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# A STUDY OF RENAL ABNORMALITIES IN HIV INFECTED PATIENTS AND ITS CORRELATION WITH CD4 COUNT AND ART REGIMEN

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**Abstract**

**Background:** Renal disease is a recognized complication of HIV infection, with chronic kidney disease (CKD) prevalence reported between 3.5% and 32.6%. Tenofovir disoproxil fumarate (TDF) has been associated with nephrotoxicity, and lower CD4 counts are linked to higher risk of renal impairment. Early identification of renal dysfunction in HIV-positive individuals is critical for timely intervention.

**Objectives:** To determine the prevalence of renal damage in the form of proteinuria and reduced creatinine clearance/eGFR in HIV-infected patients, and to assess its correlation with antiretroviral therapy (ART) regimen and CD4 T-cell count.

**Methods:** This cross-sectional observational study included 300 HIV-positive patients (aged 18–70 years) attending a tertiary care hospital. Data collected included demographics, ART regimen, CD4 count, urine analysis, 24-hour urine protein, and renal function tests. Creatinine clearance (Cockcroft–Gault) and eGFR (MDRD) were calculated. Patients were categorized based on ART regimen (TDFbased vs. zidovudine [AZT]-based) and CD4 count (<200, 200–350, >350 cells/µl).

**Results:** Of 300 patients, 196 (65.33%) were male; mean age was ~39 years. TDF-based regimen was used in 158 (52.6%) patients, AZT-based in 120 (40%), and 22 (7.3%) were not on ART. Proteinuria was present in 24% of patients, significantly higher in the TDF group (88.9%) than AZT group (13.8%) ($p<0.05$).

**Conclusion:** Proteinuria and reduced renal function are common among HIV-infected patients, particularly in those on TDF-based regimens and with CD4 counts <200 cells/µl. Regular renal function monitoring is recommended at diagnosis and quarterly for patients on TDF or with advanced HIV disease.

**Keywords**: HIV, Tenofovir, Chronic kidney disease, Proteinuria, CD4 count, eGFR, Creatinine clearance

## INTRODUCTION

In 2007, India's AIDS prevalence rate stood at approximately 0.30%—the 89th highest in the world. The main factors which have contributed to India's large HIV-infected population are extensive labour migration and low literacy levels in certain rural areas resulting in lack of awareness and gender disparity.[1] The total number of people living with HIV/AIDS (PLHIV) in India is estimated at around 20.9 lakh in 20114. India has demonstrated an overall reduction of 57% in estimated annual new HIV infections (among adult population) during the last decade from 2.74 lakh in 2000 to 1.16 lakh in 2011 4. Human immunodeficiency virus (HIV) is a lentivirus (a member of the retrovirus family) that causes acquired immunodeficiency syndrome (AIDS)[2], a condition in humans in which progressive failure of the immune system allows life-threatening opportunistic infections and cancers to thrive.[3,4] HIV affects all organs including the kidneys. Renal disease is now widely recognized as a frequent complication of HIV.[5] Glomerular disease with proteinuria and renal failure are complications of HIV infection. Renal disease related to ART and its complications, or comorbid conditions appear to be growing in importance as the natural history of HIV infection evolves and the life expectancy of HIVinfected individuals increases due to initiation of ART. With the increasing prevalence of people living with HIV infection, it is projected that the population with HIV-infection and End Stage Renal Disease (ESRD) will increase exponentially over the next decade.[6]

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.[7] Further the usage of certain drugs like tenofovir (TDF) as a first line drug in patients with seropositive status and anaemia increases the risk of renal damage hence the correlation with ART regimen becomes important.[8] Patients with lower CD4 T cell counts are at an increased susceptibility to develop renal damage.[9]

In recognition of the burden of renal disease among HIV-infected persons, the Infectious Diseases Society of America(IDSA) recommends screening for kidney disease using urinalysis and a calculated estimate of renal function upon diagnosis of HIV.[5] Thus our study aims to identify the prevalence of renal damage in the form of proteinuria and estimated creatinine clearance in HIV infected patients and its correlation with different ART regimen and CD4 T cell count.

## METHODOLOGY:

This was a cross-sectional observational study conducted at a tertiary care hospital in which 150 patients that met the inclusion criteria set 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). The study was done as per ICMR Schedule Y Guidelines for conduct of Human Research in India. Data collection was done for 2 year and the study period was 18 months.

300 patients aged 18- 70 years., detected positive by three Rapid method as per NACO guidelines were included

## EXCLUSION CRITERIA:

1.Patients with other comorbid conditions like hypertension, diabetes.
2.Patients having pre exisiting renal disorder.
3.Pregnant females.
4.Patients on nephrotoxic drugs like aminoglycosides, amphoterecin, etc.

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. Urine albumin (spot and 24 hour urine protein) , was calculated

for each patient. Those patients who had proteinuria of greater than or equal to 1+ on a first-morning macrourinalysis, or a 24 hour urine protein excretion > 30 mcg/mg were subjected to a repeat firstmorning macroscopic urinalysis, and 24 hour urine protein examination 1 month later to exclude physiological causes of proteinuria or proteinuria secondary to infection.
In patients with evidence of CKD, imaging of the kidneys via ultrasound or Xray was done to gain information on the presence of stones, extrarenal and intrarenal lesions, and kidney size. The ART regimen was noted down in each patient and the patients were divided in two groups based on ART regimen. Patients who were on TLN/TLE were taken as TDF based regimen and those on ZLN/ZLE were taken as Zidovudine (AZT) based regimen for statistical analysis. Nevirapine and Efavirenz have a similar mechanism of action and have no effects on renal functions. Hence the groups were divided based on TDF and AZT.
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:
GFR (ml/min/1.73m$^2$ )= 186 *[serum creatinine (mg/dL)]$^{-1.154}$
*[age (years)]$^{-0.203}$
*[0.742 if female] *[1.212 if black]

All the collected data was entered in Microsoft Excel sheet. It was then evaluated to SPSS v20 software for statistical analysis. All the Quantitative data was presented as mean and standard deviation and compared using student's t-test. Qualitative data was presented as frequency and percentage and analysed using chi-square test (Fisher's exact test was used in case of 2x2 contingency tables). P-value of < 0.05 was considered as significant.

**RESULTS**

300 patients either admitted or visiting the Out Patient Department in the Tertiary care hospital were studied. In our study we 196 (65.33%) were males and 104 (34.61%) were females out of 300 patients that were included. **M**ajority of the patients , 158 (52.67%) were in the age group was 31-40 years , followed by 82 (27.33%) that were in the age group 41-50 years and minimum 2 (0.66%) were less than 20 years of age.

**Mode of transmission:**

All the patients in our study were observed to have heterosexual mode of transmission of HIV infection, it also being the most common in general population. Of the total 300 patients 158 (52.6%) were on TDF based ART regimen, 120 (39.47%) were on zidovudine (AZT) based ART regimen and 22 (7.3%) were not on ART. Out of the 158 patients on TDF based regimen 34 (21.5%) were on TLE and 124 (77.5%) were on TLN, and out of the 120 patients on AZT based regimen 16 (13.3%) were on ZLE and the remaining 104 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.

Table 1 : Distribution of patients according to CD4 T-cell count

| CD4 Count | Number of patients | % |
|---|---|---|

| (cells/µl) | | |
|---|---|---|
| **< 200** | 64 | 21.36 |
| **200-350** | 70 | 23.33 |
| **> 350** | 166 | 55.33 |
| **TOTAL** | 300 | 100 |

Out of the total 300 patients enrolled in our study, 64 (21.36%) patients had CD4 < 200 cells/µl, 70 (23.33%) had CD4 200-350 cells/µl and 166 (54.33%) had CD4 > 350 cells/µl.

**Table 2 : Distribution of patients according to stage of CKD and eGFR**

| eGFR(ml/min/1.73m²) | Stage of CKD | Number of patients | Percentage (%) |
|---|---|---|---|
| **>90** | I | 144 | 44.66 |
| **60-89** | II | 128 | 42.66 |
| **30-59** | III | 24 | 8 |
| **15-29** | IV | 4 | 1.33 |
| **< 15** | V | 10 | 3.33 |

The number of patients with eGFR values > 90 ml/min/1.73m$^2$ as per the MDRD equation was 67 (44.66%), 64(42.66%) patients had eGFR in the range of 60-89ml/min/1.73 m $^2$. Majority of the patients were asymptomatic, only 14 patients had symptoms the most common symptom observed was vomiting seen in 8 patients, followed by fever seen in 8 patients. 106 (66.7%) of the total 158 of TDF group were males, and out of the 120 patients in the AZT based ART regimen group 82(68.3%) were males. However, there was no statistically significant difference. 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 years, but there was no difference.

**Table 3: 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** | AZT | 60 | 31.24 | 17.06 | **< 0.05** |

| | | | | | |
|---|---|---|---|---|---|
| **ART (months)** | 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 months; 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 ($p < 0.05$). TDF based ART regimen was introduced later in the guidelines.

**Table 4 : 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 eGFR** | AZT | 60 | 83.75 | 23.77 | **< 0.05** |
| | TDF | 79 | 61.59 | 27.09 | |
| | AZT | 60 | 103.46 | 23.11 | **< 0.05** |

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 mg% and in the other group was 0.86 mg% ( $p< 0.05$); the mean serum albumin in TDF group was 3 g/dl and in the other group was 3.15 g/dl ( $p< 0.05$); the mean creatinine clearance in the TDF group was 61.59 ml/min and in the other group it was 83.75 ml/min ( $p<0.05$) ; the mean eGFR in TDF group was 78.47 ml/min/1.73m$^2$ and in the other group it was 103.46 ml/min/1.73m$^2$ ($p<0.05$). There was a significant association between abnormal renal parameters and TDF based ART regimen. The mean creatinine clearance in the TDF group was 61.59 ml/min and in the other group it was 83.75 ml/min which was statistically significant ( $p<0.05$) ; the mean eGFR in TDF group was 78.47 ml/min/1.73m$^2$ and in the other group it was 103.46 ml/min/1.73m$^2$ which was statistically significant ($p<0.05$). There was a significant association between low creatinine clearance and eGFR and TDF based ART regimen.

In our study it was observed that 36 (24%) patients had proteinuria of which 31 (88.88 %) were on TDF based regimen and 5 (13.8%) were on AZT based ART regimen. This association was of statistical significance($p<0.05$).

**Table 5 : 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 | 64 | 46.33 | 24.87 | 4.20 | **< 0.05** |
| | 200-350 | 70 | 65.94 | 29.99 | 5.07 | |

| | | | | | | |
|---|---|---|---|---|---|---|
| **eGFR** | > 350 | 166 | 81.41 | 22.78 | 2.49 | **< 0.05** |
| | < 200 | 64 | 61.75 | 32.83 | 5.55 | |
| | 200-350 | 70 | 83.56 | 30.58 | 5.17 | |
| | > 350 | 166 | 103.47 | 30.46 | 3.32 | |

In our study, it was observed that the mean creatinine clearance was 46.33 ml/min in patients with CD4 count < 200 cells/µl, it was 65.94 ml/min in patients with CD4 200-350 cells/µl and 81.41ml/min in patients with CD4>350 cells/µl. And this is statistically significant ($p<0.05$) Also the mean values of eGFR in patients with CD4 < 200 cells/µl was 61.75 ml/min/1.73 $m^2$ , in those with CD4 200 - 350 cells/µl was 83.56 ml/min/1.73 $m^2$ and 103.47 ml/min/1.73 $m^2$ in those with CD4> 350 cells/µl. And this is statistically significant ($p<0.05$)

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

In our study, proteinuria quantification on a 24 hour urine collection has shown that, proteinuria increases as the value of CD4 count decreases and this was statistically significant ($p<0.05$). After a month, 72 patients had proteinuria quantified on a 24 hour urine sample. Out of these 72 patients, 30 had CD4< 200 cells/µl the mean proteinuria being 1.16 in this group; 24 had a CD4 200-350 cells/µl and the mean proteinuria was 0.82 in this group; 18 patients had a CD4 > 350 cells/µl and the mean proteinuria in this group was 0.52 . These values were of statistical significance ($p<0.05$).

In our study 17 (12.23%) patients had glucosuria out of which 30 (89.47%) were on TDF and 4 (10.52%) were AZT based regimen and this was found to be statistically significant ($p<0.05$).

## DISCUSSION

A broad spectrum of renal disease has been reported in patients with AIDS. 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 [10,11]. Many individuals with HIV disease develop at least transient alterations in renal function during the course of their infection. These can range from minor changes in fluid or electrolyte homeostasis to end-stage renal disease requiring dialysis. Screening for early stages of CKD, therefore, requires measurement of urinary albumin-to-creatinine or protein-to-creatinine ratios. These “spot” quantitative urine measurements of abnormal glomerular function are accurate, correlate with 24-hour urine measurements, and avoid the inconvenience and difficulty in collection of timed urine specimens in clinical practice . Patients with stage III and stage IV CKD have more severe reduction in GFR. These patients are at high risk for developing ESRD (stage V CKD) and death and should, therefore, be carefully evaluated to determine the etiology and severity of their disease.[12]

The benefits of screening for stage I–II CKD have been unequivocally demonstrated in diabetic kidney disease, in which identifying and treating patients with microalbuminuria (a urinary albuminto-creatinine ratio 30 mg/g), macroalbuminuria (an albumin-to-creatinine ratio of 300 mg/g), or overt proteinuria (a protein-to-creatinine ratio of 300 mg/g) can slow or prevent the progression of kidney disease.[13] All the patients in our study were observed to have heterosexual mode of transmission of HIV infection, it also being the most common in general population. This was in concordance with another study done by Anant et al [14], where the most common mode of HIV transmission was heterosexual (78.2%).

Majority of the patients (143) were asymptomatic, only 7 patients had symptoms the most common symptom observed was vomiting seen in 4 patients, followed by fever seen in 4 patients and oliguria which was also observed in 4 patients, 3 patients had edema feet , 3 had puffiness of eyes and 2 had loose motions as their presenting complaint, 1 hadbreathlessness and 1 had hematuria as the presenting complaint. Majority of our patients were recruited from the HIV clinics where they come

for a regular monthly follow up for medications. These patients are screened for OIs and adverse reaction to drugs and treated for the same. Hence majority of them were asymptomatic.

Nevirapine and efavirenz belong to the same class of antiretroviral drugs and are associated with very little or no renal abnormalities, whereas TDF have an adverse renal profile [15,16]. Also 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. 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 m 2.This is in concordance with other studies done by Jacobson LP et al [15] 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 and Longenecker CT et al[16] who compared 335 HIV infected people with 230 control and the estimated relative risk of stage III - V in this study was 6.5 [17] and other studies that were reviewed by Islam et al [18] in a meta- analysis done in 2012.

In our study it was observed that 90 (30%) patients had albuminuria on spot urine sample. We observed that out of these 90 patients, 78 (86.66%) were on TDF based regimen and only 12 (13.33%) were on AZT based ART regimen ($p<0.05$). In our study it was observed that 72 (24%) patients had proteinuria on the 24 hour urine quantification , out of which 62 (88.88 %) were on TDF based regimen and 10 (13.8%) were on AZT based ART regimen($p<0.05$). The mean proteinuria in the TDF group was 0.86 +0.66 g/l and in AZT group was 0.58+ 0.35 g/l .

In a review done by Scarpino et al in 2013, they concluded that patients recieving TDF based therapy are at a greater risk of developing renal tubular damage as evidenced by proteinuria as compared to those on other regimen.[19] In a metanalysis done by Islam et al, where four cohort and one case control study was included in the analysis and it was concluded that the relative risk for proteinuria in patients on TDF based therapy was 1.56 which was statistically significant ($p<0.001$).[18] The reason for this is TDF acts on the proximal tubular epithelium in the kidney and causes mitochondrial damage to the tubules leading to nephrotoxicity.[17]

In our study, 90 (31.33%) had albuminuria, out of the which 36 (48.5%) had CD4<200 cells/µl, 28 (35%) had CD4 200-350 cells/µl and 52 (17.8%) had CD4 > 350 cells/µl ($p<0.05$). There was an inverse correlation between albuminuria and CD4 cell count. In our study, proteinuria quantification on a 24 hour urine collection has shown that, proteinuria increases as the value of CD4 count decreases. After a month, 36 patients had proteinuria quantified on a 24 hour urine sample. As there is a statistically significant difference, proteinuria has an inverse correlation with CD4 count.

This was in concordance with a Kenyan study, done by Wools-Kaloustian et al., 2007 where 216 antiretroviral-naïve patients with an average CD4 count of 383 cells/$mm^3$ were screened for renal disease. Although not statistically significant, there was a trend to more severe renal insufficiency and heavier proteinuria in those with a CD4 count <200 cells/$mm^3$.[17] In their study, Chioma Pedro Emem et al found a negative correlation between proteinuria and CD4 count and concluded that as CD4 count decreases proteinuria increases and so does renal damage.[20] Another study done by Abrahem et al, albuminuria was observed in 29 (27%) patients, and it revealed a significant negative correlation with CD4 count ($p < 0.01$). Patients with CD4 cells < 350 cells/mm3 disclosed a 3.5 fold increased risk of albuminuria as compared with patients with CD4 > 350 cells/mm3.[8] An Indian study done in Jammu Kashmir by JP Singh et al also observed that there was a significant correlation between CD4<200 and presence of microalbuminuria. Similar findings were observed in studies done by Lynda Anne Szczech et al[9] and Winston JA et al[21]

The reason for this could be that CD4 count is considered as a surrogate marker for HIV viral load and activity. [22] 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.[17] Moreover, persistently low CD4 count forma a surrogate marker for increased viral load and disease activity which is an important predictor of onset of renal disease. In our study, it was observed that the mean creatinine clearance was 46.33 ml/min in patients with CD4 count < 200 cells/µl, it was

65.94 ml/min in patients with CD4 200-350 cells/µl and 81.41ml/min in patients with CD4>350 cells/µl ($p<0.05$). Also the mean values of eGFR in patients with CD4 < 200 cells/µl was 61.7 ml/min/1.73 $m^2$ , in those with CD4 200 - 350 cells/µl was 83.56 ml/min/1.73 $m^2$ and 103.47 ml/min/1.73 $m^2$ in those with CD4> 350 cells/µl. ($p<0.05$)

Thus we concluded that the risk of having CKD increases with decline in the CD4 count as documented by eGFR calulation 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[19], Wools-Kaloustian et al.,[17] 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/$mm^3$ [21]. Limitations: Being a single-centre, cross-sectional study, the findings may not be generalizable to all people living with HIV, particularly those from different geographic regions, demographic profiles, or healthcare settings. The exclusion of patients with pre-existing renal disease or comorbidities may have led to an underestimation of the true prevalence of renal dysfunction in the wider HIV-positive population. Renal function assessment was limited to creatinine clearance, estimated glomerular filtration rate (eGFR) using the MDRD formula, and urine protein by dipstick, without the use of more sensitive biomarkers such as cystatin C, microalbuminuria, or confirmatory imaging/histopathology. Additionally, variations in the duration of antiretroviral therapy were not accounted for, which could have influenced the observed renal outcomes.

## CONCLUSION

Prevalance of proteinuria is common in HIV infected patients. Proteinuria is more common in patients treated with TDF based ART regimen and proteinuria increases with advanced stages of HIV infection. Decline in eGFR values and creatinine clearance is seen with advanced stages of HIV infection and is more common with TDF based ART regimen. We recommend that at the time of HIV diagnosis all patients should be assessed for existing kidney disease with a screening urine analysis for proteinuria and a calculated estimate of renal function . Patients on TDF based regimen and CD4<200 cells/µl should undergo urine analysis and estimates of renal function every 3 months.

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