

# Risks and Benefits of Tenofovir in the Context of Kidney Dysfunction in Sub-Saharan Africa

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(See the Major Article by Mulenga et al on pages 1473–80.)

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Chronic kidney disease (CKD) remains a serious complication among individuals infected with human immunodeficiency virus (HIV). Recent studies highlight the burden of CKD in sub-Saharan Africa, where up to 25% of HIV-infected individuals starting antiretroviral therapy (ART) have decreased estimated glomerular filtration rates (eGFRs) and 72% have microalbuminuria [1]. Both of these conditions have important implications for the selection of antiretroviral regimens and monitoring for kidney disease.

Tenofovir disoproxil fumarate (TDF) is the most prescribed antiretroviral worldwide for the first-line treatment of HIV infection because of its effective antiviral activity, favorable resistance and safety profiles, and availability as a combination single-tablet regimen for once-daily

dosing. However, TDF has been associated with proximal tubular dysfunction, acute kidney injury, and CKD in developed countries, especially among older persons or those with advanced HIV infection, preexisting kidney disease, lower body mass index, or with concurrent use of boosted protease inhibitors [2–4]. These findings, however, cannot be extrapolated to sub-Saharan Africa due to differences in the timing of antiretroviral initiation, CKD risk factors, and underlying kidney disease etiologies. Examining the effect of TDF on the risk for kidney function decline among HIV-infected patients in sub-Saharan Africa is therefore necessary to inform screening and monitoring strategies in this setting.

In this issue, Mulenga and colleagues compared the impact of TDF-containing vs non-TDF-containing regimens on subsequent kidney function and death among >60 000 HIV-infected individuals aged  $\geq 16$  years who initiated combination ART in Zambia [5]. This is the largest study of its kind, and the authors should be commended for its successful completion in a region in which undertaking such studies is challenging. The researchers found a statistically significant eGFR decline at 6 and 12 months of follow-up among individuals with

previously normal baseline kidney function irrespective of ART regimen ( $-15$  mL/minute in the TDF and  $-17$  mL/minute in the non-TDF groups). Compared with those on non-TDF regimens, patients who initiated TDF with normal eGFR or mild to moderate kidney disease had lower eGFR during follow-up. While these differences may represent those already present at baseline, TDF users with baseline normal eGFR or mild kidney disease were 2–3 times more likely than their non-TDF counterparts to progress to advanced kidney disease. This is in line with a recent meta-analysis demonstrating that TDF use was associated with a clinically modest renal function decline [4]. However, if the observed trend persists, this rate of annual decline would exceed what the Kidney Disease: Improving Global Outcomes guidelines on CKD [6] regards as rapid kidney disease progression, a risk factor for end-stage renal disease. Therefore, long-term follow-up of kidney function is critical to understanding this observation.

A major finding of this study is that patients, even those receiving TDF, with severe kidney disease at ART initiation had improvement in kidney function. Whereas Reid and colleagues [7], in the Development of Antiretroviral Therapy trial

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in Uganda and Zimbabwe, observed that those with mild to moderate kidney dysfunction experienced the largest improvement in eGFR, the current study is the first to demonstrate this in a larger subpopulation with severe kidney disease. However, the observations by Mulenga and colleagues in Zambia conflict with previous findings in the US-based HIV Outpatient Study; among 19 participants with kidney disease who received TDF, approximately 25% had worsening kidney function [8].

Differences in the etiology of kidney disease present in sub-Saharan Africa vs developed countries likely underlie the disparate observations. For example, HIV-associated nephropathy (HIVAN), which leads to rapid kidney function decline and reverses with ART [9], is highly prevalent among HIV-infected individuals in sub-Saharan Africa. In this study, those with severe kidney disease may have underlying HIVAN and benefit from more effective viral suppression with TDF-based regimens. Conversely, HIVAN is now quite rare in developed countries [10] in which CKD is increasingly driven by traditional risk factors and drug toxicity. Consequently, TDF exposure may exacerbate kidney disease in this context.

In this study, mortality risk increased with worsening baseline kidney function, consistent with previous findings [11, 12]. Although causes of death were not reported, CKD (like HIV infection) strongly contributes to cardiovascular disease [13, 14], a growing concern in sub-Saharan Africa [15]. CKD and HIV may lead to cardiovascular disease through similar mechanisms, including endothelial dysfunction, chronic inflammation, and progressive atherosclerosis [16]. Studies are needed to determine the relative contribution of kidney disease to the growing cardiovascular disease burden in sub-Saharan Africa.

Of concern is the finding that among patients with normal kidney function, those on TDF had 21% higher mortality

risk compared with non-TDF users. Interestingly, those on TDF with baseline kidney dysfunction had slightly better or similar survival compared with non-TDF users. These estimates, however, may be biased by informative dropout, especially in light of the greater likelihood of TDF users having more advanced HIV infection and missing eGFR measurements during follow-up compared with non-TDF users (30% vs 15%). Moreover, details on the demise of patients were lacking and may have included older patients with other comorbidities.

Although Mulenga et al's study is a critical step forward, its limitations must be considered when interpreting its results and considering possible implications for the management of HIV-infected patients in sub-Saharan Africa. First, this study did not account for TDF-related proximal tubular injury. While proximal tubular injury may present insidiously, it can lead to overt acute kidney injury as well as osteomalacia [3]. Second, the follow-up period was short, precluding assessment of long-term TDF-related renal effects. Long-term evaluation is necessary, as a prior study among US veterans suggests that the risk of proteinuria, rapid kidney function decline, and CKD occurs beyond the first year of TDF initiation [2].

This study by Mulenga and colleagues represents the largest observational study focused on the burden of kidney disease in the context of TDF-based regimens for the primary treatment of HIV-infected individuals in sub-Saharan Africa. The independent, strong association between kidney function at ART initiation and mortality emphasize the importance of kidney disease prevention. To that end, studies are warranted to determine whether earlier ART initiation, particularly in those who are genetically susceptible to developing HIV-mediated renal diseases, mitigates the risk of developing kidney disease. The prevalence of genetic risk variants that place individuals of African descent at risk for progressive

kidney disease, especially HIVAN, may exceed 25% of the general population in certain areas of sub-Saharan Africa [17]; therefore, genotyping for these variants may eventually identify a large portion of HIV-infected patients who may benefit from early viral suppression or screening for kidney disease prior to initiation of potentially nephrotoxic antiretroviral medications.

Of note was the number of patients who had normal serum creatinine levels but impaired kidney function; reliance on absolute serum creatinine values may lead to TDF administration to patients with preexisting kidney disease. Although the incidence of progression to moderate or severe kidney dysfunction was small among TDF users, this small proportion represents nearly 500 HIV-infected individuals in this study. Moreover, those with eGFRs above the usual threshold for TDF avoidance experienced greater odds of eGFR decline. Therefore, careful monitoring of kidney function after TDF initiation remains important to prevent development or progression of kidney disease, particularly in the context of limited resources to provide life-sustaining treatments for those who progress to end-stage renal disease [18]. The conundrum, however, lies in how patients should be monitored for kidney disease. Future studies should focus on whether or not simple tools, such as the combination of serum creatinine-based GFR estimates and a urine dipstick, could cost-effectively identify patients at greatest risk of TDF-related toxicity. However, as with many efficacious agents, the therapeutic benefit of TDF to the majority of patients must be weighed against the potential harm to a small subset.

## Notes

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