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Unusual new HIV drug resistance mechanism revealed

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For the more than one million people with HIV/AIDS in the United States (and the over 34 million people living with HIV/AIDS around the world), antiretroviral drugs such as efavirenz and other so-called non-nucleoside reverse transcriptase inhibitors (NNRTIs) in combination with other antiretrovirals can be a lifeline, because they slow the progress of viral infection, prolonging life. Unfortunately, studies have shown that these benefits themselves can be short-lived in the clinic: therapy with NNRTIs can lead to single (or "point") mutations in the HIV genetic code—mutations that make the virus resistant to the drugs.

Researchers at the University of Pittsburgh School of Medicine now have a good idea why. In work to be presented at the 58th Annual Biophysical Society Meeting, which takes place in San Francisco from Feb. 15-19, cell biologist Sanford Leuba and his colleagues offer new insight into how NNRTIs function and how therapy-induced point mutations actually confer drug resistance.

NNRTIs work by blocking the action of an enzyme called reverse transcriptase, which HIV uses to convert its own genetic material (in the form of RNA) into single-stranded copies of DNA, which can then be inserted into the genome of the human cells they've infected. Once incorporated, this DNA instructs the host to create new copies of the virus, propagating the infection to new cells and over time attacking the immune system, which can lead to full-blown AIDS.

Using a number of imaging techniques and computer modeling, Leuba

and his team showed that, normally, the binding of efavirenz results in the formation of a molecule-sized "salt bridge" that holds the reverse transcriptase in an open state when it is attached to the template it uses in making DNA copies. "The reverse transcriptase can still bind the template, but it continually slides," Leuba explained, "preventing the enzyme from polymerizing nucleotides. The virus cannot replicate."

The point mutations that cause resistance to efavirenz, the researchers found, prevent that salt bridge from forming, "allowing the reverse transcriptase to function normally," he says. "This type of inhibition, which does not involve drug-binding affinity, has not been described previously."

Based on the work, Leuba said, "We have ideas about how to begin designing a new generation of NNRTIs."

More information: The presentation "A Gripping New Mechanism of Drug Resistance in HIV-1 Reverse Transcriptase" by Grant Schauer, Nic Sluis-Cremer and Sanford Leuba will be at 1:45 p.m. on Tuesday, February 18, 2014 in Hall D in San Francisco's Moscone Convention Center. Abstract: tinyurl.com/km59vnu

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