Tenofovir-Associated Decline in Renal Function

To the Editor—We read with interest the article by Goicoechea et al. [1] on the role of antiretroviral medications and tenofovir-associated kidney dysfunction. The authors concluded that regimens based on ritonavir-boosted protease inhibitor (PI/r) were associated with a greater decline in kidney function than regimens based on non-nucleoside reverse-transcriptase inhibitors (NNRTIs) among patients receiving tenofovir. However, the majority (75%) of patients in their analysis who were receiving a PI/r-based regimen were receiving lopinavir/ritonavir, and a similar proportion (79%) of patients who were receiving an NNRTI-based regimen were receiving efavirenz. Thus, we suggest that their findings may relate more to the specific effect of lopinavir/ritonavir regimens, versus that of efavirenz-based regimens, on tenofovir-associated kidney dysfunction, rather than to PIIs or NNRTIs as a class.

We performed similar analyses in an observational cohort with a larger sample size and found that amprenavir-based regimens were associated with a greater decline in kidney function than efavirenz-based regimens among 445 patients who initiated tenofovir treatment [2]. Our findings also suggested that ritonavir boosting did not account for the differences between agents. In addition, the concurrent use of didanosine with tenofovir was associated with an increased risk of kidney dysfunction.

A second issue in the article by Goicoechea and colleagues is the decision to only include patients who received tenofovir for >48 weeks. The authors stated that 48 (24%) of 199 patients did not start or discontinued tenofovir before week 40 and were excluded. It is not clear whether patients who discontinued use of tenofovir before 48 weeks did so because of kidney dysfunction. In our cohort, severe declines in kidney function, although uncommon, occurred on average 3–4 months after initiation of tenofovir treatment (P<0.001) whereas more moderate declines generally occurred after 6 months (mean, 7 months [range, 1–33 months]) [2].

In conclusion, the article by Goicoechea et al. [1] provides interesting information on risk factors for tenofovir-associated kidney dysfunction. Future studies of larger cohorts of patients are needed to examine the roles of all individual medications, rather than the roles of classes of medications, in tenofovir-associated kidney dysfunction.

Heidi M. Crane, Bryan Kestenbaum, Robert D. Harrington, and Mari M. Kitahata
Department of Medicine, University of Washington, Seattle, Washington

References


Potential conflicts of interest: none reported.

Reply to Crane et al.

To the Editor—Several reports have shown an increased risk of renal toxicity when tenofovir disoproxil fumarate (TDF) is coadministered with a protease inhibitor (PI)–based regimen instead of with a nonnucleoside reverse-transcriptase inhibitor (NNRTI)–based regimen [1, 2]. Do these findings represent overlapping toxicities from individual medications or an unexpected drug interaction involving a common metabolic pathway? Several lines of evidence suggest the latter. First, HIV drug accumulation in renal proximal tubule cells is a process determined by uptake from the blood and excretion into the urine by renal transporters, such as multidrug resistance protein (MRP)–2 [3]. Second, tenofovir has been shown to be substrate of MRP-2 and MRP-4 [4, 5], and its transport can be inhibited by most PIs (including ritonavir, lopinavir, amprenavir, saquinavir, and atazanavir [4, 6, 7]). Third, PI coadministration decreases tenofovir renal clearance in HIV-infected patients [8] and increases plasma exposure by 20%–30% [9]. Potentially, PI coadministration inhibits MRP-2–mediated renal transport of tenofovir, leading to increased intracellular accumulation and increased toxicity.

Historically, prediction of clinically significant drug interactions during drug development was based primarily on interaction studies with cytochrome P450–metabolizing enzymes. However, it is now known that alterations in the function of drug transporters can significantly alter drug absorption, distribution, and elimination. Because the Food and Drug Administration has only recently encouraged submission of reports on drug transporter function [10], a detailed understanding of the impact of clinically