Stopping Tenofovir Doesn't Always Reverse Kidney Damage

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Kidney damage caused by tenofovir (found in Viread, Truvada and Atripla) may not reverse itself after a year of discontinuing the drug, according to new study results published ahead of print on the website for the Journal of Acquired Immune Deficiency Syndromes (JAIDS).

As recently as the 17th Conference on Retroviruses and Opportunistic Infections, held last month in San Francisco, researchers have confirmed that tenofovir is associated with an increased risk of renal insufficiency and chronic kidney disease (CKD). According to results from the ongoing EuroSIDA study, tenofovir was associated with a 16 percent increased risk of CKD per year of exposure to the drug, even after adjusting the data for other risk factors for kidney damage, such as high blood pressure and diabetes.

The EuroSIDA and other investigators suggest that tenofovir's negative effects on the kidneys are often reversible, usually within 12 months of stopping the drug. However, JAIDS study author Karen Wever, MD, of St. Vincent's Hospital in New York City and her colleagues point to weaknesses in the data supporting this claim.

According to Wever's group, three reports note that renal function rapidly normalizes after the drug is discontinued by adults with tenofovir-associated kidney toxicity. "However," they write, "each report described only one or two patients and based their conclusions on the fact that serum creatinine"—a waste product from protein that becomes elevated in the blood if the kidneys aren't functioning properly—"returned to normal at some time after tenofovir cessation. Serum creatinine, however, is an insensitive measure of renal function and less sensitive than estimated glomerular filtration rate (GFR)."

In fact, persistent reductions in the GFR—not increases in serum creatinine levels—is the criteria needed to diagnosis renal insufficiency and CKD. In short, GFR is a calculation of the fluid volume passing through the kidneys using measurements of serum creatinine levels, along with pertinent age, gender, body size and race data.
Wever's group defined renal insufficiency as a GFR estimate below 90 (mL/min/1.73 m2). A diagnosis of CKD is much more conservative: A GFR less than 60 after being measured twice at least three months apart.

Using GFR estimates, Wever's group set out to determine the reversibility of tenofovir-renal insufficiency in 24 HIV-positive men who ceased using the drug because of kidney toxicity.

Before starting tenofovir, the patients' GFR average was 74, indicating some degree of renal

insufficiency before commencing therapy with the drug.

During therapy with tenofovir, their GFR average fell to 51. Thirteen months after stopping tenofovir, the average GFR hovered at 58. This post-tenofovir measurement, compared with the average pre-tenofovir GFR calculation, was statistically significant—too great to have occurred by chance.

Wever and her colleagues reported that only 10 (42 percent) patients reached their pre-tenofovir GFR during the 13-month follow-up period.

Those who experienced rapid declines in their GFRs while receiving tenofovir were the most likely to experience rapid improvements in their GFRs upon stopping treatment with the drug. “This suggests that more acute renal damage is less likely to be permanent,” the authors write.

Wever’s team also found that shorter duration of tenofovir therapy was associated with the greatest GFR improvements in the study.

The use of a protease inhibitor with tenofovir, as opposed to a nucleoside reverse transcriptase inhibitor, was also associated with more rapid GFR improvements upon stopping tenofovir. Though protease inhibitors are not toxic to the kidneys, Wever’s team writes, they can increase tenofovir levels in the blood and kidneys, potentially leading to greater tenofovir toxicity. “The greater improvement of renal function in those who had received tenofovir together with a protease inhibitor might therefore be explained by withdrawal of a higher tenofovir concentration.”

In conclusion, Wever’s group writes, “improvements in renal function after tenofovir cessation is variable and incomplete, particularly in patients with more gradual decline in GFR who are not receiving a protease inhibitor.” They also suggest using a GFR below 90, as opposed to a CKD-defining GFR below 60, when determining whether to discontinue tenofovir treatment “to avoid permanent renal dysfunction.”
