ORIGINAL PAPER

JMS Journal of Medical Science

Lipid profile after switching from TDF (tenofovir disoproxil)-containing to TAF (tenofovir alafenamide)-containing regimen in virologically suppressed people living with HIV

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DOI: https://doi.org/10.20883/medical.e808

Keywords: antiretroviral therapy, tenofovir disoproxil fumarate, tenofovir alafenamide, lipids, cholesterol, low-density lipoproteins

Received: 2023-02-01
Accepted: 2023-07-19
Published: 2023-09-26

How to Cite: Łomiak M, Gajek Z, Stępnicki J, Lembas A, Mikuła T, Wiercińska-Drapało A. Lipid profile after switching from TDF (tenofovir disoproxil)-containing to TAF (tenofovir alafenamide)-containing regimen in virologically suppressed people living with HIV. Journal of Medical Science. 2023;92(4):e808. doi:10.20883/medical.e808

ABSTRACT

Background. Tenofovir disoproxil fumarate (TDF) or its prodrug, tenofovir alafenamide fumarate (TAF), is currently being recommended in treatment of HIV infection. The distinct pharmacological properties of these two forms of this drug make TAF treatment less nephrotoxic and lead to a better impact on bone density. Nevertheless, a rising concern about TAF's possible metabolic adverse effects exists. This study aimed to evaluate the effects on the lipid profile among ART (antiretroviral therapy) patients switching from a TDF-containing to a TAF-containing regimen in the first year after the switch.

Methods. Demographic and clinical data of HIV-positive ART-experienced patients treated in the infectious diseases department was retrospectively collected. Lipid profile change concerning baseline BMI, age, and time of ART duration were analysed.
Results. In the group of 36 patients, there was a significant increase in total cholesterol levels (+18.43mg/dl, SD=23.86mg/dl, p<0.0001) and LDL levels (+13.75mg/dl, SD=23.05mg/dl, p=0.001) in the first 12 months after switching from a TDF-containing to a TAF-containing regimen. There were no statistically significant changes in both HDL and TG levels observed. Analysis of total cholesterol and LDL levels in specific subpopulations revealed a significant increase within the first year after the switch in patients younger than 40 years old and in those whose BMI was within the normal range.
Conclusions. The data suggests that switching from TDF to TAF in ART-experienced patients may be associated with worsening lipid parameters. Early detection and management of dyslipidemias among HIV-positive patients are needed.

Introduction

The main aims of antiretroviral therapy (ART) in HIV-positive patients are undetectable viral load, reduction of transmission of the virus, restoration of the immune system and decrease in AIDS-associated mortality [1]. Effective and safe antiretroviral drug availability led to an improvement in life expectancy among people living with HIV (PLWH) to the point where it is close to the non-infected population [2,3]. Nevertheless, in the era of worldwide access to long-term treatment of HIV infection, currently, the main causes of mortality are non-AIDS-associated comorbidities such as metabolic and cardiovascular diseases [4]. The incidence of ischemic heart disease, arterial hypertension, diabetes mellitus, or dyslipidemia is significantly higher among PLWH compared to healthy individuals [5]. The pathophysiology processes leading to these observations are complex and involve endothelial dysfunction associated with the chronic inflammatory state despite suppression of virus replication, immune system dysregulation, high incidence of traditional risk factors (e.g. smoking), or side effects of drugs included in ART [6].

Tenofovir alafenamide (TAF) and tenofovir disoproxil (TDF) are two forms of tenofovir that are currently recommended in the treatment of HIV infection [7]. TAF displays non-inferior antiviral properties compared with TDF in both HIV infection treatment and pre-exposure prophylaxis [8,9]. TAF is the next-generation tenofovir prodrug with a distinct pharmacological profile. The active metabolite of these two drugs (tenofovir diphosphate) can achieve even 25 times higher concentrations in peripheral mononuclear blood cells following consumption of TAF compared with TDF [10]. Pharmacological studies have shown that tenofovir undergoes active uptake by white blood cells when its precursor is TAF [11,12]. Hence, it is possible to significantly decrease the dosage of TAF compared with TDF, leading to a better safety profile – lower nephrotoxicity risk and lesser damage to bone structural integrity [13].

Nevertheless, recent reports bring up a concern about the substitution of TDF with TAF in ART due to a possible increase in cardiovascular risk after the switch of these drugs [14]. In this single-centre retrospective study, we aimed to evaluate whether switching treatment from a TDF-containing regimen to a TAF-containing regimen is associated with worsening serum lipids parameters in the ART-experienced cohort

Patients and methods

We analysed data gathered in routine care patients' charts admitted to our department. The research included patients that met the general inclusion criteria as follows: confirmed HIV infection, age over 18 years, no active neoplastic disease, switching from TDF-based regimen to TAF-based regimen, and confirmed efficacy of virologic suppression on TAF-based regimen (<200 copies/mL of HIV RNA after at least six months from treatment initiation). Patients were treated with various antiretroviral regimens that included TDF, such as TDF/emtricitabine/lopinavir/ritonavir, TDF/emtricitabine/darunavir/

ritonavir and TDF/emtricitabine/efavirenz. They were later switched to TAF-based regimens: TAF/elvitegravir/emtricitabine/cobicistat or TAF/emtricitabine/rilpivirine.

Lipid concentration measures were taken, including total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL) concentration, and triglycerides (TG). These measures were taken firstly at the beginning of TAF-containing ART (at the moment of the switch from TDF-containing ART) and then 12 months after switching from TDF-containing ART. Additional information that was collected included duration of HIV infection, duration of ART, number of previous treatment schemes, route of infection, HIV RNA viral load and CD4+ count at the moment of infection diagnosis, CD4+ at the time of switching of ART regimens, co-infection with other sexually transmitted diseases (STDs). Optimal values of lipid parameters were distinguished according to Adult Treatment Panel Guidelines III and were <200 mg/dl for total cholesterol, <100 mg/dl for LDL, <150 mg/dl for TG and >40 mg for HDL in plasma serum [6].

Paired t-tests were applied to compare changes in concentration of described lipid parameters using GraphPad Prism 8.4.3 software. The statistical significance of the results was a p-value <0.05.

Results

Study population

A total of 106 patient history charts were analysed. Eventually, 36 patients met the inclusion criteria. All the patients in the study group were Caucasians and predominantly male. The median ART duration among patients was nine years, and more than half had changed their ART regimen more than two times. Importantly, we observed a high prevalence of co-infection with other sexually transmitted diseases in the study group. More than half of patients declared the most possible transmission by sexual contact and belonged to the group described as "men having sex with men". **Table 1** presents all baseline characteristics of the study group.

Lipids parameters changes in the study population

Our data indicates a high frequency of patients whose lipid parameters were not optimal at the beginning of the study at the time of the switch from TDF-containing to TAF-containing regimen. Twelve months after switching, the number of patients with different types of dyslipidemia increased from 6 to 10 for total cholesterol levels, 13 to 20 for LDL levels, 12 to 17 for TG levels, and 8 to 11 for HDL levels (**Figure 1**). Mean values of lipid parameters at the time of switching regimens were 162.5 mg/dl (SD = 36.04 mg/dl) for total cholesterol, 91.48 mg/dl (SD = 29.14 mg/dl) for LDL, 48.17 mg/dl (SD = 15.13 mg/dl) for HDL and 138.8 mg/dl (SD = 68.65 mg/dl) for TG. We observed a significant increase in total cholesterol levels (+18.43 mg/dl, SD = 23.86 mg/dl, p < 0.0001) and LDL levels (+13.75 mg/dl, SD = 23.05 mg/dl, p = 0.001) in first 12 months after switching from TDF-containing to TAF-containing regimen (**Figure 2**). Changes in both HDL and TG levels were not statistically significant.

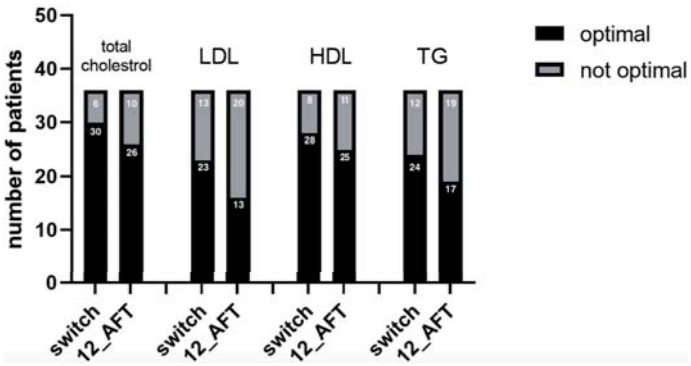

Figure 1. Number of patients with optimal and non-optimal lipid parameters at the time of the switch of ART regimen and 12 months after the switch.

Table 1. Descriptive baseline characteristics for the study population.

	Study group (n = 36)
Age in years, median (IQR)	42 (13.25)
Male, n (%)	32 (87.50)
Female, n (%)	4 (12.50)
Caucasian, n (%)	36 (100.0)
Height (cm), median (IQR)	178 (6.50)
Weight at the time of switching TDF to TAF (kg), median (IQR)	75 (10.75)
BMI at the time of switching TDF to TAF in kg/m^2, median (IQR)	24.20 (3.90)
Duration of HIV infection in years, median (IQR)	9 (5.00)
Duration of HIV treatment in years, median (IQR)	9 (4.50)
Number of patients that in the past had two different ART regimens before switching to a TAF-based regimen, n (%)	14 (38.90)
Number of patients that in the past had three or more different ART regimens before switching to a TAF-based regimen, n (%)	22 (61.10)
Declared route of infection	
– MSM, n (%)	18 (50.0)
– HET, n (%)	12 (33.30)
– IDU, n (%)	2 (5.60)
– no information, n (%)	4 (11.10)
– Co-infection with other STDs (HCV, HBV, syphilis), n (%)	16 (44.40)
Viral load at the time of HIV infection diagnosis (HIV RNA copies/mL), median (IQR)	100892 (368443.00)
CD4+ count at the time of HIV infection diagnosis, median (IQR)	273(183.75)
CD4+ count at the time of the switch to a TAF-based regimen, median (IQR)	585 (346.00)
Cardiovascular comorbidities	
– Hypertension (%)	8 (22.2)
– Heart failure (%)	0 (0)
– Coronary artery disease (%)	0 (0)
– Heart failure (%)	0 (0)
– Previous myocardial infarction (%)	0 (0)
– Previous stroke (%)	0 (0)
– Diabetes mellitus (%)	0 (0)
Other drugs used	
– Statins (%)	9 (25)
– Fibrate (%)	2 (5.6)
– Acetylosalicylic acid (%)	1 (2.8)
– Vitamin K antagonists/novel oral anticoagulants (%)	0 (0)
– Beta-blocker (%)	2 (5.6)
– Calcium channels blocker (%)	3 (8.3)
– ACE-inhibitor/sartan (%)	8 (22.2)
– Diuretics (%)	2 (5.6)
– Hypoglycemic drugs (%)	0 (0)

Legend: HET – heterosexual transmission; MSM – transmission between men having sex with men; IDU – transmission through intravenous drug use; IQR – interquartile range.

During the study period, which is the first year of TAF treatment, there were eight patients treated with statin, one treated with fibrate and one on dual hypolipidemic treatment with statin and fibrate. No changes in the type of hypolipemic drug, dosage or the proportion of patients treated with hypolipemic drugs were observed during the study period.

Next, we investigated whether total cholesterol and LDL levels in individual subgroups of the study group changed regarding patients' baseline BMI, age, and ART duration. A significant increase in total cholesterol and LDL serum levels after switching to a TAF-containing regimen occurred in patients with a BMI below 25 and patients younger than 40 years old. In both sub-

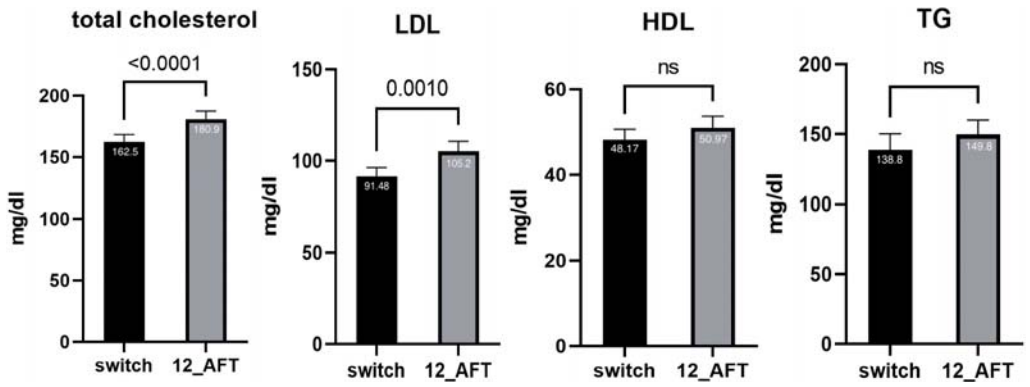

Figure 2. Mean lipid parameter levels at the time of the switch from TDF-containing to TAF-containing regimen and after 12 months of treatment with TAF-containing regimen.

Table 2. Total cholesterol and LDL changes in the study group according to BMI, age, and ART duration.

		Total cholesterol		LDL	
	Number of patients	Mean change (SD) mg/dl	p-value	Mean change (SD) mg/dl	p-value
BMI value					
<25	25	21.27 (23.59)	0.002	18.17 (23.59)	0.0008
≥25	11	11.98 (23.98)	0.13	3.8 (19.34)	0.5125
Age					
<40 years old	22	20.88 (17.79)	<0.0001	12.76 (16.24)	0.0014
≥40 years old	14	14.3 (31.32)	0.11	15.08 (31.71)	0.09
ART duration					
<10 years	21	19.72 (27.45)	0.004	13.53 (24.36)	0.0211
≥10 years	15	17.01 (18.17)	0.003	13.92 (21.66)	0.0233

groups of patients with ART duration of less than or more than ten years, we reported a significant increase in total cholesterol and LDL serum levels (**Table 2**).

Discussion

In the present study describing the effects of a switch from TDF-based to TAF-based ART regimen in a real-world setting, we have observed a significant worsening of lipid parameters among ART-experienced patients in the first year after the switch. The most prominent unfavourable changes in lipid parameters were in total cholesterol (+18.4 mg/dl) and LDL (+13.72 mg/dl) levels. At the same time, there was no significant increase in HDL and TG levels during the study period. Surprisingly, the analysis showed that the effects of regimen change leading to statistically significant worsening of total cholesterol and LDL levels occur mainly among younger patients (below 40 years old) and patients with normal baseline BMI. The study group included in this study consisted of relatively young patients (median age 42), explaining the low rate of cardiovascular comorbidities observed. Nevertheless, we have observed a high rate of patients without optimal lipid parameters after one year after the change of ART regimen and just before the switch. These observations bring concern about the inadequate treatment of lipid disorders or underdiagnosing of dyslipidemias among PLWH. There is an urgent and unfulfilled need for an active search for metabolic disorders in that group of patients. Presented data may help identify groups of patients at a higher risk of developing metabolic disturbances after switching from TDF to TAF, among whom additional surveillance on lipid parameters should be performed.

Since the beginning of the global HIV/AIDS pandemic, which has already resulted in nearly 40 million deaths, the possibilities of treatment for patients infected with HIV have significantly

widened. Currently, long-term treatment with safe antiretroviral drugs provides suppression of HIV replication and reduces its transmission. Regarding the high efficacy of that treatment, prevention of ART-related adverse effects and maintenance of adherence are the main pitfalls that medical professionals need to face. In the era of widely available ART, the population of HIV-positive patients is ageing, which leads to an overlap of HIV-associated as well as age-associated health problems, including neurodegenerative disorders, malignancies, and cardiovascular events [15].

Compared to uninfected patients, PLWH were proven to have a 1.5-2 times higher risk of cardiovascular events, including myocardial infarction, ischemic stroke, heart failure or venous thrombosis [16]. It is the consequence of the interplay of traditional risk factors (such as the high rate of cigarette smokers), chronic viral infection triggering inflammation, and adverse metabolic effects of ART components [18]. Chronic inflammation resulting from the hyperactivity of T cells, macrophages, monocytes and dendritic cells producing excess cytokines causes damage to the endothelium [19]. That exact process results in the formation of necrotic tissue with a mass of foam cells containing LDL, known as atherosclerotic plaques – a morphological manifestation of atherosclerotic disease. High levels of LDL and non-HDL cholesterol were associated with an increase in cardiovascular mortality in the general population, which should be considered when choosing ART components [20]. The worsening of lipids profile after switching ART components brings concerns about the potential atherogenic effect of certain drugs. This phenomenon is especially interesting when TDF is replaced with its newer generic formulation TAF. **Supplementary Table 1** depicts available data from research papers regarding TAF-associated dyslipidemia after the switch from TDF-containing ART.

The treatment with TAF/FTC/EVG/c compared to TDF/FTC/EVG/c results in a higher increase in total cholesterol, LDL, HDL, and TG in 48 weeks among ART-experienced patients [21]. Also, in a phase-3-clinical trial evaluating the safety of switching from RPV/FTC/TDF to RPV/FTC/TAF, researchers reported a significant increase in total cholesterol, LDL, HDL, and TG after 96 weeks among patients who switched from TDF to TAF compared to those who remained on TDF-containing ART [22]. Similar observations to our results were made by research groups from Finland and Ireland that reported the worsening of lipid parameters after switching from TDF-based to TAF-based ART [23,24]. The most significant change was in the total cholesterol and LDL classes. While patients' HDL levels increased only slightly, they were still statistically significant. Another TDF-to-TAF switch study showed nearly the same extent of lipid parameter changes in the time observation during six months. Thus, longer use of TAF in the ART regimen does not lead to more severe dyslipidemia in further months of treatment [25]. This hypothesis is consistent with data obtained by Huhn et al. [26], where patients` dynamics of lipid changes occurred mainly in the first 48 weeks after the ART switch, with only minimal changes from 48 to 96 weeks of observation after initiating HIV infection treatment. After the switch, total cholesterol and LDL levels worsen primarily in patients without baseline hypercholesterolemia [27]. In our group, therefore, we noticed significant changes in the mentioned parameters among patients under 40 years of age and with a normal BMI. However, switching from TDF to TAF in patients with baseline hypercholesterolemia resulted in a significant decrease in LDL/HDL and TC/HDL ratios, markers of ischemic heart disease risk [28]. Interestingly, the effect of TAF on lipids by switching from TDF to TAF is reversible when setting the patient back on TDF-containing ART [29]. That confirms reports about the lipid-lowering properties of TDF on all lipid fractions that may be associated with plasma levels of TFV [30]. Although the lipid-lowering effect of TDF seems to be comparable to some statins, it is still unknown whether the changes in lipid parameters in such cases correspond with a reduction of death risk from cardiovascular events in the future as it was proven to be associated with statin use [31]. It should be stressed that the exact mechanism of TDF improving lipid parameters is unclear. It probably involves actions other than the suppression of HIV replication since this phenomenon was also observed in treating HBV infection [32] and HIV pre-exposure prophylaxis [33].

Both our and other researchers' findings indicate the unfulfilled need for screening for dyslipidemia and assessing the cardiovascular risk of HIV-positive patients treated with ART.

Supplementary Table 1. Current knowledge about the impact of TAF-based ART regimen after switching from TDF-based regimen on lipid parameters among ART-experienced HIV+ patients.

		Median or mean change of lipid parameters (mg/dl)					
No. of patients	Time of observation (weeks)	Total cholesterol	LDL	HDL	TG	Additional information	Study
110	48 weeks on TDF-based ART; 48 weeks on TAF-based ART	+12.50* (median)	+8.20* (median)	+3.00* (median)	+ 4.00 (median)	– presented changes in lipid parameters are between one year before the ART switch and one year after – 13% increase in ASCVD risk scores after switching to TAF	[14]
Included in the analysis: for total cholesterol and TG – 385 for HDL and LDL – 70	12	+20.00* (mean)	+10.00* (mean)	+6.00* (mean)	+23.00* (mean)	– results demonstrate a reversible effect on lipids parameters by switching from TDF to TAF and back	[29]
194	24	+ 14.30* (mean)	+ 9.67* (mean)	+1.90* (mean)	+11.50* (mean)	– the use of statins significantly reduced the risk of worsening lipid panel after switching to TAF	[24]
189	48	+29.00* (mean)	+20.90* (mean)	+3.30* (mean)	+28.90* (mean)	– presented changes in lipid parameters occurred in the group of patients without any lipid-lowering therapy – it was necessary to prescribe almost twice as many lipid-lowering drugs in a group of patients on TAF-based ART compared with TDF-based ART	[21]
Included in the analysis: for total cholesterol – 431 for LDL – 423 for HDL – 426 for TG – 430	12 (median)	+15.00* (mean)	+9.00* (mean)	+5.00* (mean)	+12.00* (median)	– TC, HDL and LDL increased after the switch in patients without HC, while in HC patients, there were no significant variations in TC and LDL, but with a decrease in TC/HDL and LDL/HDL ratio and an increase in HDL	[27]
221	34	+19.00–34.00* (median) depending on other ART agents	+14.00–25.00 (median) depending on other ART agents	+4.00–7.00 (median) depending on other ART agents	+7.00–21.00 (median) depending on other ART agents	– after switching from TDF to TAF, the proportion of patients with LDL above their CV target increased significantly	[39]
347	24	+21.00* (mean)	+14.00* (mean)	+7.00* (mean)	+16.00* (mean)	– despite an increase in total cholesterol, triglycerides and LDL cholesterol after the TDF-to-TAF switch, no difference was found in the LDL:HDL cholesterol ratio, an essential predictor of cardiovascular risk	[25]
490	42	+23.20* (median)	+15.50* (median)	+3.50* (median)	+15.50* (median)	– the increases in lipid concentrations were similar between the participants receiving a non-NRTI, protease inhibitor or INSTI-based ART. Using a boosting agent (ritonavir or cobicistat) did not affect the observed changes in lipid concentrations.	[23]
148	24	+13.40* (mean)	+7.60* (mean)	+3.80* (mean)	+3.00* (median)	– changes in blood lipids did not determine a significant variation in cardiovascular risk scores after six months from the switch	[40]
4328	17 (median)	+12.00* (median)	+8.00* (median)	+2.00* (median)	+14.00* (median)	– 59% of patients with an elevated ASCVD risk were not prescribed statins at any point on or after their first lipid panel after switch	[41]
Included in the analysis: for total cholesterol – 98 for LDL – 95 for HDL – 96 for TG – 98	9 months-2.5 years	+8.70* (mean)	+1.70 (mean)	+2.90* (mean)	+20.00* (mean)	– -study presents underutility of statins after switching from TDF to TAF	[42]
118	52 weeks	no data	+16.00* (median)	no data	+28.00* (median)	– -TAF-based therapy had a statistically significantly worse effect on lipid parameters than TDF- based therapy	[43]

* statistically significant change
ASCVD – atherosclerotic cardiovascular disease

A high proportion of patients with dyslipidemia bring concern about the insufficient administration of lipid-lowering agents in the HIV-positive population. In recent years, the problem of the so-called "statin gap" has been addressed in multiple research papers, indicating that PLWH is less likely to be treated with statins according to current lipid-lowering treatment recommendations compared with HIV-negative patients [34]. What is more, the intensity of treatment has been reported to be inadequate in the context of choosing the type of statin and its daily dosage [35, 36], which may be the result of physicians' fear of potential drug-drug interactions. The metabolism of some statins and ART drugs includes the influence on cytochrome P450, which results in a higher (but still low) risk of drug toxicity and attenuation of the effect of therapy [37]. Nevertheless, the administration of lipid-lowering therapy should be considered a milestone in the long-term care of HIV-positive patients. Potential interactions with antiretrovirals can be managed by careful selection of the appropriate statin or another drug [38]. Also, other factors contributing to non-optimal lipid parameters among patients should be considered, such as non-adherence, suboptimal physician-provider/patient relationships, or overestimating the effect of diet control.

It is essential to mention that this study has some limitations that need to be addressed. Firstly, the sample size was relatively small, with no comparator group that would consist of patients continuing TDF-based treatment. The study's disadvantage is the need for more data about other factors influencing lipid parameters, such as dietary habits or physical activity. Nevertheless, our research provides data from a real-world setting with a comparatively long observation period of one year, which still needs to be discovered among currently published articles.

In conclusion, the presented data suggest that TAF could worsen the lipids parameters in ART-experienced patients, especially those younger than 40 and within the normal BMI range. This effect should be taken into consideration by both clinicians and patients when deciding to include TAF in ART. All PLWHs should be informed of the need to monitor their lipid parameters to facilitate their detection and management of dyslipidemia. Prospective studies on the possible mechanisms behind this metabolic phenomenon, including identifying the risk factors of lipid disorders after switching to a TAF-containing regimen, are required. Professional societies should emphasise the importance of improving the quality of cardiovascular care among PLWHs through early detection and proper management of dyslipidemias.

Acknowledgements

Contributors: MŁ, JS and TM created the concept of the article; MŁ and JS performed the data research; MŁ performed data analysis and created figures; MŁ and ZG drafted the manuscript; and lastly, AL, TM and AWD critically revised the manuscript. All authors have accepted the final version of the manuscript.

Conflict of interest statement
The authors declare no conflict of interest.

Funding sources
There are no sources of funding to declare.

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