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**VIRAL "FITNESS" EXPLAINS DIFFERENT RESISTANCE PATTERNS TO AIDS DRUGS**

Some HIV medications lead to the development of drug-resistant HIV when patients take as few as two percent of their medications. For other medications, resistance occurs only when patients take most of their pills. These differences appear to be explained by the different levels of viral "fitness" of the drug-resistant HIV, say AIDS researchers in a new study.

The research, led by David Bangsberg, MD, MPH, an AIDS specialist at the University of California, San Francisco, is reported in the January 9 issue of the journal *AIDS*.

Viral "fitness" refers to the inherent ability of a virus to replicate and cause disease. Incomplete pill-taking by patients causes HIV to mutate and become resistant to the effects of the medications, while the medications that were consumed, in turn, cause the newly resistant virus to become less fit.

The type of medication also factors in. Differences in viral fitness of mutated resistant virus occur between different classes of antiretroviral drugs, said Bangsberg, who is an associate professor of medicine at UCSF and director of the UCSF Epidemiology and Prevention Interventions Center at San Francisco General Hospital Medical Center.

When patients succeed in completely suppressing HIV, which requires that patients take all or almost all of their medications as directed, resistant strains either do not occur or are suppressed, he added.

Explaining the study results, Bangsberg said, "A non-nucleoside reverse transcriptase inhibitor (NNRTI), for example, can be taken one time by a pregnant woman to prevent mother-to-child transmission, and NNRTI resistant HIV virus can develop. Yet patients taking unboosted protease inhibitors (PI) do not experience the peak risk of PI-resistant HIV developing unless they are taking most of their PIs but fall just short of full viral suppression."

The researchers found that NNRTI resistance virus has an advantage over sensitive virus even at very low levels of adherence. This happens because only a single mutation is required to create high-level NNRTI resistance and these mutations have little impact on the virus's ability to replicate. PI-resistant virus, in contrast, requires multiple mutations, each of which significantly weakens the

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ability of the virus to replicate. These PI-resistant viruses only emerge, therefore, when challenged with high concentrations of drug.

Overall, study findings showed that NNRTI resistance was found less often than PI-resistance among patients who took the pills as directed.

“We believe that when new drug classes are developed, more attention should be given in defining how virologic fitness determines how different patterns of taking medications may lead to resistance” said Steven Deeks, MD, associate professor of medicine at UCSF’s Positive Health Program at SFGHMC and senior author on the study.

Both NNRTIs and non-boosted protease inhibitors are potent antiretroviral drugs (ARVs) with demonstrated effectiveness in suppressing the HIV virus when taken in combination with other ARVs at high levels of pill-taking as directed. The standard combination therapy usually includes either one NNRTI or protease inhibitor (non-boosted or boosted with a small amount of another potent PI) and two different antiretrovirals from the nucleoside reverse transcriptase inhibitor class.

Study co-authors include Edward P. Acosta, PharmD, University of Alabama, Birmingham; Reena Gupta, BS, Harvard Medical School; David Guzman, MS, and Elise D. Riley, PhD, both at the UCSF EPI Center at SFGHMC; P. Richard Harrigan, PhD, British Columbia Centre for Excellence in HIV/AIDS; and Neil Parkin, PhD, Monogram Biosciences, South San Francisco.

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The EPI Center and PHP at SFGHMC are both components of the AIDS Research Institute (ARI) at UCSF. UCSF ARI houses hundreds of scientists and dozens of programs throughout UCSF and affiliated labs and institutions, making ARI one of the largest AIDS research entities in the world

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