A Neural Network Model Using Clinical Cohort Data Accurately Predicts Virological Response and Identifies Regimens With Increased Probability of Success in Treatment Failures

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hiv resistance response database initiative

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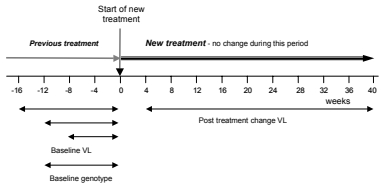
Introduction

- The RDI is gathering data from a variety of different clinical settings to populate a large relational database and model virological response from genotype
- The RDI has previously demonstrated the utility of neural networks (NN) in predicting viral load (VL) response to highly active antiretroviral therapy (HAART) from genotype using a clinical trial dataset (Seville meeting)
- Here we compare the reliability of using 'real life' clinical cohort data to model treatment response
- We also investigate the ability of the NN model to identify effective treatment regimens for real cases of treatment failure

Methods

- Data from 351 patients from the BC HIV treatment cohort were analysed, each having multiple genotypes and irregular VL measurements
- 'Treatment change episodes' (TCEs) were selected from patients having a genotype up to 12 weeks before treatment change and baseline VL up to 16, 12 or 8 weeks before treatment change, follow-up VL was within 4-40 weeks of treatment change
- 652, 602 and 539 TCEs respectively, obtained using the 3 VL windows above, were used for NN training and 10% of each was partitioned for independent testing.10 additional NN models were trained using the 8-week VL window, each with independent test sets such that each TCE appeared once in at least one test set
- Results were compared to those previously obtained using clinical trial data comprising 700 TCEs, with baseline VL and genotype at Wk 0 (time of treatment change), and follow-up VL at 8, 16, or 24 weeks
- The most accurate NN model was used to predict response to different HAART regimens for treatment failures; 139 TCEs where VL increased after a change to a regimen of ≥3 antiretroviral drugs

The 'Treatment Change Episode' (TCE)



Results - 1

- The correlation between the predicted and actual VL change for the initial 16-, 12- and 8-week baseline VL models gave R^2 values of 0.42, 0.45 and 0.55 respectively
- The model with the narrowest baseline VL window (8 weeks) most accurately predicted VL response
- The R^2 value for this model was significantly different to those for the other models ($p<0.05$) and also to that of a previous model derived using clinical trial data ($R^2=0.50$, $p<0.05$)
- VL trajectory was correctly predicted in 74%, 72% & 87% of cases (16-, 12- and 8-week models respectively)
- Again, the 8-week model was significantly more accurate than the two other models ($p<0.05$) and comparable to the clinical trial model (75%, ns)

TABLE 1: Results of NN Models

NN Model	Total TCEs in Model	R² value (training set)	R² value (test set)	VL Trajectory Prediction
Clinical Trial Model:	700	0.85	0.50	75%
Initial Cohort Models:				
-16 week VL	652	0.84	0.42	74% correct
-12 week VL	602	0.84	0.45	72% correct
-8 week VL	539	0.85	0.55	87% correct
10 NN Models:				
Model 1	539	0.85	0.56	76% correct
Model 2	539	0.86	0.52	83% correct
Model 3	539	0.85	0.56	72% correct
Model 4	539	0.87	0.35	83% correct
Model 5	539	0.86	0.48	74% correct
Model 6	539	0.85	0.52	81% correct
Model 7	539	0.87	0.75	79% correct
Model 8	539	0.87	0.36	79% correct
Model 9	539	0.86	0.44	83% correct
Model 10	539	0.84	0.34	86% correct

Results - 2

- The 10 8-week VL NN models produced R^2 values for the test sets ranging from 0.34 to 0.75 and correctly predicted viral load trajectory in 72% to 86% of cases (Table 1)
- Using the best performing model (#7) to evaluate alternative regimens in the 139 failures, in each case one or more regimens were identified that the model predicted would reduce VL (Figure 1). The median VLs for pre-TCE, post-TCE & best predicted were: 4.4, 5.0 & 2.1 logs respectively
- Of the 90 patients with baseline VLs >4 log (potentially the most difficult to 'salvage'), the median VLs for pre-TCE, post-TCE & best predicted were: 5.0, 5.2 & 2.3 logs respectively (Figure 2)

Virtual Treatments

- Indinavir, Lamivudine(3TC), Zidovudine(AZT)
- Indinavir, Lamivudine(3TC), Stavudine(D4T)
- Lamivudine(3TC), Nelfinavir, Stavudine(D4T)
- Lamivudine(3TC), Saquinavir, Zidovudine(AZT)
- Lamivudine(3TC), Nelfinavir, Zidovudine(AZT)
- Efavirenz, Lamivudine(3TC), Stavudine(D4T)
- Efavirenz, Lamivudine(3TC), Zidovudine(AZT)
- Lamivudine(3TC), Ritonavir, Zidovudine(AZT)
- Lamivudine(3TC), Saquinavir, Stavudine(D4T)
- Didanosine(DDI), Indinavir, Stavudine(D4T)
- Didanosine(DDI), Nelfinavir, Stavudine(D4T)
- Abacavir, Lamivudine(3TC), Zidovudine(AZT)
- Didanosine(DDI), Efavirenz, Stavudine(D4T)
- Lamivudine(3TC), Ritonavir, Stavudine(D4T)
- Didanosine(DDI), Indinavir, Lamivudine(3TC)
- Nelfinavir, Nevirapine, Stavudine(D4T)
- Efavirenz, Indinavir, Stavudine(D4T)
- Efavirenz, Nelfinavir, Stavudine(D4T)
- Abacavir, Efavirenz, Nelfinavir
- Lamivudine(3TC), Nevirapine, Stavudine(D4T)
- Abacavir, Efavirenz, Stavudine(D4T)
- Didanosine(DDI), Lamivudine(3TC), Zidovudine(AZT)
- Lamivudine(3TC), Nevirapine, Zidovudine(AZT)
- Ritonavir, Saquinavir, Stavudine(D4T)
- Abacavir, Lamivudine(3TC), Stavudine(D4T)
- Didanosine(DDI), Lopinavir, Ritonavir
- Lopinavir, Ritonavir, Stavudine(D4T)

Fig 1: Best Predicted Response with Alternative Treatments (all failures)

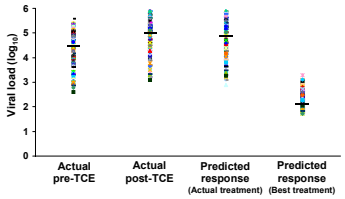
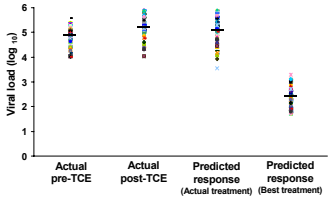


Fig 2: Best Predicted Response with Alternative Treatments (failures with VL>4logs)



Conclusions

- NN modeling using the narrowest baseline VL window gave the most accurate prediction of VL response, underlining the importance of the quality of the dataset.
- This model also showed similar predictive accuracy compared to a NN model trained with clinical trial data, establishing the feasibility of using treatment cohort data to model VL response.
- The model identified potentially beneficial treatment regimens in patients who experienced treatment failure, demonstrating the utility of using this approach to perform evaluations of multiple treatment permutations.

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