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A Study on Estimated Glomerular Filtration Rate As A Predictor of Renal Dysfunction Among Adult Hiv Patients on Highly Active Antiretroviral Therapy

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Abstract
Intoduction: *Renal dysfunction is the common complication of HIV infection with a prevalence of 30 % in HIV patients. The spectrum of renal dysfunction is multifactorial ranging from exacerbation of chronic kidney disease to acute kidney injury. Kidney disease in the setting of HIV can pose a significant challenge to patients and clinicians by increasing the risk for AIDS- defining illness, hospitalization and death.*
Objectives: *The prevalence of renal dysfunction among HIV-1 infected outpatients starting ART therapy in India is limited. Recent recommendation to include the Nephrotoxic drug tenofovir in the first-line ART regimens make clarification of this issue urgent.*
Methodology: *We screened for renal dysfunction by measuring serum creatinine, urea, microalbuminuria, USG-KUB, low CD-4 counts and opportunistic infections inn HIV- positive patients initiating ART at Coimbatore Medical College Hospital. We excluded patients with preexisting renal disease, hypertension, diabetes, pregnancy, Hepatitis B/C virus co infection. eGFR were calculated using the Cockcroft-gault equation and categorized based on Nation kidney disease foundation staging of Chronic Kidney Disease. eGFR calculated at the end of the study was compared with Age, Gender, Weight, CD4 counts, Urea, Creatinine and with different types of ART regimen used by the study population.*
Results: *Only 21 of the enrolled patients had normal eGFRabove 90ml/min/1.73m^2(Grade-0 or 1) . Grade 2 was present in 37 and 42 had grade 3 dysfunction or less. Microalbuminuria was detected in 47 % of patients. Mean eGFR was 68.28 . 70 % of patients fall under Tenofovir based regimen. Of which 64% patients fall in eGFR< 90 ml/min and in particular 38% falls under eGFR< 60ml/min which indicates moderate to severe renal dysfunction.*
Conclusion: *Renal dysfunction was highly prevalent in this population of HIV positive out patients initiating first ART in Coimbatore medical college hospital. This highlights the critical and underappreciated need to monitor renal function in HIV – positive patients, particularly given the increasing use of tenofovir in first line ART.*

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I. Introduction

Renal dysfunction is the common complication of HIV infection with a prevalence of 30% in HIV infected patients. The spectrum of kidney dysfunction is broad, ranging from exacerbation of common kidney diseases to acute and chronic conditions.[1] The causes of renal dysfunction are multifactorial which includes HIV infection per se, opportunistic infections, co-morbidities, and anti retroviraltherapy . AIDS-related kidney disease, especially HIV AN (HIV associated Nephropathy) has become a relatively common cause of end-stage renal disease (ESRD) requiring renal replacement therapy and may be associated with progression to AIDS and death.[2]

Elevated serum creatinine is the first evidence of renal dysfunction. Increase in Serum creatinine from baseline should prompt an evaluation. The estimated Glomerular filtration rate (eGFR) is a direct measure of kidney function and reduces before the onset of symptoms of Renal failure. Severity of kidney disease directly correlates with decrease in GFR which can be calculated in the clinical setting using one of the three most commonly used equations:

1. Cockcroft - Gault (CG) formula
2 Modification of Diet in Renal Disease formula (MDRD)

3. Chronic Kidney Disease Epidemiology Consortium formula (CKD-EPI)

Any of these equations may be used to follow trends in creatinine ,as part of determining GFR. Cockcroft-Gault equation is the most commonly used which estimates GFR using serum creatinine measurements and anthropometric variables. The incidence and spectrum of kidney diseases in HIV have been dramatically altered by ART .The risk for ESRD has been reduced and survival on dialysis is expected to improve with newer antiretroviral drug therapies. Patients with HIVAN who are on effective ART have a slower decrease in GFR and less incidents of fulminant renal failure .HAART is responsible for at least a 30% reduction in new ESRD cases from HIVAN[3] .However, initiation of ART may not have a beneficial effect on the natural history of other forms of CKD, such as IgA nephropathy and diabetes, which could be mistaken for HIVAN when a biopsy is not obtained. The present study was undertaken with an aim to investigate the factors associated with decline in estimated GFR using CG formula among the patients initiated on Highly Active AntiRetroviral Therapy (HAART) and its correlation with renal dysfunction and progression to end stage renal failure.

II. Objectives

1. To study the Renal Changes in Adult HIV Patients following first line HAART initiation using estimated Glomerular filtration rate (eGFR).
2. To study the Renal changes and decline in eGFR with respect to the different HAART regimens after the HAART initiation by using Cockcroft - Gault formula.
3. To consider that close monitoring of Renal function is important ,as the current use of specific anti-retrovirals may result in an increased risk of eGFR decline in HIV - 1 infected patients on HAART.

III. Methodology

Source of study :

Newly diagnosed HIV positive patients who are attending ART clinic and admitting in Medical wards at Coimbatore Medical College Hospital.

Design Of Study : Cross sectional study

Period Of Study : August 2013 to June 2014

Sample Siz : 100 patients

Study population :100 patients who are attending ART clinic and admitting in Medical units at Coimbatore Medical College Hospital were randomly selected as per the inclusion and exclusion criteria. Out of these, 44 were men and 56 were women. The mean age of subjects was 40.8 years with a range of 20-81 years. Written informed consent was obtained from each HIV positive patients enrolled in the study.

Inclusion criteria:

All newly diagnosed adult HIV positive patients as per the NACO guidelines , who was started on HAART and who are attending ART clinic and also patients who were admitted in Medical units at Coimbatore Medical College Hospital.

Exclusion criteria :

- Patients with Chronic renal failure
- Patients with diagnosed systemic causes of renal diseases (eg., SLE, Systemic Sclerosis, Rhematoid arthritis and other rheumatological& connective tissue disorders)
- Patients who are known Diabetic or Hypertensive or any other comorbid illness .
- Patients with associated Hepatitis B/ C virus infection
- Pregnant women and children age less than 15 years
- Patients with poor adherence (> 80 %)
- Patients receiving other nephrotoxic drugs / NSAIDS.
- Pregnancy

Data Collection

The 100 newly diagnosed HIV positive patients were included in the study. Detailed history - including duration of disease, any past history of antiretroviral drug and other medications , treatment regimen started , WHO staging of the HIV disease were obtained . Patients were examined in detailed for assessing any symptoms and signs of renal failure .Blood samples were taken for screening
baseline renal function for urea, creatinine and also for CD4 count . Baseline eGFR was calculated using Cockgroft - Gault equation . Patients were followed up over a period of 10 months and any opportunistic infections developed among patients during study period was noted. At the end of 10 months, patients were assessed for Urea , Creatinine , CD4 counts by drawing blood samples and eGFR was calculated using CG formula. Urine routine and USG KUB was done .

IV. Statistical Analysis

All the dates were entered in a data collection sheet in an Excel format and analyzed using SPSS Software. Numerical values were reported using mean and standard deviation or median. Categorical values are reported using number and percentages. Probability value (p) value less than 0.05 was considered a statistically significant.

Results

The present study is a prospective study . Cross- sectional data for 100 patients diagnosed to have HIV infection who was attending ART clinic and Medical units at CMCH during the period of August 2013 to June 2014 , were recruited for the purpose of this study.

STAGING Of KIDNEY DAMAGE BASED ON Egfr (END Of Study)	
GFR Normal >90 Ml/Min/1.73m^2	- **21**
GFR Mild 60-90 Ml/Min/1.73m^2	- **37**
GFR Mod-Sev<60 Ml/Min/1.73 M^2	- **42**
	-
WHO CLINICAL STAGING AFTER ART	
T1	- **67**
T2	- **7**
T3	- **12**
T4	- **14**
HAART REGIMEN	
TLN	- **28**
TLE	- **42**
ZLN	- **22**
ZLE	- **8**

A total of 100 patients were selected for the study .Of the 100 HIV infected patients , starting ART at CMCH ,44 males and 56 females. Among them patients were distributed across the age spectrum of 20to 81 years. Females accounts for 56% of study population and the mean age was 40.08. The patients were distributed in all the clinical stages of HIV disease from Tl to T4. And four types of regimen was taken by the patients TLN (28), TLE(42), ZLN (22) ,ZLE (8). Out of 100 patients , at the end of study 21% patients with Normal GFR (>90), 37% with mild reduction (60-90) and 42% with mod- severe reduction in eGFR (<60), ten months after initiating ART, with majority of GFR decline in Tenofovir based regimens .

In this present study , majority are females with 56% of study population and males constitutes 44% of study population

Relationship Between Gender And E Gfr_E

Relationship between Gender and eGFR_E				
eGFR_E				
SEX	**Mean**	**Minimum**	**Maximum**	**No of Cases**
Female	64.91	24	129	56
Male	74.83	32.4	143	44
Total	69.28	24	143	100

ANOVA					
eGFR_E					
	Sum of Squares	df	Mean Square	F	P Value
Between Groups	2426.471991	1	2426.471991	3.6773460	**0.06**
Within Groups	64664.63995	98	659.8432648		
Total	67091.11194	99			

The average eGFR for female is 64.91 and for male is 74.83 The ANOVA test indicates that the difference of average in eGFR between male and female is not statistically significant.

Distribution Of Cases According To Estimated Glomerular Filtration Rate Before And After Art

Category (eGFR ml/min)	eGFR_ B (Baseline)	eGFR_E (End of 10th mon)	Difference eGFR (B- E)
< 60(Mod-sev)	22	42	20
60-90 (Mild)	46	37	9
>90 (Normal)	32	21	11
Total	100	100	40

The overall average mean eGFR at the end of study in this sample is 69.28 In this study , before starting ART most patients , 46 % were in 60-90 category and 32% were in >90 category and at the end of study after HAART initiation , 79% of patients were in eGFR< 90 ml/min . Of which ,42 % in <60 (mod - severe) and 37% in 60-90 eGFR(mild reduction) . Approximately 20 % of patients with normal baseline eGFR falls into severe decline in eGFR after ART introduction .

Comparison of egfr_e across urea.

Dependent Variable	Mean WEIGHT (kg)	(I) eGFR_E	(J) eGFR_E	Mean Difference (I-J)	Std. Error	P Value
UREA_E (End of study)	29.9	<60	60-90	2.418	1.174	0.104
	42		>90	3.381*	1.391	**0.0.44**
	49.86	60-90	<60	2.418	1.174	0.104
	37		>90	0.963	1.422	0.777
	49.48	>90	<60	-3.381*	1.391	**0.044**
	21		60-90	-0.963	1.422	0.777

It is indicated that between less than 60 and greater than 90 eGFR_E, the average levels of Urea_E is different . Average levels of UREA_E is higher for <60 eGFR_E as compared to >90 eGFR_E with P value of 0.044. No significant difference of levels of Urea is indicated, between 60-90 category and <60 category of eGFR and also between 60-90 and >90 category. Mean urea was 28.3 mg/dl with minimum of 16 and maximum of 44.

Comparison Of Egfr Across Creatinine

Dependent Variable	Mean WEIGHT (kg)	(I) eGFR_E	(J) eGFR_E	Mean Difference (I-J)	Std. Error	P Value
CREATININE (End of study)	1.26	<60	60-90	03349*	0.0566	0
	42		>90	05476*	0.0671	0
	0.93	60-90	<60	-.3349*	0.0566	0
	37		>90	02127*	0.0686	0.007
	0.71	>90	<60	-05476	0.0671	0
	21		60-90	-.2127	0.0686	0.007

Average levels of creatinine is significantly higher for <60 eGFR as compared to 60-90 and >90 eGFR levels. Also creatinine average is higher for 60-90 eGFR_Eas compared >90 eGFR_E levels. In the present study, it shows that increase in creatinine vale from baseline is directly proportional to decline in eGFR from 90-60 and <60. Mean creatinine value is 1.028 with minimum of 0.5 and maximum of 1.8.

Distribution Of Cases According To Urine Albumin

Microalbuminuria	No of patients	Percent
Nil	53	53%
Trace	24	24%
1+	12	12%
2+	8	8%
3+	3	3%
Total	100	100.0

In the present study, albuminuria was noted in 47 patients(47%). Of the 47, who had albuminuria, 24 had Trace, 12 had 1+8 had 2+ and 3 had 3+ albuminuria.

Correlation Between Urine Alubmin And Egfr_E

Relationship between URINE_ALB and eGFR_E (No of Cases)					
	eGFR-E	**<60**	**60-90**	**>90**	**Total**
Urine **ALB** `	Nil	6	27	20	53
	Trace	15	9	0	241
	1+	10	1	1	12
	2+	8	0	0	8
	3+	3	0	0	3
Total		**42**	**37**	**21**	**100**

Symmetric Measures					
		Value	**Asymp.Std. Errora**	**Approx. Tb**	**Approx Sig.**
Interval by Interval	Pearson's R	-0.609	0.049	-7.599	0.000
Ordinal by Ordinal	Spearman Correlation	-0.682	0.058	-9.243	0.000

No of valid Cases		100			

In the present study, there was a negative correlation between Urine albumin and eGFR at the end of study and the P vale is significant 0.000. This study shows that, as the grades of urine albumin increases, eGFR declines, Category with eGFR<60 ml/min shows high albuminuria with 23% in 1+, 19% in 2+ and 7% in 3+ range.

Different Types Of Art Regimen Taken By The Patient During Study

Regimen	No Of Patients	Percentage
Tln (A)	28	28%
Tle (B)	42	42%
Zln(C)	22	22%
Zle(D)	8	8%
Total	**100**	**100%**

In present study, 4 types of ART regimen was taken up by the patients with TLN (28%), TLE (42%), ZLN(22%) and ZLE(8%) Majority of patients are in Tenofovir based regimen.

Table 34 : Relationship Between The Art Regimen And Egfr_E During Study

Relationship Between REGIMEN And Egfr_E (No Of Cases)							
	Egfr_E	**<60**	**60-90**	**>90**	**Total**	**%**	
REGIMAN	TLN(A)	13	11	4	28	28%	70%
	TLE(B)	25	15	2	42	22%	
	ZLN(C)	1	8	13	22	22%	30%
	ZLE(D)	3	3	2	8	8%	
TOTAL		42	37	21	100	100%	

Among the ART regimen used in this study, Tenofovir based regimen(AB) accounts for 70 cases (70%) and Zidovudine based regimen (CD) accounts for 30% of cases.

Relationship between REGIMEN and eGFR_E eGFR_E						
REGIMEN	eGFR_E	Mean	Mini	Max	No of Cases	% of Cases on Total Sample
AB Tenofovir based	<=90	56.7	24.0	88.4	64	64%
	>90	103.5	90.6	124.6	6	6%
	Total	60.7	24.0	124.6	0	70%
CD Zidovudine	<90	67.8	37.8	87.6	15	15%
	>90	110.6	94.6	143.0	15	15%
	Total	89.2	37.8	143.0	30	30%
Total	<=90	58.8	24.0	88.4	79	79%
	>90	108.6	90.6	143.0	21	21%
	Total	69.3	24.0	143.0	100	100%

eGFR_E Tukey HSD	**Multiple comparisons Regimens**			
(I) REGIMEN_2_eGFRE_2	**(J) REGIMEN_2_eGFRE_2**	**Mean Difference (I-J)**	**Std.Error**	**P Value**
AB<=90	AB>90	-46.76	6.79	0.00
	CD<=90	-11.12	4.56	0.08
	CD>90	-53.92	4.56	0.00
AB>90	AB<=90	46.76	6.79	0.00
	CD<=90	35.64	7.68	0.00
	CD>90	-7.16	7.68	0.79
CD<=90	AB<=90	11.12	4.56	0.08
	AB>90	-35.64	7.68	0.00
	CD>90	-42.80	5.81	0.00
CD>90	AB<=90	53.92	4.56	0.00
	AB>90	7.16	7.68	0.79
	CD<=90	42.80	5.91	0.00

The multiple comparisons table indicates

Regimen AB with eGFR<90 is having significantly lower eGFR as compared to AB with eGFR<90
Regimen AB with eGFR<90 is having significantly lower eGFR as compared to CD with eGFR>90
Regimen AB with eGFR<90 is having significantly lower eGFR as compared to CD with eGFR<90
Regimen CD with eGFR<90 is having significantly lower GFR as compared to CD with eGFR>90

TENOFOVIR BASED REGIMEN TREATED PATIENTS HAS SIGNIFICANTLY LOWER EGFR COMPARED TO ZIDOVUDINE BASED REGIMEN

correlation between who clinical staging and egfr_e

Relationship between WHO CLINICAL STAGE and eGFR (No of Cases)					
	eGFR_E	**<60**	**60-90**	**<90**	**Total**
STAGE	T1	24	28	15	67
	T2	7	4	1	12
	T3	10	3	1	14
Total		42	37	21	100

Relationship between WHO CLINICAL STAGE and eGFR (No of Cases)					
	eGFR_E	**<60**	**60-90**	**<90**	**Total**
STAGE	T1	24	28	15	67
	T2	7	4	1	12
	T3	10	3	1	14
Total		42	37	21	100

Symmetric Measures					
		Correlation Value	**Asymp. Std. Error**	**Approx. Tb**	**P Value**
Interval by Interval	Pearson's R	-0.239	0.088	-2.436	0.017
Ordinal by Ordinal	Spearman Correlation	0.203	0.096	-2.054	0.043
No of Valid Cases		100			

Distribution Of Who Stage And Egfr_E (As Per Frequency)

In the present study, there was a negative correlation between WHO clinical stage and eGFR and the P value is 0.017 which is significant. As the stage of the disease increases decline in eGFR also increases. In T4 Stage out of 14 cases, 10 cases (71%) are in <60 category but in T1 out of 67 only 24 cases (36%) are in <60 category.

Table 37 : Correlation Between Oi's And Egfr_E

Relationship between OIS and eGFR_E (No of Cases)					
	eGFR_E	**<60**	**60-90**	**>90**	**Total**
OIS	No	20	21	8	**49**
	PT	3	7	2	**12**
	Acute GE	2	1	3	**6**
	Tb Meningitis	1	1	0	**2**
	CNS Toxoplasmosis	2	0	0	**2**
	Tb lymphadenitis	0	0	2	**2**
	OC + HIV myelopathy	1	0	0	**1**
	Tb spine	0	1	0	**1**
	OC	0	0	2	**2**
	SEBORRHOEA	1	0	1	**2**
	PPE	1	2	0	**3**
	PCP	0	1	0	**1**
	PT+PCP	4	0	0	**4**
	PT+OC	0	1	0	**1**
	CMV RETINITIS	1	0	0	**1**
	HIV Myelopathy	1	0	0	**1**
Total		**42**	**37**	**21**	**100**

Symmetric Measures					
		Correlation Value	Asymp. Std.Error	Approx. Tb	P Value
Interval by Interval	Pearson's R	-0.091	0.094	-0.908	0.366
Ordinal by Ordinal	Spearman Correlation	-0.029	0.102	-0.291	0.772

No of Valid Cases		100			

In the present study, there was no correlation between opportunistic infection and eGFR at the end of study is visible from the table. Also P value is not significant.

Correlation Between Baseline Cd4 Count And Egfr

Relationship between CD4_COUNT_B and eGFR_B (No of Cases)						
				eGFR_B	**Total**	**%**
		<60	**60-90**	**<90**		
CD4_COUNT_B	P(<100)	4	11	3	18	18%
	Q(100-200)	10	14	6	30	30%
	R(<200)	8	21	23	52	52%
Total		22	46	32	100	

Distribuition Of Cd4_Count_B Across Egfr_B

In this study, baseline CD4 count less than 200 was noted in 48%, of these 18 patients had<100 count and 30 patients had 100 to 200 count Majority of patients with decline in CD4 count<200 are in eGFR60-90 category.

Correlation Between Cd4 Count And Egfr At The End Of Study

Relationship between CD4_COUNT_E and EGFR_E (No of Cases)						
		eGFR_B			Total	%
		<60	**60-90**	**>90**		
CD4_COUNT_B	P(<100)	4	11	3	15	18%
	Q(100-200)	10	14	6	30	30%
	R(>200)	8	21	23	52	52%
Total		22	46	32	100	

In this study, basline CD4 count less than 200 was noted in 48% of these 18 patients had<100 count and 30 patients had 100 to 200count Majority of patients with decline in CD4 count<200 are in eGFR 60-90 category.

Correlation Between Cd4 Count And Egfr At The End Of Study

Relationship between CD4_COUNT_E eGFR_E (No of Cases)						
		eGFR_B			Total	
		<60	60-90	>90		
CD4_COUNT_E	P(<100)	1	1	0	2	2%
	Q(100-200)	11	6	4	21	21%
	R(>200)	30	30	17	77	77%
Total		42	37	21	100	

Distribution Of Cd4_Count_E Across Egfr_E

In this study, CD4 count at the end of study which is less than 200 were noted in 24% of patients of which 2 patients had<100 and 21 patients had 100to 200 CD4 counts. Majority of patients with decline in CD4 count<200 are in less than 60 eGFR category.

V. Conclusion

This study signifies that Tenofovir based regimen is the basis for most of the decline in renal function in patients on ART. Renal dysfunction is highly prevalent in the study population . This highlights the critical and underappreciated need to monitor renal function in HIV positive patients attending ART clinic at CMCH , particularly in this era where Tenofovir is being used in first line ART regimen in majority of patients as recommended by WHO.So frequent screening of renal function at regular intervals is mandatory in Tenofovir based regimen when compared to other regimens to avoid the further complications in a HIV patient, who is already suffering a incurable dreadful disease . We also recommend assessment of renal function of HIV infected patients prior to initiation of HAART to guide the choice and dosing of Antiretroviral drugs.

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