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EDITORIAL COMMENTARY

Renal Function and Tenofovir Disoproxil Fumarate for Preexposure Prophylaxis: How Safe Is Safe Enough?

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(See the major article by Mugwanya et al on pages 1050–7.)

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Recent studies have demonstrated that daily use of oral tenofovir disoproxil fumarate (TDF), with or without emtricitabine (FTC), for preexposure prophylaxis (PrEP) against human immunodeficiency virus (HIV) infection can decrease the incidence of HIV infection in diverse populations, including men who have sex with men (MSM), transgender women, at-risk heterosexuals, and persons who use injection drugs [1–4]. In these studies, efficacy was directly correlated with medication adherence. Based on the evidence from these studies, in 2012 the Food and Drug Administration approved once-daily, coformulated TDF and FTC (TDF-FTC) for use as PrEP, and in 2014 the Centers for Disease Control and Prevention issued guidelines recommending TDF-FTC PrEP for HIV prevention [5]. Subsequent studies of PrEP use by at-risk MSM in care settings have observed high levels of adherence and very low HIV infection incidences despite high rates of sexually transmitted infections, suggesting that PrEP can be highly effective under real-world conditions [6, 7].

As PrEP is a prophylactic intervention and not a treatment for established disease, potential PrEP users and their clinicians will need to weigh carefully the benefits of its use against the potential risks of experiencing medication toxicities from daily exposure to TDF-FTC. When used as treatment for HIV infection, TDF has been associated with acute and chronic kidney injury [8], including small decreases in the glomerular filtration rate and damage to renal proximal tubules. In the efficacy studies of PrEP, renal adverse events were rare and did not differ in frequency among participants randomly assigned to use active drug or placebo. However, a meta-analysis of randomized studies with TDF-based PrEP found that participants assigned to use PrEP had a 36% increased risk of an elevated creatinine level, although nearly all of these elevations were mild and normalized after discontinuation of PrEP [9].

While primary safety analyses from randomized studies have tended to focus on whether TDF-based PrEP affects rates of glomerular filtration, less attention has been given to its effect on proximal tubular function, which could also have important safety implications. In this issue of *The Journal of Infectious Diseases*, Mugwanya et al analyzed data from the Partners PrEP study, a randomized, placebo-controlled study of daily PrEP with TDF or TDF-FTC among HIV-uninfected African men and women in HIV-serodiscordant partnerships, to ascertain rates of proximal tubular dysfunction and whether its occurrence predicts decreased renal function [10]. In an analysis that compared rates of proximal tubulopathy among participants assigned to receive TDF-FTC or placebo, the authors found that, over a median drug-exposure period of 24 months, tubular damage was rare (occurring in <2% of participants) and that rates of tubular dysfunction did not differ by treatment assignment. In an additional, nested case-control analysis restricted to participants who received active drug (either TDF or TDF-FTC), the authors found that rates of proximal tubular dysfunction did not differ among participants who experienced a clinically significant decline in renal function (defined as a 25% decrease in estimated glomerular filtration rate) and those who did not experience declines in renal function. Based on these findings, the authors conclude that routine monitoring for markers of tubular damage to predict decreases in renal function is not likely to be an efficient strategy in care settings. However, because 1 participant assigned to TDF-FTC developed severe Fanconi syndrome while using potentially nephrotoxic medications in addition to PrEP, the authors also suggest that monitoring for tubular dysfunction may be prudent for individuals at increased risk for renal injury.

Although it is reassuring that TDF-based PrEP has not been associated with proximal tubular dysfunction or serious nephrotoxicity in randomized studies, caution is warranted when extrapolating these findings outside of controlled studies. These studies did not enroll individuals with abnormal renal function or risk factors for kidney disease, so the safety of TDF-based PrEP for such individuals is not known. Participants in these studies also generally received PrEP for <2 years, and some participants were not

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adherent to PrEP, so rates of renal adverse events could potentially be higher when PrEP is consistently used for a longer duration. Data from an open-label study of TDF-FTC for PrEP among MSM and transgender women suggest that renal outcomes with PrEP may differ in some subpopulations. This study found that 1 in 5 participants aged >40 years had a clinically relevant decline in creatinine clearance rate (ie, to ≤70 mL/minute) within the first year of PrEP use and that individuals with a lower baseline level of renal function (creatinine clearance rate, <90 mL/minute) or those with greater exposure to TDF (as measured by drug levels in hair) were more likely to have a decline in renal function [11]. These findings suggest that clinicians may need to increase the intensity of renal function monitoring for patients who are older or who have low-normal renal function before initiating PrEP, as guidelines recommend that PrEP be discontinued if the creatinine clearance rate decreases to <60 mL/minute.

For patients who are at risk for acquiring HIV and also for experiencing renal toxicities with TDF-based PrEP, it would be ideal to have additional agents for PrEP that confer an even lower risk of nephrotoxicity than TDF. The development of tenofovir alafenamide (TAF), a prodrug of tenofovir that has been demonstrated to be as efficacious as TDF for HIV treatment but less likely to influence renal function [12], presents an intriguing possibility for these patients. In April 2016, the Food and Drug Administration approved a coformulated tablet containing TAF and FTC for HIV treatment, so clinicians may be considering whether off-label use of TAF-FTC for PrEP would be appropriate for PrEP for those at greatest risk for renal injury. However, early pharmacokinetic studies have raised questions about using TAF for PrEP [13]. In healthy women, oral dosing of TAF achieved lower concentrations in plasma and genital mucosal tissues than TDF [13]. The finding of low mucosal concentrations raises questions as to whether TAF will provide protection against sexual exposure to HIV. A study of TAF-FTC for use as PrEP in nonhuman primates similarly found that concentrations of TAF were low in genital compartments [14]. Despite these low concentrations, however, TAF-FTC was protective against retroviral infection in nonhuman primates, suggesting that studies to evaluate its efficacy in humans should be pursued and that correlates of tenofovir-based protection may not yet be fully understood.

In addition to TAF-FTC, other agents and novel formulations for delivering PrEP are being studied that are also expected to have favorable renal safety profiles. Examples include an intravaginal ring containing dapivirine, a nonnucleoside reverse transcriptase inhibitor, that was recently shown to be safe and efficacious in African women [15] and a long-acting injectable integrase inhibitor, cabotegravir, that will be studied in a large efficacy trial beginning in 2016 [16]. Until additional PrEP formulations are available, however, it would be useful if there were other ways to use TDF-FTC for PrEP that might minimize the likelihood of renal injury. Pericoital use of TDF-FTC for PrEP might be expected to result in less renal toxicity as compared to daily use, by limiting an individual's exposure to TDF. One study demonstrated the efficacy of pericoital TDF-FTC for PrEP among MSM, but this study also found that mild, albeit reversible, elevations in the creatinine level were more frequent among those assigned to receive active drug [17]. Because study participants used an average of 4 TDF-FTC pills per week because of frequent sexual contacts, it remains unknown whether less frequent use of episodic PrEP would be equally efficacious and result in fewer creatinine level elevations than daily use.

Overall, the evidence from numerous trials, including the current study by Mugwanya et al, suggests that daily TDF-FTC PrEP is safe and effective for many individuals at risk for HIV, as long as clinicians remain vigilant for early signs of renal dysfunction. Although the availability of newer agents without renal toxicity will be welcome, clinicians should not let the perfect be the enemy of the good, and they should be encouraged to prescribe TDF-FTC as PrEP for patients with normal renal function who are at risk for HIV acquisition.

Notes

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