Dyslipidemia in HIV positive patients on first line antiretroviral therapy

Salame R N[a*], Patil P L[b]

[a]Assistant Professor, Department of Medicine, Shri. VNGMC Yavatmal, Maharashtra, INDIA.
[b]Professor and HOD, Department of Medicine, Government Medical College, Gondia, Maharashtra, INDIA.
Email: rohit1241986@gmail.com

Abstract
Background: Abnormalities of lipid metabolism are common in human immunodeficiency virus (HIV)-infected patients and tend to be accentuated in those receiving highly active antiretroviral therapy (HAART). However, data on lipid profile of treatmentnaïve. HIV-infected patients in India are limited. So, the study was conducted to describe the pattern of lipid profile among treatmentnaive HIV-I positive patients and changes following HAART initiation in a tertiary care center. **Methods:** An observational prospective study was conducted on 120 normotensive, non-diabetic and non-obese, treatment-naive HIV-infected patients, out of which 65 were men and 55were women of age more than18 years, after applying appropriate inclusion and exclusion criterias. The study was carried out at ART center, in our tertiary care center for a period of 2 years from Dec 2012 to Nov 2014. HIV-I treatment naïve patients were put on different first line ART regimen according to NACO guidelines. Fasting lipid profiles were analyzed enzymatically. Values of lipid parameter were retrieved at the initiation of HAART then patients were followed after 3 and 6 months of HAART therapy. **Results** The study concluded that there was significant change in the lipid parameters following initiation of HAART, there was increase in mean TC,TG and LDL-C values at 3 months and further increase at 6 months with statistically highly significant P value(< 0.001). At the end of 6 month compared to baseline there was highly significant change in Triglycerides(139.33 ± 23.82 to 145.77 ± 24.42), TC(147.11 ± 28.36 to 153.77 ± 28.74) and LDL (92.55 ± 11.94 to 98.11 ± 12.94) respectively , P value (< 0.001). There was no statistical difference in HDL value at the end of 3 month [p value (0.684)] as compared to baseline value, but at the end of 6 month it significantly changes 41.22 ± 2.38 to 38.55 ± 2.69 p value (< 0.001). **Conclusions:** With the use of first-line antiretroviral therapy regimens were associated with raised total cholesterol, LDL-cholesterol, and triglycerides, an established atherogenic lipid profiles Therefore we recommend that Lipid profiles should be performed at baseline before commencement of antiretroviral therapy and then periodically through treatment follow-up to monitor any rising trends .Lipid profile results can therefore be a good index for disease progression, intervention and management of HIV patients.
Keywords: Highly active antiretroviral therapy; Human immunodeficiencyvirus; Low density lipoprotein; Very low density lipoprotein;High density lipoprotein; Triglyceride; Total cholesterol.

[*]**Address for Correspondence:**
Dr. Salame R N, Assistant Professor, Department of Medicine, Shri. VNGMC Yavatmal, Maharashtra, INDIA.
Email: rohit1241986@gmail.com

INTRODUCTION

The introduction of antiretroviral therapy in mid 1990s led to substantial improvement in the prognosis of HIV/ AIDS patients, with reduction in morbidity and mortality due to opportunistic disease and consequent improvement in quality of life.[1] Dyslipidemia is a frequent side effect of antiretroviral therapy, especially in combinations that include protease inhibitors (PIs) and nucleoside reverse transcriptase inhibitors (NRTIs). Hypertriglyceridemia, already known to be associated with HIV infection, is the most common lipid abnormality; it occurs alone or in association with hypercholesterolemia, especially in patients with evidence of body fat abnormalities[2].The mechanisms responsible for lipid profile changes in

HIV/AIDS infected patients are proven to be complex and to date are not fully understood but are probably multifactorial. It is suggested that various conditions and complex interactions involving the direct and indirect effects of antiretroviral medications and HIV infection itself have played a role in development of dyslipidemia[3,4,5].

Many of the patients have been noted to have a characteristic set of body habitus changes associated with fat redistribution, consisting of truncal obesity coupled with peripheral wasting. These changes may develop at any time ranging from about 6 weeks to several years following the initiation of HAART[6]. HAART causes increase in TC and low density lipoprotein (LDL)[7]. Dyslipidemia is influenced by genetic factors, alcohol, co- morbid conditions like diabetes mellitus, hypothyroidism etc.Following the initiation of ART, more pronounced atherogenic changes in the lipid profile has been increasingly observed[8].

Initially it was associated with exposure to protease inhibitors (PI) but subsequently exposure to nucleoside reverse transcriptase inhibitors(NRTIs) particularly stavudine (d4T) and zidovudine (AZT) were recognized as being central to the development of this syndrome, even though it has been less well studied[9,10]. Food ha The prevalence of dyslipidemia and other risk factor for cardiovascular disease is significant in HIV/AIDS patients receiving ART, ranging from 20% to 80% depending upon population investigated[11]. In view of high prevalence of dyslipidemia and increased risk for cardiovascular disease among patients with HIV which is matter of concern of public health.

Therefore this study has been undertaken to find out whether dyslipidemia exists in our population with HIV positive patients on first line anti- retroviral therapy at our tertiary health care Centre and also to assess comparative changes of serum lipid profile in HIV positive patients on different first line drug regimen and determine the changes in its different fractions with different regimen.

MATERIALS AND METHODS

We conducted an observational prospective study on 120 HIV-1 positive treatment naïve patientsof more than 18 years of age.Out of which 65 were males and 55 were females. The study was carried out at ART center, medicine OPD and wards in a tertiary care hospital for a period of 2years from December 2012 to November2014. HIV-1 positive treatment naïve patients more than 18 years of age were started on first line ART as per the NACO guidelines were included in the study.Patients were followed at 3 months and 6 months interval and results were compared with the baseline values of lipid profile . Patients with HIV-II , age less than 18 years,

with past history of diabetes mellitus, hypertension, ischemic heart disease, renal failure, hepatic failure and acute or chronic pancreatitis were excluded from the study. Patients who were already taking lipid lowering agents were also excluded. After obtaining informed consent from the subjects, 12h fasting venous blood samples were collected from median cubital vein aseptically. Serum was separated and analysed on the same day. HIV infection was diagnosed by ELISA methods and patients were put on ART as per NACO guidelines. Out of 120 patients 73 patients were put on ZLN, 28 patients were on TLN, 10 were on ZLE and 9 were on TLE. Clinical, and laboratory data -were recorded at the start of the study and after 3 and 6 months of initiatonof HAART. TC was analysed by enzymatic method (Cholesterol esterase, cholesterol oxidase and peroxidase)[11], HDL-C by precipitation (end point) method[12], TG by enzymatic method (Glycerolphosphateoxidaseand peroxidase;Endpoint)[13]. LDL values were calculated by using indirect metthod of Friedewald equation[14]. Finally dyslipidemia was defined as per the United States National Cholesterol Education Program, Adult Treatment Panel (NCEP- ATP) III guidelines as total cholesterol > 200mg/ dl, HDL-C < 40mg/dl, LDL-C > 130mg/dl, triglycerides > 150mg/dl, and TC/HDL-C > 5.

RESULTS

In our study 120 HIV-I positive patients started on ART were studied, out of which Minimum age was 19 years and maximum age was 66 years. Mean age of patient was (34.48 ± 8.35). Maximum numbers of patients were in the age group of 31-40 (49.1%). Out of total 120 patients, 65 were male (54.16%) and 55 (45.84%) were females. No transgender subjects were included. Males to females ratio was 1.18: 1Predominantly heterosexual transmission was observed in 106 (88.33%). Multiple modes of transmission were thought of in 10 patients (8.33 %), whereas in 4 (3.33 %) subjects the exact mode of transmission could not be ascertained.

In our study about 86 % of the patients were married at the time of presentation. Most patients were from lower socio-economic group majority being Laborers. Out of 120 HIV-I positive patients, 73 HIV-1 positive patients were put on ZLN regimen, out of which 47 (64.38%) were males and 26 (35.62%) were females. 28 (23.33%) HIV-1 positive patients were put on TLN regimen, out of which 12 (42.85%) were males and 16 (57.15%) were females. 10 HIV -1 positive patients were put on ZLE regimen, out of which 3 (30 %) were males and 7 (70%) were females. 9 (7.5%) HIV-1 positive patients were put on TLE regimen, out of which 3 (33.33%) were males and 6 (66.67%) were females

Table 1: Changes of lipid parameter on TLE regimen after 3 months and 6 months follow up :

Lipid parameter	Baseline	3 month	6 month
TG	139.33 ±23.82	141.11 ±23.51	145.77 ± 24.42
P VALUE		0.0277, S	< 0.001,HS
TC	147.11 ± 28.36	149.77 ± 29.63	153.77 ± 28.74
P VALUE		0.0388,S	< 0.001, HS
HDL	41.22 ± 2.38	41.00 ± 3.12	38.55 ± 2.69
P VALUE		0.6846, NS	<0.001 HS
LDL	92.55 ± 11.94	94.77 ± 11.80	98.11 ± 12.94
P VALUE		0.032,S	<0.001HS

As per Table no:1 shows changes in lipid parameters put on TLE regimen, there was significant change at the end of 3 month as compared to baseline in TG (139.33 ± 23.82 to 141.11 ±23.51) P value (0.027), TC(147.11 ± 28.36 to 149.77 ± 29.63) P value (0.038) and LDL (92.55 ± 11.94 to 94.77 ± 11.80) P value (0.032) respectively. At the end of 6 month compared to baseline there was highly significant change in TG (139.33 ±23.82 to 145.77 ± 24.42), TC (147.11 ± 28.36 to 153.77 ± 28.74) , LDL (92.55 ± 11.94 to 98.11 ± 12.94) P value (0.001). There was no statistical difference in HDL value at the end of 3 month (41.22 ± 2.38 to 41.00 ± 3.12) P value (0.684)as compared to baseline value, but at the end of 6 month it significantly changes (41.22 ± 2.38 to 38.55 ± 2.69)P value(< 0.001).

Table 2: Changes of lipid parameter in TLN regimen after 3months and 6 months follow up:

Lipid parameter	Baseline	3 month	6 month
TG	113.03 ±31.03	112.25 ±31.58	116.64 ±33.95
P VALUE		0.04,S	0.0002,HS
TC	134.46 ± 29.10	137.96 ± 29.25	142.81 ± 29.68
P VALUE		0.0198,S	<0.001,HS
HDL	44.85 ± 4.22	46.07 ± 4.20	46.17 ± 3.98
P VALUE		0.2643, NS	0.944,NS
LDL	87.42 ± 15.34	88.5 ± 14.73	89.57 ± 14.30
P VALUE		0.034,S	0.022,S

Table no 2shows changes in lipid parameters put on TLN regimen, there was significant change at the end of 3 month as compared to baseline in TG (113.03 ±31.03 to 112.25±31.58) P value (0.04), TC(134.46± 29.10 to 137.96± 29.25) P value (0.0198) and LDL (87.42±15.34 to 88.5±14.73) P value (0.034) respectively. At the end of 6 month compared to baseline there was highly significant change in TG (112.25±23.82 to 116.64± 33.95) P value (0.002), TC (137.96± 29.25 to 142.81± 29.68) P value (<0.001) , LDL (88.5± 14.73 to 89.57± 14.30) P value (0.022). There was no statistical difference in HDL value at the end of 3 month (44.85± 4.22 to 46.07± 4.20) P value (0.2643) as compared to baseline value, and also at the end of 6 months (46.07 ± 4.20 to 46.17± 3.98) P value (.0944).

Table 3: Changes of lipid parameters in ZLE regimen after 3 months and 6 months follow up:

Lipid parameter	Baseline	3 month	6 month
TG	132.72 ± 29.40	134.40 ± 31.47	143.28 ± 31.86
P VALUE		0.008,HS	<0.001,HS
TC	141.65 ± 27.46	143.60 ± 29.52	153.40 ±30.06
P VALUE		0.011,S	<0.001, HS
HDL	44.28 ± 4.08	44.08 ± 4.03	44.04 ± 3.88
P VALUE		0.1006,NS	0.1435,NS
LDL	90.20 ± 12.18	91.40 ± 12.48	96.21 ± 13.18
P VALUE		0.003,HS	< 0.001, HS

Table no:3 shows changes in lipid parameters put on ZLE regimen, there was significant change at the end of 3 month as compared to baseline in TG (132.72 ± 29.40 to 134.40 ±23.51) P value (0.008), TC(141.65 ± 27.46 to 143.60± 29.52) P value (0.011) and LDL (90.20± 12.18 to 91.40±12.48) P value (0.003) respectively. At the end of 6 month compared to baseline there was highly significant change in TG (134.40±31.47 to 143.28± 31.86), TC (143.60± 29.52 to 153.40± 30.06) , LDL (91.40± 12.48 to 96.21 ± 13.18) P value (< 0.001). There was no statistical difference in HDL value atthe end of 3 month (44.28± 4.08 to 44.08± 4.03) P value (0.1006) and also at the end of 6 months (44.08± 4.03 to 44.04± 3.88)P value (0.1435).

Table 4: Changes of lipid parameters in ZLN regimen after 3 months and 6 months follow up:

Lipid parameter	Baseline	3 month	6 month
TG	134.84 ± 29.49	136.43 ± 31.81	144.23 ± 31.69
P VALUE		0.0275,S	<0.001,HS
TC	143.20 ± 27.13	144.86 ± 29.44	155.02 ± 29.66
P VALUE		0.0101, S	<0.001, HS
HDL	44.31 ± 4.24	44.20 ± 4.38	44.19 ± 3.99
P VALUE		O.408,NS	0.4899,NS
LDL	91.06 ± 12.18	92.08 ± 12.62	97.30± 13.06
P VALUE		0.021,S	<0.001,HS

Table no:4 shows changes in lipid parameters on ZLN regimen, there was significant change at the end of 3 month as compared to baseline in TG (134.84 ± 29.49 to 136.43 ±31.81) P value (0.0275), TC(143.20 ± 27.13 to 144.86 ± 29.44) P value (0.0101) and LDL (91.06 ± 12.18 to 92.08 ± 12.62) P value (0.021) respectively. At the end of 6 month compared to baseline there was highly significant change in TG (136.43 ±31.81 to 144.23 ± 31.69), TC (144.86 ± 29.44 to 155.02 ± 29.66) , LDL (92.08 ± 12.62 to 97.30 ± 13.06) P value (< 0.001). There was no statistical difference in HDL value at the end of 3 month (44.31± 4.24 to 44.20± 4.38) P value (0.408) and also at the end of 6 months (44.20± 4.38 to 44.19± 3.99) P value (0.4899).

DISCUSSION

This hospital based observational prospective study was conducted in our parent institute from December 2012 to November 2014. A total of 120 HIV-I patients subjects started on first line ART attending the ART Centre/ Medicine OPD and admitted in Medicine ward were studied. It is well known that Protease Inhibitors (PIs) induce derangements of lipid profile during ART[15,16,17]. However, evidence in support of the adverse effects of NRTI's (Zidovudine, Stavudine, Lamivudine) and NNRTI's (Nevirapine, Effavirenz) on lipid profile in HIV patients on ART is limited. Our study showed that ART patients (Zidovudine ± Lamivudine ± Nevirapine) had significantly high level of Total Cholesterol, LDL-Cholesterol, Triglycerides. There was no significant difference in HDL-C levels between these group. An association between dyslipidemia and myocardial infarction. Our study showed that with the use of first line HAART the prevalence of dyslipidemia is more as compared to ART naïve patients. Increase in Triglyceride level is more in all regimen as compared to other lipid parameters. At 3 month follow up mean change in Triglyceride, Total cholesterol and LDL vales was more in ZLE regimen as compared to other regimen, while HDL remains unchanged. At 6 month follow up mean change in Triglyceride, Total cholesterol and LDL vales was more in ZLN regimen as compared to other regimen, while mean HDL value is more in TLE regimen as compared to other regimen. This finding was similar with finding of Jagjeet singh, *et al.*[18]

HIV-1 infection causes a specific pattern of dyslipidemia, resulting from a combination of increased production and decreased clearance of lipoproteins. It has been seen that out of 18 differentially expressed proteins in HIV-infected cells, six enzymes/kinases are expressed exclusively in HIV-infected cells (CO3, P3C2B, KPCB, FAS,ACSL1 and GPX1) and one isomerase (PDIA3) is slightly down regulated after chronic HIV infection.

These further enhance fatty acid synthesis, secrete TGs, increase the quantity of LDL, alter the lipid transport and metabolism and oxidize lipids. HAART induces raised levels of TC, LDL and TG, and variables effects on HDL levels[19,20,21,22]. The pathogenesis of HAART-associated dyslipidemia is complex, and several factors are involved, including direct effects of HAART on lipid metabolism, endothelial and adipocyte cell function and mitochondrial dysfunction. Cytokines, especially TNF-α, interleukin-1 and interleukin-6, which mediate the host acute-phase response to infection and inflammation, also mediate changes in lipid metabolism and HAART leads to activation of these proinflammatory cytokines. TNF suppresses lipoprotein lipase activity in adipose tissues. IFN-α increases TG by two main mechanisms: a decrease in TG clearance and an increase of *de novo* hepatic lipogenesis and VLDL production. Both decreased TG clearance and increased hepatic very low density lipoprotein over production have been found in HIV-positive patients, and the hepatic increased lipogenesis correlates to IFN-α. HIV-infected patients are very much prone to infections both acute and chronic with multiple pathogens such as HSV-1, HSV-2, CMV, *H. pylori*, *C. pneumonia* and hepatitis A virus. These infections lead to continuous low-level production of cytokines, increasing TG and TC, and lowering HDL concentrations producing an atherogenic lipid profile. Acute infections might increase TG by the way of hormones(steroids) or cytokines other than TNF-α or IFN-α. Also, endotoxins released by bacteria decrease macrophage LPL mRNA, independently of TNF. They interfere with processingof LPL oligosaccharide chains and disrupt the surface of the vascular endothelium. As LPL is normally anchored to heparin sulfate proteoglycans on the endothelial surface, damage of the latter by endotoxin would release LPL into the circulation, enabling it to be rapidly cleared by the liver. Derangements of lipid metabolism associated with HAART have been described particularly in patients on treatment regimens including PIs and d-4T, but also for treatment regimens including NVP and EFV[23,24]. However, the increased risk of cardiovascular diseases associated with the significant lipid derangement is well known and would therefore suggest that HAART may actually have harmful effects on the cardiovascular system.

An association between dyslipidemia and myocardial infarction (MI) and cardiovascular disease (CVD) has been recognized. The association between high serum cholesterol levels, especially high LDL-C, and CVD is causal and independent of other risk factors while increasing clinical evidence suggested that elevated triglycerides may be an independent risk factor for CVD. Low HDL-C can also act synergistically with other lipid to increase CVD[23].

We recommend that lipid profile measurements at baseline, It could become an important parameter to increase survival and improve treatment outcome. Therefore lipid profiles should be screened before and after start of antiretroviral therapy; then periodically at 3 month, 6 month etc. through treatment follow-up to monitor any rising trends.

CONCLUSION

From the above findings, it is evident that HIV-1 replication alone without any influence of antiviral drugs or other human genetic factors induces changes in serum lipid profile parameters which could be used to determine

HIV-infected persons with high risk of myocardial infarction before enrolment for HAART. Therefore, fasting plasma lipid profile should be done of all HIV-infected persons before starting HAART with periodic repetitions after enrolling on HAART, since significant increases in plasma TG, TC and LDL-C concentrations have been reported in HIV patients on HAART. Lipid profile results can therefore be a good index for disease progression, intervention and management of HIV patients.

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