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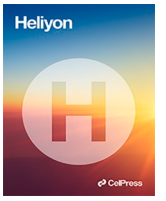

Research article

Liver function tests, CD4$^+$ counts, and viral load among people living with HIV on dolutegravir compared to efavirenz-based cART; a comparative cross-sectional study

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ABSTRACT

Background: Recently, dolutegravir-based therapy has become the first-line treatment when compared to others. However, dolutegravir-associated side effects in the liver and levels of efficacy haven't been addressed yet in underdeveloped countries such as Ethiopia.
Objective: The purpose of this study was to compare liver function tests, CD4$^+$ counts, and viral load among people living with HIV on dolutegravir and efavirenz-based antiretroviral regimens at Debre Markos Comprehensive Specialized Hospital in Northwest Ethiopia.
Methods: An institutional-based comparative cross-sectional study was carried out from May 20 to July 10, 2020. An equal number of dolutegravir and efavirenz-prescribed patients (n = 53 each) for 6 months and above were included, and a judgmental sampling technique was used. A comparison of categorical and continuous parameters was analyzed with chi-square and an independent *t*-test, respectively, using SPSS version 26. A multivariable logistic regression was conducted and considered statistically significant at a p-value of <0.05.
Results: The magnitude of liver enzyme (AST/ALT) abnormalities was 22.4 % (12/53) and 30.2 % (16/53) among dolutegravir- and efavirenz-prescribed patients, respectively. The dolutegravir group had significantly higher mean CD4$^+$ counts than the efavirenz group (589.40 ± 244.38 vs. 450.64 ± 203.54 cell/mm^3; p = 0.002). The efavirenz group had a significantly higher mean viral load than the dolutegravir group (783.83 ± 476.82 vs. 997.98 ± 439.11 cp/ml; p = 0.032). There was a statistically insignificant difference in AST (p = 0.709) or ALT (p = 0.687) between dolutegravir and efavirenz-based regimens. The multivariable logistic regression analysis revealed that BMI ≥25 kg/m^2 was associated with liver enzyme abnormalities (AOR = 6.60, 95 % CI: 1.17, 42.82).
Conclusion: A dolutegravir-based regimen was more likely to result in patients achieving higher efficacy for viral suppression and a CD4$^+$ count increase. Although the differences were statistically insignificant, the mean AST and ALT levels were marginally higher in efavirenz-treated groups than in dolutegravir-treated groups.

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1. Introduction

The human immunodeficiency virus (HIV) is a retrovirus that affects immune system cells and causes a decrease in $CD4^+$ T-cell count and immunological function, which can lead to life-threatening opportunistic infections, HIV-related malignancies, and acquired immunodeficiency syndrome (AIDS) [1]. Drugs targeting various viral replication pathways have evolved over the last 30 years, allowing for the development of new antiretroviral treatments (ARTs) [2]. The World Health Organization (WHO) currently recommends first-line combination antiretroviral therapy (cART) for people living with HIV (PLWH) who have not previously received treatment. This treatment should comprise one of the following types of drugs: integrase strand transfer inhibitors (INSTIs), boosted protease inhibitors (PIs), or non-nucleoside reverse transcriptase inhibitors (NNRTIs). In addition to one of these classes, the cART regimen should contain two nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) [3–6].

In the past, efavirenz (EFV), a NNRTI, was commonly used as the preferred first-line ART for PLWH who had not received prior treatment [7]. However, several studies have reported that this combination can lead to drug resistance, adverse side effects, and drug interactions in most patients [8]. Consequently, dolutegravir (DTG), an INSTI, is now being recognized as the preferred first-line ART [9]. The 2019 guidelines from WHO recommend a DTG-based ART (50 mg) as the preferred first-line ART, with an EFV-based ART (400 mg) as a substitute [10]. This recommendation is also applicable in Ethiopia, where DTG-based ART is indicated as the primary antiretroviral medication according to the current ART guidelines [11].

In several randomized controlled trials, it has been demonstrated that the regimen containing DTG has the ability to lead to substantial reductions in HIV ribonucleic acid (RNA) levels and increases in $CD4^+$ cell counts when compared to the regimen containing EFV [12,13]. In a study conducted in Brazil, it was found that over 90 % of individuals who started treatment with a DTG-based regimen achieved viral suppression (VS) (<50 copies/ml) within the first year of treatment. This proportion was higher compared to the 84 % rate observed for those on the EFV-base regimen. Compared to EFV-based ART, DTG-based ART is linked to higher improvements in $CD4^+$ T-cell count [14,15]. However, in the SPRING-1 clinical study, both DTG and EFV-based cART led to a comparable increase in $CD4^+$ T-cell counts [16].

During the time of highly active antiretroviral therapy (HAART), liver damage is frequent in PLWH [17]. Liver disease in PLWH may result from the HIV infection itself, ART, or comorbidities, including co-infection with the hepatitis virus [18]. It is challenging to determine the impact of each drug in a HAART regimen on hepatotoxicity [19]. In recent years, there have been a small number of reports linking the use of INSTI with liver enzyme elevation [20–23]. In the SINGLE clinical study, discontinuation of the study regimen due to liver toxicity occurred less frequently in the group receiving DTG compared to the group receiving EFV [15]. Nevertheless, in extensive clinical studies, treatment with DTG led to alanine transaminase (ALT) enzyme elevations exceeding three times the upper limit of normal (ULN) in 2 % of patients [24].

It is thought that the prolonged utilization of ART may contribute to metabolic abnormalities, including liver damage and treatment failure. Thus, ART-related metabolic abnormalities lead to the discontinuation of ART in patients with therapy. Aside from clinical studies, little is known about the liver toxicity of DTG-based therapy [25] and, to the best of our knowledge, there is no published data available that has been done, and no sample data reported has compared the effects of DTG and EFV-based therapy on hepatotoxicity, viral suppression, and immune recovery in Ethiopia as well as in the study area. Therefore, this study aimed to compare liver function tests, $CD4^+$ counts, and viral loads of PLWH on DTG and EFV-based therapy and to identify factors associated with liver enzyme abnormalities in patients with HAART.

2. Methods

2.1. Study area and period

The study was carried out at Debre Markos Comprehensive Specialized Hospital (DMCSH) from May 20 to July 10, 2020. DMCSH is situated in the Debre Markos City Administration, which is located 300 km from Addis Ababa, the country's capital, and 264 km from Bahir Dar, the capital city of Amhara Regional State. DMCSH serves around 3.5 million people in its catchment area. Since 2005, it has provided comprehensive HIV/AIDS care and support services to over 3716 adults undergoing follow-up. Along with general healthcare services, DMCSH offers HIV/AIDS interventions such as diagnosis, treatment, and monitoring.

2.2. Study design and study population

An institution-based comparative cross-sectional study was carried out among PLWH on DTG and EFV-based ART. We enrolled all ART-naive PLWH with the age of 18 years and above who were on DTG or EFV-based therapy (along with two NNRTI/NRTI) for over 6 months. We excluded patients with cognitive impairment, immediate intensive care requirements, pregnant and breastfeeding women, and those known to have chronic liver disease, hepatitis B virus, and hepatitis C virus for both groups.

2.3. Sample size determination and sampling technique

The sample size was determined using Epi Info7 version 7.2.2.2 by taking the prevalence of hepatotoxicity of 2 % among DTG and 25 % among EFV-based ART from the previous study [15,26]. DTG to EFV-based regimen ratio of 1:1, 95 % confidence interval (CI), power of 90 %, and it becomes 106. The study included 53 participants in both the EFV and DTG-based groups. The judgmental

sampling method was applied; all consecutive DTG and EFV-based prescribed individuals who met the inclusion criteria were included.

2.4. Data collection and laboratory analysis

A semi-structured interviewer-administered questionnaire adapted from the WHO step-wise approach to chronic disease risk factor surveillance questions [27,28] was used for data collection. After written consent was obtained, we collected sociodemographic characteristics such as age, gender, educational level, marital status, occupation, and residence. The checklist was used to collect clinical data from the patient's medical record, including baseline (AST/ALT, $CD4^+$ T-cell counts, and VL), current regimen type, duration of HIV and ART, and WHO clinical stage of AIDS. Besides, anthropometric characteristics (weight and height) were collected from the study participants. Two oriented nurses from the DMCSH ART clinic gathered the data. Finally, each participant provided about nine (9) milliliters of fasting venous blood. Blood samples were accurately labeled in vacutainer tubes and promptly sent to the laboratory for examination. Liver function tests [aspartate transaminase (AST)/ALT) enzyme determination] were analyzed by the BS-200 Chemistry Analyzer (Diamond Diagnostics, USA) after being centrifuged for 10 min at 10,000 relative centrifugal force. Samples for CD4 T-cell count (cells/μl) were collected in ethylenediaminetetraacetic acid (EDTA) vials and analyzed using a Becton Dickson flow cytometer. Viral load (copies/mL) samples were collected in EDTA vials and examined with the COBAS® Ampliprep/COBAS® TaqMan polymerase chain reaction (PCR) analyzer. Experienced medical laboratory technologists collected the blood, separated the serum, and carried out the laboratory analysis.

2.5. Data processing and analysis

Data were entered, and analysis was done by the statistical package for the social sciences (SPSS) version 26.0 software. Data are presented as frequency, percentage, and mean ± standard deviation (SD) for descriptive data, while chi-square tests for categorical variables and independent t-tests for continuous variables were used to compare groups. The normal distribution of data was checked by the Shapiro-Wilk normality test and visual inspection of the histogram and Q-Q plots. We used logistic regression to identify factors associated with liver enzyme abnormalities. Factors that had a p-value <0.25 in the bivariable logistic regression were included in the multivariable logistic regression. The adjusted odds ratios (AOR) were determined, and a *P*-value of <0.05 was considered statistically significant. The Hosmer and Lemeshow tests were performed to evaluate the goodness of fit of the model.

2.6. Data quality control and management

One supervisor oversaw the data collection process, and the data collectors received a half-day orientation. The questionnaire was translated into Amharic and then back-translated into English by experts to ensure consistency. A pretest of the questionnaire was carried out at Debre Markos Health Center. Liver function tests, $CD4^+$ counts, and VL were collected following standard operation procedures (SOP), and analysis was performed after running quality control samples. The collected data were reviewed daily to ensure completeness.

2.7. Operational definitions

Abnormal liver enzyme: an increase in ALT or AST of grade 1, 1.25 X ULN (upper limit of normal). Grade 2: 2.5 X ULN for patients with baseline ALT in the normal range, or 2.5 X baseline value if the baseline value was higher than the ULN. Grade 3: >5 X ULN for patients with baseline ALT or AST in the normal range, or >3.5 X baseline value if the baseline value was higher than the ULN. Grade 4: >10 X ULN for patients with baseline ALT or AST in the normal range, or >5 X baseline value if the baseline value was higher than the ULN. Upper-limit normal values were defined as ALT = 32 IU/L and AST = 32 IU/L for women and ALT = 41 IU/L and AST = 41 IU/L for men [29,30].

Anthropometric measurements: The study participants' weight was assessed with a standard balance, and their heights were assessed using a height-measuring device attached to the balance. Then, the body mass index (BMI) was determined by dividing weight (kg) by height (m^2). According to the WHO classification, BMI falls into four categories: underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (>25.0–29.9 kg/m^2), and obesity (≥30 kg/m^2) [31].

Efficacy: measured by the proportion of patients with VS and the change in $CD4^+$ cell count from baseline [32].

Severe hepatotoxicity: ALT/AST levels >5 times the ULN [33] or grade 3 or 4 ALT/AST [34,35].

Viral suppression: defined as a VL of 1000 cp/mL after 6 months of ART initiation [36].

3. Results

3.1. Socio-demographic and clinical characteristics of the respondents

A total of 106 individuals, 53 DTG and 53 EFV-based treated PLWH, participated in this study. The average age of DTG and EFV-treated participants was 37.85 ± 11.26 and 31.43 ± 6.82 years, respectively. About 30.2 % (16/53) of DTG and 75.5 % (40/53) of EFV-based prescribed participants were females. The clinical characteristics extracted from the patients' medical records revealed that the normal baseline $CD4^+$ counts at ART initiation, about 225 ± 119.97 cell/mm^3 and 253.85 ± 110.50 cells/mm^3, were the mean

$CD4^+$ counts of DTG and EFV-prescribed participants, respectively, whereas about 8119.97 ± 4917.94 cp/ml and 7378.08 ± 5139.55 cp/ml were the mean VL of DTG and EFV-treated patients, respectively (Table 1).

Significant variations were seen in sex, age, and duration of treatment among the groups tested ($P < 0.05$). PLWH on DTG were older (37.85 years vs. 31.43 years; $p = 0.001$), male (69.8 % vs. 24.5 %; $P < 0.001$), and had a shorter duration on ART (8.51 months vs. 14.58 months; $P < 0.001$) than those on EFV. Otherwise, there were no significant variations among DTG and EFV-prescribed participants in socio-demographic and clinical characteristics ($P > 0.05$) (Table 1).

3.2. Liver enzyme abnormalities

After initiating ART, about 22.4 % (12/53) of DTG and 30.2 % (16/53) of EFV-prescribed participants had liver enzyme abnormalities (AST/ALT). Hepatotoxicity grade 3 in AST/ALT level was found to be 5.7 % (3/53) of DTG and 9.4 % (5/53) of EFV-prescribed participants. About 5.7 % (3/53) of DTG-treated and 13.2 % (7/53) of EFV-treated patients had hepatotoxicity grade 2. Hepatotoxicity grade 1 was found in 11.3 % (6/53) of DTG-based and 7.5 % (4/53) of EFV-prescribed participants. The independent *t*-test found a statistically insignificant difference between the mean AST/ALT levels in the two groups (Table 2).

3.3. Immunologic and virologic outcomes

Among the total study participants, the median increase in $CD4^+$ counts for DTG and EFV-based prescribed study participants was 331 cells/mm^3 and 281 cells/mm^3, respectively ($p = 0.008$). An independent *t*-test revealed that mean $CD4^+$ counts were found to be significantly higher in DTG-based (589.40 ± 244.38 cells/mm3) compared with EFV-based (450.64 ± 203.54 cells/mm3) prescribed patients ($p = 0.002$). Also, patients on DTG-based regimens had a lower mean VL (783.83 ± 476.82 cp/ml) compared with EFV-based regimens (997.98 ± 439.11 cp/ml) ($p = 0.032$) after excluding viral load below the limit of detection (Table 2).

3.4. Factors associated with liver enzyme abnormalities

In bivariate logistic regression, residence, educational level, marital status, occupation, baseline liver enzyme level, HIV infection duration, level of BMI, ART duration, current VL, and treatment regimen type were found to be associated with current liver enzyme

Table 1
Socio-demographic and clinical characteristics of PLWH on DTG and EFV-based therapy at DMCSH, Northwest Ethiopia, 2020 (n = 106).

Variables	Category	Regimen type		p-value
		DTG (n = 53)	EFV (n = 53)	
Age (years) mean ± (SD)		37.85± (11.26)	31.43± (6.82)	0.001[a]
Sex	Male	37 (69.8)	13 (24.5)	p < 0.001[a]
	Female	16 (30.2)	40 (75.5)	
Education level	No education	16 (30.2)	14 (26.4)	0.805
	Primary	11 (20.8)	14 (26.4)	
	Secondary	16 (30.2)	13 (24.5)	
	College & above	10 (18.9)	12 (22.6)	
Marital status	Single	12 (22.6)	7 (13.2)	0.456
	Married	18 (34.0)	25 (47.2)	
	Divorced	15 (28.3)	14 (26.4)	
	Widowed	8 (15.1)	7 (13.2)	
Residence	Urban	28 (52.8)	36 (67.9)	0.112
	Rural	25 (47.2)	17 (32.1)	
Occupation	Farmer	13 (24.5)	6 (11.3)	0.152
	Merchant	6 (11.3)	14 (26.4)	
	Employed	12 (22.6)	13 (24.5)	
	Labor worker	14 (26.4)	10 (18.9)	
	Other	8 (15.1)	10 (18.9)	
HIV infection duration mean ± (SD) (months)		25.51 ± 34.29	16.98 ± 12.73	0.093
ART duration mean ± (SD) (months)		8.51 ± 2.29	14.58 ± 6.60	P < 0.001[a]
WHO stage	1	31 (50.0)	22 (41.5)	0.193
	2	12 (22.6)	19 (35.8)	
	3	10 (18.9)	12 (22.6)	
BMI (kg/m^2)	<18.5	7 (13.2)	9 (17.0)	0.291
	18.5–24.99	34 (64.2)	38 (71.7)	
	≥25	12 (22.6)	6 (11.3)	
Baseline AST (IU/L)		30.87 ± 15.28)	35.21 ± 15.57	0.151
Baseline ALT (IU/L)		31.66 ± 13.56	32.0 ± 13.66	0.898
Baseline CD4 cells/mm^3 mean± (SD)		225 ± 119.97	253.85 ± 110.50	0.260
Baseline viral load at ART initiation		8119.870 ± 4917.94	7378.08 ± 5139.55	0.449

DTG, Dolutegravir; EFV, Efavirenz; LFT, liver function tests; BMI, body mass index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CD4, cluster of differentiation 4; HIV, human immunodeficiency virus; ART, antiretroviral therapy; SD, standard deviation; IU, international units.

[a] = P−value <0.05.

Table 2
Comparison of liver enzymes, CD4 count, and HIV viral load using an independent *t*-test between PLWH on DTG and EFV at DMCSH, Northwest Ethiopia, 2020 (n = 106).

Variables	Study group	Number	Mean ± SD	Mean difference	95%CI	p-value
AST (IU/L)	EFV- based	53	56.04 ± 34.31	6.25	−9.35–21.84	0.429
	DTG- based	53	49.79 ± 45.83			
ALT (IU/L)	EFV- based	53	56.47 ± 34.11	7.25	−7.14–21.85	0.321
	DTG- based	53	49.25 ± 40.24			
$CD4^+$ counts (cells/mm^3)	EFV- based	53	450.64 ± 203.54	−138.76	−225.38-(-52.12)	0.002[a]
	DTG- based	53	589.40 ± 244.38			
HIV viral load (cp/ml)	EFV- based	46	997.98 ± 439.11	214.15	18.89–409.40	0.032[a]
	DTG- based	41	783.83 ± 476.82			

HIV, human immunodeficiency virus; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SD, standard deviation; IU, international units; DTG, dolutegravir; EFV, efavirenz; cp/ml, copies per litre.

[a] = P−value <0.05.

abnormalities at a *P*-value <0.25. These were further analyzed by multiple logistic regression, and the result revealed that BMI ≥25 kg/m^2 (AOR = 6.60, 95 % CI: 1.12–42.82) was identified as a determinant of liver enzyme abnormalities (Table 3).

4. Discussion

This study was aimed at comparing liver function tests, $CD4^+$ counts, and viral load among PLWH on DTG and EFV-based therapy in a clinical setting. The median increase in $CD4^+$ cells from baseline with DTG was +331 cells/mm^3, which was significantly higher than the +281 cells/mm^3 in the EFV group (p = 0.008). These findings were in line with a SINGLE clinical study showing that DTG-based treatment led to significantly greater median increases in $CD4^+$ counts than EFV (+267 vs. +208 cells/mm^3; p < 0.001) [15]. Contrary to our study, in the SPRING-1 study, both drugs, DTG and EFV, achieved a comparable median increase in $CD4^+$ counts from baseline (+338 vs. +301 cells/mm^3; p = 0.155) [16]. We found that the mean $CD4^+$ counts of DTG-treated subjects were higher than those treated with EFV. Patients treated with DTG (589.40 ± 244.38 cells/mm^3) had a significantly elevated mean $CD4^+$ cell count in comparison to patients treated with EFV (450.64± cells/mm^3). In line with this study, Snedecor et al. also revealed that the rise in

Table 3
Factors associated with liver enzyme abnormalities in PLWH on HAART at DMCSH, Northwest Ethiopia, 2020 (n = 106).

Variables	Category	ALT/AST level		COR	AOR	p-value
		Normal	Abnormal			
Residence	Urban	44 (68.8)	20 (31.3)	1	1	
	Rural	34 (81.0)	8 (19.0)	1.93 (0.76–4.91)	1.20 (0.21–6.88)	0.836
Educational level	No education	25 (83.3)	5 (16.7)	1	1	
	Primary	18 (72.0)	7 (28.0)	0.51 (0.14–1.88)	0.40 (0.05–3.06)	0.380
	Secondary	23 (79.3)	6 (20.7)	0.77 (0.21–2.86)	0.48 (0.06–3.94)	0.499
	College above	12 (54.5)	10 (45.5)	0.24 (0.07–0.86)	1.60 (0.10–26.95)	0.743
Occupation	Farmer	15 (78.9)	4 (21.1)	1	1	
	Merchant	17 (85.0)	3 (15.0)	1.51 (0.29–7.86)	4.76 (0.52–43.30)	0.167
	Employee	10 (40.0)	15 (60.5)	0.17 (0.05–0.69)	0.41 (0.03–5.83)	0.509
	Labor	20 (83.3)	4 (16.4)	1.33 (0.28–6.21)	4.20 (0.46–38.29)	0.203
	Other	16 (88.9)	2 (11.1)	2.13 (0.34–13.40)	4.90 (0.46–52.17)	0.189
Marital status	Single	17 (89.5)	2 (10.5)	1	1	
	Married	27 (62.8)	16 (37.2)	0.19 (0.04–0.97)	0.41 (0.05–3.17)	0.391
	Divorced	21 (72.4)	8 (27.6)	0.31 (0.06–1.65)	0.54 (0.06–4.61)	0.571
	Widowed	13 (86.7)	2 (13.3)	0.77 (0.09–6.17)	0.97 (0.05–18.95)	0.984
Baseline LFT	Normal AST & ALT	72 (78.3)	20 (21.7)	1	1	
	Abnormal AST & ALT	6 (42.9)	8 (57.1)	0.21 (0.07–0.67)	0.20 (0.03–1.25)	0.086
HIV infection duration (Mos.)		28 (26.4)	78 (73.6)	0.97 (0.95–0.99)	0.95 (0.91–1.00)	0.057
ART duration (Mos.)		28 (26.4)	78 (73.6)	0.91 (0.85–0.98)	0.88 (0.76–1.00)	0.056
BMI (kg/m^2)	<18.5	13 (81.3)	3 (18.8)	1	1	
	18.5–24.9	54 (75.0)	18 (25.0)	0.69 (0.18–2.71)	4.28 (0.42–44.04)	0.222
	≥25	11 (61.1)	7 (38.9)	0.36 (0.08–1.75)	6.60 (1.02–42.82)	0.048[a]
Current HIV RNA level cp/ml	TND	14 (68.4)	6 (31.6)	1	1	
	20–1000	49 (80.3)	13 (19.7)	1.89 (0.59–5.98)	4.17 (0.77–22.76)	0.099
	≥1000	15 (61.5)	9 (38.5)	0.74 (0.21–2.58)	0.77 (0.12–4.86)	0.782
Treatment regimen	EFV-based cART	37 (69.8)	14 (30.2)	1	1	
	DTG-based cART	41 (77.4)	12 (22.6)	1.06 (0.62–3.53)	1.17 (0.24–5.75)	0.846

CI, confidence interval; COR, crude odd ratio; AOR, adjusted odds ratio; HIV, human immunodeficiency virus; Mos., months; LFT, liver function tests; TLC, total leucocyte count; ALT, alanine aminotransferase; AST, aspartate aminotransferase; DTG, Dolutegravir; EFV, Efavirenz; RNA, ribonucleic acid; BMI, body mass index; TND, target not detected (VL < 20).

[a] = P-value <0.05.

$CD4^+$ count was significantly higher with DTG than EFV [37]. Overall, it is difficult to compare various studies and provide a definite answer about $CD4^+$ counts increasing after ART because there is significant variation in the inclusion criteria and between individuals, as well as numerous factors influencing the rate of $CD4^+$ recovery [38,39].

This study also showed that the proportion of ART-naive PLWH achieving VS with DTG was 81.1 % (43/53) over a median follow-up time of 8.51 ± 2.29 months, and EFV was 73.6 % (39/53) over a median follow-up time of 14.58 ± 6.60 months ($p = 0.024$). This study is consistent with a study conducted in Cameroon ($p < 0.001$) [40]. The findings of this real-world analysis regarding the efficacy of DTG and EFV differ from the results observed in clinical trials involving ART-naïve PLWH. Viral suppression in the DTG group (81.1 % in our study) was lower as compared with 88 % in the group that received DTG, abacavir (ABC), and lamivudine (3 TC) in the SINGLE clinical trial and 88 % in the group that received DTG and two NRTIs in the SPRING 1 clinical trial. Similarly, VS in the EFV group was observed in 73.6 % of participants in our study, lower as compared with 81 % in the SINGLE clinical trial and consistent with 72 % in the SPRING 1 clinical trial. We found that 81.1 % of the patients achieved VS in DTG-based ART, which is lower than the estimated national average of 93 % in a study conducted in Uganda [41]. A retrospective study done in Brazil showed that over 90 % of patients who started DTG achieved VS (<50 cp/ml) after the first year of treatment, compared to 84 % for EFV-based therapy [42]. Discrepancies between clinical trials and these studies might be due to effects in part to the promotion of patient retention in clinical trials, and VS was defined differently; VS defined SINGLE clinical studies [15] and SPRING 1 clinical study [16], HIV-1 RNA at < 50 cp/ml. The mean follow-up of months may also explain this difference. According to clinical studies, DTG has been found to be more effective than EFV [16,43,44]. Meta-analyses have suggested indirect evidence of the superiority of DTG over other antiretroviral drugs [45–47]. Over the follow-up period, DTG initiators showed favorable virologic efficacy compared with EFV initiators. In line with these, our study showed that DTG initiators were more likely to achieve VS than EFV ($p = 0.024$). This may be as a result of the higher adherence [42] and reduced number of side effects with DTG, which is more favorable than their EFV-based regimen.

In addition, the present study also compares the magnitude of liver enzyme abnormalities among PLWH on DTG and EFV-based therapy. The magnitude of liver enzyme abnormalities was 22.4 % (12/53) in DTG and 30.2 % (16/53) in EFV-prescribed participants. The finding of this study greater than the result of a SINGLE clinical trial carried out in the USA, which reported a prevalence rate of 2 % and 5 % among patients treated with DTG and EFV, respectively [15]. These could be related to the fact that in clinical trials, individuals may be withdrawn due to drug adverse effects, and as the disease develops and chronic inflammation increases, there is a significant possibility of increases in these liver enzymes in the real-world [19]. Besides this, conflicting definitions and terminology linked to liver enzyme elevation, inter-laboratory heterogeneity in ULN expression, and the utilization of an ethnically varied study group all pose obstacles for cross-study comparisons. This study revealed that there was no significant difference in the mean AST/ALT levels between the two groups. A study conducted in the USA supports this claim [15].

PLWH may present multiple risk factors for biochemical abnormalities, and a precise etiology is rarely clearly defined [48]. However, the risk factors linked to these abnormalities tend to vary among various geographical areas and individuals [49]. Our findings demonstrated a strong association between liver enzyme abnormalities and a BMI ≥25 kg/m^2. Patients who had a BMI of ≥25 kg/m^2 were 6.60 times more likely to develop liver enzyme abnormalities (ALT/AST) than their counterparts. This is consistent with a study carried out in Switzerland [50]. The possible explanation could be the fact that there was a strong association between the level of liver enzymes and increasing BMI. Moreover, individuals with a higher BMI tend to have a greater degree of fatty infiltration in their liver [51].

This is a comparative cross-sectional study, so we are unable to establish causal links between the factors and outcomes being examined. Besides, the study was conducted on small study participants, and the non-probability method was used, making it difficult to draw an inference about the general population. Moreover, because of financial constraints, this study didn't encompass all pertinent liver enzymes that are used for the diagnosis of hepatotoxicity.

5. Conclusion

The results of the present study assess serum liver function tests, $CD4^+$ cell counts, and VL of DTG compared with EFV-treated groups. Our research found that DTG raises $CD4^+$, while VL was higher in EFV than in DTG-prescribed patients. The results support the Ethiopian Ministry of Health's decision to change its first-line ART recommendations from EFV to DTG. Liver function test abnormalities are common among PLWH on HAART. The current study showed a higher elevation of both serum AST/ALT enzyme abnormalities in both DTG- and EFV-prescribed participants. Although the differences were statistically insignificant, the mean AST/ALT levels were slightly elevated in EFV than in the DTG-prescribed participants. In our study, liver enzyme abnormalities were found to be significantly associated with a BMI ≥25 kg/m^2. These results highlight the need for monitoring and management of liver enzyme abnormalities in PLWH with an increased BMI. Moreover, it is necessary to conduct additional studies with a larger number of participants using a prospective study design to ascertain the incidence of liver abnormalities and establish causal relationships.

Ethical considerations

Ethical clearance was granted by the ethical committee of the School of Medicine, College of Medicine and Health Sciences, University of Gondar (Reference No: 1952/03/2020). A support letter was also obtained with protocol number Ref: Bioc-79/07/2012 from the Department of Biochemistry, and submitted to DMCSH. Permission for data collection was obtained from DMCSH. Each participant provided written informed consent prior to the collection of data. Personal data was anonymized and kept secure, ensuring the confidentiality of all participants throughout the study.

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Data availability statement

Data will be made available on request.
No additional information is available for this paper.

CRediT authorship contribution statement

Enyew Fenta: Writing – original draft, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Dr Tabarak Malik:** Writing – review & editing, Visualization, Software, Data curation. **Meseret Derbew Molla:** Writing – review & editing, Validation, Supervision, Data curation. **Adane Adugna:** Writing – review & editing, Visualization, Software. **Mohammed Jemal:** Writing – review & editing, Validation, Software, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine Transaminase
AOR	Adjusted odds ratios
ART	Antiretroviral therapy
AST	Aspartate Transaminase
BMI	body mass index
cART	combined antiretroviral therapy
CD4	clusters of differentiation 4
CI	confidence interval
DMCSH	Debre Markos Comprehensive Specialized Hospital
DTG	Dolutegravir
EFV	Efavirenz
HAART	Highly Active Antiretroviral Therapy
HIV	Human immunodeficiency virus
INSTI	Integrase strand transfer inhibitor
NNRTI	Non-nucleoside reverse transcriptase inhibitor
PLWH	people living with HIV
SD	Standard deviation
ULN	The upper limit of normal
VL	Viral load
VS	viral suppression
WHO	World Health Organization

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