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Original Research Article

Incidence of Tenofovir related Nephropathies in HIV Infected Patients: A Study from Tertiary Care Centre

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Abstract:
Background: *India has the third highest number of estimated people living with human immunodeficiency virus (HIV) in the world. Tenofovir (TDF) is an effective and widely used drug in treatment for both HIV and hepatitis B virus infection. Tenofovir is widely used in combination antiretroviral therapy including as a fixed dose combination pill. Several case reports and case series reported afterwards found tenofovir to be associated with nephropathy.*
Aim: *To study the incidence of tenofovir related nephropathies in HIV infected patients and to study the correlation of tenofovir induced nephrotoxicity with CD4 count.*
Material and Methods: *200 patients on TDF based Antiretroviral therapy (ART) were included in hospital based prospective study based on inclusion and exclusion criteria. Baseline study variables serum creatinine value, urine-routine and microscopy, 24 hour urinary protein and CD4 count were recorded and patients were followed up for 6 months and study variables were compared. Statistical analysis were done by SPSS version 22.1.*
Results: *All patients had normal baseline renal function and urine routine and microscopic examination and were on tenofovir containing ART regimen. Mean age was 36.86 years and Sex ratio was 1.38:1. After six months of therapy 26 patients (13%) developed proteinuria. 20 patients (10%) had +1 proteinuria, 5 patients (2.5%) had +2 proteinuria and 1 patient (0.5%) had +3 proteinuria. Total 147 patients (73.5%) had weight gain and 53 patients (26.5%) had weight loss after taking tenofovir based ART for 6 months. Improvement in CD4 count was seen in 88.5% patients. Improvement in CD4 count was seen in 21 out of 26 patients having proteinuria. Decline in CD4 count was seen in total 11.5% patients. In this study, 12.5% patients had increase in creatinine levels and decrease in creatinine clearance was found in 13% patients.*
Conclusion: *Use of tenofovir based ART regimen is associated with increased incidence of nephropathy despite improvement in CD4 count and body weight significantly.*
Keywords: *Tenofovir, Nephropathy, HIV, CD4, ART.*

Introduction

According to WHO, each year around 2.6 million more people become infected with HIV and 1.8 million die of AIDS[1]. The worst affected region is the Sub Saharan Africa[2]. India has the third highest number of estimated people living with HIV in the world. According to the HIV estimations 2012, the estimated number of people living with HIV/AIDS in India was 20.89 lakh[3]. India has demonstrated an overall reduction of 57% in the annual new HIV infections among adult population from 2.74 lakh in 2000 to 1.16 lakh in 2011, reflecting the impact of various interventions and scaled-up prevention strategies under the National AIDS Control Program (NACP)[4]. The trend of annual AIDS deaths is showing a steady decline since roll out of the free Anti-Retroviral Therapy (ART) programme in India in 2004.It is estimated that around 1.5 lakh lives have been saved due to ART till 2011.

Tenofovir (TDF) is an effective and widely used drug in treatment for both human immunodeficiency virus (HIV) and hepatitis B virus infection[5]. Tenofovir is widely used in combination antiretroviral therapy including as a fixed dose combination pill[6]. The first efficacy and safety trial conducted in HIV-infected patients found tenofovir to be an effective drug with a good safety profile and minimal risk. However, several case reports and case series reported afterwards found tenofovir to be associated with a host of renal complications including acute kidney injury (AKI), renal failure, chronic kidney disease (CKD) and proximal tubular injury[7]. Subsequent observational cohort studies have found tenofovir to be associated with significant but modest decline in glomerular function. The WHO recommends that serum creatinine screening must be conducted before initiation of TDF and that patients with compromised renal function should not be started on TDF[8]. However, laboratory monitoring is not a requirement for the initiation of ART[9].

Material & Methods

This study was a hospital based prospective study of one year duration, carried out in P.G. Department of medicine S.N.M.C. Agra, in patients attending ART centre of hospital. HIV positive patients on tenofovir based ART regimen and who were more than 18 years of age were followed 6 monthly for any decline in kidney function and status of CD4 count.

Study variables

- Serum creatinine
- Urine-routine and microscopy
- 24 hour urinary protein
- CD4 count

Aim

To study the incidence of tenofovir related nephropathies in HIV infected patients.

Objectives

1. To evaluate the nephrotoxic effect of tenofovir in HIV infected patients.
2. To study the correlation of tenofovir induced nephrotoxicity with CD4 count.

Inclusion Criteria

1. HIV patients on tenofovir based ART regimen.
2. HIV Patients with at least one baseline creatinine value and urine routine and microscopy recorded.
3. Male or female adult HIV patients aged 18 years or older at baseline.

Exclusion Criteria

The following patient categories were excluded from the study:

1. Patients on tenofovir based ART regimen who are younger than 18 years of age.
2. Patients on Tenofovir based ART regimen who had no recorded values of serum creatinine and urine routine and microscopy at baseline.
3. Patients having any pre existing kidney disease.
4. Patients on tenofovir based ART regimen who are hepatitis B positive.
5. Patients on ATT.

Steps:

Step-1: New patients on tenofovir containing ART regimen were selected according to inclusion and exclusion criteria.

Step-2: Baseline serum creatinine, urine routine and microscopy and CD4 count of selected patients were recorded.

Step-3: Patients were followed up at 6 months interval with serum creatinine, urine routine and microscopy, CD4 count and 24 hour urinary protein.

Step-4: Impairment in renal function, calculation of incidence of nephropathy and CD4 count correlation was recorded.

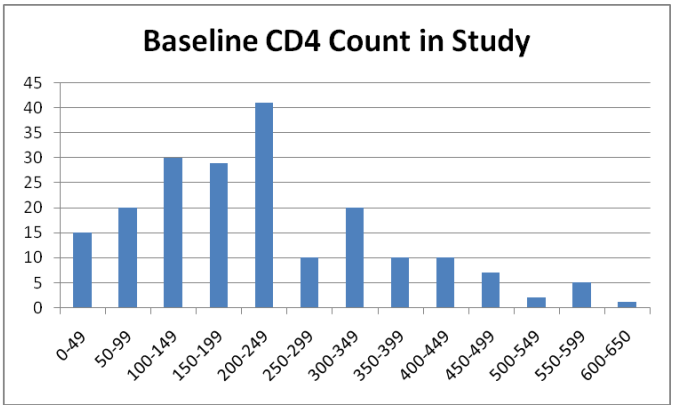
Cockroft Gault Equation

Estimated GFR =[{ (140 - Age)*Body weight} / 72* s. creatinine] * 0.85(in females)

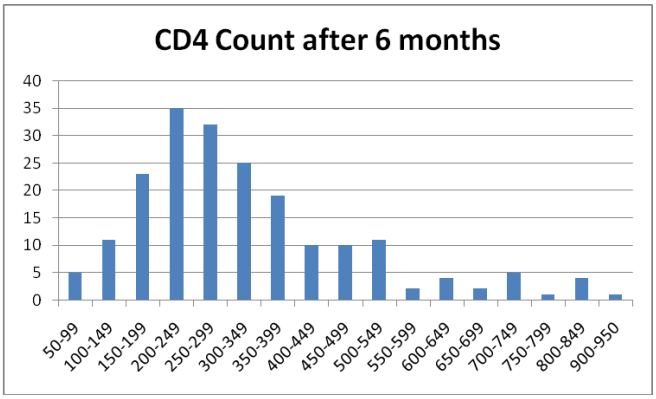
Results

In this study total 200 patients were taken from ART centre who satisfied the inclusion and exclusion criteria. All patients had normal baseline renal function and urine routine and microscopic examination and were on tenofovir containing ART regimen. Minimum age in the study was 19 years and maximum age in the study was 60 years with a mean age of 36.86 years in this study. Out of total 200 patients 84 patients (42%) were female and 116 patients (58%) were male. Sex ratio was 1.38:1.

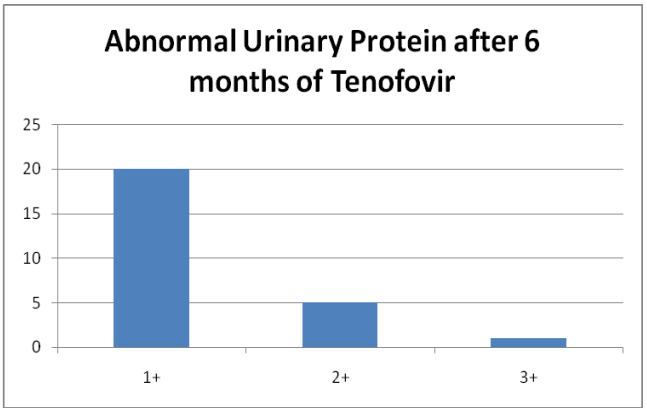
In this study baseline CD4 count was less than 50 in 15 patients (7.5%), less than 100 in 35 patients (17.5%), less than 250 in 135 patients (67.5%), more than 250 in 65 patients (32.5%) and more than 350 in 35 patients (17.5%).



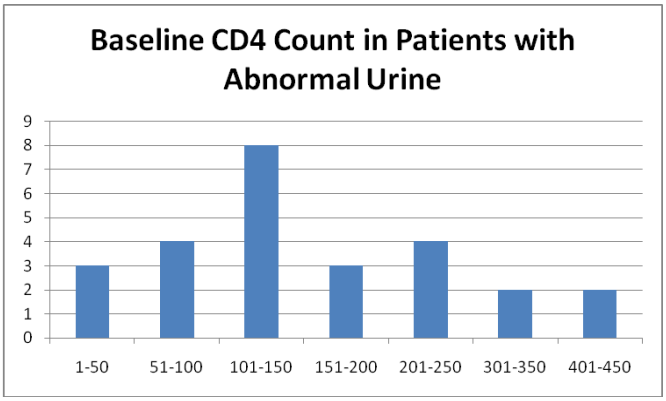
After six months use of tenofovir containing ART regimen, CD4 count was less than 50 in 5 patients (2.5%), less than 100 in 16 patients (8%), less than 250 in 74 patients (37%), more than 250 in 126 patients (63%) and more than 350 in 69 patients (34.5%).



There was no proteinuria when tenofovir based ART regimen was started. After six months of therapy 26 patients (13%) developed proteinuria. 20 patients (10%) had +1 proteinuria, 5 patients (2.5%) had +2 proteinuria and 1 patient (0.5%) had +3 proteinuria.



In patients with proteinuria baseline CD4 count was less than 50 in 3 patients (1.5% of total patients), less than 100 in 7 patients (3.5% of total), less than 250 in 22 patients (11% of total patients), more than 250 in 4 patients (2% of total patients) and more than 350 in 2 patients (1% of total patients included in study).



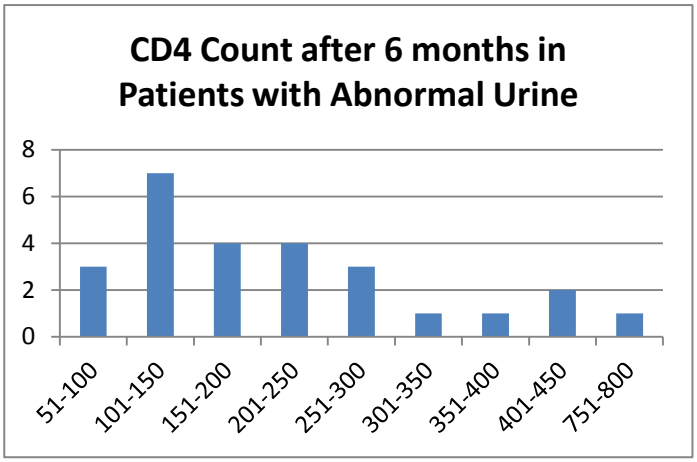
Decline in CD4 count was seen in total 23 patients (11.5%), out of which 5 patients (2.5%) had decline in renal function and 18 patients (9%) have no decline in renal function after six months intake of tenofovir based ART regimen. All patients with decline in renal function had baseline CD4 count less than 250.

Improvement in CD4 count was seen in 177 patients (88.5%). Improvement in CD4 count was seen in 21 out of 26 patients having proteinuria.

Baseline haemoglobin was less than 5 g/dL in 1 patient (0.5%), 5-7 g/dL in 5 patients (2.5%), 7-9 g/dL in 28 patients (14%), 9-11 g/dL in 96 patients (48%), 11-13 g/dL in 49 patients (24.5%), 13-15 g/dL in 20 patients (10%) and more than 15 g/dL in 1 patients (0.5%) in study.

Six months after tenofovir based regimen intake haemoglobin was 7-9 g/dL in 14 patients (7%), 9-11 g/dL in 72 patients (36%), 11-13 g/dL in 86 patients (43%) and 13-15 g/dL in 28 patients (14%).

Among 26 patients (13%) having deranged renal function, baseline haemoglobin was 5-7 g/dL in 1 patient (0.5%), 7-9 g/dL in 7 patients (3.5%), 9-11 g/dL in 14 patients (7%), 11-13 g/dL in 4 patients (2%). Six months after tenofovir based regimen intake haemoglobin was 7-9 g/dL in 6 patients (3%), 9-11 g/dL in 10 patients (5%), 11-13 g/dL in 9 patients (4.5%) and 13-15 g/dL in 1 patient (0.5%). In 20 patients (10%) haemoglobin concentration increased despite decline in renal function however haemoglobin concentration decreased in 6 patients (3%) with declining renal function.



The minimum baseline body weight of the patient included in study was 39.7 Kg, maximum body weight was 68 Kg and average body weight was 47.81 Kg. One patient (0.5%) had baseline body weight less than 40 Kg, 142 patients (71%) had baseline body weight of less than 50 Kg and 58 patients (29%) had baseline body weight of 50 Kg or more.

The minimum body weight of patient after intake of tenofovir based ART for 6 months was 33 Kg, maximum weight was 63.1 Kg and average weight was 48.88 Kg. 2 patients (1%) had body weight less than 40 Kg, 128 patients (64%) had body weight of less than 50 Kg and 72 patients (36%) had body weight of 50 Kg or more after taking tenofovir based ART for 6 months.

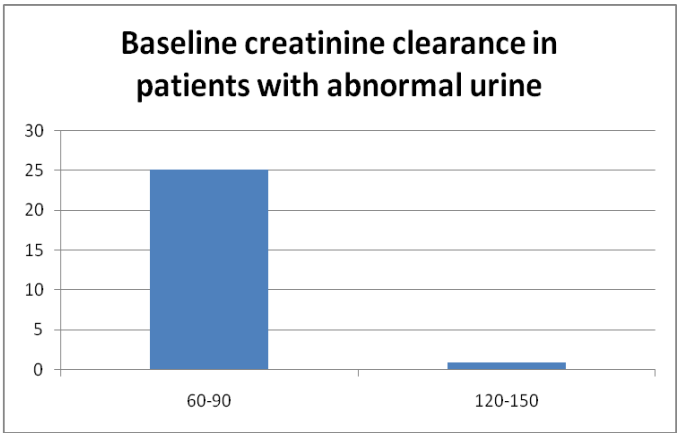
Total 147 patients (73.5%) had weight gain after taking tenofovir based ART for 6 months and 53 patients (26.5%) had weight loss after taking tenofovir based ART for 6 months. 12 patients (6%) had weight gain but developed renal dysfunction and 135 patients (62.5%) have weight gain without renal dysfunction. 14 patients (7%) had weight loss and renal dysfunction in the form of proteinuria, increased serum creatinine, increased blood urea and decreased creatinine clearance.

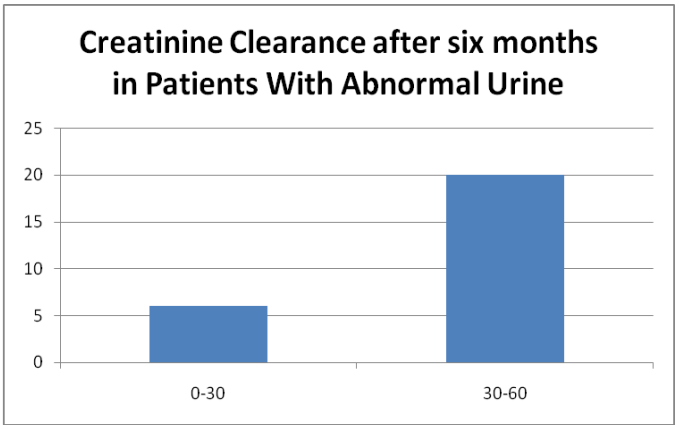
Baseline serum creatinine was less than 1 mg/dl in 167 patients (83.5%), 1-1.5 mg/dl in 32 patients (16%) and more than equal to 1.5 mg/dl in 1 patient (0.5%). After taking tenofovir based ART for 6 months, 157 patients (78.5%) had serum creatinine levels less than 1, 17 patients (8.5%)

had serum creatinine levels 1-1.5mg/dl and 26 patients (13%) had creatinine levels more than or equal to 1.5mg/dl.

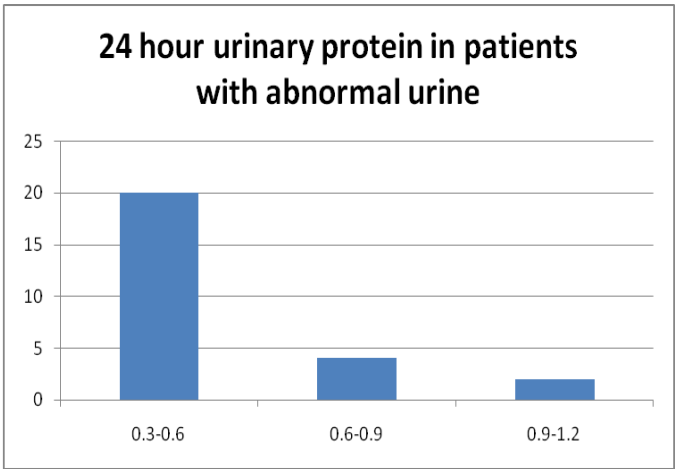
In this study 59 patients (29.5%) had insignificant increment in serum creatinine level (serum creatinine remain below 1.5 mg/dL), 115 patients (67.5%) had stationary or declining creatinine levels, 25 patients (12.5%) had significant increment in serum creatinine levels (serum creatinine above 1.5 mg/dl) and 1 patient had decrease in creatinine level but with deterioration in creatinine clearance and persistently elevated creatinine above 1.5 mg/dl. 25 patients (12.5%) had increase in creatinine levels with proteinuria and decline in creatinine clearance and 1 patient had significant decrease in creatinine level with proteinuria and decline in renal function.

In this study all patients had baseline creatinine clearance more than 60 mL/min. 96 patients (48%) had increment in creatinine clearance after taking tenofovir based ART for 6 months and 104 patients (52%) had developed decline in creatinine clearance out of which 26 patients (13%) had creatinine clearance of less than 60 mL/min.





In this study 26 (13%) patients developed derangement in 24 hour urinary protein after intake of tenofovir containing ART regimen for 6 months.



Discussion

AIDS is the epidemic of the modern era. In this disease, the morbidity and mortality arises from complications involving various organ systems. The availability of ART from NACO made HIV treatable disease in India. Between 2006 and 2012 there is 29% reduction in mortality due to HIV disease in India. The aim of therapy in HIV infected patients is to achieve clinical, virological, immunological, therapeutic and epidemiological goals[10].

Tenofovir is widely used in combination antiretroviral therapy including as a fixed dose combination pill. The first efficacy and safety trial conducted in HIV-infected patients found tenofovir to be an effective drug with a good safety profile and minimal risk. However several case reports and case series reported afterwards found tenofovir to be associated with a host of renal complications including acute kidney injury (AKI), renal failure, chronic kidney disease (CKD) and proximal tubular injury[7]. The WHO recommends that serum creatinine screening must be conducted before initiation of TDF and that patients with compromised renal function should not be started on TDF[8].

In this study, decrease in creatinine clearance was found in 13% patients after intake of TDF based ART regimen for six months. De Beaudrap *et al.*

(2010), Senegal found persistent decrease in eGFR in 30% patients receiving TDF for 12 months[11].

In this study renal impairment in the form of decrease in creatinine clearance, proteinuria and increase in serum creatinine was found in 13% patients after intake of tenofovir containing ART regimen for six months. Nishijima *et al*. (2011), Japan found that Tenofovir-related renal dysfunction occurred in 19.6% patients[12]. O'Donnell *et al.* (2011), USA found that renal impairment occurred in 14% of the cohort and was not correlated with exposure to tenofovir in univariate analyses[13].

In this study, after intake of TDF based ART regimen for six months, improvement in CD4 count was seen in 88.5% patients. Improvement in CD4 count was seen in 21 out of 26 patients having proteinuria. Decline in CD4 count is seen in total 11.5% patients. Joel E. Gallant *et al.*, California found that there is significant improvement in CD4 count. They found that the mean CD4 increase was 261 cells/mm^3 in patients on tenofovir regimen[14].

In this study, after intake of TDF based ART regimen for six months, improvement in body weight was seen in total 73.5% patients, while 26.5% patients had weight loss.

In this study, 12.5% patients had increase in creatinine levels after intake of tenofovir containing ART regimen for six months.

In this study improvement in haemoglobin concentration was found in 78.5% of patients. Fisher M et al. (2009) United Kingdom found that switching the therapy from Zidovudine/ Lamivudine to Tenofovir/ Emtricitabine in patients on Efavirenz therapy significantly increases the haemoglobin[15].

TDF is a contributing factor in renal impairment in HIV reactive patients on Tenofovir based ART regimen. Although the hemoglobin, weight and immunological status improves but still the patients with low CD4 counts remain predisposed to renal damage. Thus routine baseline renal function screening should be adopted to prevent patients with impaired renal function receiving TDF.

Conclusion

Following conclusions are based on the observation of 200 patients included in this study:

1. All patients included in study were adult and had preserved renal function and baseline creatinine clearance more than 60ml/min.
2. In this study mean age was 36.86 years with minimum age of 19 years and maximum age of 60 years. Sex ratio was 1.38:1.
3. All patients had taken tenofovir containing regimen for six months.
4. Tenofovir based ART regimen improves CD4 count in significant number of patients.
5. Tenofovir based ART regimen improves body weight in most of the patients.
6. Tenofovir based ART regimen improves haemoglobin concentration in patients.
7. Tenofovir based ART regimen is associated with derangement in renal function in the form of increase in serum creatinine levels, decrease in creatinine clearance, proteinuria and increased 24 hour urinary protein.

By this study, it can be concluded that use of tenofovir based ART regimen is associated with increased incidence of nephropathy despite improvement in CD4 count and body weight significantly. However further research work with many more subjects is required for establishment of role of tenofovir in nephropathy in HIV patients and to make suitable and acceptable recommend-ations for proper management of disease.

Conflicts of interest: None

Source of Funding: None

Ethical Issue: None

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