Medical Xpress

Ultra deep sequencing identifies HIV drug resistance at early stage

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Rare, previously undetectable drug-resistant forms of HIV have been identified by Yale School of Medicine researcher Michael Kozal, M.D., using an innovative genome sequencing technology that quickly detects rare viral mutations.

Kozal, associate professor of medicine at Yale and senior author of the retrospective study that used samples from an earlier clinical trial, presented the findings today at the 16th International HIV Drug Resistance Workshop in Barbados. “We found that the fraction of HIV patients that harbored resistance mutations is at least twice as high as previously thought,” said Kozal, who also directs the HIV Program at the VA Connecticut Healthcare System. “These low frequency resistant viral strains are not detectable by current resistance testing methods used in the clinic.”

While HIV treatment has been largely successful, with dramatic increases in survival over the last decade, a significant number of patients develop drug resistance shortly after treatment begins. This study was designed to determine if patients that fail therapy early were initially infected with drug resistant HIV strains.

Kozal and his team examined samples from 258 subjects of the FIRST study, a large multi-center five-year U.S. trial comparing three different approaches to antiretroviral therapy. The study evaluated the long-term clinical and virologic effects of three initial antiretroviral drug regimens for treatment-naïve HIV infected persons.

Kozal and colleagues used the Genome Sequencer™ system and Ultra Deep Sequencing technology, which was developed by 454 Life Sciences, to detect additional low abundant resistant variants and to predict the failure of antiretroviral therapy.

"454 Sequencing can instantly generate hundreds of thousands of long clonal sequence reads that accurately enable the sensitive detection of rare mutations," said Michael Egholm, vice president of research and development at 454 Life Sciences, a member of the Roche group. "Ultra Deep Sequencing provides an essential tool for research on viral diseases and their treatments. The ability to use 454 Sequencing to detect rare viral mutations is a crucial research tool to better understand the early stages of HIV drug resistance."

Kozal said that current genotypic resistance technology available to clinicians is limited to detecting resistance mutations that are present at levels of approximately 20 percent or greater in the circulating viral population in a patient. Therefore, the current technology used in the clinic may miss many low-level resistant HIV strains that can grow rapidly under drug selection pressure and lead to therapy failure.

"This study clearly shows that resistance HIV strains present at the one percent level can lead to premature failure of therapy," said Kozal. "It is our hope that in the future, clinicians can use this knowledge to better choose antiretroviral drug combinations that have the ability to suppress these resistant HIV strains, leading to better clinical responses in patients."

It is estimated that 22 million people have died from AIDS and over 42 million people are living with HIV/AIDS worldwide. In the U.S. alone, 40,000 new infections occur each year.

Source: Yale University