

Renal Disease Linked With HIV: A Single Center Experience

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Abstract

Introduction: HIV infection is an international health menace. In ART era, the incidence of systemic complications have reduced significantly, still renal diseases remain common in PLHIV. Current study was conducted with the goal to study renal involvement in PLHIV at a post graduate teaching multispecialty hospital of central India

Materials & Methods: Persons living with HIV attending various OPD or admitted in medicine or nephrology units of the hospital were included in this study. All enrolled patients were evaluated for renal involvement with spot urine protein creatinine ratio and serum creatinine estimation. Other investigations were performed to rule out secondary causes of renal disease. Advanced investigation was done as when required including renal biopsy in consenting patients.

Observations & Results: In present study 546 patients were evaluated, of which 78(14.3%) had renal dysfunction. Of these, 47(60.3%) patients were not on ART and 31(39.7%) patients were on ART. Of the patients not receiving ART, 47(15.9%) patients had renal dysfunction while 31(12.4%) patients on ART had renal dysfunction. The incidence of renal dysfunction was significantly low in patients on ART. Renal biopsy was performed in 11 patients and Mesangioproliferative and Membranoproliferative morphologies were the commonest finding

Conclusion: The current study shows that fair number of HIV patients has renal involvement and timely intervention in form of ART and frequent monitoring for occurrence of renal dysfunction can help the treating physician in early intervention for renal issues in PLHIV.

Key words: HIV, Renal disease, PLHIV, creatinine, ART, serum

Introduction

Human immunodeficiency virus (HIV) infection is an international menace associated with significant mortality and morbidity. The presentation has changed and life expectancy of patients has shown a lot of improvement since the availability of highly active antiretroviral therapy (HAART). In India, the government supported antiretroviral therapy(ART) programs have made

the quality of life and outcomes of persons living with HIV (PLHIV) much better.¹ These advances have also reduced the occurrence of opportunistic infections and the incidence of systemic involvements due to HIV also have reduced significantly.²

Renal diseases are common in HIV patients and the spectrum of renal involvement in HIV is very wide. These patients are at risk for both Acute kidney injury (AKI) and Chronic kidney diseases (CKD) due to medication related nephrotoxicity, HIV associated nephropathy (HIVAN), immune complex kidney disease, thrombotic microangiopathies, and renal disease due to coinfection with Hepatitis B or C virus or due to co-existent illness like diabetes, hypertension etc. superimposition of renal impairment on a complex disease such as HIV infection increases the burden of comorbidities and, predicts a worse outcome in this population.³

The spectrum of renal involvement in Indian patients cannot be directly correlated with international data due to diversity in the population and demographics of various regions. The Indian data regarding HIV related renal diseases are sparse despite having a large cohort of persons living with HIV (PLHIV). Larger and longer prospective studies are needed to assess the actual prevalence, risk factors, clinical course, morbidity and mortality of HIV related renal diseases. This will help in the early diagnosis and treatment of such diseases and hence will reduce the morbidity and mortality due to renal diseases in HIV infected patients.

The current study was conducted with objective to assess the prevalence, risk factors and spectrum of renal diseases that can be attributed to HIV and the impact of ART on the renal illness.

Material and methods

This single center prospective observational study was conducted at a post graduate teaching institute of central India with dedicated HIV care and Nephrology units. Prior to study, institutional ethic committee clearance was obtained and all procedure was followed in accordance with revised Helsinki declaration. All consecutive HIV seropositive patients (PLHIV) over the age of 18 years attending the medicine outpatient department, ART center's HIV clinic, renal clinic or admitted under general medicine or nephrology subunit, were considered for screening for renal disease.

PLHIV less than 18 years age, pregnant females, person not willing to give written consent, patients with pre-existing chronic kidney diseases not related to HIV (Renal disease due to Diabetes Mellitus, Systemic Hypertension, Collagen vascular diseases etc) and patient with diagnosed malignancy were excluded from the study. Patients with factors associated with confounding factors for proteinuria like recent heavy exercise, cardiac failure, urinary tract infection, acute inter-current illness were excluded and reevaluated on the next visit if the confounding factor were removed.

Detailed history with special focus on the duration of illness, the ART regimens taken and there adherence, CD4/CD8 count progression and any history or features of renal involvement was taken and the previous records were analyzed according to predefined format.

All patients were evaluated for renal illness with urine evaluation in form urine routine microscopy and proteinuria quantification with either 24 hour urine protein estimation or with spot protein creatinine ratio, biochemical parameters (serum creatinine, urea, uric acid, and serum sodium & potassium), hematological evaluation (complete blood picture and hemogram), radiological evaluation (Ultrasonography of kidneys and urinary bladder). Additional investigation in form of complement analysis (Complement C3, C4 levels), autoimmune disease panel (ANA, Anti DsDna, ANCA etc.) and renal biopsy with PAS, Hematoxylin & Eosin and Congo red stain were considered if deemed needful on case to case basis. Immunofluorescent microscopy and electron microscopy were not done due to lack of availability at the institute. AKI was defined by KDIGO criteria with elevation in serum creatinine or fall in urine output in 2 to 7 days.⁴

Patients having significant proteinuria (spot protein 1+ or daily estimated proteinuria more than or equal to 500 mg) or serum creatinine more than 1.5 mg% were considered as having renal function impairment or renal involvement in present study.

For statistical analysis, all the collected data was entered into Microsoft excel sheets and analyzed with Microsoft SPSS-22. Suitable parametric and non-parametric tests were applied for assessment of data namely, Chi square test for non-continuous variables, Analysis of variance for continuous variables ANOVA and Tukey pair wise analysis, Z test etc.

Results

In present study, over the period of one year 546 patients were enrolled, of which 324 (59.3 %) were males and 222 (40.3%) were females. The study population was divided into two groups based on the treatment status, and 295(54.1%) of the studied patients were ART naïve i.e. not on ART at the time of enrollment into study whereas 251(45.9%) were already on ART. Most of the studied patients were in their fourth (34.7%) and the third decade (30.2%).

Among the study population, 512 (93.8%) were outpatients and 32 (6.2%) were inpatients. Of the outpatients, 46.8% were on ART and of admitted patients 32.3% were on ART.

In present study 23.4% patients were in CDC stage 1 (CD4>500), 45.9% patients were in CDC stage 2 (CD4 200 to 499) and 30.7% patients were in stage 3 (CD4<200). Of the patients who were not on ART, 20.3% were in CDC stage 1, 40.3% were in CDC stage 2 and 39.3% were in CDC stage 3, whereas of those on ART 26.7% were in CDC stage 1, 52.6% were in stage 2 and only 20.7% were in CDC stage 3.

Duration of illness of majority of the study population (81.6%) was less than 2 years while 7% the study population had duration of illness more than 5 years. Among those who were on ART, majority (80.07%) were receiving ART over 2 years. Maximum duration of therapy among our study population was 8 years.

In the current study, of the patients already receiving ART, 52.2% patients were on Zidovudine based regimen, 46.6% patients were receiving Tenofovir based regimens while 2 of the patients were receiving protease inhibitor based therapy. The regimens being used were Zidovudine+ Lamivudine+ Nevirapine, (ZLN) regimen in 39.8% patients, Zidovudine+ Lamivudine+

Efavirenz (ZLE) regimen in 12.4% patients, Tenofovir+ Lamivudine+ Nevirapine (TLN) in 18.3% and Tenofovir+ Lamivudine+ Efavirenz (TLE) regimen in 28.3% patients.

Fifty nine (10.8%) patients had elevated serum creatinine of whom 35(59.3%) were not on ART and remaining 40.4% patients were on ART. Among the patients not on ART, 35(11.9%) had elevated Creatinine. Only 24(9.6%) patients among those on ART had elevated serum Creatinine (P value- 0.000).

In present study 58(10.6%) patients had proteinuria and of them 23(39.7%) patients were on ART whilst 35 (60.3%) patients were not on ART. Thirty five of the patients who were not on ART had proteinuria which amounted to 11.8% of all ART naive patients while 23 (9.2%) of the patients on ART had proteinuria.

Presence of significant proteinuria or elevated serum creatinine either alone or in combination, was taken as marker of renal dysfunction in current study, and cumulatively, 78(14.3%) patients of the study population had renal dysfunction. Of these, 47(60.3%) patients were not on ART and 31(39.7%) patients were on ART. Of the patients not receiving ART, 47(15.9%) patients had renal dysfunction while 31(12.4%) patients on ART had renal dysfunction(Table1)

Table 1: Renal dysfunction among the study population

Rx	Renal dysfunction (Abnormal Creatinine/Proteinuria)		Total
	Present	Absent	
Not on ART	47	248	295
	15.9%	84.1%	100%
on ART	31	220	251
	12.4%	87.6%	100%
Total	78	468	546
	14.3%	85.7%	100

In our study 71.2% patients among those who had renal dysfunction had CD4 count less than 200 and 28.8% had CD4 counts in between 200 to 499. One fourth 25% of patients with CD4 count less than 200 developed renal dysfunction whereas only 4.5% patients among those with CD4 more than 200 developed renal dysfunction (P value < 0.001). (Table2).

Table 2: Relation between Renal dysfunction and CD4 count

CD4 Count	Serum Creatinine				Total
	> 1.5	%	<1.5	%	
< 200	42	71.2%	126	25.9%	168
	25%		75%		100%
200-499	17	28.8%	234	48.1%	251
	6.8%		93.2%		100%
≥500	0	0%	127	26.0%	127
	0%		100%		100%
Total	59	100%	487	100%	546

Among those patients with renal dysfunction, 83.1% patients were diagnosed within past 3 years. 15.3% patients had duration of illness 3 to 6 years and only 1.6% patients had duration of illness more than 6 years. The influence of duration of illness on the risk of renal dysfunction was analyzed using one way ANOVA and Tukey pair wise analysis and found to be non-significant. Similarly, among those patients with renal dysfunction, 83.3% patients were on ART since less than 3 year while 16.7% patients were initiated on ART over three years duration. The impact of duration of ART on renal dysfunction was found to be statistically non-significant.

On correlating the ART regimen with occurrence of renal dysfunction, 39.1% of the patients who had renal dysfunction were on Zidovudine based regimen and 60.9% patients were receiving Tenofovir based regimen. Among those patients on Zidovudine based regimen, 6.9% patients had renal dysfunction whereas 11.9% patients on Tenofovir based regimen had renal dysfunction. These findings were statistically not significant (Table3).

Table 3: Renal dysfunction and ART regimen

Drug regimen	N	Mean	SD	SE Mean
Zidovudine based	131	0.731	0.325	0.028
Tenofovir based	118	0.807	0.385	0.035
T-Value = -1.69 P-Value = 0.093 DF = 249 Non significant				

In current study, renal biopsy was performed on 11 of the patients with renal dysfunction and histopathological analysis was done subsequently. The most common histopathological finding on histopathological examination was Mesangioproliferative glomerulonephritis (MesPGN) in five patients, followed by Membrano proliferative glomerulonephritis (MPGN) in three and acute interstitial nephritis (AIN) and renal Amyloidosis in one patient each. Renal biopsy of one patient showed no glomeruli and second biopsy could not be done as patient denied the consent for repeat procedure.

Discussion

This study was conducted on 546 PLHIV of which majority (59%) were males and most patients were in their third and fourth decades. Most of the studied patients were outpatients and less than ten percent were hospitalized.

Elevated serum creatinine and presence of significant quantifiable proteinuria were considered as diagnostic of renal involvement. Gupta et al in their study found that the incidence of renal dysfunction in a large cohort of patients was 13.8%, similar to these findings the prevalence of renal dysfunction in our study was 14.3%.⁵

Proteinuria is one of the defining criteria of CKD and is a risk marker for progression to end-stage renal disease (ESRD). HIV-associated nephropathy (HIVAN)-related risk factors, including an elevated HIV RNA level, a low absolute CD4 lymphocyte count, apolipoprotein-1 genetic polymorphism and hepatitis C and hepatitis B coinfection, are associated with proteinuria. Overt proteinuria has been encountered in 14-50 per cent of HIV/AIDS patients in various studies depending upon method of screening and patient population.^{5,6,7,8} We found that nearly 10% patients of our study population had proteinuria while another 10% had elevated serum creatinine. Our findings are similar to Antonella et al who reported prevalence of proteinuria as 20% while contrary to our findings, Gupta et al reported prevalence of proteinuria of 3.4% patients in their study population while in a study done by TM Han et al on 615 HIV positive patients in South Africa, the prevalence of proteinuria was 6.17% showing the diverse findings from various studies.^{5,9,10}

AKI is a common complication in PLHIV and is more common in patients with preexisting CKD. PLHIV have an increased risk for AKI during hospitalization, due to volume depletion, sepsis and the acute administration of nephrotoxic medications or radiocontrast. Although HAART has improved long-term outcomes of HIV-infected patients, mortality of AKI in HIV-infected patients is still high.^{5,9,10,11} Lopes JA et al reported incidence of AKI of 18% in a cohort of 489 hospitalized PLHIV, while in our study 18 patients (3%) had AKI as per the KDIGO criteria. We excluded secondary causes associated with AKI like use of non-ART nephrotoxic drugs, acute systemic illness, sepsis etc. and our cohort consisted primarily of relatively stable OPD patients unlike hospitalized patients of Lopez et al.¹² Due to these difference in studied populations and criteria for defining AKI there is a huge variation in reported incidence of AKI between different studies.^{11,12}

Various studies including those by Gupta et al have shown that the HAART use is associated with reduction in incidence, and in some cases improvement of renal dysfunction associated with HIV.⁵ Reflecting the same, in our study, 11.9% patients among those who were not on HAART had renal dysfunction whereas 9.6% patients among those on HAART had renal dysfunction and this difference was statistically significant. In another prospective cohort study done in 3329 patients who initiated ART under routine clinical care, ART initiation significantly slowed the rate of renal function decline over a median follow up of 4.8 years (loss of 1.4 after versus 2.2 mL/min per 1.73 m² per year before initiation).¹³

In our study 71.2% of the patients with renal dysfunction had CD4 count less than 200 and 25% of patients with CD4 count <200 developed renal dysfunction whereas only 4.5% patients among those with CD4 >200 developed renal dysfunction. Low CD4 count is significant risk factor for renal dysfunction in HIV patients and our findings are similar to studies done by Jotwani V et al and Kalayjian RC et al who also reported that low CD4 count is a strong risk factor for chronic kidney diseases in HIV positive patients.^{13,14}

In our study, among those patients with renal dysfunction, 83.1% patients were having duration of illness 3 years or less. 10.6% of the patients with duration of illness less than 3 years had renal dysfunction and 11.6% of the patients with duration of illness more than 3 years found to have renal dysfunction. The effect of duration of illness on the risk of renal dysfunction was found to be non-significant. Thus our study showed that there is no association between risk of renal dysfunction and duration of illness in HIV positive patients.

Tenofovir is a known tubulotoxic drug and various studies like study by Kalayjian RC et al have showed that Tenofovir is associated with an increased risk of renal impairment in HIV patients. In our study, 39.1% patients among those who had renal dysfunction were on Zidovudine based regimen and 60.9% patients were receiving Tenofovir based regimen. Among those patients on Zidovudine based regimen, 6.9% patients had renal dysfunction whereas 11.9% patients on Tenofovir based regimen had renal dysfunction. The relation between regimen of ART and risk of renal dysfunction was statistically non-significant in our study contradicting the other studies, this could be because ours was a cross sectional study whilst study by Kalayjian RC et al was long term follow up study.¹³

Renal biopsy was considered in all patients with significant proteinuria and advised strongly in patients with nephrotic range proteinuria or with active urinary sediments in form of RBC more than 5/HPF unexplained by any other cause. In present study biopsy was performed in 11 patients with renal dysfunction and histopathological analysis using light microscopy was done subsequently. Other patients with renal dysfunction denied the procedure or had contraindications for renal biopsy. The commonest pathology noted in our study were MesPGN and MPGN. The classical collapsing FSGS of HIVAN was not found in our study which is very rare in post HAART period and in Indian scenario. A report comparing the experience in European and North American centers showed that in Black patients with HIV, FSGS was the commonest lesion occurring in about 80 per cent of renal biopsies.¹⁵ In Indian experiences, Varma et al described 1 patient with collapsing FSGS and four with other variants of FSGS out of total of 25 biopsies of PLHIV, Naz et al reported first case of classical HIVAN from the State of Jammu and Kashmir while Gupta et al found two cases showing collapsing FSGS in their study involving 25 biopsies but features of classical HIVAN was absent in this study too. These studies also supports that classical HIVAN is rare in Indian population.^{5,16,17}

Conclusion

PLHIV are at increased risk of renal dysfunction due to various factors like direct HIV infection, ART and other opportunistic infection prophylaxis drugs, and factors unrelated to HIV like diabetes and hypertension. The study also confirms that HAART use is associated with reduction in occurrence of renal diseases in PLHIV but still a significant percentage of HIV positive patients have renal dysfunction even in the current era. Periodical estimation of proteinuria along with frequent monitoring of serum creatinine will help the treating teams in discovering the renal complications in PLHIV at an earlier stage. India's demographic diversity warrants more studies with involvement of multiple centers, longer follow up and intervention so as to define the pattern and risk factors specific to Indian population of various regions.

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