

Comparative Analysis of Nephrotoxicity in Patients on Tenofovir-Containing and Non-Tenofovir Antiretroviral Therapy

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ABSTRACT

The more recent generation of anti-retroviral medication (ART) has completely changed the way that HIV infections are treated. Tenofovir with lamivudine (NRTI) and one NNRT, efavirenz, make up the first-line ART. One side effect that is cause for concern is the renal tubular dysfunction linked to tenofovir. The purpose of this study was to compare the incidence of nephrotoxicity from tenofovir-based regimens to those that were not TLE-based. 50 individuals between the ages of 18 and 60 years who were already on an ART regimen were enrolled in each arm of a non-randomized cross-sectional research. TLE and ZLN were the two most commonly prescribed regimens. Four patients [8% (P-value 0.059)] developed nephrotoxicity in the TLE regimen, as in contrast to none in the non-TLE regimen. Longer exposure to the TLE regimen was a risk factor for nephrotoxicity, as 3 patients were receiving tenofovir for more than 4 years, regardless of age, body weight, or CD4 count. Anaemia was observed in 48% of patients on TLE vs. 18% in the non-TLE regimen. A minimum of one of the four criteria was aberrant in 26% of patients on a tenofovir-based regimen. Nephrotoxicity can be avoided by using tenofovir alafenamide or switching to a different treatment when early indications of renal damage are apparent.

Keywords: Nephrotoxicity, Tenofovir, Non-Tenofovir, ART regimen

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Introduction

Treatment for HIV and AIDS is being transformed by the more recent types of anti-retroviral drugs, which have decreased morbidity and increased patient longevity. By the end of 2018, the Joint United Nations Programme on HIV/AIDS (UNAIDS) projected that 37.9 million people globally were infected with HIV, of whom only 23.3 million were on antiretroviral therapy (ART) [1]. The incidence is 0.26% in India [2]. The UN 90-90-90 approach aims to raise awareness of HIV status among 90% of those living with the virus. 90% of them should be getting ART, and 90% of ART patients should exhibit viral suppression [3].

The second-largest program in the world, the National AIDS Control Program, is run and entirely funded by the Indian government. The National AIDS Control Organisation (NACO) and the state work together to cut the infection rate by half. Since 2004, the Indian government has offered ART at no cost [4]. The nationwide prevalence decreased steadily from 0.38% in 2003, 0.28% in 2012, and 0.22% in 2017, according to NACO. Additionally, ART use has resulted in a 54% decrease in annual AIDS-related mortality since 2007. Adults aged 15 to 49 years have a low frequency of less than 0.13% in Chhattisgarh, which has decreased by 4% since 2010 [5].

HAART, or highly active antiretroviral therapy, is the cornerstone of HIV infection management. Its primary goal is to inhibit HIV replication to extend and enhance the lives of those who are infected with the virus.

Coformulations of antiretrovirals and the creation of once-daily fixed dose regimens have improved adherence and patient compliance.

According to NACO guidelines 2018 [5], the current recommendations are to: (1) treat all clinical stages or CD4 counts, (2) use a triple-drug combination from two separate classes of ARVs for first-line ART, and (3) start second-line medications as soon as clinical, virological, or immunological failure has been determined. The TLE regimen, which includes (i) tenofovir with lamivudine, one non-nucleoside reverse transcriptase inhibitor (NNRTI), and one nucleoside/nucleotide reverse transcriptase inhibitor (NRTI), is the first-line ART, (ii) in children, patients below 30 kilograms of weight and in those with the previous history of renal disease use abacavir + lamivudine + efavirenz (ALE), (iii) in case of HIV-2 co-infection use tenofovir + lamivudine + lopinavir/ritonavir (TL 1/r), and (iv) if the patient is already exposed to any other regimen, e.g. zidovudine + lamivudine + nevirapine (ZLN) or zidovudine + lamivudine + efavirenz (ZLE), then the same is to be continued. Significant adverse effects of the frequently prescribed ARV drugs are shown in **Figure 1** [5].

Tenofovir	Lamivudine	Zidovudine	Efavirenz	Nevirapine
• Diarrhoea • Increased transaminases and renal toxicity-proximal renal tubular dysfunction • Bone mineral density loss	• Headache • muscle ache • Burning sensation • tingling and pain in limbs • fatigue	• Severe anaemia • neutropenia • myelosuppression • Lactic acidosis	• Severe or life-threatening rash (Stevens-Johnson Syndrome) • Persistent and severe central nervous system toxicity • neuropsychiatric manifestations	• Maculopapular rash on palms /soles, • fulminant hepatitis

Figure 1. ADRs due to ART drugs

In 2001, the FDA authorised tenofovir disoproxil fumarate (TDF), an adenosine analogue, for the treatment of HIV-1. It is also effective against HIV-2 infection, in contrast to nucleoside reverse transcriptase inhibitors. Because of its greater performance, fewer side effects, and easy dosage schedule, TDF gained notoriety [6]. However, its structural similarity to the nephrotoxic acyclic nucleotide analogues cidofovir and adefovir has sparked several safety concerns [7, 8]. The FDA has approved two versions of tenofovir: tenofovir alafenamide and tenofovir disoproxil fumarate. Bone marrow and kidney toxicity are reduced by tenofovir alafenamide. There is information on the short- and long-term adverse effects profile of antiretroviral medications in industrialised nations, but not in our nation. Therefore, it is crucial to emphasise the identification of these medications' toxicities and side effects, particularly concerning tenofovir, which is often utilised in the majority of ART centres.

Acute or chronic kidney damage is are two possible manifestations of drug-induced nephrotoxicity. According to Cooper *et al.* [9], nephrotoxicity was taken into consideration if the specified conditions were met. When Tenofovir causes nephrotoxicity, stopping the medication is the best course of action. Renal function returns to normal in a couple of weeks to months, and approximately 50% of the patients fully recover [10]. Tubular proteinuria is thought to be the most sensitive indicator of proximal tubule dysfunction since tenofovir affects the proximal tubule. Any increase in blood creatinine levels is seen as an early indicator of renal impairment, and creatinine clearance can also be computed [11].

It is advised to calculate creatinine clearance every six months following the start of Tenofovir medication. With the risk of nephrotoxicity in mind, the medication can be started without the test in a setting with limited resources. If the glomerular filtration rate is less than 50 millilitres per minute, tenofovir should not be continued. When a patient is suspected of having Fanconi syndrome, treatment should be halted; the condition resolves ten weeks after treatment is stopped [5].

According to research, probenecid, which is used to stop cidofovir nephrotoxicity [12–14], blocks the transporter that tenofovir mostly uses to enter tubular cells. However, probenecid alone caused adverse effects in 56% of patients, which restricted its use [14]. The use of rosiglitazone, a peroxisome proliferator-activated receptor-gamma agonist, to lessen tenofovir toxicity is limited because it has been linked to cardiovascular side effects, but has protected rats against tenofovir-induced proximal tubular dysfunction [15-17].

Based on these fundamental facts, a study was conducted to determine the prevalence of nephrotoxicity brought on by tenofovir disoproxil fumarate (TDF). Tenofovir/lamivudine/efavirenz-300 mg/300 mg/600 mg is the recommended once-daily dosage; NACO offers FDC for usage in institutional ART facilities. Other non-TLE regimens (ZLN, ZLA, and ZLE) were contrasted with this one. ADR profiling using the WHO UMC causality scale and analysing the lag time between the onset of tenofovir and the onset of nephrotoxicity were the secondary goals.

Aims and objectives

The objectives of this study were: (1) To find the incidence of nephrotoxicity due to tenofovir in the TLE regimen and compare it with the non-tenofovir-based anti-retroviral regimen using the laboratory criteria, (2) to identify the time duration for the onset of nephrotoxicity, and (3) to do causality assessment of ADR using the WHO causality scale [18].

Materials and Methods

This prospective observational study was conducted over 45 days in the Anti-Retroviral Therapy (ART) Centre of Dr Bhim Rao Ambedkar Memorial Hospital, Raipur, Chhattisgarh, and 50 patients were recruited in each regimen. The study was approved by the Institutional Ethics Committee. Informed consent was obtained from all participants.

The inclusion criteria were: all patients should be already enrolled for treatment at the ART centre from Dr B.R. Ambedkar Memorial Hospital, in the age group of 18-60 years, and should be on an approved ART regimen. Patients suffering from any pre-existing renal disease, cardiac disease, or any other co-morbidity, all pregnant and/or lactating females, paediatric patients, and patients taking any other nephrotoxic drugs were excluded.

In this study, the demographic details were recorded as age, sex, height, weight, residence (urban/rural), literacy status, occupation, addictions, previous history of anti-retroviral treatment, and CD 4 count at the time of the study. Nephrotoxicity was diagnosed if the following criteria were met:

Rise in serum creatinine by 0.3 mg/dL within 2 days; or increase by 1.5-1.9 times baseline within seven days; or increase in serum creatinine 0.3 but within normal limits is also indicative of serious renal injury [19] as normal range falls between 0.5 mg/dl to 1.5 mg /dl.

Hypouricemia as seen in the affection of proximal tubules (Fanconi's syndrome) (normal values: 2.6- 6.0 mg/dL). Abnormal spot urine albumin creatinine ratio in the grades of +1 and +2 (Albumin to creatinine ratio is the first preferred method to detect albuminuria in a spot urine sample)

Anemia (normal hemoglobin -12 for females and 13 for males). All pathological tests were measured at the medical college laboratories.

Statistical analysis

The results were analysed by unpaired t-test, paired t-test, and chi-square tests. Pearson's chi-square test and Fisher's exact test were used; a P-value > 0.05 is considered significant. This was done using SPSS version 23 statistics software. The ADR profiling was done by the WHO-UMC casualty scale.

Results and Discussion

One hundred of the more than 120 patients who were observed were included in the study. All inclusion and exclusion criteria were met by 50 patients in TLE and non-TLE regimens, respectively. **Table 1** displays the study population's demographics and their statistical relationship to nephrotoxicity, whereas **Table 2** shows the laboratory results of the patients who were enrolled in the study.

Table 1. Demographic profile of patients enrolled in the study (n = 100)

Variables	Total (n = 100)	TLE (n = 50)	Non-TLE (n = 50)	P-value by Fisher's exact test
Sex				
Male	50	25	25	0.245
Female	49	24	25	0.235
Transgender	1	1	0	-

Age	35.27 ± 7.85	35.12 ± 8.15	35.42 ± 7.62	-
≤ 25 years	9	7	2	-
> 25 years	94	43	48	0.046
Weight at start of ART	53.56 ± 12.02	53.34 ± 12.42	53.78 ± 11.55	-
≤ 65 Kg	87	43	44	0.241
> 65 Kg	14	7	7	0.269
Weight at time of study	54.85 ± 12.76	54.68 ± 13.89	55.02 ± 11.66	-
≤ 65 kg	81	41	40	-
> 65 kg	19	9	10	-
Duration of ART	4.29 ± 2.99 yrs	2.32 ± 1.62 yrs	6.26 ± 2.73 yrs	-
< 3 years	44	41	3	0.854
3-10 years	46	9	37	0.006
> 10 years	10	0	10	-
Residence				
Urban	65	34	31	0.137
Rural	35	16	19	0.457
Marital status				
Spouse on ART	52	27	25	0.51
Spouse not on ART	18	13	5	0.474
Spouse lost to HIV	19	8	11	0.322
Unmarried	11	2	9	-
Addiction	27	14	13	-
IV drug use	0	0	0	-
Tobacco	15	9	6	-
Alcohol	12	5	7	-
Mode of infection				
Sexual	97	49	48	-
Blood transfusion	1	0	1	-
Vertical	2	1	1	-
IV drug use	0	0	0	-
Occupation				
Driver	12	8	4	-
Unemployed/housewife	28	11	17	-
Others	60	31	29	-

Table 2. Patients' laboratory results both during the research and when they were enrolled in ATT.

Variables	Total (n = 100)	TLE (n = 50)	Non TLE (n = 50)
Serum creatinine at the time of enrolment	0.81 (0.23)	0.77 (0.20)	0.84 (0.24)
Serum creatinine at the time of the study	0.88 (0.39)	0.98 (0.49)	0.78 (0.19)
Blood hemoglobin concentration at the time of enrolment	11.31 (2.1)	11.16 (2.03)	11.46 (2.17)
Blood hemoglobin concentration at the time of the study	11.96 (2.01)	11.64 (1.92)	12.27 (2.06)
Serum uric acid at the time of the study	4.01 (0.94)	3.66 (0.97)	4.36 (0.77)
Spot urine albumin creatinine ratio			
Grade 0	96 patients	46 patients	50
Grade +1	2 patients	2 patients	0
Grade +2	2 patients	2 patients	0
CD4 count at time of study	330.79 (111.66)	269.72 (113.17)	391.86 (69.08)

Four individuals, or 8% of the TLE sample, met the criteria for the diagnosis of nephrotoxicity in this study. None of the patients in the non-TLE arm met the aforementioned requirements. A Fisher exact P-value of 0.059, which is almost significant, supported this. Only 9% of the 46% of patients who had ART for 4–10 years also received a TLE regimen; yet, Fischer's exact test revealed a P-value of 0.006. The four individuals who experienced nephrotoxicity all had CD4 counts ranging from 100 to 300, which were statistically significant (0.025) according

to Pearson's chi-square test. At the beginning of ART, they were anaemic, and their haemoglobin levels continued to drop. All four of these patients had abnormal spot urine albumin-creatinine ratios.

Table 3 lists the clinical and demographic characteristics of each of the four patients who received a nephrotoxicity diagnosis. Only one patient suffered from an alcohol addiction, whereas the rest did not. Three of the patients were from rural locations, and one was from an urban area. Whereas two lost their spouses to the disease's adverse effects, two of them were married, and their spouses were HIV positive and on ART.

Table 3. Laboratory results and the demographics of individuals with nephrotoxicity diagnoses.

Variables	Patient 1	Patient 2	Patient 3	Patient 4
Age	42	32	44	37
Sex	Male	Female	Female	Male
Marital status	Widower	Married	Widow	Married
Residence	Rural	Urban	Rural	Rural
Addiction	None	None	None	Alcohol
Time since start of ART.	4 years	7 years	1 year	4 years
Weight				
Baseline	59 kg	47 kg	66 kg	110 kg
At the time of the study	56 kg	36 kg	60 kg	105 kg
Serum creatinine				
Baseline	1.1	1.1	1.0	1.3
At the time of the study	3.6	1.7	1.6	2.8
Creatinine clearance				
Baseline	73.01 mL/min	64.09 mL/min	88 mL/min	121.05 mL/min
At the time of the study	21.17 mL/min	31.76 mL/min	50 mL/min	48.54 mL/min
Hemoglobin				
Baseline	10.28	8.0	12.5	12.4
At the time of the study	9.42	7.9	12.31	11.8
Serum uric acid	2.2	2.4	2.2	2.4
Spot urine albumin-creatinine ratio	+2 150/10	+1 80/200	+2 150/50	+1 30/100
CD4 count	194	258	333	342

Serum creatinine levels at baseline and during the trial period, as determined by the paired T test, indicated a positive correlation (0.233) with significant correlation and dependence (0.020) for all 100 patients when comparing TLE with non-TLE-based regimens. Baseline serum creatinine and TLE regimen had a moderately positive association (0.574) at the time of the investigation. This connection was significant (0.000) and dependent (0.001). The relationship was positively associated (0.375) and significant (0.007) in the non-TLE regimen, while the reliance was not significant (0.067). Additionally, there was a substantial positive correlation (0.710) between haemoglobin levels at baseline and during the research, and there was also a significant correlation (0.000). When comparing the TLE group to the non-TLE group, serum uric acid was shown to have a negative association (-0.220), and the correlation was not significant (0.125). According to the WHO causality scale, the ADRs documented are displayed in **Table 4** and were rated as POSSIBLE. According to the WHO UMC scale, ADR-nephrotoxicity was rated as PROBABLE, and these patients had to switch to a non-Tenofovir-based treatment plan.

Table 4. ADRs observed in TLE and non-TLE regimen

S. No.	A.D.R.s noted	Patients on TLE (n = 50)	Patients on Z.L.N./non TLE (n = 50)
1	Skin rashes	3 (6%)	4 (8%)
2	Drowsiness	15 (30%)	15 (30%)
3	Weakness	8 (16%)	3 (6%)
4	Loss of sleep	2 (4%)	1 (2%)
5	Confusion	4 (8%)	0 (0%)
6	Constipation	1 (2%)	0 (0%)

7	Loss of appetite	3 (6%)	6 (12%)
8	Weight loss	4 (8%)	2 (4%)
9	Nausea	14 (24%)	25 (50%)
10	Body ache	2 (4%)	0 (0%)
11	Headache	15 (30%)	15 (30%)
12	Anaemia	24 (48%)	9 (18%)

For the whole trial group, the mean peak creatinine was $0.88 (\pm 0.39)$; in individuals who experienced nephrotoxicity, the mean value rose from $1.125 (\pm 0.125)$ at baseline to $2.42 (\pm 0.95)$. **Figure 2** shows the change in serum creatinine for each of the four patients. At the time of the research, the estimated creatinine clearance similarly dropped from baseline (86.537 ± 24.03) to 37.867 ± 13.87 , which falls below the recommended threshold of < 50 ml/min as shown in **Figure 3**.

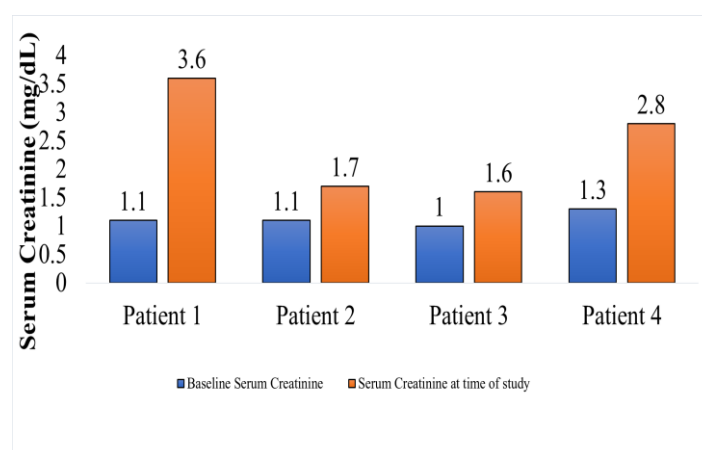


Figure 2. Figure illustrating the four patients' altered serum creatinine levels after developing nephrotoxicity

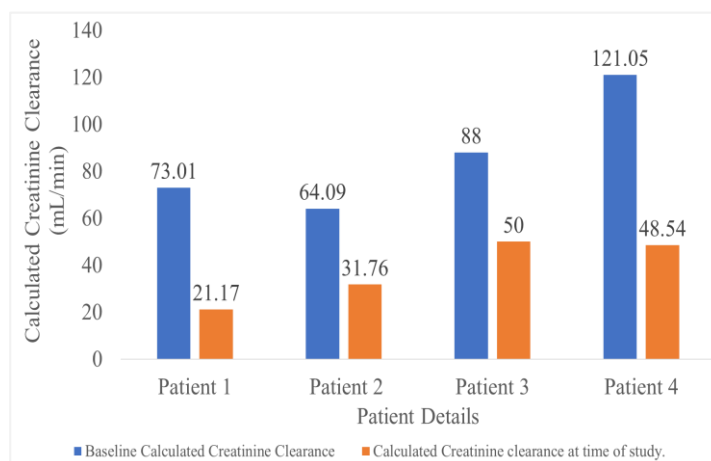


Figure 3. A decline in the four patients' calculated creatinine clearance was observed after they experienced nephrotoxicity.

Low body weight, advanced age, and a lower CD4 count were found to be risk factors for nephrotoxicity in previous studies that examined the post-marketing safety data for tenofovir (TDF) [20]. Researchers have discovered that Asian cohorts from India and Japan have higher incidences [21, 22].

According to a study, the average age of patients with nephrotoxicity was 38.75 years [5]. Nonetheless, some research has indicated that nephrotoxicity is more common in the elderly and views ageing as a separate risk factor for nephrotoxicity development [9, 23, 24]. Age is not a significant risk factor for nephrotoxicity, according to our findings. Additionally, there was no sex preponderance, which is consistent with earlier research [24]. Nonetheless, one study found that women were more prevalent than men [8]. All patients' mean weight increased between the beginning of ART and the study period, indicating that ART enhanced overall health. Although post-

marketing data identifies low body weight as a risk factor, those who experienced nephrotoxicity were not underweight either [20].

Four patients in the TLE group experienced nephrotoxicity after receiving medication for one year, four years (two patients), and seven years, indicating that tenofovir exposure for at least a year causes nephrotoxicity. However, these results contradict other research that indicates nephrotoxicity happens within the first few months of medication exposure [9, 25, 26]. It should be mentioned that 20% of patients on non-TLE regimens finished ten years of treatment without experiencing any nephrotoxicity, and that these patients had been receiving treatment for more than three years. No research describing nephrotoxicity with a non-TLE regimen was found. The majority of TLE individuals have undergone no more than three years of therapy, and multiple investigations have also demonstrated an increase in CD4 count as a reliable and effective parameter [4, 27, 28]. The prognosis of HIV infection is precisely assessed by plasma viral load (PVL) and CD4 lymphocyte count, which signifies immunological advancement. Both groups' mean CD4 count is below normal (500-1500 cells/mm³), which includes those who have established nephrotoxicity, therefore, we see no association between CD4 count and the occurrence of nephrotoxicity [28].

8% of patients on a tenofovir-containing TLE regimen who met all four criteria experienced nephrotoxicity, which is statistically significant but of moderate clinical magnitude. An incidence of 17–22% has been reported in several studies [9, 29, 30]. Other than these four TLE patients, 16% of patients had an increase in serum creatinine of 0.3 mg/dL from baseline; however, the other three parameters were normal, hence nephrotoxicity was not detected. However, as serum creatinine would not increase above the normal limit until glomerular filtration rate is less than 63 mL/min/1.73m², there may have been an underestimation of the incidence of nephrotoxicity [19]. In the TLE group, serum creatinine rose from baseline, while in the non-TLE group, it fell from baseline during the study period. This suggests that most TLE patients have impairment of their renal function. TLE was discontinued, and patients were switched to non-TLE treatment.

Proteinuria was also assessed by spot albumin creatinine ratio in the grades of +1 and +2 on urine dipstick assay in patients with reduced creatinine clearance. This result is consistent with recent research [9, 31–34] that found proteinuria in higher grades (grade 4). Nephrotoxicity could occur anywhere from one year to seven years after starting ART. According to certain research, tenofovir-associated nephrotoxicity happens within the first few months of TDF exposure [9, 25, 26].

Proteinuria was also assessed by spot albumin creatinine ratio in the grades of +1 and +2 on urine dipstick assay in patients with reduced creatinine clearance. This result is consistent with recent research [9, 31–34] that found proteinuria in higher grades (grade 4). Nephrotoxicity could occur anywhere from one year to seven years after starting ART. According to certain research, tenofovir-associated nephrotoxicity happens within the first few months of TDF exposure [35, 36]. Tenofovir alafenamide (TAF), a pro-drug formulation of Tenofovir, was recently licensed in several nations. It causes less renal damage because it doesn't interact with the transport protein needed for its accumulation in the renal proximal tubule [37, 38]. Although it wasn't accessible through ART clinics throughout the study period, TDF is currently available in India.

This study's limitations include a small study population, a brief study period, and a small number of diagnostically challenging markers (bone parameters, serum phosphate, and glycosuria). If a biopsy had been performed on the nephrotoxic patients, it might have been possible to pinpoint the precise location of the disease. Tenofovir's effect on the side effects of proximal tubulopathy, such as proteinuria, decreased bone mineral density, and bone fracture, should be evaluated in future research. This will guarantee that the cumulative toxicity that is clinically significant is not overlooked. It is urgent to use biopsy to have a better understanding of renal injury. This study was conducted in 19–20, and the ICMR announced the results in 2021 because of COVID.

Conclusion

Patients on tenofovir had an 8% incidence of nephrotoxicity, but those on the non-tenofovir regimen showed no signs of nephrotoxicity. Patients who were exposed to the medication for a minimum of one year experienced nephrotoxicity. Regardless of age, body weight, CD4 count, or other adverse drug reactions, three patients had been on tenofovir for more than four years, indicating that longer exposure to the TLE regimen was a risk factor for nephrotoxicity. Serum creatinine may be the first parameter to be abnormal in renal affection, and it requires intervention to prevent progression to nephrotoxicity. However, although serum creatinine was elevated by 0.3%

in the other 12 patients (24%) on the tenofovir regimen, they did not exhibit hypouricemia, anaemia, or a deranged urine albumin creatinine ratio.

Tenofovir disoproxil fumarate should be replaced with an abacavir-based regimen or tenofovir alafenamide as the approved treatment for tenofovir-induced nephrotoxicity. More research is required, with a bigger sample population and a longer study period. Further research is required to determine predisposing variables and identify associations between nephrotoxicity and co-morbidities, as patients with additional co-morbidities were not included in our investigations.

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Conflict of Interest: None

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References

1. Iftikhar S, Ghias M, Shahid S, Ali MR, Hassan MU, Numan A. Clinical and biochemical indicators of disease severity and neurological findings in COVID-19: a study of King Edward Medical University (KEMU), Pakistan. *Pak J Pharm Sci.* 2021;34(1):275-81.
2. Paranjape RS, Challacombe SJ. HIV/AIDS in India: an overview of the Indian epidemic. *Oral Dis.* 2016;22:10-4.
3. Jamieson D, Kellerman SE. The 90 90 90 strategy to end the HIV pandemic by 2030: can the supply chain handle it? *J Int AIDS Soc.* 2016;19(1):20917.
4. Hemasri M, Sudhapoornima P, Sowmya Sri CH, Ramya S, Avinash KKB, Kiran Kumar B. Safety and effectiveness of anti-retroviral drug regimens Zln and Tle in tertiary care teaching hospital: a prospective observational study. *J Pharm Biol Sci.* 2016;11(2):88-96.
5. State Epidemiological Fact Sheets. National AIDS Control Organisation. November. 2017;3:169-88.
6. Koh HM, Suresh K. Tenofovir-induced nephrotoxicity: a retrospective cohort study. *Med J Malaysia.* 2016;71(6):308-12.
7. Birkus G, Hitchcock MJM, Cihlar T. Assessment of mitochondrial toxicity in human cells treated with tenofovir: comparison with other nucleoside reverse transcriptase inhibitors. *Antimicrob Agents Chemother.* 2002;46(3):716-23.
8. Mwanjala MN, Urrio LJ, Mtebe MV. Prevalence and predictors of renal dysfunction among people living with HIV on antiretroviral therapy in the Southern Highland of Tanzania: a hospital-based cross-sectional study. *Pan Afr Med J.* 2022;41:137.
9. Cooper RD, Wiebe N, Smith N, Keiser P, Naicker S, Tonelli M. Systematic review and meta-analysis: renal safety of tenofovir disoproxil fumarate in HIV-infected patients. *Clin Infect Dis.* 2010;51(5):496-505.
10. Karras A, Lafaurie M, Furco A, Bourgarit A, Droz D, Sereni D, et al. Tenofovir-related nephrotoxicity in human immunodeficiency virus-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. *Clin Infect Dis.* 2003;36(8):1070-3.
11. Waheed S, Attia D, Estrella MM, Zafar Y, Atta MG, Lucas GM, et al. Proximal tubular dysfunction and kidney injury associated with tenofovir in HIV patients: a case series. *Clin Kidney J.* 2015;8(4):420-5.
12. Lalezari JP, Stagg RJ, Kuppermann BD, Holland GN, Kramer F, Ives DV, et al. Intravenous cidofovir for peripheral cytomegalovirus retinitis in patients with AIDS: a randomized, controlled trial. *Ann Intern Med.* 1997;126(4):257-63.

13. Papaleo A, Warszawski J, Salomon R, Jullien V, Veber F, Dechaux M, et al. Increased β -2 microglobulinuria in human immunodeficiency virus-1-infected children and adolescents treated with tenofovir. *Pediatr Infect Dis J*. 2007;26(10):949-51.
14. Izzedine H, Thibault V, Valantin MA, Peytavin G, Schneider L, Benhamou Y. Tenofovir/probenecid combination in HIV/HBV-coinfected patients: how to escape Fanconi syndrome recurrence? *Aids*. 2010;24(7):1078-9.
15. Tan M, Johnston S, Nicholls J, Gompels M. Dual therapy with renally adjusted lamivudine and dolutegravir: a switch strategy to manage comorbidity and toxicity in older, suppressed patients? *HIV Med*. 2019;20(9):634-7.
16. Blind E, Dunder K, De Graeff PA, Abadie E. Rosiglitazone: a European regulatory perspective. *Diabetologia*. 2011;54(2):213-8.
17. De la Prada FJ, Prados AM, Tugores A, Uriol M, Saus C, Morey A. Acute renal failure and proximal renal tubular dysfunction in a patient with acquired immunodeficiency syndrome treated with tenofovir. *Nefrol Publ of la Soc Esp Nefrol*. 2006;26(5):626-30.
18. UMC. The use of the WHO-UMC system for standardised case causality assessment. Uppsala Monit Cent [Internet]. 2018;2-7. Available from: https://who-umc.org/media/164200/who-umc-causality-assessment_new-logo.pdf
19. Fernandez-Fernandez B, Montoya-Ferrer A, Sanz AB, Sanchez-Nino MD, Izquierdo MC, Poveda J, et al. Tenofovir nephrotoxicity: 2011 update. *AIDS Res Treat*. 2011;2011.
20. Nelson MR, Katlama C, Montaner JS, Cooper DA, Gazzard B, Clotet B, et al. The safety of tenofovir disoproxil fumarate for the treatment of HIV infection in adults: the first 4 years. *Aids*. 2007;21(10):1273-81.
21. Ryom L, Mocroft A, Kirk O, Worm SW, Kamara DA, Reiss P, et al. Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D: a: D study. *J Infect Dis*. 2013;207(9):1359-69.
22. Antoniou T, Raboud JM, Chirhin S, Yoong D, Govan V, Gough K, et al. Incidence of and risk factors for tenofovir-induced nephrotoxicity: a retrospective cohort study. *HIV Med*. 2005;6(4):284-90.
23. Wyatt CM, Winston JA, Malvestutto CD, Fishbein DA, Barash I, Cohen AJ, et al. Chronic kidney disease in HIV infection: an urban epidemic. *Aids*. 2007;21(15):2101-3.
24. Cheung CY, Wong KM, Lee MP, Liu YL, Kwok H, Chung R, et al. Prevalence of chronic kidney disease in Chinese HIV-infected patients. *Nephrol Dial Transplant*. 2007;22(11):3186-90.
25. Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. *Clin Infect Dis*. 2005;40(8):1194-8.
26. Sax PE, Gallant JE, Klotman PE. Renal safety of tenofovir disoproxil fumarate. *AIDS Read*. 2007;17(2):90-2, 99-104, C3.
27. Mellors JW, Munoz A, Giorgi JV, Margolick JB, Tassoni CJ, Gupta P, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med*. 1997;126(12):946-54.
28. Egger M, May M, Chêne G, Phillips AN, Ledergerber B, Dabis F, et al. Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies. *Lancet*. 2002;360(9327):119-29.
29. Rodríguez-Nóvoa S, Labarga P, Soriano V, Egan D, Albalater M, Morello J, et al. Predictors of kidney tubular dysfunction in HIV-infected patients treated with tenofovir: a pharmacogenetic study. *Clin Infect Dis*. 2009;48(11):e108-16.
30. Nishijima T, Gatanaga H, Komatsu H, Tsukada K, Shimbo T, Aoki T, et al. Renal function declines more in tenofovir-than abacavir-based antiretroviral therapy in low-body weight treatment-naïve patients with HIV infection. *PLoS One*. 2012;7(1):e29977.
31. Petrucci KC, Baía-da-Silva DC, Val F, Valões MS, Cubas-Vega N, Silva-Neto AV, et al. Kidney function and daily emtricitabine/tenofovir disoproxil fumarate pre-exposure prophylaxis against HIV: results from the real-life multicentric demonstrative project PrEP Brazil. *AIDS Res Ther*. 2022;19(1):1-8.
32. Arribas JR, Pozniak AL, Gallant JE, DeJesus E, Gazzard B, Campo RE, et al. Tenofovir disoproxil fumarate, emtricitabine, and efavirenz compared with zidovudine/lamivudine and efavirenz in treatment-naïve patients: 144-week analysis. *JAIDS J Acquir Immune Defic Syndr*. 2008;47(1):74-8.

33. Barditch-Crovo P, Deeks SG, Collier A, Safrin S, Coakley DF, Miller M, et al. Phase I/II trial of the pharmacokinetics, safety, and antiretroviral activity of tenofovir disoproxil fumarate in human immunodeficiency virus-infected adults. *Antimicrob Agents Chemother.* 2001;45(10):2733-9.
34. Winston A, Amin J, Mallon PWG, Marriott D, Carr A, Cooper DA, et al. Minor changes in calculated creatinine clearance and anion-gap are associated with tenofovir disoproxil fumarate-containing highly active antiretroviral therapy. *HIV Med.* 2006;7(2):105-11.
35. Agrawal M, Singh P, Joshi U. Antimicrobials associated adverse drug reaction profiling: a four years retrospective study (Pharmacovigilance study). *Alexandria J Med.* 2021;57(1):177-87.
36. Mouton JP, Jobanputra N, Njuguna C, Gunter H, Stewart A, Mehta U, et al. Adult medical emergency unit presentations due to adverse drug reactions in a setting of high HIV prevalence. *Afr J Emerg Med.* 2021;11(1):46-52.
37. Surial B, Cavassini M, Calmy A, Fehr J, Stöckle M, Bernasconi E, et al. Rates and predictors of switching to tenofovir alafenamide-containing ART in a nationwide cohort. *BMC Infect Dis.* 2019;19(1):834. doi:10.1186/s12879-019-4454-9
38. Wassner C, Bradley N, Lee Y. A review and clinical understanding of Tenofovir: Tenofovir Disoproxil Fumarate Versus Tenofovir Alafenamide. *J Int Assoc Provid AIDS Care.* 2020;19:2325958220919231