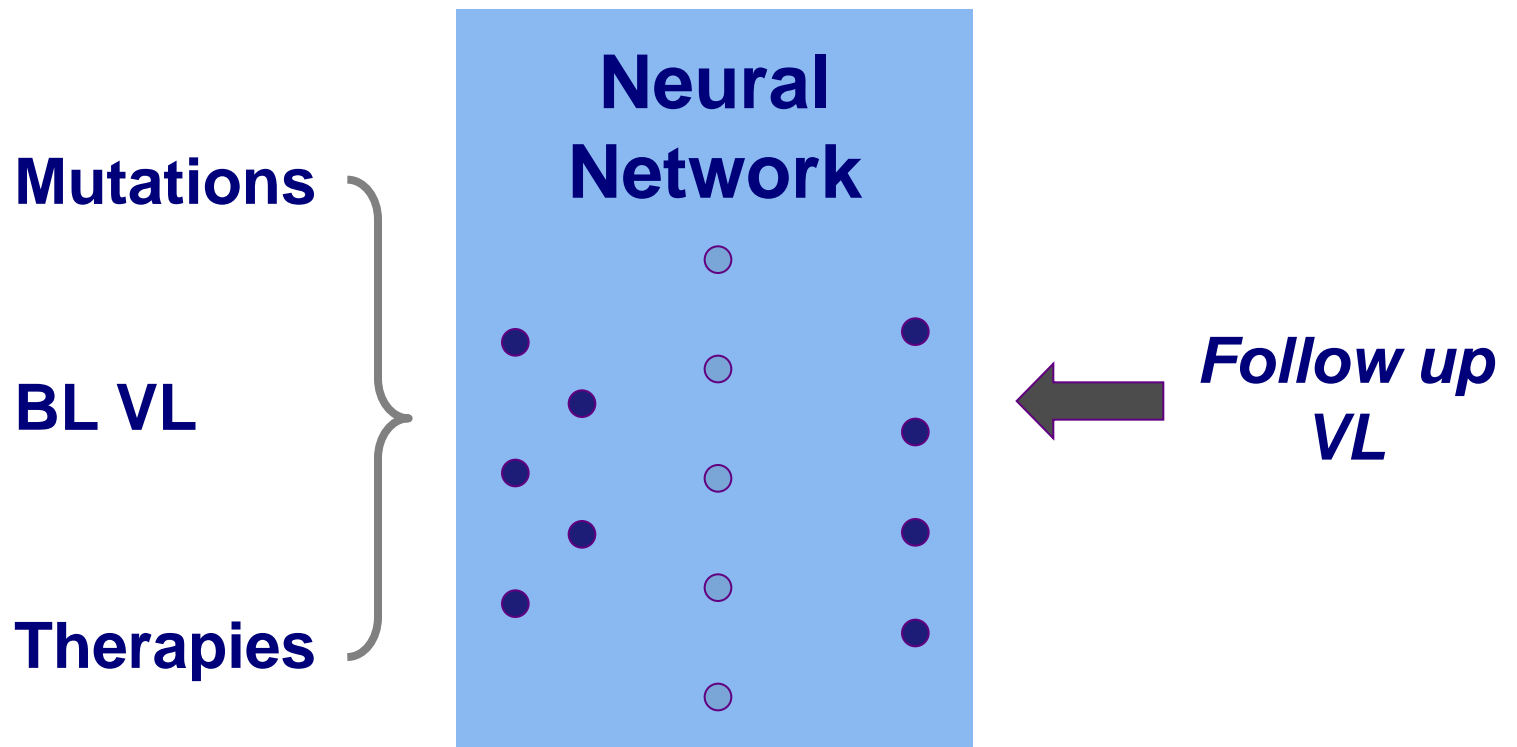
RDI approach

- Collect genotype, treatment & clinical outcome data from large numbers of patients in different clinical settings
- Apply data analysis methodologies to relate resistance to clinical response
- Develop and make freely available a resistance interpretation system to aid treatment decision-making

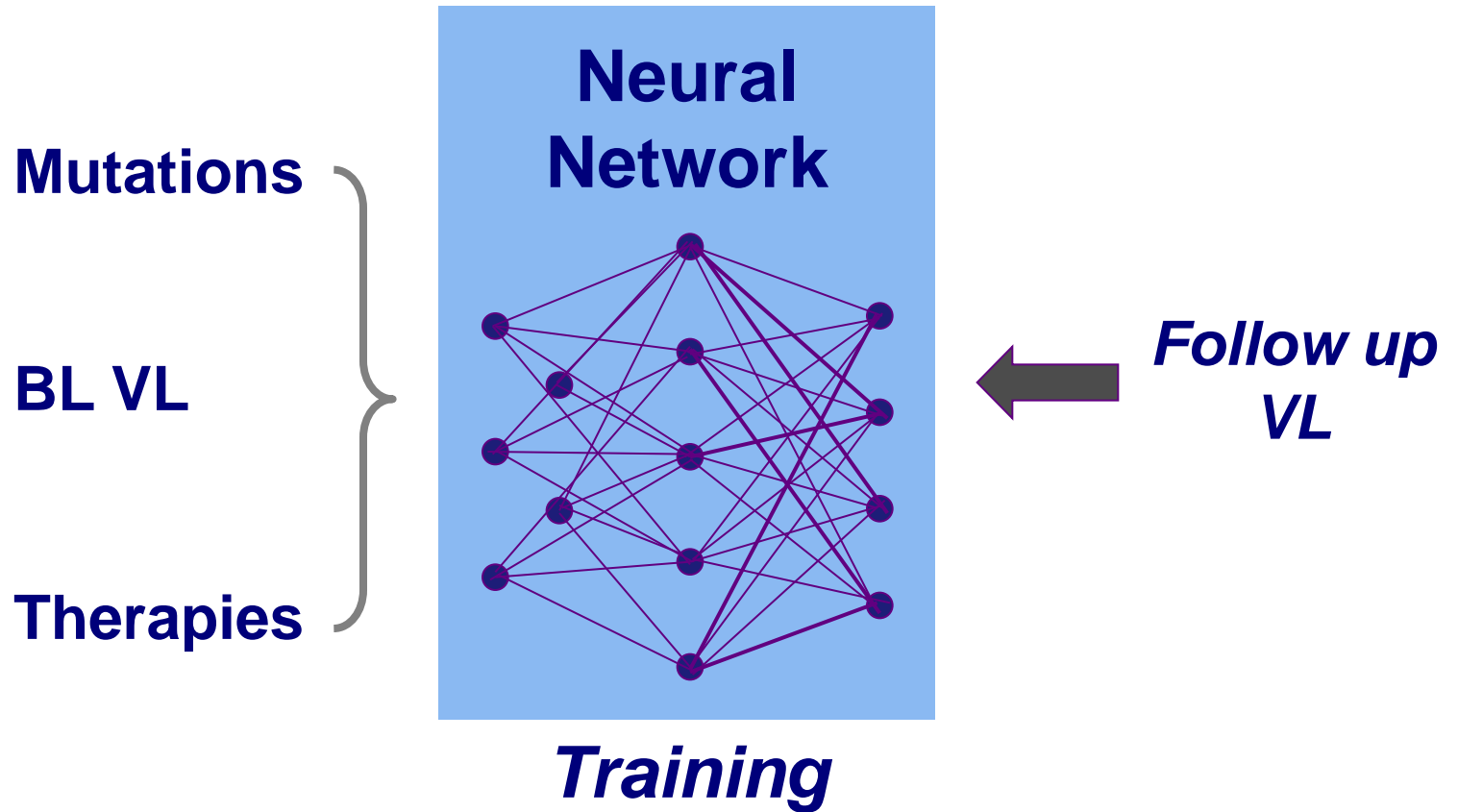
ANN model development

- Three-layer (one hidden) ANN models trained using back-propagation
- 1800 candidate ANN models trained (using different parameters e.g., learning rate, number of hidden units)
- Sub-validation sets applied to 1800 trained models & best performing models selected to make up ANN committee of 10

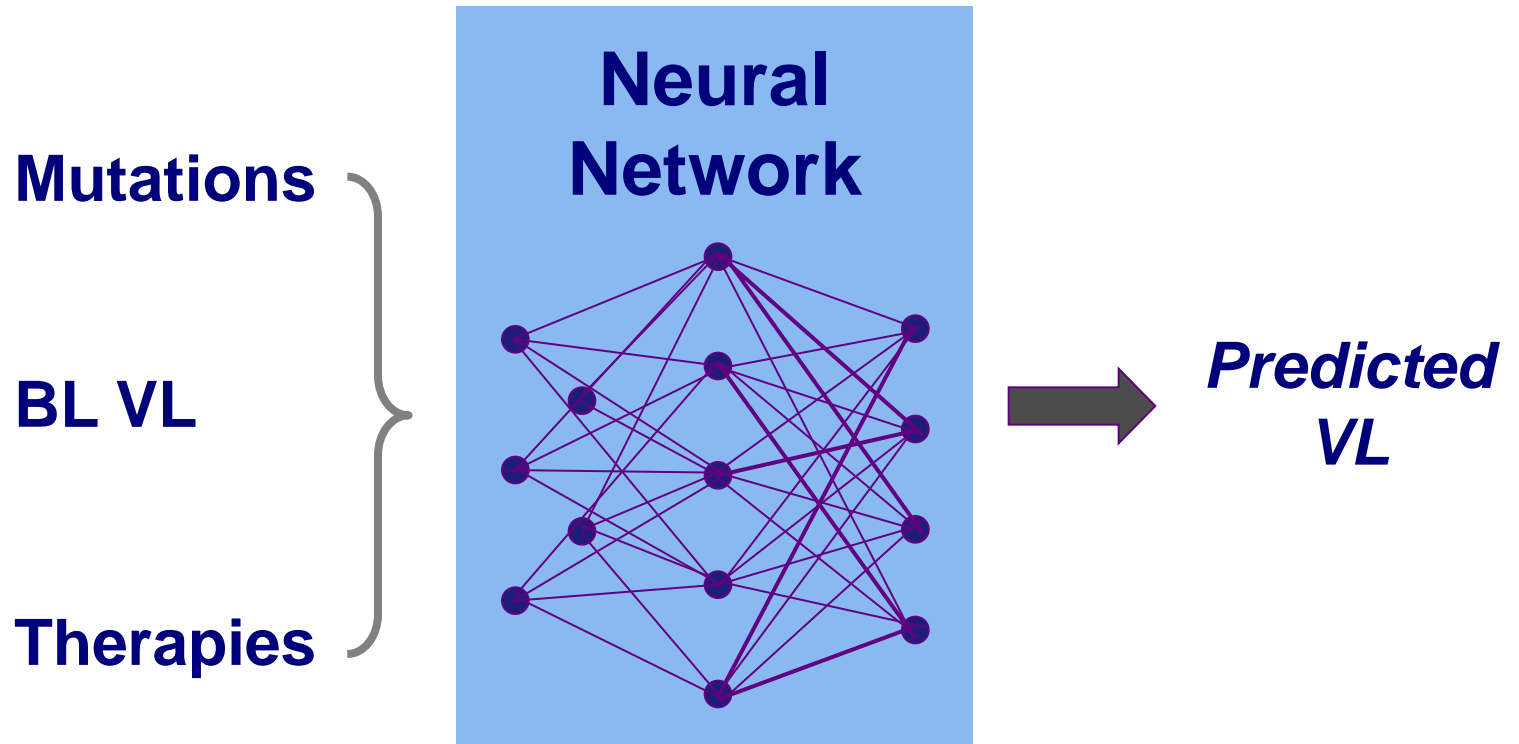
Typical Artificial Neural Network (ANN) Model



Training ANN models



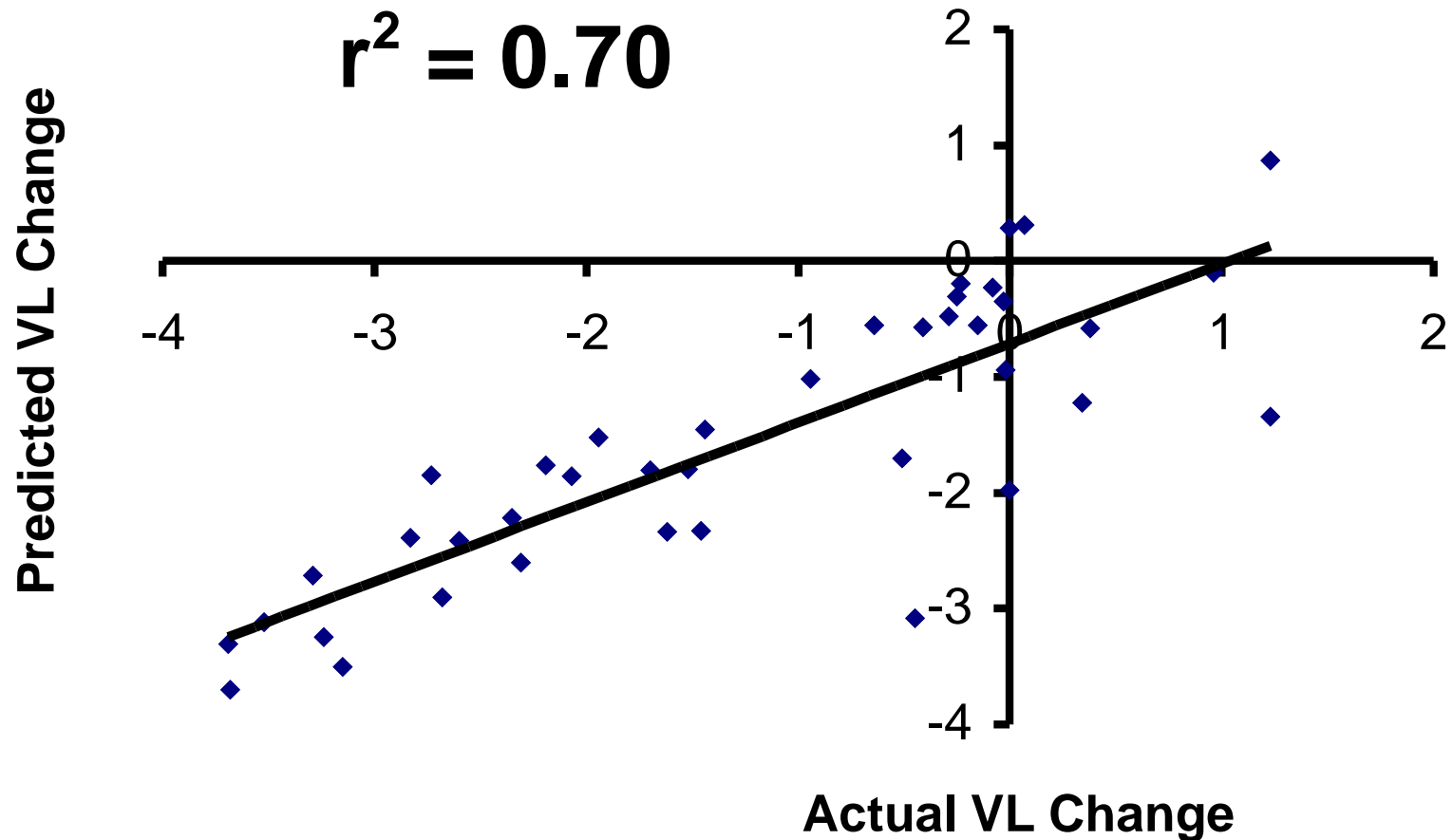
ANN model performance



Measures of ANN model performance

1. **Correlation between predicted and actual virological response (Δ viral load)**
2. Mean absolute difference between predicted and actual virological response (\log_{10}) across all test TCEs
3. Percentage correct prediction of trajectory of viral load change

Actual vs predicted change in VL for global ANN with independent test set



Study background

- Utility of genotyping limited by sensitivity for detection of resistant minority populations
- e.g. low level NNRTI mutations blunted response to EFV (Mellors *et al* 2003)
- Previous RDI study demonstrated that inclusion of historical AZT exposure variable increased accuracy of ANN in predicting virologic response to d4T, ABC and TNF-containing regimens (Larder *et al* 2004)

Study background - 2

- Detailed and precise drug history information is not always available
- Including previous exposure to every individual drug could add too many new variables for the ANN modelling
- However, the effects of previous exposure to some drugs or classes are quite well characterised and accepted

Study aim

To examine the impact of a limited number of additional drug history input variables on the accuracy of ANN models in predicting virologic response to HAART in general

ANN model with drug history

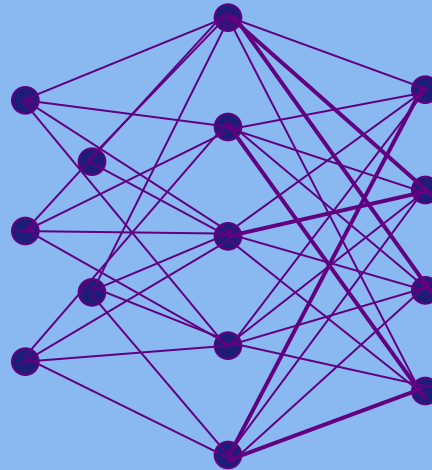
Mutations

BL VL

New
therapies

Drug history

Neural
Network



*Predicted
VL*

Methods: drug history variables

- **Four** historical drug exposure variables selected for study:
 - **AZT** (linked to broad NRTI resistance through development of NAMS)
 - **3TC** (well-characterised effects of 184V)
 - **Any NNRTI** (class resistance e.g. through K103N)
 - **Any PI** (cross-resistance through well-characterised constellation of mutations)

Methods: ANN input variables

'Basic' models (71 input variables):

- 55 mutations in RT and protease
- Drugs in new combination regimen (14 covered in these models)
- Viral load at baseline
- Time to follow up viral load

'Drug history' models 75 input variables, as above plus:

- Previous AZT, 3TC, PI, or NNRTI (each = yes or no)

Methods: ANOVA of ANN input variables

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

Methods: data partitioning

- 2,660 TCEs identified from RDI database with treatment history data that included one or more of the new variables
- TCE criteria included 24 week follow-up viral load window
- 51 TCEs from 23 patients partitioned (by patient) as independent test set

Methods: ANN training & validation

- Two committees of 10 ANN models each developed using 2,559 TCEs:
 - ‘Basic models’ (not including drug history variables)
 - ‘Drug history’ models’
- Training and validation to select ANN committee members:
 - TCEs partitioned x 10 into 90% (training) and 10% (validation), each TCE appearing in a validation set once
 - 1800 ANN models developed for each partition using different parameters (learning rates, error thresholds, no. of nodes in hidden layer, max iteration number etc)
 - Models provided input variables from validation set producing predictions of output variable, ΔVL
 - Process repeated x 10

Methods: ANN testing

- ANN models tested:
 - Correlation between predicted and actual ΔVL
 - % correct trajectory predictions
 - Absolute differences between predicted and actual ΔVL

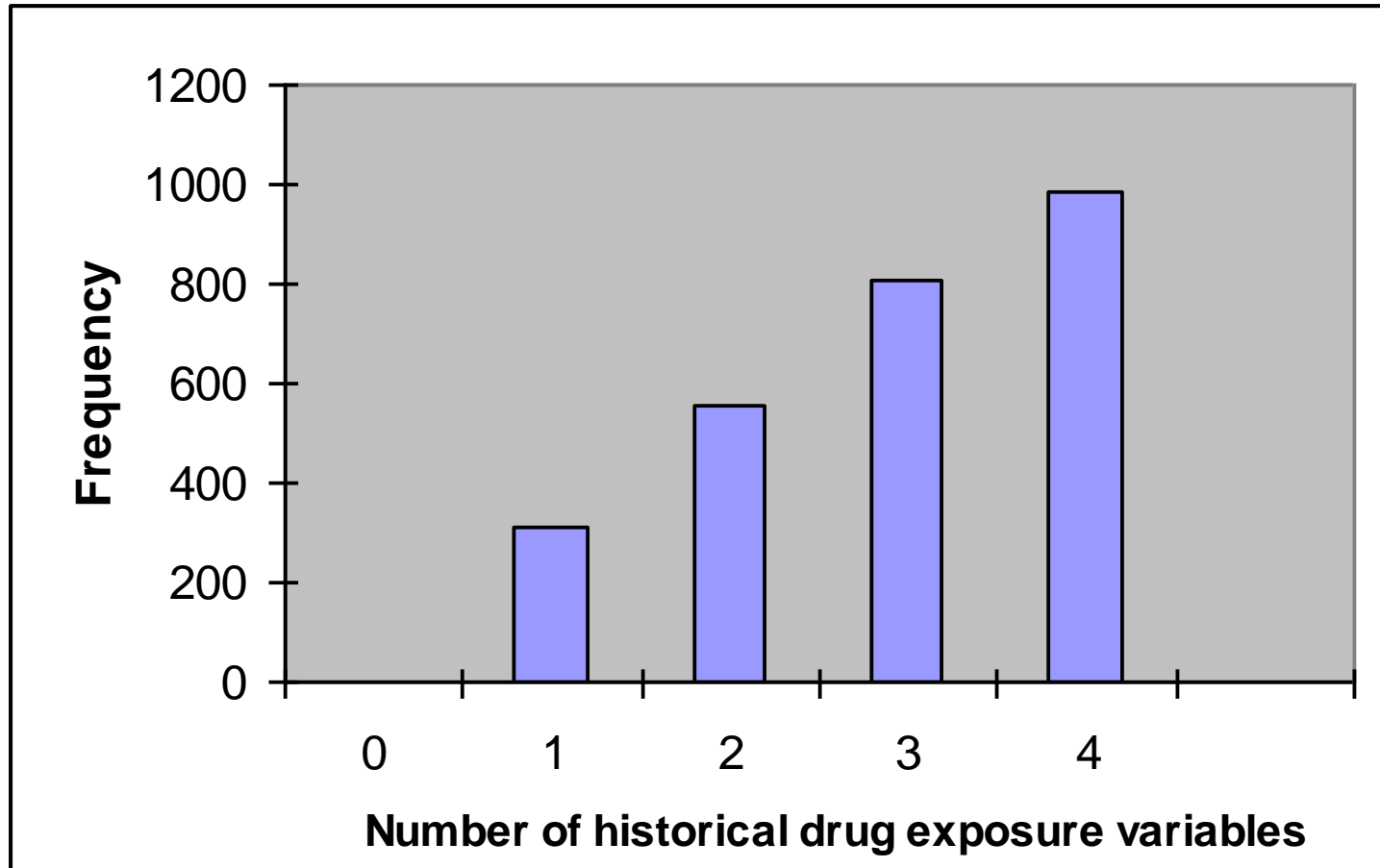
Results:

ANOVA of ANN input variables

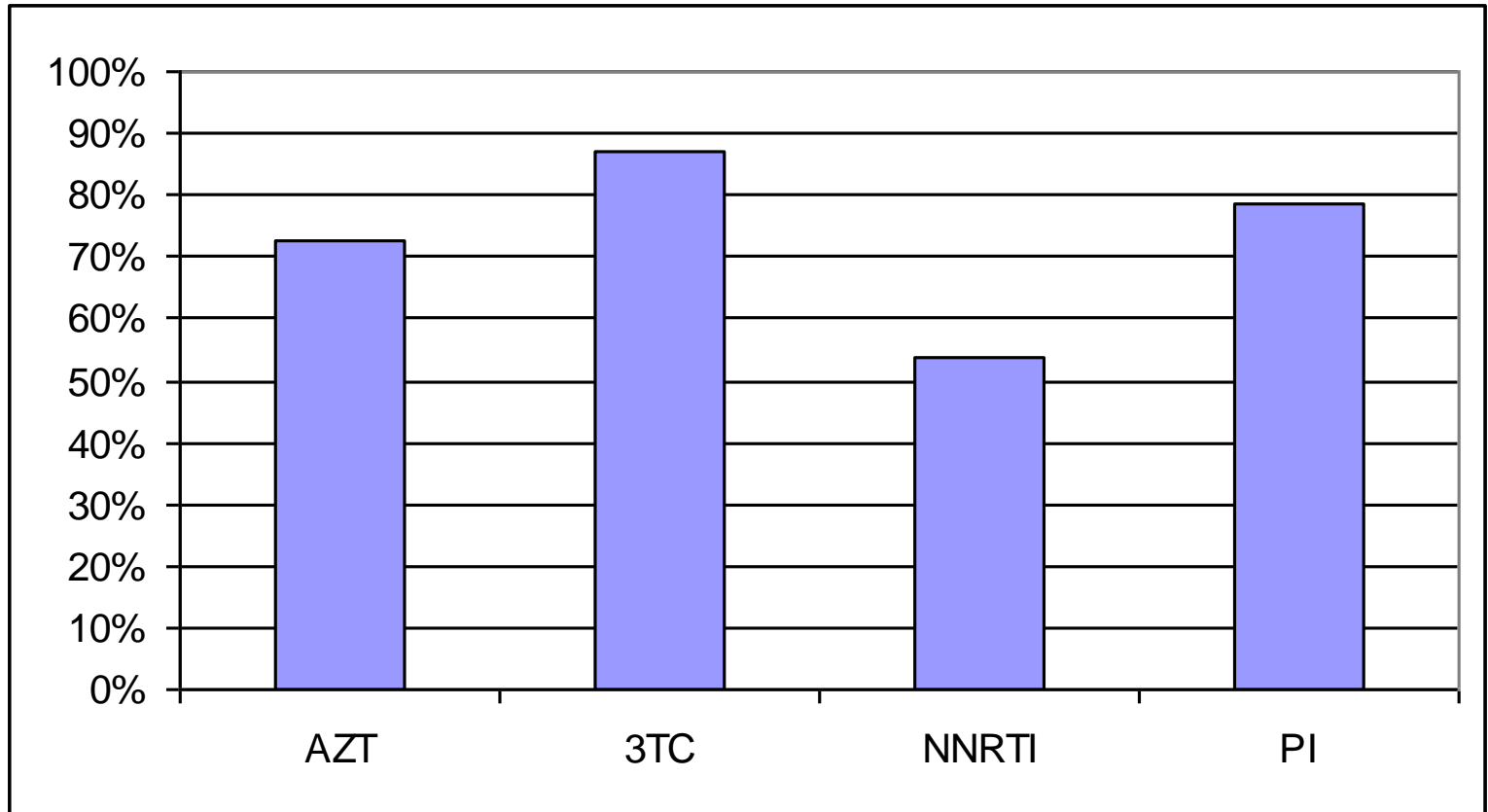
- Each of the four new historical drug exposure input variables had a significant impact on virological response

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

Distribution of historical drug exposure – all TCEs



Frequency of historical drug exposure – all TCEs

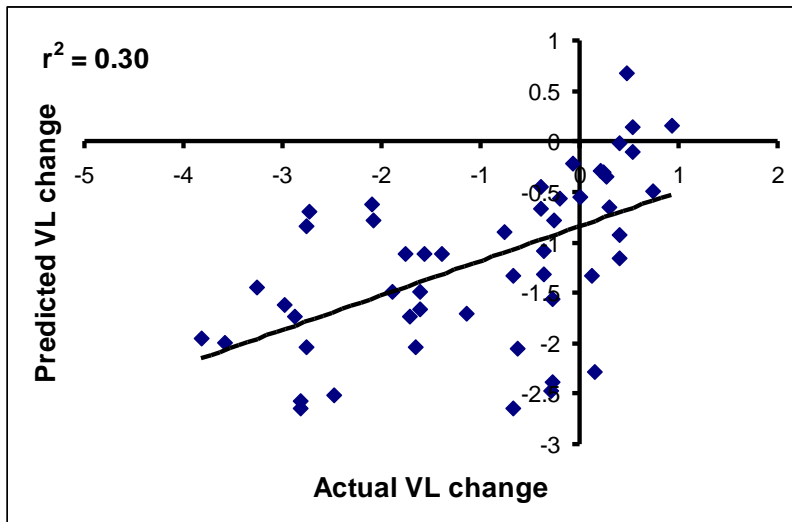


ANN model performance: correlations of predicted vs actual ΔVL

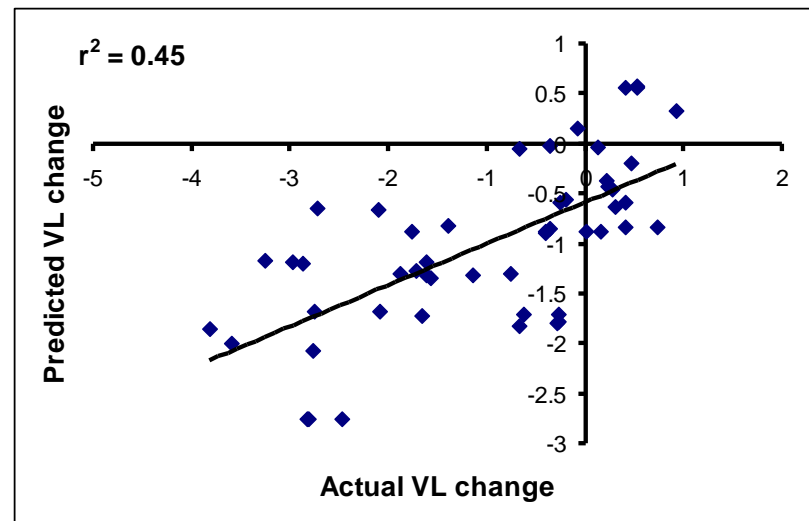
r^2 values	Basic ANN models	Drug history models
Model 1	0.17	0.35
2	0.30	0.39
3	0.25	0.34
4	0.27	0.36
5	0.18	0.13
6	0.21	0.23
7	0.07	0.22
8	0.01	0.20
9	0.35	0.30
10	0.12	0.21
Means	0.19	0.27
Statistical significance	$p < 0.01$	
Committee average	0.30	0.45

Performance of the ANN committees

Basic models



Drug History models



Results of ANN testing: summary of committee average performance

	Basic models	Drug history models	Statistical significance*
Correlation r^2 (predicted vs actual ΔVL)	0.30	0.45	P<0.01**
Trajectory (% correct ΔVL predictions)	76%	78%	P<0.05**
Absolute difference (predicted vs actual ΔVL in logs)	0.88	0.78	P=0.05

* one-tailed t-tests

** comparison performed across individual ANN mode ls

Discussion

- The addition of four binary drug history variables (AZT, 3TC, NNRTI, PI) significantly improved the accuracy with which ANN models predicted virologic response to HAART in terms of:
 - correlations between predicted and actual Δ VL
 - % correct VL trajectory prediction (individual models)
 - absolute differences between predicted and actual VLs

Conclusions

- Including drug history information improves the accuracy of ANN modelling
- Further study is warranted to extend the incorporation of drug history information and optimise the performance of ANN models
- Future data collection will include a greater emphasis on drug history information

Acknowledgements

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Acknowledgements (2)

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