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INCIDENCE AND PREDICTORS OF NEPHROTOXICITY IN HIV INFECTED PATIENTS RECEIVING TENOFOVIR BASED ART

[1]Dr. V. Ramachandran, [2]Dr. A. Kalanad, *[3]Dr. S. Mathew

[1]Physcian, Government Taluk Head Quarters Hospital Vythiri, Kerala.
[2]Assistant Professor, Department of Medicine, Government Medical College Hospital, Kozhikode, Kerala.
[3]Additional Professor, Department of Infectious Diseases, Government Medical College Hospital, Kozhikode, Kerala.

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***Corresponding Author**
Dr. S. Mathew
Additional Professor, Department of Infectious Diseases, Government Medical College Hospital, Kozhikode, Kerala.

ABSTRACT

Tenofovir based ART regimen is currently used as the first line anti retroviral therapy by NACO in India. As a part of national strategy, "Paving the way for an AIDS free India" NACO recommends initiation of ART irrespective of stage or CD4 count. The major side effects of TDF are renal toxicity and decrease in bone marrow density. A prospective Cohort Study was conducted in 202 patients, started on Tenofovir based ART to find out the incidence and predictors of nephrotoxicity. S.Creatinine 1.5 times the basal value, increase in serum creatinine more than or equal to 0.3mg/dl above the basal value, hypophosphatemia, hypouricemia, proteinuria**,** glycosuria**,** hypokalaemia & hypocalcaemia were the parameters checked. Gender, age, stage of HIV infection, CD4 count, body mass index, co morbidities (diabetes, hypertension, opportunistic infections), concomitant nephrotoxic medications, & serum creatinine level before starting treatment were the predictors of nephrotoxicity studied. Nephrotoxicity of Tenofovir was 13.9%.Average time to develop nephrotoxicity was 118 days. Average decline in creatinine clearance during renal dysfunction was 21.4 ml/min & almost all cases were asymptomatic. Nephrotoxicity was detected in the form of mild derangement of RFT and proteinuria on regular follow up. Advanced clinical stage and low CD4 count had significant association with nephrotoxicity. Single most important predictor of Tenofovir induced nephrotoxicity was CD4 count. Small sample size, short period of follow up and a smaller number of cases in the subgroups of co-morbidities were the major limitations.

KEYWORDS: Nephrotoxicity, Tenofovir, HIV, ART.

INTRODUCTION

Tenofovir disoproxil fumarate is the first nucleotide reverse transcriptase analogue approved for the treatment of HIV infection. It has a good overall safety profile, with fewer metabolic side-effects and mitochondrial toxicities when compared to other previously used first line ARTs like Zidovudine and Stavudine. Because of relatively long half-life, once daily dosing is possible and hence compliance is good. Government of India established the National AIDS Committee in 1986, which set the foundation for the establishment of National AIDS Control Organization (NACO) to oversee the policies for prevention and control of HIV infection. Tenofovir based regimen is currently used as the first line anti retroviral therapy by NACO.[1] As a part of national strategy, "Paving the way for an AIDS free India" NACO has changed their guidelines to start ART irrespective of the CD4 count there by there is an increasing use of Tenofovir.[1] The major side effects of TDF are renal toxicity,[2] and decrease in bone mineral density; renal toxicity being most significant and the overall incidence is described as 3- 5 %. Renal toxicity includes glomerular toxicity and tubular toxicity.[3]

Serum creatinine and e GFR are measurements of glomerular function. However, the main target of TDF nephrotoxicity is the proximal tubule; in severe cases TDF leads to a breakdown of solute transport in this nephron segment (renal Fanconi syndrome—FS) or acute Kidney injury (AKI). Fanconi syndrome includes aminoaciduria, glycosuria, tubular proteinuria, uricosuria and bone demineralization due to phosphate wasting. This may lead to acute renal failure and this renal toxicity can usually present after 20 weeks or more of Tenofovir therapy; resolution typically takes place within 10 weeks after the discontinuation of the therapy. Numerous case reports and case series have described FS or AKI in HIV-infected patients taking TDF. The exact incidence of TDF-induced FS is unknown, and attempts at accurate estimates are hampered by underreporting and a lack of clear diagnostic criteria, but based on the available data it is probably < 1 %. Renal biopsy specimens from patients with TDF toxicity typically

show acute tubular damage, with misshapen and swollen mitochondria in the PT on electron microscopy.[4] While cases of FS and AKI are relatively infrequent, these represent the most severe end of the toxicity. It is currently unknown whether mild PT toxicity will lead to progressive CKD over time in these patients, but chronic phosphate wasting can cause a decrease in bone mineral density. Many studies about the incidence and various risk factors for Tenofovir induced nephrotoxicity have been conducted in different parts of the world.[5,6] Only very few studies are there about the Indian population, especially South Indian population. This background led us to the present study *ie* to find out the incidence of Tenofovir induced nephrotoxicity and the risk factors affecting the same. This may help us for early detection and management of renal dysfunction

Aims & Objectives

To find out the incidence of nephrotoxicity in Tenofovir based ART receiving HIV infected patients.

To study predictors of nephrotoxicity in Tenofovir based ART receiving HIV infected patients.

MATERIALS AND METHODS

This was a Prospective Cohort Study.The study subjects were HIV infected individuals initiated on Tenofovir based ART from ART center of our institution during the study period. The sample size included 202 patients, both males and females, of age above 13 years and they were followed up for 6 months. HIV patients with baseline deranged RFT values & HIV patients taking other nephrotoxic drugs were excluded from the study. Data sharing privacy policy of NACO was met. The study group was subjected to detailed interview regarding their age, sex, addictions, dietary habits, any co morbidities like hypertension, diabetes mellitus, chronic liver or kidney disease, history of any opportunistic infections and any nephrotoxic drug intake. These patients were examined in detail.

Routine blood and urine tests were sent prior to commencement of treatment. Laboratory investigations like renal function test, random blood sugar, serum calcium, serum phosphorus, serum uric acid and urine routine examination were done on each visit *ie*. on monthly basis for up to six months.

If there was any sign or derangement in the laboratory investigations, suggestive of renal dysfunction, they were further evaluated with tests like urine albumin-creatinine ratio, creatinine clearance by Cockcroft – Gault formula and ultra sonogram of kidney –ureter-bladder. Change in dose of Tenofovir or changes in ART regimen were made according to the NACO guidelines. Predictors of nephrotoxicity studied included, Gender, Age, Stage of HIV infection, CD4 count, Body mass index, Comorbidities (diabetes, hypertension, opportunistic infections), Concomitant nephrotoxic medications, & Serum creatinine level before starting treatment

Lab results taken as evidence of renal dysfunction included S. Creatinine 1.5 times the basal value/ increase in serum creatinine value more than or equal to 0.3mg/dl than the basal value, hypophosphatemia – less than normal range with age, hypouricemia - less than normal range with age, proteinuria**,** glycosuria (nondiabetic), hypokalemia & hypocalcaemia.

RESULTS

Out of 202 patients screened, there were 94 males and 108 females. Out of 94 males, 17 men developed nephrotoxicity. 11 out of 108 females developed nephrotoxicity of Tenofovir. On analysis, p value is 0.105 – not significant.

Age distributions of cases - Cases were divided into 4 age groups 13-30, 31-45, 46-60 and above 60 years. No nephrotoxicity was found in the age group 13-30 years in which there were a total of 17 cases. In age group 31-45years, there were 95 cases, out of which 14 cases developed nephrotoxicity. In age group 46-60 years, there were 81 cases and 13 cases among them developed nephrotoxicity. There were 9 cases above 60 years and one among them developed nephrotoxicity. The mean age group developed nephrotoxicity is 46 years with a standard deviation of 8.59. On analysis p value is 0.365 and is not significant. No stage 1 disease was there in our study. Out of 157 cases of stage 2 disease 16 cases (10.2%) developed nephrotoxicity. 4 cases (26.7%) out of 15 stage 3 disease and 8 cases (26.7%) out of 30 stage 4 disease developed nephrotoxicity. The p value was 0.019. Stage of HIV had statistically significant correlation with development of nephrotoxicity.

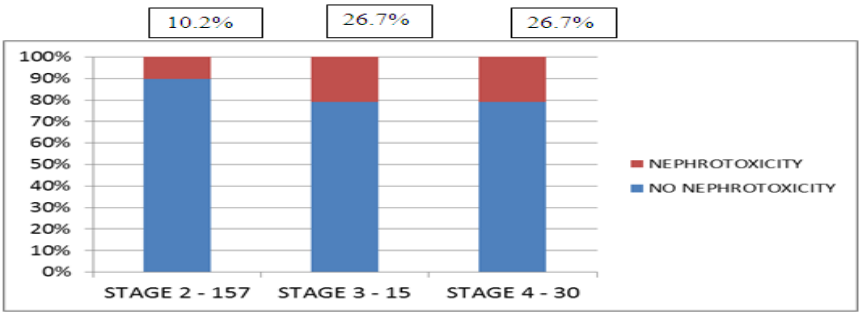

Figure 1: Stage of HIV and incidence of nephrotoxicity.

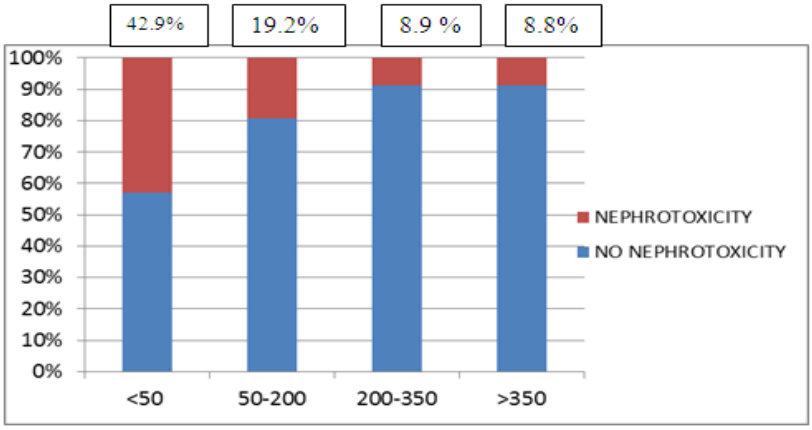

Figure 2: CD4 count and incidence of nephrotoxicity.

DISCUSSION

In this study, 202 cases were included consisting 94 males and 108 females. Male predominance was usually seen in our ART centre, but during this study period female predominance was seen. During this study period NACO guidelines recommended initiation of HAART to all HIV infected persons irrespective of the CD4 count and clinical stage.[1] Previously target CD4 count was less than 350 to initiate ART. Hence there were more females who were having CD4 count above 350 and not started on ART. This was reflected in this study as female predominance. 28 cases among them developed Tenofovir induced nephro toxicity. Incidence of nephrotoxicity in this study was 13.9%. The average time to develop Tenofovir induced nephrotoxicity was 118 days with a standard deviation of 58 days. Type of injury observed was acute kidney injury. 26 cases among them developed deranged renal function tests. 8 cases among these 26 cases were detected to have proteinuria also. 2 cases developed proteinuria without derangement in renal function test. Hypophosphatemia, hypouricemia, hypokalemia, hypocalcaemia, or nondiabetic proteinuria were not observed in any of the cases in this study. Almost all were asymptomatic. 26 cases had only mild renal dysfunction so that they continued on same ART regimen, since they did not meet the criteria to change ART regimen by NACO. Also they did not meet the criteria to decrease the dose of Tenofovir. 2 cases developed severe renal dysfunction and Tenofovir based ART regimen was stopped for both. One of them expired due to sepsis. The ART regimen was changed in the other case and her RFT came to normal in weeks and was continued on the other ART regimen (Stavudine instead of Tenofovir). The mean age group developed nephrotoxicity was 46 years with a standard deviation of 8.59. Creatinine clearance decreased in all these cases, during renal dysfunction. The average decline in creatinine clearance from baseline was 21.4 ml/min during renal dysfunction. CD4 count improved in all cases after 6 months of ART except the one who expired whose CD4 count was not rechecked.

Gender was not found to be a significant risk factor in this study. Out of 94 males, 17 men developed nephrotoxicity. 11 out of 108 females developed nephrotoxicity of Tenofovir. 18.1% of males and 10.2% percentage of females developed nephrotoxicity. Even though males were more affected, p value is 0.105 and it was not statistically significant. In a similar study conducted by Stefan Mauss et al[7], gender was not a significant risk factor for Tenofovir induced nephrotoxicity.

Age was not found to be a significant risk factor in this study. Our ART centre is offering treatment to both paediatric and adult population. Follow up of paediatric group is done in paediatric wing of institution and were not taken into this study. 5347 cases were registered in our ART centre till this study was finished. Cases were divided into 4 age groups 13-30, 31-45, 46-60 and above 60 years. A significant observation found in our study was, no nephrotoxicity was found in the age group 13-30 years where there were a total number of 17 cases. In age group 31- 45years, there were 95 cases, out of which 14 cases developed nephrotoxicity. In age group 46-60 years, there were 81 cases and 13 cases among them developed nephrotoxicity. There were 9 cases above 60 years and one among them developed nephrotoxicity. The mean age group developed nephrotoxicity is 46 years with a standard deviation of 8.59. Even though age was not a significant risk factor according to this study, some of the observations points that the possibility of age as a risk factor cannot be ruled out.In similar studies conducted by Rodriguez-Nvoaet al[8], age was not found to be a risk factor in Tenofovir induced nephrotoxicity. Stage of HIV was found to be a significant risk factor in this study. No stage 1 disease was there in our study. Out of 157 cases of stage 2 disease 16 cases (10.2%) developed nephrotoxicity. 4 cases (26.7%) out of 15 stage 3 disease and 8 cases (26.7%) out of 30 stage 4 disease developed nephrotoxicity. According to our study higher the stage of the HIV, more the chance to develop Tenofovir induced nephrotoxicity. In a similar study by Ketan K Patel et al,[9] revealed that Tenofovir

induced nephrotoxicity was higher in advanced stages of HIV.

This study revealed that CD4 count was a significant risk factor for Tenofovir induced nephrotoxicity. It was seen that lower the CD4 count, higher the chance for development of nephrotoxicity.In a similar study conducted by Nelson M R et al,[10] CD4 count was found to be a significant risk factor for tenofovir induced nephrotoxicity. Body mass index was not found to be a significant risk factor. Different studies are showing different observations; study conducted by Ketan K Patel et al,[9] revealed that body mass index was not a significant risk factor for development of Tenofovir induced nephrotoxicity. But Takeshi Nishijima et al[11]revealed low body weight was a significant risk factor for development of nephrotoxicity. Hypertension and diabetes mellituswere not significant risk factors.

In this study there were 38 cases of serious opportunistic infections. Tuberculosis and it's treatment was not a significant risk factor. There were different types of serious opportunistic infections, hence total number in each were low, significance of association of each disease with development of Tenofovir induced nephrotoxicity was doubtful since the number involved was low.Concomitant use of Tenofovir with protease inhibitors is an established risk factor for development of nephrotoxicity. There were only 3 cases using this regimen.One among them developed nephrotoxicity. Even though it was not statistically significant in this study, the possibility of it being a risk factor cannot be ruled out as the sample size in this study was small.

CONCLUSION

Nephrotoxicity of tenofovir was established in this study & the incidence was 13.9%.

Average time to develop nephrotoxicity was 118 days with a standard deviation of 58 days.

Average decline in creatinine clearance during renal dysfunction was 21.4 ml/min & almost all cases were asymptomatic. Nephrotoxicity was detected in the form of mild derangement of RFT and proteinuria on regular follow up. Gender, age, BMI, Hypertension, diabetes mellitus, serious opportunistic infection, etc had no significant association with renal dysfunction. Advanced clinical stage and low CD4 count had significant association with nephrotoxicity. Single most important predictor of tenofovir induced nephrotoxicity was CD4 count.

Small sample size, short period of follow up and a smaller number of cases in the subgroups of co-morbidities were the major limitations. As Tenofovir is nephrotoxic, all patients under tenofovir based regimen should be under regular and systematic follow up for early detection of any evidence of nephrotoxicity. The renal function status should be estimated before starting tenofovir based therapy and should be monitored regularly. Beta 2 microglobulinuria, which is more specific for proximal tubular injury can be used as a better marker for early detection of tenofovir induced nephrotoxicity. Also, Tenofovir alafenamide fumarate, a new tenofovir formulation which has less nephrotoxicity can be used instead of TDF.

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