Tenofovir Increases Risk of Irreversible Kidney Disease

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The nucleotide reverse transcriptase inhibitor tenofovir is associated with an increased risk of kidney damage and chronic kidney disease that increases over time and doesn't appear to be immediately reversible, according to a new analysis by University of California at San Francisco (UCSF) researchers that's published online ahead of print by the journal AIDS.

According to the paper, based on a review of more than 10,000 Veterans Administration medical records, the risk of proteinuria—signs of protein in the urine, a marker of kidney damage—increased 34 percent every year a person living with HIV remained on the drug. The risk of chronic kidney disease increased, annually, by 33 percent. There was also an 11 percent higher risk of rapidly declining kidney function for every year tenofovir was continued.

Importantly, Rebecca Scherzer, MD, of UCSF and her colleagues note, these increases were independent of other factors that cause kidney disease—notably age, diabetes, high blood pressure, smoking, hepatitis C virus (HCV) coinfection and various HIV-specific parameters—confirming that tenofovir therapy itself is an important risk to consider as antiretroviral treatment is started and continued.

Tenofovir—the active ingredient in Viread and a component of Atripla, Truvada and Complera—is widely prescribed, as it is considered a first-line treatment of HIV infection. "[It] is currently used in approximately half of all antiretroviral regimens and as part of post-exposure prophylaxis," Scherzer and her colleagues write.

Clinical trials leading up to the approval of tenofovir as Viread in 2001 didn't find significant kidney problems, though Scherzer's team notes that many of these studies excluded individuals living with, and at risk for, renal disease. More recent studies have reported an association with tenofovir and kidney disease, though usually in small numbers of people and typically in those who were older, with low CD4 cell counts and other HIV- and non-HIV-related health problems.

As many of these studies—some of which didn't find any obvious connection between tenofovir and kidney disease—were small and may not have been based on appropriate laboratory data, Scherzer and her colleagues turned to a national sample of closely monitored patients, notably those receiving HIV care through the Veterans Health Administration. The analysis included 10,841 veterans living with HIV starting therapy for the first time between 1997 and 2007. Patients in the

analysis were on average 46 years old when they started HIV treatment. Roughly half were black, most (more than 97 percent) were male, nearly 40 percent had high blood pressure, 7 percent had diabetes and 19 percent were smokers.

By the end of the study period, 4,303 patients had used tenofovir for an average of 1.3 years; Scherzer and her colleagues pointed out that this short follow-up time was a limitation of the study. The maximum length of tenofovir-inclusive antiretroviral therapy was about six years.

There were 3,400 incidents of proteinuria among all patients included in the analysis, notably 13 percent of those using tenofovir and 8 percent of those not using a tenofovir-inclusive regimen. Among those using tenofovir, the hazard ratio was 1.34 per year—the drug was associated with an annual 34 percent increase in the risk of protein leaking out of the kidneys, confirmed by two consecutive urine dipstick tests.

Rapid decline in kidney function—consistent drops in the estimated glomerular filtrate rate (eGFR) for at least two years—was documented 3,078 times in 9 percent of tenofovir users and 5 percent of those who never used the drug. Among those using tenofovir, the hazard ratio was 1.11—an 11 percent increase in the annual risk of a kidney-related complication associated with a higher risk of death.

As for chronic kidney disease—defined as two consecutive eGFR calculations below 60 milliliters (per minutes per 1.73 squared meters)—there were 1,712 incidents in the study population, notably 2 percent of tenofovir users and 1 percent of those who never used the drug. The annual increase in the risk was 33 percent among those using tenofovir.

All of the annual increases in the kidney disease markers were statistically significant, meaning they were too great to have occurred by chance. And importantly, the risks associated with tenofovir were documented after adjusting the data for other known risk factors. “Even after accounting for demographics, HIV-related factors, comorbidities and other antiretroviral drugs, tenofovir remained independently associated with elevated risk for each kidney disease outcome,” the authors remarked.

Interestingly, and in contrast with the findings of other studies, Scherzer and her colleagues noted that the presence of other chronic kidney disease risk factors upon starting tenofovir treatment did not affect kidney disease outcomes during therapy with the drug. “Presence of traditional [chronic kidney disease] risk factors at baseline such as pre-existing [chronic kidney disease], diabetes and hypertension did not appear to worsen the effects of tenofovir,” they wrote.

It is important to note that the risk increases reported by Scherzer’s team are relative, not absolute.* The overall risk of kidney disease among people living with HIV using tenofovir remains low and depends on underlying risk factors.

Of concern was the finding that discontinuation of tenofovir didn’t reverse the signs of kidney disease—signs of kidney problems remained for at least a year after the drug was discontinued.

“Among those who discontinued tenofovir use in our study,” Scherzer’s team writes, “time following cessation was not significantly associated with either higher or lower risks of proteinuria, or rapid decline, and appeared to be weakly associated with increased [chronic kidney disease] risk. Past users of tenofovir remained at increased risk of outcomes, compared to those never exposed to tenofovir.”

The authors concluded that “tenofovir is associated with increased risk of proteinuria, rapid decline [in kidney function] and [chronic kidney disease]. Clinicians treating HIV-infected patients should recognize that while traditional risk factors such as hypertension, older age and diabetes may increase the risk of kidney disease, tenofovir is associated with elevated risk even in patients without pre-existing kidney risk factors.”

The researchers add, however, that the risks of tenofovir needed to be weighed against its potential benefits. “Despite tenofovir’s association with progressive kidney disease, it is an important component of antiretroviral therapy that may be required in many patients to control viral load. The balance between its efficacy and probably adverse effects requires further study.”

* Generally speaking, the absolute risk of kidney disease in a white 40-year-old male with no other risk factors is very low, on the order of 0.2 percent over the next five years of his life, and increases with certain risk factors (e.g., with type-2 diabetes to 1.7 percent, with type-2 diabetes and high blood pressure to 7.2 percent). The 33 percent risk increase associated with tenofovir relates to the original underlying risk, and equates to a 0.066 percent increase in the person without any other risk factors (0.002 X 0.33) and a 2.3 percent increase in the tenofovir user with high blood pressure and diabetes (0.072 X 0.33). So the absolute risk of chronic kidney disease increases to roughly 0.27 percent in a 40-year-old white male without risk factors—still a low absolute risk—and a more moderate 9.5 percent absolute risk in a 40-year-old male with high blood pressure and diabetes.

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