A global non-profit initiative against HIV drug resistance
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hiv resistance response database initiative

RDI *e-News*

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New methodologies and data in run-up to clinical pilot study

Expert advisory group established to guide the initiative

Welcome to the fifth issue of RDI e-News. In the past year the RDI has been testing alternative modelling methodologies and collecting new data in readiness for the first clinical assessment of its approach scheduled to take place in early 2007. Some of the main developments and activities are summarised here.

Random Forests show promise

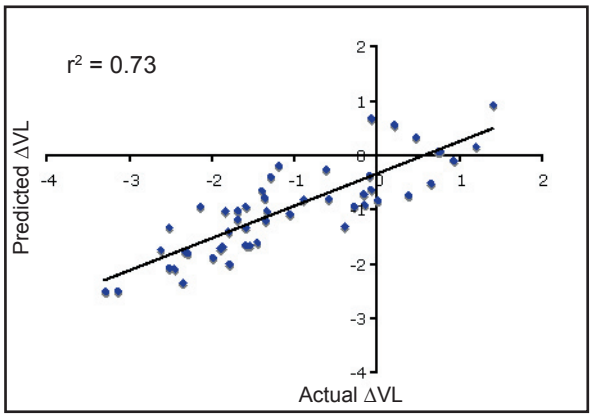
A comparison of three alternative modelling methods suggests that Random Forests (RF) may be a useful complement to artificial neural networks (ANN) in predicting virological response to HAART. The predictions produced by the RF models were as accurate as those produced by ANN and more consistent.

A potential shortcoming of ANN is that during training the models may 'over fit' the training data: they may fail to capture the true relationships between the input data (genotype, antiretroviral drugs, baseline viral load etc) and virological response, generating instead a 'local minimum' solution particular to those training data. This was considered a potential explanation for why ANN models have proved more accurate for patients from the clinics that provided training data than for those from 'unfamiliar' clinics. Alternative high level modelling methods such as RF and Support Vector Machines (SVM) are resistant to over-fitting and potentially more generalisable than ANN.

To test these alternative methods, the same 1,154 treatment change episodes (TCEs) were used to train three committees of 10 models – one of ANN, one of RF and one of SVM. There were 76 variables used for training: 55 resistance mutations; antiretroviral drugs in the new regimen (14 covered); baseline viral load; baseline CD4 count; four treatment history variables (see Issue 4) and time to follow-up viral load; and one output variable – the follow-up viral load value.

The three committees were tested with two test sets: a 'familiar clinic' test set of 50 TCEs from clinics that had contributed to the training set (randomly partitioned data from different patients) and an 'unfamiliar clinic' test set of 50 TCEs from the Dutch National ATHENA database – clinics that were not represented in the training dataset.

For the familiar clinics test set, correlations between the committees' predictions and the actual virological response data gave r^2 values of 0.69 for ANN, 0.71 for RF and 0.61 for SVM. The mean absolute differences between predicted and actual ΔVL were 0.54, 0.60 and 0.61, respectively. For the unfamiliar clinic test set the r^2 values were 0.46, 0.47 and 0.48 with mean absolute difference scores of 0.71, 0.69 and 0.73 for ANN, RF and SVM respectively. The results indicate that the new methods may be as accurate but do not show any greater generalisability than ANN.



Scatterplot for the combined predictions of the ANN, RF and SVM models.

When the performance of individual models was inspected it was clear that the ten individual RF models were more consistent and accurate than the other methods. For example the mean r^2 value for the individual RF models tested with familiar clinic data was 0.67 compared to 0.39 for ANN, raising the possibility of using smaller committees or individual RF models, perhaps in combination with ANN committees.

Mono and dual therapy data help predictions of response to HAART

A study has demonstrated that data involving sub-optimal treatments, used before the advent of HAART, contribute to the accuracy of the RDI's models in predicting virological response to HAART. The results suggest that these data contribute to the models' 'learning' about the contribution of individual drugs and their ability to make generalisable predictions about drugs in combination.

The RDI database currently includes data from the late 1980's right up to the present day, including treatment with regimens varying from monotherapy up to so-called 'mega-HAART', involving 6,7 or even 8 drugs at once. The RDI's standard approach is to use data from all types of regimen, including single and dual therapy, when training models, even though these are developed to predict responses to HAART involving three or more drugs in combination.

There is a theoretical rationale for this in that exposure of the ANN to examples of treatment and response involving single or dual therapy is likely to contribute to the ability of the ANN to model the relationships between drugs, genotypes and responses as much (or even more) than their exposure to more complex combination regimens. This theoretical assumption was tested empirically in this stage of the work programme.

Two committees of 10 ANN models were developed: one using only antiretroviral regimens involving three or more drugs in the training set ('HAART models') and one using all TCEs regardless of the number of drugs ('standard models'). The size of these training sets were set in proportion to the number of TCEs involving three or more and less than three drugs in the whole RDI database: 1,000 TCEs involving three or more drugs (not including ritonavir used as a booster) were selected at random to train the HAART models and then 154 involving fewer than three drugs were added to these to make up the training set for the standard models.

The predictions of the ANN committees correlated with the actual ΔVL values with an r^2 value of 0.69 for the standard models and 0.61 for the HAART models. The mean absolute difference between the models' predictions and the actual ΔVL values was 0.54 for the standard models and 0.61 for the HAART models. The differences in performance were statistically significant.

Long-term follow-up data contribute to predictions of short-term response.

The likely application of the RDI's approach is to provide a prediction of the short-term virological response to HAART as a treatment decision-making aid. In a similar study to that described above, models developed using TCE's with short-term follow-up viral loads (up to 24 weeks) proved somewhat less accurate than models trained with additional data with longer follow-up viral loads when predicting virological response at 12 and 24 weeks. The study provided support to RDI's strategy of including these data with longer term follow-up in its modelling.

Two committees of 10 ANN were developed, the first ('24-week models') using 1,000 TCEs with follow-up viral loads between 4 and 24 weeks after the date of treatment change, the second with the same TCEs plus an additional 300 with follow-up viral loads between 24 and 48 weeks ('48-week models'). The numbers were in proportion to the number of TCEs with these follow-up viral loads in the database as a whole. When the two committees were used to predict virological responses at 12 weeks the correlations gave r^2 values of 0.43 (24-week models) and 0.52 (48-week models). The mean absolute differences between predicted and actual ΔVL were comparable at 0.58-0.59. When the models were tested with 24-week data, the r^2 values were 0.46 and 0.54 and the mean absolute difference scores 0.67 and 0.58.

Major new data contributions

The following institutions joined the RDI during 2006, contributing significant amounts of data:

- ATHENA National Dutch HIV Database, HIV Monitoring Foundation, Amsterdam, Netherlands
- Chelsea and Westminster Hospital, London, UK
- Royal Free Hospital, London, UK
- AIDS Research Center, National Institute of Infectious Diseases, Tokyo, Japan
- Hospital of the Johann Wolfgang Goethe-University, Frankfurt, Germany.

Our thanks goes to all of you for your support.

RDI Advisory Group formed

The RDI has invited a number of collaborators and data contributors to form an advisory board to provide the initiative with ongoing expert advice and guidance. The current membership is:

1. Julio Montaner, Canada
2. Jose Gatell, Spain
3. Richard Harrigan, Canada
4. Carlo Torti, Italy
5. Brian Gazzard, UK
6. John Baxter, USA
7. Scott Wegner, USA
8. Maurizio Zazzi, Italy
9. Sean Emery, Australia
10. Victor De Gruttola, USA
11. Joep Lange, The Netherlands
12. Anna Maria Geretti, UK
13. Schlomo Staszewski, Germany

The group held its first meeting during the International AIDS conference in Toronto in August 2006.

Coming up

The RDI is currently preparing for a clinical pilot study, the first attempt to test the models developed by the RDI in clinical practice. The trial will be conducted in the USA, Canada and Italy. Physicians will be able to access the RDI system via the RDI web site, enter their patient's anonymised data and receive back a report listing the most effective HAART combinations according to the predictions of the RDI's latest models.

In addition, the RDI is planning further studies to refine its modelling techniques.

More news of these studies in the next issue.