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Impact of Antiretroviral Therapy on Renal Function of HIV- Infected Patients

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ABSTRACT

HIV/AIDS has been a major contributor to health burden since many decades. The use of certain antiretroviral treatments that effective against HIV/AIDS has are associated with toxic side effects on a number of vital organs such as the pancreas, kidneys, liver, causing morphological changes in patients treated with these drugs.Most of the regimens include tenofovir as a major component and renal toxicity is a well known complication .Hence, this study was performed to estimate the renal dysfunction due to Anti retroviral Therapy by measuring creatinine clearance and renal function tests.

Materials & Methods

The study was conducted in Department of Medicine at Pt Jawahar Lal Nehru Memorial Medical College and Hospital, Raipur after obtaining approval from the institutional ethics committee. 105 HIV/AIDS seropositive patients of 18 years and above on ART, attending ART clinic of Dr BRAM Hospital were the participants.

Observations

Patients were distributed based on age, gender, baseline CD4 counts, glomerular filteration rate and compared these parameters in patients with the different duration of HIV treatment . Spot UACR was

done and results were obtained using appropriate statistical tests.Male: female ratio was found to be 1.18:1 with slight male preponderance, mean age of starting ART was 32 years, mean CD4 counts 298 cells/microlitre, with maximum derangements from baseline RFT was observed in patients who were on ART for more than 5 years duration, statistically significant decline in GFR was observed maximum in more than 5 years treatment group, and spot UACR ratio of >300mg/g in a significant number of patients.

Conclusion

Patients who were on a longer duration of ART had more decline in GFR compared to patients who were on treatment for a shorter duration of time. Spot urine Albumin-creatinine ratio was found to be towards higher side in patients who were on ART for more than 5 years duration.

Keywords

Anti-retroviral therapy, Duration of treatment,Renal function tests, GFR, UACR, TLD Regimen.

INTRODUCTION

HIV/AIDS virus causes a decrease in immune defense mechanism hence immunosuppression, thus putting the host at risk to complications including organ damage and/or metabolic disorder [(2)]. About 32.7 million patients died from AIDS-relatedillnesses since the begining of its epidemic. This led to the advent of triple antiretroviral therapy in 1996, and it was seen that mortality due to this infection has decreased by more than three- fourth of total[(1)]. The use of antiretrovirals (ARV) since then is widely being used across the globe and as per the UNAIDS record, nearly 25.4 million people were taking antiretroviral therapy in 2020[(1)]

The use of certain antiretroviral treatments that effective against HIV/AIDS are associated with toxic side effects on a number of vital organs such as the pancreas, kidneys, liver, leading to a vriety of side effects. The most vital organ to play a key role in excretion of antiretrovirals is kidney, which is exposed to high concentrations of ART's, their metabolites, or both[(3)], which have the potential to damage the kidneys, most vulnerable being the proximal tubule, beause of a high rate of blood flow and consequently a high level of toxins, leading to development of drug related toxicity[(4)]. With the existent knowledge of side effects, antiretroviral medications with reduced side effect profile and better safety are under development, and this is being incorporated in recommendations issued in the Adult and Adolescent ARV Guidelines[(5)]. Before the start of antiretroviral therapy, it has been made mandatory to have a baseline assessment of renal functions, also during change of a regimen it is postulated to regularly monitorthe renal profile for long-term safety of the patients.

The regimens are mostly tenofovir based and risk factors for tenofovir DF- are nephrotoxicity include low CD4 cell count, hepatitis C coinfection, diabetes, older age, hence baseline hepatic or renalfunction assessment is required before initiation of regimen. Published literature has documented the risk of nephrotoxicity rises when tenofovir DF is used with a ritonavir-boosted protease inhibitor or with unboosted atazanavir (when compared with tenofovir DF plus a non-nucleoside reverse transcriptase inhibitor)[(6)]. While the other published literature, however, have emphasised that the use of ritonavir-boosted protease inhibitors and unboosted atazanavir independently predicts chronic kidney disease to a similar degree as use of tenofovir[(7)].

MATERIALS & METHODS

The study was conducted on 105 study participants in Department of Medicine at Pt Jawahar Lal Nehru Memorial Medical College and Hospital, Raipur after obtaining approval from the institutional ethics committee from September 2021 to September 2022. HIV/AIDS seropositive patients of 18 years and above on ART, attending ART clinic of Dr BRAM Hospital were the population of interest. Both female and male patients were considered to participate in the study. The patients were categorised into three subgroups, after taking their baseline renal function values, based on their duration of treatment, those who have received treatment for a 6 month to less than 2 years were in group1, with treatment duration of 2-5 years were placed in group 2, and group 3 patients werethose who were on antiretroviral treatment for the duration of more than 5 years. Renal impairment was classified according to the National Kidney Foundation clinical practice guideline based on the GFR determined by the Crcl method. Spot Urine albumin creatinine ratio was also determined for every study participant.

Inclusion Criteria:

1. Diagnosed patients of HIV aged 18 years or more of both genders and who were on Antiretroviral therapy for a minimum duration of 6 months.

Exclusion Criteria:

1. Patients not willing to give written informed consent.
2. Patients with risk factors for renal disease including Hypertension, Hepatitis B or C virus co-infections.
3. Patients with Diabetes Mellitus.
4. Pregnant and Lactating females.
5. Established case of Chronic kidney disease, Diabetic kidney diasease.
6. Patients on Hemodialysis.

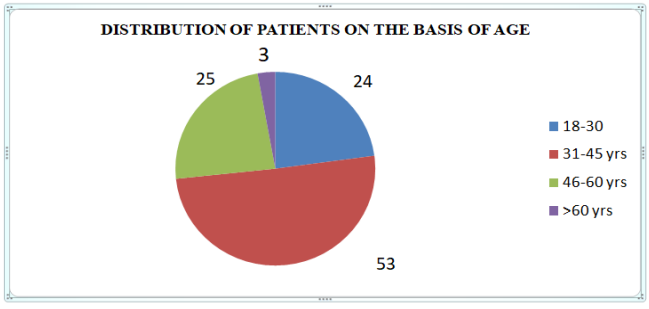
OBSERVATIONS

Table-1

Distribution of Patients Based on Gender

S. No	Gender	No. of patients	Percentage (%)
1.	Male	57	54.3%
2.	Female	48	45.7%
	Total	**105**	**100%**

In the above table patients enrolled in the study were distributed based on gender and out of 105 patients enrolled in the study, 57 patients (54.3%) were male patients and 48 were female patients (45.7%) with male : female ration of 1.18:1



The above figure shows the distribution of patients enrolled in the study, based on the age group. Age groups were divided into 4 different age groups. Patients within age group of 18-30 years constituted 24(22.8%) patients and more than 60 years were 04(3.8%). Maximum number of patients were in the age group of 31-45 years age group with 53(50.5%) patients, followed by 25 patients(23.8%)ge group of 46-60 years.

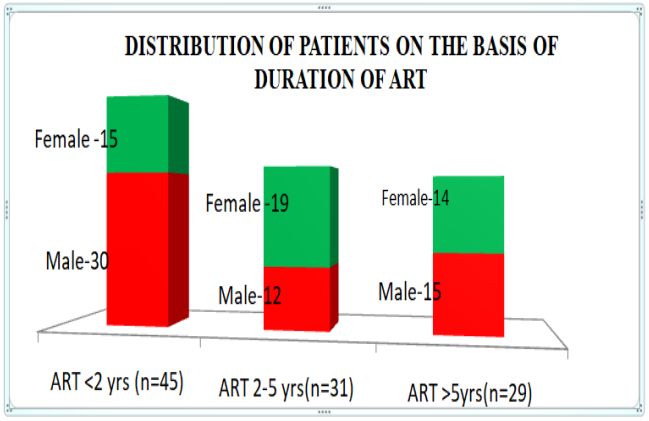
Table- 2

Distribution of Patients Based on Mean Age, CD4 Counts

S. No	Parameter	Mean	Inter-quartile range (IQR)	Mean+-SD
1.	Age	32 years	26-38 Years	1.4561
2.	CD4	298 cells/microlitre	195- 408 cells	0.8624

As per the above table, Patient distribution was done based on mean age and CD4 cell counts and in this study mean age was recorded as 32 years and mean CD4 counts as 298 cells per microlitre of blood.

Figure - 2



The above figure shows the distribution of patients on the basis of duration of their antiretroviral treatment. Total 105 patients enrolled were divided into 3 groups based on their duration of treatment. Patients who were taking ART for more than 6 months and less than less than 2 years duration had 45 patient with 66.7% male patients and 33.3% female patients, followed by 2-5 years duration of ART constituting 31 patients with 38.7% male and 61.3% female patients, and patients who were on ART for more than 5 years duration were 27.5% with 51.7% male and 48.3% female patients.

Table - 3

Distribution of Patients Based on Current Art Regimen

S. No.	ART Regimen	No. of Patients	% (Percentage)
1	Tenofovir+ lamivudine+ Dolutegravir	105	100

The above table shows the distribution of patients based on their Anti retroviral therapy regimen. Out of 105 patients, all 100% patients, current ART regimwn was TLD (Tenofovir+ Lamivudine+ Dolutegravir).

Table - 4

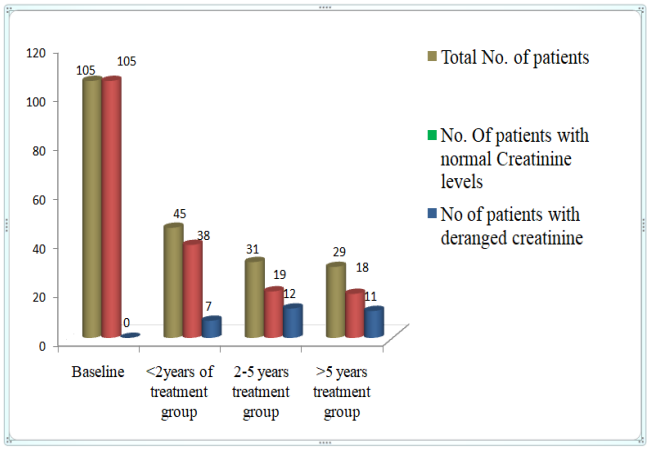
Distribution of Patients on the Basis Of Baseline & Current Blood Urea Levels

S. No	Blood urea	Total no. of patients in group	No. of patients With normal levels	No.of patients with deranged levels	p value
1.	Baseline	105	102	03	-
2.	<2 years ART group	45	38	Male - 03 Female -04	0.083
3.	2-5 years ART group	31	19	Male – 08 Female - 04	0.051
4.	>5 years ART group	29	18	Male- 06 Female-05	0.051

The above table shows the comparison of Blood urea levels, baseline, current values with the duration of treatment in 3 different groups of the study.levels Blood Urea levels were normal in 102 patients(97.1%) before the starting ART, and subsequently a repeat sample was sent and maximum rise in blood urea levels was seen in patients on ART for more than 5 years (39.3%), followed by (38.7%) in patients taking ART for a duration between 2-5 years and minimum rise in serum creatinine was seen in group who were taking ART for less than 2 years, rise in blood urea levels was seen in (15.5%).

Figure - 3

Distribution of Patients on The Basis of Baseline & Current Creatinine Levels



The above graph shows the comparison of serum creatinine levels from the baseline and with the duration of treatment in 3 different groups of the study. Creatinine levels were normal in 105 patients(100%) before initiating ART, and subsequently a repeat sample was sent and maximum rise of creatinine was seen in patients on ART for more than 5 years (39.3%), followed by (38.7%) in patients taking ART for a duration between 2-5 years and minimum rise in serum creatinine was seen in group who were taking ART for less than 2 years, rise in blood urea levels was seen in (15.5%).

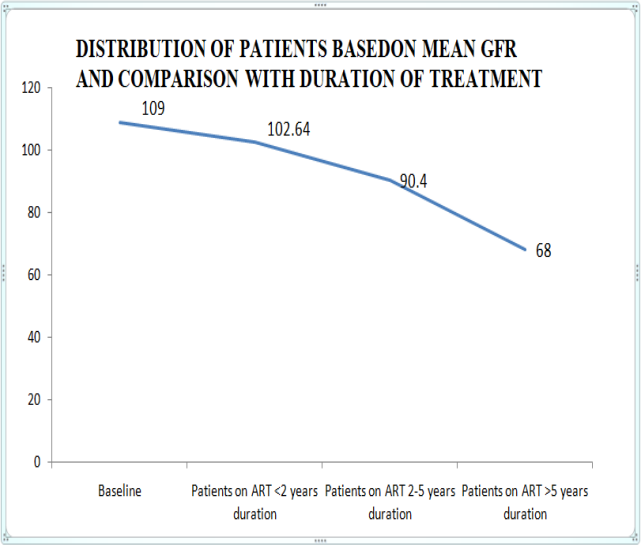
Table - 5

Comparison of Baseline RFT and CD4 Counts with the Duration of Anti-Retroviral Therapy

Parameter	No of patients (Baseline)	<2years ART Duration (n= 45)	2-5 years ART Duration (n= 31)	>5 years ART Duration (n=29)
Normal RFT	102	38	19	18
Derranged RFT (Urea, creat)	03	07	12	11
MeanCD4 counts	298	302	392	578
Paired t test - p value (CI-95%)		0.173	<0.001	<0.001

The above table and figure shows the comparison of Renal function tests in different ART duration groups with the mean CD4 counts and it was observed that Patients receiving ART for lesser than 2 years durations were having 38 patients with normal renal functions, 7 patients with deranged renal functions, and mean CD4 counts of 302 cells per microlitre, and patients with ART duration of 2-5 years were having 19 patients with normal and 12 patients with deranged renal functiona, and mean CD4 counts improved to 392 cells per microlitre. 18 patients with normal and 11 patients with deranged renal functions with substantial rise in mean CD4 counts was seen in patients taking ART for more than 5 years duration.

Figure – 4



The above table shows the distribution of patients on the basis of mean GFR and comparison between different study groups based on the duration of anti-retroviral therapy. Baseline mean GFR calculated amongst 105 study participants was 109ml/min/m2, which gradually reduced with the duration of anti-retroviral treatment, mean GFR in study group who were on ART for less than 2 years duration was 102.66ml/min/m2, in study group taking ART for 2-5 years duration was 90.40ml/min/m2, and mean GFR in study group who were taking ART for more than 5 years duration was 68ml/min/m2 suggesting decrease in GFR with the duration of ART.

Table-6

Comparison of Patients on the Basis of Duration of Art & Spot Urine Albumin-Creatinine Ratio

Spot UACR	Mean Duration of ART	No. of patients	p value	Adjusted hazard ratio (95% CI)
<30mg/g	16 months	**16/105** (15.2%)	0.056	0.41 (0.13,0.48)
30-300 mg/g	26 months	**77/105** (73.3%)	**<0.01**	0.38 (0.14, 1.03)
>300 mg/g	48 months	**12/105** (11.5%)	**<0.001**	0.35 (0.11, 0.95)

The above table shows the distribution of patients based on urinary microalbumin and creatinine ratio. 16 patients (15%) had urinary albumin and creatinine ratio below 30 mg/g with mean duration of ART of 16 months, urinary albumin-creatinine ratio of 30-300 mg/g range accounted for 77 patients (73%), with mean Duration of ART of 26 months and patients having more than 300mg/g of albumin creatinine ratio were 16 patients(12%) with mean duration of ART of 48 months. These results were statistically significant with p value of <0.01 and <0.001 in 30-300mg/g UACR and >300 mg/g UACR respectively.

DISCUSSION

In the current study which was conducted at ART centre Pt.JNM Medical College, Raipur in 2022 in 105 enrolled HIV patients on ART, patients were distributed based on gender, 57 patients (54.2%) were male patients and 48 were female patients (45.8%). This is in comparison with the study done by Takung et al 2016 which had 150 patients enrolled in their study having 64% male patients and 36% female patients[8]. The current study shows the distribution of patients enrolled in the study, based on the age group. Age groups were divided into 4 different age groups. Patients within age group of 18-30 years constituted 24(22.8%) patients and more than 60 years were 04(3.8%). Maximum number of patients were in the age group of 31-45 years age group with 53(50.5%) patients, followed by 25 patients(23.8%) in the age group of 46-60 years. This is in comparison with the already published research by Obiri - Yeboah et al in 2018 in their study participants were divided into 3 different age groups 18-30 years age group, 31-60 years age group and more than 60 years age group and the authors observed that maximum patients were in the age group of 31-60 years with 83% patients followed by 18-30 years age group with 8.6% patients and the least number of patients 8% in more than 60 years age group[9].

In present study the patient distribution was done based on mean age and CD4 cell counts and in this study mean age was recorded as 32 years and mean CD4 counts as 298 cells per microlitre of blood. This is in accordance with a study published by labarga et al in 2017 in which mean CD4 counts were 312 cells per microlitre of blood and mean age of initiation treatment was recorded as 28 years[10].

Table – 7

Comparison of the Current Studies with Published

Comparison	Mean age	Gender	Baseline CD4	Mean GFR	ART Regimen	Outcome
Present Study (2022)	32	M>F	298	109	TLD	GFR declines with the duration of ART
Oswin Mwemezi[11]etal (2018)	27	F=M	355	120	TLE/ TLD	Renal dysfunction is more with the increasing duration of ART
Tessa K, Novic etal[12] (2020)	42	M>F	513	-	TLD	GFR decline is more in patients aged>45 years.
Verma k, shuchi J[13]etal 2022	33	F>M	410	110	TLD	Early initiation is beneficial in controlling opportunistic infections.

CONCLUSION

The current study done in Pt Jawahar lal Nehru Memorial Medical College, ART centre in 105 HIV positive patients on ART concludes that there is a statistically significant difference obtained in renal derrangements in patients on Anti-retroviral therapy for more than 5 years duration with decline in GFR over time and a higher Urinary albumin Creatinine ratio in comparison to the patients who were on ART for a relatively shorter duration of time. Furthermore studies with a larger sample size are required to have more data on the renal derrangements with time and comparison in patients should be done with different HIV treatment regimens other than TLE, is needed to reach a definitive conclusion.

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