An introduction to the HIV Resistance Response Database Initiative

BACKGROUND

There are now around 25 licensed HIV drugs and combination therapy is able to reduce levels of circulating virus to very low levels in the majority of patients. Nevertheless, treatments still fail and the disease continue to progress. One of the main reasons for treatment failure is that the virus readily mutates and develops resistance to the drugs ranged against it.

Genotypic resistance tests are now in widespread use in well-resourced settings to help identify drug combinations that will overcome resistance in the individual patient. Once the test has identified mutations in a patient's virus, however, this information requires interpretation to predict what effect they will have on susceptibility of that virus to each of the available drugs. This poses tremendous challenges because there are more than 200 different mutations that can affect drug resistance in complex ways, and because of the enormous number of possible drug combinations available. Generally, this interpretation is performed by using sets of "rules" or algorithms based on review of the scientific literature. Many different interpretation systems are in everyday use, which vary in content and quality and rely heavily on data relating the genotype to phenotype, rather than to the response of patients in the clinic. Moreover, these systems can only indicate to which drugs the virus is likely to be sensitive or resistant to, they are not designed to give a relative indication of the likely response to different combinations.

THE RDI CONCEPT

The new approach pioneered by the RDI involves using computational models, trained with drug response data from tens of thousands of patients to predict how an individual will respond to any combination of HIV drugs. Many scientists and clinicians believe that this approach has the potential to greatly improve patient outcomes through individualized treatment design.

Since this approach requires an enormous amount of data, the development of the RDI database is an international collaborative initiative. A number of private and public research groups around the world have already made significant contributions to the database & continue to provide updated data.

DATA

All data entered into the RDI database is first stripped of any patient identifiers before being sent to the RDI and each data set assigned a unique identifier. The data currently required by the RDI for its computational modelling are as follows:

Mandatory data:

HIV RNA viral load measures	Viral load sample dates
HIV genotypes (RT and protease sequence data)	Genotype sample dates
CD4 counts	CD4 count dates
Details of antiretroviral drug therapy	Antiretroviral drug start and stop dates
Antiretroviral treatment history (all available)	

Optional data:

Gender	Date of birth
Measures/estimates of adherence	Viral clade
Viral load assay specifications	

PROGRESS TO DATE

The RDI is registered in the UK as an independent, not-for-profit organization, a core research team of four and an international advisory group. As of January 2019 the database held data from approximately 250,000 patients from all over the world.

Neural network, random forest and support vector machine models have been developed and have produced reliable predictions of virological response. The models consistently predict response or failure (</> 50 copies HIV RNA/ml) with 80% or more accuracy. Correlations between predicted and actual changes in viral load have been 0.7 and above. The mean absolute difference between the predicted and actual viral load values are in the region of 0.7 log copies/ml, similar to the reproducibility of the assays. Models have been developed that do not require a viral genotype in order to make their predictions with only marginal loss of accuracy. These models consistently and highly significantly out-perform the genotype resistance tests are predictors of response and are particularly useful in low and middle-income countries where genotyping may be unaffordable.

HIV-TRePS, the RDI's HIV Treatment Response Prediction System was launched in October 2010. This unique system enables healthcare professionals to obtain predictions of how their patients may respond to different combinations of antiretroviral drugs of their choice plus alternative regimens in common clinical use. The healthcare professional can input their local drugs costs and use the system to identify effective combinations within a certain budget or compare the costs of different options. It has been used in 90 countries around the world.

THE PEOPLE

Executive Group

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KEY PUBLICATIONS

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2. Revell AD, Wang D, Perez-Elias, M-J, Wood R, Cogill D Tempelman H et al. 2018 update to the HIV-TRePS system: The development of new computational models to predict HIV treatment outcomes, with or without a genotype with enhanced usability for low-income settings. *J Antimicrob. Chemother* 2018 73(8):2186-2196.
3. Revell A, Khabo P, Ledwaba L, Emery S, Wang D, Wood R, Morrow C, Tempelman H, Hamers RL, Reiss P, Van Sighem A, Pozniak A, Montaner J, Lane HC, Larder B. Computational models as predictors of HIV treatment outcomes for the Phidisa cohort in South Africa. *S Afr J of HIV Med*. 2016; 17(1): doi: 10.4102/hivmed.v17i1.450
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