Chronic Kidney Disease and associated factors among HIV/AIDS Patients on HAART at University of Gondar Referral Hospital, Northwest Ethiopia

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Abstract

Background

In developing countries, both opportunistic infections and chronic diseases account a high HIV associated mortality and morbidity. Chronic kidney diseases (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 HARRT in Northwest Ethiopia.

Methods

A hospital-based cross-sectional study with a secondary data review was conducted from February 01 to April 30, 2017, at the University of Gondar Referral Hospital, Northwest Ethiopia. The study participants were selected using a systematic random sampling technique. Socio-demographic and clinical data were collected using a semi-structured questionnaire by trained nurses. Venous blood and urine specimen was collected for serum creatinine and urine protein determination respectively. Glomerular filtration rate was estimated using the CKD–EPI estimator. Data were entered into SPSS version 20 for analysis. Bivariate and multivariate logistic regression was employed and p-value < 0.05 was considered statistically significant.

Results

A total of 336 HIV patients on HARRT participated in the study. The mean (SD) age of the participants was 39.7 (± 9.7) years. The study participants were on HAART with an average of 7.5 (± 3) years. Before ART initiation, the majority of patients had WHO clinical stage II and III, 251 (74.7%), CD4 + T cell count < 200 cells/mm^3, 221 (65.8%).The overall prevalence of CKD was 16.1%. About 27 (8.0%), 16 (4.8%), 11 (3.3%) of the participants had stage 1 and stage 2 CKD and chronic renal failure (stage 3a-5) respectively. With multivariate logistic regression analysis being male (AOR = 2.05 (1.03–4.09), p = 0.04, occupation merchant (AOR = 2.91(1.00-8.48),p = 0.049)and viral load ≥ 1000 copies/mm^3 (AOR = 3.1 (1.38-7.00), P < 0.01) were significantly associated with CKD.

Conclusions

The prevalence of CKD among HIV patients on HARRT is high. Being male, merchant and 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 with high viral load and male patients should be closely followed.

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 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 three months [11, 12].

Chronic kidney diseases 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 HIV diagnosis and initiation of HAART. 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 major impact on health, health-care costs and productivity[11, 18, 19]. The involved factors related to increased 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 coinfection with hepatitis B and C virus compared with general population[20–26].

Ethiopia is among countries where majority of CKD cases were under diagnosed and limited data both among the general population and high-risk groups such as PLWH. Hence, this study was conducted to assess CKD among HIV patients on HARRT in Northwest 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 April 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. at the time of data collection, there were about 13753 HIV patients and 5389 HIV patients on HAART.

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 in the study. Whereas, 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 study.

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 α = 0.05 and z (1-a/2) = 1.96was used for sample size determination. Including 10% non response rate, the final sample size was 423. However, a total of 336 HIV patients on HARRT participated in the study (Fig. 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 3 intervals. To determine the first-person, the lottery method was used at 1st day from the 20 patients who had under follow up. Then each 3rd client was selected for interview, chart review and blood chemistry and urine dipstick test. If the 3rd patient is not fulfilling the inclusion criteria; the next person was taken as a study subject.

Data collection and laboratory methods

Socio-demographic characteristics and clinical data were collected by trained nurses using a semi-structured questionnaire. The patient individual 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 3–5 ml of venous blood was collected aseptically from the patients and serum was separated after the sample clotted and centrifuged at 1000–2000 g for 10 minutes by trained laboratory technologist. A serum sample was immediately separated from the whole blood and transferred to nunc tube. The serum was kept frozen at -20 ºC until processed. A serum creatinine level was determined using Mindray BS-200 chemistry analyzer (Shenzhen Mindray Bio-Medical Electronics Co. Ltd, China) and reported in mg/dL. About 5 ml of urine specimen was collected using clean, dry and leak proof urine cup

for urine protein level determination. Chemical analysis of urine specimens was performed immediately after sample collection using urine dipsticks test (Multistix® Henry Schein, Inc.https://www.henryschein.com/medical-multistix.aspx). Urine protein level was reported semi-quantitatively as negative, or + 1, to + 4. Glomerular filtration rate (GFR) was estimated using CKD–EPI question[27].Chronic kidney disease was defined using eGFR and presence of albuminuria 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, with implications for health and CKD is classified based on cause, GFR category, and proteinuria category [29].

- 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 was 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 patients, 170 (50.6.4%) were married and 263(78.3%) were living in urban areas. Three hundred five (90.8%) were followers of orthodox religion (Table 1).

Table 1
Sociodemographic 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

Variables		Frequency	Percent
	Protestant	7	2.1
	Total	336	100

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 (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 was TB, 77 (22.9%). The mean plasma viral load level was 6023.46 copies/ml (range 0–245754.00 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).

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

*ADH = adherence, ARV = Antiretroviral, D4T = StavudineTDF = TenofovirDisoproxilFumarate, AZT/3TC = Zidovudine/Lamivudine, EFV = Efavirenze, NVP = NevirapineABC = abacavir, ddl = didanosine, LPV/R = lopinavir/ritonavir,

Variables		Frequency	Percent
	Pediatric 4C (AZT + 3TC + NVP)	4	1.2
Switching	No	199	59.2
	Yes	137	40.8
	Total	336	100.0
Switching	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 + ddl + LPV/R2a	10	3.0
	TDF + ddl + 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 ADH at base line	Good	321	95.5
	Fair	1	0.3
	Poor	14	4.2
ARV drug ADH 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

*ADH = adherence, ARV = Antiretroviral, D4T = StavudineTDF = TenofovirDisoproxilFumarate, AZT/3TC = Zidovudine/Lamivudine, EFV = Efavirenze, NVP = NevirapineABC = abacavir, ddl = didanosine, LPV/R = lopinavir/ritonavir,

Variables		Frequency	Percent
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

*ADH = adherence, ARV = Antiretroviral, D4T = StavudineTDF = TenofovirDisoproxilFumarate, AZT/3TC = Zidovudine/Lamivudine, EFV = Efavirenze, NVP = NevirapineABC = abacavir, ddl = didanosine, LPV/R = lopinavir/ritonavir,

Staging of kidney function and prevalence of chronic kidney disease

Using CKD-EPI GFR estimator, about 27 (8.0%) of the participants had stage 1 and 16 (4.8%) stage 2 CKD. Whereas, only 11 (3.3%) of them developed chronic renal failure (stage 3a-5). The overall prevalence of CKD defined as protein urea of $\geq +1$ and/or GFR < 60 was 16.1% (Table 3).

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	CKD N (%)
1	≥ 90, with proteinuria (≥ + 1)	27(8.0)
2	60–89, with proteinuria (≥ + 1)	16(4.8)
3a	45–59.9, with or without proteinuria (≥ + 1)	6(1.8)
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)
	Overall CKD	54(16.1%)

Associated factors of Chronic kidney disease

In bivariate logistic regression analysis associated factors gender, occupation, duration on ART; viral load was found to 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 3 times more likely to have chronic kidney disease compared with their comparison group females, housewife and viral load < 20 copies/mm^3 respectively (Table 4).

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

*COR = crude odds ratio, AOR = adjusted odds ratio Ref = reference CI = confidence interval p = significant value,

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 as 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 and their lifestyle, and the method used to estimate GFR.

This study showed, male gender was significantly associated with renal impairment and was 2.05 times more likely to have chronic kidney disease as compared with its comparison group female. The finding agrees with the study findings conducted in France [44], and South Africa[45]. The lower prevalence of CKD in females may be due to the possible protective role promoted by estrogens hormone or due to the absence of the profibrotic effects caused by testosterone [46, 47].This study also showed that being occupation merchant was independently and significantly associated with chronic kidney disease. Merchant patients were 2.9 times high risk than the comparative group housewife. In the current study more than half, (51%) of the occupation, merchant participant group were male. Since the higher prevalence of CKD on male than females might be due to the possible CKD protective role promoted by estrogens hormone in females or due to the absence of the profibrotic effects caused by testosterone hormone in females compared to males[46, 47].

In the current study patients who have had VL ≥ 1000 were three times more likely to have chronic kidney disease compared with its comparison group patents who have had viral load < 20 copies/mm^3 respectively. This result is agreed with the study conducted in America [5, 48] and Thailand [49]. High viral replication increased renal damage may be occurred due to destruction of kidney cells and the nephrons. Viral suppression would improve renal function [22, 50, 51].

Conclusion

The prevalence of CKD in our study based on glomerular filtration rate using 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.

List Of Abbreviations

ABC Abacavir

AIDS Acquired Immune Deficiency Syndromes

ART Antiretroviral Therapy

ARV Anti-retroviral 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

Declarations

Ethics approval and consent to participate

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 and head of the ART clinic. The privacy of personal information was protected and kept confidential. For the purpose of the study, codes were used instead of any personal identifiers. Data were

collected after full written consent had been obtained from each participant. Patients with abnormal test results were linked to consulting physicians for further diagnosis and treatment accordingly.

Consent for publication

Not applicable

Data Availability

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

Competing interests

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

Authors' contribution

GAM: study design, data collection, analysis and interpretation, and manuscript write-up. DDA and WNA: data analysis and interpretation, study design and supervision. All authors have read and approved the final manuscript.

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Figures

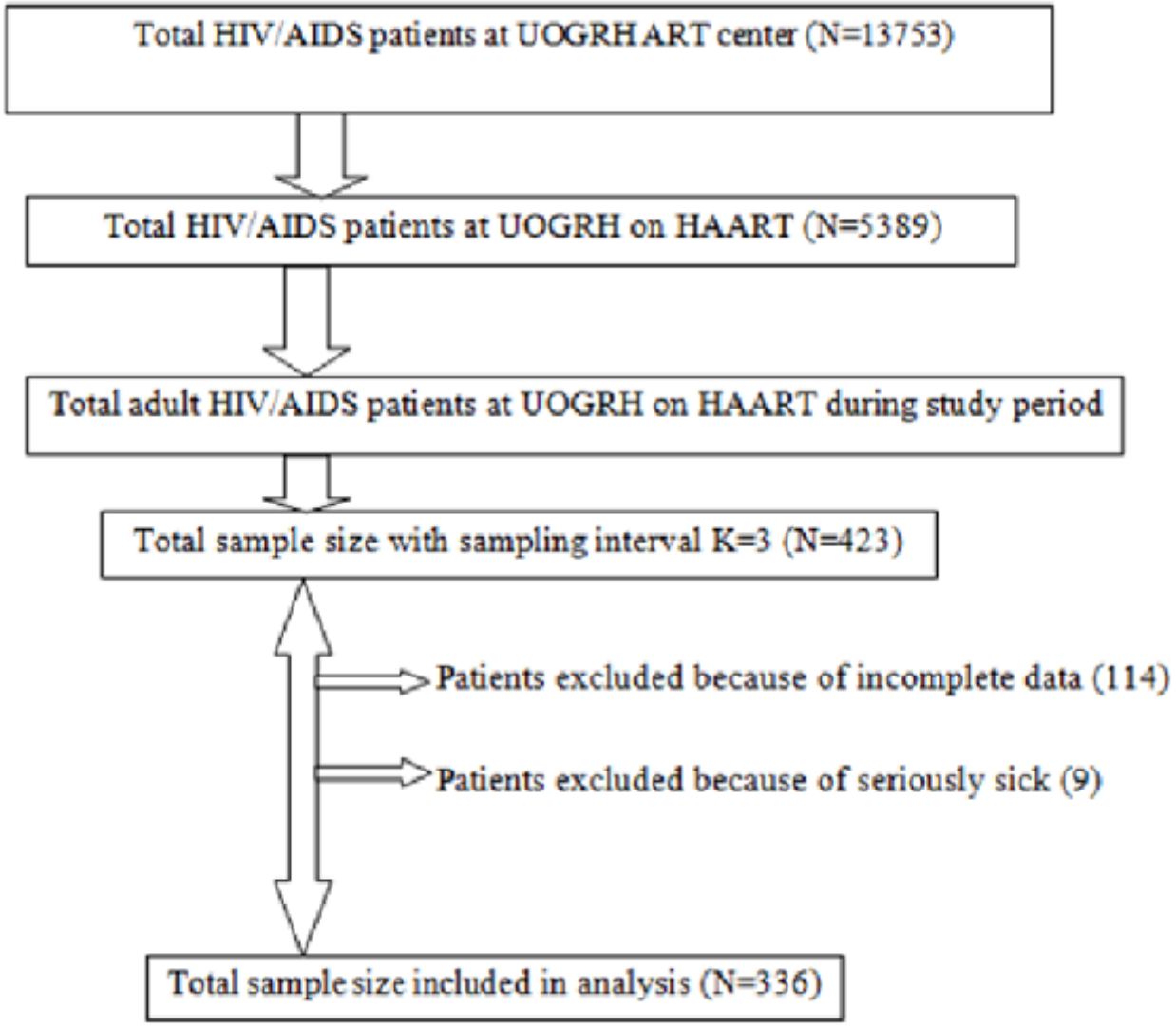

Figure 1

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