ORIGINAL ARTICLE

Outcome of HIV Related Kidney Diseases Treated with Combined Antiretroviral Therapy (cART)

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Abstract

Introduction: The safe and effective treatment of HIV-associated renal diseases with cART can decrease the progression to ESRD and also improve the morbidity and mortality secondary to renal failure.

Material and Methods: HIV positive patients with clinical kidney disease were the subjects of this study. The diagnosis of HIV was established using immunochromatographic assays. The patients were subjected to meticulous history, physical examination, laboratory investigations and kidney biopsy. Patients were treated with combined antiretroviral therapy and enalapril. They were followed at 3 months interval for one year. Short term outcome was assessed using changes in serum creatinine and proteinuria. Long term outcome assessments were done using progression to end stage renal disease and patients survival.

Result: Ten (Male=7; Female=3) HIV patients with clinical renal disease were included in this study. Their age ranged between 26-55 (Mean=40.5±8.8) years. The mean serum creatinine at the baseline, three, six, nine and twelve months was 2.46, 2.09, 2.43, 2.46 and 2.58 mg/dl respectively. The mean e-GFR by MDRD equation at 0, 3, 6, 9 and 12 months was 40.9, 45.5, 48.2, 51.1 and 52.5 ml/min/1.73m^2 respectively. The mean twenty four hour urinary protein excretion at 0, 3, 6, 9 and 12 months was 3.01, 2.82, 2.22, 2.02 and 1.79 grams respectively. Six patients showed improvement in creatinine and e-GFR, whereas worsening of renal function was seen in four patients. Proteinuria decreased in seven patients, whereas it remained unchanged in three patients. There was no mortality at the end of one year of follow up.

Conclusion: Treatment with combined ART and ACEIs slows the progression of HIV-associated kidney disease, decreases proteinuria and improves the GFR.

Introduction

HIV infection affects almost every system of the human body and the frequency of renal involvement is becoming increasingly common.[1] With the dramatic improvement in the patient survival in the era of combined antiretroviral therapy (cART), complications such as kidney, liver and cardiac diseases have become common causes of mortality in HIV positive patients.[2] There is a racial variation in HIV associated renal disease.[1] Renal disease has been reported in approximately 6.0 to 45% of HIV infected individuals in Africa, 24 to 83% of these cases had classical HIV associated nephropathy in South Africa.[3] HIV associated CKD was reported in 7.5 to 9.7% of HIV infected individuals from European countries.[3] Rates of HIV associated CKD was reported 19% in Hong Kong, 1.1 to 5.6% in Brazil, 18% in Switzerland, 27% in India and 20% in Iran.[3] HIV associated kidney disease can be caused directly or indirectly by the HIV or by the drugs used in the treatment of HIV infection.[1] The spectrum of renal involvement is wide and ranges from acute kidney injury (AKI) secondary to c-ART or nephrotoxic antimicrobials to CKD due to collapsing glomerulopathy, microangiopathy and various forms of immune complex glomerulonephritis.[1] In addition, the aging cohort of HIV-positive patients is at increased risk for kidney disease related to hepatitis B or C virus co-infection and associated comorbid diseases such as diabetes and hypertension.[4] The safe and effective treatment of HIV associated renal diseases can decrease the progression to ESRD and also improve the morbidity and mortality secondary to renal failure.However, currently there is a dearth of studies on the pattern of renal involvement and the treatment of HIV associated renal dysfunction from the Indian subcontinent. With this background, we conducted this study with the aim of observing the effect of c-ART on the outcome of HIV associated renal diseases in Indian patients at our centre.

Material and Methods

This Prospective Observational Study was conducted in the department of Nephrology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, India from November 2015 to July 2017. The study was approved by the institute ethics committee. The diagnosis of HIV was established using immunochromatographic assays. Ten HIV positive patients with clinical kidney disease were included in this study. The clinical kidney disease was defined by the presence ofproteinuria > 500 mg per day or serum creatinine >1.5 mg/dl or an active urinary sediment. Patients aged <18 or >65 years, having end stage renal disease, non-compliant to treatment or having pre-existing / coexisting renal disease attributable to other causes like diabetes, hypertension, connective tissue disorder etc. were excluded from the study.

The patients were subjected to

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meticulous history and physical examination.The laboratory investigations included urine analysis, 24 hour urinary protein estimation, serum creatinine, electrolytes, calcium, phosphate, alkaline phosphatase, SGOT, SGPT, HBsAg, Anti HCV, CD4 count and ultrasound scan of the kidneys. Serum ANA, anti-dsDNA antibodies, and complement levels were done in selected cases. Renal biopsy was done in eight patients. One patient refused biopsy whereas another one had contracted kidneys. The samples were preserved in 10% buffered aqueous formaldehyde solution for light microscopy and sent immediately for histopathologic examination. The tissue sections were cut at 2 micrometer thickness and were studied under light microscopy using hematoxylin and eosin stain, periodic acid–schiff stain, acid fuchsin orange G and periodic acid silver methamine stains. Congo red stain was used in selected patients where amyloid was suspected based on the presence of organized extracellular deposits in the glomeruli. Electron microscopy and immunofluorescence studies were not done due to lack of facility at our centre. Patients received either a combination of tenofovir 300 mg, lamivudine 300mg and efavirenz 600 mg per day or abacavir 600 mg, lamivudine 300mg and efavirenz 600 mg per day. Tenofovir based regimen was given to the patients having serum creatinine less than 1.5 mg/dl whereas abacavir based regimen was given to the patients with serum creatinine more than 1.5 mg/dl. Dose adjustment for GFR levelwas done for lamivudine. All patients received ACEI (enalapril 5 to 10 mg per day). Immunosuppressive agents were not used. Renal function test, twentyfour hour urinary protein excretion CBC and CD4 count were measured atleast every three months. The data was systematically collected, coded and analyzed using SPSS 20 software and the results were recorded as mean, median and standard deviation. Short term outcome were assessed using changes in serum creatinine and proteinuria. Long term outcome assessment were done using progression to ESRD and patients survival.

Table 1: Clinical renal syndrome at presentation (n=10)

Syndrome	Number	%age
Subnephrotic Proteinuria	2	20
Nephrotic Syndrome	2	20
Acute kidney injury (AKI)	2	20
Chronic kidney disease (CKD)	3	30
Acute Glomerulonephritis	1	10
Total	10	100

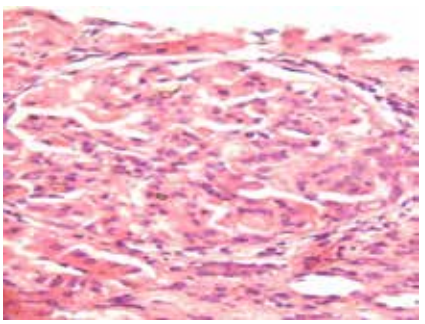


Fig. 1: Mesangioproliferative GN (H&E,400×)

Observations and Result

Ten (male =7, females = 3) patients with age range of 26 to 55 (mean = 40.5±8.8) years were included in the study.80% of the patients had acquired the infection through heterosexual contact. Physical examination revealed edema (60%), pallor (40%) and hypertension (20%) . Oliguria was noted in 20% of the patients. CKD (30%), AKI (20%), subnephrotic proteinuria (20%), nephrotic syndrome (20%) and acute glomerulonephritis (10%) were the presenting renal syndromes (Table 1). Markers of hepatitis B and C infection were negative in all patients. C3 and C4 were low in three and one patient respectively. ANA and anti-

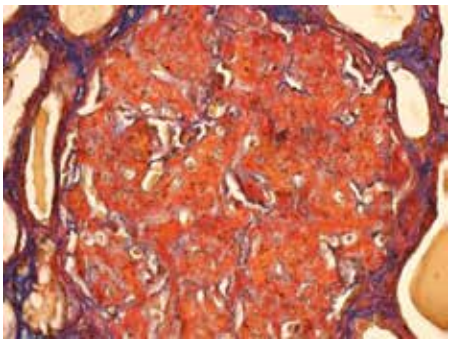


Fig. 2: Amyloid (Congo Red 400×)

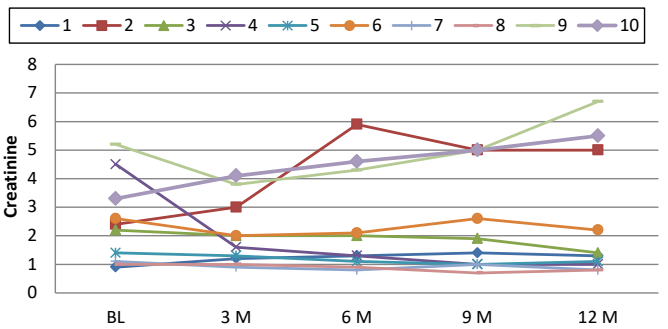


Fig. 3: Pattern of serum creatinine in individual patients at various time intervals (BL= baseline, M= month)

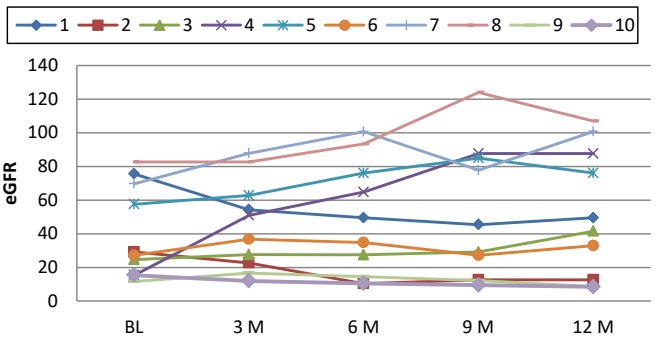
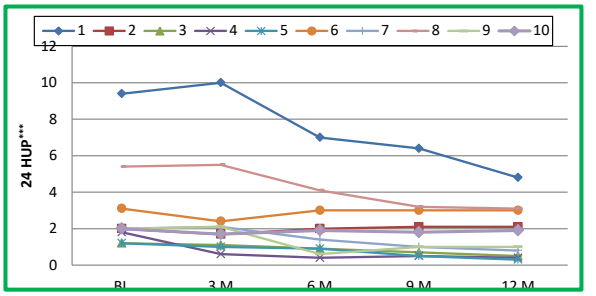


Fig. 4: Pattern of estimated GFR in individual patients at various time intervals. (BL= baseline, M= month)



*** =twenty four hour urinary protein

Fig. 5: Pattern of Proteinuria in individual patients at various time intervals. (BL= baseline, M= month)

Table 2: Parameters on followup (n=10)

Parameter	Mean ± SD	Min.	Max.
Sr. Creatinine (mg/dl)			
Baseline	2.46±1.49	1	5
3 Months	2.09±1.16	1	4
6 Months	2.43±1.82	1	6
9 Months	2.46±1.83	1	5
12 Months	2.58±2.25	1	7
eGFR ** **(ml/min/ 1.73m²)**			
Baseline	40.9±27.50	12	83
3 Months	45.5±26.78	12	88
6 Months	48.2±34.07	10	101
9 Months	51.1±39.90	10	124
12 Months	52.5±38.08	9	107
24 HUP, g/day			
Baseline	3.01±2.55	1	9
3 Months	2.82±2.86	1	10
6 Months	2.22±2.03	0	7
9 Months	2.02±1.83	1	6
12 Months	1.79±1.48	0	5
CD-4/microL			
Baseline	292.4±24.82	250	334
3 Months	323.1±28.49	288	360
6 Months	339.1±22.68	307	365
9 Months	371.1±32.71	316	411
12 Months	387.7±35.94	300	415
Hb (g/dl)			
Baseline	10.03±1.38	9	13
3 Months	10.40±1.89	8	14
6 Months	10.49±1.73	8	14
9 Months	11.86±2.62	9	16
12 Months	11.32±1.79	9	14

***using MDRD equation*; 24 HUP: Twenty four hour urinary protein

dsDNA antibodies were negative in all patients. Mesangioproliferative glomerulonephritis (Figure 1) was the commonest pattern (37.5%) of renal histology. DPGN was present in 2 (25%) patients. Amyloid nephropathy (Figure 2), membranous nephropathy and acute interstitial nephritis were present in one (12.5%) patient each.

The mean serum creatinine at the baseline, three, six, nine and twelve months was 2.46, 2.09, 2.43, 2.46 and 2.58 mg/dl respectively. The mean e-GFR by MDRD equation at 0, 3, 6, 9 and 12 months was 40.9, 45.5, 48.2, 51.1 and 52.5 ml/min/1.73m² respectively (Table 2). The trends in serum creatinine and e-GFR in individual patients during the follow up period is shown in Figures 3 and 4 respectively.

The mean twenty four hour urinary protein excretion at 0, 3, 6, 9 and 12 months was 3.01, 2.82, 2.22, 2.02 and 1.79 grams respectively (Table 2). 49% and 41% reduction in proteinuria was noted at the end of one year in the two patients with nephrotic syndrome due to diffuse endocapillary proliferative glomerulonephritis and membranous nephropathy respectively. The trends in urinary protein excretion in individual patients during the follow up period is shown in Figure 5.

Table 3: Renal and patients outcome

Outcome		Number	%age
eGFR/ creatinine	Improved	6	60
	Worsened	4	40
24 hour urinary protein excretion	Decreased	7	70
	Remained stable	3	30
Patient outcome	Survived	10	100

The mean CD4 count at 0, 3, 6, 9 and 12 months was 292, 323, 339, 371 and 387 per microL respectively suggesting an overall response to cART. The mean hemoglobin at base line 3, 6, 9 and 12 months was 10.03, 10.40, 10.49, 11.8 and 11.3 g/dl respectively (Table 2).

Six (60%) patients showed improvement in serum creatinine / estimated GFR during the study period (Table 3). Two of them had presented with AKI due to acute tubulointerstitial nephritis and mesangioproliferative glomerulonephritis with features of acute pyelonephritis. Two patients had presented with subnephrotic proteinuria due to mesangioproliferative glomerulonephritis. CKD due to endocapillary proliferative glomerulonephritis with underlying tubular atrophy and interstitial fibrosis was present in one patient. In this patient the endocapillary glomerulonephritis may have occurred in the presence of an already existing underlying chronic kidney disease. Another patient who presented with nephrotic syndrome due to membranous nephropathy also showed improvement in serum creatinine / estimated GFR during the study period.

Worsening of serum creatinine occurred in 4 (40%) patients and doubling of serum creatinine in one patient with amyloid associated CKD. The other three patients in whom worsening of serum creatinine was seen had presented with CKD, acute glomerulonephritis and nephrotic syndrome with biopsy showing diffuse endocapillary proliferative glomerulonephritis.

Proteinuria decreased in 7 (70%) and remained unchanged in 3 (30%) patients (Table 3). The three patients in whom the proteinuria did not improve (remained stable) had presented with CKD due to amyloidosis, acute glomerulonephritis (biopsy not done) and subnephrotic proteinuria due to mesangioproliferative glomerulonephritis one each.

All patients completed one year of follow up. Thus, the patient survival at one year was 100% (Table 3).

Discussion

Human immunodeficiency virus infection / AIDS is a major global health problem and HIV associated kidney diseases further increases the mortality and morbidity in the HIV infected patients.[6,7] HIV associated nephropathy (HIVAN), a peculiar collapsing variant of FSGS was the first reported renal lesion in HIV positive patients.[8] Since then, a wide spectrum of renal diseases have been reported in HIV positive patients. After the introduction of cART this spectrum has changed. There is a reduction in the incidence of HIVAN, whereas immune complex kidney diseases and comorbidity associated kidney diseases have emerged as important causes of renal dysfunction[9].

The mean age of the subjects in our study was 40.5 ± 8.89 years with a range of 26 to 54 years which is similar to the age reported in other studies.[10-13] Majority of the patients in our study were males. The male to female ratio was 2.3:1. The male predominance has also been reported in other studies from India,[3,10] Africa,[14,12] Brazil and United States.[15] The higher number of males in our study may be a reflection of higher mobility of this age group in search of livelihood, high sexual activity phase, and to some extent highly emotional and stressful life which usually prevails in this age and sex group. Heterosexual contact was the probable mode of transmission of HIV in majority (80%) of our patients. Two patients had history of blood transfusion and use of injectable medications from quakes in the past. Similar mode of transmission was reported in other studies.[16,10,17]

Edema and Pallor were present in six (60%) and four (40%) patients respectively. Hypertension and oliguria were present in two patients(20%) each. None of the patients had gross hematuria at the time of presentation. *Gupta V*[16] *et al.* reported that fever (35%), edema (27%), asymptomatic (27%), oliguria (19%), weight loss (15%), gastroenteritis (7%), and altered sensorium (4%)

were the clinical manifestation at the time of presentation. *Prakash[3] J et al.* reported edema, oliguria and gross hematuria in 8.1 %, 6.4 % and 1.6% of a total of 393 HIV positive patients of which only 136 patients had renal involvement. Vali PS[17] *et al.* reported hypertension in 40% of the patients. We excluded the patients with kidney dysfunction attributable to causes other than HIV infection. This may explain the different clinical features at the time of presentation in our study.

CKD was the presenting renal syndrome in three (30%) patients. Subnephrotic proteinuria, nephrotic syndrome and AKI were present in two patients (20%) each. One patient (10%) presented with features of acute glomerulonephritis. Another study from India reported that AKI, nephrotic syndrome, rapidly proliferative renal failure, CKD, accelerated hypertension and acute nephritic syndrome were the presenting renal syndromes.[17] This study included all HIV patients with kidney disease irrespective of etiology. In our study the mean serum creatinine, estimated GFR and twenty four hour urinary protein at the time of presentation were 2.46 mg/dl, 40.09 ml/min/1.73 m^2 and 3.01 grams respectively. The mean serum albumin, total proteins and CD4 count were 3.7 g/dl, 6.4 g/dl and 292 per micoL respectively. In a study by *Atta MG[14] at al.* the baseline mean serum creatinine, estimated GFR, proteinuria (g/day) and CD4 count respectively were 4.7 mg/dl, 20 ml/min/1.73 m^2, 7.2 grams/day and 160/microL. This cohort had a more severe disease compared to our patients. This may be because this cohort included only biopsy proven HIVAN, a more severe form of HIV associated kidney disease which occurs more commonly in advanced HIV infection and was not seen in our patients. *Booth JW[13] et al.* reported 56 cases of HIV associated immune complex disease. The mean estimated GFR and proteinuria at the time of presentation were 49 ml/min/1.73m^2 and 2.4 g/d respectively. The base line parameters in this study are comparable to our study which may be because majority of our patients also had histologic features of HIV associated immune complex disease.

ANA and anti-dsDNA were negative in all patients. C3 was low in three patients; two of them had diffuse endocapillary proliferative glomerulonephritis. Another patient who presented with acute glomerulonephritis (biopsy not done) had low C3 and C4. *Vali PS[17] et al.* reported 27 cases of kidney disease in HIV patients, of which two patients had a low serum C3 level. All patients in our study were negative for hepatitis B and hepatitis C infections. *Booth JW[13] et al.* reported 18.5% and 7.6% prevalence of hepatitis B and hepatitis C infection respectively in HIV associated immune complex kidney diseases.

Mesangioproliferative glomerulonephritis (Figure 1) and Diffuse endo-capillary proliferative glomerulonephritis was present in three (37.5%) and 2 (25%) patients respectively. Amyloid nephropathy (Figure 2), membranous nephropathy and acute interstitial nephritis were present in one (12.5%) patient each. Other studies from India,[3,16] Thailand[18] and Italy[19] have also reported Mesangioproliferative Glomerulonephritis as the most common histologic renal lesion in HIV infection. However, in contrast to our study, mesangioproliferative GN has been reported infrequently from the western world.[20] HIVAN has been consistently reported to be the most common glomerular lesion in HIV-seropositive patients from the US, Brazil, African countries, and Western Europe.[21] Classic HIVAN histopathology can be seen in adults and children at any stage of HIV infection but is most common in the advanced diseases, including AIDS.[22] West African descent is highly susceptible to classic HIVAN.[22] HIVAN has been reported to a lesser degree in Hispanic population and variably in Asian Indian cohort.[23,24] However, the disease is notably absent in Swiss–European and Thai population.[18] The current prevalence of HIVAN is declining as result of the widespread use of cART.[22]

During the follow up period serum creatinine / e-GFR and proteinuria improved in 60% and 70% of the patients respectively. Other studies have also reported improvement in HIVAN[25,26] and HIVICD[16,13] with the use of combined ART. Atta MG[14] et al. and Nicholas Weaner[26] et al. reported stabilization or increase in GFR and decrease in proteinuria in biopsy proven HIVAN patients treated with combined ART. *June Fabian [27] et al* .reported that the use of ART was associated with rapid and sustained improvement in GFR and a decrease in proteinuria irrespective of the histological class but the histological improvement was inconsistent and lagged behind the clinical response. Robert C. Kalayjiana[28] noted an improvement in renal function and patient survival in HIV positive CKD patients treated with c-ART. Thus, the results of our study are consistent with these studies.[14,27,28] The consistent improvement in proteinuria in our study may be attributed to both c-ART and use of ACEI in all patients.

The one year patient survival in the present study was 100%. *Gupta V[16] et al.* reported two deaths in 26 HIV associated kidney disease patients over a mean follow up of eight months. Both patients had received immunosuppression with low dose steroids. *Bige N et al.* reported that 71% of HIVAN patients treated with ACEI and c-ART either developed ESRD or died within two years.[29] *Post FA et al.* reported that 48% of HIVAN patients treated with c-ART and ACEI developed ESRD with in four years.[30] Patients with HIVICD had a lower cumulative progression to ESRD compared to patients with HIVAN.[31]

Conclusion

This study describes the clinico-histopathologic profile of HIV related kidney disease and the effect of combined antiretroviral therapy on its outcome. Treatment with combined ART and ACEIs slows the progression of kidney disease, decreases proteinuria and improves the GFR. Further well designed and adequately powered studies are needed in Indian patients to classify the histologic patterns of HIV associated kidney diseases, explore the treatment option and to document long term patient and renal outcomes on combined antiretroviral therapy.

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