Section: General Medicine

Original Research Article

A STUDY OF RENAL FUNCTION TEST IN NEWLY DETECTED HIV PATIENT ON INITIATION OF ANTI-RETROVIRAL THERAPY

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Abstract

Background: The objective is to record and observe clinical and investigational findings which suggest renal impairment in newly detected HIV patients initiating on ART. **Materials and Methods:** The present study was carried out in the Department of General Medicine and ART center of KC General Hospital, Malleshwaram, Bengaluru during the period of 18 months from Sept 2019 to May 2021. **Result:** 1/3rd of study population belong to 4th and 5th decade. Male gender was the dominant sex forming 2/3rd of study population. 1/4th of the study subjects presented with opportunistic infections and other 3/4th were sero-positive, asymptomatic and incidentally detected. Normal GFR at initiation of ART showed steady decline over a period of 6months but flattened out over 2nd half of study period. Inspite of continuation of therapy with Tenofovir Disoproxil Fumarate, initial decline of eGFR noticed in 1st 6 months was not noticed in 2nd half the study period. **Conclusion:** With prevalence of HIV increasing and longevity of HIV affected is increasing due to Highly Active Antiretroviral Therapy. Renal disease is becoming important cause of mortality and morbidity as HIV has become a manageable chronic disease. Study subjects co-infected with Hepatitis B and Hepatitis C showed progressive but less steeper decline over the complete study period. Improvement in CD4 status and BMI was seen in all study subjects except the Hepatitis B and Hepatitis C co-infected ones.

INTRODUCTION

Globally, 36.9 million people were living with Human Immunodeficiency Virus (HIV) at the end of 2017. The prevalence of HIV varies widely between geographical regions. Approximately 2.4 million population were estimated to be infected with HIV in India in 2017.

With the prevalence of HIV increasing, the size of HIV infected population and longevity of HIV affected patients are increasing due to the Highly Active Anti-retroviral therapy (HAART). Renal disease is becoming an important cause of morbidity and mortality in population with HIV infection. As HIV infection has become a chronic disease.[1]

HIV-related renal impairment can present as acute or chronic kidney disease. In contrast to AKI due to pre-renal and post-renal causes, renal forms of AKI in HIV-infected patients are often related to HIV-mediated viral or immunological disease, or to treatment-related toxicity, both of which have changed since the introduction of highly active antiretroviral therapy (HAART).[2]

The distribution of HIV-associated kidney diseases has changed over time and continues to vary across geographic regions worldwide. The reasons for this diversity are complex and include a critical role of APOL1 gene variants and possibly other genetic factors, disparities in access to effective antiviral therapies, and likely other factors that we do not yet fully understand.

Renal disorders are encountered at all stages of HIV infection. HIV-related renal impairment can present as acute or chronic kidney disease; it can be caused directly or indirectly by HIV and/or by drug-related effects that are directly nephrotoxic or lead to changes in renal function by inducing metabolic vasculopathy and renal damage. Acute renal failure is frequently caused by the toxic effects of antiretroviral therapy or nephrotoxic antimicrobial substances used in the treatment of opportunistic infections. Chronic renal disease can be caused by multiple pathophysiological mechanisms, leading to HIV-associated nephropathy, a form of collapsing focal glomerulosclerosis, thrombotic microangiopathy, interstitial nephritis and various forms of immune complex glomerulonephritis.[3]

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Rates of HIV-associated chronic kidney disease (CKD) vary widely between calendar periods, populations and settings. Renal disease has been reported in approximately 6.0–48.5% of HIV-infected individuals in Africa,[4] 24–83% of these cases were classic HIVAN in South Africa.[5] A cross-sectional study of 31 European countries, Israel and Argentina reported HIV-associated- CKD in 3.5–4.7% of HIV-infected individuals.[6]

HIV associated kidney disease burden is increasing worldwide. In developing countries like India, limited financial resources and lack of infrastructure put a severe strain on existing health policies in the light of the increasing burden of HIV associated renal disease. Acute kidney injury (AKI) is an important cause of hospitalization and morbidity in human immunodeficiency virus (HIV)-positive patients. However, the data on AKI in such patients is limited. Many of the renal manifestations represent complications of concurrent infections in a severely immunocompromised host, or side effects of the plethora of treatments required to manage patients with HIV infection. Several studies have indicated that risk factors for acute injury include underlying CKD, advanced HIV disease (whether measured by CD4+ cell count or HIV viral load), and HCV coinfection. AKI is predictive of poor health outcomes in HIV-infected patients as well as in the general population, with even an asymptomatic increase in serum creatinine being associated with increased risk of heart failure, cardiovascular events, end stage renal disease (ESRD), and death.

Naaz et al,[7] from India reported first case of classical HIVAN from the State of Jammu and Kashmir, a low incident belt for HIV. Subsequently another study from India reported two patients of HIVAN presented with nephritic range proteinuria with renal involvement in HIV infected children.[8]

MATERIALS AND METHODS

The Prospective observational study was conducted among newly detected HIV positive patients not started on ART who will visit OPD, ART and admitted in wards of K C General Hospital, Malleswaram, Bengaluru from the period of Sept 2019 to May 2021..

Study sample size: All the 100 eligible HIV positive who were fulfilling inclusion and exclusion criteria underwent Renal Function Test, Hepatitis B and C

Inclusion Criteria

- Age between 18 to 50 years.
- Recently detected HIV positive not started on ART.
- Subjects willing to give informed written consent.

Exclusion Criteria

- Patients with a history of prior renal dysfunction, chronic illness like diabetes mellitus, hypertension known to cause renal dysfunction prior to detection of HIV infection.
- History of prolonged usage of drugs that is known to cause renal dysfunction.

Methodology: Detailed history with detailed demography and clinical examination was done, Study subjects were looked for opportunistic infection and details of drugs in use was noted.

Blood test was done for ruling out diabetes melitus, hypertension and renal dysfunction

Laboratory Investigations

Investigation done including

- Complete Blood Count,
- Blood Urea Nitrogen,
- Serum Creatinine,
- Serum Electrolytes,
- FBS & PPBS,
- Urine routine and microscopy,
- Ultrasound Abdomen,
- Hepatitis B and Hepatitis C,
- CD4 count and
- Other investigations if required

eGFR was calculated and the patient was followed up after 3 months, 6 months & 1 year. eGFR was compared during the follow up.

Ethical Clearance: The study has been approved by Ethical Committee of KC General Hospital, Malleshwaram, Bengaluru.

Method of Study: During the period of data collection 410 newly detected HIV subjects were screened for diabetes, hypertension and past history of renal dysfunction. Out of which 100 subjects were included in the study who were fulfilling inclusion and exclusion criteria.

A detailed history was taken and examination done as per proforma. all study subjects underwent hematological test and renal function test, assessment of eGFR.

Statistical Analysis: Data was entered into Microsoft Excel (Windows 7; Version 2007) and analyses were done using the Statistical Package for Social Sciences (SPSS) for Windows software (version 22.0; SPSS Inc, Chicago). Descriptive statistics such as mean and standard deviation (SD) for continuous variables, frequencies and percentages were calculated for categorical Variables were determined. Association between Variables was analyzed by using Chi- Square test for categorical Variables. Bar charts and Pie charts were used for visual representation of the analyzed data. Level of significance was set at 0.05.

RESULTS

During the period of data collection 410 newly detected HIV subjects whoever started on TLE(Tenofovir, Lamivudine, Efavirenz) regime according to NACO/KSAPS guidelines were screened for diabetes, hypertension and past history of renal dysfunction. Out of which 100 subjects were included in the study who were fulfilling inclusion and exclusion criteria. A detailed history was taken

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and examination done as per proforma. all study subjects underwent hematological test and renal function test, assessment of eGFR.

It is found to be 22% in the age group of 20 – 30 years, 30% in the age group of 31 – 40 years and 48% in the age group of 41 – 50 years with Mean SD of 38.06(8.08).

In this analysis of study subject the gender is found to be 65% to be Male, where three transgender were included in it and 35% were females.

In this analysis of study subject, 35% of them were single/unmarried, 65% of them were married - in which 16% of them expired, 25% were positive and 24% were found to be negative.

In this analysis of study subjects, we found that 86% of them were found to be negative for Hepatitis B and C, 4% of them were found to be Hepatitis B positive, 6% of them were found to be Hepatitis C positive and 4% of them were found to be positive for both Hepatitis B and C. [Table 2]

In this analysis of Hb% at beginning of the study period, we found that 5% of the study subjects were 6.5 - 7.9 (severe anaemia), 13% of the study subjects were 8 - 9.9 (moderate anaemia), 56% of the study subjects were 10 - 11.9 (mild anaemia) and 26% of the study subjects were >12 (normal). [Table 3]

In this analysis, At 0 month, 7% of study subjects were under 18.5 kg/m^2, 76% were between 18.5 kg/m^2 - 22.9 kg/m^2, 11% were between 23 kg/m^2 - 24.9 kg/m^2 and 6% were above 25 kg/m^2. At 3 months, 7% were under 18.5 kg/m^2, 73% where between 18.5 kg/m^2 - 22.9 kg/m^2 , 14% were between 23 kg/m^2 - 24.9 kg/m^2 and 6% were more than 25 kg/m^2.

At 6 months, 7% less than 18.5 kg/m^2 , 74% between 18.5 kg/m^2 - 22.9 kg/m^2 , 13% between 23 kg/m^2 - 24.9 kg/m^2 and 96% more than 25 kg/m^2. At 12 months, 3.2% less than 18.5 kg/m^2 , 67% between 18.5 kg/m^2 - 22.9 kg/m^2 , 17% between 23 kg/m^2 - 24.9 kg/m^2 and 8% more than 25 kg/m^2. [Table 4]

In this analysis, At 0 month 15% of the study subjects were found to have less than 50 cd4 count, 10% were between 50 - 100, 23% between 100 - 250, 34% between 250 - 500 and 18% were more than 500. At 12 months, 1.1% of the study subjects were found to have lesser than 50 cd4 count, 2.1% between 50 - 100, 15.8% between 100 - 250, 42.1% between 250 - 500 and 38.9% more than 500. [Table 5]

In this analysis, At 3 month 20% of the study subjects were between 60 - 89 GFR and 80% were above 80 GFR. At 6 months, 69% of the study subjects were above 90 GFR, 28% were 60 - 89 GFR, 2% were between 30 - 44 GFR and 1% were less than 15 GFR. At 12 month, 68.4% of the study subjects were more than 90 GFR and 31.6% were between 60 - 89 GFR.

In this analysis, At 3 months Hepatitis B positive, 100% of the study subjects were more than 90 GFR. At 6 months Hepatitis B positive, 25% of the study subjects were between 60- 89 GFR and 75% of the of the study subjects were more than 90 GFR. At 12 months Hepatitis B positive, 25% of the study subjects were between 60 - 89 GFR and 75% of the study subjects were more than 90 GFR.

In this analysis, At 3 months 20% Hepatitis C of the study subjects were between 60 - 89 GFR and 80% of the study subjects were more than 90 GFR. At 6 months, Hepatitis c positive of the study subjects were 60% between 60 - 89 GFR and 40% of the study subjects were more than 90 GFR. At 12 months, Hepatitis C positive of the study subjects were 60% were between 60 - 89 GFR and 40% more than 90 GFR.

Table 1: Distribution of Study Subjects according to the Spouse Status (N=100)

Spouse Status	No.	Percent
Positive	25	25
Negative	24	24
Single	35	35
Expired	16	16

Table 2: Showing severity of Anaemia (N=100)

Hb	No.	Percent
<6.5 (Life Threating)	0	0
6.5-7.9 (Severe)	5	5
8.0-9.9 (Moderate)	13	13
10.0-11.9 (Mild)	56	56
≥ 12 (Normal)	26	26
Mean (SD)	10.81 (1.50)	
Range	7.0-16.0	

Table 3: Subjects according to the BMI (N=100)

BMI	At 0 Month n (%)	At 3 Months n (%)	At 6 Months n (%)	At 12 Months n (%)
<18.5	7 (7.0)	7 (7.0)	7 (7.0)	3 (3.2)
18.5-22.99	76 (76.0)	73 (73.0)	74 (74.0)	67 (70.5)
23.0-24.99	11 (11.0)	14 (14.0)	13 (13.0)	17 (17.9)
≥25.0	6 (6.0)	6 (6.0)	6 (6.0)	8 (8.4)
Mean (SD)	21.05 (1.98)	21.27 (1.98)	21.48 (2.04)	21.90 (1.91)
Range	16.81-26.35	16.81-25.97	14.71-26.35	18.11-26.40
P Value	-	0.005*	<0.001*	<0.001*
*Paired t Test, P Value Significant				

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Table 4: Study Subjects according to the CD4 Count (N=100)

CD4 Count	At 0 Month n (%)	At 12 Months n (%)
<50	15 (15.0)	1 (1.1)
50-100	10 (10.0)	2 (2.1)
100-250	23 (23.0)	15 (15.8)
250-500	34 (34.0)	40 (42.1)
>500	18 (18.0)	37 (38.9)
Mean (SD)	288.32 (214.22)	485.65 (265.02)
Range	7-858	15-1335
P Value	<0.001*	Significant

Table 5: Distribution of Study Subjects according to the GFR (N=100)

GFR	At 0 Month n (%)	At 3 Months n (%)	At 6 Months n (%)	At 12 Months n (%)
<15			1 (1.0)	
15-29				
30-44			2 (2.0)	
45-59				
60-89		20 (20.0)	28 (28.0)	30 (31.6)
>90	100 (100.0)	80 (80.0)	69 (69.0)	65 (68.4)
Mean (SD)	106.68 (7.99)	100.84 (13.24)	94.87 (18.08)	94.65 (15.93)
Range	90.14-124.15	63.43-125.20	11.94-122.65	59.02-122.65
P Value	-	<0.001*	<0.001*	<0.001*
*Paired t Test, P Value Significant				

Table 6: Association between GFR and Hepatitis B (N=100)

GFR	At 3 Months n (%)		At 6 Months n (%)		At 12 Months n (%)	
	Positive	Negative	Positive	Negative	Positive	Negative
60-89		20 (21.7)	2 (25.0)	26 (28.3)	2 (25.0)	28 (32.2)
>90	8 (100.0)	72 (78.3)	6 (75.0)	63 (68.5)	6 (75.0)	59 (67.8)
P Value		0.14		0.953		0.676

Table 7: Association between GFR and Hepatitis C (N=100)

GFR	At 3 Months n (%)		At 6 Months n (%)		At 12 Months n (%)	
	Positive	Negative	Positive	Negative	Positive	Negative
60-89	2 (20.0)	18 (20.0)	6 (60.0)	22 (24.4)	6 (60.0)	24 (28.2)
>90	8 (80.0)	72 (80.0)	4 (40.0)	65 (72.2)	4 (40.0)	61 (71.8)
P Value		1		0.124		0.041*

DISCUSSION

With the advent of Highly Active Antiretroviral Therapy longevity of HIV affected subjects is increasing. Renal disease is becoming an important cause of morbidity and mortality in the population with HIV infection as HIV infection has tendency to progress to a chronic disease.

eGFR was calculated in newly detected HIV subjects attending the ART centre, OPD and IPD of K C General Hospital at 3 months, 6 months and 1 year. A total of 100 subjects were studied who were newly detected HIV positive and ART naïve were screened and selected as study subjects. In this study, it is found that a gradual increase in percentage of study subjects according to age in each decade was noted in agreement with marriageable age increase in sexual activity and duration of manifestation of disease after initial contact.

In this study, male constituted two thirds of the study population. less number of females because pregnant women were not included in the study as development of GDM or pregnancy induced hypertension and increase in weight of pregnant women during the course of pregnancy may come in the way of estimating eGFR. Three study subjects were transgender however because of body habitus they were considered as male.

In this study, there were 65 study subjects that were married out of which 25 study subjects' spouses were positive for Retroviral status, 24 were negative for Retroviral status, among which 17 were male and 7 were female. 16 spouses expired and the reason for death of these spouses couldn't be ascertained. 35 study subjects were single with male to female ratio being 2.5 :1.

In this study, 76 subjects were asymptomatic(spouses of women who were positive during ANC, screening for blood donation, pre operative work up), 16 subjects were presented with Tuberculosis, 4 subjects had mucocutaneous candidiasis, 2 subjects with herpes zoaster(recurrent and multi dermatomal), 1 subject with weight loss and 1 subject presented with recurrent UTI.

In this study, 76% of the study population were incidentally diagnosed with retroviral disease during spouse ANC check-up, screening for blood donation and pre-operative workup, therefore general physical status of the study subjects were normal as they were seropositive and asymptomatic. Improvement in BMI was seen with drug therapy after six months of initiation of therapy.

Concomitant viral infection was seen in 20 study subjects of which herpes zoster manifesting opportunistic infection was seen in 2 subjects. 8 study subjects were Hepatitis B positive and 10 study

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subjects were Hepatitis C positive out of which 4 subjects tested positive for both Hepatitis B and C. Hepatitis B and C viral infection is known to alter the course of HIV illness and known to affect renal function on their own.

In this study, there is been steady decline in eGFR during course of follow-up of one year in HIV co-infected with Hepatitis B and Hepatitis C similar decrease in eGFR was noticed in HIV without co-infection at the end of 6 months but it plateaued off of between 6 to 12 months. The steady decline in eGFR of a seen in all subjects irrespective of comorbidities could be attributed to the drug therapy that they were initiated with but it was offset in the second six months of study period where decline in eGFR was plateaued in spite of continuation of drug therapy with improvement in their immune status reflected by improvement in CD4 count. Stopping of cotrimoxazole supplement therapy could be another reason since renal dysfunction is known with long term usage of this drug.

We found 3 of these subjects showed aberration in the form of drastic decline in their eGFR (less than 44ml/min//1.73m2). All 3 subjects were negative for Hepatitis B and C. However, they were detected to have extensive pulmonary tuberculosis. 1 of the subject was diagnosed as MDR TB. All 3 subjects expired during the course of the study, however their data was included because they were present for more than ⅔ of study period.

Mentioned below are earlier studies on renal dysfunction in HIV subjects. However, due to heterogeneity in their study subjects comparative studies were not found.

Antoniou et al 2017, this study showed 74% subject developed grade 1 increase in serum creatinine during follow-up, no subjects developed grade 2 or higher nephrotoxicity. 15 subjects (8.7%) had increase in serum creatinine greater than 1.5 X baseline value during follow-up, 4 subjects (2.3%) discontinued TDF because of increase in serum creatinine. In this study subjects were not ART naive.[9]

Leonard Msango et al 2010, This study 129 (36%) out of 355 subjects had normal eGFR above 90ml/min/1.73m2. Grade 2 renal dysfunction (eGFR between 60 and 89ml/min/1.73m2) was present in 137 subjects (38.6%) and 87study subjects (25%) had Grade 3 renal dysfunction (eGFR between 30-59ml/min/1.73m2). Renal function was checked only at the beginning of the ART therapy.[10]

Dorcos orbiri Yeboah et al, Participant with mean age of 45.5 years with 228 (65.4%) where tenofovir based regime the mean is eGFR decreased from 112.4 ml/min/1.7 m2 at baseline to 103.4 ml/min/1.73m2 at 6 months of ART. In this study other regimens have also been used along with tenofovir and subjects were not ART naive.[11]

In this study, out of hundred HIV positive subjects it was found that at 3 months 20 subjects (20%) were in mild renal dysfunction(eGFR between 60 and 89ml/min/1.73m2) and 80 subject where normal eGFR (>90ml/min/1.73m2) with mean eGFR of 100.84 ± 13.24, At 6 months 28 subjects(28%) were in mild renal dysfunction (eGFR between 60 and 89ml/min/1.73m2) and 69 subject (69%) were normal eGFR (>90ml/min/1.73m2) with mean eGFR 94.87 ± 18.08. At 12 months 30 subjects (31.6%) were in mild renal dysfunction (eGFR between 60 and 89ml/min/1.73m2) and 65 subjects (68.4%) were normal eGFR (>90ml/min/1.73m2) with mean eGFR 94.6 5 ± 15.93.

CONCLUSION

With prevalence of HIV increasing and longevity of HIV affected is increasing due to Highly Active Antiretroviral Therapy. Renal disease is becoming important cause of mortality and morbidity as HIV has become a manageable chronic disease. /3rd of study population belong to 4th and 5th decade. Male gender was the dominant sex forming 2/3rd of study population. 1/4th of the study subjects presented with opportunistic infections and other 3/4th were sero-positive, asymptomatic and incidentally detected. Normal GFR at initiation of ART showed steady decline over a period of 6months but flattened out over 2nd half of study period. Inspite of continuation of therapy with Tenofovir Disoproxil Fumarate, initial decline of eGFR noticed in 1st 6 months was not noticed in 2nd half the study period. Study subjects co-infected with Hepatitis B and Hepatitis C showed progressive but less steeper decline over the complete study period. Improvement in CD4 status and BMI was seen in all study subjects except the Hepatitis B and Hepatitis C co-infected ones.

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