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Effect of Clinical Study of Moringa oleifera on Body mass index, Low density lipoprotein and Triglyceride level in Patients on Tenofovir/lamivudine/efavirenz Combination Therapy

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Original Article

Abstract:

Background and aim: HIV/AIDS drugs usually have undesirable side effect. *Moringa oleifera* is a plant that has been uses for various beneficial purposes. The aim of this study is to investigate the potential benefits of *Moringa oleifera* on blood triglyceride and low density lipoprotein (LDL) levels in patient receiving tenofovir/lamivudine/efavirenz (TLE) combination therapy.

Methods: The protocol was designed as a Longitudinal Randomized Comparative Trial (LRCT) involving 140 HIV adult subjects (56 men and 84 women) who had already been on TLE (300/300/600mg) combination therapy for at least 6 months prior to the study. They were enrolled from a teaching hospital in Nigeria. *M. oleifera* capsules (200mg) were given to the subjects to be used from the first day as visit 0 until visit 1 (four weeks after) and 2 (12 weeks after). Blood samples of subjects were collected at visits 0, 1 and 2 and serum analyzed for triglyceride and LDL levels

Results: There was a significant decrease in serum LDL level ($P<0.01$) at visit 1 compared to visit 0. There was also significant ($P<0.01$) improvement compared to visit 0 and visit 1. There was a significant decrease in blood triglyceride level ($P<0.01$) at visit 1 compared to visit 0 of TLE combination. At visit on day 2, there was a further significant decrease in triglyceride level compared to visit 0 Conclusion: *M. oleifera* may

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be useful in improving blood triglyceride and LDL levels of patients receiving TLE combination.

Conclusion: *M. oleifera* may be useful in improving blood triglyceride and LDL levels of patients receiving TLE combination.

Keywords: Moringa oleifera, blood, glucose, Tenofovir, Tenofovir / Lamivudine/Efavirenz

INTRODUCTION

There are at least six classes of drugs, which are commonly used in combination, to treat HIV infection. Antiretroviral (ARV) drugs are basically classified by the phase of the retrovirus life-cycle that the drug acts or inhibits[1]. Well-known combinations include two nucleoside reverse-transcriptase inhibitors (NRTI) and one non-nucleoside reverse-transcriptase inhibitor (NNRTI), protease inhibitor (PI) or integrase inhibitors also referred to as integrase nuclear strand transfer inhibitors (INSTIs) as a base. The life cycle of HIV can be as short as about 1.5 days from viral entry into a cell, through replication, assembly, and release of additional viruses, to infection of other cells[2]. HIV lacks proofreading enzymes to correct errors made when it converts its RNA into DNA via reverse transcription. Its short life cycle and high error rate result in the virus mutating very rapidly, leading to a high genetic variation[3]. The more active the copies of the virus, the greater the possibility of the infection acquiring resistance to antiretroviral drugs[4].

These drugs can also help reduce the risk of HIV-related issues, stop the virus from progressing, and reduce the rate of transmission to others. Moreover, antiretroviral drugs improve quality of life and increase life expectancy[5]. People experience side effects in different ways and degree [6]. However, these may go away after a few weeks of treatment. There are several classes of antiretroviral drug, and if one causes side effects, another may not [5,6]. Advances in antiretroviral therapies to treat the disease have led to improved life quality and fewer complications from the infection than ever before. However, this may require given potent antiretroviral medications for many years[7].

HIV drugs have significantly improved over the years, and severe side effects have become less likely than the past. However, HIV drugs can still cause side effects[8]. Some are mild, while others are more severe or even life-threatening. Side effects may also worsen if the drug is taken for the long term. It is likely that other medications interact with HIV drugs, causing side effects. Other health

conditions can also worsen the side effects of HIV drugs.

Antiretroviral formulations inhibit HIV at certain stages of the viral life cycle [9], such as binding, fusion and entry, reverse transcription and integration, proviral transcription, cytoplasmic expression replication, assembly and budding, release, and maturation [10]. Some metabolic side effects of antiretroviral drugs include bone demineralization, increased cholesterol and triglyceride levels, and abnormalities in fat distribution [5,7]. Lipodystrophy is a common metabolic adverse event that is associated with central adiposity, peripheral fat wasting, cushingoid feature, lipomas, and breast hypertrophy[5]. In particular, HIV-infected patients with abnormal fat distribution or lipoatrophy may experience dyslipidemia, which has become a serious issue [3,5,7]. In some HIV-infected individuals, serious metabolic events may lead to discontinuation of treatment or switching to another regimen with fewer side effects [5,7].

Moringa oleifera Lam (Moringaceae) is a highly useful plant, well distributed in different countries, particularly in the tropical and subtropical regions. It has a wide range of medicinal uses with high nutritional value. Different parts of this plant contain a profile of important minerals, and are a good source of protein, vitamins, beta-carotene, amino acids and various phenols. The M. oleifera leaves are consumed fresh, dried, or as extract [11-13]. Some communities consume it in their regular diets, whereas others use it as a nutritional supplement and for medicinal reasons, mainly diabetes. Common diseases such as malaria, cut, typhoid fever, swellings, high blood pressure and diabetes are treated with the leaves[14]. They are also used to increase milk production in lactating women [15-18], sediment impurities of water[19], detoxification of free radicals [20,21], improving immunity (to manage HIV/AIDS) and treating related symptoms. The aim of this study is to investigate the clinical effect of *M. oleifera* with tenofovir/lamivudine/efavirenz (TLE) (300/300/600mg) regimen on blood low-density lipoprotein (LDL) and triglyceride levels.

METHODS

The protocol was designed as a Longitudinal Randomized Comparative Trial (LRCT) as applied in clinical investigation involving more than one patient treatment groups over a period of time. This study was designed according to a part of the FDA (Food and Drug Administration)/WHO Phases during randomized controlled clinical trials (RCCTs) of drugs. Groups were evaluates in 3 phases as commencement, 4weeks follow-up and 12 weeks after beginning of treatment (completion of drug administration).

Recruitment procedure

Participants were recruited from the HIV Clinic of the Outpatient Section of University of Port Harcourt Teaching in Rivers State. Prospective participants were officially and properly informed prior to the exercise, doubts were cleared and benefits x-rayed to the patients.

Procedures

The study protocol was designed as a Longitudinal Randomized Comparative Trial (LRCT) with a total of 140 adult HIV patients (56 men and 84 women) who had already been on tenofovir/lamivudine/efavirenz (300/300/600mg) TLE combination therapy for at least six months. Subjects were categorized into groups as underweight, normal weight, over weight and obese. On visit 0, blood samples of the subjects already on TLE regimen (without *M. oleifera* or any supplements) for at least 6 month were taken for analysis. M *M. oleifera* capsules (200mg) were given to each subject to be taken daily from beginning (baseline) to 12 weeks after beginning of the study. Blood samples were collected from the participants at each visit (1 and 2) and analyzed for LDL and triglyceride levels, respectively.

Data collection

Anthropometric parameters (weight and height) and blood samples of the participants were divided into different categories. After duly signed consent forms were obtained from them, their blood samples were examined at the UPTH Hematology Research Laboratory.

Blood samples

Analysis of samples was done at the Hematology Laboratory of UPTH, Rivers State, Nigeria. Computerized

clinical chemistry analyzer (VS10) (Vitro Scient) equipped with the principle guided by Beer-lambert's law was used to measure concentration of biochemical parameters.

Data analysis

Data were presented in tables of SPSS (IBM® version 23) and MATLAB (version 17). Descriptive statistics were used to express variable characteristics while categorical data as frequency (percentage) and post hoc Dunnett's T3 test of multiple comparisons were used to compare mean values, while binary logistic regression was used to determine factors contributing to the changes in variables. Variable interactions were tested at 95% confidence interval, with $P \leq 0.05$ considered as significance level.

Ethical considerations

Ethical approval

Ethical approval was obtained from the University of Port Harcourt Research Ethics Committ'se (UPH/R&D/REC/--)

Patient consent

In line with the ethical requirements, the ethical considerations below were taken into account while carrying out the study:

i. Beneficence (the duty to do good, and with due consideration of the best interests of the subjects);
ii. Non-maleficence (the obligation of avoidance of harm to the subjects as much as possible);
iii. Respect (giving the deserved respect to all subjects); and
iv. Justice and confidentiality (ensuring fairness and unconditional privacy protection)

Individual who did not volunteer to participate were not forced to do so. Volunteering individuals provided informed consent before beginning of the study.

Results

LDL and triglyceride level s of ART subjects receiving TLE at visit 0

Six of our participants were underweight, 76 had normal weight, 44 were overweight, and 14 were obese (Tables 1 and 2).

Table 1: Socio-demographic and anthropometric characteristics of participan

Sex		N	Mean±SD	SE
Age (yr)	Male	53	39.11±10.46*	1.43
	Female	87	35.63±8.33	0.89
	Total	*140*	*36.01±9.41*	*0.77*
Weight (kg)	Male	53	69.00±9.76	1.3
	Female	87	66.43±12.1	1.25
	Total	*140*	*67.38±11.3*	*0.92*
Height (m)	Male	53	1.71±0.09**	0.01
	Female	87	1.64±0.08	0.01
	Total	*140*	*1.66±0.09*	*0.01*
BMI (kgm-^{2})	Male	53	23.77±3.26	0.44
	Female	87	24.79±4.60	0.47
	Total	*140*	*24.41±4.17*	*0.35*

Table 2: Post-hoc (Dunnett's T3) multiple comparison of the metabolic profile of HIV patients on TLE NOT receiving Moringa oleifera supplement at different visit

Parameters	Visits	Mean±SD	Min.	Max.	SE	95% CI for mean	
						Lower limit	Upper limit
TG (mmol/l)	Visit 0	1.24±0.47	0.30	2.30	0.05	1.14	1.35
	Visit 1	1.27±0.37	0.24	2.21	0.04	1.19	1.35
	Visit 2	1.15±0.47	0.23	3.18	0.05	1.05	1.25
	Total	1.22±0.44	0.23	3.18	0.03	1.17	1.28
LDL ((mmol/l	Visit 0	2.17±0.77	0.53	4.43	0.08	2.00	2.34
	Visit 1	2.08±0.67	0.87	3.73	0.07	1.93	2.22
	Visit 2	2.08±0.47	1.28	3.78	0.05	1.98	2.18
	Total	2.11±0.65	0.53	4.43	0.04	2.03	2.19

ART: Antiretroviral Therapy

ARV: Antiretroviral

TLE: Tenofovir/lamivudine/efavirenz

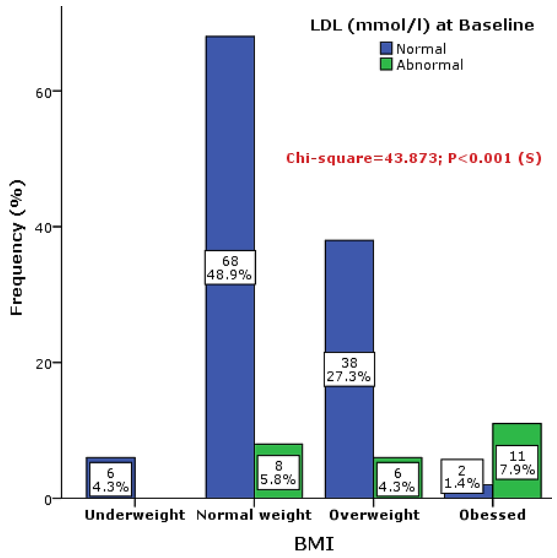

Figure 1: Body mass index-associated low density lipoprotein (LDL) classification and distribution at visit 0 (baseline)

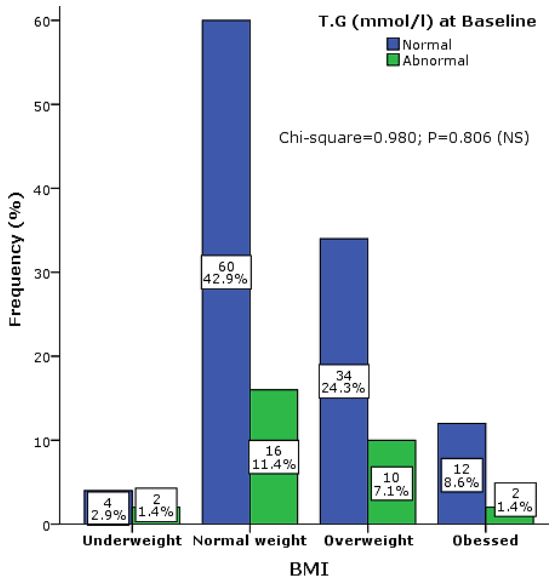

Figure 2: Body mass index-associated triglyceride classification and distribution at visit 0 (baseline)

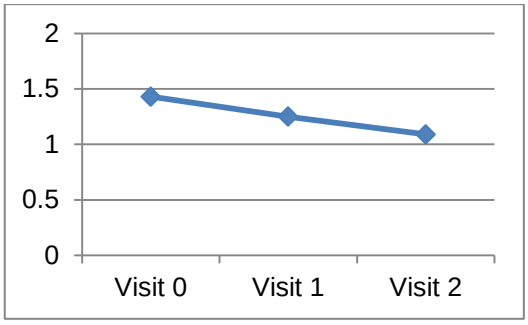

Figure 1: Serum level of triglyceride in TDF patients receiving Moringa oleifera (TDF+M) supplement at different visits

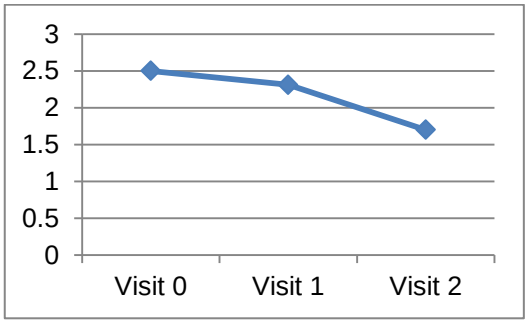

Figure 2: Level of low density lipoprotein in TDF patients receiving Moringa oleifera (TDF+M) supplement at different visits

Effect of M. oleifera on ART patient receiving TLE at visit 1

A statistically significant decrease ($P<0.001$) was observed in LDL level observed in the mean values of TLE/M. oleifera subjects between visit 0 and visit 1. There was also a significant decrease ($P<0.001$) in triglyceride level in visit 1 compared to visit 0. In addition, there was no difference between TLE/M. oleifera (visit 1) and TLE/non M. oleifera (visit 1) in serum triglyceride levels of the subjects (Tables 2- 6)

Effect of M. oleifera on ART patient receiving TLE at visit 2

A statistically significant ($P<0.001$) decrease in LDL and triglyceride levels was observed in values of the TLE/M. oleifera subjects between visit 0 and visit 2, while there was no significant differences ($P<0.001$) between TLE/non M. oleifera (visit 2) and TLE/non M. oleifera (visit 0) in the serum levels of LDL and triglyceride (Tables 1 and 2).

Discussion

Severe side effects have been reported with all ARV drugs; and in the earlier periods, when combination antiretroviral therapy (ART) is introduced [21,22], adverse effects are among the most common reasons for switching or discontinuing treatment and lack of patient adherence to medication [23,24]. Fortunately, recent ARV drugs are associated with fewer severe toxic effects than regimens used previously [25]. In a study, less than 10% of ART-naive patients enrolled in randomized trials experience treatment-limiting adverse events [26]. However, the long-term side effects of ART may be underestimated because most clinical trials use more specific inclusion criteria that exclude subjects with

certain underlying medical history/conditions, and the duration of participant follow-up is usually short [27-29]. It should be noted that HIV patients in the current study have been on TDF ART for at least six months prior to the study and there are strong indications that the type of ARV-T, duration and application is well associated with "the severity of metabolic syndromes"[15,23,29]. Regarding classification of BMI (underweight, normal, overweight and obese), this study showed a linear relationship to the LDL cholesterol and triglyceride (TG) (classified as normal and abnormal). Despite the slight improvement of TG and LDL-C at visit 1 (4 weeks after administration of M. oleifera supplement, no significant decrease was observed; however, a significant decrease in both the mean values as well as proportion of subjects with high TG and LDL-C was observed at visit 2 when compared to the TDF-NM group that showed a reverse result, which indicates the positive gradual effect of M. oleifera supplement. These observations agree with several other studies reporting the hypocholesterolemic and hypoglycemic effects of M. oleifera [30-33,35].

Kumar and Mandapaka[35] noted that M. oleifera used in dietary form reduced serum CHOL, PHOSLIPID, TG, VLDL, LDL, cholesterol to phospholipid ratio and atherogenic index, but there was an increase in HDL/HDL-total cholesterol ratio. The antilipidemic property of M. oleifera observed in this study agrees with the findings of Ghasi et al.[36] and Dubey et al.[37] as they reported that the presence of a bioactive phyto-molecule, called β-sitosterol, plays a substantial role. Different parts of M. oleifera have also been demonstrated to be rich sources of unique glucosinolates, carotenoids, flavonoids, phenolic acids, tocopherols, (PUFAs), highly bioavailable minerals, folate, and polyunsaturated fatty acids, most of which have been known to possess various pharmacological activities [38-40]. M. oleifera leaves, used as vegetables in various countries of the world, have been shown to have positive effects on blood and immune system [41-43]. Aqueous and alcoholic extracts of leaves and roots of M. oleifera have been found to exhibit strong in vitro antioxidant, anti-diabetic, cardiovascular, hepatoprotective and anti-cancer activities [44-46]. These effects

may be responsible for improvement of BMI, metabolic profile and lipid profile of patients on ARV therapy.

Conclusion

M. oleifera may be useful for patients on antiretroviral regimen are suffering from side effects of the drug. Further studies may be necessary to understand molecular and pharmacological activities and mechanisms of action of this plant to improve the metabolic profile of patients on HIV drugs.

Conflict of interest

The authors declare that there is no conflict of interests.

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