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Renal Profile in HIV Seropositive Patients on Highly Active Anti Retroviral Therapy (Haart) Compared with Haart-Naïve Patients

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Abstract: ***Since the emergence of AIDS, renal disease has been recognized as a common complication associated with HIV infection, which significantly contributes to morbidity and mortality in patients. Methods:An institution based cross-sectional observational study was conducted from November 2017-March 2019, among HIV positive adult (>15 years) patients attending the ART clinic in Lady Hardinge Medical College (LHMC) and Associated Hospitals, New Delhi. Those on HAART for more than 3 months and naive patients were recruited after taking consent. Patients with pre-existing renal disorders not related to HIV (Diabetes/ Hypertension/Chronic liver disease, Hepatitis B/C positive) and those having structural abnormality of kidneys on Ultrasound imaging were excluded. The Markers of kidney damage in the study was determined by ≥ 1 of the following 1) UACR ≥30mg/g 2) eGFR less than 60 ml/min/1.73 m², which was calculated using Cockcroft-Gault equation. Results: A total of 100 patients with complete data were analysed. The predominant age group having renal impairment was formed by 30-40 years age group (37.78%). The prevalence of renal impairment is higher in HAART-naive patients (52.9%) as compared to those on HAART (36.7%) patients with p value of 0.045; which indirectly shows the nephroprotective role of HAART. The prevalence was found to be 40% in females and 60% in males. The mean UACR for naïve kidney damage patients was 119.23±26.3mg/g and for those on ART was 31.71±17.1 mg/g with p-value of 0.00084. The predictors of kidney damage include low CD4 count, low haemoglobin and (WHO) stage III/IV disease. Our study also revealed the higher prevalence(30.61% (p value 0.035)of renal impairment in tenofovir based HAART taking patients as compared to those on HAART without tenofovir.Conclusion:As there is higher prevalence of renal impairment in HAART-naive as compared to those on HAART patients, early initiation of HAART is recommended. Although HAART showed reno-protection, Tenofovir (TDF) based HAART was found to have higher prevalence of renal impairment. Therefore, regular assessment of renal function is required to assess baseline parameters prior to commencement of treatment with HAART and also to monitor ART nephrotoxicity.***

Keywords: HIV/AIDS, on highly active anti-retroviral therapy (HAART), HAART naive, renal profile, UACR(Urine Albumin-to-Creatinine ratio), eGFR (estimatedglomerular filtrationrate)

1. Introduction

Human Immunodeficiency virus (HIV), the causative agent of Acquired Immunodeficiency Syndrome (AIDS) is a challenging public health problem worldwide.Since the emergence of AIDS, renal disease has been recognised as a common complication associated with HIV infection (Scott[1] and Paul [2], 2007). The association between HIV infection and renal disease was first reported as far back as 1984 by Herman[3] et al and Klotman in New York and Miami. Renal disease in HIV can also result from the use of HAART and their associated adverse effects. Also, Patients with HIV/AIDS are at a higher risk of developing pre-renal azotemia due to volume depletion resulting from salt wasting, poor nutrition, nausea or vomiting (Moro[4]et.al,2007).Despite reductions in morbidity and mortality owing to widespread use of HAART, renal impairment is still more common in HIV positive patients than in general population with prevalence of 5-30%. HIV infected patients are at a greater risk for development of a variety of acute and chronic renal disease (Ross[5] et al,2000).Thespectrum of renal diseases among HIV-infected patients can be 1) HIV associated Nephropathy (HIVAN) 2) cARTinduced Nephropathy 3) Non-HIV related kidney diseases.Kidney damage in HIVAN results from variety of mechanisms including direct viral cell injury and host susceptibility factors. Viral infection of podocytes and tubular epithelial cells including dedifferentiation, proliferation and apoptosis. Different viral gene products are key determinants for these process specially APOL1 gene[6]. Acute renal failureoccurs in 20% of HIV patients.

HIVAN is a disease with unique clinical, pathologic and epidemiologic features that progresses rapidly to end stage renal disease (ESRD). Increased survival of HIV patients under HAART has let to complex interactions of HIV infection with prevalent chronic diseases often leading to renal disease. Environmental factors or genetic susceptibility or underlying diseases (Diabetes, metabolic syndrome, hypertension, atherosclerosis) may synergize with HIV infection or HAART to accelerate the loss of kidney function, leading to chronic kidney disease (CKD) presenting as decreased eGFR, increased urinary protein excretion or other abnormal urinary findings.All aspects of medical management become more difficult when a patient with HIV infection develops renal failure (AIDS clinical care [7] 2007).

2. Objectives

Primary Objective**:** To compare the prevalence of renal disorders in HIV positive patients on HAART with HAART- naive patients.

Secondary Objective: To determine the relevant assessment parameters for renal function in sero-positive patients**.**

3. Materials and Methods

An institution based cross-sectional observational study was conducted from November 2017-March 2019, among HIV positive adult (>15 years) patients attending the ART clinic in Lady Hardinge Medical College (LHMC) and Associated Hospitals, New Delhi.A total of 100 patients who presented in ART clinic LHMC who were meeting the inclusion and exclusion criteria were enrolled in the study after taking informed consent. Out of 100 participants, 51 were HAART naive and the remaining 49 were on HAART.

Inclusion Criteria: More than15 years HIV positive patients attending the ART clinic OPD Lady Hardinge Medical College 1) Those on HAART for more than 3 monthsas well as HAART-naive patients 2) Given written, informed consent for participation in the study.

Exclusion Criteria: a)Patients who do not give consent and Age <15yearsb)Patients with pre-existing renal disorders not related to HIV (Diabetes/ Hypertension/ Chronic liver disease, Hepatitis B/C positive) on the basis of clinico-investigative profile.c) Those having structural abnormality of kidneys on Ultrasound imaging.Markers of kidney damage (one or more of following)

1) UACR more than or equal to 30mg/g
2) eGFR less than 60 ml/min/1.73m^2.

Recommended equation for estimation of glomerular filtration rate (GFR) using serum creatinine concentration (pcr), age, sex, Race, and body weight: Cockcroft-Gault equation.Estimated creatinine clearance (mL/min), eGFR ={(140 -age) X body weight in kg X 0.85(for females)}/72 X serum creatinine.

Venous samples were drawn and mid-stream urinary sample were taken.Complete Blood Count was analyzed using hematology autoanalyzer Sysmex KX 21. Urea was analyzed by enzymatic method based on preliminary hydrolysis of urea with urease (Sentinel diagnostics reagent). Creatinine was measured using chemical method, Jaffe reaction. The machine used was the Olympus AU480.UACR AND UPCR was measured using Beckman Coulter AU 680-2 SL.Nno2016034716. USG abdomen was done to detect any renal dysfunction. The Toshiba Nemio XG ultrasound machine was used in our study. For Viral serology (HBsAg and anti-HCV), the Monolisa HBsAg ULTRA kit and the Monolisa HCV Ag-Ab ULTRA kit was used. Renal biopsy was not done in any patient as no indication was there. Both fasting and post prandial were taken. CD4 count was measured by using FACS Calibur^{TM}.

Due to the cross-sectional nature of our study, we could not adequately assess the duration for development and persistence of declining eGFR. Data collected by above materials and methods was tabulated on excel sheet. Quantitative variables are expressed as mean ±sd and compared between groups using unpaired t-test. Qualitative variables are expressed as frequencies/ percentages and analyzed using Chi-square/ Fisher's Exact test. A p-value < 0.05 is considered statistically significant. The data is tabulated in MS Excel and analysis performed using IBM SPSS version 20.0 software.Correlationbetween renal dysfunction with BMI, Duration of HAART, CD4 count, age, anemia, serum creatinine, UACR, Type of ART were carried out in the patients.

4. Observations and Results

Kidney damage were found in 45 (45%) patients with significant p value of < 0.001. Out of 45 PLHIV/PLHA with renal dysfunction, 27 (60%) are HAART niave and 18 (40%) are on HAART with prevalence of 52.9% in naive and 36.7% on HAART patients which is statistically significant with the p value of 0.045. Out of 100participants, 39(39%) were females and 61 (61%) were males. Kidney damage were found in 18(40%) femalesand 27 (60%) males, which is not statistically significant with p value 0.42.The age distribution of the kidney damage were slightly higher among 30-40 years; with 17(37.78%) participants were found to have kidney damage in this group. The mean age of the kidney damage was 36.67 ± 9.15 SD.

Table 1: Age-wise prevalence of renal dysfunction in PLHIV

Kidney Damage→	Yes		No	
Age (years) ↓	n	%	n	%
< 20	2	4.44%	8	14.55%
10 - 20	14	31.11%	22	40.00%
30 - 40	17	37.78%	20	36.36%
40 - 50	7	15.56%	4	7.27%
50 - 60	5	11.11%	0	0.00%
≥ 60	0	0.00%	1	1.82%
TOTAL	45	100%	55	100%

The mean weight (in kg) of the participants having kidney damage were 48.05 ± 9.21 and mean body mass index BMI (in kg/m²) was 25.07 ± 33.06. The differences in mean of body mass index (BMI) between the patients with kidney damage and those without kidney damage as demonstrated by this study is not statistically significant with p value 0.167. The mean eGFR in ml/min/1.73m was found to be 93.30 ±43.53 in study populations with kidney damage. The mean UACR in the kidney damage patients was found to be 111.51 ±95.98 (mg/g) which are statistically significant with p value <0.001.Out of 45 kidney damage patients, only 5 patients were found to have eGFR < 60 ml/min/1.73m²; 25 patients have eGFR between 60-90 ml/min/1.73m² while the 15 patients have more than 90 ml/min/1.73m². The mean eGFR in female and male are respectively 118.15 ±38 and 113.74 ±60 mi/min with p value 0.697.There are 4 individuals on HAART with Creatinine clearance ≤60 ml/min but only one naïve patient. The percentages of individuals with Creatinine clearance in between 60 & 90 ml/min are greater in those who are on HAART [15(60%)] than that of naive [10(40%)]. Serum uric acid was higher in HIV subjects both on HAART and treatment-naive groups.

The level of serum uric acid was higher in treatment-naive groups compared with patients on HAART. Serum creatinine level was comparable in treatment-naive groups and those on HAART.

The mean UACR for naive kidney damage patients was 119.23±26.3mg/g and for those on ART was 31.71±17.1 mg/g with statistically significant p-value of 0.00084. The means of eGFR and CD4 count for naïve and on HAART patients with renal impairment are given in table no.2.

Table 2: Comparison of means of parameters for naive and on HAART patients

	Naïve with kidney damage Mean ± SD	On ART with kidney damage Mean ± SD	P-value
UACR mg/g	119.23±26.3	31.71±17.1	0.00084
eGFR ml/min/1.73m²	80.66±26.2	113.33±17.5	0.014
CD4 count cells/mm³	239±17	435±26	0.024

*eGFR in (ml/min/1.73m²

The mean duration (in years) of participants on HAART having kidney damage were 3.08 ± 1.73 with a significant p value of 0.011. The mean systolic blood pressure in participants with kidney damage was 114.71 ± 9.99 mmHg, which was almost similar to that of PLHA patients without kidney damage 116.18 ± 8.58 mmHg. There is no significant correlation of BP with kidney damage In PLHA patient. There is a significant reduction in haemoglobin (mean Hb-10.08 ±3.02 g/dl) level in patient with kidney damage with p value of <0.001. There is also statistically significant association of lower platelet (p value <0.011) and raised serum urea level (p value 0.009) with renal dysfunction**.** However, there was no significant difference in FBS and PPBS level in PLHA with kidney damage or without damage. There was a significant (p value=0.02) reduction in CD4+ cell count in HIV patients who have kidney damage compared with those without kidney damage, with mean CD4 count being 368.91 ±265.03. The pattern of urinalysis result in the study population shows more patients with proteinuria/albuminuria (45%), erythrocyturia (11.11%) and leukocyturia (0%). Participants on ART regime containing tenofovir was found to have higher prevalence of kidney damage as compared to those on tenofovir spared ART regime. 15 (83.33%) out of 18 participants who are on ART associated with kidney damage; are found to be on tenofovir based ART regime (TLE). The prevalence of TDF associated nephropathy is found to be 30.61% with statistically significant p value of 0.035. However, association of ZLN with renal impairment is found to be statistically insignificant with p value of 0.117.

Table 3: Relevant Parameters of Renal Function

Kidney Damage→	Yes		No		p-value
	mean	±SD	mean	±SD	
Duration of ART (years)	3.08	±1.73	4.81	±2.77	0.011
BP (Systolic) mmHg	114.71	±9.99	116.18	±8.58	0.215
BP (Diastolic) mmHg	74.31	±7.76	74.40	±7.27	0.477
MAP mmHg	87.78	±7.36	88.33	±6.94	0.351
Hb (g/dl)	10.08	±3.02	12.26	±2.52	<0.001
TLC (cells/µL)	6966.22	±3480.41	6422.55	±2308.42	0.176
Platelet (cells X 10^5/µL)	1.70	±0.89	2.15	±1.01	0.011
Blood Urea (mg/dl)	33.08	±28.75	23.31	±7.92	0.009
Serum Creatinine (mg/dl)	0.88	±0.57	0.89	±1.82	0.481
FBS (mg/dl)	87.22	±12.13	83.87	±7.8	0.050
PPBS (mg/dl)	125.80	±16	125.11	±6.22	0.385
CD4 Count (cells/mm³)	368.91	±265.03	503.67	±360.08	0.020

5. Discussion

Several renal syndromes and diseases may be associated with HIV infection and it remains an important risk factor for the development of end stage renal disease. The prevalence of kidney damage among Indians was found to be 17.3% among PLHA (Gupta et al [8]).The present study was conducted to compare the prevalence of renal dysfunction and to assess renal function abnormalities in HIV infected patients on HAART as compared to HAART-naive.The results show significantly (p<0.05) higher prevalence of renal disorder in HAART-naive patients (52.9%) as compared to those on ART (36.7%). This result is comparable to the figure reported by Agaba et al [9](51.8%) and Nefrol et al [10] (47.6%).The finding in this study of 45% as having kidney damage (based on defining criteria) is almost consistent with those findings of prevalence of 55.8% (GFR <90 ml/min) by Susman (2005) [11], 48.5% by Andia et al (2005) [12] and 38.0% by Chioma et al (2008) [13]. However it is not agreement with the findings found in study by HerryMapesi et al [14] which showed (15.7%) had renal impairment.In this study, 30 (30%) patients were found to have reduced eGFR< 90mi/min. Out of 45 kidney damage patients,only 5(11.1%) patients were found to have eGFR< 60 ml/min/1.73m²(stage 3 CKD); 25(55.5%) patients have eGFR between 60-90 ml/min/1.73m²(stage 2 CKD) while the 15(33.3%) patients have more than 90 ml/min/1.73m². There was no patient having eGFR less than 30 ml/min.Out of 5 patients having eGFR< 60ml/min, 4 are on HAART and onlyone was(2.2%) naive patient. The percentages of individuals with Creatinine clearance in between 60 & 90 are greater in those who are on HAART [15(60%)] than that of naive [10(40%)]. The mean eGFR among renal dysfunction is found to be 80.66±26.2 mi/min in Naïve and 113.33±17.5 ml/min for on ART patients with p-value of 0.014.The finding of 11.1% of the patients having eGFR of <60 ml/min is in agreement with findings in other studies (Gupta et al, 2004[8], Ronald et al, 2005[15]and Chi Yuen et al, 2007[16]. The decline in eGFRfound in 30 patients is likely to be as a result of invasion of the glomeruli by the HIV as well as due to side effects of HAART[tenofovir] mostly.A 2010 meta-analysis involving 17 large studies found that TDF was associated with a statistically significant decrease of creatinine clearance of 3.92 mL/min and a risk of renal dysfunction[17]. Schwartz et al. (2005) [18], found that HAART reduced the AIDS growth rate and the progression to HIV-positive ESRD and the mortality rate. This is supported by other studies Szczech et al (2005)[19] and Kimmel(2003)[20], suggested that HAART is associated with decreased prevalence of renal disease and its progression in HIV-infected patients with chronic renal disease. This result however is not in consistent with the findings of Kanai and

Hanabusa (2005) [21] of Japan, who reported cases of renal disease associated with Tenofovir containing HAART. Indinavir is highly soluble in acidic urine but relatively insoluble in more alkaline urine, predisposing to the development of crystals at typical urine pH levels. In our study, 15(83.33%) out of 18 participants who are on ART associated with kidney damage are found to be on tenofovir based ART regime (TLE). The likely tenofovir associated renal disease prevalence is found to be 33.33% which is slightly lower as compared to that found by other study (55.8%) Susman[11]. The mean duration (in years) of participants on HAART having kidney damage were 3.08 ± 1.73 with a significant p value of 0.011.

Tenofovir nephrotoxicity is characterized by proximal tubular cell injury and may result in partial or complete Fanconi syndrome, AKI or CKD. Drug withdrawal is the main therapeutic option which usually results in improvement of clinical manifestations of renal impairment, which may be only partial. Thus, prevention of nephrotoxicity by careful monitoring of high-risk populations is paramount. Nephroprotection theoretically can be achieved by preventing tenofovir entry into proximal tubular cells. Drugs are under trial. Probenecid, an inhibitor of OAT1[organic anion transporter], is used to prevent cidofovir nephrotoxicity and can also be used for ten of ovir toxicity[22,23,24]. Hexadeciloxypropyl-tenofovir (CMX157) and Novel ribose-modified NtRTI[25] are currently being in clinical trial. They are less cytotoxic to proximal tubular cells than acyclic nucleotides. These include GS-9148 and its oral prodrug GS-9131. The clinical development of any of these strategies will result in the availability of less cytotoxic albeit effective NtRTI drugs. For predictors of renal impairment, we found association between renal disease and low CD4 count, low Haemoglobin, World Health Organizaton (WHO) stage III/IV disease[26].The mean CD4+ count in our study was significantly lower on patients associated with renal diseaseboth HAART-naive and on HAART patients.There was significant decrease in body mass index in PLHA in our study. However, the differences in mean of body mass index (BMI) between the patients with kidney damage and those without kidney damage is found to be statistically non-significant. There was a significant (p value=0.02) reduction in CD4+ cell count in HIV patients who have kidney damage compared with those without kidney damage, with mean CD4 count being 368.91 ±265.03.35 participants were found to have CD4 count < 300 cells/mm³. Out of 35 patients, 21(60%) were found to have kidney damage.The mean CD4 count among kidney damage patients was found to be 239±17 cells/mm³ in naïve and 435±26 cells/mm³ for on ART patients with significant p-value of 0.0248.Agbaji et al.[27] showed in their study that there is an association between age and CKD in HIV patients; Older age was a predictor of CKD. However, our study did not show such relationship, despite the fact that the mean age of the subjects in their study and ours was almost the same.In our study, the age distribution of patients showed that 30-40years age group(37.78%) forms the predominant age group followed by 10-20 years age group. This finding is consistent with a previous observation in sub-saharan Africa, where 74% of those infected with HIV were in the age group 15-49 years (Fausi,1999[28]; Gayle and Hill, 2001[29]). This findingmay be due to the middle age group involvement in economically productive ventures, coupled with physical well being with a quest for sexual adventure.

In our study, the results showed that low Haemoglobin was associated with renal damage in PLHA patients. We found that there is a significant reduction in haemoglobin (mean Hb-10.08 ±3.02 g/dl) level in patient with kidney damage with p value of <0.001. In our study there is no significant difference in serum creatinine level between patients with kidney damage and those without renal impairment. Our study also showed that there was no association between SBP, DBP, FBS, PPBS and kidney damage, which may be explained by the exclusion of hypertensive and diabetic patients in our study.

6. Strength of the Study

This research is significant as there is paucity of data and lack of sufficient literature in study field regarding “the renal profile in HIV seropositive patients on highly active antiretroviral therapy (HAART) compared with HAART-naive patients” specially in India.The study uses urine albumincreatinine ratio (UACR) and eGFR (calculated by Cockroft-Gault formula) to identify the renal dysfunction in sero-positive patients, which is advisable in hospital setting specially in ART centre.This study successfully showedthe higher prevalence of renal disease in HAART-naive (52.9%)on-HAART patients(36.7%) with statistically significant p value of 0.045.The study also successfully proved the reno-protective nature of HAART.This study has successfully identified the risk factors and predictors of renal disorder associated with PLHA patients.Despite limited resources, this study is comprehensive in assessing the renal function ofHIV/AIDS patients. This could be a help in the diagnostic, therapeutic and prognostic purposes, and therefore reduce the morbidity and mortality among this group of patients in India.

7. Limitations of the Study

This study was done exclusively in a tertiary care government hospital, So the study may not be extrapolated or generalised on a large population as patient comes from limited territory and of lowermost socioeconomic class specially in India.Sample size of the study was small and limited to patients presenting to ART clinic in LHMC. It was carried out in a single center, there is need for a multi-center study to give a better picture of the prevalence in India.Single assessment of urine protein/albumin and eGFR was used to identifyRenal impairment; hence we could not differentiate between acute and chronic kidney diseases. Therefore, we need to take caution in interpretation of the results as they showed loss of renal dysfunction rather than CKD.As renal biopsy was not done in any patients, we could notidentify the histological type of the renal dysfunction.

8. Conclusion and Recommendations

This study showed that the prevalence of renal impairment is higher in HAART-naive patients (52.9%) as compared to those on HAART (36.7%) patients with p value of 0.045;

which indirectly shows the nephroprotective role of HAART.The mean UACR for naïve kidney damage patients was 119.23±26.3mg/g and for those on ART was 31.71±17.1 mg/g with statistically significant p-value of 0.00084.

In our study, the age distribution of patients showed that 30-40 years age group (37.78%) forms the predominant age group having renal impairment followed by 10-20 years age group.The predictors of renal impairment in HIV/AIDS patients include low CD4 count (mean=239±17in naïve & mean=435±26cells/mm³ in on-ART patients),low Haemoglobin [Hb-10.08 ±3.02 g/dl (p value of <0.001)] and (WHO) stage III/IV disease.Our study also revealed the higher prevalence of renal impairment in tenofovir based HAART taking patients as compared to those on HAART without tenofovir. The data from our study will influence the decisions on ART selection and provisioning in India.This can also act as a guide in implementing potentially diagnostic, preventive and therapeutic strategies to whittle down the renal diseasesand therefore reduce the morbidity and mortality among this group of patients in India.Therefore, regular assessment of renal function is required to identify renal impairment, to monitor disease progress and to assess baseline parameters prior to commencement of treatment with HAART and also after HAART started to monitor ART nephrotoxicity.

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