Predicting response to HIV therapy

Brendan Larder* speaks to Francesca Lake, Managing Commissioning Editor: Dr Larder is one of the world’s leading experts in the fields of HIV drug resistance and pharmacogenomics. Dr Larder is a graduate of Cambridge University (UK) and started his professional career studying herpes viruses at the University, gaining his PhD in Virology. Moving to Wellcome (London, UK) in 1985, Dr Larder went on to discover HIV drug resistance. His seminal work on azidothymidine resistance and its genetic basis was achieved while working for the Wellcome Research Laboratories and published in 1989. Since then, Dr Larder has continued to pioneer understanding in the field, unraveling the genetic basis of resistance to several other HIV drugs and developing many of the laboratory techniques for studying HIV drug resistance, including phenotyping and genotyping methodologies. Dr Larder left Glaxo Wellcome in 1997 to set up the UK subsidiary of Belgian diagnostics group Virco (Mechelen, Belgium). During the next 4 years Dr Larder helped Virco to become a leader in HIV drug resistance testing and developed a revolutionary new approach to the interpretation HIV genotypes – the Virtual Phenotype. This provided interpretation of individual patient genotypes, by matching them with genotypes in a large relational database and retrieving and averaging the phenotypes from those matched viruses. Dr Larder was appointed Chief Scientific Officer of Visible Genetics following their acquisition of Virco’s Cambridge research group in September 2001. After leaving Visible Genetics in late 2002, Dr Larder instigated the formation of the HIV Resistance Response Database Initiative, or RDI. The RDI has established the largest database in the world of patient data relating to antiretroviral treatment outcomes and has developed online models that predict how individual patients will respond to different drug combinations.

How did you become interested in studying HIV drug resistance?

My background is actually in virology and molecular virology, which was the subject of my PhD. In the mid-to-late 1980s I was studying herpes viruses, in particular the interaction between herpes simplex virus and what was, at the time, a new antiviral called acyclovir. Those studies were aimed at elucidating the mechanisms of herpes virus resistance to acyclovir. When HIV and AIDS started to become more prominent in the 1980s, I thought there were some parallels with my work on herpes virus DNA polymerase, as HIV has a reverse transcriptase that is similar to a polymerase. With those parallels in mind, I thought it would be useful to apply the information and knowledge that I’d gained from the herpes area to HIV. At that time, I also moved from an academic post at the University of Cambridge (UK) to the Wellcome Research Laboratories (London, UK), at the time when Wellcome was just starting to develop the first antiretroviral, azidothymidine. What I wanted to do was to pre-empt the potential for resistance to...
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azidothymidine, which is how I got involved in the HIV drug resistance field.

When & why did you decide to instigate the formation of the HIV Resistance Response Database Initiative?
The HIV Resistance Response Database Initiative (RDI) was founded in 2002. We wanted to collect data or information from multiple clinical groups, research groups, clinics and hospitals from around the world and to make one big database. At the time, individual groups were working on comparatively small data sets of HIV response in patients and drug resistance, but it’s a very complex issue with many resistance mutations, lots of different patient responses and lots of different drugs. Our feeling was that by accumulating tens of thousands of patients’ worth of data, we would have a better chance of using the data to develop accurate models of treatment response and of trying to make more sense of the relationships between resistance and drug response.

How did the concept of HIV Treatment Response Prediction System originally arise?
Can you give our readers a brief explanation of what HIV-TRePS is and how it works?
HIV Treatment Response Prediction System (HIV-TRePS) started with the RDI, which is a relatively small not-for-profit group. We spent quite a lot of time accumulating data, asking different clinical groups to collaborate with us and to allow us to combine their data in a common format that could be data mined. As we were doing that, we were developing computer modeling techniques to try to produce models that could predict response based on, for example, patient resistance profiles, CD4 counts, viral loads and treatment history. We did that for quite a number of years and today we have approximately 150,000 patients worth of data and have produced numerous models and iterations of the models. Once these were getting fairly accurate, approximately 80% accuracy in predicting response to combination therapy, we made a system that is basically an add-on to the RDI website, allowing individual physicians to obtain customized predictions of their individual patients’ responses to different combinations of antiretrovirals. It’s a free system and once a physician has registered, they can enter their patients’ details online, which would consist of treatment history, viral loads, CD4 counts and, if available, the resistance mutations, although this isn’t necessary. They can then ask the system to give an output of the prediction of the best combinations that would likely be effective for that patient.

The system is quite customizable so the physician can decide what drugs they would like to see modeled and can discard certain drugs if they can’t or don’t want to use them, for example if the patient is intolerant to them or they are not available. If they also input the cost of the drugs at their local clinics, or in their country, they can ask the TRePs system to show combinations that are cheapest, which is quite relevant to resource-limited settings. They can also input their own combination; if they think drugs ‘A’, ‘B’ and ‘C’ are their preferable drugs, they can ask the system to model those and see what the response is predicted to be, relative to a myriad of other combinations produced by the models.

The system’s output is the probability of the patient’s viral load going below 50 copies at a certain time after treatment, which again, the physician can choose. It’s a very flexible system and it’s quite powerful. Once the data has been input by the physician, a report with the predictions is output as a PDF or as an email, within about a minute.

One of the key features of HIV-TRePS is that it can effectively predict treatment response without the need of a viral genotype. Is genotyping still a relevant tool when monitoring HIV treatment response success?
The reason we developed models that don’t require a viral genotype is because a lot of treatments are now being rolled out in resource-limited settings such as sub-Saharan Africa, India, South America and southeast Asia. Very few of those settings commonly have access to genotyping, which is a sophisticated and expensive tool. It’s the access and the expense that is the issue. So we thought that if we can produce a model that doesn’t require genotyping, it would be useful for those settings. The models that we have developed are now virtually as accurate as those that do require a genotype for their predictions. They have been shown in studies to be significantly more accurate than using a genotype with the commonly used interpretation systems to predict how patients will respond to their therapy.

Whether genotyping will still play a role in the future, I think it certainly will in clinics in countries where resources are not limited and genotyping has become an established tool in the diagnostics of HIV treatment and infection. It
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**Interview**

The RDI has recently joined forces with Load Zero foundation. How are you hoping this will impact on the future of HIV-TRePS?

The Load Zero foundation is a very interesting initiative that has acquired access to a large number of viral load tests and is providing those tests to clinics and clinical settings in resource-limited settings, where the clinics wouldn’t usually be able to access viral loads. For example, fairly small clinics and in places that are not easy to transport clinical samples to large diagnostic clinical centers. This should bring a lot of benefit to resource-limited settings, enabling people to detect treatment failure early and pre-empt the development of extensive drug resistance. However, one of the big issues is then what to treat with next. So what we thought, and the reason we formed this collaboration, is if we can ‘bolt on’ a TRePS prediction to the viral load information, the clinical information and the treatment information with these patients in these settings, that would give the physician even more information and knowledge gained from the hundreds of thousands patients in the database as to what to do next. Not only are these clinics resource limited, but knowledge has always been a world where people want to hold on to their own data and produce their own results from it, which is fine, but once you get to the point where you have very large and complex problems, such as with HIV therapy, they can really only be solved, or attempted to be solved, by sharing considerable amounts of data. That’s one of the things we’ve actually managed to do, despite it being a massive challenge. People were very skeptical to begin with and dubious as they basically weren’t used to doing that.

**Question**

What were the main challenges that had to be overcome during the development of HIV-TRePS in order to make it sufficiently effective?

One of the challenges with the TRePS system was the creation of the user interface that integrates the models, as the system will access different models based on whether the doctor chooses to use genotype or not to use genotype. The system has a number of different models that can be accessed and we update them every 6 months to 1 year.

However, the major challenges in developing the system were related to gathering enough data together from a sufficient variety of clinical and geographical settings to allow us to develop a relevant and accurate model that can be generalized to different populations around the world. We found that we really needed to accumulate tens of thousands of patients worth of data and we now have approximately 150,000. When we are developing models, we can’t use all of the data as we apply strict criteria to the data required for the study and do not permit any missing pieces of information. For example, when a patient has their treatment changed we need to know what drugs they’ve been changed to, what drugs they’ve been changed from, what the dates were and what the viral loads were around the time the treatment was changed, and so on. So sometimes we have patients’ data that are incomplete and doesn’t have a recent viral load or the treatment history.

Along with those data set issues, an ongoing challenge has been to persuade clinics, pharmaceutical companies and research institutes to be brave enough to share their data with us in the form of this large collaboration. Science will probably still be used and, my guess is, with technology advancing the way it is, it will become cheaper. It will always be a useful fallback to see genotypes, particularly when new drugs are being introduced into the clinic, of which there have been a number in the recent past. It’s also useful for general epidemiological studies, just to have an idea of the nature of the circulating resistant viruses in the general population and to work out why and what can be done about it. For all of those reasons, genotyping is likely to stay relevant. How relevant it will be in resource-limited settings is a matter of debate and it really depends on accessibility and the cost of the testing. My guess is that in the foreseeable future, widespread use is not going to be practical.

**Question**

Has it become easier to input more data into the system as it has become more popular & are people now more willing to share their patient data?

I think they are; people aren’t completely giving up their data to the RDI, as they retain their rights to it and all the data remains anonymous. Everyone who has contributed has a say in what happens to the data and, in any publications in which their contribution is significant, they will be listed as coauthors or will be acknowledged in that publication. I think as we’ve become a bit more successful and more high profile in what we’re doing then, yes, people are more willing to share their data.
and experience of HIV treatment and specifically drug resistance is fairly limited as well. So this is a way of getting some of that experience and information out to the field in areas where they wouldn’t usually be able to access it at all.

How would you like to see the treatment of HIV progress in the next 5–10 years?
If you look over the last 20–25 years, there has been amazing progress from having no drugs at all and not really understanding the nature of AIDS or HIV, to going through a period of monotherapy with single drugs, where people were failing because of resistance, and then realizing that combinations could work better. That’s the situation we’re in currently; where infected people can be treated very successfully with one combined pill of per day, and monitored, and can have a long and fulfilling life. I think over the next 5–10 years the real thoughts are looking towards whether HIV can be cured. There’s quite a lot of research work and clinical work that’s investigating the possibility of cure, as well as refining development of current antiretrovirals and producing new ones that could be used in the face of continual resistance in some patients. There’s also research into refining and really reducing the price of antiretroviral drugs so that they’re universally accessible, along with the essential diagnostics that go hand in hand with the treatment. It would be nice to see in the next 5–10 years the real thoughts are looking towards whether HIV can be cured.

Finally, if you had unlimited resources, what research would you instigate & why?
My interest has segued slightly from virology and molecular virology through to an interest in computer modeling. I think I would put resources into using supercomputers with very powerful models and expanding that into different fields of medicine. I think in the future, as is starting to happen now, patients’ treatment for many different diseases is being increasingly individualized. So you can imagine in the future a patient will see their physician, who will run a number of tests and receive very rapid results electronically, to give an accurate ‘menu’ of how that patient should be treated. A different patient with the same disease that a doctor sees next may be treated differently owing to their individual genetic makeup or for any number of reasons that influence how drugs work. But knowing all of that and getting all of that information is a big job and will require many collaborations and some very high-powered computing. So one thing I would really like to do is to put together a lot of the work that is starting to be done with human genomics and with infectious agents, for example. So if you combine human genomics and HIV infections, this could be a very powerful way of modeling response to therapy and really expand that type of modeling to different diseases.

You believe then, that supercomputers are basically the key to providing personalized medicine?
Yes, I think that the issues that are starting to become fairly obvious now are that we’re able to generate a huge amount of data and information on people, genomes and disease, but the challenge is how to process that information and what do we do with it? I think the RDI, and what we’ve done with TRePS, could be viewed as a small example of what might be done and what is starting to be done with other diseases and other situations. Cancer is an important example, because massive amounts of information are being generated from a genetic and a genomics point of view, but how all that information is processed and assimilated will be the real challenge in the future. I think that’s where resources need to be directed.

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