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# Clinical and Etiological Profile of Chronic Kidney Disease in HIV Positive Patients

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**Abstract:** ***Aim: To study various clinical manifestations and etiological factors of chronic kidney disease in HIV positive patients. Introduction: HIV infection affects multiple organs and kidney is a common target. Chronic kidney disease (CKD) is a frequent complication of HIV infection, occurring in 3.5-48.5%, and occurs as a complication of HIV infection, other co-morbid disease and infections and as a consequence of therapy of HIV infection and its complications. Materials and Methods: Single centric, observational, cross sectional, descriptive study conducted in Department of medicine of a tertiary care hospital in period of 12 months. Total 55 patients admitted in medicine wards, OPD patients, SACEP referred cases were included in study. Patients with HIV positive and has CKD, Serum creatinine >1.5mg/dl for 3 months, Patient with proteinuria > 500 mg /24 hrs and AKI (Acute Kidney Injury) on CKD were included and HIV positive with AKI due to any cause were excluded. Results: The most common etiology for CKD was Tenofovir induced irreversible nephropathy in 22 patients (40 %) followed by Diabetic Nephropathy in 8 patients (14.55 %) and Hypertensive nephropathy in 4 patients (7.27 %). Other etiologies noted were Chronic pyelonephritis in 4 patients (7.27 %), Obstructive uropathy seen in 4 patients (7.27 %) and FSGS in 3 patients (3.64 %). ADPKD etiology was noted in 2 patients (3.64 %), Analgesic nephropathy in 1 patient (1.82 %), Nephrocalcinosis in 1 patient (1.82 %) and Tubulointerstitial nephritis noted in 1 patient (1.82 %), no specific etiology was found in 6 patients (10.91 %). The most common symptom was fever with nausea & vomiting (20%) &sign was Edema (facial & pedal) (67.27 %). Conclusion: Due to lack of awareness of tenofovir (TDF) induced nephropathy and improper renal function monitoring on tenofovir based regimen in Indian population due to which tenofovir induced irreversible damage was the most common etiology found in our study.***

**Keywords:** CKD (Chronic Kidney Disease), HIV (Human Immunodeficiency Virus), TDF (Tenofovir Disoproxil Fumarate)

## 1. Introduction

Broad spectrum of renal disease are reported in patients with AIDS, and range from acid base disturbances, acute renal failure, and glomerular diseases like immune complex glomerular disease, IgA nephropathy, membranous nephropathy, membranoproliferative, mesangial proliferative, diffuse proliferative, or crescentic glomerulonephritis. [2] including a distinctive form of sclerosing glomerulopathy [HIVAN] which develops in 5 to10%ofpatients. Progression to end stage kidney disease has been reported to be more likely when high grade proteinuria, severely reduced eGFR, hepatitis B and/C co-infection, diabetes mellitus, extensive glomerulosclerosis, and chronic interstitial fibrosis are present.

There is increasing concern that HIV being epidemic in this region, is contributing to the increasing prevalence of renaldys function in Sub-Saharan Africa [3] The etiology of renal dysfunction includes; HIV-associated nephropathy (HIVAN), HIV immune complex kidney disease (HIVICK), drugs used for treatment of opportunistic infections, antiretroviral therapy (ART), use of non-steroidal anti-inflammatory drugs (NSAIDS), herbal medicines, other co morbid conditions namely diabetes mellitus, hypertension and Hepatitis B & C. The consequences of renal dysfunction range from acute kidneyinjury (AKI), chronic kidney disease, end stage renal disease (ESRD) or death [4].

Though CKD is common in PLHIV, not many Indian studies which throw light on different angles including etiological profile and risk factors, which are unique to our population. Hence this study was done in our Centre with objective to determine various risk factors, epidemiological aspects, clinical profile of patients of PLHIV with CKD. Our Hospital, is a tertiary care hospital and State AIDS Clinical Expert Panel (SACEP) meetings are conducted here for evaluation and management of toxicities, complications and virological failure patients. Hence we have large no of patients of PLHIV coming for treatment and also for consultation to our center for the work up, selection and dose adjustment for Anti-retroviral therapy in patients of PLHIV with CKD. Hence the current study was done. This was an observational study conducted in the department of medicine of a tertiary care hospital after obtaining permission from the institutional ethics committee. The present study included 55 patients diagnosed to have HIV infection and came to OPD / IPD / referred cases for SACEP fulfilling the inclusion and exclusion criteria.

## 2. Materials and Methods

**Study Design**
This was a single centric, observational, cross sectional, descriptive study

**Study Site**
The study was conducted in Department of medicine of a tertiary care hospital.

**Study duration**
The study was conducted for a period of 12 months from 1st January 2020 to 31st December 2021

**Study population**
All patients admitted in medicine wards, OPD patients, SACEP referred cases and ARTOPD patients included during the12 months of the study.

**Sample size: The sample size calculated was 55.**

## 3. Methodology

**Ethical considerations**
The study was initiated after obtaining approval from the institutional ethics committee and MDACS (Mumbai District AIDS Control Society). A written informed consent was taken from the patients, once they were stable.

**Selection criteria**
Participants were selected based from the following selection criteria

**Inclusion criteria**
Patient with HIV positive and has CKD (Chronic Kidney Disease)
1) Serum creatinine >1.5mg/dl for 3 months And/ Or
2) Patient with proteinuria>500mg/24hrs
3) AKI (Acute Kidney Injury) on CKD
4) Patients who are ready to give written informed consent
5) Patients who are willing to be part of the study

**Exclusion criteria**
1) Patients with HIV positive with AKI due to any cause.
2) Patients who were not ready to give written informed consent
3) Patients who were not willing to be part of the study.

**Statistical analysis**
Categorical variables were presented in number and percentage (%) and continuous variables were presented as mean± SD and median. Normality of data was tested by Kolmogorov-Smirnov test. A p value of <0.05 was be considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 21.0.

## 4. Study Procedure

The study was initiated after approval from Institutional ethics committee and MDACS (Mumbai District AIDS Control Society), Mumbai. All the patients presenting to medicine ward, OPD patients, SACEP referred cases and ART OPD patients who meet the inclusion and exclusion criteria were part of the study. Written informed consent in the language understandable was obtained from patients or their legal representative whenever possible. All patients were subjected to full clinical examination including vital signs assessment such as heart rate, respiratory rate, blood pressure, temperature.
The following parameters were studied:
1) Urine routine for the presence or absence of protein uria by dipstick method.
2) Spot Urinary Albumin Creatinine ratio (ACR)
3) Serum creatinine for the presence or absence of renal failure (according to The AIDS Clinical Trials creatinine level greater than 1.5 mg/dL defined as acute renal failure (ARF) and if it persists for more than 3 months it is defined as chronicrenal failure (CRF).
4) Ultrasound of abdomen for the assessment of renal sizes, echo texture and cortico medullary differentiation. Also for screening of abdominal tuberculosis as an opportunistic infection.
5) 24 hour urine protein for the presence or absence of significant proteinuria (>500mg/day).
6) CBC, Urea, Serum Calcium, Serum electrolytes, serum Phosphorus, LFT, HBA1Cetc.
7) Fundoscopy examination.
8) Opportunistic infection / Co-infection screening (Chest xray, CT brain, Stoolr/m, Hep B s antigen, anti Hepcanti body, CSF-Cryptococcal antigen whenever necessary)
9) ART Medication history including all baseline regimen, then ART regimen till deranged serum creatinine, date of change of ART regimen, subsequent serum creatinine levels and current serum creatinine level.
10) Renal biopsy in patients, after taking written consent to study the various renal manifestations in HIV infected patients.
11) Baseline and current CD4 count, Current Viralload level.

**Case Definition**
Any HIV positive patient with CKD (Chronic Kidney Disease)-
1) Serum creatinine>1.5mg/dlfor3monthsAnd/Or
2) Patient with proteinuria >500mg/24hours
3) AKI (Acute Kidney Injury) on CKD, was enrolled in study and evaluated as per proforma.

**Data Analysis:**
Qualitative And Quantitative Data Analysis done from Collected data In Microsoft Excel Sheet. The data in the proformas of all the 55 patients enrolled in the study was entered into the SPSS software. Categoric variables in the study were compared using Chi square test. Relative Risk is calculated using odd ratio. P value of <0.05 was significant. Results displayed in Tabular and Graphical form.

## 5. Summary

- This was an observational study conducted in the department of medicine at tertiary care hospital after obtaining permission from the institutional ethics committee. The present study included 55 patients diagnosed to have HIV infection and came to OPD / IPD / referred cases for SACEP fulfilling the inclusion and exclusion criteria.
- The average age of patients enrolled in our study was51.72 ± 8.67. Most of the patients in the present study in the age group of 40 to 50 years (38.2%) followed by those in the age group of 50 to 60 years (36.4%).
- Male predominance was seen in our study 42 (76%).
- Male to Female ratio of (3: 1).
- The most common HIV was Type 1 seen in 46 patients (83.63 %) followed by Type 2 seen in 7 patients (12.72 %) and Type (1 & 2) seen in 2patients (3.63%).
- The most common etiology noted was Tenofovir induced irreversible nephropathy in 22 patients (40 %) followed by Diabetic Nephropathy in 8patients (14.55 %) and Hypertensive nephropathy in 4 patients (7.27 %). Other etiologies noted were Chronic pyelonephritis in 4 patients (7.27 %), Obstructive uropathy seen in 4 patients (7.27 %) and FSGS in 3 patients (3.64 %). ADPKD etiology was noted in 2 patients (3.64 %), Analgesic nephropathyin 1 patient (1.82 %), Nephrocalcinosis in

1patient (1.82 %) and Tubulointerstitial nephritis noted in 1 patient (1.82 %), no specific etiology was found in 6 patients (10.91%).

**Table 1:** Distribution of patients according to Etiological profile

| **Etiological profile** | Frequency | Percentage |
|---|---|---|
| ADPKD | 2 | 3.64 |
| Analgesic Nephropathy | 1 | 1.82 |
| Chronic pyelonephritis | 4 | 7.27 |
| DM Nephropathy | 8 | 14.55 |
| FSGS | 3 | 5.45 |
| HTN Nephropathy | 4 | 7.27 |
| Nephrocalcinosis | 1 | 1.82 |
| Obstructive uropathy | 3 | 5.45 |
| TDF Induced | 22 | 40.00 |
| Tubulointersitial nephritis | 1 | 1.82 |
| Not Known | 6 | 10.91 |
| Total | 55 | 100 |

- The most common symptom was fever with nausea and vomiting (20%) followed by Facial puffiness (16.36%) and decrease in urine output (10.9 %).

**Table 2:** Distribution of patients according to Clinical Symptoms

| Clinical Profile | Frequency | Percentage |
|---|---|---|
| Asymptomatic | 4 | 7.27 |
| Bilateral lower limb swelling | 3 | 5.45 |
| Breathlessness | 8 | 14.55 |
| Decrease in appetite | 2 | 3.64 |
| Decrease in urine output | 6 | 10.91 |
| Facial puffiness | 9 | 16.36 |
| Fever, Vomiting, Nausea | 11 | 20.00 |
| Fatigue, Generalised weakness | 5 | 9.09 |
| Headache, seizures | 2 | 3.64 |
| Loose motions | 1 | 1.82 |
| Pain in abdomen | 3 | 5.45 |
| Rt Lower limb gangrene | 1 | 1.82 |
| Total | 55 | 100 |

- The most common sign in the present study was Edema including both facial & pedal (67.27%) followed by pallor (58.18%) and Combined pallor with edema (43.64%).

**Table 3:** Distribution of patients according to Clinical signs

| Signs | Pallor | Percentage | Edema | Percentage | Pallor With Edema | Percentage |
|---|---|---|---|---|---|---|
| Present | 32 | 58.18 | 37 | 67.27 | 24 | 43.64 |
| Absent | 23 | 41.82 | 18 | 32.73 | 31 | 56.36 |
| Total | 55 | 100.00 | 55 | 100.00 | 55 | 100.00 |

- The most common comorbidity was Hypertension 22 patients (40 %). Of the 22 patients 3 patients were newly diagnosed hypertension, followed by Diabetes mellitus in 14 patients (25.45%), Ischemic heart disease in 6 patients (10.91%) and Obesity in 5 patients (9.09%).
- The most common ultrasonography of abdomen finding noted was Bilateral medical renal disease with normal sized kidney with maintained CMD in 26 patients, followed by Bilateral medical renal disease with partial loss of CMD in 9 patients, Bilateral Contracted small kidneys found in 6 patients, out of which Partial CMD maintained in 5 patients. Remaining 1 patient of Bilateral Contracted small kidneys had loss of CMD, Bilateral medical renal disease with complete loss of CMD finding seen in 3 patients, Unilateral contracted small kidney with loss of CMD seen in 2 patients, Bilateral enlarged kidneys with multiple cyst seen in 2 patients, Obstructive Uropathy seen in 3 patients and Right sided Non Obstructive renal calculi seen in 1 patient. Single left sided kidney with partial loss of CMD, right kidney agenesis seen in 1 patient.
- Albuminuria was noted in all cases. Of these 39 patients (70.9 %) had Macroalbuminuria followed by 11 patients (20%) had Microalbuminuria and remaining 5patients (9%) had Nephroticrange albuminuria
- 24 hours urinary proteinuria-Significant proteinuria was found in 47 patients (85.45 %) and Nephrotic range proteinuria was found in 8 patients (14.55%).
- The most common histological finding on renal biopsy noted was FSGS in 3 patients (75 %) and remaining 1patient (25 %) had Tubulointerstitial nephritis.
- The most common fundoscopic findings noted was NPDR seen in 7 patients (12.73) followed by Grade 2 hypertensive retinopathy noted in 6 patients (10.91%) and Grade 3 Hypertensive retinopathy in 4 patients (7.27%). Normal fundoscopy was noted in 36 patients (65.45%)
- Hypocalcemia was noted in 40 patients (72.73%) and remaining 15 (27.27%) patients had normal serum calcium level.
- Hyperphosphatemia was noted in 45 patients (81.81%) and remaining 10patients (18.19 %) had normal serum phosphorous level.
- The most common CKD Stage noted was stage4 seen in 24 patients (43.64 %) followed by stage 3 B in 17 patients (30.91 %) and stage 5 in 11 patients (20 %). All 11 patients in stage 5 were on hemodialysis.
- The most common CD4 count was > 500 seen in 21 (38.18%) patients followed by patients between CD4 count between 200-500 seen in 20 patients (36.36%), CD4 count between 100-200 found in 6 patients (10.90%) and CD4 count Below < 100 in 8 patients (14.54%).
- The most common opportunistic infection in the present study was Pulmonary tuberculosis in 5 patients (9.09 %) followed by Hepatitis B viral co-infection in 3 patients (5.45%) followed by Abdominal tuberculosis in 2 patients (3.64%).

## 6. Discussion

In the present study shows that total 41 patients were started on Tenofovir based baseline regimen out of which, Tenofovir (TDF) based baseline ART regimen causing irreversible renal damage was found in22 (53.66) %patients. The most common Baseline Tenofovir (TDF) based regimen

causing irreversible damage was TLE in 12 patients (29.27%) followed by TL+ATV/ Rin4patients (9.76%) &TL+LPV/Rin4patients (9.76 %). Out of 22 Tenofovir (TDF) based regimen causing irreversible damage patients, 3 patients (7.31%) required haemodialysis. Remaining 19 patients (46.34%) had renal damage due to other causes which is described in above table. Remaining 19 patients (46.34%) had renal damage due to other causes such as Diabetes mellitus, hypertension & ADPKD etc. As per NACO guideline October 2018, TENOFOVIR (TDF 300 mg) + LAMIVUDINE (3TC 300 mg) +EFAVIRENZ (EFV 600 mg). (TLE) as Fixed Dose Combination (FDC) in a single pill once a day recommended as a First-line ART regimen for: All ARV naive PLHIV patients with HIV-1 infection, age > 10 years, and body weight >30 kg irrespective of CD4 Count. Before this, since long duration Tenofovir (TDF) was recommended as a component of first-line ART regimen, hence majority of patients who exposed Tenofovir (TDF) for long duration are affected primarily along with lack of adequate renal function monitoring. In India, Renal function monitoring was not done properly in many ART centers due to lack of awareness of tenofovir induced nephropathy in initial few years there was no 6 monthly regular monitoring of serum creatinine in spite of guideline, hence patients continued to receive Tenofovir based ART regimen for long duration despite of Tenofovir induced damaged renal function. Also initially patients with renal toxicity due totenofovir were continued on tenofovir as per adjusted doses of tenofovir as per create clearance (the guideline was changed later) hence most of them ultimately landed up in irreversible renal damage. According to Lourembam Gayatrietalin North eastern India study found high prevalence of renal dysfunction among HIV patients receiving tenofovir- based ART regimen, Hence tenofovir usemustbeaccompaniedbymoreintensiverenalmonitoringparticularlyinpatients at risk of renal dysfunction. 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 % [5]However, retrospective cohort studies from Asian region have shown similarly high rates of renal dysfunction. A study conducted by Kyuong HL et al [6] among HIV infected Koreans found a prevalence of 27%.13 One of the postulated explanations forthis is the lower BMI of the patients in Asia as well as genetic predisposition.17Polymorphism in the genes encoding proximal tubular transportes, such as theABCC2andABCC4genes, have been postulated to increase the plasma concentration of tenofovir and hence an increased risk of nephrotoxicity. According to Patel KK et al [7] study done on Tenofovir-associated renal dysfunction in clinical practice from western India found that, TDF-based treatment is associated with mild but reversible renal dysfunction. Patients receiving PI/rare at a higher risk of renal dysfunction compared to those receiving NNRTI-based ART. [8]The results of the present study are in contrary to above mentioned study, due to all patients in the above mentioned study were monitored for tenofovir induced acute kidney injury (AKI), after starting tenofovir serum creatinine monitoring was monitored every 3 monthly and 6 monthly, when AKI detected Tenofovir was stopped, hence reversible and mild kidney dysfunction found. However our cohort had patients who were not monitored with regular serum creatinine after starting tenofovir in various ART centres and had many co-morbidities like diabetes, hypertension etc. Due to prolonged and continued use of tenofovir in spite of deranged creatinine due to lack of awareness of medical officers & lack of guidelines atthat time for prompt stopping of tenofovir, led to tenofovir induced irreversible and severe renal damage

## 7. Limitations

Our study has several limitations. The study was conducted on small sample size. A limitation of our study that we were unable to assess further follow up &outcome of patients. Also our experience may be quite different from other parts of the world affected by HIV pandemic. In 22patientsno other cause of renal failure was found, and since this patients had chronic tenofovir exposure in spite of having deranged renal parameters, in this patients tenofovir was assumed to be the cause of irreversible renal damage, however we could not performed renal biopsies due to resource limitation.

**Declaration**

I confirm that I have read, understand, and agreed to the submission guidelines, policies, and submission declaration of the journal. I confirm that all authors of the manuscript have no conflict of interests to declare. I confirm that the manuscript is the authors' original work and the manuscript has not received prior publication and is not under consideration for publication elsewhere. On behalf of all Co-Authors, I shall bear full responsibility for the submission. I confirm that all authors listed on the title page have contributed significantly to the work, have read the manuscript, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission. I confirm that the paper now submitted is not copied or plagiarized version of some other published work. I declare that I shall not submit the paper for publication in any other Journal or Magazine till the decision is made by journal editors.

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