

Neural Network Model Identifies Potentially Effective Drug Combinations For Patients Failing Salvage Therapy

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Introduction

- One of the main challenges in HIV care remains the identification of effective combination antiretroviral therapy (ART) for salvage patients
- The RDI is gathering data from a variety of different clinical settings to populate a large relational database and model virological response to ART from genotype using neural networks (NN)
- Here we develop NN models using clinical cohort data including heavily pre-treated, salvage patients
- We investigate the ability of NN models to identify effective alternative treatment regimens for salvage patients experiencing continued treatment failure despite having treatments changed according to current clinical practice

Methods

- Data from 511 patients from two clinical cohorts were analyzed
- 747 'treatment change episodes' (TCEs, **Figure 1**) were obtained: episodes with a genotype ≤ 12 weeks and a viral load (VL) ≤ 8 before treatment change and follow-up VL within 4-40 weeks
- Thirteen NN models were trained, each using 690 randomly selected TCEs and evaluated using the remaining 57 TCEs, as independent test sets
- 108 salvage failure TCEs were identified (baseline VL of ≥ 4 logs and an increase in VL following treatment change)
- The best NN model was then used to predict virological response to 38 common treatment regimens (**Table 1**) for each case (4104 individual virtual response predictions)

Fig 1: The Treatment Change Episode (TCE)

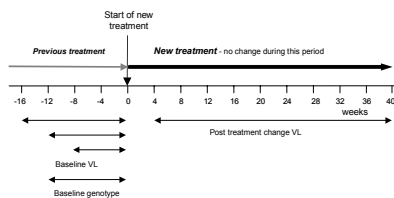


Table 1: Virtual Treatments

- Indinavir, Lamivudine(3TC), Zidovudine(AZT), Ritonavir
- Indinavir, Lamivudine(3TC), Stavudine(d4T)
- Lamivudine(3TC), Neftravir, Stavudine(d4T), Ritonavir
- Lamivudine(3TC), Saquinavir, Zidovudine(AZT), Ritonavir
- Lamivudine(3TC), Neftravir, Zidovudine(AZT), Ritonavir
- Efavirenz, Lamivudine(3TC), Stavudine(d4T)
- Efavirenz, Lamivudine(3TC), Zidovudine(AZT), Ritonavir, Saquinavir, Stavudine(d4T)
- Lamivudine(3TC), Ritonavir, Zidovudine(AZT), Ampiclavir
- Lamivudine(3TC), Saquinavir, Stavudine(d4T), Ritonavir
- Lamivudine(3TC), Indinavir, Stavudine(d4T)
- Diclofenac(DDI), Indinavir, Stavudine(d4T)
- Abacavir, Lamivudine(3TC), Zidovudine(AZT), Didanosine(DDI), Efavirenz, Stavudine(d4T)
- Lamivudine(3TC), Ritonavir, Stavudine(d4T)
- Didanosine(DDI), Indinavir, Lamivudine(3TC), Ritonavir
- Nelfinavir, Nevirapine, Stavudine(d4T)
- Efavirenz, Indinavir, Stavudine(d4T), Ritonavir
- Efavirenz, Neftravir, Stavudine(d4T)
- Abacavir, Efavirenz, Neftravir
- Abacavir, Efavirenz, Stavudine(d4T)
- Didanosine(DDI), Lamivudine(3TC), Zidovudine(AZT)
- Lamivudine(3TC), Nevirapine, Zidovudine(AZT)
- Lamivudine(3TC), Ritonavir, Saquinavir, Stavudine(d4T)
- Abacavir, Lamivudine(3TC), Stavudine(d4T)
- Lopinavir
- Lopinavir, Ritonavir, Stavudine(d4T), Lamivudine(3TC)
- Didanosine(DDI), Lopinavir, Ritonavir, Lamivudine(3TC)
- Tenofovir, Efavirenz, Lamivudine(3TC)
- Ampiclavir, Efavirenz, Lamivudine(3TC)
- Lamivudine(3TC), Ritonavir, Stavudine(d4T), Lopinavir

Results - 1

- The correlation between the predicted and actual VL change for the 13 NN models gave a mean R^2 value of 0.65 (**Table 2**) - examples of scatter plots are shown in **Figure 2**
- The 13 NN models produced a mean correct trajectory prediction rate of 78%
- The best model identified one or more regimens that were predicted would reduce VL in all 108 salvage failure cases
- The median actual change in VL for these cases was +0.4 logs whereas the median change using the best regimens from the NN predictions was -2.6 logs (**Figure 3**)

TABLE 1: Results of NN Models

NN Model	R ² value (test set)	VL Trajectory Prediction
Model 1	0.38	81% correct
Model 2	0.76	74% correct
Model 3	0.62	84% correct
Model 4	0.64	84% correct
Model 5	0.66	72% correct
Model 6	0.68	84% correct
Model 7	0.79	72% correct
Model 8	0.64	72% correct
Model 9	0.70	81% correct
Model 10	0.62	77% correct
Model 11	0.53	83% correct
Model 12	0.63	79% correct
Model 13	0.78	73% correct

Figure 2: Examples of Predictions by NN models

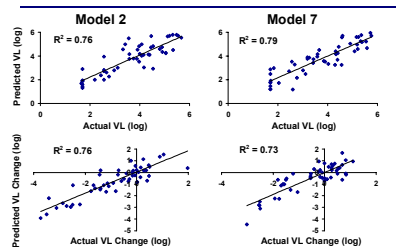
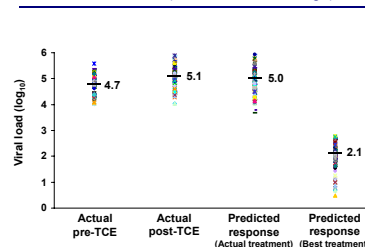


Figure 3: Best Predicted Response with Alternative Treatments (failures with VL > 4 logs)



Conclusions

- NN modeling identified potentially effective treatment regimens in all patients who experienced treatment failure
- The NN model predicted that substantial reductions in viral load would result from these alternative treatments
- This demonstrates the potential utility of this approach in supporting treatment decision making in salvage therapy.

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