

Introduction

The goal of the RDI is to create a sufficiently large relational database to correlate baseline HIV-1 resistance genotypes and drug therapy to virological response. The ultimate aim is to collect data from 5,000 - 10,000 individuals. Baseline genotype, viral load (VL) and treatment data, plus week 24 VL from clinical studies is being collected in a customised Oracle database. In this study, we wished to develop neural network (NN) models to predict virological failure, using initial data already collected.

Methods

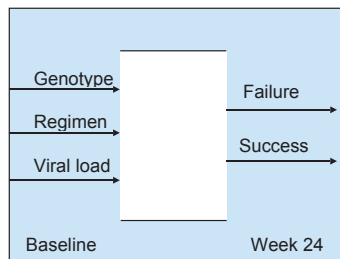
Data from the BC Center for Excellence in HIV/AIDS, Vancouver, Canada, Visible Genetics (VGI) and the University of Siena, Italy were analysed and the following information selected for the study:

1. Genotype mutations appearing with a frequency >0.5% in at least 2 out of 3 datasets, together with mutations previously reported as having a significant impact on drug susceptibility
2. Antiretroviral drugs used with a frequency >0.5% in at least 2 out of 3 groups
3. Patient samples with the following information:
 - Baseline genotype
 - Details of antiretroviral regimen
 - For continuous models, VL pre-therapy and for at least one time point (weeks 8, 16 or 24)
 - For dichotomous models, VL pre-therapy and at week 24
 - No therapy change during the period of 24 weeks

Based on these criteria, 400 patient samples were selected. From these, approximately 800 'cases' (VL from weeks 0-8, 0-16, or 0-24) were derived and used for construction of continuous NN models to predict VL change. 115 cases were removed at random to test the accuracy of the NN models derived. 63 were selected at random as a validation set against which the NN models were tested iteratively during development.

215 cases were selected for the construction of the dichotomous models to predict virological success/failure (VL \leq 400 copies/mL) with 21 removed at random as a test dataset and the remaining 194 used to train the models. The modelling diagram is shown in Figure 1.

Figure 1: Modelling Diagram



Results:

Drug parameters

12 frequently used drugs were selected for the analysis: indinavir, nelfinavir, ritonavir, saquinavir, lopinavir, AZT, ddl, d4T, abacavir, 3TC, efavirenz, and nevirapine.

Genotype parameters

49 codons were selected: 20 in protease (10, 20, 24, 30, 32, 33, 36, 46, 47, 48, 50, 54, 63, 71, 73, 77, 82, 84, 88, 90) and 29 in RT (41, 44, 62, 65, 67, 69, 70, 74, 75, 77, 98, 100, 101, 103, 106, 108, 115, 116, 118, 151, 179, 181, 184, 188, 190, 210, 215, 219, 236).

Three final NN models were tested, two complex ones involving all 62 parameters (49 mutations, 12 drugs and time or baseline viral load) and a simplified model involving 38 parameters. The simplified model was developed by grouping drugs with similar resistance profiles (Indinavir = Ritonavir = Lopinavir, AZT = ddl = d4T, and Efavirenz = Nevirapine), reducing the number of drug parameters to 6 and by only including mutations with a frequency >2% instead of

>0.5%, reducing the number of mutations to 31 (13 in protease: 10, 20, 30, 36, 46, 54, 63, 71, 73, 77, 82, 84, 90, and 18 in RT: 41, 44, 67, 69, 70, 98, 103, 115, 116, 118, 151, 179, 181, 184, 190, 210, 215, 219).

62-parameter Continuous Model:

The correlation between predicted and actual absolute VL change for the training set gave an R^2 value of 0.85 ($p < 0.0001$) (Figure 2).

For independent test and validation sets, the correlation was reduced, but still highly significant, with an R^2 value of 0.5 ± 0.05 ($p < 0.0001$) (Figures 3). The VL trajectory was correctly predicted in 75% ($\pm 1.8\%$) of cases in the test sets.

Figure 2

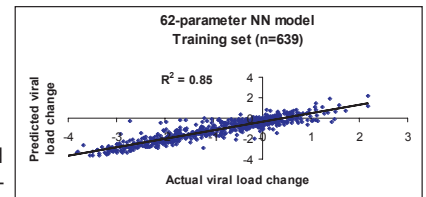
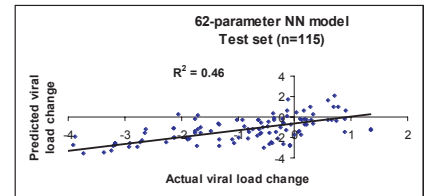


Figure 3



38-parameter Continuous Model:

The correlation between the predicted and actual absolute VL change for the training set gave an R^2 value of 0.85 ($p < 0.0001$). Of interest, the simplified NN model appeared slightly less accurate in predicting absolute VL change (average $R^2 = 0.47 \pm 0.05$ for test and validation sets) or the VL trajectory ($72 \pm 1.8\%$ correct for the test and validation sets). However, these differences between the two models were not statistically significant ($p > 0.05$).

62-parameter Dichotomous Model:

Correct prediction of failure based on baseline genotype and treatment was achieved in 100% of cases in the training data set and an average of $82\% \pm 1.6\%$ of cases in multiple cross validation data sets. Example results are shown in Table 1.

Table 1: Example results of predicting virological failure

Genotype	Baseline		Virological response at week 24	
	Therapy regimen	Viral load (log10)	Actual	Predicted
Pattern 1	d4t, 3TC, Efavirenz	3.85	F	F
Pattern 2	d4t, Abacavir, Efavirenz	3.89	S	S
Pattern 3	AZT, Abacavir, 3TC	4.94	F	F
Pattern 4	AZT, 3TC, Nelfinavir	4.29	F	F
Pattern 5	AZT, 3TC, Abacavir, EFV	3.80	F	S
Pattern 6	d4T, Indinavir, Nelfinavir	4.85	F	F

Pattern 1: PI (15, 20, 37, 38, 57, 62, 63, 69, 71, 90), RT (41, 49, 101, 108, 173, 174, 178, 181, 184, 190, 196, 211, 214, 215, 221, 237, 238)
 Pattern 2: PI (10, 13, 15, 19, 20, 35, 36, 37, 41, 54, 69, 71, 74, 75, 89), RT (68, 122, 123, 135, 162, 165, 173, 174, 177, 178, 184, 200, 207, 211, 214, 235)
 Pattern 3: PI (37, 63, 69, 77), RT (83, 90, 101, 103, 174, 178, 211, 214)
 Pattern 4: PI (13, 15, 19, 30, 35, 36, 37, 57, 62, 63, 72, 88), RT (122, 123, 135, 184, 200)
 Pattern 5: PI (6, 37, 64, 70), RT (60, 103, 108, 135, 142, 207, 211, 214, 221, 227, 245)
 Pattern 6: PI (10, 37, 71, 77, 93), RT (41, 43, 67, 74, 100, 103, 122, 123, 166, 177, 184, 202, 210, 214, 215, 219, 228)

F: Failure S: Success

Conclusion:

Initial development of NN models resulted in successful training with a limited dataset and demonstrated that it is possible to use this approach to predict the absolute VL change and VL trajectory from complex input variables. The dichotomous models gave a high average prediction rate of >82%, suggesting that this approach is also useful in predicting virological failure from genotype and therapy regimens.