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ORIGINAL RESEARCH

Chronic Kidney Disease and Associated Factors Among HIV/AIDS Patients on HAART in Ethiopia

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Background: In developing countries, both opportunistic infections and chronic diseases account a high HIV-associated mortality and morbidity. Chronic kidney disease (CKD) associated with HIV infection has got increased attention in sub-Saharan Africa as a result of the high HIV prevalence and due to the late diagnosis and initiation of HAART. Thus, this study was conducted to assess CKD and associated factors among HIV patients on HAART in Ethiopia.

Methods: A hospital-based cross-sectional study with a secondary data review was conducted on 336 on HIV/AIDS patients on HAART from February to July 2017 at University of Gondar Referral Hospital. The study participants were selected using a systematic random sampling technique. Socio-demographic and clinical data were collected using a semi-structured questionnaire at their follow-up date with interview and chart review. Three to five milliliters of venous blood and five milliliters of urine specimen were collected for serum creatinine and urine albumin determination, respectively. Data were entered into SPSS version 20 for analysis. Glomerular filtration rate was estimated using the CKD-EPI estimator. Bivariate and multivariate logistic regression was employed and p-value <0.2 and < 0.05, respectively, was considered statistically significant.

Results: The prevalence of CKD on the study participants was 54 (16.1%) (95% CI, 12.2–20.4%). By stage, about 27 (8.0%) had stage 1 (persistent proteinuria with eGFR ≥ 90 mL/min/1.73 m^2), 16 (4.8%) had stage 2 (persistent proteinuria with eGFR of 60–89.9 mL/min/1.73 m^2), 6 (1.8%) had stage 3 (eGFR 30–59.9 mL/min/1.73 m^2 with or without proteinuria) and 5 (1.5%) had stage 5 ((kidney failure), eGFR<15mL/min/1.73 m^2 with or without proteinuria). With multivariate logistic regression analysis, being male (AOR=2.05 (1.03–4.09), p=0.04), being merchant (AOR=2.91 (1.00–8.48), p=0.049) and having viral load≥1000 copies/mm^3 (AOR=3.1 (1.38–7.00), P<0.01) were significantly associated with CKD.

Conclusion: The prevalence of CKD among HIV patients on HARRT is high. Being male, merchant and having viral load ≥1000 copies/mm^3 were associated factors of CKD. Patients should be regularly monitored and screened for early diagnosis and management of CKD. Those patients who have being merchant with high viral load and male patients should require close monitoring.

Keywords: chronic kidney disease, HIV/AIDS, HAART, Ethiopia

Background

Globally, an estimated 36.7 million people were living with Human immunodeficiency virus (HIV) in 2016. The majority of people living with HIV are in sub-Saharan Africa. In the era of combined antiretroviral therapy, the life expectancy of people living with HIV (PLWH) has increased.[1–3] With longer life spans, however, PLWH is developing chronic medical conditions.[4–6] The morbidity and mortality associated with HIV

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infection were due to opportunistic infections. However, in developed countries, opportunistic infections have been replaced by chronic diseases. Whereas in developing countries like Ethiopia, both the opportunistic infections and chronic diseases account a high HIV-associated mortality and morbidity.[7] One of the most commonly diagnosed chronic diseases is chronic kidney disease (CKD).[8–10] Chronic kidney disease is defined as kidney damage or reduced kidney function that persists for more than 3 months.[11,12]

Chronic kidney diseases associated with HIV infection have got increased attention in sub-Saharan Africa as a result of the high HIV prevalence and due to the late HIV diagnosis and late initiation of highly active antiretroviral therapy (HAART) before the recommendation of initiation of HAART for any person diagnosed with HIV. A research finding showed an increasing prevalence of kidney disease in PLWH compared with the general population, being related to increased mortality and morbidity.[13–15] HIV-infected patients are five times more likely to develop kidney disease as compared to HIV non-infected.[16] A recent systematic review and meta-analysis in sub-Saharan Africa reported a 6.42% prevalence of CKD among HIV patients in which the majority of them were in stage 3 CKD.[17] Chronic kidney disease prevalence is increasing globally and recognized as a global public health problem with a major impact on health, healthcare costs and productivity.[11,18,19] The involved factors related to increasing the prevalence of kidney disease in PLWH were a direct effect of the virus itself, closely related to the immune status; prolonged use of antiretroviral therapy (tenofovir, indinavir, and others); frequent use of concomitant therapy with nephrotoxic drugs; an increase of comorbidities such as diabetes mellitus, dyslipidemia, and hypertension; high prevalence of co-infection with hepatitis B and C virus compared with the general population.[20–26]

Ethiopia is one of the countries where the majority of CKD cases among the general population and high-risk groups such as peoples living with HIV patients have limited data in consequence of underdiagnosing. Hence, this study was conducted to assess CKD among HIV patients on HAART in Ethiopia.

Materials and Methods

Aim

The aim of this study was to assess the prevalence of CKD among HIV/AIDS patients and its associated factors.

Study Area, Design, and Population

A hospital-based cross-sectional study was conducted from February 01 to July 30, 2017, at the University of Gondar Referral Hospital (UOGRH), which is located in the North Gondar zone, 747 km from the capital city of the country, Addis Ababa. Gondar has an estimated population of more than 206,987 (98,085 males and 108,902 females) based on the 2008 central statistical agency data. Currently, 13,753 HIV patients and 5389 on ART patients are attending at the University of Gondar Referral Hospital.

Adult HIV/AIDS patients who received HAART in UOGRH were the study population. Those adult HIV/AIDS patients, who received HAART for more than 6 months, visited UOGRH during the study period and consented to be involved in the study were included. But patients who were seriously sick and unable to give response, diabetic, and hypertension were excluded from the study. In addition, patients with incomplete laboratory and clinical data such as baseline adherence, baseline drug regimen, HIV/AIDS WHO stage, weight, etc. were excluded from the study too.

Sample Size Determination and Sampling Technique

Based on single population formula and systematic random sampling technique with the following assumption, P = population proportion (estimated prevalence) = 0.5 to yield maximum sample size, precision d, 0.05, by assuming 95% confidence interval $\alpha = 0.05$ and z (1-a/2) = 1.96 was used for sample size determination. Including 10% non-response rate, the final sample size was 423. However, a total of 336 HIV patients on HAART participated in the study (Figure 1).

During the three-month data collection period, 1320 HIV/AIDS patients on HAART (> 6 months) were expected to visit the hospital for follow-up. The average number of HIV/AIDS patients per day under follow-up was 20.Sampling intervals (K value) was calculated with 1320/423 = 3.12 = 3. Thus interviews, chart review and blood and urine specimen collection for chemistry analysis and urine dipstick were conducted at three intervals. To determine the first-person, the lottery method was used on first day from the 20 patients who had under follow-up. Then, each third client was selected for an interview, chart review and blood chemistry and urine dipstick test. If the third patient is not fulfilling the inclusion criteria; the next person was taken as a study subject.

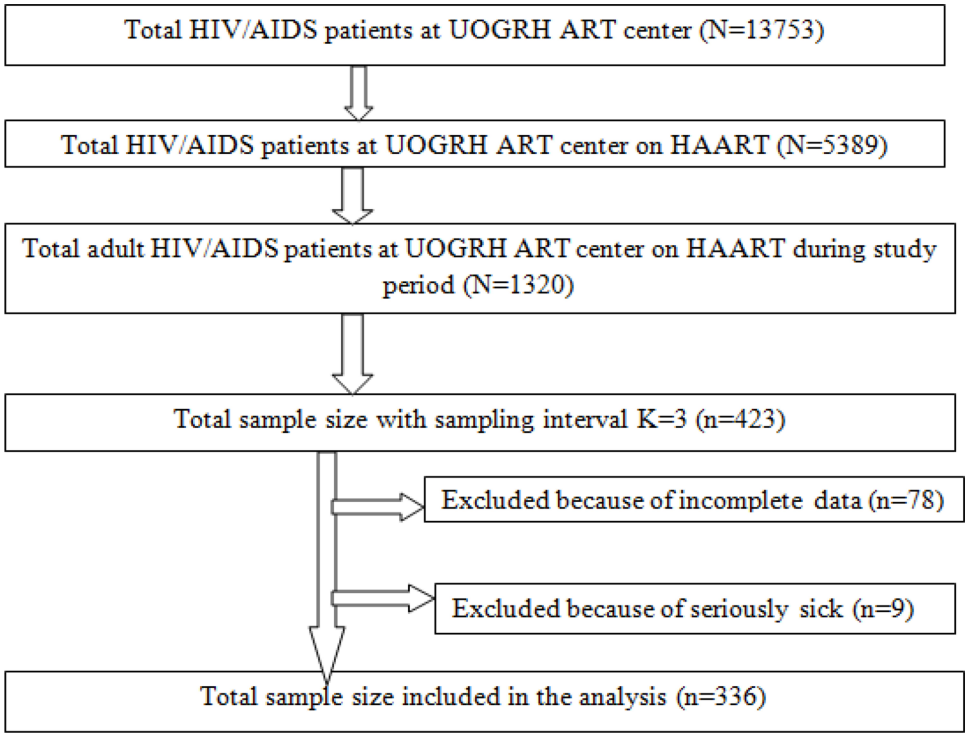

Figure 1 Schematic representation of the sampling procedure adult HIV/AIDS patients on HARRT at University of Gondar Referral Hospital from February to April 2017.

Data Collection and Laboratory Methods

Socio-demographic characteristics and clinical data were collected by trained nurses using a semi-structured questionnaire. The patient individual was interviewed and the chart was also reviewed for relevant information. Variables included age, gender, residence, education, occupation, viral load, CD4 count, co-infections, base line CD4+ count, regimen type, WHO stage, duration of follow-up time, etc.

About 3–5mL of venous blood with serum (gel) separator tube and 5mL of urine specimen using clean, dry and leak-proof urine cup were collected from the patients for creatinine and urine albumin level determination, respectively. For creatinine determination, a serum sample was immediately separated from the collected venous blood after the blood sample clotted and centrifuged at 1000–2000g for 10 mins. The separated serum was transferred to a nunc tube and kept frozen at −20 ºC until processed. A serum creatinine level was determined by kinetic Jaffe reaction using Mindray BS-200 chemistry analyzer (Shenzhen Mindray Bio-Medical Electronics Co. Ltd, China) and reported in mg/dL. Chemical analysis of urine specimens for urine albumin level determination was performed immediately after the sample collection using urine dipsticks test (Multistix® Henry Schein, Inc. https://www.henryschein.com/medical-multistix.aspx). Urine albumin level was reported semi-quantitatively as negative, or +1, to +4. All the participants with positive urine albumin and creatinine above the normal range (0.6 to 1.2 milligrams (mg) per deciliter (dl) in adult males and 0.5 to 1.1 mg per deciliter in adult females) were also checked their serum creatinine level and urine albumin for a second time after 3 months of the first check-up for confirmation of CKD. Glomerular filtration rate (GFR) was estimated using CKD-EPI question.[27]

Chronic kidney disease was defined using the average of the two consecutive creatinine eGFR and presence of urine albumin and classified into five stages according to the classification of Kidney Disease Improving Global Outcomes (KDIGO).[28]

Variables' Definition

Chronic kidney disease is defined as abnormalities of kidney structure or function, present for ≥3 months and evaluated by at least two measurements, with implications for health and CKD is classified based on cause, GFR category, and proteinuria category.[29]

- Persistent proteinuria, a positive urine albumen is positive too after 3 months of screening

- Stage 1, persistent proteinuria with eGFR ≥ 90 mL/min/1.73 m^2
- Stage 2, persistent proteinuria with eGFR of 60–89.9 mL/min/1.73 m^2
- Stage 3, eGFR 30–59.9 mL/min/1.73 m^2 with or without proteinuria
  - 3A (eGFR 45–59.9mL/min/1.73 m^2)
  - 3B (eGFR 30–44.9mL/min/1.73 m^2)
- Stage 4, eGFR 15–29.9 mL/min/1.73 m^2 with or without proteinuria
- Stage 5, (kidney failure), eGFR<15mL/min/1.73 m^2 with or without proteinuria.

HAART experienced: taking HAART for more than 6 months which is composed of two NRTIs plus an NNRTI.[30]

Underweight, normal weight, overweight and obesity were defined as a BMI <18.5 kg/m^2, 18.5–24.9 kg/m^2, 25–29.9 kg/m^2 and ≥30 kg/m^2, respectively.[31]

Hypertension: defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg or taking medication for blood pressure-lowering.[32]

Adherence: adherence was calculated as No. of the dose of HAART taken/No. of prescribed doses of HAART x 100%. Good adherence, >95%, fair adherence, 85–95% and poor adherence, < 85% doses take.[33,34]

Data Processing and Analysis

The completeness of the data was checked and entered into SPSS version 20 for analysis. During analysis, descriptive statistics such as percentage, mean and standard deviation were used. Bivariate logistic regression was used to assess the crude association between independent and dependent variables, and with p-value ≤ 0.20 were considered for multivariate logistic regression. Finally, logistic regression was used to identify independent predictors of CKD and p-value < 0.05 was considered statistically significant.

Results

Socio-Demographic Characteristics

A total of 336 HIV/AIDS patients who received HAART were enrolled in the study. Of these, 215 (64%) of them were females and 121 (36%) were males. The mean (SD) age of the participants was 39.7 (±9.7) years, range 18–69 years. One hundred thirty-three (39.6%) of the study participants were within the age group of 30–39 years. At the time of study almost half of the patients, 170 (50.6%) were married and 263 (78.3%) were living in urban areas. Three hundred five (90.8%) were followers of orthodox religion (Table 1).

Clinical Characteristics of HIV/AIDS Patients

The study patients were on ART with a minimum of 1 up to 12 years with an average time of 7.5 (± 3) years. Before ART initiation majority of patients had WHO clinical stage II and III, 251 (74.7%), CD4+T cell count < 200 cells/mm^3, 221 (65.8%), good adherence 321 (95.5%) and on AZT +3TC +NVP 121 (36%) regimen followed by TDF+3TC+EFV 62 (18.5%).

Majority of study participants, 326 (97%) were on WHO clinical stage I, 28 (8.3%) had CD4+T count <200 cells/mm^3, 333 (99.1%) had good adherence and 126

Table 1 Socio-Demographic Characteristics of HIV/AIDS Patients on HARRT at the University of Gondar Referral Hospital, 2017

Variables		Frequency	Percent
Age	18–29	39	11.6
	30–39	133	39.6
	40–49	110	32.7
	≥50	54	16.1
Marital status	Single	72	21.4
	Married	170	50.6
	Divorced	69	20.5
	Widowed	25	7.4
Gender	Female	215	64
	Male	121	36
Resident	Urban	263	78.3
	Rural	73	21.7
Occupation	Farmer	43	12.8
	Merchant	44	13.1
	Student	13	3.9
	Government employ	33	9.8
	Daily laborer	52	15.5
	House life	81	24.1
	Private employ	53	15.8
	Other	17	5.1
Educational status	Illiterate	99	29.5
	Primary school	85	25.3
	Secondary school	119	35.4
	Tertiary	33	9.8
Religion	Orthodox	305	90.8
	Muslim	24	7.1
	Protestant	7	2.1
	Total	336	100

Table 2 Clinical Characteristics of HIV/AIDS Patients on HARRT at the University of Gondar Referral Hospital, 2017

Variables		Frequency	Percent
Duration on ART in year	≤6	110	32.7
	>6	226	67.3
Mean ART duration in year	7.5 year (± 3)		
Base line WHO stage	WHO stage I	40	11.9
	WHO stage II	72	21.4
	WHO stage III	179	53.3
	WHO stage IV	45	13.4
WHO stage during data collection	WHO stage I	7	2.1
	WHO stage II	326	97
	WHO stage III	3	9
Type of Opportunistic infection	No	238	70.8
	Protozoa	4	1.2
	Helminths	8	2.4
	Hepatitis viruses	2	0.6
	Fungal infections	1	0.3
	TB	77	22.9
	Mixed	6	1.8
Initial regimen	D4T + 3TC +NVP	66	19.6
	D4T+3TC+ EFV	28	8.3
	AZT +3TC+NVP	121	36.0
	AZT+3TC+EFV	25	7.4
	TDF+3TC+EFV	62	18.5
	TDF+3TC+NVP	25	7.4
	D4T+3TC+NVP	5	1.5
	Pediatric 4C (AZT +3TC+NVP)	4	1.2
Patients who switched	No	199	59.2
	Yes	137	40.8
	Total	336	100.0
Patients who switched either first or second	To 1st line drug	126	37.5
	To 2nd line drug	11	3.3
Second regimen	AZT +3TC+NVP 1c	52	15.5
	AZT+3TC+EFV1d	22	6.5
	TDF+3TC+NVP1e	21	6.3
	TDF+3TC+EFV1f	31	9.2
	ABC + ddI +LPV/R2a	10	3.0
	TDF + ddI +IPV/R 2c	1	0.3
Reason of switching drug	Toxicity	93	27.7
	Pregnancy	5	1.5
	TB	16	4.8
	Clinical failure	17	5.1
	Age	6	1.8
ARV drug adherence at base line	Good	321	95.5
	Fair	1	0.3
	Poor	14	4.2
ARV drug adherence During data collection	Good	333	99.1
	Poor	3	0.9
Base line CD4 count	≤199	221	65.8
	200–349	95	28.3
	350–499	16	4.8
	≥500	4	1.2
CD4 count during data collection	≤199	28	8.3
	200–349	89	26.5
	350–499	92	27.4
	≥500	127	37.8
Viral load	Undetected	178	53.0
	0–19	66	19.6
	20–999	42	12.5
	≥1000	50	14.9
	Total	336	100
Component of immunological failure	CD4 falling more than 50%	22	6.5
	CD4 falling below Baseline	12	3.6
	CD4 persistently below 100	3	9
	Total	37	11.0

(*Continued*)

(37.5%) switched to first-line or second-line regimen, 11 (3.3%). The most common reason for switching was toxicity, 93 (27.7%) followed by clinical failure, 17 (5.1%). The common opportunistic infections observed during their ART follow-up were TB,77 (22.9%). The mean plasma viral load level was 6023.46 copies/mL (range 0–245,754.00 copies/mL). Among all the study participants, 27 (8.0%), 16 (4.8%), 6 (1.8%) and 5 (1.5%) of patients during follow-up were stage I, stage II, stage III and stage V, respectively (Table 2).

Staging of Kidney Function and Prevalence of Chronic Kidney Disease

Using CKD-EPI GFR estimator, the overall prevalence of CKD was 54 (16.1% (95% CI, 12.2% - 19.9%)). By stage, about 27 (8.0%) had stage 1, 16 (4.8%) had stage 2, 6 (1.8%) had stage 3 and 5 (1.5%) had stage 5 (Table 3).

Associated Factors of Chronic Kidney Disease

In bivariate logistic regression analysis associated factors like gender, occupation, duration on ART, viral load was found to

Table 3 Stages of Kidney Functions Using the CKD-EPI Estimator Among HIV/AIDS Patients on HARRT at the University of Gondar Referral Hospital, 2017

Stages of CKD	GFR Estimation	CKDN (%)
1	≥ 90, with proteinuria (≥+1)	27 (8.0% (95% CI, 5.4%-11.0%))
2	60–89, with proteinuria (≥+1)	16 (4.8% (95% CI, 2.7%-7.6%))
3a	45–59.9, with or without proteinuria (≥+1)	6 (1.8% (95% CI, 0.6%-3.3%))
3b	30–44.9, with or without proteinuria (≥+1)	0 (0)
4	15–29.9, with or without proteinuria (≥+1)	0 (0)
5	< 15, with or without proteinuria (≥+1)	5 (1.5% (95% CI, 0.3%-2.8%))
	Overall CKD	54 (16.1% (95% CI, 12.2% - 20.4%))

be a p-value of < 0.2. When it was analyzed with multivariate logistic regression analysis being male, occupation (merchant) and VL ≥ 100 copies/mm^3 were significant factors (p < 0.05) for chronic kidney disease. Male patients on follow-up (AOR=2.05 (1.03–4.09), = 0.04), merchant patients (AOR=2.91 (1.00–8.48), P=0.049) and patients who have had VL ≥ 1000 (AOR= 3.1 (1.38–7.00), P < 0.01) were 2, 2.9 and three times more likely to have chronic kidney disease compared with their comparison group female, housewife, and viral load < 20 copies/mm^3 respectively (Table 4).

Discussion

The current study assessed the prevalence and associated factors of CKD in HIV patients on HAART using the commonest estimator of kidney function method CKD-EPI. The finding of this study revealed a high frequency of CKD and the related risk factors mostly being male, occupation merchant and patients with VL ≥ 1000. The prevalence of CKD, 16.1% was consistency with the previous study conducted in Ethiopia, 12.1%,[33] Ghana, 14.5%,[35] Nigeria, 15.3%[36] and Tokyo, 13%.[37] However, the result was higher than compared to a study conducted in Uganda, 6%,[38] Nigeria, 6.9%,[39] Brazil, 8.4%,[40] Southwest Ethiopia, 7.6%,[41] Tanzania, 1.1%,[42] and Lesotho, 5.5%.[43] The observed differences could be due to study design, study area, their lifestyle, and the method used to estimate GFR.

Our finding showed, being male was significantly associated with renal impairment and it was 2.05 times more likely to have chronic kidney disease as compared with its comparison group female. Our finding disagrees with the

Table 4 Bivariate and Multivariate Analysis of Chronic Kidney Disease Associated Factors Among HIV/AIDS Patients on HARRT at the University of Gondar Referral Hospital 2017

Variables		CKD		COR (95% CI)	p-value	AOR (95% CI)	p-value
		Yes	No				
Gender	Female	183	26			Ref	
	Male	93	28	2.19 (1.22–3.94)	0.009	2.05 (1.03–4.09)	0.04*
Occupation	Farmer	38	4	0.96 (0.27–3.40)	0.95	0.63 (0.16–2.51)	0.51
	Merchant	32	13	3.71 (1.40–9.82)	0.008	2.91 (1.00–8.48)	0.049*
	Student	10	3	2.74 (0.62–12.05)	0.18	1.13 (0.22–5.90)	0.89
	Governmental employee	72	13	1.165 (0.64–4.21)	0.30	1.18 (0.42–3.30)	0.76
	Daily laborer	57	13	2.08 (0.81–5.36)	0.13	1.52 (0.55–4.16)	0.42
	Household wife	73	8	Ref	Ref	Ref	
Duration on ART in year	≤6	196	30	1.82 (1.01–3.30)	0.05	1.06 (0.21–5.37)	0.95
	>6	86	24	Ref		Ref	
Viral load category	Undetectable	156	22	Ref		Ref	
	<20	56	10	1.27 (0.57–2.84)	0.57	1.13 (0.49–2.61)	0.78
	20–999	35	7	1.42 (0.56–3.58)	0.46	1.30 (0.48–3.48)	0.60
	> 1000	35	15	3.04 (1.43–6.45)	0.004	3.10 (1.38–7.00)	0.01*

Note: *Has significant association.
Abbreviations: COR, crude odds ratio; AOR, adjusted odds ratio; Ref, reference; CI, confidence interval; p, significant value.

findings done in Burundi and Spain[4,44] but it was concurred with the study findings done in France[45] and South Africa.[46,47] In addition, our study also showed that being an occupation merchant was independently and significantly associated with chronic kidney disease. Occupation merchant patients were 2.9 times high risk than the comparative group housewife. In our study more than half (51%) of the occupation merchant participants were males. Hence, the lower prevalence of CKD among females and the higher prevalence of CKD among males may be due to the possible protective role encouraged by estrogen hormone or due to the absence of the profibrotic effects caused by testosterone hormone in females compared to males.[48,49]

In our study patients who have had VL ≥ 1000 were three times more likely to have chronic kidney disease contrasted with its comparison group patients who have had viral load < 20 copies/mm^3 respectively. Our result is in line with the study done in America[5,50] and Thailand.[51] High viral replication increased renal damage possibly occurred due to the destruction of kidney cells, and the nephrons with the virus. Consequently, viral load suppression would improve renal function on the other hand if the viral load is not suppressed it lead to chronic kidney disease.[22,52,53]

Conclusion

The prevalence of CKD in our study based on the glomerular filtration rate using the CKD-EPI method was high (16.1%). Male gender, merchant, and VL ≥ 1000 were associated factors of chronic kidney diseases CKD among HIV patients on HARRT. Hence, HIV patients on HARRT should be regularly screened for early diagnosis and management of CKD. Those patients with high viral load and male patients should be closely followed.

Abbreviations

ABC, Abacavir; AIDS, Acquired Immune Deficiency Syndromes; ART, Antiretroviral Therapy; ARV, Antiretroviral Virus; AZT/3TC, Zidovudine/Lamivudine; CKD, Chronic Kidney disease; DDI, Didanosine; EFV, Efavirenze; ESRD, end-stage renal disease; eGFR, estimated glomerular filtration rate; GFR, glomerular filtration rate; HAART, Highly Active Antiretroviral Therapy; HIV, Human Immune Deficiency Virus; LPV/R, Lopinavir/ritonavir; NNRT, Non-Nucleoside Rivers Transcriptase; NRT, Nucleoside Rivers Transcriptase; NVP, Nevirapine; OI, Opportunistic Infections; PLHIV, People Living with Human Immune Deficiency Virus; PIs, Proteinase Inhibitors; TDF, TenofovirDisoproxilFumarate; VL, Viral Load.

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Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki after ethical clearance was acquired from the Research and Ethical Review Committee of School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar. The permission letter was taken from the clinical director of the University of Gondar Specialized Referral Hospital. Written informed consent was obtained from each study participants after reading and clearly explaining the reason, procedure, period, possible risks and benefits of the research in Amharic translated full participant information sheet. For this purpose, a consent form, and a participant information sheet was attached as a cover page of each questionnaire. Patients who were not willing to participate in the study were not forced to participate. The privacy of personal information was protected and kept confidential by excluding their name during the period of data collection. The laboratory results from the study participants were communicated to their physicians for appropriate management.

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Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version

to be published, and agree to be accountable for all aspects of the work.

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Disclosure

We declare that we do not have any conflict of interests.

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