ORIGINAL ARTICLE

Lipid Profile Improvement after Switching to Dolutegravir-Based Regimen in People Living with HIV: A Cohort Study

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Background: Integrase inhibitor (INSTI) based antiretroviral therapy is the mainstay for people living with HIV (PLHIV). Due to its favorable efficacy and safety profile, dolutegravir (DTG) is widely used in combination with nucleoside reverse transcriptase inhibitors (NRTIs). TLD, a fixed-dose combination of tenofovir disoproxil fumarate (TDF), lamivudine (3TC), and DTG, is the first-line treatment for PLHIV in Thailand. However, data on metabolic complications from DTG-based regimens in the Thai population have not been thoroughly investigated.

Materials and Methods: A cohort study non-randomized trial was conducted at Buddhachinaraj Hospital, Phitsanulok, Thailand. Data on demographics, baseline antiretroviral regimens, and metabolic profiles such as triglycerides, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), fasting blood sugar, and aminotransferases, were collected at baseline and six months after switching to a DTG-based regimen in virologically suppressed PLHIV between November 1, 2022 and August 31, 2023. Informed consents were obtained from all participants.

Results: One hundred thirty-eight PLHIV were enrolled, with a majority being men, at 59%, and a median age of 47.5 years (IQR 36.2, 55.1). Median CD4 count was 608 cells/mm^3 (IQR 452, 805) and median duration of antiretroviral treatment was 13 years (IQR 8, 18). Underlying conditions included dyslipidemia with 44.2%, hypertension for 29.7%, and type II diabetes for 14.5%. Of the participants, 107 out of 138 (77.5%) were on TDF, 3TC, or emtricitabine (FTC) combined with a non-nucleoside reverse transcriptase inhibitor (NNRTI) such as efavirenz (EFV) or rilpivirine (RPV) as their baseline regimen. After six months, significant changes were observed in median triglycerides, from 138.5 to 97.5 mg/dL ($p<0.001$), total cholesterol from 201 to 173 mg/dL ($p<0.001$), and LDL cholesterol from 117 to 103 mg/dL ($p<0.001$). Median body weight increased from 63.2 to 63.35 kg ($p<0.001$).

Conclusion: DTG, a second-generation INSTI, is widely used as a key antiretroviral therapy in Thailand. While it demonstrates favorable effects on lipid profiles, body weight gain, which is a crucial factor for cardiovascular outcomes, should be monitored closely.

Keywords: Integrase inhibitor; People living with HIV (PLHIV); Dolutegravir (DTG); Triglyceride; Total cholesterol; LDL-cholesterol; HDL-cholesterol; Fasting blood sugar; Aminotransferase

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To date, HIV management has advanced to include all individuals living with HIV, regardless of CD4 count. Integrase inhibitor-based regimens are now the mainstay of antiretroviral therapy (ART) due to their favorable efficacy and fewer adverse events[1]. Dolutegravir (DTG), a second-generation integrase inhibitor, offers a high barrier to resistance and can be administered once daily, often combined with nucleoside reverse transcriptase inhibitors (NRTIs)[2]. The single-tablet regimen containing tenofovir disoproxil fumarate (TDF), emtricitabine (FTC), and DTG is widely used for ART-naïve patients and those switching from older regimens for better adherence and fewer side effects[1].

Long-term ART has been associated with metabolic complications, including dyslipidemia[3], hepatic issues[4], and cardiovascular problems[5], particularly with regimens containing efavirenz, nevirapine, and protease inhibitors. While DTG appears to have a neutral effect on serum lipids[6], weight gain remains a concern, especially among women[7].

Due to its efficacy and minimal adverse effects, the single-tablet regimen TLD, which is TDF, 3TC, and DTG, has been promoted for all ART- naïve individuals and those switching due to side effects from efavirenz or protease inhibitors in Thailand.

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However, the metabolic complications of DTG-based regimens in the Thai population have yet to be investigated.

Materials and Methods

A cohort study non-randomized trial at Buddhachinaraj Hospital was carried out between November 1, 2022 and August 31, 2023. All people living with HIV who were virologically suppressed, which is HIV viral load of less than 20 copies/mL, and currently on ART in various regimens were included. The patients switched to TLD or a 2-drug regimen containing DTG and lamivudine (3TC) for TDF-induced renal complications. Triglyceride (TG), total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, fasting blood sugar (FBS), alanine aminotransferase (ALT), and body weight (BW) were evaluated at baseline and at six months after switching. Participants who were currently on lipid-lowering agents will not have their regimen or dosing modified during the study period. Participants with documented DTG, 3TC, or tenofovir resistance were excluded. From the previous study, LDL cholesterol decreased by 10.9±27 mg/dL at 12 months after switching to DTG, with a power of 80%, an alpha error of 5%, and 30% of participants lost to follow-up. Therefore, by two-dependent means model[8], at least 64 participants were included.

The present study was approved by the Human Research Ethics Committee of Buddhachinaraj Phitsanulok Hospital (EC No. 022/66). The present research was conducted according to the Declaration of Helsinki, The Belmont Report, CIOMS Guideline and the International Conference on Humanization in Good Clinical Practice. All participants had given informed consent.

Statistical analysis

The data were analyzed using R version 4.4.1. Participants were described using frequency for categorical variables and median (interquartile range, IQR) for continuous variables. Univariable analysis comparisons for TG, TC, LDL, HDL, FBS, ALT and BW variations were performed at before and after switching using Wilcoxon signed-rank test and adjusted for each ART regimens. Differences were considered significant for p-values less than 0.05.

Results

During the present study, 138 participants living with HIV were included with a median age of 47.5 years (IQR 36.2, 55.1). Eighty-one (59%) were male. The median CD4 count was 608 cells/mm³ (IQR 452, 805). Underlying diseases other than HIV infection were dyslipidemia, hypertension, and type II diabetes mellitus, which were at 44.2%, 29.7%, and 14.5%, respectively. Forty-eight out of 138 participants (34.8%) were currently on lipid-lowering agents. The baseline antiretroviral regimen in 107 out of 138 patients (77.5%), were combinations of TDF, 3TC, or FTC and non-nucleoside reverse transcriptase inhibitor (NNRTI) as efavirenz or rilpivirine. Following this, 10.9% were on a combination of zidovudine (AZT), 3TC, or FTC and NNRTI as efavirenz or rilpivirine, and 8% were on a combination of abacavir (ABC), 3TC, or FTC and NNRTI as efavirenz or rilpivirine. Another five out of 138 (3.6%) were on a combination of any NRTI and boosted protease inhibitor-based regimen as lopinavir or atazanavir with ritonavir. The median duration of antiretroviral regimens at baseline was 13 years (IQR 8, 18). One hundred twenty-eight out of 138 (92.8%) were switching to TLD, and another nine (7.2%) were on the ABC, 3TC, and DTG regimen as described in Table 1.

Table 1. Characteristics of study patients

Characteristics	Numbers
No. of PLHIV; n (%)	138 (100)
Age (years); median (IQR)	47.5 (36.2, 55.1)
Sex; n (%)	
Male	81 (58.7)
Female	57 (41.3)
Comorbidities; n (%)	
Dyslipidemia	61 (44.2)
Hypertension	41 (29.7)
Diabetes mellitus	20 (14.5)
Others	5 (3.5)
No underlying disease	1 (0.7)
CD4 at baseline (cell/mm^3); median (IQR)	351 (452, 805)
Antiretroviral duration at baseline (years); median (IQR)	13 (8, 18)
Antiretroviral regimen at baseline; n (%)	
TDF, 3TC or FTC, NNRTI (EFV or RPV)	107 (77.5)
AZT, 3TC or FTC, NNRTI (EFV or RPV)	15 (10.9)
ABC, 3TC or FTC, NNRTI (EFV or RPV)	11 (8.0)
Others	5 (3.6)
Lipid lowering agent; n (%)	48 (34.8)
New antiretroviral regimen after switching; n (%)	
TDF, 3TC or FTC, DTG	128 (92.8)
ABC, 3TC or FTC, DTG	10 (7.2)

PLHIV=people living with HIV; TDF=tenofovir disoproxil fumarate; 3TC=lamivudine; FTC=emtricitabine; NNRTI=non-nucleoside reverse transcriptase inhibitor; EFV=efavirenz; RPV=rilpivirine; ABC=abacavir; AZT=zidovudine; DTG=dolutegravir; IQR=interquartile range

Table 2. Effects on metabolic profile at baseline containing of various regimens and six months after switching to DTG based regimen

Metabolic effects	Initial antiretroviral regimen											
	All regimens (n=138); median (IQR)			TDF/3TC/NNRTI (n=107); median (IQR)			AZT/3TC/NNRTI (n=15); median (IQR)			ABC/3TC/NNRTI (n=11); median (IQR)		
	Before	After	p-value	Before	After	p-value	Before	After	p-value	Before	After	p-value
TG (mg/dL)	138.5 (90.3, 215.5)	97.5 (69.5, 167)	<0.001	126 (89.5, 209.5)	92.5 (67, 163)	0.1148	162 (102.5, 475)	131 (79, 199)	0.012	167 (135, 221)	111 (84, 204.5)	0.413
TC (mg/dL)	201 (178.2, 235)	173 (146, 197.5)	<0.001	199 (178, 236)	175 (148.5, 199)	<0.001	215 (188.5, 221.3)	169 (146, 175)	0.021	192 (182.5, 219.5)	187 (145.5, 214)	0.464
LDL (mg/dL)	117 (95, 140)	103 (81, 123)	<0.001	120 (101, 143)	104 (87.5, 123.8)	<0.001	110 (92, 136)	82 (76, 116)	0.068	91 (78.5, 108)	90 (72.5, 132)	0.683
HDL (mg/dL)	53 (47.3, 64)	44 (37, 51)	<0.001	52 (46, 62)	44 (37.5, 50.5)	<0.001	53 (48.5, 72.5)	37 (48.5, 45)	0.068	64 (53.5, 66)	57 (40, 62.5)	<0.001
FBS (mg/dL)	96 (89, 104)	92 (88, 110.2)	<0.001	96 (89, 104)	92 (88.3, 108.3)	0.022	101 (96, 125.5)	100.5 (91.3, 138.7)	0.609	93 (84, 96)	93 (87, 95)	1
ALT (U/L)	29 (22, 40)	29 (19, 41)	0.218	30 (23, 42.8)	29 (19, 41.5)	0.037	24 (22, 39.5)	39 (32, 49)	0.126	27 (20, 35.5)	29 (22, 35.5)	0.756
BW (kg)	63.2 (51.4, 73)	63.35 (53.3, 72.5)	<0.001	63.4 (52.5, 73)	64 (54, 72.5)	0.019	67 (54.5, 71.5)	65 (53.5, 73.8)	0.972	57.5 (50, 62.45)	57.5 (50.0, 62.45)	0.483

TG=triglyceride; TC=total cholesterol; LDL=low density lipoprotein; HDL=High density lipoprotein; FBS=fasting blood sugar; ALT=alanine aminotransferase; BW=body weight; TDF=tenofovir disoproxil fumarate; 3TC=lamivudine; NNRTI=non-nucleoside reverse transcriptase inhibitor; AZT=zidovudine; ABC=abacavir; IQR=interquartile range

Effects on triglyceride

Table 2 and Figure 1 shows that all participants had a median baseline TG level of 138.5 mg/dL before switching, regardless of lipid-lowering agent. After switching to a DTG-based regimen, TG levels were significantly decreased to 97.5 mg/dL without modification of lipid-lowering agent from baseline. From the initially TDF/3TC/NNRTI-based regimen, the median TG level was also decreased from 126 to 92.5 mg/dL, the same as the ABC/3TC/NNRTI-based regimen, which decreased from 167 to 111 mg/dL, but it was not statistically significant except for the initially AZT/3TC/NNRTI-based regimen, which significantly decreased from 162 to 131 mg/dL.

Effects on total cholesterol

Table 2 and Figure 1 shows that the median TC significantly decreased from 201 to 173 mg/dL after switching to a DTG-based regimen. Especially for initial baseline regimens containing TDF/3TC/NNRTI and AZT/3TC/NNRTI, which decreased from 199 to 175 mg/dL and 215 to 169 mg/dL, respectively. For the ABC/3TC/NNRTI regimen, there was also a decrease, but it was not statistically significant.

Effects on LDL-cholesterol

Table 2 and Figure 1 shows that the LDL decreased significantly in overall regimens from 117 to 113 mg/dL. In the TDF/3TC/NNRTI initial regimen, there was a significant decrease from 120 to 104 mg/dL. Similarly, other regimens showed a similar trend, but the changes were not statistically significant.

Effects on HDL-cholesterol

Table 2 and Figure 1 shows that after switching, HDL levels significantly changed regardless of the initial antiretroviral regimens. Median HDL levels were significantly decreased from 53 to 44, 52 to 44, and 64 to 57 mg/dL for overall, TDF/3TC/NNRTI, and ABC/3TC/NNRTI, respectively.

Effects on FBS, ALT, and BW

Table 2 and Figure 1 shows that after switching to a DTG-based regimen, all participants showed a significant decrease in FBS from 96 to 92 mg/dL, but BW increased from a median of 63.2 to 63.35 kg. In addition, in the baseline TDF/3TC/NNRTI regimen, it affected in the same direction. Moreover, ALT was significantly improved after switching from TDF/3TC/NNRTI to a DTG-based regimen, from a median of 30 to 29 U/L.

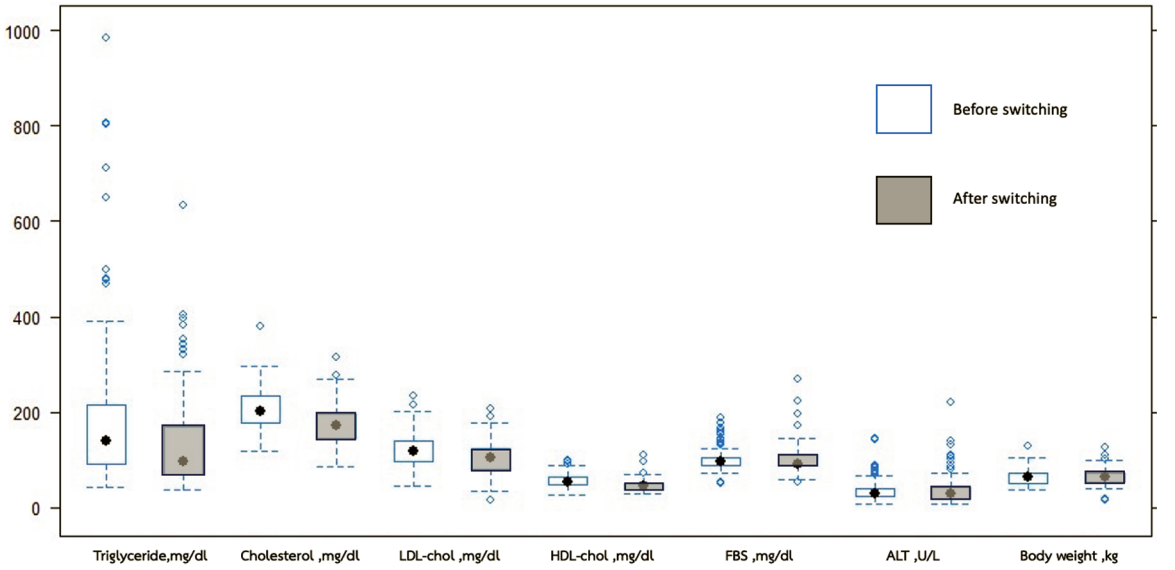

Figure 1. Effects on metabolic profiles at baseline containing of various regimens and six months after switching to DTG based regimen.

Discussion

Non-communicable diseases (NCDs) are a growing global concern, with risk factors identified by the World Health Organization (WHO) including diabetes, high cholesterol, hypertension, alcohol use, tobacco use, obesity, and physical inactivity[9]. HIV can increase the risk of atherosclerosis and coronary artery inflammation by activating the immune system. Comorbidities such as hepatitis B or C, smoking, and alcohol consumption further elevate NCD risks in people living with HIV[10]. ARTs, particularly protease inhibitors, are linked to hypercholesterolemia and metabolic syndrome[11] that occurs in more than 50% after two years of therapy[12]. Switching from protease inhibitors to efavirenz or rilpivirine is recommended for better compliance through single-tablet regimens. However, efavirenz is associated with neuropsychiatric, which are suicidal ideation, encephalopathy, catatonia, psychosis, and ataxia[13] and hepatic side effects[14], leading to the promotion of TLD as TDF, 3TC, and DTG, as the first-line regimen in Thailand.

The present study found that switching to a DTG-based regimen significantly reduced TGs, TC, and LDL cholesterol, similar to the previous findings with ABC, 3TC, and DTG[15]. High efavirenz concentrations correlate with increased plasma lipid levels by increased lipid uptake and cholesterol biosynthesis in hepatic cells[16], particularly in individuals with the CYP2B6 slow metabolizer genotype[17]. Additionally, switching to DTG improved FBS, although its impact on HbA1C remains unexamined. ALT levels also improved, suggesting that DTG may reduce hepatic complications linked to NNRTIs. While HDL cholesterol levels decreased after switching, the TG/HDL ratio showed improvement in previous studies but was not investigated here.

The switch to a DTG-based regimen also correlated with BW gain due to a "return to health" effect from reduced catabolism associated with HIV. Limited studies suggest that DTG may increase hunger and lower leptin levels[18], which effect is similar to a previous study of a regimen containing DTG that increased BW more than efavirenz regimen[19].

Overall, the study indicates benefits in lipid profiles after switching to TLD, now the first-line regimen in Thailand since 2022[20]. However, data on metabolic effects in the Thai population remain limited.

Limitations of the present study include its non-randomized design, which may affect lifestyle factors, and its short duration of six months, necessitating longer-term follow-up on NCD outcomes, particularly cardiovascular events in the Thai population.

What is already known on this topic?

Integrase inhibitor-based regimen is currently the mainstay for ART with favorable efficacy and less adverse event. Metabolic complication in the studies showed neutral effect on lipid profile.

What does this study add?

This study shows metabolic outcomes on TG, TC, LDL cholesterol, HDL cholesterol, FBS, ALT, and BW six months after switching regimen in Thai patients.

Conflicts of interest

The author declares no conflict of interest.

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