A Retrospective Cohort Study on the Risk of Kidney Disease in HIV Positive Individuals Receiving Tenofovir Based Regimens

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ABSTRACT

Introduction: Exposure to tenofovir often leads to the development of some irreversible high risk for kidney disease events. In Human Immunodeficiency Virus (HIV) patients, the prolonged treatment with tenofovir use frequently causes mild-to-moderate nephrotoxicity. Hence, there is a need to further investigate the efficacy and the adverse effects associated with tenofovir use to combat the decreased morbidity and mortality associated with the declined kidney function.

Aim: To investigate the risk of kidney disease associated with tenofovir use.

Materials and Methods: A retrospective cohort study was conducted at the tertiary care centre in northern India, from August 2009 to January 2017 and analysed during January to May 2021. The patients with HIV infection who were administered Tenofovir, Lamivudine and Efavirenz (TLE) and Zidovudine, Lamivudine and Nevirapine (ZLN) were included. The patients were divided into two group based on the TLE and ZLN regimen they received. These patients were on a regular follow-up for

six months. The data was assessed on the basis of serum creatinine and estimated Glomerular Filtration Rate (eGFR) (using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation), body weight and Cluster of Differentiation (CD4) count.

Results: Out of 703 patients, 364 patients were administered with TLE, while 339 patients received ZLN. In both the groups, the number of patients were between the age 21-40 years was significantly higher, followed by patients between the age 41-60 years. The mean weight and CD4 count of the patients in both the groups significantly increased with the progression of time (p<0.001). The creatinine levels at baseline and at 24 months were comparable in both the groups, p>0.05. The mean eGFR level was significantly lowered in TLE group (112.2 mL/min/1.73 m²) compared to ZLN group (123.5 mL/min/1.73 m²) at 24-months follow-up (p<0.001).

Conclusion: Overall results demonstrate that increasing exposure to tenofovir was associated with a higher incidence of CKD. The serum creatinine levels were comparable between the TLE and ZLN group.

INTRODUCTION

With the advent of Highly Active Antiretroviral Therapy (HAART), HIV is considered a chronic condition, with the majority of HIV infected patients successfully reaching an optimal immune and virological outcome a few months after starting HAART. Treatment with HAART has led to a dramatic increase in the survival of HIV infected patients reducing the incidence of opportunistic infections, Acquired Immunodeficiency Syndrome (AIDS) related malignancies, and improving the patients' quality of life vis-a-vis the pre-HAART era [1].

However, this switch from acute to chronic disease is associated with an increased incidence of Chronic Kidney Disease (CKD), Glomerular Filtration Rate (GFR) (under 60 mL/min), which has been reported in up to 60% of HIV-infected patients [2,3]. Globally, in patients with access to Antiretroviral Therapy (ART), CKD in people living with HIV infection is now attributed to non HIV associated conditions and a higher prevalence of CKD and earlier onset is observed in HIV patients as compared to age-matched uninfected individuals [3].

CKD in patients with HIV infection could be due to both HIV and non HIV related factors. One of the factors associated with an increased risk of CKD in HIV positive patients is the use of some antiretrovirals (ARVs) [4]. Among all cases of renal impairment in HIV infected patients, around 0.5–14% of renal impairment is caused due to ARVs [4].

Tenofovir Disoproxil Fumarate (TDF) has been shown to be associated with CKD in HIV infected patients [4]. Exposure to TDF is an independent risk factor for reduction in renal function (OR 1.67, 95% CI 1.33-2.08) and was strongly associated with renal tubular dysfunction and CKD [3]. Additionally, patients receiving third drug along with TDF containing

regimens may pose higher risk of CKD [5]. It has been demonstrated that patients who received TDF along with ritonavir boosted protease inhibitor are more prone to develop CKD than Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs) like nevirapine, delavirdine, efavirenz and etravirine [4]. The pharmacokinetics of few ART may be modified in patients with HIV infection with CKD; hence, use of TDF based regimens should be avoided in patients with a creatinine clearance of <50 mL/min [6].The chances of developing CKD with HIV infection are even more in older patients with low eGFR [7].

A retrospective cohort study suggests that there is a higher risk of developing eGFR <60 mL/min/1.73 m² with TDF treatment, in western India [8]. After considering the adverse side-effects associated with TDF, it is necessary to perform renal parameter monitoring at regular intervals, in order to prevent the severe renal toxicity [9]. Hence, the present study was conducted in which patients receiving TLE and ZLN treatment were compared, to assess the increased kidney disease risk associated with the tenofovir use and to study the renal outcomes in patients with TDF treatment.

MATERIALS AND METHODS

This was a retrospective cohort study, conducted at the tertiary care centre in northern India, from August 2009 to January 2017. The analysis of the data was done from January 2021 to May 2021. A cohort of HIV infected patients who were administered based on ART were enrolled in the present study. It was ensured that all the patients' details remained anonymous and the identities were not revealed at any stage of the study. The study was conducted following the Helsinki guidelines, and under the supervision of the Head of the Department.

Inclusion criteria: Patients of age above 18 years, who were registered at the HIV clinic, receiving ART TLE or ZLN, who were on regular follow-up for at least six months, and whose data were available of atleast on six month follow-up were included in the present study.

Exclusion criteria: Patients with irregular follow-up/lost to follow-up, whose records were incomplete, had pre-existing CKD, with acute kidney injury, who were on any form of renal replacement therapy and ritonavir-boosted regimen were excluded.

Patients were assessed on the basis of serum creatinine and eGFR (using CKD-EPI equation), body weight and CD4 count [10].

STATISTICAL ANALYSIS

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20.0. Categorical variables were presented as number (percentage) and compared using Pearson's Chi-square test. Continuous variables were presented as mean (standard deviation) compared using Kolmogorov-Smirnov Z test (for comparison between two groups). A p-value <0.05 was considered as statistically significant.

RESULTS

Of the total 2,590 registered patients, 703 patients were enrolled in the present study. Out of the 703, 364 patients were administered with TLE, while 339 patients received ZLN. The number of patients were more in the age group of 21-40 in TLE group (260), as well as in ZLN group (272). In both the groups, majority of patients were male. The demographic characteristics is shown in [Table/Fig-1]. The mean weight significantly increased in TLE and ZLN groups from 50 kg at baseline to 54.6 kg at 24 months, and 49.8 kg at baseline to 54.7 kg at 24 months. The mean CD4 levels also increased significantly from baseline (254.0 cells/mm^3) to 24 months (488.8 cells/mm^3) in TLE group, and in ZLN group, it increased from 197.3 cells/mm^3 at baseline to 403.7 cells/mm^3 at 24 months [Table/Fig-2]. The creatinine levels at baseline and at 24 months were comparable in both the groups, p<0.005. The mean eGFR level was significantly

Parameters	TLE (n=364)	ZLN (n=339)	p-value (Chi-square test)
Age (years), Mean±SD	35.9±10.8	35.2±8.4	0.874
Age group (years)	**n (%)**	**n (%)**	
≤20	7 (1.9)	2 (0.6)	
21-40	260 (71.4)	272 (80.2)	0.026
41-60	89 (24.5)	62 (18.3)	
≥60	8 (2.2)	3 (0.9)	
Sex			
Male	201 (55.2)	207 (61.1)	0.117
Female	163 (44.8)	132 (38.9)	

[Table/Fig-1]: Demographic characteristics of the patient.
Data given as n (%), TLE: Tenofovir, lamivudine and dolutegravir, ZLN: Zidovudine, lamivudine and nevirapine

Parameters	TLE (N=364) Mean±SD	ZLN (n=339) Mean±SD	p-value (Mann-Whitney U test)
Weight (in kg)			
Baseline	50.0 (11.3)	49.8 (10.0)	0.623
6 months	51.8 (11.3)	51.6 (10.9)	0.291
12 months	52.6 (11.3)	53.6 (11.0)	<0.001
18 months	55.1 (12.3)	54.0 (12.3)	0.001
24 months	54.6 (10.9)	54.7 (11.7)	>0.05
p-value (Independent sample t-test)	<0.001	<0.001	
Creatinine (mg/dL)			
Baseline	0.8 (0.7)	0.7 (0.7)	<0.001
6 months	0.8 (0.8)	0.6 (0.6)	<0.001
12 months	0.8 (0.7)	0.6 (0.2)	<0.001
18 months	0.8 (0.8)	1.0 (0.6)	<0.001
24 months	0.8 (0.8)	0.6 (0.5)	>0.05
p-value (Independent sample t-test)	<0.005	<0.005	
eGFR (mL/min/1.73m²)			
Baseline	117.8 (120.2)	121.4 (122.2)	0.002
6 months	115.1 (119.7)	123.4 (126.4)	0.813
12 months	116.0 (21.3)	124.2 (126.0)	0.085
18 months	115.7 (17.5)	124.9 (128.1)	0.001
24 months	112.2 (120.2)	123.5 (126.0)	<0.001
p-value (Independent sample t-test)	>0.005	>0.005	
CD4 (cells/mm³)			
Baseline	254.0 (165.5)	197.3 (123.7)	<0.001
6 months	400.6 (201.0)	245.3 (159.5)	<0.001
12 months	434.2 (233.0)	298.4 (163.1)	<0.001
18 months	463.6 (281.4)	372.4 (168.7)	0.011
24 months	488.8 (259.5)	403.7 (183.0)	0.250
p-value (Independent sample t-test)	<0.001	<0.001	

[Table/Fig-2]: Comparison of parameters between TLE and ZLN groups.
Data given as Mean±SD, CD4: Cluster of differentiation 4; eGFR: Estimated glomerular filtration rate; TLE: Tenofovir, lamivudine and dolutegravir; ZLN: Zidovudine, lamivudine and nevirapine

lowered in TLE group (112.2 mL/min/1.73 m^2) compared to ZLN group (123.5 mL/min/1.73 m^2) at 24 months follow-up (p<0.001).

DISCUSSION

The rising prevalence of CKD in HIV infected individuals is a cause of concern. One of the contributing factors to the development of CKD in this patient population is the use of some ARV, especially TDF and some ritonavir-boosted protease inhibitors. In resource-limited settings, routine monitoring of renal function during ART is not recommended. However, the problem of TDF-related nephrotoxicity is being reported increasingly [11].

Tenofovir Disoproxil Fumarate (TDF) can sometimes lead to acute kidney injury and proximal tubular dysfunction [12]. In the Asia-Pacific region, HIV infected individuals with older age, lower baseline eGFR and PI-based ART were associated with higher risk of renal dysfunction during the use of TDF [11]. The magnitude and trajectory of eGFR may vary with calculation of eGFR, done by MDRD or CKD-EPI equations. Patients with baseline eGFR ≥90 mL/min receiving tenofovir experienced significant decline in eGFR level over time, when Modification of Diet in Renal Disease or CKD-EPI equations were used to estimate eGFR. However, patients with eGFR <90 mL/min could not find any significant reduction regardless of which estimating equation was used [13]. In settings with limited access to laboratory testing, monitoring guidelines should consider focusing on higher risk patients. It is not clear whether to discontinue the TDF treatment when mild eGFR reduction was observed during treatment. Though patients receiving TDF-based regimen reported high complete or partial renal recovery rate, they discontinued the treatment due to appearance of nephrotoxicity [14].

In the current study, the creatinine level remained stable. Previous literature reported that in TDF induced nephrotoxicity, creatinine level may remain constant with lowering eGFR level which is attributed to tubular dysfunction [15]. Secondly, weight gain observed in these patients may be associated with GFR estimation. Serum creatinine has low prediction value for change in eGFR in HIV patients treated with ART. It is recommended that patients who were on ART should be thoroughly monitored for renal impairment during initial four months. However, appearance of renal impairment after four months of tenofovir based ART regimen is not so common [16].

Incidence of renal loss was higher among women and patients with CD4 nadir <200 cell/mm^3 who use tenofovir as ART [17]. In the

present study, CD4 count did not decrease, which could be the reason for stable creatinine levels.

When TLE and ZLN treatment modalities are compared, it is seen that the ADR associated with ZLN are more severe than the ADR in TLE [18]. The incidence of opportunistic infections was also higher in ZLN group when compared to TLE group, however a retrospective study suggests that both TLE and ZLN are equally effective treatment in improving the immunological status of HIV infected patients [19]. Zidovudine is a well-absorbed deoxythymidine analog, which can also cross the Blood Brain Barrier (BBB) [20], and tenofovir is a nucleotide analogue having broad tissue distribution because of its low-molecular size [21]. The ZLN regimen is a very effective treatment modality in HIV-infected patients. However, the only limitation of ZLN regimen is its possibility to develop haematological toxicity. Hence, it should be used cautiously in patients with haematological disorders like anaemia [22].

Clinicians may use monitoring tools including Data Collection on Adverse Effects of Anti-HIV Drugs (D:A:D) risk score for, routine measurements of eGFR, and proteinuria to identify risk factors [23]. Sometimes individuals may require an intervention. Long-term renal safety has been associated with use of Tenofovir Alafenamide (TAF), alternative of TDF. Outcomes of renal safety are still awaited for the long-term use of TAF but available short-term data suggest that little decline in eGFR level with low risk of proteinuria. Alternative dual therapy antiretroviral regimen is a promising therapy and exclusion of nucleoside (tide) reverse transcriptase class and PI/rs can help to reduce burden of drug which can, further reduce the toxicity. But the long-term safety outcomes of these dual therapies are still unknown. Further prospective studies are required to address preventive measures and predictive factors associated with renal impairment in HIV-infected patients [24].

Limitation(s)

The present study was a retrospective, comparative cohort study, from a single Institution. Multicentric, randomised trials with a larger sample size and longer follow-up are necessary to confirm these findings.

CONCLUSION(S)

Overall results demonstrate that increasing exposure to tenofovir was associated with a higher incidence of CKD. The levels of serum creatinine and CD4 were comparable between the TLE and ZLN group.

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