Modelling response to HIV therapy without a genotype: an argument for viral load monitoring in resource-limited settings

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In the absence of widespread access to individualized laboratory monitoring, which forms an integral part of HIV patient management in resource-rich settings, the roll-out of highly active antiretroviral therapy (HAART) in resource-limited settings has adopted a public health approach based on standard HAART protocols and clinical/immunological definitions of therapy failure. The cost-effectiveness of HIV-1 viral load monitoring at the individual level in such settings has been debated, and questions remain over the long-term and population-level impact of managing HAART without it. Computational models that accurately predict virological response to HAART using baseline data including CD4 count, viral load and genotypic resistance profile, as developed by the Resistance Database Initiative, have significant potential as an aid to treatment selection and optimization. Recently developed models have shown good predictive performance without the need for genotypic data, with viral load emerging as by far the most important variable. This finding provides further, indirect support for the use of viral load monitoring for the long-term optimization of HAART in resource-limited settings.

Keywords: computational modelling, antiretroviral therapy, HIV/AIDS, access

The first decade of the new millennium has seen the roll-out of highly active antiretroviral therapy (HAART) to communities in resource-limited settings hardest hit by the HIV-1 epidemic. The WHO reports that >4 million people in low and middle income countries were receiving HAART by the end of 2008, an increase of more than a million over 2007.[1] While this falls far short of the 10 million that could benefit, a 10-fold increase in access over 5 years is a major achievement. This dramatic expansion of treatment in resource-limited settings brings with it enormous challenges for the future, not least of which is the need to monitor patients and modify their treatment regimens as required to sustain viral suppression and prevent clinical deterioration.

Experience in the developed world has demonstrated that HAART does not eradicate HIV and, over time, mutant variants that are drug resistant to one or more components are often selected. A timely change to the regimen is then required in order to reassert viral suppression. This principle lies at the heart of a clinical management template that includes regular viral load monitoring to detect increased viral replication as early as possible, followed by a resistance test to identify specific viral resistance mutations, interpretation to indicate which drugs may be affected and a change of regimen to drugs to which the mutant virus is presumed susceptible.[2,3] Treatment changes are routinely achieved within a few weeks of the detection of resistant virus, minimizing the risk of progression, accumulation of resistance mutations and the risk of onward transmission of resistant virus.

This approach has been suitable in settings that have access to regular viral load evaluations, genotyping and the choice of ~25 drugs, but it is a very different picture in resource-limited settings. Here, cost and logistical constraints mean that viral loads and genotypes are usually unavailable, treatment changes are triggered clinically or immunologically, and typically there are only ~10 drugs available, organized into strict public health protocols with no scope or basis for individualization. This pared-down clinical strategy, with late switching of failing regimens, increases the risk of significant complex patterns of resistance at the individual and population levels.[4,5] This compromises the potential for subsequent antiretroviral treatment success and ultimately increases the chances of disease progression.

There is, therefore, a major debate in progress regarding the relative importance of laboratory monitoring in resource-limited settings. The recent Development of Antiretroviral Therapy in Africa (DART) study, whilst finding a significant survival advantage among patients with CD4 and other laboratory monitoring compared with those monitored clinically, concluded that the added

benefit was not cost-effective in the short term.[6,7] The study did not include viral load monitoring, which is not included in the WHO guidelines for antiretroviral treatment, and there is a lack of robust evidence of its cost-effectiveness in such settings.[8] However, the studies of laboratory monitoring that do exist examine the short- to medium-term outcomes for the individual but not, for example, the potential long-term impact of late and inadequately guided treatment changes on resistance, subsequent treatment outcomes and the spread of resistance among the wider population. On current evidence, the jury is out on the potential cost-effectiveness of viral load monitoring in resource-limited settings.

The HIV Resistance Response Database Initiative (RDI) is a not-for-profit research organization established in 2002 to collect data from clinical practice to train computational models to predict virological response to HAART. The aim is to make these models freely available over the Internet as an experimental tool to help optimize HAART. Over several years, data from 57000 patients have been collected, and considerable progress has been made in terms of developing and refining modelling methodologies. Artificial neural networks and random forest (RF) models have been developed that make predictions of virological response following a change to the antiretroviral regimen that correlate well with the actual viral load changes observed.[9] Studies also showed that the models were most accurate in their predictions for patients from 'familiar' settings, i.e. those settings from where the data used to train the models were obtained.[10]

Recent models have been developed that predict the probability of the viral load going below 50 copies/mL with an accuracy of ~80%.[11] The models use ~80 variables, including the viral load, CD4 count, treatment history and genotype, from immediately before the treatment change to make their predictions. The premise on which this work was based was to improve the ability to predict response to therapy over the use of a genotype with current interpretation methods. The models have consistently proved more accurate predictors of response than genotypic sensitivity scores from common rules-based interpretation systems.[11–13]

With the roll-out of HAART in resource-limited countries, it is especially critical that the best use is made of the limited treatment options available. However, doing so without the use of genotyping presents a major challenge. This raised the question of whether computational modelling could play a role.

As an initial attempt to address this question, we took data from >3000 treatment change episodes (TCEs) from clinics in North America, Europe, Japan and Australia that had recently been used to train a single RF model. This model predicted virological response among 100 independent test cases with an accuracy of 82%, using 82 baseline variables (including genotype). We removed the genotype data (53 of the 82 variables) from this dataset and repeated the study. The new model was able to predict virological responses for the same test set with an accuracy that, at 78%, was only slightly diminished.[13] While genotyping plays an important role in optimizing therapy, it appears that use of other data, including treatment history information, in the modelling can partially compensate for its absence.

Encouraged by this, we set out to develop models that were more relevant to clinical practice in a resource-limited context.

As we did not have sufficient data from such settings, we selected TCEs that involved drugs in common use in these countries. Two RF models were trained using >8000 TCEs without the use of genotypes, one with comprehensive and one with simplified treatment history information. Both models predicted virological response for 400 independent test cases with an accuracy of ~82%. The models were able to identify alternative regimens (involving the same restricted range of drugs) that they predicted would have reduced viral load to below 50 copies/mL in almost half of the cases of actual treatment failure.[11] They identified regimens that were predicted to be more effective than those that failed in almost all cases.[11] A secondary analysis of the input variables used for these models revealed that the baseline viral load was by far the most important variable (considerably more so than CD4 counts, for example) for the models in making these predictions.

These studies suggest that with viral load monitoring in place, computational models could play an important future role in optimizing antiretroviral therapy in resource-limited settings. Even in the absence of resistance testing, this approach could potentially maximize virological suppression, minimize failure, preserve treatment options and reduce the spread of resistance at the population level.

Viral load monitoring has long been established and empirically supported as key to the effective management of HIV in richer countries. Our findings indicate that it is also likely to be the single most important laboratory monitoring tool for effective long-term treatment strategies in less wealthy settings and, after initial screening, where resources are limited, viral load monitoring could be considered a priority over CD4 determination.

Encouraged by our results, the RDI aims to develop free web-based systems using computational models to support treatment optimization in resource-limited settings.

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None of the authors has anything to declare.

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