Mathematical model helps design efficient multi-drug therapies

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For years, doctors treating those with HIV have recognized a relationship between how faithfully patients take the drugs they prescribe, and how likely the virus is to develop drug resistance. More recently, research has shown that the relationship between adherence to a drug regimen and resistance is different for each of the drugs that make up the "cocktail" used to control the disease.

New research conducted by Harvard scientists could help explain why those differences exist, and may help doctors quickly and cheaply design new combinations of drugs that are less likely to result in resistance.

As described in a September 2 paper in Nature Medicine, a team of researchers led by Martin Nowak, Professor of Mathematics and of Biology and Director of the Program for Evolutionary Dynamics, have developed a technique medical researchers can use to model the effects of various treatments, and predict whether they will cause the virus to develop resistance.

"What we demonstrate in this paper is a prototype for predicting, through modeling, whether a patient at a given adherence level is likely to develop resistance to treatment," Alison Hill, a PhD student in Biophysics and co-first author of the paper, said. "Compared to the time and expense of a clinical trial, this method offers a relatively easy way to make these predictions. And, as we show in the paper, our results match with what doctors are seeing in clinical settings."

The hope, said Nowak, is that the new technique will take some of the guesswork out of what is now largely a trial-and-error process.

"This is a mathematical tool that will help design clinical trials," he said. "Right now, researchers are using trial and error to develop these combination therapies. Our approach uses the mathematical understanding of evolution to make the process more akin to engineering."

Creating a model that can make such predictions accurately, however, requires huge amounts of data.

To get that data, Hill and Daniel Scholes Rosenbloom, a PhD student in Organismic and Evolutionary Biology and the paper's other first author, turned to Johns Hopkins University Medical School, where Professor of Medicine and of Molecular Biology and Genetics Robert F. Siliciano was working with PhD student Alireza Rabi (also co-first author) to study how the HIV virus reacted to varying drug dosages.

Such data proved critical to the model that Hill, Rabi and Rosenbloom eventually designed, because the level of the drug in patients – even those that adhere to their treatment perfectly – naturally varies. When drug levels are low – as they are between doses, or if a dose is missed – the virus is better able to replicate and grow. Higher drug levels, by contrast, may keep the virus in check, but they also increase the risk of mutant strains of the virus emerging, leading to drug resistance.

Armed with the data from Johns Hopkins, Hill, Rabi and Rosenbloom created a computer model that could predict whether and how much the virus, or a drug-resistant strain, was growing based on how strictly patients stuck to their drug regimen.

"Our model is essentially a simulation of what goes on during treatment,"

Rosenbloom said. "We created a number of simulated patients, each of whom had different characteristics, and then we said, 'Let's imagine these patients have 60 percent adherence to their treatment – they take 60 percent of the pills they're supposed to.' Our model can tell us what their drug concentration is over time, and based on that, we can say whether the virus is growing or shrinking, and whether they're likely to develop resistance."

The model's predictions, Rosenbloom explained, can then serve as a guide to researchers as they work to design new drug cocktails to combat HIV.

While their model does hold out hope for simplifying the process of designing drug "cocktails," Hill and Rosenbloom said they plan to continue to refine the model to take additional factors – such as multiple mutant-resistant strains of the virus and varying drug concentrations in other parts of the body – into effect.

"The prototype we have so far looks at concentrations of drugs in blood plasma," Rosenbloom explained. "But a number of drugs don't penetrate other parts of the body, like the brains or the gut, with the same efficiency, so it's important to model these other areas where the concentrations of drugs might not be as high."

Ultimately, though, both say their model can offer new hope to patients by helping doctors design better, cheaper and more efficient treatments.

"Over the past 10 years, the number of HIV-infected people receiving drug treatment has increased immensely," Hill said. "Figuring out what the best ways are to treat people in terms of cost effectiveness, adherence and the chance of developing resistance is going to become even more important."