While Rare, Drug Resistance After Contracting HIV on PrEP Can Occur

January 15, 2015

For the first time, a study has shown that, although rare, resistance to Truvada (tenofovir/emtricitabine) can develop if someone contracts HIV while taking the drug as pre-exposure prophylaxis (PrEP). In previous studies this had only been found to occur if someone turned out to be acutely, or very newly, infected with HIV when they started taking PrEP. (An HIV test may yield a false negative if conducted during an acute infection, possibly leading someone to enter a PrEP study under the false impression that he or she does not have the virus.)

Publishing their findings in the Journal of Infectious Diseases, researchers analyzed plasma samples from the 121 study participants who contracted HIV in the Partners PrEP Study. They tested the samples for HIV that had resistance mutations associated with emtricitabine or tenofovir. The study was a Phase III, randomized, double-blind, placebo-controlled trial in which the HIV-negative member of 4,747 mixed-HIV status heterosexual couples was assigned to receive Truvada or tenofovir as PrEP, or a placebo.

Out of those who tested HIV positive during the study, 25 were assigned Truvada, 38 were assigned tenofovir and 58 were assigned the placebo. Drug levels in the plasma indicated that 26 participants had taken PrEP during or after acquiring the virus. Out of this group, five people had evidence of resistance mutations associated with their PrEP regimen: four of seven (57 percent) of those who took Truvada, and one of 19 (5.3 percent) who took tenofovir. The difference in resistance rates between the two groups was the result of the development of the emtricitabine-related resistance mutation M184IV.

Of the five participants who had drug resistance, three were found to have been acutely infected when they started the trial, leaving two people who were HIV-negative when they enrolled. These two people are key, because their cases indicate that there is a possibility of contracting HIV while taking PrEP and then developing drug resistance, although this chance is apparently rare.

The authors state that that risk of drug resistance may be higher in those who are taking PrEP around the time that they are infected and in those who, because of infrequent follow-up testing, take PrEP for an extended period after contracting the virus. Truvada as PrEP is highly effective if taken daily as prescribed, but loses efficacy if taken less frequently. U.S. Food and Drug Administration protocol recommends that people taking PrEP undergo HIV testing every three months. The participants in this study were tested monthly.

The study found that resistance was more likely to develop to the emtricitabine component of Truvada, meaning that only taking tenofovir instead of Truvada, which also emtricitabine in addition to tenofovir, would lower the risk of resistance. However, the authors state that this risk must be weighed against the 49 percent increased efficacy of Truvada over tenofovir as PrEP that was found in the Partners study.

In an accompanying editorial, Robert M. Grant, MD, MPH, a professor at the University of California, San Francisco, who led the iPrEx study that proved PrEP's efficacy among men who have sex with men (MSM) in 2010, and Teri Liegler, PhD, an associate professor at UCSF, write, "Fear of drug resistance is now raised as we consider rolling out PrEP." However, they add, "Fomenting fear of drug resistance is also misguided if it distracts us from fear of HIV itself, by far the greater threat to human health."

Grant and Liegler point out that while five people developed drug resistance during this trial, an estimated 123 infections were prevented, along with any other secondary infections those cases of HIV may have caused. Additionally, the drug resistance that developed was mostly to emtricitabine, not tenofovir, which is one of the most vital antiretrovirals on the market. This, the authors state, "leaves multiple options for successful combination antiretroviral therapy."

The editorial writers also suggest that drug resistance may be more likely to develop as a result of HIV transmitted through vaginal sex rather than anal sex. In the Partners PrEP trial, there was detectable drug in 49 percent of those taking tenofovir when they contracted HIV and 28 percent of those taking Truvada. This is compared with just 9 percent of the MSM taking Truvada in the VOICE study.

In other words, Truvada, when present in the body, apparently did a better job in of preventing HIV among MSM than among heterosexuals. If PrEP had a higher rate of failure in protecting the heterosexuals from HIV when it was present in the body, then the higher likelihood of its presence at the point of seroconversion would in turn raise the likelihood of drug resistance.

To read the editorial, click here.

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