THE PREVALENCE AND PREDICTORS OF RENAL DYSFUNCTION IN HUMAN IMMUNO DEFICIENCY VIRUS POSITIVE PEOPLE AT JIMMA UNIVERSITY SPECIALIZED HOSPITAL SOUTH WEST ETHIOPIA.

BY:

YISHAK ALI, MD

A SENIOR RESEARCH PAPER SUBMITTED TO THE DEPARTMENT OF INTERNAL MEDCINE, COLLEGE OF PUBLIC HEALTH AND MEDICAL SCIENCE, JIMMA UNIVERSITY; IN PARTIAL FULLFILMENT FOR THE REQUIREMENTS OF SPECIALIZATION IN INTRNAL MEDCINE.

AUGUST, 2012

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YISHAK ALI, MD

ADVISORS:

1. DANIEL YILMA, MD

2. FASIL TESSEMA, MSc

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Abstract

Background

Renal disease is a significant cause of morbidity and mortality among people living with the human immunodeficiency virus (HIV).However, little is known about renal dysfunction among people living with HIV/AIDS in Sub-Saharan Africa.

Methods; A cross-sectional survey was conducted from May to July, 2012 at outpatient HIV-clinic in Jimma university specialized hospital (JUSH). Renal dysfunction was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m2 and/or detectable urine protein. Multiple binary logistic regression analysis was used to analyze associated factors for renal dysfunction in HIV infected individuals.

Results; A sample of 321 patients was included in the study. The mean (±SD) age of patients was 36 ± 9.74 and, 58.3% were females. The median current CD4 count was 328cells/mm3.The prevalence of renal dysfunction was 15.9% (n=51). Factors associated with renal dysfunction were age, CD4 count and duration of tenofovir use. Accordingly for age,(OR 3.6 for age group (31-42) , p <0.025),(OR 4.5 for age group (43-53) , p <0.025) and (OR 22.7 for age group 54+,p <0.001) compared to age group (19-30), lower CD4 nadir (OR 9.7 for CD4 < 200 cells/mm3 compared to CD4 ≥ 200cells/mm3, p <0.001), and duration of tenofovir use (OR 18.5 for duration ≥ 12months compared to non users , p<0.001).

Conclusion; Renal dysfunction was relatively common in these HIV positive individual. Likewise longer duration of tenofovir use, individuals having CD4 nadirs of < 200 cells/mm3 and increasing age were found to be associated with increased risk of renal dysfunction. So, screening for urine protein and serum creatinine should be routine. Further studies with long-term follow-up to see the incidence of CKD and related risk factors is mandatory.

Acknowledgement

I would like to thank my advisors Dr Daniel Yilma and Mr.Fasil Tessema for the very detail, exhaustive and constructive comments and advices they gave me from the very beginning to completion of this study paper. Likewise, Jimma University College of public health and medical sciences, Department of internal medicine for giving me this chance to conduct the study.

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Acronyms

AIDS Acquired immune deficiency syndrome

ART Antiretroviral therapy

BMI Body mass index

BUN Blood urea nitrogen

CKD Chronic kidney disease

eGFR Estimated glomerular filtration rate

ESRD End-stage renal disease

HAART Highly active antiretroviral therapy

HBs Ag Hepatitis B surface antigen

HCV Hepatitis C virus

HIV Human immunodeficiency virus

HIVAN HIV-associated nephropathy

JUSH Jimma University specialized hospital

MDRD Modification of diet in renal disease

NKF National kidney foundation

OI opportunistic infection

OR Odds ratio

PLWHA People leaving with HIV/AIDS

SSA Sub-Saharan Africa

TDF Tenofovir

Chapter 1: Introduction

1.1. Background Information

As patients infected with HIV live longer while taking ART, kidney diseases have emerged as significant causes of morbidity and mortality. Black race, older age, hypertension, diabetes, low $CD4^+$ cell count, and high viral load remain important risk factors for kidney disease in this population. Chronic kidney disease (CKD) should be diagnosed in its early stages through routine screening and careful attention to changes in glomerular filtration rate (GFR) or creatinine clearance. Hypertension and diabetes must be aggressively treated. Antiretroviral regimens themselves have been implicated in acute or chronic kidney disease. The risk of kidney disease associated with the widely used agent tenofovir continues to be studied, although its incidence in reported clinical trials and observational studies remains quite low. Future studies about the relationship between black race and kidney disease, as well as strategies for early detection and intervention of kidney disease, hold promise for meaningful reductions in morbidity and mortality associated with kidney disease.(1)

The first reports of acquired immune deficiency syndrome (AIDS)-related renal failure, published in the mid-1980s, described cases of what we now recognize as HIV-associated nephropathy (HIVAN) [2]. Before effective antiviral therapy became available, HIVAN was so frequent and its clinical features were so dramatic—heavy proteinuria and rapid progression to end-stage renal disease (ESRD) in immune suppressed black persons—that HIVAN became almost synonymous with HIV-associated CKD. As HIV spread through the black community, the ESRD incidence increased substantially, and by the early 1990s, HIVAN became the third leading cause of ESRD in black persons aged 20–64 years [3].

Since that time, the incidence and spectrum of kidney diseases in HIV-infected patients have been altered by the widespread use of highly active antiretroviral therapy (HAART). The clinical course of kidney disease is more indolent, the risk of ESRD has been reduced by 40%–60%, the 1-year survival rate while undergoing dialysis has increased from 25% to 75%, and kidney transplantation is a viable option [4–7].

Despite these improvements, risk factors for kidney disease are highly prevalent among HIV-infected patients, and kidney disease remains a significant cause of morbidity and mortality, even among those patients receiving HAART.

1.2. Statement of the problem

CKD has become an important co-morbidity among HIV-infected persons (8). Since the introduction of HAART, the number of deaths due to opportunistic infections has significantly declined, while a greater proportion of patients are developing chronic conditions not traditionally related to HIV, such as cardiovascular, liver, and kidney disease (9,10). As the prevalence of HIV infection increases as a result of improved survival, the prevalence of renal dysfunction is projected to increase (11).

CKD during the pre-HAART period was largely a result of HIV-associated nephropathy (HIVAN), which was associated with African American ethnicity and low CD4 count (12, 13). The introduction of HAART has resulted in significant change in the epidemiology of renal disease among HIV patients, with a substantial reduction in the incidence of HIVAN (14). Even with the benefits of HAART, CKD remains common among HIV patients. A recent study showed that despite HAART use, kidney function loss continued to occur among HIV-infected persons (15). Contributing factors to renal disease among HIV patients includes the aging of the population, concurrent medical conditions such as diabetes mellitus and hypertension, and uncontrolled viremia (15,16).

In addition, certain antiretroviral medications may contribute to loss of renal function. Some studies have linked tenofovir with renal insufficiency, while others have not shown this finding (17, 18).

Patients from Sub-Saharan Africa (SSA) are of particular concern, since they accumulate CKD risk factors both related to HIV (late HIV diagnosis, OI, nephrotoxic OI- or HIV-related drugs) and non-related (hypertension, diabetes and ethnicity) [26,29]. Data on people leaving with HIV/AIDS (PLWHA) renal function in SSA are scarce, despite being the area hardest hit by the pandemic. Data that is available on CKD prevalence in PLWHA ranges from 6% to 45%, although a variety of definitions have been used [29-33].

Very little data are available on the worldwide prevalence of CKD in people with HIV. This is also true regarding the prevalence and impact of HIV-related renal disease in sub-Saharan

Africa (34) .Until recently, there have been few data regarding the epidemiology of renal disease associated with HIV infection in Africa. Recently, several reports have begun to appear, highlighting our lack of knowledge about renal diseases in this region and the importance of further study in this area.

Kidney disease is a significant cause of morbidity and mortality among persons infected with the HIV. However, the prevalence and factors contributing to renal dysfunction had not been determined among HIV-infected patients in Ethiopia and other sub Saharan countries. So, the purpose of this study is to determine the prevalence and factors contributing to renal dysfunction in ambulatory patients attending ART clinic at JUSH.

Chapter 2: Literature Review

Renal dysfunction in HIV infected patients could potentially be caused by many factors .The factors identified through different literatures proposed to be responsible for renal dysfunction in HIV are demographics, antiretroviral/nonantiretroviral medications, co morbidities (hypertension, diabetes mellitus, hepatitis C virus [HCV] infection, hepatitis B virus [HBV] infection), CD4+ counts, viral load, and duration patients were monitored at the clinic.

Diabetes mellitus and hypertension are the 2 most frequent causes of CKD in the general population. They increase the CKD risk 10-fold and account for 71% of all ESRD cases [35, 38]. Diabetes and hypertension are increasingly common among persons with HIV infection. The prevalence of diabetes was 14% in the Multicenter AIDS Cohort Study, 4-fold higher than in seronegative control persons [39], and was associated with cumulative exposure to nucleoside reverse-transcriptase inhibitors but not protease inhibitors (PIs) [40, 42]. Among those included in the Multicenter AIDS Cohort Study, the prevalence of hypertension is 3-fold higher than in age- and sex-matched control persons (34.2% vs. 11.9%; P<.001), and hypertensive persons with HIV infection are more likely to have insulin resistance and metabolic syndrome (64.3% vs. 16.9%; P<.001) [43]. In a cross-sectional analysis of 129 HIV-infected patients with CKD, the prevalence of documented hypertension and the prevalence of diabetes mellitus were 55% and 20%, respectively [44], which underscores the importance of optimizing blood pressure and achieving glycemic control as a means of minimizing the impact of CKD concomitant with HIV infection.

Race is an important risk factor for CKD. Black persons comprise 10% of the general population in the United States but account for >30% of patients with ESRD [35]. Young, male blacks have an 11-fold increased risk of CKD, compared with their white counterparts [45]. Five new cases of ESRD develop for every 100 cases of CKD in black persons, whereas only 1 new ESRD case develops for every 100 cases of CKD in whites [46]. The burden of kidney disease in black persons with HIV infection, compared with their HIV-infected white counterparts, is similarly disproportionate. Among persons with HIV infection who receive

dialysis, 91% are black [35]. Black race increases the risk of microalbuminuria and proteinuria by at least 2-fold [47, 48]. In a comparison between blacks and whites in an analysis of >2 million patients who received care through the Veterans Administration system, the multivariate hazard ratio for ESRD in HIV-infected persons was 4.56 (95% CI, 3.44–6.05) [49]. The natural history of CKD is also considerably more aggressive in HIV-infected blacks than in whites. Among 4259 patients observed in the Johns Hopkins HIV Clinical Cohort from 1990 through 2004, the risk for incident CKD was 2-fold higher among blacks (hazard ratio 1.9; 95% CI, 1.2–2.8). After CKD diagnosis, however, the decrease in GFR was 6-fold more rapid among blacks, which dramatically increased the likelihood of progression to ESRD (hazard ratio, 17.7; 95% CI, 2.5 –127) [50].

The aging of an HIV-infected population is another important pathway by which the incidence of CKD can be expected to continue to increase. GFR normally decreases with age. The prevalence of CKD in the elderly population now approaches 50% [53]. Other risk factors for CKD in HIV-infected patients are high viral load, low $CD4^+$ lymphocyte count, and hepatitis C virus co infection [47]. The importance of recognizing CKD is underscored by the strong correlation between CKD and both morbidity and mortality. In the HIV Epidemiology Research Study, proteinuria or an elevated serum creatinine level was associated with an increased risk of hospitalization and mortality [54, 55]. In the Women's Interagency HIV Study, elevated creatinine level and proteinuria were similarly predictive of an increased risk of an AIDS-defining illness and mortality [56].

Isolated case reports of nephrotoxicity have been reported with almost all agents of ART, but renal disease has been associated with indinavir and tenofovir more often than with other drugs [57, 58]. Indinavir causes nephrolithiasis and chronic interstitial nephritis in as many as 12% of patients who receive it. Decreases in GFR in tenofovir-treated patients have been reported. In the Johns Hopkins Cohort, GFR decreased to a greater extent in tenofovir-treated patients than in non–tenfovir-treated patients (19 vs. 11 mL/min), an effect restricted to treatment-experienced patients (59)

A cross-sectional study in HIV Clinic, Naval Medical Center San Diego, California at two military clinics with open access to care to determine the impact of HIV factors, including antiretroviral therapy, on renal function, 717 was evaluated. Twenty-two patients (3%) had renal dysfunction. Factors associated with renal dysfunction in the multivariate logistic analyses included older age (odds ratio [OR] 2.0 per 10 year increase, p ¼0.006), lower CD4 nadir (OR 0.6 per 100 cell change, p ¼0.02), and duration of tenofovir use (OR 1.5 per year use, p ¼0.01)(60).

A study in China on 322 patients, the prevalence of hypertension, diabetes mellitus and CKD were 7.4%, 10.6% and16.8%, respectively. Eighteen patients (5.6%) had GFR<60 ml/min/1.73 m2while 44 patients (13.7%) had spot urine P/Cr >0.3. Among those with urine P/Cr >0.3, 38 patients had 24-h urine collection. Using univariate analysis, CKD was found to be significantly (P<0.05) associated with age, hypertension, diabetes, use of indinavir, lower CD4 count and peak viral load. Multivariate logistic regression revealed older age (P<0.001), lower CD4 count (P ¼0.02) and use of indinavir therapy (P 0.04) were associated with development of CKD (61).

A cross-sectional study in Japan of 788 HIV-infected outpatients including 706 men was conducted. The prevalence of CKD and that of CKD > or = stage 3 was 14.9% and 9.4%, respectively. The pro-portion of each stage was as follows: stage 1, 15 patients (1.9%); stage 2, 28 patients (3.6%); stage 3, 66 patients (8.4%); stage 4, 1 patient (0.1%); stage 5, 1 patient (0.1%); and stage 5D, 6 patients (0.8%). Comorbidities such as hypertension and diabetes were found in 55.4% and 27.0% in patients with CKD > or = stage 3, respectively. Urinalysis showed 71 patients (9.1%) with proteinuria and 44 patients (5.6%) with hematuria (62).

The prevalence and nature of CKD were assessed in Burundi on 300 patients CKD prevalence in patients was 45.7%, 30.2% of whom being classified as stage 1 according to the national kidney foundation (NKF) classification, 13.5% as stage 2 and 2% as stage 3(63).

One of the few large cohort studies in Zimbabwe on 25,000 Zambians taking ART. At the time they initiated treatment, one-third of all cohort members had eGFR values below 90 mL/min, indicating some degree of renal impairment. Only 3,209 individuals (12.4%)

appeared to have a renal insufficiency: about three quarters of these cases were classified as mild, 20.0% were moderate, and 5.3% were severe (64).

Other studies have simply reported proteinuria, albuminuria and serum creatinine. For instance, a Nigerian study that defined renal disease in terms of the presence of proteinuria or abnormal serum creatinine found the prevalence of renal disease to be 38% in a cohort of 400 HIV-positive people, most of whom were ART-naïve (65).HIV-positive study cohorts in Cote d'Ivoire (both ART-naïve and ART-experienced) and Tanzania (unspecified ART status) respectively had 26% and 28% prevalence of albuminuria (66, 67).

Isolated screening studies suggest that many sub-Saharan African countries have high prevalence of kidney disease. Small studies in Kenya (11.5% had stage 3 or higher CKD) and Uganda also found high prevalence of reduced eGFR in HIV-positive people. The Kenyan cohort was ART-naïve, and the ART status of the Ugandan cohort was not specified (33, 68).

2.1. Significance of the study

Kidney disease is a significant cause of morbidity and mortality among persons infected with HIV. However, the prevalence and factors contributing to renal dysfunction had not been determined among HIV-infected patients in Ethiopia. Until recently, there have been few data regarding the epidemiology of renal disease associated with HIV infection in Africa. Recently, several reports have begun to appear, highlighting our lack of knowledge about renal diseases in this region and the importance of further study in this area. So this study will have its own input to fill this gap and it will be a base line study in this area.

Chapter 3: Objective of the study

3.1. General objective

To assess the prevalence and predictors of renal dysfunction in HIV infected individuals on follow up at ART clinic, JUSH.

3.2. Specific objective

1. To assess the prevalence of renal dysfunction in HIV infected individuals on ART at ART clinic, JUSH.

2. To assess predictors of renal dysfunction in HIV infected individuals on ART at ART clinic, JUSH.

Chapter 4: Methods and Material

4.1. Study area and period

The study was conducted at JUSH ART clinic from May to July, 2012. The hospital is located in Jimma town in Jimma zone in South West of Oromia region about 350 km from the capital city, Addis Ababa. JUSH is one of teaching hospitals in the country. It has both undergraduate and post graduate programs, paramedical and medical departments. The hospital gives health service at inpatient and outpatient level as being a referral center for 15 million populations in the South West region of the country. According to the ART clinic report, as outpatient level, chronic HIV care and service is delivered for a total of 6,520 patients from which 2,149 patients are on ART. Service is given by trained nurses, medical resident & internist.

4.2. Study Design

Hospital based cross-sectional study design was used.

4.3. Population

4.3.1. Source population

All adult HIV infected patients, on ART who are on follow up at ART clinic JUSH.

4.3.2. Study population

All adult HIV infected patients, on ART who are on follow up at ART clinic JUSH from May to July, 2012.

4.4. Inclusion and Exclusion criteria

4.4.1. Inclusion

- HIV positive individuals on ART, age >18 years and willing to give informed consent.
- Whose last CD4 count determined not more than six month.

4.4.2. Exclusion

- Those age <18
- Those pre ART
- Those unwilling to give informed consent.
- Whose last CD4 count determined more than six month.

4.5. Sample size determination and sampling technique

4.5.1. Sample size determination

According to the ART clinic report, a total of 1,562 HIV positive patients are expected to visit the clinic during the study period. The prevalence of renal dysfunction in the context of HIV varies according to the particular definition used however results of different study show prevalence of renal dysfunction in the context of HIV to be between 6% and 45%. For this study prevalence will be taken as 45% by adding non-response rate of 5%, the required sample size will be

$$n = \frac{Z^2_{1-\alpha/2} P(1-P)}{d^2} = \frac{1.96^2 \times 0.45 \times 0.55}{0.05^2} = 380$$

Where:

P = Taken as 50%

d =Margin of error 5% Z= The standard normal value at 95% confidence level (1.96),

And because sampling is from a finite population of size, N=1562 then the final sample size will be corrected as

Adding 5% non response rate the, final sample size will be, n = 306 + 15 = 321

4.5.2. Sampling technique

Systematic random sampling method was employed to select and approach each study subjects. The sampling interval was N~4 that is every 4^{th} HIV positive patients was selected. The first study subject to be interviewed was chosen by a lottery method out of 1,562 individuals. If the selected study subject refuses to participate in the study, he or she was considered as non-respondent.

4.6. Measurement and variables

4.6.1. Data collection instrument

Structured interviewer administered questionnaire was used to collect the data which is developed after reviewing different relevant literatures and similar studies. The questionnaire was initially prepared in English then translated into Amharic language and Afaan Oromo then again was translated back to English to check for any inconsistencies. The questionnaire contains socio-demographic factors, co-morbidities, HIV related factors, initiation of HAART and specific drugs, anthropometry to calculate BMI, creatinine and BUN to estimate GFR and urine dipstick to estimate urine protein and other parameters.

4.6.2. Study Variables

Independent Variables

- Age,
- Sex,
- Place of residence
- Presence of Hypertension,
- Diabetes mellitus,
- Chronic hepatitis C
- Chronic hepatitis B
- Duration of seropositivity
- Tenofovir use
- Duration of tenofovir use
- Cotrimoxazole use
- Duration of cotrimoxazole use
- Anthropometry

Dependent Variable

- Serum creatinine
- Urine dipstick

4.6.3. Data Collection Process

Data for this study was collected from patient card review, patient interview at ART clinic using structured questionnaire, performing blood tests for BUN and Cr, tests for HBs Ag antigen and anti HCV and urine dipstick at JUSH laboratory and measuring weight and height during patient interview. Data from card review will be those variables which are beyond an individual's knowledge to be interviewed to minimize knowledge gap like, the type of ART regimen, cotrimoxazole use and if the patient is on tenofovir duration of

tenofovir use. During patient interview Age, Sex, place of residence & duration of seropositivity will be included. Hypertension and Diabetes mellitus will be assessed by card review & patient interview based on the definition given.

4.7. Data processing & analysis

After data collection, each questionnaire was checked for completeness. Data was entered into a database, cleaned and checked for outliers, missed values and missed variables were analyzed using SPSS 20. Tables, graphs and descriptive summaries was determined to describe the study variables. Univariate analysis such as chi square test was performed to see the existence of association between dependent and independent variables.

Finally stepwise logistic regression model was used to identify independent predictors of renal dysfunction in HIV infected individuals. Variables which had P value <0.1 were entered for the multivariable logistic regression model. Interaction between variables was tested and reported. P value < 5% was used to declare statistical significance.

4.8. Data Quality Control

To achieve a good data quality:

- ✓ Questionnaires was prepared in English and translated into Amharic language and then back to English by the third person to keep its consistency.
- ✓ Data collectors was selected based on ability to speak the local language and previous experience of data collection.
- ✓ Vague points and other problems encountered about the questionnaire were given explanations and clarifications. Closer supervision was undertaken during data collection.
- ✓ A total of eleven personnel were trained for one day on the objective of the study, each variable on the questionnaire and its implication, demonstration and practical session on interviewing, record reviewing and laboratory sample collection, labeling, transportation, storage and testing procedures as per the standard. The participants were given appropriate manuals and guidelines during the training.
- ✓ Every questionnaire was crosschecked daily by the principal investigator.

- ✓ Problems faced were discussed over night with data collectors and laboratory personnel's.
- ✓ Pre-testing for questionnaire with number of sample [5%] were conducted and care were taken not to mix up those who already participated in pre-testing of the questionnaires.

4.9. Ethical Considerations

Patient's confidentiality, equity of services and interests of patients was kept for all during the study period. There were not been risky procedure done to patients. By caring out standard universal pre-questions of sample collection from clients and also the laboratory results were attached to the patients card and accordingly modification of drugs were done based on the laboratory results. Ethical clearance was obtained from ethical committee of the university. The willingness of the respondents and verbal informed consent were obtained from study participants before inclusion into the study.

4.10. Operational definition

- **Adult**-individual age ≥18
- **Renal dysfunction**– when eGFR<60ml/min/1.73m2 or
  - Urine dipstick +1 and more or
  - eGFR <60 and urine dipstick +1 and more.
- **Hypertension** –Blood pressure greater than 140/90 mm Hg on at least two of any three prior clinic visits,
  -By a physician diagnosis, or
  -The use of an antihypertensive medication
- **Diabetes mellitus**- By physician diagnosis or receipt of an anti diabetic agent
- **Chronic hepatitis B-**A positive surface antigen test (HBsAg)
- **Chronic hepatitis C**- A positive antibody test or detectable viral load

- **Renal function-** Can be reliably estimated from the serum creatinine by calculating the creatinine clearance or GFR through use of the Cockcroft-Gault or MDRD equations. Neither the Cockcroft-Gault nor the MDRD equations has been specifically validated in the HIV-infected population. The MDRD equation was derived from patients with low GFR and therefore can yield variable results in persons with normal renal function [40].

  Nonetheless, these estimates remain the most highly validated formulas available, and both equations are more sensitive than measurement of serum creatinine alone. In this particular study MDRD equation will be used without considering race to avoid over estimation of GFR in women for all patients.

- **MDRD-** Equation from the Modification of Diet in Renal Disease study Estimated GFR (mL/min per 1.73 m^2) = 1.86 x $(P_{Cr})^{-1.154}$ x $(age)^{-0.203}$

  Multiply by 0.742 for women

  Multiply by 1.21 for African Americans]

Staging	**eGFR**
I=	>=90
II=	60-89
III=	30-59
IV=	15-29
V=	<15

- **Proteinuria**- was estimated by Urine dipstick and considered significance for those who have +1,+2, +3 and above

- **BMI**- was measured by using weight and height of an individual BMI=Wt/Ht^2 (kg/m^2)

- **Rural** – place of residence was considered as rural if the area has the following properties low density housing, farms & recreational lands.
- **Urban** – place of residence was considered as urban if the area has the following properties; moderate density housing, public building, shopping center offices & industrial parks.

4.11. Dissemination of the Study Result

The final result of this study will be presented to Jimma University, College of Public Health and Medicine and to the department of internal medicine if need be it will be disseminated to Other governmental and nongovernmental organization who are concerned with HIV infection and its consequence and to policy makers to publish the result.

4.12. Limitations

We acknowledge several limitations to our study because of financial and resource limitation.

Urine protein was determined in this study by urine dipstick which is not the standard way of urine protein measurement because it cannot detect microalbuminuria which is the early indicator of renal dysfunction as a result it will underestimate the prevalence of proteinuria in particular and renal dysfunction in general.

Impaired kidney function due to acute renal failure versus gradually developing chronic renal insufficiency was not differentiated in this study.

In addition, calculations of eGFR were based on single measurements of serum creatinine, which may be subject to variations due to laboratory or patient factors like wise a single measurement of urine protein without ruling out other possible causes of proteinuria may over estimate the prevalence of renal dysfunction.

Chapter Five; Result

A total of 321 patients were included in the study. The mean (±SD) age was 36 ± 9.74 and 58.3% were females and the majorities were urban 77%. The prevalence of Diabetes, Hypertension, Hepatitis B and Hepatitis C were 0.9%, 3.7%, 5.3% and 0.3% respectively. The mean (±SD) BMI was 21 Kg/m2 ±3.1 .The median duration of HIV diagnosis was 48 months (2-180 months). The median current CD4 count was 328 cells/mm3 (4 - 1265 cells/mm3) of which 78% were ≥200 cells/mm3 and 22% were < 200 cells/mm3.The current use of cotrimoxazole was 82%.The median duration of Cotrimoxazole use was 20 months (2-108 months). The current use of TDF was 49.5%.The median duration TDF use was 11 months (1-71 months) of which 23% were ≥12 months and 77% were < 12 months. Demographic and clinical characteristics of the study were summarized in Table 1 below.

Table 1.Demographic and clinical Factors Associated with Renal dysfunction among HIV-Infected individuals

Factor	**Total N=321**	
Demographic	No	%
Age(mean)	35.8	20-65
19-30	88	27.4
31-42	157	48.9
43-53	52	16.2
54+	24	7.5
Place of residence		
Urban	247	77
Rural	74	23

Medical condition		
Diabetes	3	0.9
Hypertension	12	3.7
Hepatitis B	17	5.3
Hepatitis C	1	0.3
BMI, mean	20.7	12-32
Hiv related		
Duration of Hiv dx in months, median	48	2-180
Current CD4,median	328	4-1265
≥200	251	78.2
<200	70	21.8
Drug related		
Cotrimoxazole use	262	81.6
Duration of CPT use, median	20	2-108
Current TDF	159	49.5
Duration of TDF, months median	11	1-71
≥12	74	23.1
<12	247	76.9

Among the study cohort, 49 patients (15.3%) had an eGFR <90 mL/min/1.73 m2 .The prevalence of an eGFR of <60 mL/min/1.73 m2 was 11% (n =35). Of those with an eGFR of <60, 2 (0.6%) patients had an eGFR of <30 and no patient had an eGFR of <15 mL/min/1.73 m2.The prevalence of urine protein was 6.7% (n=21) as measured by urine dipstick. Six patients (1.8%) had eGFR of <60 and proteinuria. The prevalence of renal dysfunction in this study defined as an eGFR <60 mL/min/1.73 m2 and/or urine protein was 15.9% (n=51).

HIV patients with renal dysfunction were more likely to be older (OR 3.6 for age gr per 10 year increase in age, p <0.001), have hypertension (OR 1.2, p <0.001) , and a lower CD4 nadir (OR 1.34 for CD4 <200 compared to CD4 ≥200 cells/mm, p =0.001) and long duration cotrimoxazole use(p=04).The effect of antiretroviral medications was examined on renal dysfunction. In univariate analyses, current receipt of tenofovir was significantly associated with renal dysfunction (OR 1.56, P<0.001) and long duration of TDF use (0R 2.5 for TDF >12months as compared to TDF <12months, p <0.001). The factors associated with renal dysfunction in the univariate models are summarized in Table 2 below.

Table 2. Univariate AND Multivariate Analysis OF Factors Associated with Renal dysfunction among HIV-Infected individuals

Factor	**Total N=321**		**Normal renal fun. N=270**		**Renal dysfunction N=51**		**Univariate**		**Multivariate**	
							OR	**P value**	**OR**	**P value**
Demographic	No	%	No	%	No	%				
19-30	88	27.4	83	30.7	5	9.8				0.004
31-42	157	48.9	136	50.4	21	41.2			3.6	0.025
43-53	52	16.2	41	15.2	11	21.5			4.5	0.025
54+	24	7.5	10	3.7	14	27.5			22.6	0.000
Gender										

female	187	58.3	155	57.8	32	72	0.92	0.478		
Male	134	41.7	115	42.6	19	38	1.14			
Place of residence										
Urban	247	77	205	76	42	84	0.92	0.318		
Rural	74	23	65	24	9	26	1.36			
Medical condition										
Diabetes	3	0.9	3	1.1	0		0.98	0.572		
Hypertension	12	3.7	2	0.7	10	20	1.2	<0.001	0.082	5.5
Hepatitis B	17	5.3	15	5.5	2	4	0.98	0.228		
Hepatitis C	1	0.3	1	0.3	0		0.99	0.663		
BMI, mean	20.7	12-32	20.6	12-32	20.7	13-29		0.647		
Hiv related										
Duration of hiv dx in months, mean	48	2-180	48.4	2-180	52.7	4-160		0.878		
Current CD4,mean	328	4-1265	388	7-1265	290.8	4-1163				
>200	251	78.2	220	81.4	31	62	0.47			
<200	70	21.8	50	18.5	20	40	1.34	0.001	0.000	9.7
Drug related										
Cotrimoxazole use	262	81.6	218	80.7	44	88	0.93	0.349		
Duration of CPT use, median	20	2-108	223	2-108	44	3-96		0.04	1.01	0.06
Current TDF use	159	49.5	119	44	40	80	1.56	<0.001	1.16	0.806
Duration of TDF, months										
≥12	74	23.1	40	14.8	34	68	0.22	<0.001	18.4	<0.001

<12	247	76.9	230	85	17	34	2.5		

Multivariate logistic regression models were built and included the following variables: age, hypertension, current CD4 count, cotrimoxazole use, use of tenofovir and duration of tenofovir use. Table 3 shows the reduced (final) multivariate logistic regression model. older age groups (OR 3.6 for age group (31-42) , p <0.025),(OR 4.5 for age group (43-53) , p <0.025) and (OR 22.7 for age group 54+,p <0.001) compared to age group (19-30), lower CD4 nadir (OR 9.7 for CD4 < 200 cells/mm3 compared to CD4 ≥ 200 cells/mm3, p <0.001), and duration of tenofovir use (OR 18.5 for duration ≥ 12months compared to non users , p<0.001) remained independently associated with renal dysfunction. Hypertension(OR 5.5, p= 0.082), Use of tenofovir (OR 1.16 , P=0.8) and long duration of cotrimoxazole use (OR 1.06 ,P=0.06) were no longer significantly associated with renal dysfunction and dropped from the final model.

Chapter Six; Discussion

The prevalence of renal impairment as defined by an eGFR <60 mL/min/1.73 m2 and/or urine protein was 15.9% among the studied HIV positive people. The prevalence by an eGFR <60 mL/min/1.73 m2 and urine protein is 11% and 6.3% respectively.

This study had a similar out come with a Zambian study which revealed 12.4% prevalence of renal insufficiency as defined by an eGFR <60 mL/min/1.73 m2 which is 11% in this study though didn't considered proteinuria (64). A study in Kenya 11.5% had stage 3 or higher CKD which is consistent with this study which is 11% but the Kenyan cohort was ART-naïve and didn't considered urine protein (33, 68).Cross-studies' comparison of renal dysfunction prevalence is hampered by the heterogeneity of definitions used, such as chronic kidney failure with a GFR below 60 ml/min/1.73m2 or a combination of definitions assessing the presence of proteinuria together or not with the GFR.

A study in China which have similar definition with this study revealed CKD prevalence of 16.8% which is comparable with this studies prevalence of renal dysfunction ,15.9%(n=51).Similarly the prevalence of renal dysfunction as defined by an eGFR <60 mL/min/1.73 m2 and urine protein in this study was 11% and 6.3% respectively which the Chinese study revealed 5.6% with GFR<60 ml/min/1.73 m2 while 13.7% had spot urine P/Cr >0.3.(61).The discrepancy in urine protein could be they used the more sensitive way of urine protein detection, the spot urine p/cr, unlike in this study which used the urine dipstick which detects only gross proteinuria. A similar study in Japan showed the prevalence of CKD > or = stage 3 was 9.4% and proteinuria of 9.1% which has a comparable result with this study 11% and 6.3% respectively (62).

The prevalence of renal dysfunction in this study was relatively higher than some of the above mentioned studies this could be explained by variations in patient population characteristics including demographic characteristics, stage of HIV infection, and access to health care services. Of note, our population was relatively diagnosed with HIV late in the

course of infection, and had no open access to medical care and the fact that both eGFR and proteinuria was used to define renal dysfunction could also contributed for the discordance.

Factors associated with renal dysfunction in our HIV population included older age , lower CD4 counts and longer tenofovir use. Older age is an established risk factor for a decline in creatinine clearance in the general population (69).Similarly, older age has been independently associated with renal function decline among HIV-infected subjects (70-72).Regarding low CD4 count ,the finding of this study are concordant with other studies showing that prior AIDS and a history of low CD4 counts are risk factors for future kidney disease(73,74). These data suggest that avoiding the occurrence of low CD4 cell counts, by early HIV diagnosis and treatment, may be important components of preventing future kidney disease among HIV patients; further studies are needed.

In addition to age and lower CD4 counts, duration of tenofovir use was also significantly associated with renal dysfunction. Early clinical trials revealed a low incidence of renal dysfunction among HIV patients who received tenofovir. As more HIV patients were prescribed tenofovir, reports of Fanconi syndrome and renal proximal tubulopathy associated with tenofovir were published (75, 76). Subsequent studies have demonstrated tenofovir use as a predictor of renal impairment (69,77-79,80,81). Similar to our study, a recent analysis linked the cumulative exposure of tenofovir to renal failure, suggesting that long-term use of this medication may result in an increasing risk of nephrotoxicity (82).

Chapter Seven; Conclusion and recommendation

7.1. Conclusion

The prevalence of renal dysfunction is high in this study population. Like wise longer duration of tenofovir use, individuals having CD4 nadirs of < 200 cells/mm3 and Increasing age were also associated with increased risk of renal dysfunction.

This study contributes to the current knowledge regarding HIV patients who may be at greatest risk for kidney dysfunction in the ambulatory setting. This study has shown renal dysfunction has become an important co morbidity for HIV-infected patients with higher prevalence

7.2. Recommendation

Whereas previous studies mainly focused on HIVAN, there is now a need to shift towards a more comprehensive review of all the potential risk factors associated with CKD. HIV is a chronic disease and patients are now exposed to a range of non HIV-specific kidney risk factors, such as arteriosclerosis, hypertension or diabetes mellitus.

The prevalence of renal dysfunction in HIV patients is high based on the findings of this study. So, screening for urine protein and serum creatinine should be routine.Further studies with long-term follow-up to see the incidence of CKD and to see the risk factors is mandatory.

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Annex-II QUESTIONNAIRE

College of public Health and Medical Sciences, Department of Internal Medicine

Questionnaire on the prevalence & predictors of renal dysfunction in HIV patients in ART clinic who are on HAART JUSH,2012.

Part I. Socio demographic characteristics

1. Ser. No _____
2. Age _____
3. Sex
   A. Male
   B. Female
4. Place of residence
   A. Urban
   B. Rural

Part II. Concurrent medical Conditions

5. Were you diagnosed to have Diabetes mellitus?
   A. Yes
   B. No
6. Were you diagnosed to have Hypertension?
   A. Yes
   B. No
7. Chronic Hepatitis C
   A. Positive
   B. Negative
8. Chronic Hepatitis B
   A. Positive
   B. Negative

9. Anthropometry

A. Weight _____

B. Height _____

Part III. HIV related factors

10. When was HIV diagnosis made? _____

11. What is the current CD4 Count? _____

Part IV. Drug related factors

12. Cotrimoxazole use

A. Yes

B. No

13. If yes to the above question what is the duration? _____

14. What is the HAART regimen?

A. ZVD/3TC/EVF

B. ZDV/3TC/NVP

C. D4T/3TC/NVP

D.D4T/3TC/EVF

E.TDF/3TC/NVP

F.TDF/3TC/EVF

G. Others specify_____

15. If on tenofovir containing regimen what is the duration of tenofovir use?

_____

Part V. Renal function testes

16. RFT

A. Cr _____

B.BUN _____

17. Urine dipstick for protein

A. Protein _____

B. Glucose _____

C. RBC _____

D. Cells _____

E. Others specify _____

Declaration

I THE UNDERSIGNED, THIRD YEAR INTERNAL MEDICINE RESIDENT DECLARE THAT THIS THESIS IS MY ORIGINAL WORK IN PARTIAL FULFILLMENT FOR THE REQUIREMENTS FOR THE SPECIALITY CERTIFICATE IN INTERNAL MEDICINE. *ALL THE SOURCES OF THE MATERIALS USED FOR THIS THESIS AND ALL PEOPLE AND INSTITUTIONS WHO GAVE SUPPORT FOR THIS WORK ARE FULLY ACKNOWLEDGED.*

NAME DR YISHAK ALI

SIGNITURE_____

PLACE OF SUBMISSION – JIMMA UNIVERSITY, COLLEGE OF PUBLIC HEALTH & MEDICAL SCEINCES, DEPARTMENT OF INTERNAL MEDICINE

DATE OF SUBMISSION_____

THIS THESIS WORK HAS BEEN APPROVED BY MY ADVISORS.

Dr. Daniel Yilma, Internist, Department of Internal Medicine, JUSH

SIGNITURE _____

Mr. Fasil Tessema, MSc, Department of statistics ,JU

SIGNITURE _____