

Original Research Article

A study of renal dysfunction among HIV-infected patients on tenofovir based ART regimen in the Northeast part of India

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ABSTRACT

Background: Tenofovir is an integral part of the currently used antiretroviral therapy (ART) regime. However, nephrotoxicity has been a concern. This study has been undertaken to evaluate the prevalence and risk factors of renal dysfunction among HIV-patients on tenofovir containing ART regime.

Methods: This cohort study was conducted at Regional Institute of Medical Sciences. HIV-patients newly started on tenofovir containing ART regime were subjected to detailed history, thorough physical examination, and routine investigations. Serum creatinine levels and creatinine clearance were measured at regular intervals.

Results: Mean age of the patients was 42.37 ± 10.8 years. Most of the patients had normal BMI (66%) and 22% were obese while 12% of the cases were underweight. Majority of the patients had CD4 count less than 350 cells/cumm. Renal dysfunction, defined as creatinine clearance < 50 ml/min, developed in 9% of the patients at 3 months and in 33% of the patients at 6 months. Old age, low CD4 cell count, HCV co-infection, and advanced HIV infection were found to be important risk factors.

Conclusions: Development of renal dysfunction is common among HIV patients receiving tenofovir-based ART regimen. Old age, low CD4 cell count, HCV co-infection, and advanced HIV infection were found to be important risk factors.

Keywords: Antiretroviral, Creatinine clearance, Renal dysfunction, Tenofovir

INTRODUCTION

Highly active antiretroviral therapy (HAART) has revolutionized the management of HIV-AIDS with drastic reduction in morbidity and mortality. The improvement in prognosis has changed the leading causes of morbidity and mortality in HIV infected patients from infectious to non-infectious causes with kidney disease increasingly emerging as significant.¹ The etiology of kidney disease in HIV infected patients is often multifactorial, reflecting an interplay between the host and viral factors, as well as exposure to nephrotoxic agents.²⁻⁵

Improved survival among patients with HIV infection is anticipated to result in an increase in the long term development of HAART-associated metabolic complications, such as diabetes and dyslipidemia, which in turn, can contribute to vascular changes and decreased renal function.⁶ While HAART has been demonstrated to reduce the incidence and severity of HIV-associated nephropathy (HIVAN), use of antiretroviral drugs have been associated with a number of toxicities, including those affecting the kidney.^{7,8}

Tenofovir disoproxil fumarate (TDF) is an acyclic nucleotide analogue reverse transcriptase inhibitor

approved for the treatment of HIV in combination with other antiretroviral drugs. It has gained popularity because of its convenient once daily dosing, antiviral efficacy, and relatively favourable side-effect profile, making it one of the most widely prescribed antiretroviral drugs for the treatment of HIV-1.⁹ However, multiple case reports and studies have linked TDF use with renal dysfunction.

With the new NACO guidelines to initiate ART irrespective of CD4 count and clinical stage, and to start TDF based ART regime for all treatment naïve patients unless contraindicated, the number of HIV patients exposed to tenofovir is increasing.¹⁰ There is very limited data on TDF associated renal dysfunction among HIV patients in the North Eastern part of India where the prevalence of HIV infection is relatively high. Hence, this study was taken up to estimate the prevalence of TDF associated renal dysfunction and to identify factors increasing the risk of development of renal dysfunction in HIV infected patients on tenofovir containing ART regime.

The study was conducted with the aim to estimate the prevalence of renal dysfunction among HIV patients on tenofovir containing ART regimen and to determine the risk factors for the development of renal dysfunction.

METHODS

This cohort study was undertaken in a Centre of Excellence, ART, under the National AIDS Control Organization, Government of India, attached to the Department of Medicine of a teaching institute in northeastern India. Ethical clearance was obtained from the Institutional Ethics Committee. Informed consent was obtained from all participants. The study recruited HIV-infected patients aged 18 years and above who were newly started on tenofovir-based ART regimen. We excluded patients known to have earlier renal disease as well as those with Diabetes Mellitus, Hypertension and connective tissue disease. We also excluded patients currently on nephrotoxic drugs like aminoglycosides, amphotericin B, acyclovir, sulfonamides etc.

Each enrolled patient provided a detailed history and underwent thorough clinical examination. CD-4 cell count was estimated using automated analyser and Fluorescent Activated Cell Sorter (FACS) manufactured by BD Biosciences, 2350, Qume Drive, San Jose, CA 95131-1807, USA. Serum creatinine levels were estimated using Randox Autoanalyser by Jaffe’s method. Serum creatinine levels were estimated again at 3 months and 6 months. Creatinine Clearance (CrCl) was calculated using the Cockcroft-Gault formula.¹¹

$$CrCl (ml/min) = \frac{(140 - \text{age in years}) \times \text{weight in kg}}{\text{Serum creatinine in mg/dl} \times 72}$$

(In female subject the whole product need to be multiplied by 0.85).¹¹

Impaired renal function was defined as creatinine clearance <50 ml/min.¹²

Body mass index (BMI) of the patients was categorized using WHO Asian classification.¹² Patients were screened for HBsAg by Virucheck and for HCV-Ab by Flaviscreen.

Data collected were checked for completeness and consistency. Data were analyzed using descriptive statistics (mean, proportions, percentages, and standard deviations) and Chi-square test. IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY) was used to analyze the data. P <0.05 was considered statistically significant.

RESULTS

There were 132 patients fulfilling the inclusion criteria were enrolled for the study, and during the study period 2 patients died due to cryptococcal meningitis and 1 patient died of cerebral toxoplasmosis, while 29 patients were lost to follow-up. So, 100 patients were analyzed for the study.

Mean age of the patients was 42.37±10.8 years. 54 patients were males and 46 were females. Majority of the patients were HIV newly detected patients (55%) while 19 percent of the patients had HIV for more than 10 years. Most of the patients had normal BMI (66%) and 22% were obese while 12% of the cases were underweight. Majority of the patients had CD4 count less than 350 cells /cumm which constituted 79% of the cases. There were no cases of HBV co-infection while 6 patients had HCV co-infection.

All the patients had normal baseline creatinine clearance. At 3 months of follow up 9 patients had creatinine clearance of <50 and after 6 months another 24 patients had low creatinine clearance so a total of 33 patients had low renal clearance accounting to 33%. This finding was found to be statistically significant (p<0.05) (Table 1).

Table 1: Distribution of patients based on creatinine clearance at baseline, 3 months and 6 months.

Creatinine clearance	At baseline (%)	3months (%)	6 months (n=90)	Chi-square test
<50	100 (100.0)	91 (91.0)	67 (73.6)	Value=49.5 p=0.00
≥50	0 (0.0)	9 (9.0)	24 (26.4)	
Total	100 (100.0)	100 (100.0)	91 (100.0)	

Renal dysfunction was more in the age group of >50 years. High BMI group had increased risk and the finding was statistically significant ($p < 0.05$) (Table 2). Development of renal dysfunction was more among the newly detected patients and those with duration of HIV more than 10 years (Table 3). Development of renal dysfunction was also more among patients with low CD4 count (Table 4).

Table 2: Relation between BMI and renal dysfunction.

BMI	Renal dysfunction	No renal dysfunction	Total	Chi-square test
<18.5	1 (3.0)	11 (18.3)	12 (12.0)	Value=9.4 df-2 p-0.015
18.5-24.9	20 (60.6)	46 (68.7)	66 (66.0)	
25.0-29.9	12 (36.4)	10 (14.0)	22 (22.0)	
≥30	0 (0.0)	0 (0.0)	0 (0.0)	
Total	33 (100.0)	67 (100.0)	100 (100.0)	

Table 3: Relation between duration of HIV infection and renal dysfunction.

Duration of HIV infection	Renal dysfunction	No renal dysfunction	Total	Chi-square test
Newly detected	22 (66.7)	33 (53.3)	55 (55.0)	Value =0.44 df-3 p-0.932
Upto 5	2 (6.0)	10 (13.3)	12 (12.0)	
6-10	3 (9.0)	11 (15.0)	14 (14.0)	
>10	6 (18.3)	13 (18.3)	19 (19.0)	
Total	33 (100.0)	67 (100.0)	100 (100)	

Table 4: Relation between CD4 cell count and renal dysfunction.

CD4	Renal dysfunction	No renal dysfunction	Total	Chi-square test
<350	31 (93.9)	48 (71.6)	79 (79.0)	Value =1.13 df-1 p-0.31
≥350	2 (6.1)	19 (28.4)	21 (21.0)	
Total	33 (100.0)	67 (100.0)	100 (100.0)	

DISCUSSION

In the present study, majority of the patients were in the age group of 31 to 50 years constituting 60% of the study population. This finding may be explained by the fact that this age group, being the most sexually active, is most vulnerable to get infected with HIV.

The study population had an almost equal number of male and female patients. Fifty five percent of the

patients were newly detected HIV cases, and majority of the patients (79%) had baseline CD4 cell count below 350 cells/cumm.

The serum creatinine level of all patients were checked prior to initiation of tenofovir-based ART regimen as per NACO guidelines. So all the patients included in the study had normal baseline serum creatinine level. Also, the creatinine clearance were normal for all the patients at baseline.

Renal dysfunction, defined as creatinine clearance < 50 ml/min, developed in 9% of the patients at 3 months and in 33% of the patients at 6 months of exposure to tenofovir.

Abdominal ultrasonography was done for patients who developed renal dysfunction and was found to be normal in all the patients. This rules out the presence of renal parenchymal disease as well as obstructive pathology that might have caused the decline in renal function. Urinalysis of patients with renal dysfunction showed trace to 1+ proteinuria in only 30% of the patients and glycosuria in 47% of the patients.

The renal proximal tubular cell is the main target of tenofovir toxicity due to its complement of cell membrane transporters that favour tenofovir accumulation. Tenofovir accumulates in the cytoplasm of proximal renal tubular epithelial cells, inhibiting mitochondrial DNA polymerase and causing dysfunction of the oxidative respiratory chain and energy deprivation. This acquired renal tubular mitochondriopathy eventually drives epithelial cells to apoptosis, resulting in proximal tubular damage and renal injury.¹³

The prevalence of tenofovir-related renal dysfunction found in this study was higher than previously reported randomized controlled trials and cohort studies from western countries which showed a prevalence ranging from 4% to 11%.^{14,15}

However, retrospective cohort studies from Asian region have shown similarly high rates of renal dysfunction.^{13,16,17} A study conducted by Kyuon HL et al among HIV infected Koreans found a prevalence of 27%.¹³ One of the postulated explanations for this is the lower BMI of the patients in Asia as well as genetic predisposition.¹⁷ Polymorphism in the genes encoding proximal tubular transporters, such as the ABCC2 and ABCC4 genes, have been postulated to increase the plasma concentration of tenofovir and hence an increased risk of nephrotoxicity.¹⁸

The results of this study further showed that old age, low CD4 cell count, Hepatitis C co-infection, and advanced HIV infection were the important risk factors for development of renal dysfunction in patients on tenofovir-based ART regimen. This finding was comparable to the findings in many previous

studies.^{17,19,20} A cross-sectional study conducted by Wantakishi et al had shown that old age and low CD4 count were risk factors for development of tenofovir-related renal dysfunction.²⁰

Besides the ones found in this study, other reported risk factors for the development of renal function with tenofovir include concomitant use of protease inhibitors, pre-existing kidney disease, diabetes and concurrent use of other nephrotoxic drugs.^{17,21} In this study patients with pre-existing renal disease, comorbidities like Diabetes, Hypertension, SLE, etc, and use of other nephrotoxic drugs were excluded. All the patients were on TLE regime and hence there was no concomitant use of protease inhibitors in any of the patients.

A study by Sadre A et al showed low BMI as a risk factor for tenofovir-related renal dysfunction whereas, in our study renal dysfunction was more common in patients with normal and high BMI.²² This contradicting result is supported by a study conducted by Kyoung HL et al which showed that tenofovir-related renal dysfunction had no relationship to BMI.¹³

This study found a high prevalence of renal dysfunction among HIV patients receiving tenofovir-based ART regimen. Old age, low CD4 cell count, HCV co-infection, and advanced HIV infection were found to be important risk factors for the development of renal dysfunction. Hence, tenofovir use must be accompanied by more intensive renal monitoring particularly in patients at higher risk of renal dysfunction. Measurement of serum creatinine and creatinine clearance at frequent intervals is essential.

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