

# A Study to Evaluate Lipid Profile in Treatment Naïve HIV Positive Patients

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**Abstract** HIV infection is associated with lipid abnormalities in treatment naïve patients. CD4 count is used for monitoring the HIV infection. Primary objective was to evaluate and correlate lipid profile and CD4 counts in HIV infection. Secondary objective was to evaluate the feasibility of using Lipid profile to monitor the HIV infected treatment naïve patients instead of CD4 counts. 112 patients were selected based on a criteria from ART center in tertiary care center. CD4 counts were assessed and Lipid profile was evaluated enzymatically. A correlation study was done between the lipid profile and the CD4 count and clinical stages of infection. Cholesterol showed no significant correlation in any stage. HDL-C showed significant correlation ( $p < 0.05$ ) with stage 2 and 4 disease. LDL-C showed no significant correlation in any stage. TGL showed significant correlation ( $p < 0.05$ ) at stage 4 disease. Hence, HDL-C and TGL can be used as indicators of lipid status and for infection progression in treatment naïve HIV patients, while Cholesterol and LDL-C has no role to play.

**Keywords** Lipid profile · Treatment naïve HIV infected patients · NACO based clinical staging

## Introduction

According to National AIDS control organization, HIV infects 2.5 million people in India. There has been improved long term survival and quality of life in patients with HAART therapy [1]. However, with the advent of HAART therapy, especially the regimens containing protease inhibitors, has been deemed to be the cause for dyslipidemia that features as increase in triglycerides (TGL) and low density lipoprotein cholesterol (LDL-C) and lipodystrophy [2–8]. As a result, this predisposes patients on HAART therapy to cardiovascular and cerebrovascular disease risk [8–12]. Lipid abnormalities were also seen in HIV infected patient who are not on HAART therapy [13–16]. Constans [17] proposed that HIV-1 infection predisposed individuals to develop coronary heart disease.

Demographic differences influence lipid levels in treatment naïve HIV infected individuals [18]. Although studies about lipid profile in HIV infected individual have been done in India, there aren't many published data to substantiate for patients who are treatment naïve. Also the lipid abnormalities have not been documented in the earliest stages of HIV infection [19].

In our study, we hypothesized that there is no difference in lipid profile in treatment naïve HIV patients and apparently healthy individuals.

The primary objective of this study was to evaluate and compare lipid profile in treatment naïve HIV patients and apparently healthy individuals. The specific objective was to correlate lipid profile and CD4 counts in early stages of HIV infection. Secondary objective was to evaluate the feasibility of using Lipid profile to monitor progression of infection in HIV infected treatment naïve patients instead of CD4 counts.

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## Materials and Methods

### Study Design

This observational study was of a case control design and it was done at St. John's Medical College Hospital from Sep 2008 to Jan 2011. The apparently healthy individuals formed the controls while the cases were treatment naïve HIV patients. We compared lipid profile between the two groups to evaluate lipid dysfunction.

### Setting

Apparently healthy individuals were recruited from Health Plan Clinic, a part of health services in St. John's Medical College and Hospital. At the same time, treatment naïve HIV infected individuals were selected from a population of HIV infected individuals attending the ART clinic for counseling and further management. The ART center is a part of the tertiary care hospital, St. Johns Medical College and Hospital, Bangalore.

### Subjects

#### *Control group*

120 apparently healthy individuals were recruited from Health Plan Clinic. Individuals belonging to age group of 20–60 years, belonging to either sex with negative HIV status (based on medical records) were selected. Exclusion criteria used for selecting the cases were used for controls as well.

#### Cases

112 treatment naïve HIV infected individuals of either sex belonging to age group of 20–60 years were included in the study. Following exclusion criteria was followed: HIV infected individuals on HAART treatment, lipid lowering drugs, BMI > 30 (since, obesity can be a confounding factor), history of heavy alcohol consumption, diabetes, pre-existing renal disease, malabsorption syndrome or liver disease. These patients were selected randomly from the population attending the clinic.

The cases or patients were categorized in two ways: Based on CD4 counts and based on NACO guidelines. Based on CD 4 counts, the patients were further divided into 3 groups: Group A: <200 cells; Group B: 201–499 cells; Group C: >500 cells. Based on NACO guidelines of clinical staging, the patients were allocated to 4 groups: Stage 1—Group 1; Stage 2—Group 2; Stage 3—Group 3; Stage 4—Group 4.

### Data Source

Patient's demographic details, history of alcohol consumption and drug history were collected. Patients were clinically evaluated for HIV staging and CD4 counts were analysed. And the control group was evaluated for lipid profile only. 12 h fasting blood sample was collected by venipuncture for lipid profile from the patients. Lipid profile constituted of Total Cholesterol, HDL-C, LDL-C and TGL. Lipid profile was evaluated by enzymatic methods using completely automated Siemens Dimension RxL Max with dedicated reagent.

### Bias

There was a potential information bias with respect to control group. The individuals in the control group were recruited based on absence of history of exposure and in a few based on lab reports.

The study was approved by the Research Society for the financial support and Institutional ethical review board. Written consent was obtained from all the patients before their recruitment.

All the quantitative outcome variables were checked for distribution by using Tests of Normality (Kolmogorov–Smirnov test). Descriptive statistics (using SPSS package 16.0) was used to obtain mean, Standard Deviation (SD) and 95 % Confidence Interval (95 % C I) for all the biochemical parameters and CD4 counts. Two-way Analysis of Variance (ANOVA) was used to compare the lipid profile in males and females between the groups. Correlation analysis was done to evaluate for correlation between biochemical parameters and CD 4 counts (as per CDC guidelines) as well as with clinical staging (as per NACO guidelines).

## Results

One hundred and twelve cases selected for the study had 60 males and 52 females and they belonged to the mean age ( $\pm$ SD in years) of 33.3 ( $\pm$ 8.4) with mean BMI ( $\pm$ SD in kg/m<sup>2</sup>) of 23.35 ( $\pm$ 4.03). Amongst the 120 controls, 50 males and 70 females belonging to mean age ( $\pm$ SD in years) of 41.8 ( $\pm$ 12.3) and mean BMI ( $\pm$ SD in kg/m<sup>2</sup>) of 22.84 ( $\pm$ 3.24).

Table 1 gives the descriptive statistics of controls and cases based on Clinical staging (NACO guidelines). When the control group was compared with HIV infected treatment naïve subjects, there was a significant decrease in total cholesterol, HDL-C and significant increase in TGL. However, there were no statistically significant changes in LDL-C between the control and cases though the LDL-C

levels are lower than in controls. When the cases were further subdivided based on NACO guidelines into different stages, there was a statistically significant decrease in total Cholesterol, HDL-C in stage 2 and 3 when compared to controls. In addition, there was a significant increase in TGL in stage 4 in comparison to controls (refer Table 1). One of the subjects was excluded from the analysis because of high TGL (TGL > 1119 mg/dL). The patient was fasting at the time of sample collection and the sample was reevaluated to check for errors.

Table 2 depicts the descriptive statistics of biochemical parameters in subjects with CDC grouping. In Table 3, comparison between different clinical stages of HIV is given. HDL-C showed a significant decrease from stage 1 to stage 3 ( $p$  value 0.006) and TGL showed a significant increase from stage 1 to 3 ( $p$  value 0.027). Comparison of lipid profile between different groups as per CDC guidelines shows that there is significant difference in TGL between group A and group C (Table 4).

Correlation analysis between different stages (as per NACO guidelines) indicates that there is significant correlation between HDL-C and stage 2 while TGL correlates

significantly in stage 2 and 4 (Table 5). And there is significant correlation between CD4 count and HDL-C while other parameters of lipid profile show no significant correlation.

## Discussion

Our study was conducted to determine the correlation of lipid profile and CD4 counts in treatment naïve HIV patients in India. Bacterial, viral and parasitic infections are known to induce lipid abnormalities [20–24]. Such lipid abnormalities are also seen in HIV infections that could be due to acute phase response induced by infection. Cytokines (TNF, interleukins and interferon) produced in an infection result in host response that causes lipid profile changes [14, 25, 26] such as increased serum TGL and low HDL-C [25–28]. Immune activation in HIV infection is associated with lipid abnormalities as evidenced by correlation between lipid and various immune markers such as neopterin and  $\beta$ -2 microglobulin [29]. Acute phase reactants such as haptoglobin had good predictive value for disease in CD4 lymphocyte count [30].

**Table 1** Descriptive statistics of biochemical parameters in Subjects with clinical staging (as per NACO guidelines)

Clinical staging		Cholesterol Mean $\pm$ SD	HDL-C Mean $\pm$ SD	LDL-C Mean $\pm$ SD	Triglycerides Mean $\pm$ SD	CD4 counts Mean $\pm$ SD
Control	Male ( $n = 50$ )	174.0 $\pm$ 33.2	44.6 $\pm$ 8.9	100.9 $\pm$ 25.4	86.7 $\pm$ 28.7	Not done
	Female ( $n = 70$ )	155.3 $\pm$ 29.8	52.1 $\pm$ 12.1	106.4 $\pm$ 28.6	91.9 $\pm$ 32.3	Not Done
	Both Sex ( $n = 120$ )	169 $\pm$ 31	48 $\pm$ 11	103 $\pm$ 27	89 $\pm$ 30	Not done
Stage 1	Male ( $n = 14$ )	152.4 $\pm$ 48.7	30.8 $\pm$ 8.7	82.4 $\pm$ 38.3	149.4 $\pm$ 102.5	375.3 $\pm$ 246.2
	Female ( $n = 23$ )	161.0 $\pm$ 38.1	38.4 $\pm$ 10.1	101.4 $\pm$ 29.4	119.2 $\pm$ 45.4	442.4 $\pm$ 343.8
	Both Sex ( $n = 37$ )	157.7 $\pm$ 41.9	35.5 $\pm$ 10.1	94.2 $\pm$ 33.8	130.6 $\pm$ 72.6	411.6 $\pm$ 300.8
Stage 2	Male ( $n = 9$ )	147.3 $\pm$ 26.0	28.2 $\pm$ 10.3	89.3 $\pm$ 16.9	125.2 $\pm$ 43.0	122.0 $\pm$ 61.4
	Female ( $n = 11$ )	151.2 $\pm$ 20.4	32.7 $\pm$ 4.6	86.6 $\pm$ 10.0	129.2 $\pm$ 42.5	240.5 $\pm$ 139.2
	Both Sex ( $n = 20$ )	149.5 $\pm$ 22.5*	30.7 $\pm$ 7.8*	87.9 $\pm$ 13.2*	127.4 $\pm$ 41.7	204.9 $\pm$ 131.7
Stage 3	Male ( $n = 24$ )	150.0 $\pm$ 36.6	26.0 $\pm$ 10.7	92.5 $\pm$ 27.2	175.2 $\pm$ 206.7	149.3 $\pm$ 56.8
	Female ( $n = 12$ )	156.6 $\pm$ 66.7	32.8 $\pm$ 10.2	85.8 $\pm$ 50.0	148.5 $\pm$ 52.5	122.9 $\pm$ 70.0
	Both Sex ( $n = 36$ )	152.2 $\pm$ 47.8*	28.3 $\pm$ 10.9*	90.3 $\pm$ 35.7	139.1 $\pm$ 50.0	139.8 $\pm$ 62.2
Stage 4	Male ( $n = 13$ )	157.2 $\pm$ 51.1	33.2 $\pm$ 14.4	110.5 $\pm$ 47.8	148.6 $\pm$ 76.9	198.2 $\pm$ 175.9
	Female ( $n = 6$ )	151.6 $\pm$ 28.5	28.0 $\pm$ 8.0	100.0 $\pm$ 24.0	130.6 $\pm$ 48.9	117.5 $\pm$ 85.3
	Both Sex ( $n = 19$ )	155.6 $\pm$ 45.2	31.7 $\pm$ 12.9	107.6 $\pm$ 42.1	143.6 $\pm$ 69.3*	180.3 $\pm$ 161.7
Overall	Male ( $n = 60$ )	151.7 $\pm$ 41.0	29.0 $\pm$ 11.2*	93.6 $\pm$ 34.8	155.9 $\pm$ 144.0*	222.0 $\pm$ 186.4
	Female ( $n = 52$ )	156.9 $\pm$ 42.2	34.8 $\pm$ 9.4*	94.4 $\pm$ 32.4	129.4 $\pm$ 46.9*	280.1 $\pm$ 266.6
	Both Sex ( $n = 112$ )	154.1 $\pm$ 41.4	31.7 $\pm$ 10.8*	94.0 $\pm$ 33.6	143.7 $\pm$ 110.9*	248.7 $\pm$ 227.6

SD standard deviation

\* indicates that there was statistically significant difference between the stages when compared to controls ( $p \leq 0.05$ )

**Table 2** Descriptive statistics of biochemical parameters in Subjects with CDC grouping

Groups based on CD 4 counts		Cholesterol Mean $\pm$ SD	HDL-C Mean $\pm$ SD	LDL-C Mean $\pm$ SD	Triglycerides Mean $\pm$ SD
Group A (CD4 count < 200 cells)	Male ( $n = 38$ )	156.2 $\pm$ 47.1	29.2 $\pm$ 11.4	96.4 $\pm$ 34.5	140.3 $\pm$ 52.9
	Female ( $n = 27$ )	144.4 $\pm$ 28.4	27.9 $\pm$ 9.6	83.3 $\pm$ 22.9	144.6 $\pm$ 74.2
	Both Sex ( $n = 65$ )	151.3 $\pm$ 40.5	28.7 $\pm$ 10.6	90.9 $\pm$ 30.7	142.1 $\pm$ 62.3
Group B (CD4 count 201 – 499 cells)	Male ( $n = 17$ )	162.7 $\pm$ 49.2	35.6 $\pm$ 11.2	109.2 $\pm$ 43.6	139.2 $\pm$ 68.3
	Female ( $n = 16$ )	142.9 $\pm$ 36.1	32.6 $\pm$ 7.0	82.3 $\pm$ 28.6	127.4 $\pm$ 38.3
	Both Sex ( $n = 33$ )	153.1 $\pm$ 43.8	34.1 $\pm$ 9.4	96.2 $\pm$ 38.9	133.5 $\pm$ 55.3
Group C (CD4 count > 500 cells)	Male ( $n = 5$ )	151.3 $\pm$ 40.5	40.8 $\pm$ 11.7	116.0 $\pm$ 45.1	129.4 $\pm$ 73.2
	Female ( $n = 8$ )	153.1 $\pm$ 43.9	40.0 $\pm$ 7.8	95.4 $\pm$ 22.8	85.8 $\pm$ 32.0
	Both Sex ( $n = 13$ )	170.7 $\pm$ 38.7	40.3 $\pm$ 9.03	103.3 $\pm$ 33.0	102.5 $\pm$ 53.6

SD standard deviation

**Table 3** Comparison of lipid profile between different stages (As per NACO guidelines) in treatment naïve HIV infected individuals

Parameters	Comparison between different stages as per NACO guidelines											
	Stage 1 & 2		Stage 1 & 3		Stage 1 & 4		Stage 2 & 3		Stage 2 & 4		Stage 3 & 4	
	Mean*	P**	Mean*	P**	Mean*	P**	Mean*	P**	Mean*	P**	Mean*	P**
Cholesterol	8.28	1.00	5.56	1.00	2.11	1.00	−2.72	1.00	−6.16	1.00	−3.44	1.00
HDL-C	4.79	0.62	7.24	<b>0.024</b>	3.76	1.00	2.45	1.00	−1.02	1.00	−3.47	1.00
LDL-C	6.37	1.00	3.91	1.00	−13.39	0.99	−2.46	1.00	−19.76	0.43	−17.31	0.45
Triglyceride	3.22	1.00	−35.68	1.00	−12.99	1.00	−38.9	1.00	−16.21	1.00	22.69	1.00

\* Mean is mean difference between the groups; \*\* *P* is the *p* value, bold *p* value indicates that it is statistically significant**Table 4** Comparison of lipid profile between different groups (As per CDC guidelines) in treatment naïve HIV infected individuals

Parameters	Comparison between different stages as per CDC guidelines					
	Group A and B		Group A and C		Group B and C	
	Mean*	P**	Mean*	P**	Mean*	P**
Cholesterol	−1.86	1.00	−19.43	0.38	−17.57	0.59
HDL-C	−5.43	<b>0.04</b>	−11.62	<b>0.001</b>	−6.19	0.19
LDL-C	−5.19	1.00	−12.32	0.69	−7.13	1.00
Triglyceride	23.67	0.95	54.62	0.32	30.95	1.00

\* Mean is mean difference between the groups; \*\* *P* is the *p* value, bold *p* value indicates that it is statistically significant

In our study, it was observed that total cholesterol was significantly lower than the apparently healthy subject that is in accordance with few published studies that have reported hypocholesterolemia in early stages [31]. And hypocholesterolemia is associated with altered immune function due to effect of cytokines [15, 16]. However, cholesterol did not correlate with clinical staging and CD4 counts. Interestingly, certain studies have shown that

hypercholesterolemia is associated with history of AIDS defining events [32].

In our study, HDL-C shows a significant overall correlation with the CD4 counts, more so in patients with CD4 < 500 cells. Also there was significant correlation with clinical stage 2 and stage 4 of HIV infection. We observed a significant decrease in HDL-C levels in patients with decreasing CD4 counts, reinforcing that, HDL is a good marker of disease progression [29, 31, 33]. This could be due to increased Cholesterol ester transfer protein (CETP) activity resulting in increased transfer of cholesterol esters from HDL to apo B-containing lipoproteins. This has been substantiated by negative correlation between HDL-C and CETP levels activity and further high activity of CETP diverts cholesterol to Very low density lipoprotein and LDL-C thus contributing to atherosclerosis [30]. Consequently, HDL particles become less protective against atherosclerosis [16]. Another possible reason for HDL-C decrease could be due to Cytokines such as tumor necrosis factor, interleukins and interferons [30]. Further, reduction in HDL-C could impair Prostaglandin I stabilization and thus increasing the risk of thrombotic events

**Table 5** Correlation of lipid profile with clinical staging (As per NACO guidelines) and different groups (As per CDC guidelines) in treatment naïve HIV infected individuals

No. of cases = 111		Cholesterol	HDL-C	LDL-C	Triglyceride
Clinical staging	Pearson correlation	−0.030	−0.200*	0.086	0.096
	Sig. (2-tailed)	0.757	0.035	0.370	0.316
CD4 count	Pearson correlation	0.142	0.345*	0.129	−0.166
	Sig. (2-tailed)	0.136	0.000	0.178	0.081

Sig. is significance or  $p$  value  $\leq 0.05$

[34]. HDL cholesterol also indicates the role of immune activation in HIV. Zangerle et al. reported a decrease in HDL in patients CD4 count  $< 500$ , while no difference in others plasma lipids were seen. A high level of HDL may be protective against HIV, since apo A1, the main lipoprotein of HDL, inhibits syncytium formation [35].

In our study, LDL-C shows no correlation with CD4 counts or clinical staging. There is no significant difference in LDL-C among various groups of CD4 counts or clinical stages of infection. Constans et al. reported low levels of LDL-C in patients with CD4 below  $400/\text{mm}^3$ . Low level of HDL-C and LDL-C is associated with elevated  $\beta_2$  microglobulin [15].

TGL was shown to be significantly elevated when compared to controls. Hypertriglyceridemia is thus an indicator of advanced disease and severe immune impairment [29, 36, 37] as also seen in our study. It is associated with wasting syndrome, immune impairment and secondary infection. Cytokines such as IL-6, Interferon- $\gamma$ , Interferon  $\alpha$  and tumor necrosis factor mediate acute phase response which causes an increase in VLDL and consequently a rise in triglycerides [14, 16, 28, 38]. Reduced activity of lipoprotein lipase resulting in delayed clearance of lipoprotein as well as increased hepatic lipogenesis, either by increased acid synthesis of fatty acid re-esterification has shown to contribute to hypertriglyceridemia [16, 27, 37, 39] Low HDL and high triglyceride levels seen with advancing HIV infection, may impair the competence of both humoral and cellular system through changes in lipid membrane metabolism [40]. Fernandes Miranda et al. reported HDL reduced progressively with CD4  $< 200/\text{mm}^3$ . VLDL related hypertriglyceridemia was seen in association with CD4  $< 50/\text{mm}^3$ .

Markers of advanced HIV disease such as low CD4 lymphocyte count, high HIV RNA level and history of AIDS defining events were all associated with higher concentrations of VLDL, cholesterol and triglycerides [31].

The shortcomings of the study were that the number of participants in stage 4 was comparatively lower. And the cytokines, haptoglobulin and  $\beta_2$  microglobulin were not evaluated in these patients. Moreover, the objective was to evaluate whether the lipid profile could be used instead of CD4 counts in those health centers that do not have the facility for CD4 count evaluation. HDL-C and TGL can be used to monitor the status of infection progression to

certain extent but to institute therapy, it is important to consider the CD4 counts and the clinical status.

## Conclusion

HDL-C and TGL can be used as one of the indicators for Infection progression in treatment naïve HIV patients. A rise in TGL occurs in patients with CD4 count below 200. To monitor the lipid status in treatment naïve HIV infected patients, HDL-C and TGL can be used while Cholesterol and LDL-C has no role to play.

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