# Computational modeling of drug resistance to guide treatment decisions for HIV patients

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The Antibody and Product Development group is led by Samuel Ken-En Gan (back row, second from the left). Postdoctoral fellow Chinh Tran-To Su (back row, second from right) was the first author of this study. Credit: A*STAR Bioinformatics Institute

A bioinformatic examination of HIV mutations documented in clinics could help guide the selection of antiretroviral therapies.

Through structural modeling and computational analyses, A*STAR researchers have shown how changes in the HIV genome that make the virus resistant to one antiretroviral drug can often induce resistance more broadly to other drugs of the same class. The findings suggest that some of these drugs—known as protease inhibitors because they block critical

viral proteases—should be prescribed before others.

Such a strategy could help "delay the onset of drug resistance, thereby prolonging drug effectiveness, improving quality of life and lowering treatment costs," says Samuel Ken-En Gan, the study's senior author from the A*STAR Bioinformatics Institute.

Gan and his team modeled the structures of more than two dozen mutated proteases that clinicians found made HIV resistant to any one of seven different protease-blocking drugs. These mutations arose in patients who were taking just one of these drugs, but they impacted the efficacy of other protease inhibitors, too. The A*STAR team showed that cross-resistance can develop easily across five of the seven protease inhibitors, but less so for the other two.

That kind of information, says Chinh Tran-To Su, a postdoctoral fellow in Gan's lab, "could help guide the selection of drugs for the first and subsequent lines of treatment."

Take the protease inhibitor lopinavir, for example. The analysis found that resistance to any other protease inhibitor would probably induce resistance to lopinavir as well. That means it's not very useful if taken by patients after other drugs have started to fail. However, since resistance to lopinavir does not seem to affect how well the other six protease inhibitors will work, Gan and Su conclude that lopinavir should be considered as the drug of choice for patients who are getting their first protease inhibitor.

Should resistance then emerge to lopinavir, the analysis indicates that patients should try one of the four other protease inhibitors that are prone to cross-resistance, while saving the two that are least affected by cross-resistance as agents of last-resort.

Clinical implementation of these recommendations will be needed to test the predictions of the computational modeling. But as Gan notes, the insights gleaned from his group's structural analysis would be hard to come by any other way. "This paper," he says, "represents a landmark analysis using bioinformatics to go where experimental labs and clinical trials cannot easily investigate."

**More information:** Chinh Tran-To Su et al. Structural analyses of 2015-updated drug-resistant mutations in HIV-1 protease: an implication of protease inhibitor cross-resistance, *BMC Bioinformatics* (2016). DOI: 10.1186/s12859-016-1372-3

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