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NEPHROTOXICITY IN PATIENTS ON TENOFOVIR VS NON-TENOFOVIR CONTAINING ART REGIMEN: AN OBSERVATIONAL STUDY

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ABSTRACT

Treatment of Human Immunodeficiency Virus (HIV) infection has been revolutionized by the newer generation of Anti-Retroviral therapy (ART). The first-line ART comprises of NRTI (Tenofovir plus Lamivudine) and one NNRT, Efavirenz. The renal tubular dysfunction associated with Tenofovir is an adverse effect of concern. This study was undertaken to find the incidence of nephrotoxicity due to Tenofovir based regimen in comparison to non TLE regimen. A nonrandomised cross-sectional study with 50 patients between 18-60 years already on ART regimen were included in each arm- TLE and non TLE. Nephrotoxicity was diagnosed if there was: 1) increase serum creatinine 2) Decrease Serum Uric Acid 3) abnormal spot urine albumin creatinine ratio 4) decrease blood haemoglobin concentration. Statistical analysis was done using Fischer's exact test. TLE and ZLN were the two most frequently prescribed regimen. Four patients [8% (p value 0.059)] developed nephrotoxicity in the TLE regimen as compared to none from the non-TLE regimen. Longer exposure to TLE regimen was a predisposing factor for nephrotoxicity as 3 patients were on tenofovir for more than 4 years but independent of age, body weight, or CD4 count. Anaemia was observed in 48% of patients on TLE vs 18% in non TLE regimen. 26% of patients on Tenofovir based regimen had an abnormality in at least one of the four parameters. Using Tenofovir alafenamide or shifting to an alternate regimen when early signs of renal injury are visible will prevent nephrotoxicity.

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Introduction

Human Immunodeficiency Virus (HIV) and acquired immunodeficiency syndrome (AIDS) treatment has been revolutionised by the newer generation of Anti-Retroviral medications, which have reduced the morbidity and extended the lifespan of the patients. The incidence of HIV infection worldwide is estimated to be around 37.9 million individuals by the end of 2018, according to the Joint United Nations Programme on HIV/AIDS (UNAIDS), of which only 23.3 million were receiving Antiretroviral Therapy (ART) [1]. In India, the prevalence is 0.26% [2]. The goal of the UN 90-90-90 strategy is to make 90% of people living with HIV aware of their disease status. Of these, 90% of people should be under ART care, and 90 % of patients receiving the ART should show viral suppression [3].

The National AIDS control program is implemented and fully funded by the Government of India and is the second-largest program globally. It functions with the help of the state and the National AIDS Control Organisation (NACO) to reduce the infection by 50%. ART is provided free of cost by the government of India since 2004 [4]. NACO reported a consistent decline in the national prevalence from 0.38% in 2003, 0.28% in 2012. and 0.22% in 2017. Annual AIDS-related deaths also declined

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after the use of ART since 2007 by 54%. Chhattisgarh has a low prevalence of less than 0.13% in adults (15-49 years) and reported a 4% decline since 2010 [5].

Highly active anti-retroviral therapy (HAART), is the central pillar for managing HIV infection. It mainly focuses on subduing HIV replication to prolong and improve the quality of life in patients with HIV infection. Better adherence and patient compliance have been ensured by coformulations of anti-retrovirals and the development of once-daily fixed dose regimens.

Current Recommendations as per NACO guidelines 2018 [5] are to: (1) Treat all clinical stage or CD4 count, (2) Use first-line ART for treatment n using a triple-drug combination from two different classes of ARVs. (3) When failure has been identified clinically, virologically or immunologically start second line drugs. The first-line ART comprises of (i) Nucleoside/nucleotide reverse transcriptase inhibitor (NRTI), Tenofovir plus Lamivudine and one Non-nucleoside reverse transcriptase inhibitor (NNRTI), Efavirenz collectively known as (TLE regimen). (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 l/r), (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].

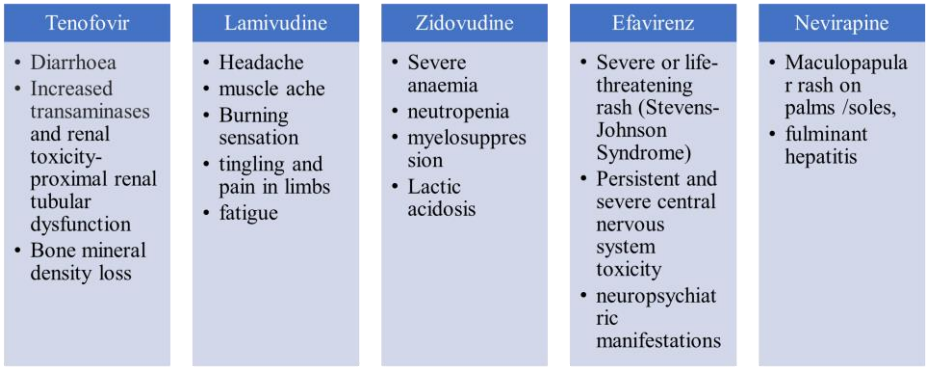

Figure 1. ADRs due to ART drugs

Tenofovir Disoproxil Fumarate (TDF) is t tan adenosine analogue approved by the FDA for the treatment of HIV-1 in 2001. Unlike the Nucleoside Reverse transcriptase inhibitors, it is also useful against HIV-2 infection. TDF became famous because of the convenient dosing schedule, better efficacy, and less side effect [6]. But the resemblance of its structure to that of nephrotoxic acyclic nucleotide analogues adefovir and cidofovir has raised various concerns about its safety [7, 8]. Tenofovir alafenamide and tenofovir disoproxil fumarate are two formulations of tenofovir approved by FDA. Tenofovir alafenamide has fewer renal and bone marrow toxicities. The short and long-term adverse effects profile of Anti-Retroviral drugs in developed countries is available but similar data is not available for our country. Therefore, it is important to stress upon identifying adverse effects /toxicities of these drugs, especially Tenofovir, used frequently in most ART centres.

Drug-induced nephrotoxicity can present either as acute or chronic kidney injury. Nephrotoxicity was considered if the given criteria were fulfilled, as Cooper RD *et al.* [9]. The most effective treatment for Tenofovir-induced nephrotoxicity is the discontinuation of the drug. Around half of the patients completely recover, and renal function comes to baseline level in a few weeks to months [10]. Tenofovir affects the proximal tubule, so tubular proteinuria is considerede most sensitive test of proximal tubule dysfunction. Creatinine clearance may also be calculated, and any rise in serum creatinine level is considered as early signs of renal damage [11].

Calculating creatinine clearance every 6 months after initiation of Tenofovir therapy is recommended. However, in resource-limited setting, the drug can be started without the test keeping the risk of nephrotoxicity in mind. Tenofovir should not be continued if glomerular filtration rate is < 50 ml/min. Treatment should be stopped in patients suspected with Fanconi syndrome, and resolution t occurs within ten weeks after therapy is discontinued [5].

Studies have noted that probenecid, used to prevent cidofovir nephrotoxicity, [12-14], inhibits the transporter primarily responsible for tenofovir entry into tubular cells. But,56% of patients developed adverse reactions due to probenecid itself, limiting its use [14]. Rosiglitazone, a peroxisome proliferator-activated-receptor-gamma agonist showed protection in rats from Tenofovir-induced proximal tubular dysfunction [15] but has been associated with Cardiovascular adverse effects [16, 17], so use of these drugs to reduce tenofovir toxicity is limited.

With this basic information this study was done and focused on the incidence of nephrotoxicity due to Tenofovir Disoproxil Fumarate (TDF). It is prescribed as once-daily dosing (Tenofovir/Lamivudine/Efavirenz-300mg/300mg/600mg) –FDC available through NACO for use in institutional ART centres. This regimen was compared with other non-TLE (ZLN, ZLA, ZLE) regimens. The secondary objectives were to analyse the lag time between the start of Tenofovir and the development of nephrotoxicity and do ADR profiling using the WHO UMC causality scale.

Aims and Objectives

The objectives of this study were: (1) To find the incidence of nephrotoxicity due to Tenofovir in TLE regimen and compare it with 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 respectively. The study was approved by the institutional Ethics Committee. Informed consent was obtained from all participants.

The inclusion criteria were: all patient should be already enrolled for treatment at 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 patient 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:

1. Rise in Serum creatinine by 0.3mg/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 0.5mg/dl to 1.5mg /dl.
2. Hypouricemia as seen in the affection of proximal tubules (Fanconi's Syndrome) (normal values: 2.6- 6.0mg/dL).
3. 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)
4. Anemia (normal hemoglobin -12 for females and 13 for males). All pathological tests were measured at 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 Fischer's exact test were used; p value greater than 0.05 is considered significant. This was done using SPSS version 23 statistics software. The ADR profiling was done by WHO-UMC Casualty Scale.

Results and Discussion

A total of over 120 patients were observed, of which 100 patients were enrolled in the study. 50 patients in TLE and non-TLE regimens, respectively, fulfilled all the inclusion and exclusion criteria. Demographics of the study population and its statistical correlation with nephrotoxicity is shown in **Table 1**, and the laboratory parameters of patients enrolled in this study are illustrated in **Table 2**.

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 Fischer'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 years	35.12 ± 8.15yrs	35.42± 7.62yrs	-
≤25 years	9	7	2	-
>25 years	94	43	48	0.046
Weight at start of ART	53.56±12.02kg	53.34±12.42kg	53.78±11.55kg	-
≤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±1.62yrs	6.26±2.73yrs	-
<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. Laboratory parameters of patients at the time of enrolment for ATT and at the time of study.

Variables	Total (n=100)	TLE (n = 50)	Non TLE (n=50)
Serum Creatinine at time of enrolment	0.81 (0.23)	0.77 (0.20)	0.84 (0.24)
Serum Creatinine at time of study	0.88 (0.39)	0.98 (0.49)	0.78 (0.19)
Blood Hemoglobin concentration at time of enrolment	11.31 (2.1)	11.16 (2.03)	11.46 (2.17)
Blood Hemoglobin concentration at time of study	11.96 (2.01)	11.64 (1.92)	12.27 (2.06)
Serum Uric Acid at time of 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)

In this study, four patients fulfilled the criteria for the diagnosis of nephrotoxicity and constituted a total of 8% of TLE population. No patient from the non-TLE arm fulfilled any of the mentioned criteria. This was supported by a Fischer exact p value of 0.059 which is nearly significant. 46% patients received ART for the duration of 4-10 years of which only 9% received TLE regimen, but it showed p value of 0.006 on Fischer's exact test. All four patients who developed nephrotoxicity had CD4 count between 100 to 300 and on Pearson's Chi square test was found to be statistically significant (0.025). They were anemic at the start of ART and their hemoglobin levels declined further. Spot Urine Albumin-Creatinine ratio was found abnormal is all four of these patients.

The demographic and clinical parameters of all the four patients who were diagnosed with nephrotoxicity are mentioned in **Table 3**. Only one patient had an addiction of alcohol while others had no addiction. one patient was from urban area while three were from rural areas. Two of them were married and their spouse were also HIV positive and receiving ART, while the other two had lost their spouse due to disease complications.

Table 3. Laboratory parameters and Demographic profile of patients diagnosed with nephrotoxicity.

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	59kg	47kg	66kg	110kg
At time of study	56kg	36kg	60kg	105kg
Serum Creatinine				
Baseline	1.1	1.1	1.0	1.3
At time of study	3.6	1.7	1.6	2.8

eCreatinine Clearance				
Baseline	73.01 mL/min	64.09 mL/min	88 mL/min	121.05 mL/min
At time of 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 time of 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

For all 100 patients; on comparing TLE with Non-TLE based regimen; Serum Creatinine values at baseline and at the time of study with Paired t test showed positive correlation (0.233) with significant correlation and dependent (0.020). For TLE regimen, Baseline Serum Creatinine and at the time of the study were moderately positively correlated (0.574), and the correlation was significant (0.000) and also dependent (0.001). In the non-TLE regimen, the relation was positively correlated (0.375) and the correlation was significant (0.007) but the dependency is not significant (0.067). Haemoglobin at baseline and at the time of study also showed strong positive correlation, which is significant (0.710) and dependency is also significant (0.000). Serum Uric acid was found to be negatively correlated (-0.220), and the correlation is not significant (0.125) when the TLE group was compared to the non-TLE group. ADR reported are shown in **Table 4** and were graded as POSSIBLE on WHO Causality Scale ADR-Nephrotoxicity was graded as PROBABLE as per WHO UMC Scale and these patients had to be shifted to a non-Tenofovir based regimen.

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%)

The mean peak creatinine was 0.88 (±0.39) for the entire study group, in patients who developed nephrotoxicity the mean value increased from 1.125(±0.125) at baseline to 2.42(±0. 95). The change in serum creatinine of the individual four patients is depicted in **Figure 2**. Estimated Creatinine clearance also decreased from baseline 86.537 ±24.03 to 37.867 ±13.87 at the time of the study, which is below <50ml/min as per guidelines as illustrated in **Figure 3**.

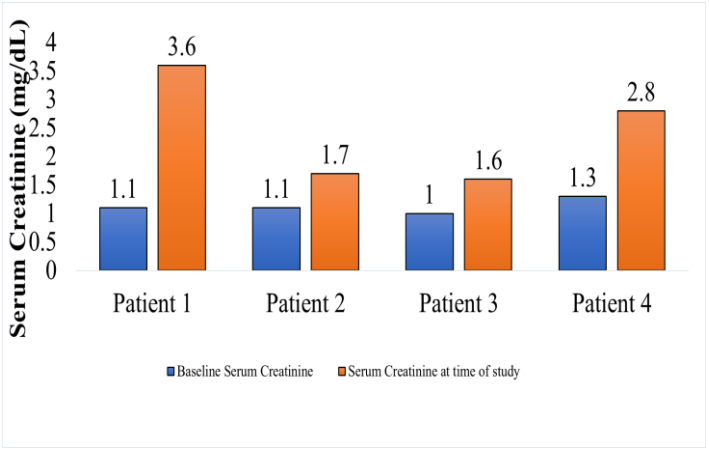

Figure 2. Figure showing change in serum creatinine of the four patients who developed nephrotoxicity

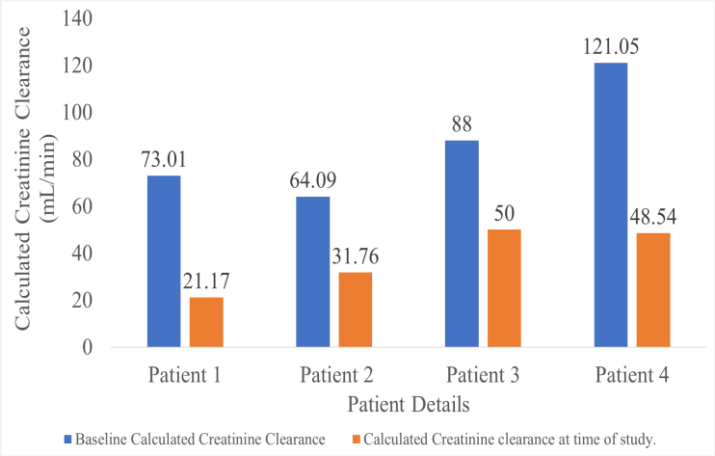

Figure 3. Showing fall in Calculated Creatinine Clearance of the four patients who developed nephrotoxicity.

Earlier studies that analysed the post marketing safety data for tenofovir (TDF) identified advanced age, low body weight and lower CD4 count as risk factors for nephrotoxicity [20]. Researchers have found a greater incidence in Asian cohorts from Japan and India [21, 22].

The mean age of patients diagnosed with nephrotoxicity was 38.75 which is similar to a study [5]. However, some studies have reported a predominance of nephrotoxicity in the older population and consider old age as an independent risk factor for the development of nephrotoxicity [9, 23, 24]. As per our findings, age is not a significant risk factor for nephrotoxicity. There was no sex predominance also, which is parallel with other study [24]. However, Female gender predominance was observed by one study [8]. The increase in mean weight of all patients from start of ART to the time of study shows that ART improved general wellbeing. Patients who developed nephrotoxicity were also not underweight, whereas post-marketing analysis reports low body weight as a risk factor [20].

In the TLE arm, 4 patients developed nephrotoxicity and had received treatment for 1year, 4 years (2 patients) and 7 years suggesting at least one year exposure to tenofovir leads to nephrotoxicity. But this findings do not corroborate with other studies which state that nephrotoxicity occurs within first few months of drug exposure [9, 25, 26]. It may be noted that patients in non-TLE regimen had received treatment for a duration of more than 3 years and 20% of these patients had completed ten years of treatment without any signs of nephrotoxicity. We could not find any study reporting nephrotoxicity with non-TLE regimen.

The mean CD4 count of patients in both groups is below normal (500-1500 cells/mm^3 including those who developed Nephrotoxic, therefore we see no correlation of CD4 count and occurrence of nephrotoxicity. Better CD4 count in ZLN regimen is due to the fact that most patients in the ZLN have received therapy between 4-10 years, which implies that longer treatment with ART improves CD4 count, a marker of treatment outcome. Most patients of TLE have completed less than 3 years of therapy. Various studies have also shown an improvement in CD4 count as safety and efficacy parameter [4, 27, 28]. Prognosis of HIV infection is precisely defined by Plasma Viral Load (PVL) and CD4 lymphocyte count which signifies immunological improvement [28].

Nephrotoxicity was observed in 8% patients on Tenofovir containing TLE regimen who fulfilled all four criteria which is statistically significant but in clinical terms the magnitude was moderate. Some studies report an incidence of 17-22% [9, 29, 30]. Increase in serum creatinine by 0.3mg/dL from baseline was observed in 16% patients other than these four patients on TLE but other three parameters were normal, so they were not diagnosed as nephrotoxicity. However, there might be a chance that incidence of nephrotoxicity was underestimated because serum creatinine would not rise above the normal limit until Glomerular filtration rate is <63/mL/min/1.73m^2 [19]. Serum Creatinine in TLE group increased from baseline, whereas in non-TLE regimen serum creatinine decreased from baseline at the time of study, suggesting affection of the renal function in most patients of TLE arm. TLE was stopped and patients shifted to non TLE regimen.

Patients who have decreased creatinine clearance also had proteinuria analysed by spot albumin creatinine ratio in the grades of +1 and +2 on urine dipstick assay. This finding is in line with other studies [9, 31-34] who however reported proteinuria in higher grades (grade 4). The time from initiation of ART to occurrence of nephrotoxicity was variable: 1 year to 7 years. Some studies suggest that Tenofovir associated nephrotoxicity occurs within first few months of exposure to TDF [9, 25, 26].

Previous studies have found association of various Adverse Drug Reactions (ADRs) affecting all body system with both TLE and non-TLE based regimen but the frequency and severity were higher with ZLN regimen [7] which is similar to our findings. In a study conducted in 2020 also shows that anti-retroviral agents account for 21.73% ADRs, and TLE alone accounts for 16.42% ADRs [35]. Anemia was the most common ADR in TLE arm which could be attributed to bone marrow suppression due to Tenofovir. Another study conducted in South Africa, 2021, showed 8.4% (20 cases) ADRs were related to drugs used in management of HIV and 6 cases for drug induced renal impairment with TDF and/Rifamicin [36]. Recently a pro-drug formulation of Tenofovir: Tenofovir alafenamide (TAF), has been approved in several countries. as it does not interact with

the transport protein required for its accumulation in Renal proximal tubule and therefore leads to less renal toxicity [37, 38]. TDF is available in India but was not available through ART centres at the time of study, but is available now.
The limitation of this study is small study population, short study period, and limited number of markers (bone parameters, serum phosphate and glycosuria) which were diagnostic challenges. Biopsy of the Nephrotoxic patients, if done, could have helped in identifying the exact site of pathology.
Further studies should assess the impact of Tenofovir on the consequence of proximal tubulopathy like proteinuria, altered bone mineral density and bone fracture. This will ensure that clinically important accumulative toxicity is not missed. The use of biopsy to better understand kidney damage is need of the hour. This study was done in 19-20, and due to Covid, the results were declared in 2021 by ICMR. Covid duties during 2020-2021 delayed the publication process on part of the authors.
Govt. of India has included Tenofovir alafenamide in its regime now.

Conclusion

The Incidence of Nephrotoxicity was 8% is patients on Tenofovir, while no nephrotoxicity was observed in patients on the non-Tenofovir regimen. Nephrotoxicity was observed in patients who were exposed to the drug for at least one year. Longer exposure to TLE regimen was a predisposing factor for nephrotoxicity as 3 patients were on tenofovir for more than 4 years but independent of age, body weight, or CD4 count or other ADRs. Though serum creatinine was raised by 0.3% in other 12 patients (24%) on Tenofovir regimen but they did not have hypouricemia, anemia or deranged Urine Albumin Creatinine ratio suggesting serum creatinine may be the earliest parameter to be deranged in renal affection and mandates intervention to prevent progression to nephrotoxicity.
The approved management of Tenofovir induced nephrotoxicity is shift to Abacavir based regimen or use of Tenofovir Alafenamide instead of tenofovir disoproxil fumarate. Further studies with a larger study population and longer duration is necessary. Patients with other co-morbidities were excluded from our studies, so it is necessary to conduct further studies to find correlations of nephrotoxicity with co-morbidities and ascertain predisposing factors.

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Conflict of interest: None

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Ethics statement: Ethical approval was obtained from institutional ethics committee (No./MC/Ethics/2019/84).

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