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Tenofovir Associated With Nonreversible Kidney Disease

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November 28, 2011 (Philadelphia, Pennsylvania) — Tenofovir for the treatment of HIV infection is associated with an increased risk for events indicative of kidney disease, and the risk does not appear to be reversible after drug treatment is discontinued. Rebecca Scherzer, PhD, research statistician at the University of California at San Francisco School of Medicine, reported these findings here at Kidney Week 2011: American Society of Nephrology 44th Annual Meeting.

Dr. Scherzer noted that HIV disease itself is associated with an increased risk for kidney disease, even with highly active antiretroviral therapy (HAART), and there has been controversy over whether tenofovir also raises the risk.

Tenofovir is a first-line treatment for HIV. It is used in about half of all antiretroviral regimens and for postexposure and preexposure prophylaxis.

Early clinical trials of the drug found little or no nephrotoxicity, but the trials excluded individuals with renal impairment or other risk factors. More recent experience with tenofovir indicates that a higher risk for toxicity is associated with older age, lower CD4 T cell count, and other comorbidities.

In a retrospective cohort study of 10,841 HIV-infected treatment-naive veterans initiating antiretroviral therapy at the San Francisco Veterans Affairs Medical Center from 1997 to 2007 (the modern HAART era), Dr. Scherzer and colleagues used statistical modeling to identify any association between tenofovir cumulative exposure and kidney outcomes. They looked specifically at the first occurrence of proteinuria, a rapid decline in kidney function (defined as an annual decline in estimated glomerular filtration rate [eGFR] of 3 mL/min per 1.73 m² or greater), or an eGFR below 60 mL/min per 1.73 m² (indicative of chronic kidney disease [CKD]).

The average age of the cohort was 46 years, and only about 2.3% of the cohort was female. Patients with kidney failure at baseline and anyone missing laboratory values were excluded.

"We found that each year of exposure to tenofovir is associated with a 34% increased risk of proteinuria, an 11% increased risk of rapid decline, and a 23% risk of CKD," Dr. Scherzer reported. "Similarly, when we looked at ever vs never exposure to tenofovir, ever exposure was associated with a 60% increased risk of proteinuria, a 36% [increased risk for] rapid decline, and a 38% [increased risk] for incident CKD; all of these are statistically significant."

After multivariate adjustment for antiretroviral drugs, demographics, baseline comorbidities, and current measurements, each year of exposure to tenofovir was independently associated with an increased risk for all 3 end points. Time off of tenofovir did not appear to lessen the risk for kidney disease events.

Risk for Kidney Disease Outcomes Associated With Cumulative Tenofovir Exposure

Outcome	Hazard Ratio (95% Confidence Interval) Per Year of Tenofovir	*P* Value
Proteinuria, n = 3400 events	1.34 (1.25-1.45)	<.0010
Rapid decline, n = 3078 events	1.11 (1.03-1.18)	=.0033
CKD, n = 1712 events	1.23 (1.12-1.35)	<.0010

The researchers also looked at risk factors for tenofovir renal toxicity. When the participants were stratified by subgroup at baseline, the researchers found that several factors, including age, race, CKD, and other comorbidities, were associated with increased risk for proteinuria.

When all the other antiretroviral drugs were considered, "tenofovir was the only drug that was associated with an increased risk of all 3 outcomes," Dr. Scherzer noted. Scattered negative findings occurred with other drugs, such as an increased risk for CKD with indinavir.

The study was limited because there was no direct measure of eGFR and because of the relatively short mean exposure to tenofovir of 1.3 years (maximum, 6 years). The results might not generalize to nonveterans, women, or patients not receiving regular clinical care, the investigators caution.

"There is strong evidence that tenofovir may cause clinically significant toxicity to the kidney," Dr. Scherzer concluded. She said it remains an important component of effective antiretroviral therapy, and that many patients require tenofovir to control their viral loads. She recommended that clinicians monitor serum creatinine and urine protein levels of these patients.

In light of the efficacy but also the potential toxicity of tenofovir, session moderator Areef Ishani, MD, MS, chief of nephrology at the Minneapolis Veterans Affairs Medical Center and assistant professor of medicine at the University of Minnesota in Minneapolis, who was not involved in the study, told *Medscape Medical News*: "I think there are a couple of risk reduction strategies — you can switch to other agents, and you can see that only 50% of individuals are using tenofovir during the study, so it looks like there are other agents available."

He said the risk of not suppressing the HIV viral load has to be balanced against the risk of diminishing kidney function. "The risk of HIV is clearly bad, and what's the risk of having a GFR go down by 3% or proteinuria? These have to be quantitated with the individual patient.... I think what happens commonly is that people are monitored for progression of kidney disease; if it's bad enough, you can switch them to something else."

The study had no commercial funding. Dr. Scherzer and Dr. Ishani have disclosed no relevant financial relationships.

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