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Left Ventricular Systolic Dysfunction in the Antiretroviral Therapy Era: A Call for Comprehensive Cardiovascular Management in People Living with HIV in Ethiopia

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Abstract **Background:** Access to antiretroviral therapy (ART) has transformed HIV infection into a chronic disease. However, cardiovascular disease (CVD) is now a leading cause of morbidity and mortality among people living with HIV (PLWH). This study assessed the prevalence and predictors of left ventricular systolic dysfunction (LVSD) among PLWH in Ethiopia. **Methods:** An institution-based cross-sectional study involving 156 PLWH was conducted. Medical records were reviewed, and a structured questionnaire was used to collect data on demographics, clinical characteristics, medications, and echocardiography findings. Binary logistic regression identified factors associated with LVSD ($p<0.05$). **Results:** LVSD prevalence was 19%, with ischemic heart disease (75%) as the primary cause. Echocardiography revealed abnormalities in 40% of participants, with ischemic heart disease (16.6%) being the most frequent. Dyslipidemia (51.6%) and hypertension (30.8%) were the most common traditional risk factors. After adjusting for covariates, diabetes mellitus (AOR=14.7, p=0.009), age (AOR=12.2, p=0.073), sex (AOR=7.4, p=0.006), presence of cardiac signs (AOR=6.6, p=0.011), duration of HIV illness (p=0.005) and ART exposure (p=0.03), and stage IV HIV (AOR=8.9, p=0.008) were independent predictors of LVSD. **Conclusion:** LVSD is prevalent among PLWH in Ethiopia, with ischemic heart disease being the leading cause. Traditional risk factors and HIV-related factors contribute to LVSD. These findings highlight the need for comprehensive CVD management strategies in PLWH.

Keywords: *HIV, ART, left ventricular systolic dysfunction, People living with HIV (PLWH), cardiovascular disease, ischemic heart disease*

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1. Introduction

HIV/AIDS remains one of the leading public health concerns, with an estimated 38.4 million people infected globally in 2021. According to estimates, new infections have decreased significantly, with 1.5 million persons worldwide contracting HIV, a 32% decrease from 2010. As of the end of 2021, antiretroviral therapy (ART) has been initiated for 75% of patients with HIV infection, and over 650,000 individuals worldwide passed away from AIDS-related illnesses, a 68% decrease from the high of 2 million in 2004 and 1.4 million in 2010. The majority of HIV-positive people reside in low- and middle-income countries, mainly in sub-Saharan Africa [1].

AIDS info Global data on HIV Epidemiology and Response 2021 report states that there are 610,000 adults and children living with HIV in Ethiopia. Ethiopia experienced an improvement in ART coverage from 3% in 2005 to 78% in 2021. During the same period, there was a considerable decline in HIV incidence and AIDS-related deaths [2].

Cardiac disorders were recognized early in the epidemic of acquired immunodeficiency syndrome (AIDS). Patients are now living longer due to effective antiretroviral therapy (ART), and even in low- and

middle-income nations, the infection has turned into a chronic one [3,4,5]. People living with HIV infection (PLWH) now experience cardiovascular disease as a primary source of morbidity and mortality [6].

Despite more prolonged survival due to the widespread use of effective antiretroviral therapy (ART), especially in resource-rich nations, additional comorbidities have also emerged, including hypertension, metabolic abnormalities (hyperglycemia, hyperlipidemia, lipodystrophy), and accelerated atherosclerosis, including coronary artery disease [7,8,9,10,11,12]. As a result, cardiovascular disease has become a leading cause of morbidity and mortality among HIV patients despite the reduced overall mortality [13,14,15]. For instance, the percentage of deaths attributable to heart disease rose from 5 to 10 percent between 1996 and 2006 in a study from the United States of death certificates that included HIV infection [16].

An analysis of the proportionate CVD mortality in HIV-infected people from 1999 to 2013 using data from the Wide-Ranging Online Data for Epidemiologic Research (WONDER) web database from the Centers for Disease Control and Prevention showed that HIV-positive people's overall mortality dropped from 15,739 in 1999 to 8,660 in 2013, however within the same period, CVD deaths rose from 307 to 400. As a result, the relative CVD mortality rate for people living with HIV increased considerably between 1999 and 2013 (p 0.0001) compared to the general population [17].

A wide range of cardiac and vascular manifestations can occur in HIV-infected patients. Although the particular form of heart disease varies depending on the setting, persons with HIV have been documented to have some cardiac abnormalities more frequently than the general population [6,18].

According to various studies, the prevalence of cardiovascular abnormalities among HIV-positive people is variable and ranges from 28% to 73%, including asymptomatic cases. It encompasses a wide range of conditions, which include pericardial effusion, myocarditis, dilated cardiomyopathy, endocarditis, coronary artery disease, pulmonary hypertension, vasculitis, aneurysm development, and cardiac tumors [6,18].

Cardiac conditions affecting PLHIV are more frequently variable across different geographical regions. For instance, PLHIV patients in higher-income countries often have hypertension, CAD, atherosclerosis, and metabolic syndrome. In the Contrary, Sub-Saharan Africa has a comparatively lower prevalence of CAD and is more frequently affected by heart failure (HF) caused by HIV-associated cardiomyopathy and TB-associated pericarditis [15]. Thus, complications of HIV infection are comparable to the illness in the pre-ART era in some resource-constrained situations where medical treatment is limited [8].

Cardiac disorders were recognized early in the epidemic of acquired immunodeficiency syndrome (AIDS). Since patients with HIV infection are now living longer where access to effective antiretroviral therapy (ART) is available even in low- and middle-income nations, the infection has turned into a chronic one. People living with HIV infection (PLWH) now experience cardiovascular disease as a primary source of morbidity and mortality [3,4,5,19].

According to various studies, the prevalence of cardiovascular abnormalities among HIV-positive people is variable and ranges from 28% to 73%, including asymptomatic cases. Although the particular form of heart disease varies depending on the setting, persons with HIV have been documented to have some cardiac abnormalities more frequently than the general population [6,18]. Geographic location, HAART availability, and immunosuppression level are the three variables that affect the frequency and pattern of cardiac symptoms in HIV-positive individuals. Depending on these variables, there are significant differences in the range of cardiac conditions affecting PLWH across different countries. Furthermore, studies suggest that some anti-retroviral medications raise the risk of coronary artery disease [20].

There are two extremes of cardiovascular complications encountered among PLWH: in resource-limited settings where access to HAART is scarce, pericarditis, cardiomyopathy, and pulmonary hypertension are the three most prevalent conditions of HIV-associated cardiac disease. Whereas in affluent countries, where access to HAART is pervasive, atherosclerosis-related cardiovascular illness predominates [21]. Thus, the cardiovascular manifestations of HIV seem to be unpredictable based on the ART coverage and screening strategies across different countries. Yet, no study in our country has assessed LV dysfunction among PLWH. Even though there are no specific studies among PLWH, CVDs are the primary cause of death in Ethiopia, according to a systematic review of the Global Burden of Disease (GBD) 2017 survey data [22].

2. Methods and Materials

An Institution-based cross-sectional observational study was conducted among HIV patients on follow-up at the TASH ART clinic from August 1/2023 to December 30/ 2024 G.C. All adult patients (>18 years old) with HIV infection at the anti-retroviral therapy follow-up clinic of Tikur Anbessa Specialized Hospital during the study period and willing to participate included in the study. Data was collected by reviewing patients' medical records and interviewing them using a structured questionnaire. The questionnaire was written in English and translated into the local language by interviewers. It included sociodemographic characteristics (Age, Gender, Religion, Civil Status, Address, Educational Level, Occupation, Monthly Income), Behavioral factors (current/previous smoking history, number of pack-years), alcohol consumption& some of the clinical characteristics (History of Hypertension, DM, medications (antihypertensives, anti-diabetic &statins). Additional clinical factors, such as CD4 count, duration of HIV illness, time since ART initiation, WHO staging, ART medication regimen, and frequency of ART medication switch, as well as recent anthropometric measurements and recent blood pressure measurements, were extrapolated from the charts of the patients and doctors I care (Electronic medical records).

Echocardiography was extrapolated from the patients' charts and electronic medical records. Standard blood pressure measurement was obtained using a digital sphygmomanometer for participants who did not have

blood pressure records on their charts and electronic medical records. Patients were then categorized as having hypertension or not based on the 2020 ISH/2018 ESC Blood pressure category.

3. Sample Size Determination

The sample size was determined using the formula for a single population proportion, considering a prevalence of 12% of LV systolic dysfunction in PLWH from a previous study.

The sample size was calculated by assuming a Confidence interval of 95%, 5% margin of error, & 10% non-response rate.

$n = (Z\alpha/2)2 \times P(1-p)/ d2$

Final sample size=156

Sampling procedures – A consecutive sampling method was used.

4. Operational Definitions

Heart failure is a clinical syndrome with signs and symptoms brought on by a structural or functional cardiac defect and supported by increased natriuretic peptide levels as well as/or by concrete proof of pulmonary or systemic congestion.

LV Systolic dysfunction is defined as LVEF below 50%.

Hypertensive heart disease is a constellation of changes in the left ventricle, left atrium, and coronary arteries due to chronic blood pressure elevation, which increases the workload on the heart, inducing structural and functional changes. These changes include hypertrophy of the left ventricle, which can lead to heart failure.

Cardiomyopathy is a heterogeneous group of diseases of the myocardium, usually with inappropriate ventricular hypertrophy or dilatation.

Ischemic heart disease: myocardial impairment due to an imbalance between coronary blood flow and myocardial requirement caused by a change in the coronary circulation. **Atherosclerotic cardiovascular disease includes:**

- Coronary heart disease (CHD) manifested by fatal or nonfatal myocardial infarction (MI), angina pectoris, and heart failure.
- Cerebrovascular disease manifested by fatal or nonfatal stroke and transient ischemic attack.

5. Statistical Analysis

Descriptive statistics were used to summarize the baseline demographic characteristics, clinical characteristics & cardiovascular risk factors. The bivariate/univariate binary logistic regression analysis was performed on each independent variable with LV systolic dysfunction. Finally, multivariable logistic regression analysis was done after adjusting for other covariates to show the association between the dependent & independent variables.

6. Result

Sociodemographic characteristics of the study participants

Of 156 patients included in the study, fifty-seven percent of the study participants were male, and 26.9% were in the age group of 40-49 years. Forty-three percent of the study participants completed primary education, and 55.8% live in Addis Ababa. Almost half of the participants were married, and 32.1% were non-employed.

Table 1. The sociodemographic characteristics of study participants having HIV infection at the anti-retroviral therapy (ART) follow-up clinic of Tikur Anbessa Specialized Hospital, 2023

Variable	frequency	Percent
Age of the study participants		
Male	89	57.1
Female	67	42.9
Age in years		
18-29	17	10.9
30-39	39	25.0
40-49	42	26.9
50-59	33	21.2
>=60	25	16.0
Level of education		
Illiterate	32	20.5
Primary	33	21.2
Secondary	67	42.9
collage and above	24	15.4
Residence		
Addis Ababa	87	55.8
Out Of Addis Ababa	69	44.2
Marital status		
Married	77	49.4
Single	44	28.2
Divorce	17	10.9
Widowed	18	11.5
Current occupation		
Government Employee	30	19.2
Private sector Employee	27	17.3
Retired	32	20.5
Self-employed	12	7.7
Student	5	3.2
Non-Employed	50	32.1

HIV AIDS related characteristics of the study participants

The mean duration of HIV illness was 9.57 years, and the mean duration of ART was 9.78 years. Almost sixty percent of the study participants had ART shifts. Most (94.2%) were on the first-line regimen, of which 3TC+TDF+DTG accounted for 66.6%. Over forty percent of the participants had>499 CD4 count, and 35.3% had clinical stage 1 illness.

Characteristics of cardiovascular clinical manifestations

Thirty-seven percent (n=58) of the study participants had cardiac disease symptoms; dyspnea accounts for 79.3%, followed by orthopnea and cough. Twenty-five percent of the participants also had a clinical sign of cardiac disease, and from those cardiac signs, edema accounts for 38.5%, followed by cardiac murmur. Fifty-

eight percent of the participants had risk factors for cardiac disease, and from those risk factors, dyslipidemia accounts for 47(51.6%), followed by hypertension 28(30.8%) and DM 17(18.7%). Most participants (55.7%) had FBS of <100, and 26.6% had FBS between 100-125. Most participants (44.9%) had a normal body mass index.

The prevalence of left ventricular dysfunction among PLWHIV.

In this study, the prevalence of left ventricular dysfunction among people living with HIV was 19%, as shown in the figure below. Ischemic heart disease contributes to 75% of LV systolic dysfunction, followed by DCM 20% and CRVHD 3%.

The pattern of cardiac disease among study participants

Almost 16 percent of the study participants had ischemic heart disease followed by hypertensive heart disease 11(7%). Cardiomyopathy accounts for nearly 4% (Figure 1).

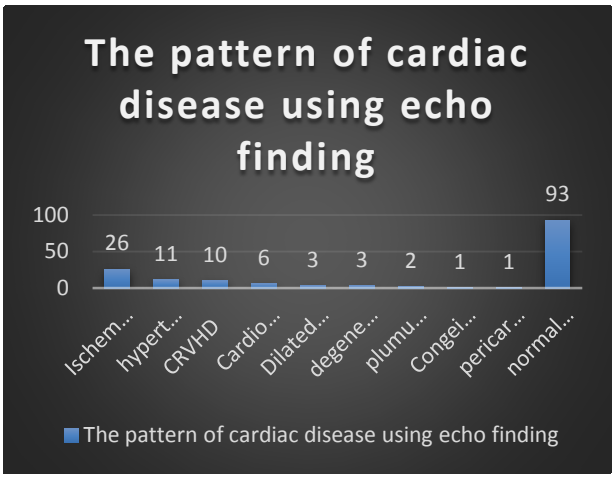

Figure 1. The pattern of cardiac disease among people living with HIV, 2023

Table 2. HIV ADIS-related characteristics of the study participants

Variable	Frequency	Percent
Duration of HIV in years (mean ±SD)	9.51±5.05	
Duration waiting in ART drug (Mean ±SD)	9.78±8.38	
Shift of ART regimen		
Yes	93	59.6
No	63	40.4
Types of ART regimen		
First line	147	94.2
Second line	7	4.5
Third line	2	1.3
Primary ART regimen		
Baseline CD4 count		
≤200	42	26.9
201-499	51	32.7
>499	63	40.4
Clinical stage		
stage I	55	35.3
stage II	34	21.8
stage III	37	23.7
stage IV	30	19.2

Table 3. Characteristics of cardiovascular clinical manifestations of the study participants

Variable	frequency	Percent
Symptom-related cardiac disease		
Yes	58	37.2
No	98	62.7
The specific types of symptoms (n=58)		
Dyspnea	46	79.3
Body swelling	6	10.3
cough	7	12.1
Orthopnea	9	15.5
Others	11	18.9
Clinical signs of cardiac disease		
Yes	39	25
No	117	75
The specific types of cardiac disease sign (n=39)		
Cardiac murmur	9	23.1
Edema	15	38.5
Rales	6	15.4
Raised JVP	1	2.6
Hepatomegaly	2	5.1
Others	11	28.2
Presence of cardiac risk factor		
Yes	91	58.3
No	65	41.7
The list of cardiovascular risks (n=91)		
Hypertension	28	30.8
Dyslipidemia	47	51.6
DM	17	18.7
Alcoholic	13	14.3
Obesity	2	2.2
Smoking	6	6.6
Others	3	3.3
Fasting blood sugar		
<100	90	57.7
100-125	42	26.9
>125	24	15.4
Body mass index		
<18.5	36	23.1
18.5-24.9	70	44.9
25-29.9	50	32.1

Table 4. One-way Nova test on HIV duration

Variable	Left ventricular dysfunction		p-value
	Yes	No	
Duration of illness	11.97±4.25	8.95±5.07	0.005*
Duration of ART treatment	10.86±4.08	9.54±5.04	0.03*

*Statistically significant

One-way nova test on HIV duration

The mean duration of illness among left ventricular dysfunction was 11.97, while for those without LV dysfunction was 8.95, and the difference was significant. That means that as the duration of illness increases, the chance of left ventricular dysfunction is substantial.

Factors determining left ventricular dysfunction

Odd ratio and 95%CI were used to measure the strength of association between the independent variable and left ventricular dysfunction. Accordingly, sex, presence of a cardiac symptom, sign, DM, FBS, CD4 count, and clinical

stage were associated with left ventricular dysfunction by bivariate logistic regression. The multivariate logistic regression revealed that male study participants had 7.4 folds increase in left ventricular dysfunction compared to females (AOR=7.4, 95%CI=1.78, 30.38) and study participants whose age ≥60 years had 12.2 folds increase in left ventricular dysfunction compared to the age of 18-29 years (AOR=12.2, 95%CI=1.79, 87.20). The study participant having cardiac signs had 6.6 folds increase in left ventricular dysfunction compared to those without clinical signs (AOR=6.6, 95%CI=1.54, 28.15), and those participants having DM had 14.7 folds increase in left ventricular dysfunction compared to their nondiabetic counterparts (AOR=14.7, 95%CI=1.93, 112.21). Study participants with clinical stage IV HIV had an 8.9-fold increase in left ventricular dysfunction compared to clinical stage I HIV individuals (AOR=8.9, 95%CI=1.77, 44.46).

Table 5. The bivariate and multivariate logistic regression of association between the independent variable and left ventricular dysfunction among PLWHIV, TASH, 2023. (* statistically significant)

Variable	Left ventricular dysfunction		COR with 95%CI	P-value	AOR with 95% CI
	Yes	No			
Sex					
Male	23	66	3.5(1.35, 9.29)	0.006*	**7.4(1.78, 30.38)**
Female	6	61		1	
Age in years					
18-29	1	16		1	
30-39	7	32	3.5(0.39, 30.95)	0.050	14.8(1.0, 29.14)
40-49	8	34	3.8(0.43, 32.71)	0.080	10.6(0.75, 48.48)
50-59	5	28	2.9(0.31, 26.66)	0.379	3.6(0.21, 61.56)
≥60	8	17	7.5(0.84, 67.15)	0.073	**12.2(1.79, 87.20)**
Presence of cardiac symptom					
Yes	22	36	7.9(3.12, 20.22)	0.459	18(0.38, 8.75)
No	7	91		1	
Presence of cardiac sign					
Yes	15	24	4.6(1.96, 10.79)	0.011*	**6.6(1.54, 28.15)**
No	14	103		1	
DM					
Yes	7	10	3.7(1.28, 10.83)	0.009*	**14.7(1.93, 112.21)**
No	22	117		1	
FBS					
<100	12	78		1	
100-125	8	34	1.5(0.57, 4.08)	0.598	1.5(0.35, 6.11)
>125	9	15	3.9(1.39, 10.88)	0.342	0.45(0.09, 2.36)
BMI					
<18.5	13	23	4.1(1.39, 12.34)	0.116	3.8(0.72, 20.38)
18.5-24.9	10	60	1.2(0.41, 3.62)	0.943	0.95(0.21, 4.26)
25-29.9	6	44		1	
CD4 count					
≤200	11	31	2.4(0.89, 6.71)	0.228	2.5(0.57, 10.86)
201-499	10	41	1.7(0.61, 4.62)	0.376	1.9(0.46, 7.84)
>499	8	55		1	
Clinical staging of HIV					
I	7	48			
II	7	27	1.8(0.56, 5.61)	0.135	3.2(0.69, 14.95)
III	2	35	0.39(0.08, 2.00)	0.938	1.1(0.13, 9.11)
IV	13	17	5.2(1.79, 15.33)	0.008*	**8.9(1.77, 44.46)**

7. Discussion

In our study, echocardiographic abnormalities were observed in 40% of the participants. We found a lower prevalence of cardiac abnormalities compared to studies conducted in Cameroon and India, with 100% and 74%, respectively [23,24]. This difference can be partly attributed to the exclusion of asymptomatic patients and the inclusion of admitted patients in those studies. However, our findings were comparable to findings in other studies [25,26].

We also found Significant cardiac abnormalities and ischemic heart disease, accounting for 16.6%, followed by hypertensive heart disease at 7%. DCM accounts for 3.8%. This differs from studies conducted in India, Ghana, Mozambique, and Cameroon, where pulmonary hypertension, Rheumatic heart disease, and pericardial effusion were the predominant findings. [23,24,25,26]. These discrepancies may be due to differences in sociodemographic and HIV/AIDS-related characteristics of the study participants, including young study participants. The majority had a very low CD4(<200) count compared to our study population, where the

majority (40%) had CD4≥200, and most of the participants were aged> 40 years.

Left ventricular systolic dysfunction was identified in nearly one-fifth of the patients, accounting for 19%. 72% of these cases were observed in individuals over 40, with a relatively higher prevalence in men. This discovery is comparable with a study done in Ghana, which reported a left ventricular systolic dysfunction prevalence of 17.5% but was lower than studies done in India (26%) and Cameroon (37%) [23,25]. This difference may be attributed to various factors, including more advanced clinical stages, lower CD4 count, the inclusion of ART-naive, and admitted patients in those studies[4,23,25].

Ischemic heart disease (IHD) emerged as a significant contributor, accounting for 75% of LV dysfunction, followed by DCM at 20% of the cases of LV dysfunction in our study.

Sex and age above 60 were a significant predictor of LV systolic dysfunction. Male participants had 7.4 times higher odds of experiencing LV systolic dysfunction compared with female counterparts. Additionally, individuals aged above 60 years demonstrated 12.2 times higher odds of having LV systolic dysfunction compared to younger study participants (age 18-29 years). This is consistent with other studies [27,28,29].

51.6% of our patients had dyslipidemia, and 30.8% had established hypertension. The proportion of these traditional risk factors was also similar in other studies [30,31,32,33]. Different studies reported dyslipidemia and hypertension as the main risk factors for CVD among individuals with HIV [34,35,36,37]. However, we did not find a significant association between dyslipidemia, hypertension, and left ventricular dysfunction. This discrepancy might be because most of our patients were screened early and managed for these traditional risk factors. We found that the prevalence of DM among those with LV dysfunction was 31.8% and 18.7% among the study participants. Our findings indicated a higher prevalence of DM than studies in other parts of Ethiopia, such as Harar, Gondar, and Jimma, 7.1%, 8%, and 6.4%, respectively. However, it is consistent with other studies [30,31,33,38,39,40].

The association between DM and CVD is well-established in individuals with HIV (38-40). Worm et al.'s study conclusively demonstrated DM as a commonly found significant risk factor for CVD in HIV-infected patients [12]. This study revealed that individuals with HIV and diabetes exhibited a 14.7 times higher likelihood of developing LV dysfunction as compared to non-diabetic counterparts.

In our study, a significant proportion of participants with LV systolic dysfunction had a baseline CD4 count above 200 (N=18,62%). Most participants were on first-line regimens (N=148, 94%), 3TC+TDF+DTG accounting for two-thirds of the regimens. Our study highlighted a significant association between the duration of ART exposure and the duration of HIV illness with LV systolic dysfunction. The mean duration of HIV illness among those with left ventricular dysfunction was 11.97 years. In contrast, for those without LV systolic dysfunction, it was 8.95 years. Individuals in clinical stage 4 HIV exhibited an 8.9-fold increase in the likelihood of developing left ventricular dysfunction compared to those in clinical stage 1 HIV. These findings are consistent with other studies [41,42,43].

Strengths and limitations of the study

Our study offers valuable insights into cardiovascular health in people living with HIV (PLWH) in Ethiopia. However, some limitations require consideration. Firstly, missing viral load data for some participants hinders a complete picture of their viral status. Secondly, using the most recent CD4 count, regardless of the timeframe, may only partially capture changes in immune function over time. Additionally, challenges in obtaining echocardiograms for those with prior procedures might limit the accuracy of cardiac assessments. Finally, conducting the study within a single institution restricts the generalizability of the findings to the broader population, as healthcare access, demographics, and other factors can vary significantly across different settings. Despite these limitations, our study provides a strong foundation for future research. By addressing these constraints in upcoming studies, researchers can gain a deeper understanding of cardiovascular risks in PLWH and ensure the applicability of findings to diverse populations and healthcare environments.

Abbreviations

ART - Antiretroviral Therapy
CVD - cardiovascular disease
DM - Diabetes Mellitus
DTG - Dolutegravir
FBS - Fasting Blood Sugar
HAART - Highly Active Antiretroviral Therapy
HIV - Human Immunodeficiency Virus
IHD - ischemic heart disease
LVEF - Left Ventricular Ejection Fraction
LVSD - Left Ventricular Systolic Dysfunction
PLWH - People Living With HIV
TDF - Tenofovir Disoproxil Fumarate
3TC - Lamivudine
WHO - World Health Organization

Declarations

Author Contributions: conceptualization, Methodology, Investigation, Analysis, and Writing of the manuscript- Abinet Tekalign Manyahilal, Dufera mekonnen, Amanuel Gebreselassie Tesfaye

Methodology, Data curation, Drafting, Interpretation, and Supervision and edition of the manuscript- Gebeyehu Tessema Azibte, Zekarias Seifu Ayalew, Biruk Abate legesse, Samuel Tsehaye Gebremedhin

All authors revised the manuscript and have approved the final version of the manuscript.

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Ethical clearance

Institutional Review Board Statement: The study was conducted by the Declaration of Helsinki and approved by the Institutional Review Board of Addis Ababa University, College of Health Sciences.

Informed Consent Statement: Informed consent was

obtained from all subjects involved in the study.

Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article.

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Conflicts of Interest: The authors declare no conflicts of interest.

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