hiv resistance response database initiative

RDI e-*News*

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Neural Network identifies effective salvage drugs

Nature covers the news

New data presented by the RDI at the 12th International Workshop on HIV Drug Resistance in Cabo Mexico and the 2nd IAS conference on HIV Pathogenesis and Treatment demonstrated that artificial intelligence (AI) could find potentially effective treatments for patients whose drug therapy is failing, despite having their treatment changed by their physicians according to current clinical practice.

"These patients had high viral loads and were failing because of drug resistance, despite multiple changes to their treatment and the use of current resistance tests", commented Professor Julio Montaner MD, Professor of Medicine and Chair in AIDS Research, at the BC Centre, University of British Columbia, Canada, describing the results presented at Cabo. "Today's results hold out the possibility of being able to reverse the process of treatment failure for such patients, using artificial intelligence to help us identify the best possible drug combination for the individual."

Cohort data produces accurate NN model

In the study presented at Cabo, a Neural Network model was developed using data from hundreds of patients in the BC cohort. It was able to predict how individual patients responded to different combinations of drugs from the genetic code of their virus with 79% accuracy.

The model was then fed the HIV genotypes from 139 failing patients. In every case it identified an alternative drug combination that it predicted would be effective. On average these alternative treatments were predicted to reduce the viral load by over 2 logs (99%). Based on its 79% accuracy, had the system been used to select new drug combinations for these patients, 110 of the139 patients might have responded to treatment instead of failing.

"We were very excited when we saw the scale of these results" commented Dr Brendan Larder, Chair of the RDI's Scientific Core Group. "This is the first time that we have used this technique specifically to look for alternative treatments for patients experiencing multiple treatment failures."

These results were produced from the research described in the last issue of RDI e-*News*. The abstract and presentation from the Cabo meeting are available on the RDI web site.

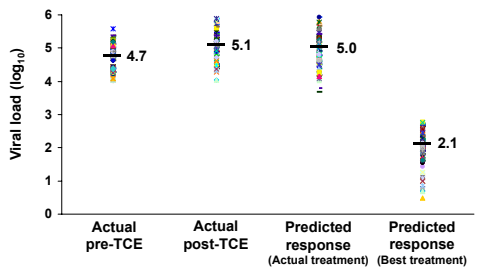
The results were impressive enough to lead Nature magazine to run an article on the RDI in the 19th June issue, a copy of which is attached.

Second study confirms and extends findings

Encouraged by these results, the BC data were combined with data from the NIAID treatment cohort and new neural network models developed. The models achieved even greater accuracy than those developed from the BC data, with a mean percentage correct prediction of viral load trajectory of 81%. The most accurate model produced a correlation (r^2) between predicted and actual viral load change of 0.76.

This model was then used to identify alternative effective regimens for 108 cases of treatment failure. Alternatives were successfully identified in all cases and the median reduction in viral load for the best alternative in each case was -2.86 logs (See figure from Paris presentation below). This compares with a median actual increase in viral load of +0.41log from the prescribed drugs, or an improvement of approximately 3 logs, demonstrating the potential utility of this approach in supporting treatment decision-making in the salvage setting.

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



Press release, abstracts and posters available at http://www.hivrdi.org

Nature article

Clinical data marshalled to treat HIV

Tom Clarke, London

A database is set to help doctors treat HIV. It attempts to identify the best drug combinations to keep a patient's infection in check, on the basis of genetic sequences of drug-resistant strains of the virus.

The international collaboration that is developing the system — the HIV Resistance Response Database Initiative (RDI) — unveiled its latest results on 12 June at the 12th International HIV Drug Resistance Workshop in Los Cabos, Mexico. And although the system isn't the first to deduce information about the drug resistance of particular HIV strains, it is the first to attempt to do so on such a scale, and to be based on clinical results.

"We're aiming to produce tools that can predict treatment response in actual patients," says Brendan Larder, a virologist who chairs the initiative's core group. The system could eventually be available to all physicians online, enabling them to use a patient's HIV gene sequence to help to predict what drug treatment options would be most successful.

Rapidly mutating HIV strains readily develop resistance to drugs. Up to half of all patients living with HIV must switch drug combinations at least once to control their viral load. Studies have identified about 200 mutations associated with resistance to the 16 drugs commonly given to control the virus.

Doctors already use computer models to establish the optimal combination of two or three drugs that should be given to treat a particular, resistant strain of HIV. But that is an inexact business, given that a patient's virus may harbour as many as 40 drug-resistance mutations. Also, input to the existing computer models usually derives from the ability of different strains to survive in test-tube experiments — which may not reflect the outcomes in patients.

"What's missing is a link to clinical response," says Joep Lange, director of the National AIDS Therapy Evaluation Center in Amsterdam. "At the moment, a lot of mistakes are being made." Because the RDI software 'learns' from real patient data, it could surmount these problems, he says.

The latest test of the software showed that the system could correctly predict which drug combinations would bring HIV under control, and by how much, 78% of the time.

This isn't reliable enough for clinical use, Larder admits. But the latest results are from the 750 cases in the original database. And data from about 4,000 patients at AIDS treatment centres in Europe and North America are currently being added. Once that happens, "we hope to achieve 90% accuracy", says Larder.

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Current activities

Working to provide access to the database
The database is taking shape and we are starting to work on the research query function (RQF). This will enable the RDI database to be queried freely by anyone visiting the RDI web site. Users will sign-on via a user interface on our site and will be presented with a menu of database search options. Use of these will enable the visitor to define and submit their research question. The search will be conducted automatically and the results made available in real time on-line or via email.

Keep the data coming!
Over the coming months a major priority of the RDI will be importing reviewing, editing and inputting the data from many thousands of patients that has been pledged to the initiative by clinical centres all over the world. Central to the goal of the RDI is the development of a substantial database of genotypes, treatment information and virological outcome. Currently we have data from around 5,000 patients. Our aim is in the region of 20,000.

Gilead and Boehringer Ingelheim provide RDI support

Gilead Sciences of Foster City, California, USA and Boehringer Ingelheim of Ridgefield Connecticut, USA have provided financial support and given or pledged data qualifying the companies for Founding Corporate Supporter status. Gilead has provided data from several hundred patients treated with combination therapy including the company's new drug Tenofovir, the first nucleotide analogue reverse transcriptase inhibitor to be approved for HIV therapy.

"We decided to support the RDI because drug resistance is a major problem and their approach has the potential to help physicians select the most effective regimens to overcome resistance in individual patients", commented Gilead scientist Michael Miller. "It is important that the RDI has sufficient data to be able to model and predict responses to combinations including tenofovir".

The support provided by these companies entitles them to substantial research conducted by the RDI on the database on their behalf. Such research could, for example, provide valuable insight into how patients who's HIV has different combinations of mutations responds to those companies' drugs, in different combination therapy settings.

"The database and artificial intelligence tools that we are developing will unlock much of the mystery of why one patient and their virus respond to combination X and the next does not", commented RDI CEO Dr Andrew Revell. "Obviously this is of critical interest to the pharmaceutical industry and we are pleased and grateful that companies such as Gilead and Boehringer have the vision to see the importance of supporting this global initiative and working with us as we unlock this information".

Funding update

As a not-for-profit initiative we are, of course, dependent on funding. We are extremely grateful to the following for support:

Gilead Sciences Inc.
Founding Corporate Supporter

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SAIC-Frederick
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Boehringer Ingelheim

HIV and Hepatitis.com

Common questions

The following questions and answers are based on the most common questions we have received through the RDI web site and email in the past few months.

What data do you need?

The RDI requires data relating to what we call a Treatment Change Episode (TCE), i.e. an instance when a patient has their combination antiretroviral therapy changed. The essential data relating to the TCE are:

1. Baseline viral load at time of treatment change or shortly before
2. Baseline genotype at time of treatment change or shortly before
3. Details of the new treatment regimen
4. Follow up viral load(s)

Additional data such as reason for treatment change, measures of adherence, previous treatment history etc are welcomed.

Why aren't you collecting phenotypes and using your techniques to predict phenotype from genotype?

We collect phenotypic information when available. Unfortunately we have had little opportunity to do so as the bulk of resistance data linked to clinical outcomes is genotypic.

We are not modelling phenotype from genotype, as the phenotype is still an indirect and imperfect predictor of whether or not a patient will respond to a certain combination of drugs in the clinic, which is ultimately what physicians and patients are interested in. The RDI's approach maps genotype directly onto virological response to combination regimens in patients in the clinic, cutting out the inference required with current resistance interpretation methods.

If you have any suggestions for how this newsletter could be improved or if you have any questions about the RDI please contact us at info@hivrdi.org.

And don't forget: the latest information on the RDI can always be found at: www.hivrdi.org