

Tenofovir Disoproxil Fumarate-Associated Renal Dysfunction Among Adult People Living with HIV at the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia, 2019: A Comparative Retrospective Cohort Study

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Background: The use of tenofovir disoproxil fumarate (TDF) has been reported to be a significant contributor to renal dysfunction. However, patients in Ethiopia may be different than in other parts of the world, and findings from such studies may not apply in this setting. **Objective:** This study aimed to assess TDF-associated renal dysfunction among adult people living with HIV (PLHIV) at the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia.

Methods: This retrospective cohort study included adult PLHIV between January 2015 and June 2019. The Chronic Kidney Disease Epidemiology (CKD-EPI) equation was used to estimate glomerular filtration rate (eGFR). Renal dysfunction was defined as eGFR <60 mL/min/1.73 m². Data were entered into Epi Info™ 7 and analyzed by using SPSS® software version 20. The Kaplan–Meier method was used to estimate the survival curves. Cox proportional hazards models were used to identify predictors of renal dysfunction using a 95% confidence interval and p-value ≤ 0.05 as a statistical significance.

Results: Out of 400 participants, 200 were TDF-based ART groups, and 200 were non-TDF-based ART groups. The incidence of renal dysfunction of TDF and the non-TDF group was 28.31 per 100 person-years (PYs) and 12.53 per 100 PYs, respectively. Adult PLHIV taking TDF-based regimens were 1.70 (adjusted HR = 1.70; 95% CI = 1.02–2.82) times at higher risk of renal dysfunction than non-TDF-based regimens. Age ≥55, diabetes mellitus, concurrent nephrotoxic drug use, and combined use of ritonavir-boosted protease inhibitors were also associated significantly with renal dysfunction.

Conclusion: The incidence rate of renal dysfunction among TDF users is higher than non-TDF users. Exposure to TDF is a significant risk of renal dysfunction in adult PLHIV. Clinicians should regularly monitor the renal function of adult PLHIV who are taking TDF.

Keywords: antiretroviral therapy, renal dysfunction, tenofovir disoproxil fumarate, estimated glomerular filtration rate, northwest Ethiopia

Introduction

Tenofovir disoproxil fumarate (TDF) is an oral prodrug of tenofovir, an NRTI with activity against retroviruses, including HIV-1 and HIV-2.¹ It is a widely used drug in combination with other antiretroviral drugs for the treatment of HIV owing to its

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favorable pharmacodynamics and pharmacokinetic properties.² Its long intracellular half-life permits once-daily dosing, lowers pill burden, and facilitates adherence.³

Although TDF is assumed to be a relatively safe drug, its effect on renal function is questioned by different studies.^{4–6} It is one of the potential risks of renal dysfunction among HIV patients.^{7–12} TDF induced nephrotoxicity was reported in as many as 0.5–45% of HIV-positive patients.¹³

A Systematic Review and Meta-analysis of 17 studies done in Southern America, Northern America, and Asia showed that there was a significantly greater loss of kidney functions among the TDF recipients than controls.¹⁴ Similar reports were also released from African countries.^{15–19}

However, due to the lack of renal function monitoring, the inadequacy of management, limited accessibility of dialysis and kidney transplant procedures in case of renal failure the occurrence of a renal problem in HIV patients can be worst in low- and middle-income countries.²⁰ Also, patients may not be capable of affording renal function tests as well as for available treatment costs.

Moreover, TDF-induced renal toxicity causes regimens discontinuation in a significant number of individuals.^{7,21} This may expose individuals to viral rebound and unexpected drug resistance. Its burden on survival and quality of life is becoming worse.²² Generally, the occurrence of renal dysfunction is worrisome and should not be neglected in PLHIV who received TDF-based antiretroviral regimens.

Following the 2016 WHO recommendation, a TDF-based regimen is being provided for all eligible HIV-infected adolescents (10 to 19 years or weight ≥ 35 kg and adults in Ethiopia.^{23,24} However, a study showed that the use of TDF for a longer duration of time increases the risk of TDF-induced renal dysfunction.²⁵ In addition to this, the risk of renal dysfunction due to the use of TDF is tended to be higher in developing countries; where the relative bodyweight of the users is low.²⁶ So, the risk of TDF renal toxicity may be high in sub-Saharan countries where most HIV infected individual lives in poor economic status and malnutrition are high. The risk of renal toxicity is also high due to the concomitant use of Nephrotoxic drugs like anti-TB medication in developing countries.²⁵ The late presentation of patients in developing countries like Ethiopia with high viral load and low CD4 count may increase the risk of renal toxicity.^{8,25} There are

only a few studies that tried to assess the magnitude of the renal problem on patients taking TDF in Ethiopia; however, none of the studies did not compare the magnitude of the renal problem on patients taking TDF and non-TDF-based regimens.^{17,27} Moreover, uncovering the problem may result in being over-dependent on TDF instead of seeking a relatively safer drug-like Tenofovir alafenamide.²⁸ Therefore, this study aimed to assess TDF-associated renal dysfunction among adult people living with HIV(PLHIV) at the University of Gondar Comprehensive Specialized Hospital (UoGCSH).

Materials and Methods

Study Area and Period

A retrospective cohort study was conducted on adult PLHIV attending to ART clinic at UoGCSH, Northwest Ethiopia from May 01/2019 to August 30/2019. This data was obtained from follow-up laboratory data of adult PLHIV and their charts. The hospital is located in the Central Gondar administrative zone, Amhara National Regional State, which is about 750 km far from Addis Ababa, which is the capital city of Ethiopia. According to the 2007 population and housing census report, the total population size of Gondar town was estimated to be 206,987. Currently, Gondar town has one comprehensive specialized Hospital and eight governmental Health Centers. UoGCSH is a teaching hospital, which serves more than five million people in the North Gondar zone and the people around the neighboring zones. The HIV care service of the Hospital was initiated in 2005. It has 7 outpatient units, one voluntary testing and counseling unit, one pharmacy, and one laboratory. Since 2005, in which the hospital started ART, 7581 adults and 738 pediatrics patients have been enrolled in HIV care. Currently, 5600 adults are actively following their treatment.

Study Design

An institution-based retrospective cohort study was conducted on medical records of adult PLHIV who were registered at the ART clinic of the University of Gondar Comprehensive Specialized Hospital, Northwest Ethiopia from January 2015 to January 2019. Adult PLHIV who were not taking TDF-based ART regimens were used as unexposed groups (non-TDF users), and adult PLHIV who were taking TDF-based ART regimens were used as exposed groups (TDF users). The medical records of eligible patients were reviewed from the earliest time 2015 until

administrative censoring (January 2019). The minimum follow up period was 3 months from the start of ART regimens. It is a time at which the first renal function tests are done, in most cases, after the start of ART regimens in the hospital. So each patient was followed until the last recorded renal function test. We recorded the outcome of interest “renal dysfunction” at its first occurrence or incidence.

Population

The source population was all adult PLHIV on ART attending ART Clinic of UoGCSH. Whereas, the study population was all adult PLHIV attending to ART clinic in UoGCSH starting from January 2015 to January 2019.

Inclusion and Exclusion Criteria

All adult PLHIV treated with TDF or non-TDF-based ART regimens from January 2015 up to June 2019 were included in the study. Pregnant women, adult PLHIV with no baseline creatinine value record, no renal function test on follow-up at least two times, and who had renal dysfunction before initiating ART were excluded from the study.

Sample Size Determination and Sampling Procedure

Sample Size Determination

The sample size calculation was done by using STATA version 14. It was begun by determining the expected (required) number of events (e). Then, the following formula was used for calculating the sample size: $n1 = n2 = \frac{(z_{\alpha/2} + z_{\beta})^2}{\theta^2 p(1-p)}$.^{29–31} By using an equal sample size for two population proportion ($P1=0.263$, $1-P = 0.737$), level of significance ($\alpha=0.05$), power of the study ($\beta=0.8$), and the effect size ($HR = e^{\theta}=1.719$)³² from a previous study the sample size was summarized as follows. $n1 = \frac{(z_{\alpha/2} + z_{\beta})^2}{\theta^2 p(1-p)} = \frac{(1.96 + 0.8416)^2}{0.5418^2 * 0.263(0.737)} = 137.94 = 138$; $N = n1 * 2 = 138 * 2 = 276$. For possible missed data and loss to follow up, a 10% contingency was considered. With this, the minimum sample size was determined to be 304. However, to increase the power of the study, the sample size was extended to 400.

Sampling Technique

First, the lists of all adult PLHIV who were on ART medication were obtained from the electronics dispensing tool (EDT) at the ART pharmacy and the registration book of the ART clinic. Then, we have classified the patients

into two groups (patients taking TDF and non-TDF-based regimens) based on the information obtained from the EDT and registration book, and separately entered into two XL sheets to avoid possible repetition using the 6 digit chart number. Then, we applied systematic random sampling to select the charts for data collection. When the collected chart failed to fulfill the inclusion criteria, we used the immediate next chart by using the list from the XL sheets. We stopped data collection when data was collected from 400 charts, 200 charts from TDF, and 200 charts from non-TDF-based regimens.

Study Variables

The independent variables of the study were the socio-demographic characteristics (age, BMI, weight, occupation, and educational status); drug-related factor (TDF and non-TDF ART regimens, concurrent use of ART, anti TB drug, cotrimoxazole, concurrent use of a nephrotoxic drug); disease-related factors like HIV (viral load, CD4, WHO stage (I, II, III, IV), OIs (TB, PCP, Toxoplasmosis, Bacterial Pneumonia, and others)), and comorbidities (Hypertension, Diabetes mellitus, Cancer, and others). However, the dependent variable of the study was renal dysfunction.

Operational Definitions

Renal dysfunction is defined as $GFR < 60 \text{ mL/min/1.73 m}^2$ (with or without kidney damage), calculated using the abbreviated chronic kidney disease epidemiology (CKD-EPI) equation, according to the Kidney disease outcome Quality Initiative which includes moderate (stage 3) kidney disease.^{33,34}

Baseline serum creatinine (SCr) is defined as the first recorded SCr before ART initiation.

An adult is an age greater than or equal to 18 years.

Measurement

For calculating the eGFR, CKD-EPI was used, because it is preferred over MDRD to determine more accurate eGFR, and it gives better risk prediction.^{33,35} For calculating the eGFR, the following equations were used for the respective individuals:

For female individual who had $Scr \leq 0.7$, it was calculated by using the equation, $eGFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{age} \times 1.159$ (if black). Whereas when $Scr > 0.7$, it was calculated by using the equation, $eGFR = 144 \times (Scr/0.7)^{-1.209} \times (0.993)^{age} \times 1.159$ (if black). For male individuals who had a $Scr \leq 0.9$, the equation, $eGFR = 141 \times (Scr/0.9)^{-0.411} \times (0.993)^{age} \times 1.159$ (if black) was used.

However, when $\text{Scr} > 0.9$, $\text{eGFR} = 141 \times (\text{Scr}/0.9)^{-1.209} \times (0.993)^{\text{age}} \times 1.159$ (if black) was used. Where the serum creatinine was in mg/dL, eGFR was in mL/min/1.73m², and the age is in a year.

An eGFR cutoff value of less than 60mL/min/1.73m² was used to dichotomize patients into renal dysfunction and relatively normal renal function. This cutoff point had been used in many previous studies done internationally.^{6,10,15,16,21,26,36–39} The < 60 mL/min/1.73m² threshold is usually recommended for adjustment of the dose of medications in most guidelines.^{33,40,41}

Data Collection

Data Collection Procedures and Quality Control

The data were collected retrospectively from patients' laboratory data and patient charts by one diploma nurse and one clinical pharmacist after one-day training were given to data collectors and supervisors on the objectives of the study, the contents of the questionnaire, and the issues related to confidentiality. A data abstraction format designed based on previous studies ([Annex I](#))^{15–17,42} was used for collecting the data from the patient charts. It was pretested on 10% of the sample size at Felege Hiwot Referral Hospital in Bahir Dar city. Based on the findings of the pre-test, some questions were modified and some others were added (BMI, BUN). The data extracted for the pre-test was not included in the main analysis. The data collection was supervised, checked for consistency and completeness daily.

Data Processing and Analysis

After the data were checked for its consistency and completeness, it was entered into Epi Info™ 7 software. Then it was transformed to SPSS® (IBM Corporation) software version 20 and analyzed. The result was interpreted and presented using appropriate tables and figures. Descriptive statistics, such as mean and standard deviations for normally distributed continuous data frequencies, and percentages for categorical data was calculated. Pearson chi-square and Fisher's exact test of independence were used to determining the significant difference between TDF exposure and non-TDF exposure at baseline. The IR was calculated for the entire study period by STATA software version 14 (STATA Corp, College Station, TX, USA). To calculate the incidence rate of renal dysfunction among people on ART, the total duration of follow-up for the whole cohort in person-year (PY) was used.

The survival analysis was carried out, as this study has considered time-to-event data, the Cox proportional hazard

model was fitted to determine the risk of TDF on renal dysfunction. The Kaplan–Meier curve was used to estimate the median duration of renal dysfunction. It was also used to compare the hazard and the survival functions of the survival analysis between TDF and non-TDF-based regimens. The Log rank test was used to compare whether there is a significant difference between TDF and Non-TDF groups on the survival curves. Both bivariate and multivariate Cox proportional hazard models were used to identify the predictors. Variables with a p-value < 0.2 in the bivariate analysis were entered into the multivariate proportional hazard model. Ninety-five percent CI of hazard ratio and p-value < 0.05 in bivariate and the multivariate Cox proportional hazards model was considered as a level of significance. Cox proportional hazard model fitness was checked using the Schoenfeld residuals.

Ethical Considerations

The ethical clearance was obtained from the ethical clearance committee of the school of pharmacy, University of Gondar (UOG) before conducting the research. Permission to access all necessary patients' data for the study was obtained from the medical director of the UoGCSH. Confidentiality of the information regarding patients' data was ensured in such a way that the assessment was used for the study purpose only. The collected data would not be used other than the purpose of the study and not be accessed by a third party other than the purpose of the study. The collected data was secured in a locked cabinet. Patient consent was not applicable. This study was conducted in accordance with the Declaration of Helsinki.

Results

Baseline Socio-Demographic

Characteristics of the Study Subjects

Out of 400 participants, 238 (59.50) were females, the Median age of the patients was 42 (15) years, and 240 (60.00%) of the participants were in the age range between 36 and 55years. Statistically significant differences were seen in residence and educational level of the participants between the TDF and Non-TDF groups with a p-value of 0.02 and 0.01 respectively. Similarly, the occupational status of participants was found to be significantly different ($P=0.03$) between the two groups. The median weight of participants at baseline was 50 (13) Kg. Nearly half of the study subjects, 197 (49.3%), had a bodyweight of < 50 kg. On the other hand, the median BMI of the study

participants was 20.8 (4) kg/m². With this, nearly three-quarters of the study respondents, 291 (72.8%), had a BMI of ≥ 18.5 kg/m² (Table 1).

Clinical Characteristics of the Study Subjects

The number of patients with diabetes mellitus 13 (3.3%), hypertension 19 (4.8%), and cancer 7 (1.8%) at baseline was comparably low in both TDF and non-TDF-based groups, with p -value = 0.78, 0.81, and 0.45 respectively. As well, comparable number of patients between the two groups (TDF vs non-TDF) was seen on the following baseline clinical characteristics: opportunistic infection except bacterial pneumonia ($p=0.02$), the median baseline serum creatinine (IQR) (0.63 (0.28)mg/dl), the proportion of concomitant administration of anti- TB drugs (107 (26.8%) vs 94 (23.5%)) and cotrimoxazole (188 (47%) vs 191 (47.8%)), and relatively high use of concurrent NNRTIs (174 (43.5%) vs 182 (45.5%)). However, the two groups had statistically significant difference on the following baseline clinical characteristics: the WHO clinical stage ($p=0.040$) of participants, patients with other comorbidities ($p=0.01$), the median baseline CD4 (166.5 (166) cells/mm, $p = 0.01$), the median baseline eGFR (132 (-28) mL/min/1.73 m², $p = 0.02$), the median baseline BUN (11 (8), $p=0.01$), and the proportion of concurrent administration of nephrotoxic drugs (58 (14.5%) vs 36 (9%)) ($p=0.01$) (Table 1).

The Incidence of Renal Dysfunction Among Study Participants

Renal dysfunction was occurred in 55 (27.5% with 95% CI=22.5–35.5%) of the study participants who were taking TDF-based regimens and in 26 (13% with 95% CI=8.5–18%) of participants who were taking non-TDF-based regimens, with an estimated incidence rate of 28.31 (CI=22.64, 35.41) and 12.53 (CI=8.75, 17.95) per 100 person-years (PYs), respectively. The overall median follow-up time was 1(IQR=0.75) years; 0.75 (IQR=0.75) years for the TDF-based regimen, and 1(IQR=0.50) years for the non-TDF regimen. The Log rank test comparing the distribution of the two hazard curves showed that TDF users had a significantly higher risk probability of renal dysfunction over time than non-TDF users ($\chi^2=15.122$; $df=1$; $P=<0.001$) (Figure 1). The Log rank test comparing the distribution of the two survival curves showed that TDF users had a significantly shorter survival probability over time

than non-TDF users ($\chi^2=15.122$; $df=1$; $P=<0.001$) (Figure 2).

Predictors of Renal Dysfunction

After controlling for the effects of potentially confounding variables using multivariate Cox regression model, TDF-based treatment regimens, the age of 55 and above, diabetes mellitus, concurrent use of nephrotoxic drugs, and concurrent ART were found to be statistically significant predictors of renal dysfunction.

Accordingly, patients on TDF-based regimens were 1.70 times higher risk for renal dysfunction than patients on non-TDF-based regimens (AHR = 1.70; 95% CI =1.-02–2.82; $p=0.04$). Those individuals in the age of 55 and above were 2.81 times more likely at high risk of renal dysfunction than those individuals in the age group between 18 and 35 (AHR = 2.81; 95% CI = 1.23–6.42; $p=0.02$). Having diabetes mellitus increases the risk of developing the outcome 2.52 times as compared to those who have not diabetes mellitus (AHR = 2.52; 95% CI = 1.11–5.72; $p=0.03$). Concurrent nephrotoxic drug use was 2.24 times higher risk than patients who did not report concurrent nephrotoxic drug use (AHR =2.24; 95% CI = 1.22–4.13; $p=0.01$). Concurrent ART had also a significant effect, those who took PI/r were 2.14 times at higher risk as compared to those who took NNRTIs (AHR = 2.14; 95% CI = 1.15–4.10; $p=0.02$) (Table 2).

Discussion

This study tried to compare the incidence rate of renal dysfunction, determine the risk of TDF on renal function and identify factors associated with renal dysfunction among adult PLHIV infection taking ART medication. Accordingly, the incidence rate of renal dysfunction is recorded nearly on a quarter of TDF exposed groups (28.31 per 100 PYs) and around one-tenth (12.53 per 100 PYs) of non-TDF exposed groups. Adult PLHIV taking TDF-based regimens had a relatively higher incidence rate of renal dysfunction than non-TDF groups. TDF users had a significantly higher risk probability and shorter survival probability of renal dysfunction over time than non-TDF users. This is in line with the previous studies done in Japan, Canada, and Korea.^{11,42–44}

However, the incidence rate of renal dysfunction in both TDF-based and non-TDF-based regimens is relatively higher as compared to studies done in Japan (9.84 and 4.55 per 100 person-years respectively),⁴⁴ Canada (7.35

Table I Baseline Socio-Demographic and Clinical Characteristics of Adult PLHIV on TDF versus Non-TDF Regimens at University of Gondar Comprehensive Specialized Hospital, January 2015–January 2019 (N=400)

Variables	Categories	Total Participant (N=400)	TDF Group (N=200)	Non-TDF Group (N=200)	P-value
Baseline sociodemographic characteristics		Frequency (%)	Frequency (%)	Frequency (%)	
	Sex	Female Male	127 (31.8) 73 (18.2)	111 (27.8) 89 (22.2)	0.063
	Age(Year)	18–35 36–55 >55 Mean age	57 (14.2) 120 (30.0) 23 (5.8)	67 (17.2) 120 (30) 11 (2.8)	0.068
	Baseline Weight(kg)	>60 50–60 <50	43 (10.8) 63 (15.8) 94 (23.5)	38 (9.5) 59 (14.8) 103 (25.8)	0.653
	BMI (kg/m ²)	<18.5 ≥18.5	53 (13.2) 147 (36.8)	56 (14.0) 144 (36.0)	0.736
	Educational Status	No educated Primary Secondary Diploma and above	66 (16.5) 50 (12.5) 45 (11.2) 39 (9.8)	53 (13.2) 58 (14.5) 68 (17) 21 (5.2)	0.007*
	Occupation	Farmer House Wife Merchants Employee Un Employee	14 (3.5) 69 (17.2) 29 (7.2) 70 (17.5) 18 (4.5)	16 (4) 65 (16.2) 32 (8.0) 50 (12.5) 37 (9.2)	0.036*
	Residence	Rural Urban	64 (16) 136 (34)	44(11) 156(39)	0.024*
Clinical characteristics of study participants	Diabetes mellitus	Yes No	7 (1.8) 193 (48.2)	6 (1.5) 194 (48.5)	0.778
	Hypertension	Yes No	10 (2.5) 190 (47.5)	9 (2.2) 191(47.8)	0.814
	Cancer	Yes No	5 (1.2) 195 (48.8)	2 (0.5) 198 (49.5)	0.449 ^a
	Other comorbidities**	Yes No	29 (7.2) 171 (42.8)	13 (3.2) 194 (46.8)	0.009*
	WHO Stage	Stage I Stage II Stage III Stage IV	60 (15) 31 (7.8) 73 (18.2) 36 (9)	47 (11.8) 54 (13.5) 67 (16.8) 32 (8)	0.040*
	Tuberculosis	Yes No	74 (18.5) 126 (31.5)	66 (16.5) 134 (33.5)	0.402
	PCP	Yes No	4 (1) 196 (49)	2 (0.5) 198 (49.5)	0.685 ^a

(Continued)

Table I (Continued).

Variables		Categories	Total Participant (N=400)	TDF Group (N=200)	Non-TDF Group (N=200)	P-value
	Toxoplasmosis	Yes No	10 (2.5) 390 (97.5)	8 (2) 192 (48)	2 (0.5) 198 (49.5)	0.055
	Bacterial Pneumonia	Yes No	35 (8.8) 365 (91.3)	24 (6) 176 (44)	11 (2.8) 189 (47.2)	0.021*
	Other OIs***	Yes No	175 (43.8) 225 (56.3)	80 (20) 120 (30)	95 (23.8) 105 (26.2)	0.131
	Cotrimoxazole	Yes No	379 (94.8) 21 (5.3)	188 (47) 12 (3)	191 (47.8) 9 (2.2)	0.501
	Anti TB Drug	Yes No	201 (50.3) 199 (49.8)	107 (26.8) 93 (23.2)	94 (23.5) 106 (26.5)	0.194
	Concurrent Nephrotoxic Drugs****	Yes No	94 (23.5) 306 (76.5)	58 (14.5) 142 (35.5)	36 (9) 164 (41)	0.009*
	Concurrent ART	NNRTIs Ritonavir-boosted PIs	356 (89) 44 (11)	174 (43.5) 26 (6.5)	182 (45.5) 18 (4.5)	0.201
	Baseline Serum Creatinine	<0.60 0.60–1.20	191 (47.8) 209 (52.3)	105 (26.2) 95 (23.8)	86 (21.5) 114 (28.5)	0.057
	Baseline eGFR	≥90 60–89	385 (96.3) 15 (3.8)	197 (49.2) 3 (0.80)	188 (47) 12 (3)	0.018*
	Baseline BUN	<7 7–20 >20	85 (21.3) 268 (67) 47 (11.8)	48 (12) 121 (30.2) 31 (7.8)	37 (9.2) 147 (36.8) 16 (4)	0.013*
	CD4	<200 200–499 ≥500	249 (62.3) 137 (34.3) 14 (3.5)	111 (27.8) 78 (19.5) 11 (2.8)	138 (34.5) 59 (14.8) 3 (0.8)	0.006*
	Viral load (Copies/mL) (N=50)	< 1000	28 (7)	27 (54)	1 (2)	0.576 ^a

Notes: ^aFisher exact test, *significant ($P < 0.05$). ***Oral candidiasis, herpes zoster, HIV wasting syndrome, **anemia, dyslipidemia, heart failure, ****vancomycin, ceftazidime, ceftriaxone, ciprofloxacin, angiotensin converting enzyme inhibitors, NSAIDs, PPIs.

Abbreviations: ART, antiretroviral therapy; BMI, body mass index; BUN, blood urea nitrogen; CD4, cluster of differentiation; eGFR, estimated glomerular filtration rate; NNRTI, non-nucleoside reverse transcriptase inhibitor; OIs, opportunistic infections; PCP, pneumocystis carinii pneumonia; PIs, protease inhibitors; TB, tuberculosis; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization.

and 5.58 per 100 person-years respectively),¹¹ and Korea (9.66 and 5.14 per 100 person-years respectively).⁴²

The 28.31 per 100 PYs incidence rate of renal dysfunction in adult PLHIV who started TDF-based ART regimens in this study is also higher than non-comparative studies done in Japan (10.5 per 100 person-years),⁸ USA/Europe/Australia (1.33 cases/1000 person-years),²¹ and Malaysia (12 per 100 person-years).⁷

This variation may be due to Socio-demographic and clinical factors, Genetic polymorphism in renal proximal

tubule cell transporter proteins, duration of follow-up time, the slight difference in the definition of renal dysfunction, and the equation used to calculate the eGFR. For instance, the longer duration of follow-up in this study may explain the relatively higher incidence rate of renal dysfunction in this study than the study done in Malaysia.⁷ According to previous studies, TDF-induced renal dysfunction increases with the use of TDF for a longer duration.^{19,45} The other possible explanation may be attributed to the slight difference in the definition of renal dysfunction and the equation

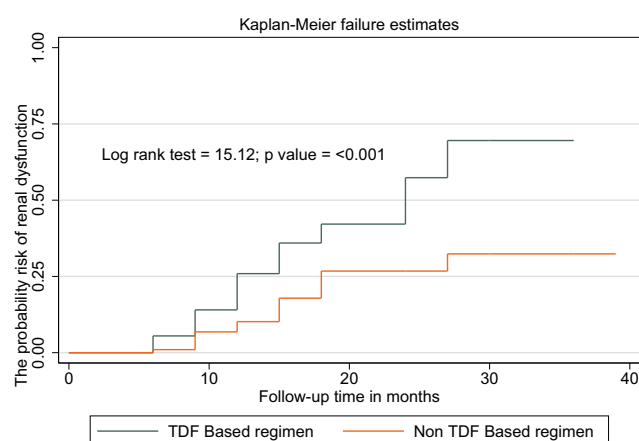


Figure 1 Two Kaplan-Meier survival curves comparing the risk probabilities against time for TDF users and non-TDF users.

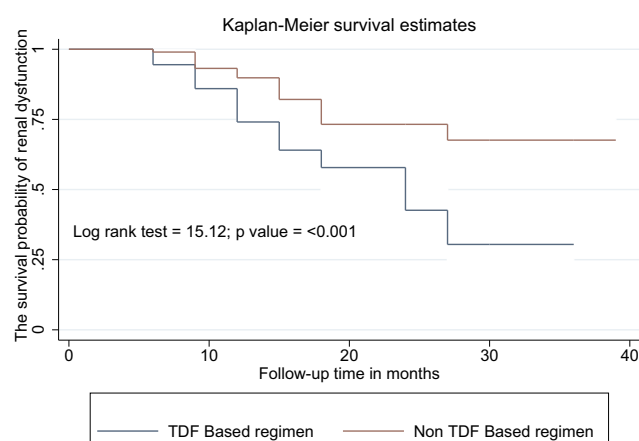


Figure 2 Two Kaplan-Meier survival curves comparing the survival probabilities against time for TDF users and non-TDF users.

used to calculate the eGFR in the studies. In this study, renal dysfunction was defined as eGFR <60 mL/min/ 1.73m^2 . However, in the studies conducted in Japan and Korea, it was defined as a $>25\%$ decrement in eGFR.^{42,44} Likewise, this study used the CKD-EPI equation for calculating eGFR, but the study conducted in Japan used the MDRD equation.⁴⁴

The proportion of TDF-related renal dysfunction for these studies was 27.5%. (22.5–35.5%). This is in line with the study conducted at Gondar University Hospital, previously,²⁷ at Tikur Anbessa Specialized Hospital in Ethiopia 25.4%,¹⁷ and Madrid 22%.⁹ However, higher than the study done in Lesotho 19 (55%) and Zambia.^{16,43} This may be due to the study done in Lesotho used relatively lower eGFR, below 50mL/min, for defining renal dysfunction, and the shorter follow-up period of the study done in Zambia than this study.

After adjusting for possible confounders, the TDF-based regimen was significantly associated with renal dysfunction. Patients treated with TDF-based regimens were 1.70 times at higher risk for renal dysfunction than patients on non-TDF-based regimens. This is consistent with many previous studies, which reported that its use predicted or associated with renal dysfunction significantly.^{9–12,15,21,32,43,44,46} As well, other studies reported that the use of TDF-based regimens associated with a greater decline of renal function than non-TDF-based regimens or ART naïve patients.^{26,37,47–50} However, some studies reported that the use of TDF failed to show any association with renal dysfunction.^{4,5,16,22,42} Similarly, a prospective cross-sectional study conducted in Uganda shows there were no significant differences in the adjusted mean differences of eGFR, serum urea, serum creatinine, fractional tubular reabsorption of phosphate and serum phosphates when patients on TDF-ART were compared with those on non-TDF containing ART. There were no differences in renal function even when different durations on Tenofovir were compared.⁴

The difference seen in the strength of the association and even the absence of association may be due to the slight difference in the definition and stage of renal dysfunction used by the different studies. For example, in the study done in Europe/USA/Australia TDF use was an independent predictor for confirmed eGFR of ≤ 70 , but it was not a significant predictor of CKD.²¹ Some of the study defines renal dysfunction as eGFR <60 or <50 mL/min/ 1.73m^2 ,^{2,6,10,15,16,21,26,36–39,45,46} and the other used a $\geq 25\%$ decline in eGFR.^{7,8,17,42,44,47} Also, different stages of CKD, stage I, stage II, stage III, and CKD stage IV were also be used.¹²

Moreover, the dose, the duration of exposure to TDF, the administration of a concomitant nephrotoxic drug, and the presence of a comorbid condition may enhance the toxic effect of TDF. Hence, the occurrence and even the presence and the magnitude of the risk may be influenced. Many previous studies support the occurrence of renal dysfunction may depend on the duration of use of TDF,^{19,45} the dose of TDF,³⁸ the combined use of TDF with PI/r,^{11,18,21,36,46,50} and concurrent use of other nephrotoxic drugs.^{8,26} As well the magnitude of the risk may increase with more severe renal dysfunction.⁴⁶ However, patients with more severe renal disease at the baseline were excluded in this study. Possibly, the difference in genetic factors, study design, sample size, and statistical model may partially explain the discrepancy

Table 2 Cox Regression Analysis of Predictors for Renal Dysfunction Among Adult PLHIV on TDF versus Non-TDF Regimens at the University of Gondar Comprehensive Specialized Hospital (UoGCSH), January 2015–January 2019 (N=400)

Variable	Renal Dysfunction					
	Yes	No	CHR (95% CI)	p value	AHR (95% CI)	p value
Treatment Regimens						
TDF Based Regimen	55	145	2.37(1.48–3.79)	<0.01	1.70(1.02–2.82)	0.04*
Non-TDF Based Regimen	26	174	1		1	
Age(Year)						
18–35	13	113	1		1	
36–55	53	187	2.26(1.23–4.16)	0.01	1.63(0.84–3.13)	0.15
>55	15	19	4.50(2.13–9.46)	<0.01	2.81(1.23–6.42)	0.01*
Residence						
Rural	24	84	1.83(1.13–2.97)	0.01	1.42(0.83–2.41)	0.20
Urban	57	235	1		1	
Baseline Weight						
>60	18	63	1		1	
50–60	25	97	0.75(0.41–1.38)	0.36	0.90(0.48–1.68)	0.74
<50	38	159	0.65(0.37–1.15)	0.14	0.77(0.43–1.39)	0.39
WHO Stage						
Stage I	19	88	1		1	
Stage II	10	75	0.82(0.38–1.76)	0.61	0.83(0.37–1.86)	0.65
Stage III	30	110	1.19(0.67–2.12)	0.54	0.57(0.26–1.23)	0.15
Stage IV	22	46	1.91(1.03–3.54)	0.04	0.90(0.38–2.13)	0.81
Tuberculosis						
Yes	40	100	1.69(1.09–2.61)	0.02	1.46(0.62–3.45)	0.38
No	41	219	1		1	
Bacterial Pneumonia						
Yes	14	21	1.80(1.01–3.21)	0.05	1.41(0.70–2.99)	0.63
No	67	298	1		1	
Diabetes mellitus						
Yes	7	6	2.60(1.19–5.68)	0.05	2.52(1.11–5.72)	0.03*
No	74	313	1		1	
Hypertension						
Yes	9	10	2.00(1.00–4.00)	0.05	1.05(0.46–2.38)	0.90
No	72	309	1		1	
Anti TB Drug						
Yes	50	151	1.69(1.08–2.64)	0.02	1.22(0.59–2.51)	0.59
No	31	168	1		1	
Concurrent nephrotoxic Drugs						
Yes	34	60	2.15(1.38–3.34)	<0.01	2.24(1.22–4.13)	0.01*
No	47	259	1		1	
Concurrent ART						
NNRTIs	66	290	1		1	
Ritonavir-boosted PIs	15	29	1.50(0.85–2.62)	0.16	2.14(1.15–4.10)	0.02*

Note: *Significant (P < 0.05).

Abbreviations: CHR, cured hazard ratio; AHR, adjusted hazard ratio; CI, confidence interval; ART, antiretroviral therapy; PIs, protease inhibitors; TB, tuberculosis; TDF, tenofovir disoproxil fumarate; WHO, World Health Organization; NNRTI, non-nucleoside reverse transcriptase inhibitor.

seen between the current study and the studies done in Korea, Uganda, and Lesotho.^{4,16,42}

The age difference was detected as independent predictors of renal dysfunction. Age ≥ 55 had a 2.81 times higher risk of renal dysfunction as compared to those who were between the ages of 18–30 years. This finding was supported by studies conducted in Myanmar, Malaysia, the Asian Pacific, Canada, Vietnam, Madrid, Nigeria, and Lesotho, Ethiopia (TASH), Japan, South Africa, and Zimbabwe.^{7–11,15–18,36,37,39,49} It is known that age greater than 50 years old is an established risk factor for TDF-induced renal dysfunction. This can be explained by the age-related structural and physiological deterioration of the kidney.²³

Diabetes mellitus was another independent predictor of renal dysfunction; those who were diabetes patients had a 2.52 times higher risk for renal dysfunction as compared to those non-diabetic patients. This result was in line with studies conducted in a middle-income country, Myanmar and Zimbabwe.^{37,39,49}

Concomitant use of concomitant nephrotoxic drugs was another independent predictor for renal dysfunction; those who were received concomitant nephrotoxic drugs had a 2.24 times higher risk for renal dysfunction as compared to those who were not received the concomitant nephrotoxic drug. This result was similar to a study conducted in Japan.²⁶

Moreover, concomitant ART (cART) were other predictors of renal dysfunction; adult PLHIV taking ART regimens containing ritonavir-boosted protease inhibitors had a 2.14 times higher risk of renal dysfunction as compared to ART regimens containing Non-Nucleoside reverse transcriptase inhibitors. This evidence was supported by studies conducted at the University of California, in the Asian Pacific, in South Africa, in Canada, and a multicenter study done in the USA, Europe, and Australia.^{11,18,21,36,50} This may be because the plasma concentrations of TDF increase by decreasing elimination when the drug is co-administered with some ritonavir-boosted protease inhibitors (PI/r). However, this finding is contradicted with studies conducted in Malaysia, Japan, Vietnam, Madrid-Spain, and New York.^{7–10,12,26,44} This may be due to less frequent prescribing patterns of PI/r-based ART and the difference in the types of PI/r used in these countries.

This study implies that HIV-infected patients who are living in developing countries like this study area and being treated with ART medication have multiple risk factors for developing renal dysfunction. Although HIV/AIDS by itself and HIV-related comorbidities may

deteriorate renal function if they are not treated with ART and other proper medication, ART medications like TDF may also be responsible for significant renal dysfunction. The occurrence of renal dysfunction/the incidence and the magnitude of the risk may vary depending on the patient's genetic polymorphism, the duration, the dose of exposure to TDF, and presence of comorbid conditions like DM, being elder age, prescription of potentially nephrotoxic drugs, and concomitant ART medications. So that taking precaution in high-risk adult PLHIV and considering alternative drug like TAF (tenofovir alafenamide) which has a comparable viral suppression and better renal safety profile may be helpful.^{51,52}

Limitation of the Study

Despite we have tried to invest our best efforts throughout the study, the study may not be out of any limitation. The retrospective nature of the study may have limited our possible best efforts to include all patients due to data incompleteness. We believe that this study should be interpreted with the following precaution: first, the study might have a systematic bias because of the observational nature of the study. So that unmeasured bias may limit the generalizability of the findings. Second, the presence of difference on some of the baseline characteristics like more other-comorbidities, bacterial pneumonia, concurrent nephrotoxic, and BUN>20 in TDF group than non-TDF groups may slightly modify (increase) the effect of the exposure. However, the presence of slightly more patients with an eGFR between 60 and 90 in non-TD, an eGFR>90mg/dl in the TDF group, and the presence of more patients with lower CD4 levels in the TDF group may also affect (decrease) the effect conservatively. We also did not study the potential effect of treatment adherence level on renal function due to the retrospective nature of the study. We have not included data from urinalysis which is not routinely done in most cases. We also did not assess the potential mechanism of renal toxicity due to the unavailability of the markers.

Conclusion

HIV-infected adult patients with TDF-based ART regimens use showed a higher incidence rate of renal dysfunction than those with non-TDF-based ART regimens. HIV-infected adult patients who take TDF-based ART regimens may be at significantly high risk of renal dysfunction than patients on a non-TDF-based ART regimen. Patients with age ≥ 55 , diabetes patients, patients with concomitant

nephrotoxic drugs, and the use of ritonavir-boosted protease inhibitors may require higher attention.

Recommendation

To Health Care Providers Managing HIV Patients

Health care providers involving in the management of adult PLHIV should closely monitor patients who have age greater than 55 years old, presence of diabetes mellitus, concurrent use of nephrotoxic drugs, and ritonavir-boosted protease inhibitors for changes in renal function while they are on ART. So, renal function monitoring is especially recommended for these patients.

To Governmental and Policymakers

The government, policymakers, and all stakeholders involving in the care of adult PLHIV should find a possible way to make available TAF containing regimens, which is a preferred option to TDF, for patients living in resource-poor settings like Ethiopia. They should also strengthen careful follow-up and regular renal function monitoring of patients on TDF.

To Researchers

We strongly recommend to researchers conduct a prospective long-term comparative cohort study with a large sample size to come up with strong evidence.

Abbreviations

3TC, lamivudine; ABC, abacavir; AHR, adjusted hazard ratio; AIDS, acquired immunodeficiency syndrome; AKI, acute kidney injury; ART, antiretroviral treatment; ARV, antiretroviral; ATV/r, atazanavir boosted with ritonavir; AZT, zidovudine; BMI, body mass index; BUN, blood urea nitrogen; CD4, cluster of differentiation 4; CHR, cured hazard ratio; CI, confidence interval; CKD, chronic kidney disease; CKD-EPI, chronic kidney disease epidemiology; CrCl, serum creatinine clearance; DNA, deoxyribonucleic acid; EDT, electronics dispensing tool; eGFR, estimated glomerular filtration rate; HAART, highly active antiretroviral therapy; HIV, human immunodeficiency viruses; MDRD, Modification of Diet in Renal Disease; MRP4, multidrug resistance protein 4; mtDNA, mitochondrial DNA; NNRTIs, non-nucleoside reverse transcriptase inhibitor; OAT1, organic anion transporter 1; PIs, protease inhibitors; SPSS, Statistical Package for the Social Sciences; TAF, tenofovir alafenamide; TB, tuberculosis;

TDF, tenofovir disoproxil fumarate; UoGCSH, University of Gondar Compressive Specialized Hospital; UoG, University of Gondar; WHO, World Health Organization.

Data Sharing Statement

All relevant data are in the manuscript.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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