*CIBTech Journal of Pharmaceutical Sciences ISSN: 2319–3891 (Online)*
*An Open Access, Online International Journal Available at http://www.cibtech.org/cjps.htm*
*2015 Vol.4 (1) January-March, pp.32-42/Girma et al.*
***Research Article***

# EFFECT OF 1ST LINE HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY (HAART) ON THE DEVELOPMENT OF RENAL FAILURE IN HUMAN IMMUNODEFICIENCY VIRUS (HIV)-INFECTED PATIENTS ATTENDING ART CLINIC OF ST. PAUL'S GENERAL SPECIALIZED HOSPITAL, ADDIS ABABA: A RETROSPECTIVE CROSSECTIONAL STUDY

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## ABSTRACT
In HIV/AIDS patients renal dysfunction is a severe complication of advanced HIV disease. In addition to HIV, HAART also contributes to the development of renal failure. A total of 518 HIV infected patients of which 259 control groups and the rest 259 HAART receiving were included in the study. Of the 259 patients with HAART at baseline, 2(0.8 %) and 3(1.2%) showed serum creatinine and serum urea greater than 1.8mg/dl and 50mg/dl respectively. Of 259 controls 2(0.8%) showed serum urea greater than 50mg/dl and none of them had creatinine values of greater than 1.8mg/dl. Among HAART receiving 154 and 104 were female and male respectively, and of whom 2(0.8%) females and 1(0.4%) male showed abnormal urea value (greater than 50mg/dl). Abnormal creatinine value was found among HAART receiving males 3(1.2%) while HAART receiving females had normal creatinine value. Among controls, 1(0.4%) male and females had abnormal urea value and none of them had abnormal creatinine value. Although, some renal abnormalities has been observed on HAART receiving patients, our study showed that there was no statistically significant difference in renal abnormalities compared to controls ($p>0.05$). Therefore, the study confirms the need for further follow up for prolonged period of time to see the actual effect of HAART treatment on renal failure in Ethiopian patients. Furthermore, lack of sensitive indicators of renal failure examination like gromerular filtration rate and microalbuminurea in the study area limits the diagnosis of the condition as early as possible.

***Keywords:*** *HAART, Creatinine, Urea, St. Paul Hospital*

## INTRODUCTION
HIV infection results from 1 of 2 similar retroviruses (HIV-1 and HIV-2) that destroy $CD4^+$ lymphocytes and impair cell-mediated immunity, increasing the risk of certain infections and cancers. Initial infection may cause nonspecific febrile illness. Risk of subsequent manifestations related to immunodeficiency is proportional to the level of $CD4^+$ lymphocytes. Manifestations range from asymptomatic carriage to AIDS, which is defined by serious opportunistic infections or cancers or a CD4 count of < 200/$\mu$L. Transmission of HIV requires contact with body fluids specifically blood, semen, vaginal secretions, breast milk, saliva, or exudates from wounds or skin and mucosal lesions that contain free virions or infected cells (Buchacz *et al.*, 2006; World Health Organization, 2008). Transmission is more likely with higher levels of virions, as is typical during primary infection, even when people are asymptomatic. Transmission by saliva or droplets produced by coughing or sneezing, although conceivable, is extremely unlikely (Buchacz *et al.*, 2006; World Health Organization, 2008).
T helper cell also known as $CD4^+$ T cells are a sub-group of lymphocytes that play an important role in establishing and maximizing the capabilities of the immune system. They express the CD4 protein on their surface. Helper T cells become activated when they are presented with peptide antigens by MHC class II molecules that are expressed on the surface of Antigen Presenting Cells. Once activated, they

divide rapidly and secrete small proteins called cytokines that regulate or assist in the active immune response. Cytotoxic T cells destroy virally infected cells and tumor cells, and are also implicated in transplant rejection. These cells are also known as $CD8^+$ T cells since they express the CD8 glycoprotein at their surface. These cells recognize their targets by binding to antigen associated with MHC class I, which is present on the surface of nearly every cell of the body (FMOH/FHAPCO, 2007a).

Sub-Saharan Africa remains the region most heavily affected by HIV. In 2008, Sub-Saharan Africa accounted for 67% of HIV infections worldwide, 68% of new HIV infections among adults and 91% of new HIV infections among children. The region also accounted for 72% of the world's AIDS-related deaths in 2008.The epidemic continues to have an enormous impact on households, communities, businesses, public services and national economies in the region. In 2008, an estimated 1.9 million people living in Sub-Saharan Africa became newly infected with HIV, bringing the total number of people living with HIV to 22.4 million. The number of people living with HIV in sub-Saharan Africa slightly increased in 2008, in part due to increased longevity stemming from improved access to HIV treatment. Adult HIV prevalence declined from 5.8% in 2001 to 5.2% in 2008. In 2008, an estimated 1.4 million AIDS-related deaths occurred in Sub-Saharan Africa. This number represents an 18% decline in annual HIV-related mortality in the region since 2004 (World Health Organization, 2008).

In Ethiopia, according to the single point estimate, the national HIV prevalence is 2.1%. Free ART program for HIV infected patients was launched in January 2005. According to the Federal Ministry of Health monthly HIV Care and ART up date of December 2008, 175,612 ever started ART and 128,935 patients are currently on ART (FMOH/FHAPCO, 2007a; FMOH/FHAPCO, 2007b; FMOH/FHAPCO, 2008).

The use of combination of drugs, particularly HAART since the mid-1990s has resulted in significant and sustained reductions in morbidity and mortality from HIV infection, including significant declines in HIVAN. There are more than 20 approved antiretroviral drugs with five classification but not all are licensed or available in every country. Because adequate antiretroviral therapy can cause significant long-term morbidity, it is not recommended for everyone. Current indications include a $CD4^+$ count of < 350/μL and HIV RNA level of > 55,000 copies/ml. The increase in $CD4^+$ count indicates a corresponding decrease in risk of opportunistic infections, other complications, and death (Roling *et al.*, 2006; World Health Organization, 2005).

The five classes of antiretroviral include- Nucleoside reverse transcriptase inhibitors (NRTIs), Non-nucleoside reverse transcriptase inhibitors (NNRTIs), Protease inhibitors (PIs), Entry Inhibitors, and Integrase inhibitors. The mechanism of action of NRTI is that, they are an analog of thymidine, cytosine, adenine, or guanine which will be triphosphorylated inside lymphocytes to active compound and incorporate into the growing HIV viral DNA strand by reverse transcriptase. The only nucleotide analog currently in use is tenofovir (TDF), which di-phosphorylated to active compound (Winston *et al.*, 2007; Zager, 2004).

The NNRTIs are agents that directly bind to reverse transcriptase to inhibit transcription without requiring prior phosphorylation to be active. Both nucleoside and non-nucleoside RTIs inhibit the same target, the reverse transcriptase enzyme. Unlike NRTIs, which bind at the enzyme's active site, NNRTIs act allosterically by binding to a distinct site away from the active site known as the NNRTI pocket. Protease inhibitors bind to protease enzyme preventing the cleavage and inhibiting the assembly of new HIV viruses. Entry inhibitors block the chemokine receptor CCR5 which HIV uses as a coreceptor to bind and enter a human macrophage. Intregrase inhibitors has structural motif which possesses metal-chelating functions, and it interact with divalent metals (Zager, 2004; Schetz *et al.*, 2005).

## MATERIALS AND METHODS

### *Methods*

### *Research Setting and Context*

St. Paul's General Specialized Hospital is found in the capital city, Addis Ababa in the Gulelle sub-city. This hospital is selected due to the ease access and sufficient availability of the data. According to

FMOH, a total of 5953 patients were enrolled for ART in St. Paul's General Specialized Hospital (FMOH/FHAPCO, 2007b).

***Study Design and Participants***

Retrospective and cross-sectional study from clinical and biochemical data was conducted from October to December 2013. The study was conducted on HIV positive patients attending ART clinic of St. Paul General Specialized Hospital. The source population was all HIV/AIDS patients attending the ART clinic of St. Paul's General Specialized Hospital. The study participants were those on first line HAART for 6 months with documented serum creatinine and urea values. The control groups were those patients with HIV but not yet started taking HAART. The sampling technique used was considering HIV patients taking first line HAART for a period of six month and HIV patients who were not started taking HAART as a control. Both groups were selected for having relatively completed record.

***Data Collection Procedures***

Demographic (age and sex), clinical and laboratory data were extracted from patient cards using data collecting format. Clinical data include WHO staging, hypertension and diabetes status. The laboratory data include, Urea (BUN), Creatinine, and CD4+ T lymphocyte. Data were coded to maintain confidentiality. All procedures at St Paul general specialized hospital laboratory were carried out by experiences Technicians/Technologists following standard operating procedures (SOPs).

Creatinine and urea/BUN values were performed by Hitachi analyzer of RD Germany. The assay quality control materials were used to form a reference level of each analyte for the Hitachi 917, manufactured by RD Germany. The controls were assayed by the RD which establishes concentrations for each lot and determines the mean and ±2 SD ranges for each parameter. One set of assayed controls was analyzed at the beginning of the analyzer run period to verify calibration and as an accuracy check. If the inventory of these materials becomes low, another lot was ordered on time to analyze it concurrently with the lot currently in use so that a bridge may be formed between the materials.

***Operational Definitions***

There are several explanations for the lack of an accurate incidence of ARF in the population due to lack of accepted clinical definition for ARF. Historically, most definitions have relied on an increase in the concentration of serum creatinine and BUN. In reference to creatinine nephrotoxicity is classified as, mild, moderate and sever, if the creatinine concentration is 1.7 to 3.4 mg/dl, 3.4 to 10mg/dl, and > 10mg/dl respectively. BUN value > 50mg/dl is usually indicative of nephrotoxicity

***Data Management and Analysis***

Risk factors associated with the outcome variable i.e. kidney failure were analyzed using Statistical package, Stata10 package (StataCorp, Texas). The increase in kidney failure secondary to HAART were calculated by taking the difference between the kidney failure in HIV patients of the entire study population and the kidney failure in HIV patients which were not under HAART treatment. Chi square analysis was used to compare demographic, clinical and laboratory data of individuals with and without the outcome. Multi-variate logistic regression analysis was used to identify those variables which were independently associated with outcome.

***Ethical Considerations***

The study protocol was reviewed and approved by the research and ethical committee of the Faculty of Medicine. Permission was also obtained from the hospitals where the study was conducted. Data were extracted using codes and confidentiality of results was maintained throughout the study.

## RESULTS AND DISCUSSION

***Findings***

The present study includes HIV patients who were taking HAART for a period of 6 month (**n**=259) and those who were not yet started taking HAART as control groups (n= 259) and were evaluated for renal function status (serum urea/BUN and serum creatinine values). The subjects were constructed to evaluate changes in RFTs, and the sample size was determined based on calculations made to achieve adequate power to detect differences in RFT levels. Among the study participants who were on HAART 154

(59.5%) and 105 (40.5%) were women and men respectively. Among those who did not st art HAART 172 (66.4%) and 87 (33.6%) were women and men respectively (Table 2).

***Socio Demographic Distribution of the Study Population***

The median age of HAART receiving patients was 35 years ranging from 20 to 69 years and that of control was 32 years ranging from 18 to 68 years. Majorities on HAART receiving group were between ages of 24 to 40 years; whereas majorities of controls were between ages of 25 to 40 years. HAART receiving males and female accounts for 105(40.5%) and 154(59.5%), respectively and in controls 87 (33.6%) and 172(66.4 %) were males and females, respectively (table 2). Data on marital status, educational background, religion, income level and other demographic data were missing.

**Table 2: Socio demographic distribution of the study population at ART clinic of St. Paul General Specialized Hospital, Addis Ababa, 2012-2013**

| Study groups | Variable | Frequency | Percent | Study groups | Variable | Frequency | Percent |
|---|---|---|---|---|---|---|---|
| HAART receiving | Age groups | | | Controls | Age group | | |
| | (20-24) | 16 | 6.2 | | (18-22) | 16 | 6.2 |
| | (25-29) | 59 | 22.8 | | (23-27) | 41 | 15.8 |
| | (30-34) | 46 | 17.5 | | (28-32) | 73 | 28.2 |
| | (35-39) | 67 | 25.9 | | (33-37) | 52 | 20.1 |
| | (40-44) | 26 | 10 | | (38-42) | 34 | 13.1 |
| | (45-49) | 19 | 7.3 | | (43-47) | 23 | 8.9 |
| | (50-54) | 12 | 4.6 | | (48-52) | 12 | 4.6 |
| | (55-59) | 8 | 3.1 | | (53-57) | 4 | 1.5 |
| | (60-64) | 4 | 1.5 | | (58-62) | 2 | 0.8 |
| | (65-69) | 2 | 0.8 | | (63-68) | 2 | 0.8 |
| | Sex | | | | Sex | | |
| | (Male) | 105 | 40.5 | | (Male) | 87 | 33.6 |
| | (Female) | 154 | 59.5 | | (Female) | 172 | 66.4 |

***Clinical and Biochemical Findings of Patients***

Among those receiving HAART 26(10%) of HAART were at WHO stage I while 59(22.8%) at stage II, 132 (51%) at stage III and 42(16.2%) at stage IV, where as 113(43.6%) of control groups were at WHO stage I while 79(30.5%) at stage II, 57(22%) at stage III and 10(3.9%) at stage IV (Table 3). Among HAART receiving, 11.6% and among controls 4.6% had CD4 count less than 100cells/mm$^3$, respectively.

Nearly 1.2% among HAART receiving groups and 1.9% among controls had below 50cells/$mm^3$ respectively. Control groups at stage IV were those who have been on anti-TB treatment, among the control groups with CD4 < 100cells/$mm_3$ were reported to be disappeared prior to starting HAART (Table 3).

**Table 3: Clinical and biochemical status of study population at ART clinic of St. Paul General Specialized Hospital, Addis Ababa, 2012-2013**

| Study groups | Variable | Frequency | Percent | Study groups | Variable | Frequency | Percent |
|---|---|---|---|---|---|---|---|
| HAART receiving | WHO stage | | | Controls | WHO stage | | |
| | (I) | 26 | 10 | | (I) | 113 | 43.6 |
| | (II) | 59 | 22.8 | | (II) | 79 | 30.5 |
| | (III) | 132 | 51 | | (III) | 57 | 22 |
| | (IV) | 42 | 16.2 | | (IV) | 10 | 3.9 |
| | CD4 status | | | | CD4 status | | |
| | (<200) | 117 | 45.2 | | (<200) | 26 | 10 |
| | (200-499) | 129 | 49.8 | | (200-499) | 168 | 64.9 |
| | (>500) | 13 | 5 | | (>500) | 65 | 25.1 |
| | Creatinine | | | | Creatinine | | |
| | (Normal) | 256 | 98.2 | | (Normal) | 259 | 100 |
| | (Abnormal) | 3 | 1.2 | | (Abnormal) | - | - |
| | Urea | | | | Urea | | |
| | (Normal) | 256 | 98.2 | | (Normal) | 257 | 99.2 |
| | (Abnormal) | 3 | 1.2 | | (Abnormal) | 2 | 0.2 |

Creatinine normal and abnormal indicates values less than or equal to 1.8mg.dl and greater than 1.8 mg.dl respectively, where as urea normal and abnormal indicates less than or equal to 50mg/dl and greater than 50 mg/dl respectively. The finding indicates that only 3 (1.2%) of HAART receiving patients had abnormal creatinine and urea values. None of the controls had abnormal creatinine values, where as 2(0.2%) of them had abnormal urea values. According to CDC classification CD4 values of <200 indicates below threshold, where as 200-499 and >500 indicates borderline and above threshold respectively.

***Initial Regimen Given***

The most commonly prescribed initial regimen was AZT/3TC/NVP for 97(37.5%) of cases, followed by d4T/3TC/NVP for 72 (27.8%), d4T/3TC/EFV and AZT/3TC/ EFV with equal proportion for 34 (13.1%), TDF/3TC/EPV for 13 (5%), TDF/3TC/NVP for 8 (3.1%) and TDF/AZT/3TC 1 (0.4%). Regiments d4T/3TC/EFV and AZT/3TC/NVP prescribed for the patient were 2 times and 3 times lower respectively

than for d4T/3TC/NVP and AZT/3TC/EFV. Only 1(0.4%) of patients were switched to TDf containing first line regiment (figure 2).

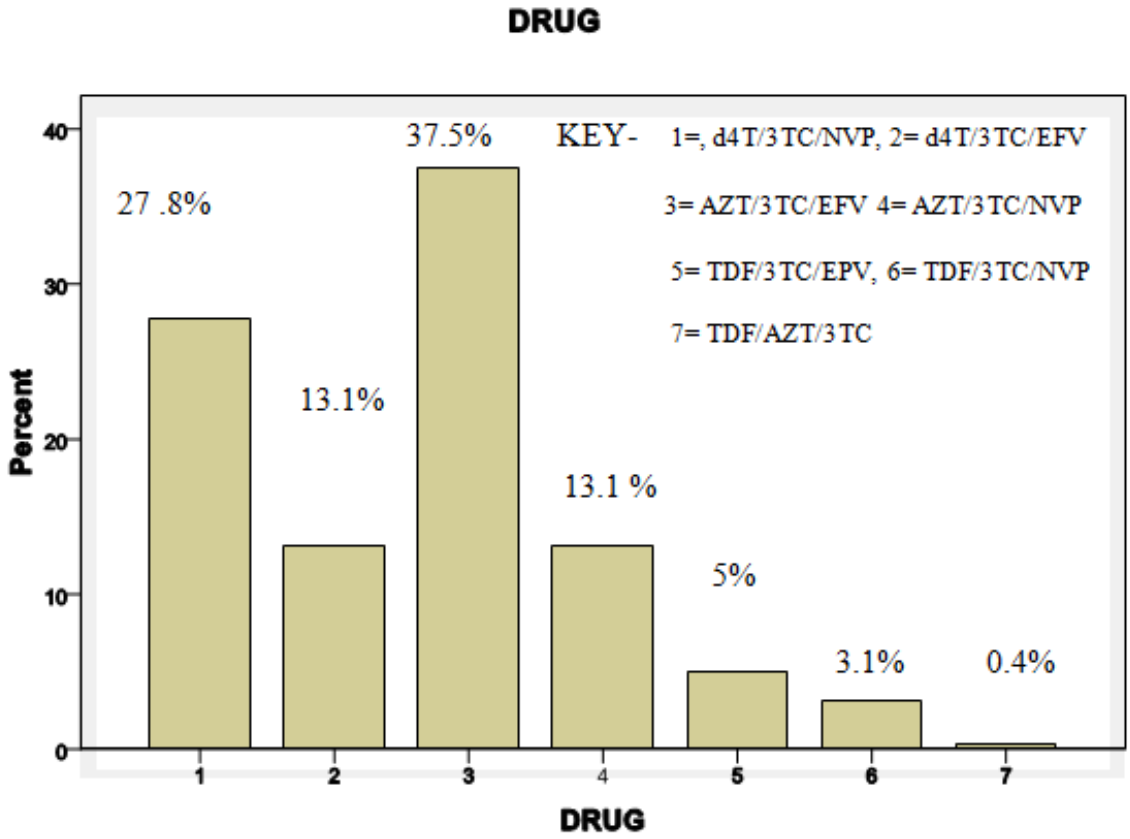


**Figure 2: Graph showing percentages of patients receiving individual first line HAART in ART clinic of St. Paul General Specialized Hospital, Addis Ababa, 2012-2013**

***Frequency of Renal Failure (Abnormal Serum Creatinine and Urea Values)***

As the aim of the study was to assess changes in renal function on HAART, our result was limited to the 259 subjects who had been taking first line HAART for a period of 6 months and who had creatinine and urea/BUN results at the end of 6 month period.

We dichotomized creatinine values at 1.8 mg/dl and urea values at 50mg/dl because HIV treatment guidelines recommend dosage modifications (decreasing dose) for several antiretrovirals with greater than the above values.

Serum concentrations of creatinine were assessed using the Jaffe reaction and urea by enzymatic method.

The National Institutes of Health Division of AIDS table for grading the severity of adult and pediatric adverse events classifies a creatinine greater than or equal to 1.4 times the upper limit of normal as moderately abnormal, which corresponded to a serum creatinine of 1.5mg per 100ml.

Mean urea values(mg/dl) for patients taking d4T/3TC/NVP2, d4T/3TC/EFF, AZT/3TC/EFV, AZT/3TC/NVP, TDF/3TC/EPV, and TDF/3TC/NVP were 23.5, 21.8, 24.0, 24.7, 26.5, and 24.3 respectively where as mean creatinine values(mg/dl) of patients taking the same drug were 0.86, 0.92, 0.96, 0.86,0.93, and 0.69 respectively.

TDF/AZT/3TC was taken by a single patient and the values of urea and creatinine were 20mg/dl and 0.7mg/dl respectively.

Mean urea value for male and female HAART receiving groups were 24.1mg/dl and 23.1 mg/dl respectively, whereas mean creatinine value was found to be 1.0mg/dl for males and 0.8mg.dl for females. In case of controls, mean urea value was found to be 23.9 mg/dl for males and 21.1 for females,

whereas mean creatinine values for males and females were 1.0mg/dl in each group (table 4). The result shows there was no significant association between regiments and renal failure.

**Table 4: Mean urea and creatinine values for study populations at ART clinic of St. Paul General Specialized Hospital, Addis Ababa, 2012-2013**

| | Sex | | UREA(Mg/Dl) | CREAT(mg/dl) |
|---|---|---|---|---|
| HAART receiving groups | Male | Mean | 24.171 | 1.023 |
| | | N | 105 | 105 |
| | Female | Mean | 23.610 | .830 |
| | | N | 154 | 154 |
| Controls | Male | Mean | 23.98 | 1.050 |
| | | N | 87 | 87 |
| | Female | Mean | 21.18 | 0.985 |
| | | N | 172 | 172 |

The median creatinine for HAART receiving was 1mg/dl, and 1.9% of 259 participants had a creatinine greater than 1.4mg/dl. The baseline median Urea values were 23 mg/dl and 1.2% of 259 participants had renal urea values over 50mg/dl. The base line median creatinine for controls was 1mg/dl, and (5%) of 259 participants had a creatinine over 1.4mg/dl. The baseline median Urea values was 21mg/dl, and 3(0.8%) of 259 participants had urea values of greater than 50mg/dl. None of the independent variables (WHO stage, HAART, sex, age and CD4 associated with anormal urea and creatinine values (table 5 and 6).

**Table 5: Uinvariable predicator of renal failure with urea as an indicator among HAART receiving groups at ART clinic of St. Paul General Specialized Hospital, Addis Ababa, 2012-2013**

| Covariate | Number at risk | No of cases with urea Normal/abnormal | Odds ratio | 95%CI | P-value |
|---|---|---|---|---|---|
| Sex (male and female) | 259 | 256/3 | - | 0.81-1.09 | 0.79 |
| Age group (20-69) | 259 | 256/3 | - | 0.219-216 | 0.22 |
| WHO (I-IV) | 259 | 256/3 | - | 0.380-0-399 | 0.39 |
| HAART | 259 | 256/3 | - | 0.914-0.925 | 0.91 |
| Abs.CD4 count | 259 | 256/3 | - | 0.24- 0.25 | 0.24 |

**Table 6: Uinvariable predicator of renal failure with creatinine as an indicator among HAART receiving groups at ART clinic of St. Paul General Specialized Hospital, Addis Ababa, 2012-2013**

| Covariate | Number at risk | No of cases with creatinine Normal/abnormal | Odds ratio | 95%CI | P-value |
|---|---|---|---|---|---|
| Sex (male and female) | 259 | 256/3 | - | 0.60-0.70 | 0.65 |
| Age group (20-69) | 259 | 256/3 | - | 0.04-0-07 | 0.06 |
| WHO (I-IV) | 259 | 256/3 | - | 0.946-0.955 | 0.95 |
| HAART | 259 | 256/3 | - | 0.58-0.60 | 0.59 |
| Abs.CD4 count | 259 | 256/3 | - | 0.59-0.61 | 0.60 |

Since the abnormalities seen were very low (<5), it was difficult to show the association of renal failure (abnormal urea and creatinine) at different level of HAART, age groups, WHO clinical staging, sex and absolute CD4 count. None of the independent variables were also associated with the development of renal failure (p>0.05).

***Discussion***

The present study aimed at assessing the effect of first lline HAART on renal failure within 6months of therapy by using serum urea and creatinine as renal function markers. The study demonstrated that the prevalence of renal failure among HAART receiving groups with first line regimen were low (1.2 % of abnormal creatinine and urea value) supporting other similar study done in King's College Hospital in London. In this study done by Roe J et al, 2274 patients were analyzed for first line HAART related renal failure between January 1998 and December 2005. Seventy-seven per cent of them took first line HAART during the study period and found that, 2(0.1%) cases of ARF related to d4T-plus-ddI use, and 2(0.1%) cases of ARF (abnormal urea, creatinine and GFR values) attributed to tenofovir. Despite the fact that 21% of all patients in the study took tenofovir containing first line regimen, only 1.4% of patients experienced ARF while taking tenofovir (Roe *et al.*, 2008; Barditch *et al.*, 2005; Horbery *et al.*, 2010).

Other study has also shown that, renal toxicity of tenofovir is much less frequent than that observed with adefovir. In the phase I/II trial, 49 patients were randomly assigned to receive daily 75 mg, 150 mg, 300 mg, or 600 mg tenofovir or placebo. As of 28 days no renal abnormalities could be attributed to tenofovir. In a phase II randomized double-blind placebo-controlled multicenter trial, 181 patients were assigned to add 75 mg, 150 mg, or 300 mg tenofovir or placebo to their background therapy. Safety assessments included the effects of tenofovir on renal parameters (creatinine, urea and GFR). After 48 weeks no renal abnormalities were observed, particularly no significant creatinine elevation as well as no differences in changes neither in urea levels, nor in the incidence of proteinuria between adefovir and placebo groups (Barditch *et al.*, 2005; Rockstroh *et al.*, 2005; World Health Organization, 2003).

However, Studies exploring the relation between treatment with the drug and kidney problems have produced contradictory results, and one recent study found that the risk of kidney dysfunction was high for tenofovir compared with other antiretroviral drugs if patients are monitored for over two years. Researchers retrospectively analysed the medical records of 1647 patients who were registered in the Kaiser Permanente cohort in California, United States, and started HIV treatment for the first time between 2002 and 2005. Changes in three key markers of kidney function were analysed: GFR; serum creatinine; and serum urea. Results showed that a significantly higher proportion of patients taking tenofovir had at least a 50% decline in GFR and mild increase in crearinine and urea values from baseline compared to those taking other drug (Horbery *et al.*, 2010; Szczech *et al.*, 2006; Berns *et al.*, 2005).

However, different studies have showed that renal failure was associated with the use of tenofovir containing second line treatment. In study done by analysis of creatinine clearance among 3316 participants taking second line drugs underway in Uganda and Zimbabwe showed that 45% had mild renal insufficiency as measured by estimated glomerular filtration rate, 7% moderate and 0.2% sever, renal insufficiency. Severe renal and moderately impaired renal function were defined as an estimated GFR of $\leq$ 30 mls/min/1.73 $m^2$ and 30–60 mls/min/1.73 $m^2$ respectively. Fifty-two individuals with normal, mild or moderate renal impairment at baseline subsequently developed grade sever renal impairment. Patients were randomized to receive nevirapine, tenofovir or abacavir with AZT/3TC. The estimated GFR did decrease in those who received tenofovir or abacavir when compared to nevirapine, and this difference persisted to 96 weeks (Menezes *et al.*, 2006; Sulkowski *et al.*, 2002; Wyatt *et al.*, 2006).

In our study the first line regimens prescribed were AZT/3TC/NVP to 97(37.5%) of cases, followed by d4T/3TC/NVP 72 (27.8%), d4T/3TC/EFV and AZT/3TC/ EFV with equal proportion 34(13.1%), TDF/3TC/EPV 13(5%), TDF/3TC/NVP 8(3.1%) and TDF/AZT/3TC 1 (0.4%). The selection of the existing first line regimen is based on the availability of fixed dose combination, toxic profile, need for laboratory monitoring, coexisting conditions (TB and hepatitis), potential for maintenance of future treatment options and special considerations for women of child bearing potential (WHO, 2005). Our

results suggest that the inability to monitor renal function should not be a contraindication in providing first-line HAART and support current WHO guidelines, which do not recommend monitoring renal function with first-line HAART in resource-limited settings. To maximize durability of first line regimen one has to deal with factors that affect the adherence of patients to HAART. One major reason for non adherence and drop out is side effects. The risk of specific side effects varies from drug to drug, from drug class to drug class and from patient to patient. Experience of the khayelitsha programme in South Africa showed that most people tolerated the first line regimen well with only 14% changing one of the HAART because of either adverse events or a contraindication to treatment with that drug (World Health Organization, 2003; Mehta *et al.,* 2002; Sherman *et al.,* 2002).

The pre HAART prevalence of renal dysfunction in this setting was less than rates observed in several cohort studies and a cross-sectional study from other countries. Two factors likely explain this discrepancy. Renal disease, such as HIV-associated HIVAN, typically worsens with advanced HIV disease, in resource-limited settings; the ability to monitor renal function is often limited and also there were no GFR test in the study area to detect the condition early. Other study done in King's College Hospital in London also showed the association of HIV in the development of renal failure. In this study 1000 patient with HIV were diagnose for renal failure prior to starting HAART, and 23% were found to have a decreased GFR and mild increase in serum creatinine and urea values (World Health Organization, 2003; Scott *et al.,* 2004; Parish *et al.,* 2004).

Where sensitive monitoring is available, patients with renal dysfunction at HAART initiation may warrant repeat renal function testing during the first few months of treatment. If renal function does not improve despite HAART, then antiretroviral dose adjustments based on renal function should be considered. Although renal function improved in the majority of participants in this study, 1.9% and 5% from HAART receiving and controls had a renal dysfunction based on creatinine as a parameter respectively, and 1.2% and 0.8% from HAART taking and controls had greater urea values, respectively. In Torero, Uganda among 1073 patients on stavudine-lamuvudine +neverapine , nearly 50% of the patient experience some form of toxicity by 18 month while around 2% toxicity was associated with renal dysfunction. Swiss cohort of 1160 patients also showed that 47% presented with clinical and 27% with laboratory adverse events including abnormal renal profile attributed to HAART by 2 years. These results indicate that the effect of HAART on renal failure might not be detected by 6 month monitoring, unless followed for a longer period (Berns *et al.,* 2005; Patton and Crouch, 1977; Peraldi *et al.,* 1999).

This study shows there is no significant association between first line HAART and renal failure compared with controls. Socio demographic, WHO stage and CD4 status of patients were found to have no significance association with development of renal failure which is consistent with similar study in Brazil where all socio demographic and WHO state of patients taking first line regimen except for gender were found to have no significant association with the development of adverse drug reaction affecting kidney (Menezes *et al.,* 2006; AIDS in Ethiopia, 2006; Kimmel *et al.,* 2004).

***Conclusion***

Although some renal abnormalities has been observed on cases, our study shows there is no significant difference on renal abnormalities between cases and control in the first line regimen and similarly CD4 levels also has no significant association with the development of renal failure which increase later with treatment. None of the socio demographic variables, the clinical records and the biochemical parameters were significantly associated with the development of renal failure. These indicate the need for further follow up for prolonged period of time to see the actual effect of HAART treatment on renal failure in Ethiopian patients. Furthermore lack of sensitive indicators of renal failure examination like gromerular filtration rate and microalbuminurea were not available in the study area to diagnose the condition as early as possible. Mild increase in creatinine value on control patients were also seen suggesting the contribution of the HIV itself on the development of renal failure.

***Competing Interest***

All authors declare that they have no conflict of interest associated with the publication of this manuscript.

***Authors' Contributions***

JG conceived and designed the study and collected data in the field, performed analysis, Interpretation of data, and draft the manuscript. MU assisted with the design, performed analysis, interpretation of data and the critical review of the manuscript. AT participated in design and performed analysis, interpretation of data, helped in drafting the manuscript and critically reviewed the manuscript.

**ACKNOWLEDGMENT**

We would thank the Medical Director and Staffs of ART Department of St. Paul Referral Hospital in providing the laboratory data necessary for the study. We are grateful to Mr. Bineyam Taye, who has been advising us on sample size determination and data analysis.

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