Clinical Epidemiology and Global Health 25 (2024) 101462

Contents lists available at ScienceDirect

Clinical Epidemiology and Global Health

journal homepage: www.elsevier.com/locate/cegh

A review of Tenofovir Disoproxil Fumarate associated nephrotoxicity among People Living with HIV: Burden, risk factors and solutions

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ARTICLE INFO

Keywords:
Nephrotoxicity
People living with HIV
Tenofovir Disoproxil Fumarate

ABSTRACT

Background: Tenofovir Disoproxil Fumarate (TDF) is one of the first-line antiretroviral therapy (ART) recommended for all treatment naïve People Living with HIV (PLHIV). However, evidence indicates increasing TDF-associated nephrotoxicity among PLHIV due to longer duration of treatment and longevity that raises clinical and programmatic concerns. This review aims to understand the extent of TDF-induced nephrotoxicity and associated factors.

Methods: The article is based on a comprehensive scoping review of journal articles, reports and guidelines related to the use of TDF-based ART regimens in electronic databases such as the National Library of Medicine (PubMed), Google Scholar, Web of Science, Scopus and other relevant search engines.

Results: The review provides evidence on the burden of nephrotoxicity due to TDF among PLHIV and its variations across geographic regions and population groups. The review highlights the key factors associated with TDF-induced nephrotoxicity which include age, gender, nutrition status (BMI), duration of treatment with TDF, baseline creatinine, baseline CD4 count, WHO HIV stage of disease and presence of comorbid conditions. The review also emphasizes the importance of baseline and regular renal monitoring and early detection of TDF-induced nephrotoxicity to avoid irreversible tubulointerstitial damage through simple laboratory investigations such as glomerular filtration rate (GFR), blood urea nitrogen, serum creatinine and creatinine clearance.

Conclusion: The burden of TDF-associated nephrotoxicity is well documented. It is critical to consider the risk factors associated with nephrotoxicity while initiating TDF. The review provides evidence for calibrating the dosage of TDF based on body weight and BMI. Considering the high burden of PLHIV in India, prevention of nephrotoxicity through targeted and regular monitoring, early diagnosis and initiation of appropriate clinical management is crucial to reduce avoidable morbidity and mortality.

1. Background

Tenofovir Disoproxil Fumarate (TDF), a nucleotide reverse transcriptase inhibitor (NRTI) is widely used as a first-line Antiretroviral therapy (ART) regimen in resource-limited settings such as India and Sub-Saharan African countries.[1] Ever since the U.S. Food and Drug Administration (FDA) approved its use in October 2001, several countries included it in their list of recommended first-line drugs for the treatment of HIV infection.[2,3] In India, the number of HIV patients on TDF steadily increased after the National AIDS Control Program (NACP) adopted the "Test and Treat policy" to initiate treatment irrespective of CD4 count and WHO clinical stage of HIV disease, as TDF based ART regime is recommended for all treatment naïve patients unless contraindicated.[4]

TDF is administered orally and is generally effective and relatively safe, however, several studies have indicated that it has nephrotoxic

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https://doi.org/10.1016/j.cegh.2023.101462
Received 15 August 2023; Received in revised form 29 October 2023; Accepted 11 November 2023
Available online 18 November 2023

potential, characterised by proximal tubular cell injury which may result in acute kidney injury (AKI), chronic kidney disease (CKD) or partial or complete Fanconi syndrome.[5] It is extensively distributed with the highest concentrations occurring in the kidney and liver.[6] The increased amount of renal toxicity occurs due to the high intracellular deposit of TDF in the renal tubules.[6] TDF can cause renal proximal tubular dysfunction and reduce the estimated glomerular filtration rate (eGFR) at a much higher level compared to other NRTIs such as Abacavir (ABC), Lamivudine (3 TC), Zidovudine (AZT).[7]

Tenofovir alafenamide (TAF) is also a NRTI which has similar efficacy to that of TDF but an improved safety profile. Studies have indicated that administration of TAF is associated with a significantly lower plasma concentration of its metabolite tenofovir (TFV), compared with TDF. As nephrotoxicity is proportional to plasma TFV exposure, TAF may result in less nephrotoxicity.[8] With the increasing evidence of nephrotoxicity associated with TDF as a first line of treatment for HIV patients, understanding the adverse health outcome of this drug is critical. This review aims to comprehensively understand the extent of TDF-induced nephrotoxicity among People Living with HIV (PLHIV), its variations among different geographies and population groups, the associated factors and potential prevention strategies that can be adopted in regular programme settings.

1.1. Methodology

This article is based on a comprehensive scoping review of journal articles, reports and guidelines related to the use of TDF-based ART regimens and associated nephrotoxicity among PLHIV, published globally. We searched the journal articles in electronic databases such as the National Library of Medicine (PubMed), Google Scholar, Web of Science, and Scopus, limiting the search of papers published until May 2023. Besides, we used general search engines to access non-peer-reviewed publications, technical guidelines and reports related to TDF-induced nephrotoxicity. We chose the documents based on their titles and abstracts, with additional references identified from the reference lists of chosen articles in English language.

The keywords used were “Tenofovir Disoproxil Fumarate”, “Treatment for People Living with HIV (PLHIV)”, “TDF associated nephrotoxicity”, “TDF induced nephrotoxicity”, “Burden of TDF”, “Nephrotoxicity among People Living with HIV (PLHIV)”, “Factors associated with TDF-induced nephrotoxicity”, “ART regimens” “first-line Antiretroviral therapy (ART)”.

We included articles or documents that provided original findings on TDF-induced nephrotoxicity and technical guidelines and documents related to TDF use. The review excluded the literature that did not expressively indicate TDF-associated renal toxicity or nephrotoxicity. The findings of the selected publications were summarised using a narrative technique. We identified major themes and patterns in the articles, analyzed and presented the findings.

2. Findings

2.1. Clinical presentations and the burden of TDF-induced nephrotoxicity among PLHIV

The key clinical presentations of TDF-induced nephrotoxicity are proximal tubular dysfunction with preserved renal function and proximal tubular dysfunction with decreased renal function. Decreased renal function may be classified as Acute Kidney Injury (AKI), Chronic Kidney Disease (CKD), or decreased glomerular filtration rate (GFR) as compared to baseline values, though within normal limits.[9]

Several studies provided substantial evidence for TDF-induced nephrotoxicity among PLHIV. Globally, the reported incidence ranges between 0.5 and 45%.[9] A meta-analysis of 13 studies with more than 5, 767 patients reported a significant and rapid loss of kidney function (−5.4 mL/min) in patients receiving TDF compared with control subjects (mean difference between groups in GFR loss estimated by the Cockroft-Gault formula: 3.9 mL/min; 95 % CI: 2.1–5.7 mL/min). Another meta-analysis of eight studies that included 7,496 patients showed a 0.7% higher (CI: 0.2–1.2) risk for Acute Renal Failure in TDF-treated patients compared to patients receiving combined antiretroviral treatment (cART) without TDF.[10] A study conducted in Thailand reported around 20% of PLHIV receiving TDF have β2-microglobulinuria, a marker of tubular dysfunction. A Zambian study reported a high burden of renal dysfunction in older patients with low CD4 counts, reporting a kidney dysfunction point prevalence of 18.6% at 18 months follow-up with TDF.[11]

In Ethiopia, the incidence of renal dysfunction among TDF and the non-TDF group was found to be 28.31 per 100 person-years (PYs) and 12.53 per 100 PYs, respectively. Adult PLHIV taking TDF-based regimens were 1.70 (CI: 1.02–2.82) times at higher risk of renal dysfunction than non-TDF-based regimens.[12] Studies conducted among registered adult PLHIV with TDF-based ART regimens in Northwest Ethiopia indicated a renal dysfunction incidence rate of 28.31 per 100 person-years, much higher than studies done in Japan (10.5), Europe/Australia (1.33), Malaysia, Canada (7.35) and Korea (9.66).[12]

In India, several studies indicated varying levels of nephrotoxicity among PLHIV who are on TDF. A study conducted in south India among PLHIV on TDF-based ART between 2002 and 2017 reported a renal dysfunction prevalence of 5.6%.[13] According to a study in south India among patients on TDF for a median period of 10 months, 39.7% developed renal failure as per RIFLE (Risk, Injury, Failure, Loss and End-stage kidney disease) Criteria.[14] A study conducted in North-Eastern India indicated low creatinine clearance of <50 among 33% of the patients who were on TDF after 6 months, showing renal impairment.[15] A study in western India among 1,271 patients on TDF revealed that 83 (6.53%) developed renal dysfunction, of which 79 had impaired serum creatinine and five had Fanconi’s syndrome.[16] All these studies have indicated similar outcomes despite the regional variations.

Although there is adequate evidence to highlight the risk for completely irreversible acute tubular damage, several studies indicated the opposite describing that the long-term use of TDF is safe for kidneys.[17,18] A few studies indicated a slight decline in kidney function or rare kidney injury as adverse effects even though it affected 1%–5% of patients.[3] The decline in kidney function can be as low as 13.3 ml/min per 1.73 m^2 after 1 year of TDF.[3] Similarly, a meta-analysis on renal safety of TDF in PLHIV concluded that TDF was associated with a loss of renal function, however, the clinical magnitude of this effect was modest which did not support the need to restrict TDF use.[5,14]

2.2. Risk factors associated with TDF associated nephrotoxicity

Several factors are associated with TDF-induced nephrotoxicity which include age, gender, nutrition status (BMI), duration of treatment with TDF, baseline creatinine, treatment with Non-nucleoside reverse transcriptase inhibitors (NNRTIs), baseline CD4 count, WHO HIV stage of disease, patients with known renal impairment at ART initiation, nephrotoxic antiretrovirals in a previous treatment regimen, the administration of a concomitant nephrotoxic drug, and presence of comorbid conditions.[13]

Age: Studies have indicated that older PLHIV on TDF-based ART regimens are more at risk of renal dysfunction or impairment. A study in South Africa revealed that PLHIV of older age (>41 years) on TDF had a lower average eGFR than the other age groups.[19] Similarly, PLHIV in Asian countries, aged greater than 60 years compared with those aged 20–29 years had a significantly higher risk of renal impairment.[20] Besides, an Indian study observed that PLHIV of older age were 45% more likely to develop renal dysfunction and TDF-related renal toxicity.[21]

Gender: Literature suggests that males are at a higher risk for TDF-induced GFR reduction.[22] A prospective, observational, multicenter study carried out in Italy indicated that nephrotoxicity was more prevalent among the male population.[23] Another study conducted in South

Africa found that males were associated with lower average eGFR levels over time.[16] Though most of the studies indicated males to be at higher risk, a study in Myanmar, among PLHIV initiated on a TDF-based ART regimen found women (aHR:1.8; 95 % CI:1.2–2.9) at a higher risk of developing renal dysfunction.[24] The higher risk for TDF-induced nephrotoxicity among women could be due to their relatively lower weight and BMI compared to men, but the dosage among men and women are same across the countries.

Weight and BMI: Several studies have highlighted low body weight and lower BMI, as key risk factors for TDF-induced nephrotoxicity due to exposure to high TDF drug concentrations. A study mentioned that Asians are susceptible to such nephrotoxicity due to TDF due to their smaller body stature in general.[25] Moreover, the risk of renal dysfunction due to TDF was reported to be higher in developing countries; where the relative body weight of the users is low.[26] Also, the risk may be higher in sub-Saharan countries where most HIV-infected individuals belong to lower economic status and have malnutrition.[13] On the contrary, a few studies mentioned that the relatively lower incidence of nephrotoxicity especially among Asians could be due to their smaller body stature and lower median body weight than other population groups.[27]

A study conducted in Myanmar among Women living with HIV (WLHIV) on TDF indicated low body weight as a risk for renal toxicity.[24] A South Indian study among PLHIVs indicated a significant risk for renal dysfunction in patients with low BMI.[21] Another study in Vietnam found that PLHIVs who had a BMI from 18.5 up to 25 kg/m2 were less likely to suffer from renal impairment compared to BMI below 18.5 kg/m2.[20] A few African studies have also indicated BMI as a risk factor for renal dysfunction among those who are on TDF.[19]

Duration on ART: Though the possible detrimental effect of long-term use of TDF on kidney function is debated, a few studies have concluded that the long-term use of TDF-based ART regimen results in declining kidney function.[28] A retrospective observational study in China specified that patients receiving ART for 144 weeks and 168 weeks were 4.1 and 8.4 times more likely to develop decreased renal function, respectively, compared to those receiving ART for 12 weeks.[28] A study in an African cohort of HIV-infected adults indicated that the prevalence of renal impairment increased from 10% at week 24–45 % at 144 weeks in TDF-exposed participants compared to an increase from 8% at 24 weeks to 14% at 144 weeks in TDF-unexposed participants and TDF exposure predicted the risk of renal impairment at 144 weeks of ART.[29] However, a few studies indicated that AKI related to Combination antiretroviral treatment (cART) including TDF is more frequent in the first year of therapy, but severe kidney dysfunction is rare.[30,31]

Baseline CD4 and WHO HIV Stage of Disease III and IV: Studies have highlighted immunosuppression and advanced stage of HIV disease as significant predictors of impaired kidney function due to TDF. A South African study found that anaemia and immunosuppression (WHO Stage III/IV and CD4 cell counts <100 cells/mm3) were associated with lower average eGFR levels over time.[19] A study in Ghana revealed that Patients with WHO HIV staging III or Stage IV at the initiation of TDF-containing ART, were at 3.8 and 3.4 times increased risk of incident renal impairment compared with patients of Stage I.[32]

Baseline creatinine clearance rate: There is a significant association between baseline clearance rate and TDF-induced nephrotoxicity.[3,9,23] A study conducted in Ghana showed that decreasing baseline creatinine clearance rate was associated with renal impairment. It indicated that for every 1 mL/min decrease in baseline CrCl rate, the risk of incident renal impairment increased by 5%. According to a study conducted in Nigeria, Creatinine clearance and GFR of patients in the TDF-treated arm were significantly lower than those of the TDF-free arm at baseline (83.7 mL/min versus 90.3 mL/min; $p < 0.001$ and 106.9 versus 108.3; $p < 0.001$).[29]

Presence of comorbidities and coinfections: Comorbidities such as diabetes, hypertension, and HCV coinfection were found to be significant risk factors for TDF-induced GFR reduction and renal dysfunction.[7,9,18,22,25,33] A study in Nigeria indicated that PLHIV on TDF with hepatitis-C seropositivity and other comorbidities were 1.6 and 2.7 times more at risk for renal impairment.[29] Studies conducted in Northwest Ethiopia found that diabetes patients had a 2.52 times higher risk for renal dysfunction as compared to non-diabetic patients. These findings are in line with studies conducted in low-income countries such as Myanmar and Zimbabwe as well.[12] Similarly, patients co-infected with HIV/AIDS and TB on ART/DOTS combined therapy had low eGFR. Studies conducted in Western and Southern India highlighted similar findings that comorbidities such as hypertension, CAD, chronic liver diseases (HCV), prolonged survival with HIV >10 years, diabetes, renal calculi and single kidney as possible risk factors for renal dysfunction.[16,21]

2.3. Impact of tenofovir, adefovir and combination ART therapy

There is increasing evidence that combination antiretroviral therapy (cART) can lead to a wide variety of nephrotoxic effects, including both AKI and CKD. The cART drugs associated with CKD include indinavir, atazanavir, tenofovir disoproxil fumarate and lopinavir/ritonavir. An observational longitudinal study in western India indicated that PLHIV on the PI/r-based regimen had higher chances of developing renal toxicity compared to patients on the NNRTI-based regimen.[16] A systematic review of African studies suggests that interaction between TDF and boosting agents such as Ritonavir may be responsible for an initial decrease in eGFR.[6] However, in contrast to the previous factors, a study in south India indicated concomitant Protease inhibitors (PI) use was not associated with increased risk for renal dysfunction ($P > 0.05$).[21]

3. Discussion

It is well documented that TDF is one of the widely used first-line ART regimens with proven efficacy across the world. As it is widely used in HIV programmes in resource-limited settings, it is essential to have a clear understanding of TDF-associated nephrotoxicity. This review highlights the burden of TDF-associated nephrotoxicity among PLHIV in different geographic regions and population groups and associated factors which have critical programmatic importance. According to the review, the burden of TDF-associated nephrotoxicity is evident and well-documented around the world. However, a few studies indicated just minimum or modest clinical significance of this adverse effect.[3,14,18,19] This could be due to the favourable efficacy and safety profile of TDF leading to fewer side effects including renal dysfunction.

Considering the critical use of TDF-based regimens across the HIV programmes, the risk factors associated with TDF-induced nephrotoxicity need to be considered while initiating TDF-based regimens. The review revealed that lower weight and lower BMI are found to be key risk factors for TDF-induced nephrotoxicity which is in concurrence with several studies including clinical trials, and in vitro and pharmacokinetic studies across the world.[7,26] The pharmacokinetic studies revealed reduced plasma TDF clearance among people with lower body weight leading to larger drug exposure and higher plasma concentrations of TDF and further more severe toxicity and renal tubular dysfunction.[7,33] Thus, PLHIV, generally having low body weight and BMI may be more vulnerable to TDF-induced nephrotoxicity.[34] However, TDF-associated renal dysfunction may not be just due to factors such as age and BMI, but due to the complex interaction of pharmacological, environmental, and genetic factors.[33] For instance, gene polymorphisms such as ABCC2, ABCC4 and COL27A1 were associated with tenfovir induced renal dysfunction.[35] Besides, concomitant use of ritonavir or cobicistat and anti-TB medication with TDF were also found to be risk factors for renal dysfunction.[17,36]

Another key finding of programmatic importance is the higher likelihood of TDF-induced nephrotoxicity among women. It is evident that the mean weight of women is relatively low compared to men across the world. For instance, the mean weight of men and women in India is

65.0 kg vs 55.0 kg respectively and the pattern is the same across the world.[37] However, TDF dosage is the same for both men and women which may have an implication on their renal function. The increased likelihood of TDF-induced nephrotoxicity among PLHIV with lower weight, lower BMI and among women emphasizes the importance of reviewing the current strategy, guidelines and the need to consider differentiated TDF dosage while initiating ART among PLHIV.

Evidence suggests that PLHIV with related comorbidities, coinfections and low CD4 levels are at higher risk for TDF-induced nephrotoxicity which emphasizes the need for early diagnosis and initiation of ART at preserved CD4 counts, as well as treatment for comorbidities, and coinfections.[20] While HIV/AIDS and related comorbidities may deteriorate renal function in the absence of ART and other relevant medications, TDF-based ART regimens may contribute significantly to renal dysfunction. Besides, as the HIV-infected population gets older with higher probabilities of comorbidities such as diabetes and hypertension, it is essential to make careful choice of ART regimen in high-risk adult PLHIV and consider alternative regimens which have better renal safety profile.[21,23,31]

Essentially, the review stresses the importance of baseline and regular renal monitoring before and after initiating TDF-based regimens, especially among PLHIV with risk factors. Many studies have also highlighted the need for regular monitoring to either alter the dose or withdraw the drug completely at the first sign of nephrotoxicity.

The WHO provides guidelines for screening and monitoring for the frequency of Kidney Function Tests/GFR which emphasizes serum creatinine and estimated GFR for TDF-based treatment regimen.[38] Studies indicated that TDF use was not associated with nephrotoxicity in PLHIV if baseline renal function was assessed and normal. However, in resource-limited settings, regular testing of kidney function has significant programmatic challenges which need to be addressed through appropriate linkage of the HIV programme, which is generally vertical in nature, with the existing health services.

Considering the higher use of TDF and higher incidence of nephrotoxicity among PLHIV, it is essential to ensure early detection of nephrotoxicity and TDF withdrawal to avoid irreversible tubulointerstitial damage and features of nephrotoxicity, through the existing programme. Regardless of the underlying aetiology of kidney disease, it may lead to death if left untreated. The finding is in concurrence with other studies that highlight the complete recovery of a significant proportion of the patients to baseline levels of renal function following TDF discontinuation after developing AKI.[39] However, cautious withdrawal of the drugs is suggested in other studies as TDF-induced renal toxicity leading to regimen discontinuation may expose individuals to viral rebound and unexpected drug resistance.[13]

Earlier diagnosis and initiation of appropriate clinical management can be done effectively by having an integrated approach between the disease control programme and existing healthcare system. A hallmark indication of nephrotoxicity is an alteration in the function of the kidney assessed by simple blood tests that include GFR, blood urea nitrogen (BUN), urine output, and serum creatinine and creatinine clearance tests. As recommended by WHO, these tests are to be part of the regular monitoring of the kidney functions.[31,38] Urinalysis, urine protein, and Albumin-to-Creatinine Ratio (ACR) can also indicate renal impairment. Currently, under the National AIDS Control Programme in India, serum blood urea nitrogen, serum creatinine, and urine for routine and microscopic examination are recommended. However, the discovery and development of biomarkers that can detect kidney dysfunction at the early stage may be required for specific diagnosis of nephrotoxicity at earlier stages. The pre-symptomatic nephrotoxicity before the marked reduction in GFR can be detected by these biomarkers of tubular dysfunction.[40] While biomarkers for regular monitoring of kidney functions have been defined in the programme, there is a need to include biomarkers that can specifically detect the early signs of kidney damage in the already existing system to prevent the morbidity and mortality of the PLHIVs on treatment.

Furthermore, nephroprotection can also be achieved by preventing TDF entry into proximal tubular cells, facilitating its exit or administering drugs that protect tubular cells from injury. Probenecid, an inhibitor of the human organic anion transporter 1 (hOAT1) gene, is used to prevent cidofovir nephrotoxicity and may also give protection against tenofovir.[9,34] However, more research may be required in regular programme settings.

4. Conclusion

The burden of TDF-associated nephrotoxicity is high as TDF is a mainstay of treatment and part of first-line regimen among PLHIV. The factors associated with nephrotoxicity provide critical evidence for developing strategies for initiation and cautious use of TDF as a first-line ART drug in the presence of risk factors for nephrotoxicity. Since TDF is an important part of the ART treatment regimen, there is a need for calibrating TDF dose based on body weight and BMI. Considering the burden of 2.4 million PLHIV in India and in pursuit of achieving the UNAIDS 95-95-95 treatment target, prevention of nephrotoxicity through targeted and regular monitoring, early diagnosis and initiation of appropriate clinical management is crucial to reduce avoidable morbidity and mortality and improve quality of life among PLHIV. The review also emphasizes the need for further research on TDF-associated nephrotoxicity among PLHIV.

Ethical statement

Ethical approval and informed consent were not required for this article as it was based on literature review.

Source of funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Author contribution

Conceptualization and Methodology E S Asirvatham, S Upadhyaya, M Periasamy.

Data curation, drafting manuscript and Editing E S Asirvatham, V Ranjan, C Garg, CJ Sarman, M Periasamy.

Revising the manuscript, critically for intellectual content E S Asirvatham M Periasamy, V Yeldandi, S Upadhyaya, B Rao.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

None.

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