The Role of Drug Interactions and Monitoring in the Prevention of Tenofovir-Associated Kidney Disease

To the Editor—Zimmerman et al. [1] described 5 patients and reviewed 22 published cases of tenofovir-associated renal injury, emphasizing the potential role of drug interactions, incomplete recovery of renal function that occurred in some cases, and intensive monitoring of kidney function. Increased exposure to tenofovir occurs when the combination of ritonavir-ritonavir or atazanavir is coadministered [2]. The statement that ritonavir causes tenofovir to accumulate in renal tubules because of inhibition of multidrug resistance protein (MRP) 2–mediated efflux is not supported by experimental evidence. Recent studies have demonstrated that another renal transporter, MRP-4, is responsible for the efflux of tenofovir, and this process is not diminished by protease inhibitors [3]. Concurrent use of ritonavir-ritonavir, didanosine, or atazanavir occurred often in their report, but analysis of an appropriate control population is necessary for one to infer meaningful associations. Although lopinavir-ritonavir use may contribute directly to toxicity, use of this agent also may be a marker of patients who have a higher risk of adverse events associated with use of multiple medications due to advanced disease. In an analysis of patients treated with tenofovir, lopinavir-ritonavir use was not associated with diminished glomerular filtration rate after controlling for other clinical variables [4].

Incomplete recovery of kidney function was described in 5 of 27 cases. Creatinine clearance had decreased to ≈17 mL/min before discontinuation of full-dose tenofovir treatment in 4 cases; this rate of clearance is considerably less than the recommended threshold for tenofovir dose adjustment of 50 mL/min [2]. In the fifth case, only 3 months of follow-up data were reported. Incomplete recovery has been observed in most forms of acute renal failure and is usually related to age, preexisting kidney disease, chronic liver disease, underlying diabetes, atherosclerotic vascular disease, or cast nephropathy [5]. One or more of these factors was present in patients with incomplete reversibility.

We agree that the optimal approach to management of acute renal failure is prevention. We strongly agree with statements regarding the importance of monitoring kidney function, proper dose-adjustments when creatinine clearance is <50 mL/min, the relative insensitivity of serum creatinine levels in estimating glomerular filtration rate, and the fact that an increase in the serum creatinine level of ≥50% or ≥0.5 mg/dL should prompt reassessment of kidney function by estimation of the glomerular filtration rate. However, the recommendation for monitoring multiple parameters of renal function every 2 weeks for 2 months and monthly thereafter in “high-risk” patients is excessive and is not supported by their data. The median duration of tenofovir treatment in this report was 10 months, and relatively subtle but meaningful increases in the serum creatinine level were overlooked. In most previously reported cases, tenofovir treatment was initiated before there was awareness of the infrequent occurrence of tenofovir-associated kidney dysfunction, and few patients underwent periodic monitoring of renal function as part of routine care (e.g., every 3–6 months).

Tenofovir is a widely prescribed antiretroviral that combines potency, convenient dosing, and a favorable safety and tolerability profile. Prospective, clinical trials have not demonstrated excess renal toxicity attributable to tenofovir, with or without concurrent receipt of lopinavir-ritonavir or atazanavir [6–9]. Patients with an adequate glomerular filtration rate (i.e., an estimated creatinine clearance of ≥50 mL/min) can safely receive tenofovir, with or without lopinavir-ritonavir, atazanavir, or didanosine. We believe that, in the vast majority of cases, monitoring of kidney function at routine clinic visits, in accordance with prescribing information [2] and published guidelines [10], should allow safe use of tenofovir.

Acknowledgments

Potential conflicts of interest. J.W. is on the Speakers Bureau at Gilead Sciences. D.H.S. is an employee of Gilead Sciences.

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References

Reply to Winston and Shepp and to Lanzafame et al.

To the Editor—We thank Lanzafame et al. [1] and Winston and Shepp [2] for their comments on our article [3]. We agree that the incidence of tenofovir-associated acute renal failure is low. The majority of patients described in the articles and/or abstracts referenced by Lanzafame et al. [1] were not receiving the combinations we described in our article. We disagree that the mechanism for the ritonavir-related increase in tenofovir concentrations has been ruled out, because the article cited [4] did not assess tenofovir concentrations. The exact mechanism producing increased proximal tubular concentrations of tenofovir when coadministered with ritonavir and/or lopinavir-ritonavir needs to be determined by further basic research. Studies have demonstrated that the concurrent use of atazanavir or lopinavir-ritonavir with tenofovir markedly increases the serum concentrations of tenofovir, potentially leading to tenofovir-associated acute and chronic kidney disease [5, 6].

Lanzafame et al. [1] recognize the effectiveness and convenient dosing of tenofovir, yet they desire to provide clinicians with recommendations for identifying high-risk patients who might develop acute renal failure and timelines for monitoring these patients. The onset for the development of acute renal failure with tenofovir has varied from 1 month to >28 months [3]. We feel that it would be prudent to monitor more closely tenofovir recipients who are concurrently receiving antiviral agents with known drug interactions (e.g., atazanavir, didanosine, ritonavir, and lopinavir-ritonavir) and who have identifiable risk factors for kidney disease. Although, in most cases, the development of acute renal failure was reversible, some patients may have cases that progress to chronic kidney disease. We agree with the current dosing recommendations and published guidelines for the safe use of tenofovir, as described by Winston and Shepp [2], and we strongly urge clinicians to follow them.

Acknowledgments

Potential conflicts of interest. All authors: no conflicts.

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References
