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Evaluation of Renal Functions among HIV-Infected Patients Using Antiretroviral Therapy.

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Abstract— The introduction of highly active antiretroviral therapy (HAART) has significantly improved the quality of life and extended the longevity of HIV-infected individuals on treatment in both developed and developing nations. However, the greatest disadvantage of long-term HAART usage is the risk of liver and kidney damage, which can be fatal. The medicines accumulate aggressively in the proximal renal tubule, causing functional disruption, with mitochondrial damage being one of the most critical targets identified. Therefore, the aim of this retrospective comparative study is one of the little studies conducted to evaluate the renal functions among PLHIV receiving antiretroviral combination compared to naive subjects, the present study consisted of 100 treated and 20 untreated subjects, their mean age was (29.41) ranging between (18-68), the gender distribution was equal (50% female, 50% males), teenage was the most predominant age group in the study. Creatinine levels were high in both treated and untreated HIV subjects, with no significant differences among them. In the treated subjects the prevalence of the high creatinine was 67%. Only 23% of the treated subjects reported elevated serum urea level, with no significant differences between the two study groups. The mean of eGFR in untreated subjects was 98.9ml/min and 77.3ml/min in treated HIV subjects. Most study subjects were had mildly reduced kidney function in both treated and untreated (55% and 50%) respectively. In un treated subjects 35% had normal kidney function and 15% had mildly to moderately reduced kidney function, In contrast to the treated subjects only 25% had normal kidney function, 14% demonstrated mildly to moderately reduced kidney function, 6% recorded moderately to severely reduced kidney function. None of the study subjects demonstrated advanced renal failure. The prevalence of renal impairment in the treated group, defined as eGFR <60ml/min/ 1.73m^2 using the Cockcroft-Gault formula was 20% in treated subjects, while it was only 15% in the untreated subjects. Notably, the prevalence rate of renal impairment among untreated HIV subjects was also high at 15% though significantly different from the HAART-treated group. The association between high creatinine and HAART usage was highly significant, higher proportion of the study subjects on FTC+ TDF + LPV/r subjects on FTC+ TAF + EVG/c had high creatinine. Subjects with mildly reduced kidney function was associated with all HAART groups, Stage 3a (with mildly to moderately reduced kidney function) were associated with receiving FTC+ TDF + RAL and FTC + TDF + EFV combinations. Most study subjects (88%) were using antiretroviral therapy containing tenofovir disoproxil fumarate (TDF) which was demonstrated to have severe renal complications in most previous studies. No significant association between gender and prevalence of abnormal kidney function among both treated and untreated subjects, eGFR was more reduced in male gender than female in untreated subjects, in the treated subjects females had more advanced cases of renal impairments with no significant difference. No significant effect of age on renal functions (creatinine and urea) in both treated and untreated subjects, eGRF was significantly reduced in HIV treated subjects, characteristically, the prevalence of renal impairment was higher in patients aged above 40 years in HAART-treated groups, there was 6 patients at stage 3b and 5 patients at stage 4.

Keywords- renal, HIV, antiretroviral, patients.

I. INTRODUCTION

The human immunodeficiency virus (HIV-1) is a virus belonging to class of Retroviruses and sub family Lentiviridae. It is rapidly mutating virus. The acquired immunodeficiency syndrome (AIDS) is a fatal chronic illness associated with increased mortality and morbidity from HIV-related conditions (Bittar *et al.*, 2012). HIV breaks down the body's immune system, infects $CD4^+$ cells initially and progressively leads to AIDS. This disease is characterized by immunosupression, secondary neoplasma and neurological manifestations (Rasheed *et al.*, 2008). HIV and AIDS continue to be a major global health tragedy despite intense efforts in international and local initiatives to address the pandemic. About 38.4 million people globally were living with HIV in 2021. About 1.5 million people became newly infected with HIV in 2021 . Approximately 650000 people died from AIDS-related illnesses in 2021. Only 28.7 million people were accessing antiretroviral therapy in 2021 (UNAIDS, 2022). Studies and reports dating from 2001 to 2020 identified the HIV prevalence and the number of registered people living with HIV in Libya as relatively low, Much of the research on HIV in Libya was conducted between 2004 to 2020 and most studies published similar HIV prevalence rates and number of subjects. They show an increase of HIV prevalence from

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0.13% in 2004 (UNGASS, 2010), to 0.2% in 2019 (World Bank, 2020). The initiation of highly active antiretroviral therapy (HAART) has been a key to reduce overall morbidity and mortality associated with human immunodeficiency virus-(HIV-1) infection and acquired immune deficiency syndrome (AIDS) (Kharsany & Karim, 2016). However, several complications of long-standing infection and long-term treatment have been recognized with increasing frequency. Renal disease is one of the highly prevalent co-morbidity in patients living with HIV (Calza, 2012). According to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification; 18.9% patients were in stage one of kidney disease, 10.7% in stage two of kidney disease, 5% in stage three of kidney disease, 0.3% in stage four of kidney disease and no patient was in stage five of kidney disease (Dauchy *et al.*, 2011). HIV-positive patients may have abnormal kidney functions that may be either due to HIV itself known as HIV-associated renal disease, a condition characterized by nephritic range of proteinuria that rapidly progresses to end-stage renal disease (ESRD) (Maggi *et al.*, 2012), or Drug-induced kidney injury which often leads to acute renal failure (ARF) indicated by an increase in serum creatinine level more than 30%(>1.3mg/dl (in females) and >1.5 mg/dl (in males), or blood urea nitrogen >20 mg/dl of baseline (Ibrahim *et al.*, 2010). However, the exact frequency of ART medication-induced renal insufficiency becomes difficult to determine (Izzedine *et al.*, 2005). HIV infected patients who are at risk of developing ARF are older and more likely to be men of black ethnicity, had lower CD4 T-cell counts, high viral load and hepatitis C co-infection, hypertension, diabetes, advanced WHO clinical stage of AIDS and abnormal BMI) (Ibrahim *et al.*, 2010; Mekuria *et al.*, 2016; Kumarasamy *et al.*, 2018). The occurrence of acute renal failure in peoples living with HIV is also associated with delayed HIV diagnosis (Post & Holt, 2009). A review of over 200 patients in New York with HIV-associated nephropathy also indicated that 90% were black and 70% were male despite the prevalence of HIV is three times more among the white people (D'Agati & Appel, 1997). Usually, first-line therapy offered to ART-naïve patients included one Non-Nucleoside Reverse Transcriptase (NNRTI) generally called efavirenz (EFV) or nevirapine (NVP), plus two Nucleoside Reverse Transcriptase NRTIs, either lamivudine (3TC) or emtricitabine (FTC), in addition to TDF (Kumarasamy *et al.*, 2018). Studies have shown, however, that some antiviral medications such as indinavir, tenofovir, and atazanavir induce defects in renal function including a reduction in glomerular filtration rate, proximal tubular damage, and acute kidney injury (Ibrahim *et al.*, 2010; Calza, 2012) Tenofovir disoproxil fumarate (TDF) belongs to the nucleoside reverse-transcriptase inhibitors (NRTI) used for the treatment of HIV/AIDS since 2001 which was approved by the US Food and Drug Administration (Calza, 2012; Tourret *et al.*, 2013; Kumarasamy *et al.*, 2018). It is needed to inhibit HIV replication by halting DNA synthesis from the RNA-dependent DNA polymerase of HIV and is a poor inhibitor of host cell α and β DNA polymerases and of mitochondrial γ DNA polymerase (Tourret *et al.*, 2013). TDF is renaly excreted via a combination of glomerular filtration and active tubular secretion causing proximal renal tubular dysfunction (Gallant *et al.*, 2005). Despite its proven efficacy, the frequent clinical use of TDF is associated with increased risk of kidney tubular dysfunction, which can manifest as reduced glomerular filtration rate, increased serum Creatinine level, Fanconi syndrome, proximal tubulopathy, nephrogenic diabetes insipidus, acute and chronic kidney injury (Maggi *et al.*, 2012, Ojeh *et al.*, 2018). Chronic kidney disease (CKD), defined as an estimated glomerular filtration rate (eGFR) below 60 ml/min or the presence of proteinuria, is present in 15–20% of patients infected with HIV (Ibrahim *et al.*, 2010). Some other studies have shown that although small decreases in the estimated glomerular filtration rate (eGFR), an increase in glucose and low molecular weight proteins in patients' urine after the use of TDF, they are not associated with increased nephrotoxicity compared to other regimens (Yombi *et al.*, 2014). Some other studies have also indicated that TDF use is safe for the kidney in clinical practice with an only modest decline in renal function which generally has been reported in patients with advanced HIV disease, decreased renal function at baseline or co-morbidities such as diabetes, and hypertension (Ababa *et al.*, 2016). Co-administration of TDF with other ART drugs may compete for the same pathway in order to be removed by active tubular secretion which may increase concentrations of either TDF itself or the other co-administered drug, resulting in renal tubular damage (Gallant *et al.*, 2005).

A. Objectives of the study:

The aim of this study was to determine the effect of antiretroviral treatment on some biochemical markers of renal functions among HIV-infected patients receiving treatment at Benghazi center of infectious diseases and immunology.

II. METHODS AND MATERIALS

A. Study design:

This retrospective was conducted in the laboratory of Benghazi center for infectious diseases and immunology during the period of 2021-2022 to evaluate renal functions in HIV subjects using different HAART.

B. Study population:

B.1 Study subjects and exclusion criteria:

About 122 confirmed HIV positive subjects attending BCIDI were screened for their renal functions. Inclusion criteria for cases were: HIV-infection in patient within the age group 20-65 years on HAART with no underlying cardiovascular,

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diabetes, kidney diseases, Tuberculosis; not pregnant; not on any medication (except HAART); and negative for hepatitis B or C virus infection.

B.2 Subjects on ARTs:

The 100 HIV positive subjects were stratified into four groups according to the treatment regimens table (2-1), These HIV-infected patients who were using ARTs drugs triple combination therapy for more than 24 weeks.

Assessed treatment regimens:

Group	ART classes	Group
Gr-1	**2NRTIs +NNRTIs**	FTC + TDF + EFV
Gr-2	**2NRTIs+ PIs**	FTC+ TDF + LPV/r
Gr-3	**2NRTIs +INSTIs + Booster**	FTC+ TAF + EVG/c
Gr-4	**2NRTIs +INSTIs**	FTC+ TDF + RAL

NRTIs: Nucleoside reverse transcriptase inhibitors, NNRT: Non-Nucleoside reverse transcriptase inhibitors, PI: Protease inhibitors, INSTI; I*ntegrase* strand transfer *inhibitor*.

B.3 Naive subjects:

Twenty (20) Age and gender matched HIV positive subjects not receiving any antiretroviral drugs at the study time.

C. Data collection:

Age, gender and treatment details including types of drugs, duration of treatment together with other laboratory parameters, were obtained from the medical records of the subjects.

D. Assessment of renal function:

Renal function was assessed by serum creatinine level, urea BUN and creatinine clearance by estimating the glomerular filtration rate (eGFR).

E. Results interpretation of creatinine and urea BUN:

Parameter	Normal range (mg/dl)
Creatinine	0.7-1.3
Urea BUN	7-20

F. Estimated glomerular filtration rate:

Estimated by the Cockcroft-Gault equation as following:

$$\textbf{CrCL (ml/min)} = \frac{(140-\text{age}) \times \text{body weight (KG)}}{\text{Serum creatinine } \left(\frac{\text{mg}}{\text{dl}}\right) \times 72} (\times\ 0.85 \text{ if female})$$

G. .2.3. Assessment of eGFR:

- Stage 1: GFR 90 ml/min, or greater (normal kidney function).
- Stage 2: GFR 60-89 ml/min, (mildly decreased kidney function).
- Stage 3a: GFR 45 - 59 ml/min, (mildly to moderately decreased kidney function).
- Stage 3b GFR 30 - 44 ml/min, (moderately to sever decreased kidney function).
- Stage 4: GFR 15-29 m;/min, (Severely decreased kidney function).
- Stage 5: GFR less than 15 ml/min, (close to or at kidney failure).

H. Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 22 software program. Descriptive statistics, Chi-square test and Independent T test, were used to test the significance of the results at 95% confidence interval.

III. RESULTS AND DISCUSSION

A. Study population:

A.1 Distribution of all study subjects:

The study comprised of 100 HIV positive subjects on different antiretroviral therapies and 20 HIV positive naive who were not receiving any treatment, as shown in table (I) and figure (I).

Table (I): *Distribution of all study subjects.*

HIV (+) Subjects	N.	Percent
Untreated (ARTs Naïve)	20	16.7%
Treated	100	83.3%
Total	120	100%

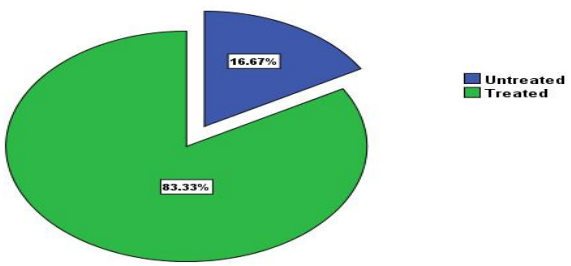

Fig. (I): *Distribution of all study subjects.*

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B. Distribution of the treated study subjects according to the ARTs regimens:

The distribution of the treated HIV positive subjects according to their treatment regimens showed that about 36% of them were receiving (FTC + TDF + EFV), 25% were receiving (FTC+ TDF + LPV/r), 22% were receiving (FTC+ TAF + EVG/c), while 17% were receiving (FTC+ TDF + RAL), as described in table (II) and figure (II).

Table (II): *Distribution of the treated study subjects according to the ARTs regimens.*

Treated HIV (+) subjects	N.	Percent
Gr-1	36	36%
Gr-2	25	25%
Gr-3	22	22%
Gr-4	17	17%
Total	100	100%

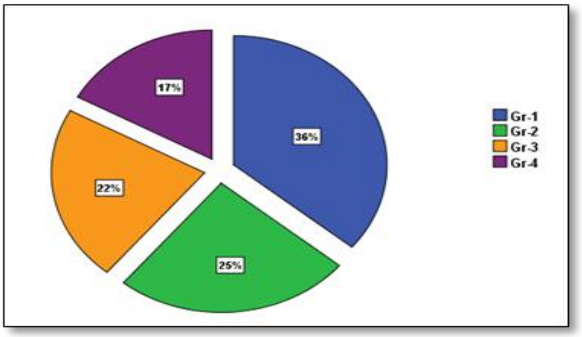

Fig. (II): *Distribution of the treated study subjects according to the ARTs regimens.*

C. Distribution of study subjects according to gender:

The study comprised of 60 (50%) females and 60 (50%) males, their distribution according to their HAART treatment is illustrated in table (III) and figure (III).

Table (III): *Distribution of study subjects according to gender.*

Gender	Treated HIV (+) subjects		Untreated (ARTs Naïve)		Total N. (%)
	N.	Percent	N.	Percent	
Female	52	52%	8	40%	60 (50%)
Male	48	48%	12	60%	60 (50%)
Total	100	100%	20	100%	120 (100%)

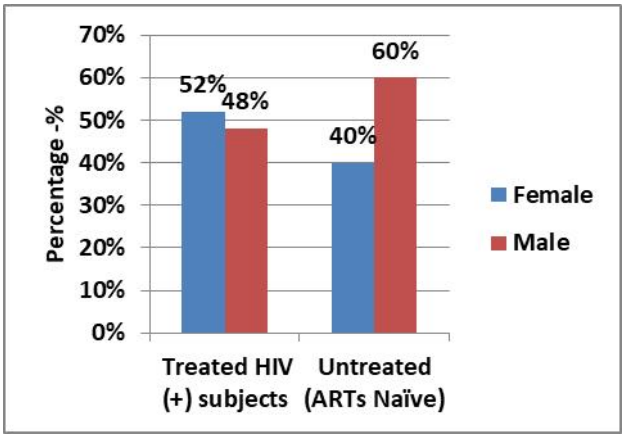

Fig. (III): *Distribution of study subjects according to gender.*

D. Distribution according to the age:

The mean age of the total population was 29.41 ±9.61 ranging between 18 and 68 years old. Among untreated HIV positive subjects the mean age was 27.6±2.99, ranging between 25 to 35 years old, while the mean age among the treated subjects was 29.77±10.42, ranging between 18to 68 years old, subjects were stratified into age groups, the distribution of the subjects according to their age is described in the table (IV) and figure (IV).

Table (IV): *Distribution of the study subjects according to the age.*

Age	Treated HIV (+) subjects		Untreated (ARTs Naïve)	
	N.	Percent	N.	Percent
≤ 25	55	55%	6	30%
26-30	16	16%	11	55%
31-35	11	11%	2	10%
36-40	4	4%	1	5%
≥ 41	14	14%	-	-
Total	100	100%	20	100%

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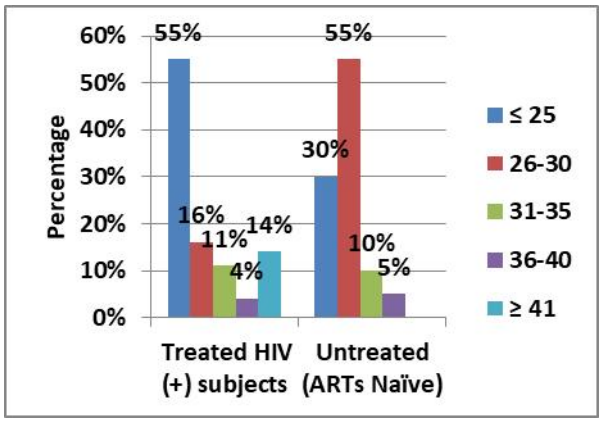

Fig. (IV): *Distribution of the study subjects according to the age.*

E. Evaluation of renal function:

E.1. SERUM CREATININE LEVEL:

- **Categories:**

Serum creatinine level was normal in only 25% of the untreated study subjects and 33% of the treated study subjects, but it was high in 75% of untreated subjects and 67% of the treated study subjects, the distribution of the study subjects according to their serum creatinine categories is described in table (V) and figure (V).

Table (V*): The distribution of the study subjects according to their serum creatinine***.**

Subjects	Creatinine	Frequency	Percent
Untreated (ARTs Naïve)	Normal	5	25%
	High	15	75%
	Total	20	100%
Treated HIV (+) subjects	Normal	33	33%
	High	67	67%
	Total	100	100%

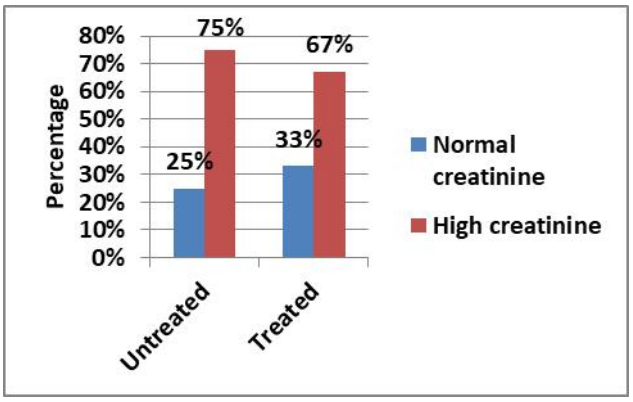

Fig. (V): *The distribution of the study subjects according to their serum creatinine.*

- **Compare means:**

The mean creatinine value in was higher in untreated HIV subjects was 1.51 mg/dl, ranging between 0.6-1.99 mg/dl, than in the treated HIV subjects was 1.48 mg/dl ranging between 0.65-2.8 mg/dl, with no significant differences according to the independent T test (p-value > 0.05), as shown in table (VI) and figure (VI).

Table (VI): *Comparing creatinine level among study subjects.*

Subjects	N.	Mean± STD	Mini.	Max.	Independent T test (Sig.)
Untreated (ARTs Naïve)	20	1.51±0.443	0.60	1.99	0.224
Treated HIV (+) subjects	100	1.48± 0.392	0.65	2.80	

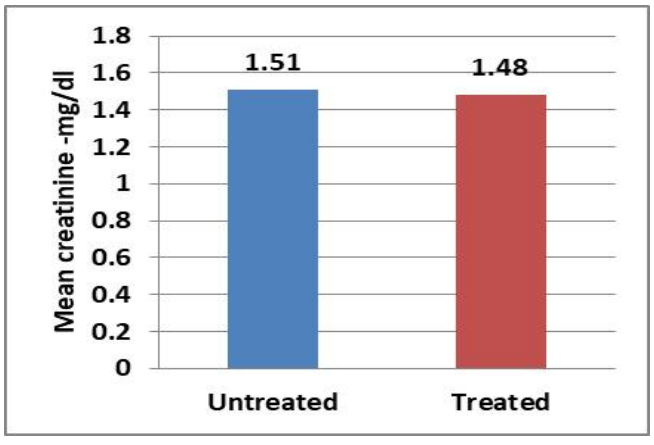

Fig. (VI): *Comparing creatinine level among study subjects.*

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F. Serum urea BUN level:

- *Categories:*

Serum urea BUN level was normal in 65% of the untreated study subjects and in 77% of the treated study subjects, but it was high in only 35% of untreated subjects and 23% of the treated study subjects, the distribution of the study subjects according to their serum urea BUN categories is described in table (VII) and figure (VII).

Table (VII): *The distribution of the study subjects according to their serum urea.*

Subjects	Urea	Frequency	Percent
Untreated (ARTs Naïve)	Normal	13	65%
	High	7	35%
	Total	20	100%
Treated HIV (+) subjects	Normal	77	77%
	High	23	23%
	Total	100	100%

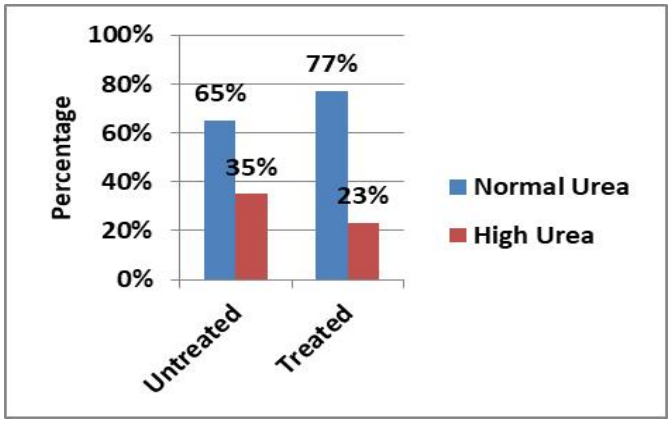

Fig. (VII): *The distribution of the study subjects according to their serum urea.*

- **Compare means:**

Untreated HIV subjects recorded higher mean of serum urea 15.97 mg/dl, ranging between 6-23mg/dl, than found in treated subjects 14.69 mg/dl, ranging between 6-29mg/dl, with no significant differences according to independent T test (p-value > 0.05), as shown in table (VIII) and figure (VIII).

Table (VIII): *Comparing urea level among study subjects.*

Subjects	N.	Mean± STD	Mini.	Max.	Independent T test (Sig.)
Untreated (ARTs Naïve)	20	15.97±5.65	6	23	0.372
Treated HIV (+) subjects	100	14.69± 5.89	7	29	

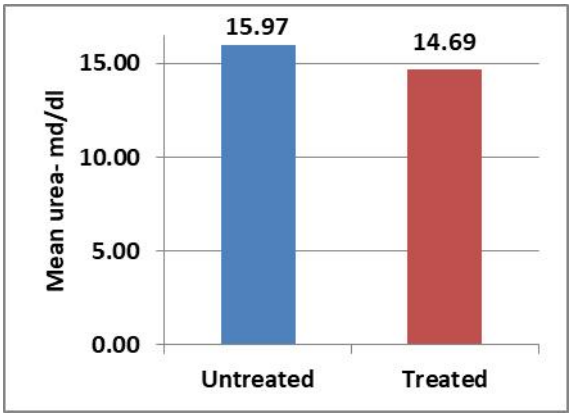

Fig. (VIII): *Comparing urea level among study subjects.*

E. ESTIMATED GLOMERULAR FILTRATION RATE (EGFR):

- **Categories:**

Most study subjects were in stage 2 (had mildly reduced kidney function), it was 50% in untreated, 55% in treated subjects). In untreated subjects 35% had normal kidney function and 15% were at stage 3b (mildly to moderately reduced kidney function), in contrast only 25% of the treated subjects had normal kidney function, 14% were at stage 3b (mildly to moderately reduced kidney function), 6% were at stage 3b (moderately to severely reduced kidney function). The prevalence of renal impairment in the HAART-treated group, defined as eGFR <60ml/min/ 1.73m2 using the Cockcroft-Gault formula was 20%.

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Table (IX): *The distribution of the study subjects according to their eGFR.*

Subjects	Urea	Frequency	Percent
Untreated (ARTs Naïve)	Stage1	7	35%
	Stage 2	10	50%
	Stage 3a	3	15%
	Total	20	100%
Treated HIV (+) subjects	Stage 1	25	25%
	Stage 2	55	55%
	Stage 3a	14	14%
	Stage 3b	6	6%
	Total	100	100%

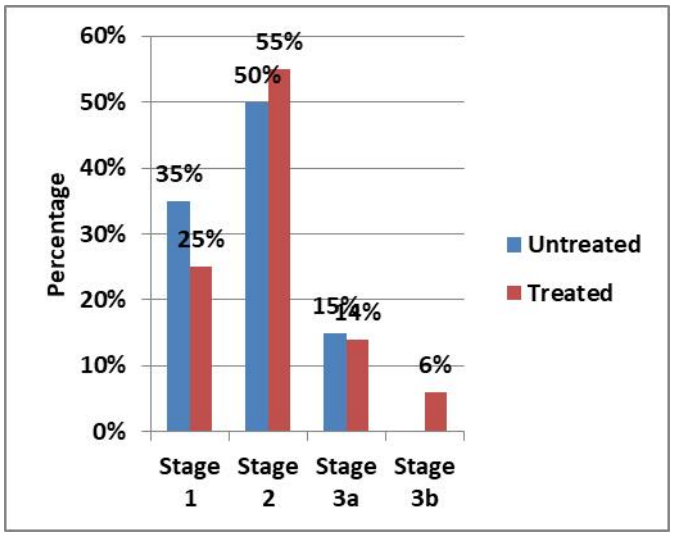

Fig. (IX): *The distribution of the study subjects according to their eGFR.*

- **Compare means:**

The mean of eGFR in untreated subjects was 98.9ml/min, ranging between 50-173ml/min, but lower eGFR was found in treated HIV subjects 77.3 ml/min, ranging between 31-124 ml/min, with a significant differences in the means among the two groups (p-value< 0.05).

Table (X): *Comparing eGFR among study subjects.*

Subjects	N.	Mean± STD	Mini.	Max.	Independent T test (Sig.)
Untreated (ARTs Naïve)	20	98.9 ± 30.87	50	173	0.043
Treated HIV (+) subjects	100	77.3±18.353	31	124	

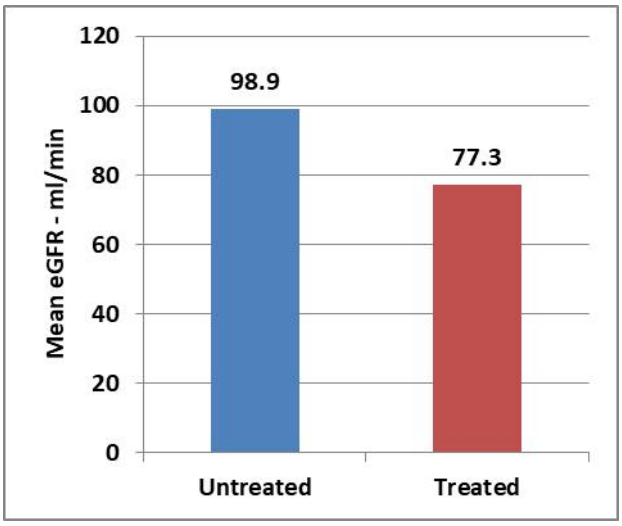

Fig. (X): *Comparing eGFR among study subjects.*

G. Effect of HAART on renal functions among treated subjects:

The association between high creatinine and HAART usage was highly significant, higher proportion of the study subjects using Gr-2 (subjects on FTC+ TDF + LPV/r) and Gr-3 (subjects on FTC+ TAF + EVG/c) had high creatinine. Subjects at stage 2 (with mildly reduced kidney function) was associated with all HAART groups, Stage 3a (with mildly to moderately reduced kidney function) were associated with Gr-4 (subjects receiving FTC+ TDF + RAL) and Gr-1(subjects using FTC + TDF + EFV), the association was highly significant according to chi-square (p-value< 0.05). There was no significant association between HAART usage and urea level.

Table (XI): *Effect of HAART on renal functions among treated subjects.*

Parameter	Gr-1	Gr-2	Gr-3	Gr-4	Total	Chi-square (Sig.)
Creatinine (mg/dl)						
Normal	21	4	5	3	33	0.001
High	15	21	17	14	67	
Total	36	25	22	17	100	
Urea (mg/dl)						
Normal	26	20	18	13	77	0.83
High	10	5	4	4	23	
Total	26	20	18	13	100	
eGFR (ml/min)						
Stage 1	17	1	6	1	15	0.004
Stage 2	15	18	12	10	55	
Stage 3a	4	3	2	5	14	
Stage 3b	-	3	2	1	6	
Total	36	25	22	17	100	

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H. Effect of gender on renal functions:

There was no significant association between gender and renal functions (creatinine and urea) (p-value > 0.05), but the association was significant in eGFR among HIV naive subjects, most males were at stage 2 (mildly reduced renal function) (p-value < 0.05).

Table (XII): *Effect of gender on renal functions.*

Subjects	Parameter	Female	Male	Total	Chi-square (Sig.)
Creatinine (mg/dl)					
Untreated (ARTs Naïve)	**Normal**	4	1	5	0.058
	High	4	11	15	
	Total	8	12	20	
Treated HIV (+) subjects	**Normal**	19	14	33	0.258
	High	33	34	67	
	Total	52	48	100	
Urea (mg/dl)					
Untreated (ARTs Naïve)	**Normal**	6	7	13	0.392
	High	2	5	7	
	Total	8	12	20	
Treated HIV (+) subjects	**Normal**	38	39	77	0.232
	High	14	9	23	
	Total	52	48	100	
eGFR (ml/min)					
Untreated (ARTs Naïve)	**Stage 1**	6	1	7	0.008
	Stage 2	2	8	10	
	Stage 3a	0	3	3	
	Total	8	12	20	
Treated HIV (+) subjects	**Stage 1**	13	12	25	0.055
	Stage 2	26	29	55	
	Stage 3a	9	5	14	
	Stage 3b	4	2	6	
	Total	52	48	100	

I. Effect of age on renal function:

There were no significant associations between age and renal functions (creatinine, urea) among both treated and untreated subjects (p-value > 0.05). eGFR was not significantly associated with age in untreated subjects, but the association was significant among treated HIV subjects, moderate to severe renal impairments were associated with old age, (p-value < 0.05).

Table (XIII): *Effect of age on renal functions.*

Subjects	Parameter	≥ 25	26-30	31-35	36-40	≤41	Total	Chi-square (Sig.)
Creatinine (mg/dl)								
Untreated (ARTs Naïve)	Normal	3	2	0	-	0	5	0.351
	High	3	9	2	-	1	15	
	Total	6	11	2	-	1	20	
Treated HIV (+) subjects	Normal	23	3	5	1	1	33	0.057
	High	32	13	6	3	13	67	
	Total	55	16	11	4	14	100	
Urea (mg/dl)								
Untreated (ARTs Naïve)	Normal	4	8	0	-	1	13	0.208
	High	2	3	2	-	0	7	
	Total	6	11	2	-	1	20	
Treated HIV (+) subjects	Normal	39	14	7	4	13	77	0.169
	High	16	2	4	0	1	23	
	Total	55	16	11	4	14	100	
eGFR (ml/min)								
Untreated (ARTs Naïve)	Stage 1	4	3	0	-	0	7	0.295
	Stage 2	2	5	2	-	1	10	
	Stage 3a	0	3	0	-	0	3	
	Total	6	11	2	-	1	20	
Treated HIV (+) subjects	Stage 1	18	4	3	0	0	25	0.000
	Stage 2	33	11	5	3	3	55	
	Stage 3a	4	1	3	0	6	14	
	Stage 3b	0	0	0	1	5	6	
	Total	55	16	11	4	14	100	

HIV affects multiple organs, including the kidney, heart, skin, and lungs. Kidney disease is the fourth most common cause of non-acquired-immune-deficiency syndrome-(AIDS)-related mortality in the people living with HIV (after oncologic, cardiac, and liver disorders) (Razzak *et al.*, 2015). HIV infection can result in a diverse clinical and histologic spectrum of renal diseases; HIV-associated nephropathy (HIVAN), HIV-associated immune complex kidney disease (HIVICK), thrombotic microangiopathy-related renal disease, and others (Menez *et al.*, 2018). Research in the last two decades has shown that early initiation of combination antiretroviral therapy (cART) in people living with HIV may result in a near-normal life expectancy (NIAID, 2022). The advent of cART in the 1990s produced a paradigm shift in the HIV, with pandemic, striking reductions in patient mortality and morbidity (Razzak *et al.*, 2015). Nevertheless, along with co-morbidities like diabetes mellitus (DM) and hypertension (HTN), chronic HIV infection may play a substantive role in the rising prevalence of chronic kidney disease (CKD) and is associated with poor health outcomes (Clark & Khan, 2010). Several treatment modalities are available for people living

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with HIV with end-stage kidney disease (ESKD), including renal replacement therapy (RRT) and renal transplantation, with excellent survival rates (Wyatt, 2012). CKD is increasingly important as a critical comorbidity for patients living with HIV: the life expectancy of appropriately treated individuals living with HIV is now similar to that of the general population (May *et al.*, 2014), the prevalence of patients with fully suppressed HIV on combined antiretroviral (ARV) treatment is increasing and the HIV population is ageing. Such patients are increasingly exposed to, and often more affected by, diseases associated with ageing, including cardiovascular disease and CKD, and the prevalence of risk factors such as smoking and dyslipidaemia is increased in this population (Mdodo *et al.*, 2015). This retrospective comparative study is one of the little studies conducted to evaluate the renal functions among PLHIV receiving antiretroviral combination compared to naive subjects, the present study consisted of 100 treated and 20 untreated subjects, their mean age was (29.41) ranging between (18-68), the gender distribution was equal (50% female, 50% males), teenage was the most predominant age group in the study

Evaluation of renal function:

Creatinine: Creatinine levels were high in both treated and untreated HIV subjects, with no significant differences among them. In the treated subjects the prevalence of the high creatinine was 67% with mean value 1.48mg/dl, the reference value in this study was ranging between 0.7-1.6 mg/dl. In fact serum creatinine has been found to be a fairly reliable indicator of kidney function. In contrast to a study conducted in Cameron, the prevalence of increased creatinine level was 25% (Samje *et al.*, 2020). According to Vadde, *et al.*, (2013), elevated serum creatinine level signifies impaired kidney function. While low levels of the waste product creatinine in the body could be a sign that the liver or muscles are not working as they should (Jao, 2010). Long term exposure to HAART may be associated with significant toxicity. The previous researches reviewed the potential nephrotoxicity of specific antiretroviral agents and the impact of antiretroviral therapy on related metabolic disorders (Vadde, *et al.*, 2013). The antiretroviral agents most strongly associated with direct nephrotoxicity include the nucleotide reverse transcriptase inhibitor, tenofovir, and the protease inhibitor, although other agents have been implicated less frequently. Tenofovir and related nucleotide analogs have primarily been associated with proximal tubular dysfunction and acute kidney injury, whereas protease inhibitors is known to cause nephrolithiasis, obstructive nephropathy, and interstitial nephritis (Jao, *et al.*, 2010).

Serum urea BUN: Urea level were studied only in few previous reports, in this study, the mean of serum urea level, still in the normal range for both studied groups. Only 23% of the treated subjects reported elevated serum urea level, with no significant differences between the two study groups. However, serum urea level is highly variable, and depends on other factors such as diet and diuresis (Valdiguié, 2000).

Estimated glomerular filtration rate (eGFR): The mean of eGFR in untreated subjects was 98.9ml/min and 77.3ml/min in treated HIV subjects. Most study subjects were had mildly reduced kidney function (stage 2), it was 50% in untreated, 55% in treated subjects. In un treated subjects 35% had normal kidney function and 15% had mildly to moderately reduced kidney function (stage 3b), in contrast only 25% of the treated subjects had normal kidney function, 14% demonstrated mildly to moderately reduced kidney function(stage 3b), 6% recorded moderately to severely reduced kidney function (stage 3b). No subjects at renal failure stage. The prevalence of renal impairment in the HAART-treated group, defined as eGFR <60ml/min/ 1.73m^2 using the Cockcroft-Gault formula was 20% in treated subjects, while it was only 15% in the untreated subjects. Notably, the prevalence rate of renal impairment among untreated HIV subjects was also high at 15% though significantly different from the HAART-treated group. This study is higher than the rate of 18.2% reported in southeast Ethiopia (Mekuria *et al.*, 2016), 21% in northwest Ethiopia (Kahsu *et al.*, 2013), 5.5% in Lesotho (Bygrave *et al.*, 2011), 6% in Uganda (Peters *et al.*, 2008) and 1.1% in Tanzania (Mpondo *et al.*, 2014), and less than reported in Cameron (Samje *et al.*, 2020). The variation in the rate compared to other studies may be related to differences in population studied, study design, sample size, and formula/definition used to classify renal impairment (Mekuria *et al.*, 2016).

Effect of HAART:

The association between high creatinine and HAART usage was highly significant, higher proportion of the study subjects using Gr-2 (subjects on FTC+ TDF + LPV/r) and Gr-3 (subjects on FTC+ TAF + EVG/c) had high creatinine. Subjects at stage 2 (with mildly reduced kidney function) was associated with all HAART groups, Stage 3a (with mildly to moderately reduced kidney function) were associated with Gr-4 (subjects receiving FTC+ TDF + RAL) and Gr-1(subjects using FTC + TDF + EFV). In general, most study subjects (88%) were using antiretroviral therapy containing tenofovir disoproxil fumarate (TDF), while (22%) were on combination containing tenofovir Alafenamide (TAF). TDF belongs to the nucleoside reverse- transcriptase inhibitors (NRTI) used for the treatment of HIV/AIDS since 2001 (Calza, 2012; Tourret *et al.*, 2013; Kumarasamy *et al.*, 2018), TDF is renaly excreted via a combination of glomerular filtration and active tubular secretion causing proximal renal tubular dysfunction (Gallant *et al.*, 2005). Despite its proven efficacy, the frequent clinical use of TDF is associated with increased risk of kidney tubular dysfunction, which can manifest as reduced glomerular filtration rate, increased serum Creatinine

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level, Fanconi syndrome, proximal tubulopathy, nephrogenic diabetes insipidus, acute and chronic kidney injury (Maggi *et al.*, 2012, Ojeh *et al.*, 2018). In contrast to TAF, which also belonging to NRTI, it may offer improved renal safety over TDF (Sax *et al.*, 2015) TAF can achieve higher intracellular levels of the active moiety tenofovir diphosphate, with lower levels of circulating tenofovir when compared with TDF. This more targeted treatment could potentially result in fewer renal complications (Ruane *et al.*, 2013; Markowitz *et al.*, 2014). TAF has been shown to be safe in mild to moderate renal impairment (30–69 mL/min), and switch from a mixture of TDF- and non-TDF-containing regimens to fixed-dose EVG/COBI/FTC/TAF in a further study resulted in no change in eGFR but significant improvements (reduction) in proteinuria (Sax *et al.*, 2015). Elvitegravir (EVG) is >99% protein bound in plasma and predominantly excreted in faeces (94%), with the remainder (6%) excreted in urine (Ramanathan *et al.*, 2011; Adams *et al.*, 2012). As its metabolism is primarily hepatic, EVG does not require dose adjustment in renal impairment (Post *et al.*, 2015). with no documented formal renal adverse effects (Elion *et al.*, 2013). Raltregravir (RAL) is 83% plasma-protein bound and excreted in both urine and faeces (32 and 51%, respectively), but dose adjustment is not needed in renal impairment (Adams *et al.*, 2012). RTG is only minimally removed during haemodialysis (Moltó *et al.*, 2010). Trial data suggest RTG may cause an increase in serum creatinine without affecting renal excretory or tubular function. The sailing study evaluated renal adverse effects in both RTGand DTG-exposed individuals as part of a non-inferiority study (Cahn *et al.*, 2013). The protease inhibitors lopinavir has been associated with renal stone formation (Post, 2014) ritonavir-boosted lopinavir (LP/r) have been associated with CKD risk that increases with cumulative exposure (Mocroft *et al.*, 2010), and may precipitate nephrolithiasis according to finding reported by (Rockwood *et al.*, 2011). In addition LP/r have all been shown to increase plasma exposures of tenofovir by approximately 20–37%. and the mechanism for this interaction is unclear (Kearney *et al.*, 2006).

The non-nucleoside reverse transcriptase inhibitors (NNRTIs have no reported significant kidney toxicity efavirenz (Rockwood *et al.*, 2011). However, some renal complications often observed in patients may indeed be related to the virus itself, according to studies carried out in Cameroon and elsewhere in the world (Wyatt *et al.*, 2008; Kalayjian, 2010;. FolefackKaze *et al.*, 2013).

Effect of gender:

No significant association between gender and prevalence of abnormal kidney function among both treated and untreated subjects, However eGFR was more reduced in male gender than female in untreated subjects, in the treated subjects females had more advanced cases of renal impairments (though not significantly different), which contradicts the report of Mekuria *et al.*, (2016) but was in agree with, Samje *et al.*, (2020) who suggested that the female gender is more predisposed to HAART-induced renal toxicity, Molu *et al.*, (2018) reported twice females than males in a study that recruited 712 HIV-infected patients in Cameroon (Wondifraw Baynes *et al.*, (2016) reported that female gender was a risk factor for CKD. The disparity in the male to female ratio may be attributed to the increased feminization of the HIV epidemic, with large number of females living with HIV.

Effect of age:

In this study, no significant effect of age on renal functions (creatinine and urea) in both treated and untreated subjects, eGRF was significantly reduced in HIV treated subjects, characteristically, the prevalence of renal impairment was higher in patients aged above 40 years in HAART-treated groups, there was 6 patients at stage 3b and 5 patients at stage 4. This finding was in co-accordance with (Gallant *et al.*, 2005; Kumarasamy *et al.*, 2018; Kefeni *et al.*, 2021), However renal function decreases with age, with the older age being a risk factor also in the general population (Sulkowsk *et al.*, 2000). In contrast Various studies found that old age is an independent predictor for renal function impairment (Shamu *et al.*, 2015). This variation may be due to the population variation and different age classification methods used. Renal function impairment that might progress to end-stage renal disease requiring dialysis and renal transplant can be diagnosed in its earlier stage through routine screening and careful attention to changes in renal functions (Msangoa *et al.*, 2011). In developing countries, where renal transplant and dialysis are rarely accessible, early detection of renal disease has clinical and financial implications for people living with HIV/AIDS (Ababa *et al.*, 2016).

IV. CONCLUSION

This retrospective comparative study is one of the little studies conducted to evaluate the renal functions among PLHIV receiving antiretroviral combination compared to naive subjects, the present study consisted of 100 treated and 20 untreated subjects, their mean age was (29.41) ranging between (18-68), the gender distribution was equal (50% female, 50% males), teenage was the most predominant age group in the study.

- Creatinine levels were high in both treated and untreated HIV subjects, with no significant differences among them. In the treated subjects the prevalence of the high creatinine was 67%.
- Only 23% of the treated subjects reported elevated serum urea level, with no significant differences between the two study groups.
- The mean of eGFR in untreated subjects was 98.9ml/min and 77.3ml/min in treated HIV subjects. Most study subjects were had mildly reduced kidney function in both treated and untreated (55% and 50%)

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respectively. In un treated subjects 35% had normal kidney function and 15% had mildly to moderately reduced kidney function, In contrast to the treated subjects only 25% had normal kidney function, 14% demonstrated mildly to moderately reduced kidney function, 6% recorded moderately to severely reduced kidney function. None of the study subjects demonstrated advanced renal failure.

- The prevalence of renal impairment in the treated group, defined as eGFR <60ml/min/ 1.73m^2 using the Cockcroft-Gault formula was 20% in treated subjects, while it was only 15% in the untreated subjects. Notably, the prevalence rate of renal impairment among untreated HIV subjects was also high at 15% though significantly different from the HAART-treated group.
- The association between high creatinine and HAART usage was highly significant, higher proportion of the study subjects on FTC+ TDF + LPV/r subjects on FTC+ TAF + EVG/c had high creatinine. Subjects with mildly reduced kidney function was associated with all HAART groups, Stage 3a (with mildly to moderately reduced kidney function) were associated with receiving FTC+ TDF + RAL and FTC + TDF + EFV combinations.
- Most study subjects (88%) were using antiretroviral therapy containing tenofovir disoproxil fumarate (TDF) which was demonstrated to have severe renal complications in most previous studies..
- No significant association between gender and prevalence of abnormal kidney function among both treated and untreated subjects, eGFR was more reduced in male gender than female in untreated subjects, in the treated subjects females had more advanced cases of renal impairments with no significant difference.
- No significant effect of age on renal functions (creatinine and urea) in both treated and untreated subjects, eGRF was significantly reduced in HIV treated subjects, characteristically, the prevalence of renal impairment was higher in patients aged above 40 years in HAART-treated groups, there was 6 patients at stage 3b and 5 patients at stage 4.
- Some renal complications often observed in patients may indeed be related to the virus itself.
- Early detection of renal disease has clinical and financial implications for people living with HIV/AIDS

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