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STUDY OF ESTIMATION OF URINARY CYSTATIN –C FOR CORRELATION OF RENAL MANIFESTATIONSWITH THE IMMUNOLOGICAL STATUS OF HIV PATIENTS

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ABSTRACT

Aim: To study the clinical manifestation of renal involvement of HIV patients and its correlation with virologic load and CD4 T- cell count, with correlation with cystatin –c as early biomarker of renal involvement in HIV patients.

Methodology: Sample of 75 known retro-positive cases who attended Dr DY Patil medical college and hospital, DY Patil Vidyapeeth, Pimpri, Pune during the study period were selected. All procedures and interventions have been established only after obtaining adequate / appropriate consent in a prescribed form. Ethical clearance has been obtained from the Ethical clearance committee in a prescribed certificate.

Results: The spectrum of HIVAN manifests ions are equally distributed among male and female population. dipstick proteinuria is the most effective measure for screening of the patients for renal manifestations in patients with HIV. the significant proteinuria with >1+ on dipstick examination in patient with all other causes excluded (hypertension, diabetes mellitus) should always warrant for further investigation. 24 hour urinary and >3gm/dl spot

Upcr >3.5gm/dl were more associated with HIVAN. Duration of ART doesn't have any correlation with the renal disease or proteinuria if patient maintains good immunological status (CD4+-T –cells >500/microL) with good adherence to the HAART. The low CD4+T -cells is associated with the early onset of renal manifestation with most values below <200 cells /microL ,and poor adherence or lack of use of HAART ,as studies have revealed that the HIV virus stimulates the PODOCYTES to differentiate and podocytopathy is the hallmark of HIVAN and cause of proteinuria.

Conclusion: Hence urinary cystatin -c which is marker of tubular dysfunction is early marker of renal disease in HIVAN patients even before theonset of nephrotic proteinuria.

Keywords: HIV, Cystatin, HAART, CD+4, Podocytopathy, ART

INTRODUCTION

HIV infection is a global pandemic with estimated 36.7 million cases globally as per UNAIDS (united nation programme for HIV/AIDS, in 2016 95% cases reside in low income countries, with 50 % belonging to children <15 years and females combined[1]. AIDS was recognized first in USA in 1981 with AIDS defining complexes, 2 years later in 1983, HIV virus was isolated from a patient with lymphadenopathy.[2]

In 1985, ELISA test was developed which allowed massive screening programme and defining the HIV epidemic .IN 2016 ALONE 1.8 million new cases of HIV infection were detected globally, with majority of cases concentrated in high risk population like sex workers and their clients, I.V drug users, transgender people, and gay men.

There is over all globally increased prevalence In PLHA (people living with HIV and AIDS) and is due to increase in life span with global increase is availability and utilization of HAART (highly active antiretroviral therapy).

Among all the world counties east and south Africa regions are the hardest hit with about 50 % cases concentrated in this area. In Asia pacific itself the population distribution is very skewed; hence more than 50% cases are concentrated in three most populous countries of the world – china, India and Indonesia[3]

Between 2000-2016 there is 40% decline in new infection across world –clearly due to HIV prevention programme and increased provision of HAART – which decreases viral load and makes them less likely to transmit the virus to their sexual partner[4]

BURDEN OF HIV IN INDIA:

The first case of HIV was detected in Chennai in 1986, among female sex workers, as per 2015, India is home to third

largest population however with global prevalence of0.3% only[1]

The national plan for control of AIDS in India in NACO-.

It was launched in 1992 earlier as national aids control programme –(NACP-1)- where emphasis was on HIV surveillance in targeted group and prevention of high-risk activities, and screening of blood and blood products.

NACP-2 IN 1999- Marked the utilization of ART in diagnosed cases of HIV. NACP-3 in 2007- focused on expansion of support and access to treatment programme.[2]

As per 2017 there are total of 21.40 lakh PLHIV cases in India and 50 % of which reside in 4 states of India – Maharashtra, Andhra Pradesh, Tamilnadu and Karnataka.[3]

Aims and objectives: -

AIM: -

To study the clinical manifestation of renal involvement of HIV patients and its correlation with virologic load and CD4 T-cell count, with correlation with cystatin –c as early biomarker of renal involvement in HIV patients.

Objective: -

To study the role of HIV infection to cause renal manifestation.

To study the correlation between the virologic load and immune status (CD4 T – cell count) and renal manifestation of HIV patient on HAART.

To study the use of urinary CYSTATIN –C as an early bio marker for predicting the renal involvement in HIV patients.

Patients with HIV/AIDS satisfying inclusion and exclusion criteria from august 2019- august 2020.

Sample size: 75 patients.

INCLUSION CRITERIA

Patients who are HIV positive aged > 18 years and admitted in Department of GeneralMedicine.

Criteria for renal involvement. Significant proteinuria - >1+ on dipstick, Progressive decline in renal function.

USG indicating of renal abnormality (large kidney or echogenic kidneys)

EXCLUSION CRITERIA

History of concomitant hypertension, diabetes mellitus Patient with history of nephrotoxic drug abuse.

Patient diagnosed or documented with any form of auto immune renal disease Patient refusal or inability to provide informed consent

METHODLOGY:

Sample of 75 cases who attended Dr DY Patil medical college and hospital, DY Patil Vidyapeeth, Pimpri, Pune during the study period were selected. All procedures and interventions have been established only after obtaining adequate / appropriate consent in a prescribed form. Ethical

clearance has been obtained from the Ethical clearance committee in a prescribed certificate. Upon enrollment in the study, written consent was obtained and duly signed by the patients in a prescribed format.

RESULTS

In the present study, 75 HIV patients were recruited whose mean age was 39.6±10 years (Figure1). Of the 75 positive cases, 52% (n=39) were males and 48% were females (n=36). The mean age of females was 36.8±9.8 years and males were 42.2±9.6 years.

These patients were given different combinations of ART regimen like TLE regimen, RALTEGRAVIR+DALTEGRAVIR/RITONAVIR etc. The mean duration of ART regimen was 10.8 ± 6.8 years. Biochemical Parameters like Hemoglobin count (Hb), WBC, Platelets, Serum creatinine, Blood Urea, Na+, K+, Cl-, TSB, SGOT, SGPT, ALT, Total Protein, Serum Albumin, Spot UPCR, 24hr-urinary Protein, CD4 count on recruitment and after six months and urinary cystatin-C were analyzed to see the effect of the regimen duration on these parameter.

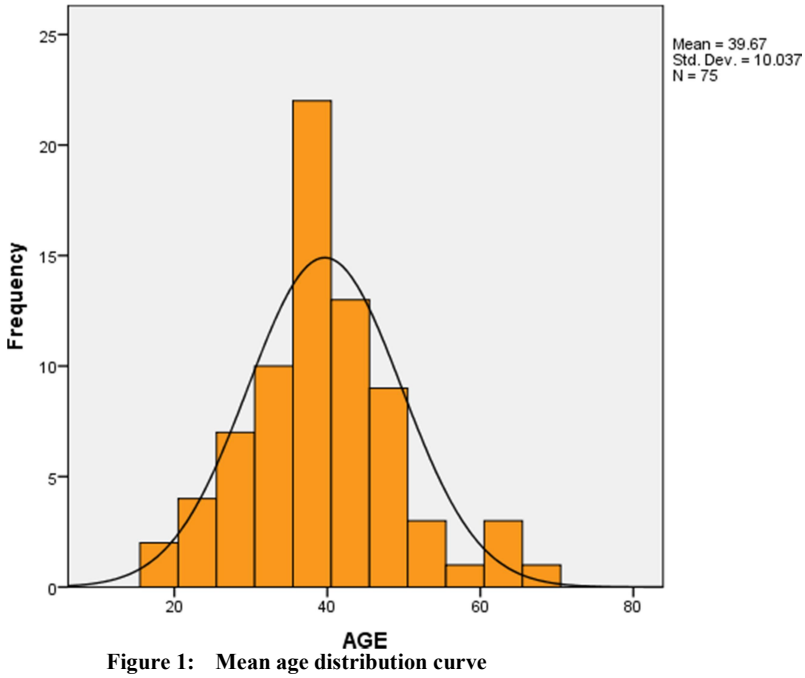

Figure 1: Mean age distribution curve

Table 1: frequency distribution table as per gender in study population

Gender	Frequency	Percentage (%)
Female	36	48
Male	39	52
Total	75	100

Table 2: age and gender wise distribution chart among study population

Age group	GENDER		Total
	Female (%)	Male (%)	
0-20	1(0.75)	1(0.75)	2
21-40	26(34.6)	17(22.6)	43
41-60	8(10.6)	18(24)	26
60-80	1(0.75)	3(4)	4
Total	36	39	75

Table 3: Different HAART regimens in study population

	Frequency	Percent
TLE	39	52
RDRi	23	30.6
RLoRi	11	14.6
TLRLoRi	1	1.4
ZLN	1	1.4
Total	75	100

Table 4: Prevalence of renal parenchymal changes in study population

	Frequency	Percent
B/L NORMAL SIZED KIDNEYS	58	77.2
B/L GRADE 1 RPD CHANGES	13	17.4
B/L GRADE 2 INCREASED ECHOTEXTURE NORMAL SIZE	3	4
B/L GRADE 3 RPD CHANGES	1	1.4
Total	75	100

Table 5: s. creatinine distribution in study population

Serum Creatinine Groups		
	Frequency	Percent (%)
<1	3	4
1.0-2	55	73.4
2.1-3	14	18.6
3.1-4	3	4
Total	75	100

The distribution of kidney size and changes in the architecture in the study population

Table 6: Distribution of 24 hour urinary protein in study population

24hr Urinary Protein		
	Frequency	Percent (%)
<1	51	68
1.0-2	7	9.4
2.1-3	12	16
3.1-4	5	6.6
Total	75	100

Dipstick proteinuria

Table 7: dipstick proteinuria prevalence in study population

Proteinuria -	Mild (+)	Moderate (++)	Gross (+++/++++)	No proteinuria
No of patients	37	14	16	8
Percentage (%)	49.3	18.6	21.3	10.6

Measure of dipstick proteinuria with CD4+ T-cell count at time of diagnosis

Table 8: dipstick proteinuria in correlation with CD4 T -cell count

CD4+ T- CELL COUNT/ micro L	<100	100-250	250-400	400-550	>550
Nil proteinuria	2	4	1	1	-
Mild (+)	5	17	4	5	6
Moderate (++)	3	6	4	1	-
Severe /gross (+++/++++)	9	3	4	-	-
	19	30	13	6	6

The effect of continuous use of HAART therapy on CD4 T –CELL count of thepatients.

The correlation studies within different parameters to see the test of significance with pearson R value analysis

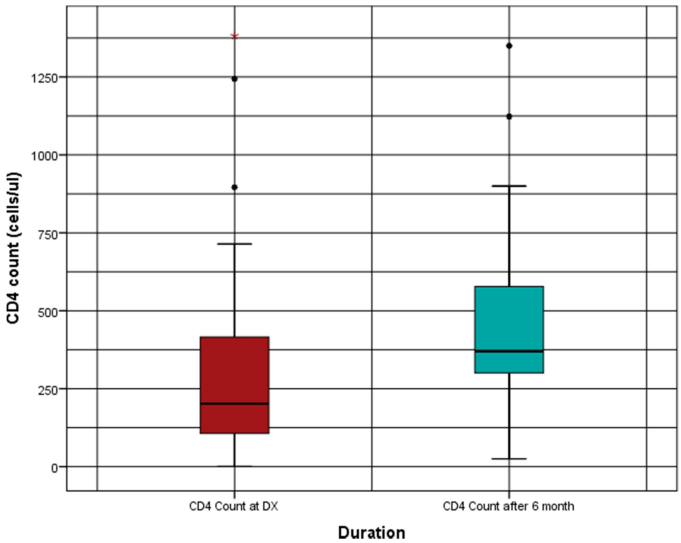

Figure 2: effect of complaint HAART on CD4 T-cell count in 6 month study period

Table 9: Pearson correlation values between different variables of study population

	Pearson's R value	p Value
CD4 at Diagnosis vs Urinary Cystatin-C	-0.32	0.005*
Blood Urea vs Urinary Cystatin-C	+0.55	0.0001*
Serum Creatinine vs Urinary Cystatin-C	+0.48	0.0001*
Duration of Therapy vs Urinary Cystatin-C	+0.32	0.005*
Spot Upcr vs Urinary Cystatin-C	+0.70	0.0001*
24hrUrinary Protein vs Urinary Cystatin-C	+0.71	0.0001*
Spot Upcr vs CD4 at Diagnosis	-0.23	0.04*
24hrUrinary Protein vs CD4 at Diagnosis	-0.26	0.03*

The following data was plotted to see the test of association between the variables

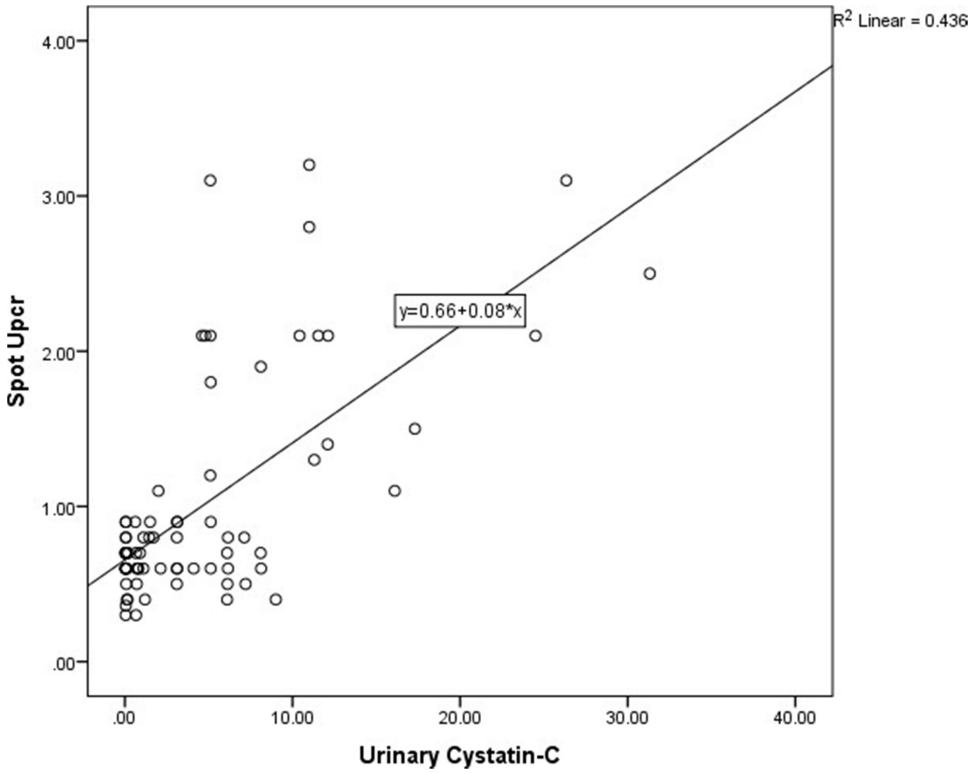

Figure 3: Pearson correlation graph between spot Upcr and urinary cystatin-c

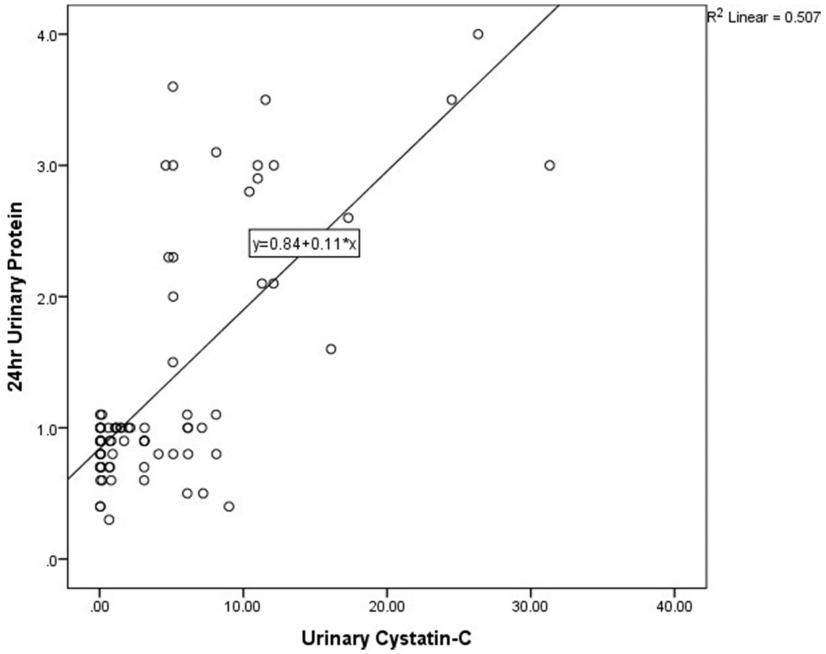

Figure 4: Pearsons correlation graph between 24 hr urinary protein and urinary cystatin-c

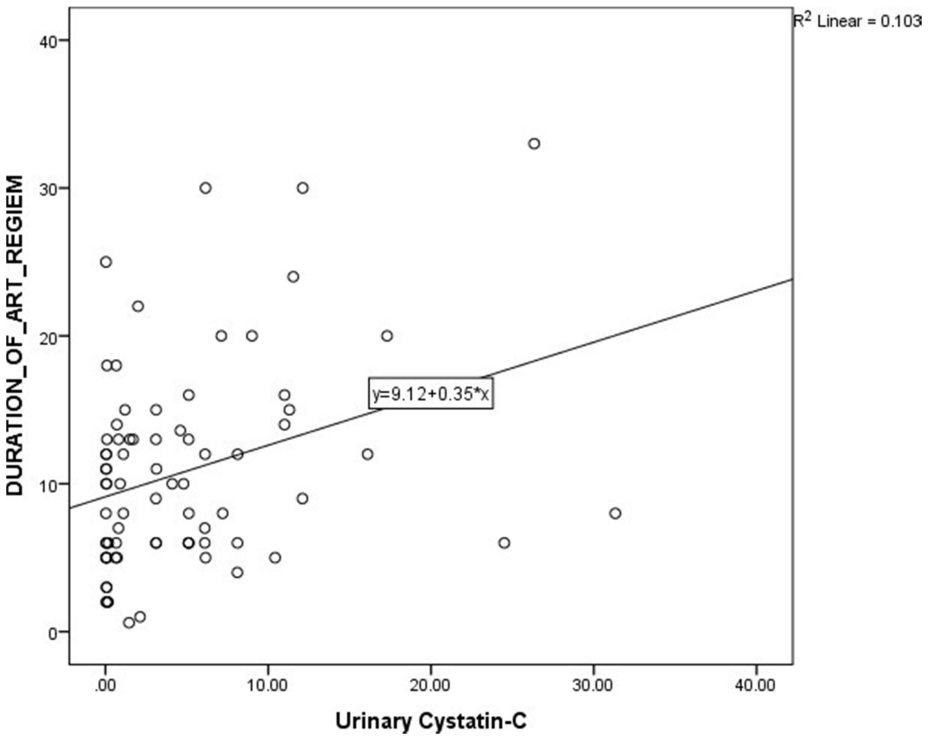

Figure 5: Pearsons correlation graph between duration of ART Regimen and urinary cystatin –c

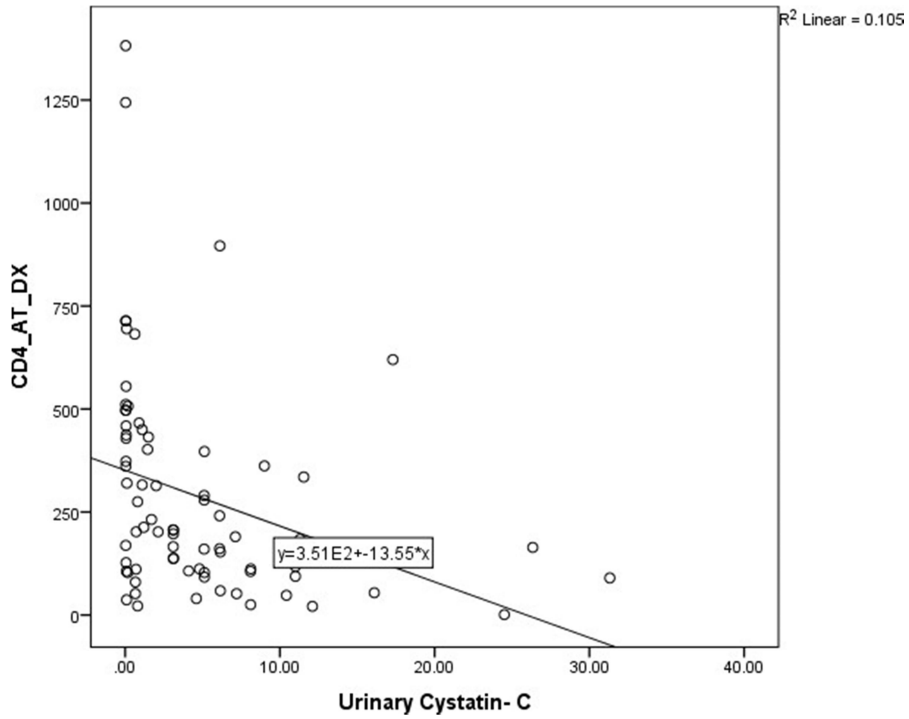

Figure 6: Pearsons correlation graph between CD4 T -cells at time of diagnosis and urinary cystatin -c

DISCUSSION

The prevalence of dipstick-positive proteinuria in HIV-seropositive patients was high (38%) and bears no relation to duration of HIV, CD4, HAART therapy and serum creatinine levels Chronic interstitial nephritis, either in isolation or superimposed on another glomerular lesion, was very common (71%). Mesangioproliferative glomerulonephritis was the most common glomerular lesion like in other Indian studies. The absence of HIVAN in our HIV patients with proteinuria was a characteristic feature as per **Wali *et al*, [5] Nephropathies in HIV patients. however,** the prevalence of dipstick is different in different studies within the Indian subset of population.

Biggs *et al* [6] to evaluate the prevalence and spectrum of the changes seen on renal biopsy of patients with HIVAN, 27 cases were enrolled with male 23 and female 413 patients were subjected to renal biopsy showing glomerular disease in 55.5 %(5/13) showing FSGS vs tubule – interstitial disease of 40 % .this study has cast doubt on assumption that renal biopsy manifestations are absent in Indian patients as all 13 patients showed a spectrum of renal involvement in HIVAN.

In the following study of 75 people suffering from HIV infection, on ART regimen The average hemoglobin was 10.97gm/dl +_1.23, the hb values were lower in patient with low cd4 T –cell count that the people with normal count.

The average wbc count 7364.3cell /microL+_6872.6 and average platelet count was 1.81+_0,2, indicating no significance variability from normal count in population irrespective of duration and type of ART used.

There was near equal prevalence number of male and female population enrolled in the study (52% vs 48%) respectively .t the mean age of females was 36.8±9.8 years and males were 42.2±9.6 years. The mean duration of use of HAART is 10.8 years in my study population with the maximum duration of 33 years and min of 1 year at the time of enrollment. the most common regimen used by the study population is TLE regimen (52%) flowed by raltegravir; dolutegravir,+ritonavir/lopinavir in 30.6% and only 1 each patient was on TL+raltegravir, lopinavir/ritonavir and on old ZLN REGIMEN. most of the female population in study group were house wife, whereas the male belong to odd jobs involving migration from homes and belonging to low socio economic class. The age wise distribution of the study population reveals that among males and females the max population under study belonged to age group 21-40 years (22.6% and 34.6%) respectively indicating that

about 57.2 % population in study in between 21-40 years ,which represents highly sexually active group which is slightly higher than the prevalence study found in HIV associated renal disease – a pilot study in north India by Vijay Gupta *et al*.

In this study the 2 other parameters were selected to assess the correlation of proteinuria ie –spot U PCR and 24 – hour urinary protein .and the renal involvement was assessed by urinary level of cystatin – c. Urine cystatin C – as a marker of tubular dysfunction. [7-9]

- Cystatin C is rapidly reabsorbed and degraded in renal tubular cells. In cases of tubular dysfunction, this is impaired and cystatin C is excreted as such in urine. The correlation was assessed with the help of Pearson correlation analysis and revealed a strong correlation between spot U pcr and cystatin –c(Pearson R value of 0.7 and p-value 0.0001) and 24 hr urinary protein and cystatin –c (pearson r value of +0.71 and p-value 0.0001) .histologically FSGS is the most common glomerular lesion in HIVAN and tubular dysfunction in the form of micro cystic tubular dilation, interstitial infiltrates and found in 60 % cases ,and urinary cystatin –c is essential a marker of tubular dysfunction presence of mild to moderate proteinuria (>1+ proteinuria) in 67.9% indicated the renal tubular dysfunction appears much earlier than actual histological picture of FSGS in HIVAN ,similar to findings The spectrum of renal histology seen in HIV with outcomes, prognostic indicators and clinical correlations.[10]

CONCLUSION

Dipstick proteinuria is the most effective measure for screening of the patients for renal manifestations in patients with HIV the significant proteinuria with >1+ on dipstick examination in patient with all other causes excluded (hypertension, diabetes mellitus) should always warrant for further investigation.

24 hour urinary and >3gm/dl spot Upcr >3.5gm/dl were more associated with HIV AN.

The low CD4+T -cells is associated with the early onset of renal manifestation with most values below <200 cells /microL ,and poor adherence or lack of use of HAART, as studies have revealed that the HIV virus stimulates the PODOCYTES to differentiate and podocytopathy is the hallmark of HIVAN and cause of proteinuria

7.60% of patients with HIVAN has tubular dysfunction without any obvious glomerular disease, hence urinary cystatin - c which is marker of tubular dysfunction is early marker of renal disease in HIVAN

patients even before the onset of nephrotic proteinuria.

Conflict of Interest

None

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Nil

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