

TO STUDY ESTIMATION OF THE CREATININE CLEARANCE AND EGFR IN HIV POSITIVE PATIENTS AND ITS CORRELATION WITH DIFFERENT ART REGIMEN AND CD4 COUNT AT TERTIARY CARE HOSPITAL IN MUMBAI, INDIA***Dr. Sushma S. Gaikwad, Dr. Dileep Asgoankar and Dr. Astha Ganeriwal**

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ABSTRACT

Introduction: Chronic kidney disease (CKD) appears to be a common complication of HIV infection in the modern era of ART. The prevalence of CKD ranges from 3.5% to 32.6%, depending on the characteristics of the study population and the criteria used to define CKD. Hence study was conducted to estimate the creatinine clearance and eGFR in HIV positive patients and its correlation with ART regimen and CD4 count. **Methods:** This prospective cross-sectional observational study was carried out in the BYL Nair Hospital, Mumbai during the period of July 2013 to December 2014 for a period of 18 months. Total 150 adult patients (age >18 years) were enrolled. Their demographic profile, clinical data along with routine blood and urine investigations, CD4 count and treatment including ART regimen namely TDF (Tenofovir based) and AZT (Zidovudine based) were recorded. Findings were tabulated and compared and result were analysed using SPSS 17. **Results:** In our study, out of the total 150 patients, 92(65.33%) were males and 58(34.6%) females with a mean age of 34.6 years. Total 79 (52.6%) patients were on TDF based ART regimen, 60 (39.47%) were on AZT based ART regimen and 11(7.3%) were not on ART. The mean creatinine clearance was 46.33 ml/min in patients with CD4 count < 200, it was 65.94 ml/min in patients with CD4 200-350 and 81.41ml/min in patients with CD4>350, which was statistically significant ($p<0.05$). Also the mean values of eGFR in patients with CD4 < 200 was 61.75 ml/min/1.73 m², in those with CD4 200 - 350 was 83.56 ml/min/1.73 m² and 103.47 ml/min/1.73 m² in those with CD4> 350. And this is statistically significant ($p<0.05$) There is an inverse correlation of CD4 cell count and eGFR and creatinine clearance. The mean creatinine clearance in the TDF group was 61.59 and in the other group it was 83.75 which was statistically significant ($p<0.05$); the mean eGFR in TDF group was 78.47 and in the other group it was 103.46 which was statistically significant ($p<0.05$). There was a significant association between low eGFR and creatinine clearance and TDF based ART regimen. **Conclusion:** Decline in eGFR values and creatinine clearance is more common in patients treated with TDF based ART regimen and with advanced stages of HIV infection.

KEYWORDS: Chronic kidney disease (CKD), HIV, eGFR.**INTRODUCTION**

HIV infection per se and pharmacologic agents used in HIV treatment and prophylaxis and treatment of opportunistic infections have been increasingly recognized to contribute to HIV associated renal diseases.

Tenofovir disoproxil fumarate (TDF) is widely used in countries around the world as a first line antiretroviral therapy regimen in the treatment of HIV according to the recent World Health Organisation guidelines.^[1,2] TDF is the most effective drug available in the armamentarium against the deadly virus. Apart from being used in treatment of HIV, TDF is also being approved as the backbone of pre exposure and post exposure prophylaxis regimens.^[3]

Renal tubular toxicity was demonstrated in vitro and in animal models when high doses of TDF were administered. Furthermore, several cases of kidney dysfunction and/or acute kidney injury have been reported in TDF recipients.^[4]

The U.S. and European observational cohort studies, retrospective reviews, and a meta-analysis by Hall and colleagues have reported kidney dysfunction associated with TDF use, have concluded that the reduction in estimated glomerular filtration rate (eGFR using Cockcroft-Gault (CG) and the Modification of Diet in Renal Disease (MDRD) equations, is mild and of questionable clinical significance.^[4] These reports are contradicted by a Veterans Health Administration observational study of over 10,000 patients which reported that TDF use was associated with higher risk for

chronic kidney disease (CKD) and rapid decline in kidney function when compared to other drug regimens.^[4]

Only handful of data in this regard is available in our clinical setting, India being home to the third largest population of people living with HIV. Thus our study aims to identify the prevalence of renal damage in the form of GFR and creatinine clearance in HIV infected patients and its correlation with different ART regimen and CD4 T cell count.

OBJECTIVE

1. To estimate the creatinine clearance and eGFR in HIV positive patients.
2. To study the correlation of the creatinine clearance and eGFR with ART regimen and CD4 count.

MATERIAL AND METHODS

This was a prospective cross-sectional observational study conducted at a tertiary care hospital in which 150 patients that met the inclusion criteria for the said study and were willing to consent for the study were enrolled from the indoor and out patient departments. The study started after the approval of Institutional Ethics committee (E CARP). Data collection was done for 1 year and the study period was 18 months.

The inclusion and exclusion criteria for the study were.

Inclusion Criteria

1. Age: 18- 70years.
2. Patients detected positive by three Rapid method as per NACO guidelines.
3. Patients willing to participate in the study.

Exclusion Criteria

1. Patients with other comorbid conditions like hypertension, diabetes.

2. Patients having pre existing renal disorder.
3. Pregnant females.
4. Patients on nephrotoxic drugs like aminoglycosides, amphoterecin, etc.
5. Patients who have an acute opportunistic infection.

Detailed clinical history and clinical examination was done in each patient. Investigations like Hb, CBC, LFT, RFT, ESR, urine routine microscopy, urine culture, RBS, 24 hour urine protein estimates, CD4 T cell count was done on each patient.

Urine albumin (spot and 24 hour urine protein), was calculated for each patient. In patients with evidence of CKD, imaging of the kidneys via ultrasound or Xray was done.

Patients were divided in two groups based on ART regimen. Patients who were on TLN/TLE were taken as TDF based group and those on ZLN/ZLE were taken as Zidovudine (AZT) based group for statistical analysis.

The severity of CKD was graded according to renal function, on the basis of estimates of either the creatinine clearance (calculated using the Cockcroft-Gault equation) or the GFR (calculated using the modification of diet in renal disease [MDRD] equation)

Cockcroft-Gault

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] * \text{weight (kg)} * [0.85 \text{ if female}]}{72 * \text{serum creatinine (mg/dL)}}$$

Simplified MDRD

$$\begin{aligned} \text{GFR (mL/min/1.73m}^2\text{)} &= 186 \\ & * [\text{serum creatinine (mg/dL)}]^{-1.154} \\ & * [\text{age (years)}]^{-0.203} \\ & * [0.742 \text{ if female}] * [1.212 \text{ if black}] \end{aligned}$$

As per the calculated eGFR the patients were divided into various stages of CKD as follows^[5]

Stage		GFR mL/min per 1.73m ²
I	Kidney damage with normal or increased GFR	≥ 90
II	Kidney damage with mildly decreased GFR	60–89
III	Moderately decreased GFR	30–59
IV	Severely decreased GFR	15–29
V	ESRD	<15

Routine standard of care was provided to all the patients in the hospital. Clinical examination, investigation findings were tabulated and compared and result were analysed using SPSS). P-value of < 0.05 was considered as significant.

RESULTS

In this study 150 patients, 98 (65.33%) were males and 52 (34.61%) were females either admitted or visiting the

Out Patient Department in the Tertiary care hospital were included.

In our study, majority of the patients, 79(52.67%) were in the age group of 31-40 years, followed by 41 (27.33%) that were in the age group 41-50 years and minimum 1 (0.66%) were less than 20 years of age.

Table 1: Distribution of patients according to ART Regimen.

Regimen	Number	Percentage
TDF based	79	52.6%
AZT based	60	40%
Not on ART	11	7.34%
Total	150	100%

In our study, out of the total 150 patients 79(52.6%) were on TDF based ART regimen, 60 (39.47%) were on zidovudine (AZT) based ART regimen and 11(7.3%) were not on ART.

Out of the 79 patients on TDF based regimen 17 (21.5%) were on TLE and 62 (77.5%) were on TLN, and out of the 60 patients on AZT based regimen 8 (13.3%) were on ZLE and the remaining 52 were on ZLN. As the number of patients who were on efavirenz in both the groups was small, we included them and those on nevirapine in a broad group and divided the patients only in two groups on the basis of TDF and AZT. Mechanism of action of both nevirapine and efavirenz being the same they were not considered separate groups.

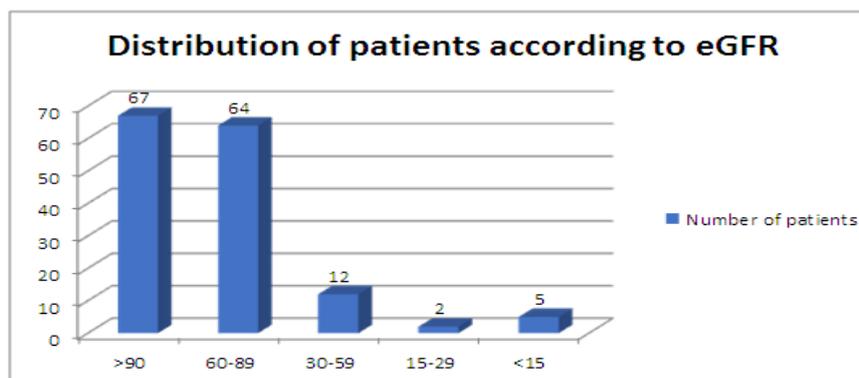
Table 2: Distribution of age according the ART regimen.

Variables	Group	N	Mean
Age	AZT based	60	39.37
	TDF based	79	38.95

In our study, the mean age in the patients of TDF based ART regimen group (TLN/TLE) was 38.95 and that in the other group was 39.37

Table 6: Distribution of patients according to stage of CKD and eGFR.

eGFR (ml/min/1.73m ²)	Stage of CKD	Number of patients	Percentage (%)
>90	I	67	44.66
60-89	II	64	42.66
30-59	III	12	8
15-29	IV	2	1.33
<15	V	5	3.33

**Figure 1: Distribution of patients according to eGFR****Table 3: Distribution of gender according to ART regimen.**

Sex	Group		Total
	AZT based	TDF based	
Female	19	26	45
	31.7%	33.3%	32.6%
Male	41	53	94
	68.3%	66.7%	67.4%
Total	60	79	139
	100.0%	100.0%	100.0%

As shown in the above table 53(66.7%) of the total 79 of TDF group were males and 26 (33.3%) were females, and out of the 60 patients in the AZT based ART regimen group 41(68.3%) were males and 19 (31.7%) were females.

Table 4: Distribution of BMI according to ART regimen.

In our study the mean BMI in males in TDF group was 20.6 kg/m² and that in AZT group was 19.20 kg/m², in females it was 19.7 kg/m² in TDF group and 18.73 kg/m² in AZT group.

Table 5: Distribution of patients according to CD4 T-cell count.

CD4 Count	Number of patients	%
< 200	32	21.36
200-350	35	23.33
> 350	83	55.33
TOTAL	150	100

Out of the total 150 patients enrolled in our study, 32 (21.36%) patients had CD4 < 200, 35(23.33%) had CD4 200-350, and 83(54.33%) had CD4 > 350

In our study out of 150 patients, the number of patients with eGFR values ≥ 90 ml/min/1.73m² as per the MDRD equation was 67 (44.66%), 64(42.66%) patients had eGFR in the range of 60-89ml/min/1.73 m², values between 30-59 ml/min/1.73m² was observed in 12 (8%) patients, 2 (1.33%) patients had value between 15- 29

ml/min/1.73m² and 5 (3.33%) patients had value less than 15 ml/min/1.73 m². Thus majority of the patients were in CKD stage I and II (131 out of 150 i.e 87.33%). 19 (12.66%) patients were found to have CKD stage III – V.

Table 7: Distribution of HIV duration, CD4 count and duration of ART regimen on the basis of ART regimen.

Variables	Group	N	Mean	SD	p-value
HIV Duration (months)	AZT	60	48.06	29.47	0.88
	TDF	79	47.24	33.53	
CD4 Count	AZT	60	428.87	237.92	0.772
	TDF	79	416.14	270.05	
Duration of ART (months)	AZT	60	31.24	17.06	< 0.05
	TDF	79	9.47	5.14	

In our study, the mean duration of HIV infection in TDF group was 47.24 months and that in the other group was 48.06; the mean CD4 in the TDF group was 416.14 and that in the other group was 428.87; the mean duration of

ART in TDF group was 9.47 months and that in the other group was 31.24 months, this was statistically significant ($p < 0.05$).

Table 8: Distribution of mean values of serum electrolytes on the basis of ART regimen.

S. Electrolytes	Group	N	Mean	SD	p-value
Serum calcium	AZT	60	8.92	0.40	0.464
	TDF	79	9.74	8.71	
Serum phosphorus	AZT	60	3.17	0.40	< 0.05
	TDF	79	2.44	0.60	
Serum sodium	AZT	60	139.82	4.05	0.292
	TDF	79	139.05	4.41	
Serum potassium	AZT	60	4.11	0.23	0.059
	TDF	79	3.98	0.48	

The mean serum calcium in the TDF group was 9.74 and that in the other group was 8.92 (p 0.464); the mean serum sodium in TDF group was 139.05 and that in the other group was 139.82 (p 0.292); the mean serum

potassium in TDF group was 3.98 and that in the other group was 4.11 (p 0.059); the mean serum phosphorus in the TDF group was 2.44 and in the other group was 3.17 which was statistically significant ($p < 0.05$).

Table 9: Distribution of renal parameters according to ART regimen.

Variables	Group	N	Mean	SD	p-value
Bun	AZT	60	10.87	2.84	< 0.05
	TDF	79	17.61	18.39	
Serum creatinine	AZT	60	0.86	0.19	< 0.05
	TDF	79	1.46	1.47	
Total protein	AZT	58	6.09	0.28	< 0.05
	TDF	79	5.97	0.25	
Serum albumin	AZT	58	3.15	0.21	< 0.05
	TDF	79	3.00	0.28	
Creatinine clearance	AZT	60	83.75	23.77	< 0.05
	TDF	79	61.59	27.09	
EGFR	AZT	60	103.46	23.11	< 0.05
	TDF	79	78.47	34.94	

In our study, the mean BUN in the TDF group was 17.61 and in the other group was 10.87 (statistically significant $p < 0.05$); the mean serum creatinine in TDF group was 1.46 and in the other group was 0.86 ($p < 0.05$); the mean serum albumin in TDF group was 3 and in the

other group was 3.15 ($p < 0.05$); the mean creatinine clearance in the TDF group was 61.59 and in the other group it was 83.75 ($p < 0.05$); the mean eGFR in TDF group was 78.47 and in the other group it was 103.46 ($p < 0.05$). There was a significant association between

abnormal renal parameters and TDF based ART regimen.

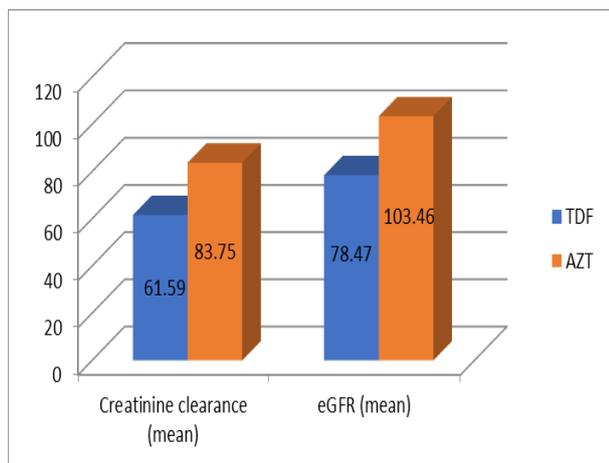


Figure 2: Creatinine clearance and eGFR according to ART regimen.

As shown in the above figure the mean creatinine clearance in the TDF group was 61.59 and in the other group it was 83.75 which was statistically significant ($p < 0.05$); the mean eGFR in TDF group was 78.47 and in the other group it was 103.46 which was statistically significant ($p < 0.05$). There was a significant association between low eGFR and creatinine clearance and TDF based ART regimen.

Table 10: Distribution of creatinine clearance and eGFR according to CD4 T-cell count.

Variables	CD4 T-cell Count	N	Mean	Std. Deviation	Std. Error	p-value (ANOVA)
Creatinine Clearance	< 200	32	46.33	24.87	4.20	< 0.05
	200-350	35	65.94	29.99	5.07	
	> 350	83	81.41	22.78	2.49	
eGFR	< 200	32	61.75	32.83	5.55	< 0.05
	200-350	35	83.56	30.58	5.17	
	> 350	83	103.47	30.46	3.32	

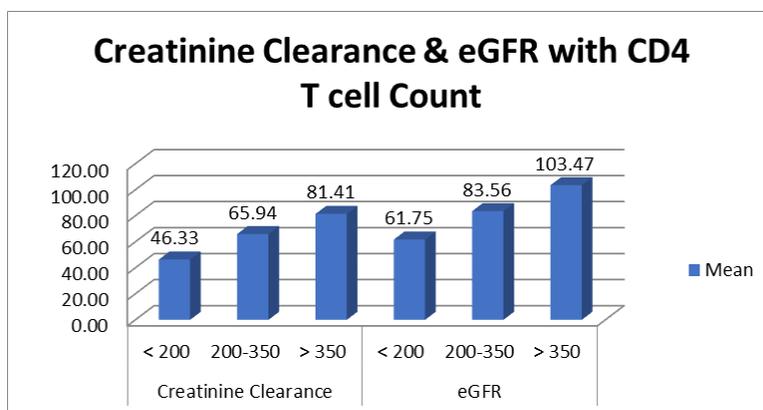


Figure 3: Distribution of Creatinine clearance and eGFR as per CD4 T-cell count.

In our study, it was observed that the mean creatinine clearance was 46.33 ml/min in patients with CD4 count < 200, it was 65.94 ml/min in patients with CD4 200-350 and 81.41ml/min in patients with CD4>350. And this is statistically significant ($p < 0.05$).

Also the mean values of eGFR in patients with CD4 < 200 was 61.75 ml/min/1.73 m², in those with CD4 200 - 350 was 83.56 ml/min/1.73 m² and 103.47 ml/min/1.73 m² in those with CD4> 350. And this is statistically significant ($p < 0.05$).

There is an inverse correlation of CD4 cell count and eGFR and creatinine clearance.

Distribution of cases according to urinalysis and USG findings

9 patients had UTI on urine analysis and the majority of them were asymptomatic and the most common organism on culture was E.coli seen in 7 patients and no organism was cultured in 2 patients.3 patients had hematuria on urine analysis but dysmorphic RBCs were not seen.

Only 2 patients had abnormal kidney size and the majority 150 had normal sized kidneys with intact corticomedullary dissociation. 1 had large kidneys, 1 had normal sized kidney with bright echotexture.

DISCUSSION

HIV-associated renal involvement was first described in 1984 and since then several forms of HIV-associated nephropathy have been described resulting from the direct effects of virus infection on the kidneys or indirect effects of intercurrent illness or medications. In the 80's, the clinical spectrum of HIV-associated renal disease was described as nephrotic and nephritic syndrome, acute kidney injury (AKI), chronic kidney disease (CKD), and non-nephrotic proteinuria (14). The classical HIV-associated nephropathy (HIVAN) is known to occur more frequently among HIV-infected individuals of African descent, and its clinical manifestations include nephrotic proteinuria, hematuria, rapidly progressive renal failure, and hypertension. HIVAN is characterized histologically by a collapsing focal segmental glomerulosclerosis (FSGS). Other HIV-associated conditions, including bacterial or viral infections and nephrotoxicity of antiretroviral therapy (ART), induce specific kidney damage such as acute tubular necrosis (ATN) and acute interstitial nephritis (AIN) (8,10). Lastly, kidney injury caused by amyloidosis, diabetes mellitus, and hypertension are also part of the spectrum of HIV-associated renal diseases because they are comorbidities that nowadays develop owing to the increased survival of these patients. For example, CKD is currently considered an independent risk factor for mortality in HIV patients.^[7]

Age, sex distribution, mode of HIV transmission and symptoms

The age of the patients studied ranged between 19 and 59 years with a mean age of 38.95 ± 8.30 years. Majority of the patients, 79 (52.67%) were in the age group was 31-40 years. In our study, 98 (65.33%) were males and 52 (34.61%) were females out of 150 patients that were included. Most common (100%) mode of HIV transmission was heterosexual mode in the study population. Renal involvement in HIV infected patients was largely asymptomatic, 94.15% patients were asymptomatic.

Distribution of patients according to CD4 count and ART regimen and duration of ART

In our study, out of the total 150 patients 79 (52.6%) were on TDF based ART regimen, 60 (39.47%) were on zidovudine (AZT) based ART regimen and 11(7.3%) were not on ART.

Out of the 79 patients on TDF based regimen 17(21.5%) were on TLE and 62 (77.5%) were on TLN, and out of the 60 patients on AZT based regimen 8 (13.3%) were on ZLE and the remaining 52 were on ZLN. As the number of patients who were on efavirenz in both the groups was small, we included them and those on nevirapine in a

broad group and divided the patients only in two groups on the basis of TDF and AZT. Nevirapine and efavirenz belong to the same class of antiretroviral drugs and have very little or no renal abnormalities, whereas TDF has an adverse renal profile.^[5,7]

The mean duration of ART in TDF group was 9.47 months and that in the other group was 31.24 months. This is because according to previous NACO guidelines, Zidovudine based ART regimen was the first choice for patients diagnosed as HIV with indications of starting ART and TDF is now the first line agent in all treatment naïve patients.^[2,8] In our study 52.6 % patients were on TDF based ART regimen, the reason being zidovudine induced anemia and pancytopenia in this group. The mean hemoglobin in patients who were shifted to TDF based regimen was 9.25 ± 1.14 .

Out of the total 150 patients enrolled in our study, 32 (21.36%) patients had $CD4 < 200$, 35(23.33%) had $CD4 200-350$, and 83(54.33%) had $CD4 > 350$. This is because we have recruited patients attending HIV clinic for monthly follow up and these patients are usually asymptomatic and on regular treatment and follow up so there are more number of patients with $CD4$ count > 350 .

Distribution of patients according to stage of CKD as per the calculated eGFR

For CKD staging purposes, the simplified MDRD equation is in general, preferred. Because studies of medications in renal failure have traditionally used the Cockcroft-Gault equation, it would be appropriate to use this estimating formula in deciding on dosage.^[6]

In our study out of 150 patients, the number of patients with eGFR values ≥ 90 ml/min/1.73m² as per the MDRD equation was 67 (44.66%), 64(42.66%) patients had eGFR in the range of 60-89ml/min/1.73 m², values between 30-59 ml/min/1.73m² was observed in 12 (8%) patients, 2 (1.33%) patients had value between 15- 29 ml/min/1.73m² and 5 (3.33%) patients had value less than 15 ml/min/1.73 m². Thus majority of the patients were in CKD stage I and II (131 out of 150, 87. 33%). 19 (12.66%) patients were found to have CKD stage III - V. This is in concordance with other studies done by Jacobson LP et al where they concluded that the relative risk of kidney disease in 542 HIV infected men with abnormal proteinuria with CKD stage III - V was 5.1 compared to 661 HIV negative men,^[9] and Longenecker CT et al who compared 335 HIV infected people with 230 control and the estimated relative risk of stage III - V in this study was 6.5.^[10] and other studies that were reviewed by Islam et al.,^[11] in a meta-analysis done in 2012.

The reason for this is tenofovir acts on the proximal tubular epithelium in the kidney and causes mitochondrial damage to the tubules leading to nephrotoxicity.^[12,13]

The reason for this could be that CD4 count is considered as a surrogate marker for HIV viral load and activity.^[14] HIV viral antigens are present in the renal tissue leading to glomerular and tubular damage this has been postulated as the mechanism for development of various glomerular diseases.^[15] Moreover, persistently low CD4 count form a surrogate marker for increased viral load and disease activity which is an important predictor of onset of renal disease.^[16]

Distribution of patients creatinine clearance and eGFR according to CD4 count

In our study, it was observed that the mean creatinine clearance was 46.33 ml/min in patients with CD4 count < 200, it was 65.94 ml/min in patients with CD4 200-350 and 81.41ml/min in patients with CD4>350. And this is statistically significant ($p<0.05$). Also the mean values of eGFR in patients with CD4 < 200 was 61.75 ml/min/1.73 m², in those with CD4 200 - 350 was 83.56 ml/min/1.73 m² and 103.47 ml/min/1.73 m² in those with CD4> 350. ($p<0.05$).

Thus we concluded that the risk of having CKD increases with decline in the CD4 count as documented by eGFR calculation and creatinine clearance. These findings are in concordance with a meta analysis done by Islam et al in 2012 where they analysed 9 studies and concluded that CD4 count has a negative correlation with eGFR^[11], Wools-Kaloustian et al., 2007 it was observed that 25% of the remaining patients had creatinine clearance (Cr Cl) < 90ml/min (normal 90ml/min), 2% had Cr Cl <60ml/min and 8% had proteinuria of >1gram/day. Although not statistically significant, there was a trend to more severe renal insufficiency and heavier proteinuria in those with a CD4 count <200 cells/mm³,^[3,17] Similar such results were observed in various other such studies.^[4,18-22]

The reason for this could be that patients with lower CD4 counts have an increased disease activity and increased renal damage as the HIV viral antigens are involved in the pathogenesis of glomerular and tubular damage.^[15]

Distribution of patients with creatinine clearance and eGFR according to ART regimen

In our study, the mean creatinine clearance in the TDF group was 61.59 and in the other group it was 83.75 which was statistically significant ($p<0.05$); the mean eGFR in TDF group was 78.47 and in the other group it was 103.46 which was statistically significant ($p<0.05$). Thus the risk of CKD is higher in the patients on TDF based regimen as suggested by lower GFR values in this subset of patients. This was in concordance with other studies done by Shubhankar et al who observed that the mean estimated creatinine clearance among patients on TDF declined from 84.1 (SD 21.0) to 62.1 (SD 26.3) mL/min/1.73 m² i.e. 26.8% decline from the baseline (p -value 0.05, 95% CI -64.4 --25.3).^[23] Similar observations were made by studies done by Islam et al,^[11] Scarpino M et al,^[24] John W Stanifer et al.^[14]

This is because approximately 20 – 30% of the TDF is excreted unchanged in the urine via active secretion by the proximal tubular cells. The free drug is actively taken up by the Organic Anion Transporter (OAT-1) receptor located at the basolateral surface of the tubular cells and concentrated in the cytosol. TDF is excreted into the tubular lumen via the multi-drug resistant proteins (MRP-2 & 4) located at the luminal surface. Although the exact mechanism of TDF induced nephrotoxicity remains unclear, it is proposed that TDF inhibits mitochondrial DNA γ -polymerase and thereby exerts its mitochondrial toxicity and leads to caspase mediated proximal tubular cell injury. The long term consequence of the damage to the proximal tubular cells leads to variety of nephrotoxic features, which includes Fanconi syndrome, chronic renal failure, acute on chronic renal failure etc.^[24]

CONCLUSIONS

Decline in eGFR values and creatinine clearance with advanced stages of HIV infection as indicated by low CD4+ T cell count. Decline in eGFR values and creatinine clearance is more common in patients treated with TDF based ART regimen. All patients at the time of HIV diagnosis should be assessed for existing kidney disease with a screening urine analysis for proteinuria and a calculated estimate of renal function.

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