LIPID PROFILE ABNORMALITIES IN PEOPLE LIVING WITH HIV AND AIDS

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CERTIFICATE

Certified that this dissertation entitled "**LIPID PROFILE ABNORMALITIES IN PEOPLE LIVING WITH HIV AND AIDS"** is a bonafide work done by D. SASI ANAND, Post Graduate Student of Internal Medicine, Institute of Internal Medicine, Madras Medical College, Chennai – 600 003, during the academic year 2005-2008.

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DECLARATION

I solemnly declare that this dissertation entitled **"LIPID PROFILE ABNORMALITIES IN PEOPLE LIVING WITH HIV AND AIDS"** was done by me at Madras Medical College and Government General Hospital during 2005-2008 under the guidance and supervision of **Prof. M. JUBILEE, M.D**. This dissertation is submitted to the Tamil Nadu Dr. M.G.R. Medical University towards the partial fulfilment of requirements for the award of **M.D. DEGREE IN GENERAL MEDICINE (BRANCH – I)**

Place:
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INTRODUCTION

After the advent of highly active antiretroviral therapy (HAART), persons infected with HIV live longer and have fewer opportunistic complications.

Metabolic toxicity of HAART, particularly dyslipidaemia, is now emerging as a major cardiovascular concern in HIV infected individuals.

Epidemiological datas suggest a link between HIV infection, HAART use and premature atherosclerosis. When HIV infected individuals are given the expected long term use of HAART, their Coronary Artery Disease (CAD) risk is likely to increase.

Therefore, strategies to minimize the CAD risk in HIV-Positive persons have focussed on risk factor modification, particularly the treatment of dyslipidaemia and the use of lipid-favourable HAART regimens.

Considering the importance of Dyslipidaemia in HIV – infected individuals, an analysis of lipid profile abnormalities in this subset of patients was made.

AIM OF THE STUDY

1) To find out the lipid abnormalities in HIV-infected patients before starting HAART.

2) To find out the lipid abnormalities in HIV-infected patients on HAART (Stavudine + Lamivudine + Nevirapine) for atleast 1 year.

3) To compare the prevalence of dyslipidaemia between these two groups.

MATERIALS AND METHODS

PLACE OF THE STUDY

This study was conducted at the Government General Hospital, Chennai. Patients admitted to the wards of Institute of Internal Mediine and ART Centre were the subjects of the study.

PERIOD OF STUDY

APRIL 2006 – AUGUST 2007

DESIGN

Prospective Study

INCLUSION CRITERIA

HIV – Positive Patients

SAMPLE SIZE

Group I – HIV Positive patients without HAART – 50

Group 2 – HIV Positive patients on HAART – 50 (Stavudine + Lamivudine + Nevirapine) for atleast 1 year.

EXCLUSION CRITERIA

- Patients with Diabetes Mellitus
- Patients with Renal, liver and Autoimmune Diseases.
- Patients on long term steroid therapy
- Patients with thyroid disorders and long standing cholestasis
- Obese patients and chronic alcoholics
- Patients on drugs like Beta Blockers, Diuretics, Cyclosporine, estrogen, Growth hormone, Retinoids , etc.

METHODOLOGY

HIV infected individuals admitted in the wards of Institute of Internal Medicine and ART Centre at Government General Hospital were chosen for the study. Random selection of patients were made in whom a detailed History and Clinical evaluation after getting an informed consent from the patients, were done.

The following investigations were done to all patients selected in this study.

1) Fasting lipid profile (Total cholesterol, Triglycerides, High Density Lipoprotein).
2) Renal Function Test (Sugar, Urea, Creatinine, and Electrolytes)
3) Liver Function Test (S.Bilirubin, SGOT, SGPT, SAP, Total Protein and Albumin)
4) Complete Blood Count (Total Count, Differential Count, ESR, Hemoglobin, PCV and Platelets)
5) Electrocardiogram and Chest X-Ray – PA view
6) CD_4 Count

METHODOLOGY OF INVESTIGATIONS

- HIV serology was done using microlisa kit.
- CD_4 count was done with Facs count (Automated Counter) manufactured by Becton and Dickinson.
- Lipid profile analysis was done on serum obtained after 12 hours of fasting. Total cholesterol, triglycerides and HDL-C are measured.

Tests were done in a single laboratory by the same person. Therefore no interpersonal error was possible.

The normal values of the parameters taken for the study were assessed and listed below.

Total Cholesterol (TC)

Desirable TC is **Less than 200mg/dl**

Borderline high TC is from 200-239mg/dl

High TC is greater than or equal to 240mg/dl

HDL Cholesterol (HDL-C)

Desirable HDL-C is greater than or equal to 40mg/dl

Low HDL-C is **less than 40mg /dl**

Triglycerides (TG)

Desirable Trigylcerides is **less than 150mg/dl**

Borderline high TG is from 150 to 199mg/dl

High TG is from 200 to 499 mg/dl

Very-high TG is greater than 500mg/dl

WHO CLINICAL STAGING (NATIONAL AIDS CONTROL ORGANISATION)

- Stage I
  - Asymptomatic
  - Persistent generalised lymphadenopathy
  - Performance scale 1:asymptomatic normal activity.
- Stage II
  - Wt. loss < 10% of body weight
  - Minor muco cutaneous manifestation
    (seborrheic dermatitis, fungal nail infection, recurrent oral ulcers, angular chelitis)
  - Herpes zoster (within last 5 years)
    Recurrent upper resp. infection (bacterial sinusitis)
    Performance scale 2: Symptomatic, normal activity.
- State 3
  - Wt loss > 10% body weight
    unexplained chronic diarrhoea >1 month unexplained fever (intermittent/continuous) > 1 month
  - Oral Thrush
  - Oral hairy leukoplakia

- Pulmonary TB within past 1 year.
- Severe bacterial infection (preumonia, pyomyositis)
- Performance Scale 3: bed ridden for <50% of day in last 1 month.

- Stage 4
  - HIV wasting synd (>10% BW loss + Unexplained fever (or) Unexplained diarrhoea >1 month chronic weakness)
  - Pneumocystitis carnii pneumonia
  - Toxoplasmosis of brain
  - Cryptosporidiasis with diarrhoea >1 month
  - Cyptococcosis (extra pulmonary)
  - Cytomegalo viral disease of organ other tran liver, spleen and lymph node
  - Herpes simplex infection, Mucocutaneous >1month (or) visceral
  - Progressive multifocal leukoencephalopathy

- Disseminated endemic mycosis, histoplasmosis, Coccidiodomycosis
- Candidiasis of oesophagus, trachea, bronchi lung
- Atypical; Mycobacterial infection
- Non typhoid salmonella septicaemia
- Extra pulmonary tuberculosis
- Lymphoma
- Kaposi sarcoma
- HIV encephalopathy
- Performance scale 4: Bed ridden for >50% of day in last 1 month.

REVIEW OF LITERATURE

The occurrence of dyslipidaemia is well recorded in HIV-infected persons, even prior to treatment with HAART. High density lipoprotein (HDL) Cholesterol (HDL-C) and Low Density Lipoprotein (LDL) - Cholesterol (LDL-C) are decreased in HIV-infected individuals compared with HIV –negative controls [(1)] Elevated triglyceride (TG) levels frequently occur in the advanced stages of HIV infection [(1-3)]

In recent years, clinicians observed elevated cholesterol and often markedly elevated triglyceride levels in HIV infected persons maintained on HAART. The dyslipidaemia was often associated with other metabolic abnormalities, including insulin resistance and lipodystrophy, characterized by accumulation of visceral fat, an enlarged dorsocervical fat pad, and atrophy of subcutaneous fat in face, buttocks and extremities. This constellation of findings has been termed the HIV-related lipodystrophy syndrome. In many ways, it resembles the rare congenital and autoimmune disease related lipodystrophy syndromes[(4)].

HAART ASSOCIATED DYSLIPIDAEMIA

Different HAART agents have different effects on the lipid profile [5]. In the Data Collection on Adverse Events of Anti-HIV Drugs (DAD) study (in which HAART use is defined on the basis of the agents the subjects were taking at the time of study enrolment), the prevalence of Total Cholesterol > 240mg/dl among persons treated with HAART that include a protease inhibitor (PI) non nucleoside reverse transcriptase inhibitor (NNRTI), or both were 22.8, 27 and 44.1% respectively (5, 6). The prevalence of HDL-C < 35mg/dl was 19.1, 27.1 and 23.8% respectively, and TG Levels >200mg/dl were recorded in 31.8, 40 and 54.3 respectively.

Thus, in patients treated with combination of PI and NNRTI, dyslipidaemia is particularly common; an effect that has been seen in multiple studies that have included patients of different ethnicities [7, 8]. Among NRTI, stavudine (d4T) appears to produce hyper lipidaemia more frequently than zidovuine (AZT) or tenofovir (TDF) (9).

ASSOCIATION WITH PROTEASE INHIVITORS

PI – containing regimens, and particularly those containing ritonavir (RTV), are frequently associated with elevations in Total cholesterol (T-

Cho), LDL-C and TG, and a decline in HDL-C levels [10, 11, 12]. The risk of hypercholesterolaemia among patients receiving RTV, Nelfinavir (NFV) and indinavir (IDV) was increased 20, 9 – and 9-fold, respectively compared with PI-unexposed patients. [10, 13].

Atazanavir (ATV) does not appear to affect TG and T-Cho levels significantly [13]. RTV use is associated with higher levels of T-chol, T-chol/HDL-C and TG compared with regimens containing IDV, NFV or amprenavir [10] Extreme hypertriglyceridaemia is seen almost exclusively in RTV-treated patients [14]. Typically, it is rapidly reversible when RTV is replaced by another PI or an NNRTI [10].

HIV RNA Levels, CD_4 Cell Count, and weight change were neither predictors of hyperlipidaemia not confounders of the relationship with PIS. In a longitudinal study, which examined time dependent factors in a multivariate analysis, the initiation of PIS was a strong independent predictor of hypertriglyceridemia [12].

Finally, vergees et al demonstrated that adherence to a PI-containing HAART regimen was associated with a greater likelihood of developing elevated LDL cholesterol and severe (>800mg/dl) hypertriglyceridemia [15].

ASSOCIATION WITH NON-NUCLEOSIDE REVERSE – TRANSCRIPTASE INHIBITORS (NNRTIS)

The NNRTIs cause alterations in the lipid profiles, although generally to a lesser degree than has been observed with PIs. NNRTIs use is associated with substantial increases in HDL-C levels to a degree not generally seen with PIs. The lipid profile changes are somewhat different with efavirenz (EFV) and nevirapine (NVP) in the DAD study [5]. Patients treated with EFV had a higher risk of elevated T-chol or TG. In a substudy of the randomized, prospective 2NN trial, both NVP and EFV were associated with an increase in HDL-c at 48 weeks but the HDL-C increase was significantly larger in the NVP group (42.5%) than in the EFV group (16). The increase of TG was smaller in the NVP group (20.1%) than in the eFV group (40%). Data from the swiss HIV Cohort study also indicates larger TG increases with EFV exposure, compare with NVP.

In a longitudinal study, Efavirenz or indinavir given with NRTIs raised T-Chol levels with 4-8 weeks of therapy, but subjects who received both efavirenz plus indinavir experienced the greatest increases in the total cholesterol level [17]. HDL – C also increased significantly among subjects receiving efavirenz. Containing regimens. In a direct comparison reported in abstract form, nevirapine recipients had smaller increases in TG levels, greater increases in HDL-C levels than did efavirenz recipients, although the differences were relatively small in magnitude [18].

Additional data are needed before any firm conclusios can be drawn regarding the relative tendencies of individual non-nucleoside analogues to alter lipid profiles.

ASSOCIATION WITH NUCLEOSIDE REVERSE – TRANSCRIPTASE INHIBITORS (NRTIs)

There are many studies suggest that the fat redistribution has been observed in PI-naïve patients taking various combinations of NRTIs [19-25]. And in a randomized trial, there was a higher incidence of lipodystrophy in patients receiving ritonavir, saquinavir, and stavudine than in patients taking the 2 PIs alone [26]. In 2 multivariable analyses of cross-sectional and

longitudinal data, the use of several NRTIs persisted as an independent risk factor for lipodystrophy [27, 28]. Among the NRTIs, stavudine had the strongest and most consistent association with fat redistribution in many of these studies.

The association between NRTIs and dyslipidaemia is less ideal. A small cross sectional study found higher triglyceride level in patient taking stavudine [20]. In a prospective but uncontrolled study, Galli et al. followed 335 PI-naive patients taking 2 NRTIs for a median exposure of 748 days. 10% of patients developed T-chol levels >250mg/dl, and 23% developed TG levels >200mg/dl [24]. Exposure to stavudine in this cohort was associated with an increased risk of developing hypertriglyceridaemia.

To summarise, there are clear evidence supports an association between PI exposure and dyslipidaemia. NRTIs may be associated with hypercholesterolemia and possibly milder hypertriglyceridaemia. However, to confirm the association of NNRTIs with dyslipidaemia, needs further datas.

KINETICS OF HAART – ASSOCIATED SERUM LIPID CHANGES

In comparative HAART trials, lipid changes are often recorded several months after starting or changing HAART [11]. However serum lipid levels typically increase within a few weeks after HAART initiation, and elevated levels are sustained therafter [11, 12, 29]. This is well documented in cohort studies of HIV – infected individuals [11, 12, 14] and in clinical PI trials [29]. Dyslipidaemia is often rapidly but only partially reversible when PIs are discontinued [30], and typically worsens within the weeks when PIs are combined with NRTIs [26] or NNRTI's. The development of hypertriglyceridaemia and impaired insulin sensitivity after short term PI treatment [31, 32, 33] stands in contrast to body fat – redistribution, which generally becomes apparent only after several months of treatment with PIs or NRTIs [34, 35].

PATHOGENESIS OF HAART – ASSOCIATED DYSLIPIDAEMIA

HAART may result in a number of metabolic disturbances, including subcutaneous lipoatrophy, truncal fat accumulation, hepatic steatosis, dyslipidaemia, insulin resistance, glucose intolerance and Type 2 Diabetes Mellitus. The exact pathogenic relationship between dyslipidaemia to lipodystrophy and insulin resistance is as yet undefined . Both PIs and

NRTIs are associated with these abnormalities; NNRTIs may also contribute to dyslipidaemia, although their exact relation to lipodystrophy is unclear [36].

The mechanisms responsible for HAART – associated dyslipidaemia are not fully elucidated and may include several factors, including HIV infection itself, the type of HAART and the concomitant presence of lipodystrophy. Evidence for a complex genetic predisposition has also emerged.

HIV Infection and Plasma Lipids

Hypertriglyceridaemia in association with low HDL-C and LDL-C, was commonly observed in HIV-infected individuals before the HAART ([1, 37-40]). Several studies have suggested the following factors as contributing to dyslipidaemia:

- The apolipoprotein E (Apo E) Genotype,
- Increased synthesis of VLDL, and

- Decreased clearance of TG-rich lipoproteins such as VLDL, intermediate density lipoproteins (IDL) and chylomicrons and their remnants [14, 41, 42].

Both hypertriglyceridaemia and hypocholesterolemia are associated with progressive HIV disease. These lipid abnormalities, may, however, reflect a non-specific response to chronic infection, as indicated by the well – documented relationship between TG concentrations and levels of inflammatory cytokines such as IFN-α and –γ or TNF [38, 40, 42]. On the other hand, low concentrations in HDL – C in a symptomatic HIV –infected patients could be due to an elevated catabolic rate of apolipoprotein (APO) A1, the main protein component of HDL partiles [43].

DYSLIPIDAEMIA IN HAART – TREATED INDIVIDUALS

Compared with HIV-infected control subjects, HAART treated HIV-positive patients had a significantly increased basal lipolysis in the Fasting state. Inspite a modest but significant increase in the rate of intraadipocyte re-esterification, the net result was an increase in the release of .free fatty acids (FFAs) into the plasma pool and into other sites with the highest

capacities for energy uptake such as the liver, visceral fat and skeletal muscle [44].

In the liver, increased uptake of FFAs enhances the synthesis of ApoB, reduces the degradation of ApoB and increases the production of VLDL particles [45].

Increased transport of FFAs into skeletal muscle results in intramyocellular lipid deposition, which is strongly associated with insulin resistance and impaired glucose disposal [45, 46].

PIs may also negatively affect glucose tolerance by directly inhibiting glucose transporter – 4, a transport molecule integral to this process[47]. Nevertheless, FFA-uptake is higher within visceral Fat deposits than skeletal muscle, perhaps due to increased sensitivity to lipoprotein lipase (LPL) activating hormones such on cortisol, in omental adipocytes. This preferential deposition of fat may be the reason for the development of visceral obesity in HAART related lipodystrophy.

Carr and colleagnes have suggested the inhibition of LDL-receptor – related protein (LRP) an another mechanism of PI-associated dyslipidaemia [48]. LRP is a hepatic receptor that plays a critical role in clearance of ApoE – containing particles that are rich in TGS, such as chylomicrons, VLDL and their remnants. However, this hypothesis remain to be substantiated [31, 49].

Elevated FFAs inhibit LPL – activity which is required for the clearance of VLDL, IDL and chylomicrons [50].

The impaired clearance of TG-rich particles occurs as a result of inhibition of LPL activity due to:

- Increased levels of Apo C3 associated with increased plasma FFAs,
- Increased levels of Apo C3 associated with decreased activation of the heterodimer peroxisome proliferators – activated receptor – α (PPAR-α) retinoic acid receptor (RXR). [14, 51].

In one model, PIs cause increased activity of sterol regulatory element binding protein (SREBP), which alters adipocyte differentiation and reduces leptin levels [52] . In hepatocytes, SREBP induces lipogenic genes, which

leads to increased hepatic very-low density lipoprotein production. The increased lipid levels and reduced leptin levels, in turn, cause insulin resistance, which further activates SREBP, then perpetuating the cycle.

The role of NRTIs in the HIV-related lipodystrophy has been attributed to mitochondrial toxicity [53] but this hypothesis has been challenged.

POSSIBLE MECHANISMS FOR HAART – ASSOCIATED DYSLIPIDAEMIA

Increased hepatic TG and cholesterol synthesis.	Increased Substrate delivery of FFA's. Insulin resistance Increased levels of SREBP – IC Improved nutritional status
Impaired clearance of TG-rich particles	Inhibition of LPL activity due to: Increased levels of ApoC3 associated with increased plasma FFAs. Increased levels of ApoC3 associated with decreased RXR-PPAR – Alpha activity Inhibition of LRP receptors (?)

GENETIC FACTORS

A genetic predisposition could explain why hyperlipidaemia occurs in some but not all patients, despite similar exposure to HAART and comparable demographic, immunological and virological characteristics. Research attention has focussed primarily on the potential role of unfavourable allelic variants of ApoE and ApoC3. ApoE is instrumental in the transport and clearance of lipoprotein remnants from the blood stream. ApoC3 inhibits the activity of lipoprotein lipase, and thereby modulates lipolysis and hepatic clearance of plasma TG.

Case reports have described HIV-infected patients who were ApoE ε2 or ε4 carriers in whom severe hyperlipidaemia was triggered by the initiation of HAART [(54)]. ApoE ε4 carriage was already been linked to hypertriglyceridaemia in advanced HIV infection in the pre-HAART era [(41)]. A more recent report showed an association of hypertriglyceridaemia with variant alleles of ApoC3 in 60 men who all were treated with PI based HAART [(51)]. TG levels were higher in carriers of three variant ApoC3 alleles than in carriers of one or two variant alleles.

An association of these ApoE and ApoC3 variants with hyperlipidaemia was recently reported in a longitudinal study of 329 HIV-

infected patients in the swiss HIV cohort study [14]. The genetic variants were relatively common : 27.7% of patients were carriers of variant alleles of ApoE (i.e., ε2 or ε4 alleles), 17.9% were carriers of all three variants of ApoE. 5.8% were carriers of variants of both ApoC3 and ApoE; and these patients were at risk for extreme and sustained hypertriglyceridaemia when exposed to RTV. The relative contribution of genotype and HAART to lipid levels was also evaluated. HAART containing a PI but no RTV, and RTV – containing HAART were associated with increases in non –HDL-C of 0.29mmol/l (11mg/dl) and 0.65mmol/l (25mg/dl), respectively. The contribution of the ApoE ε4 allele was a non – HDL-C increase of 0.27mmol/l (10.4mg/dl) ; that is, quantitatively similar to the non-HDL-C increasing effect of PI treatment [14]. This study highlighted the issues of appropriate methodology and statistical power in genetic association studies. Longitudinal modeling [12] of lipid levels in large numbers of patients may represent the most powerful approach to quantitating the contributions of genotype and HAART to dyslipidaemia. Cross-sectional analyses of lipid levels at a single time point during HAART exposure may be underpowered to detect the genetic effects. (14)

CARDIOVASCULAR RISK IN HIV-INFECTED PERSONS

Several cases of premature coronary Heart Disease (CHD) have been reported in HIV patients with dyslipidaemia associated with HAART [56-61] . In a cross sectional study, HIV infected individuals had more femoral or carotid artery atherogenic plagues than controls. However most of these patients had 1 or more established CHD risk factors like smoking, Diabetes Mellitus, Hypertension etc.

A recent large cohort study showed higher age-adjusted rates of coronary Artery Disease in HIV infected individuals compared with HIV-negative individuals (6-3 versus 2.9/1000 person – years, respectively) [62].

The most solid data linking HAART exposure to an increased cardiovascular risk to date was provided by the DAD study. In the most recent analysis of DAD data, the adjusted risk of myocardial infarction (MI) was increased by 17% for each year of HAART exposure, 16-18% for each mmol/l increase in T-Chol, and 39-48% for each doubling of the TG concentration [63].

It is clear that the benefits of HAART by far outweighs the small, absolute increase in cardiovascular risk that is presumably attributable to HAART [64]. In the DAD study, the risk of MI was 1.39/1000 patient years in those not exposed to HAART. The risk increased 2.53/1000 in those <1 year of exposure, and 6.07/1000 in those exposed to >6 years of HAART.

The exact mechanisms by which premature atherosclerosis is mediated in HIV infected person is unclear. Support for direct pro-atherogenic effects is provided by studies showing that HAART and HIV infection itself may induct endothelial dysfunction [65-67] , an early indicator of atherosclerosis associated with diminished vasodilatory properties of the endothelium.

A large proportion of HIV-infected individuals can be classified as being at high 10-year cardiovascular risk. Among 3199 HIV-infected patients evaluated in Spain in 2004, 10% of women and 29% of men were considered to be at either moderately high or high 10 year CAD risk [68]. With the improved life expectancy since the introduction of HAART and the consequent ageing of the HIV-infected population, the number of patients at high cardiovascular risk is likely to increase. This has already been shown in

the DAD cohort, in which the proportion of patients at high risk increased from 36.2% in 2000 to 44.7% in 2003 [69]. After adjusting for changes in cardiac risk factors, however, the MI risk was lower in 2003-2004 compared with 1999-2000. The exact reasons for this decrease in MI risk are not yet clear. Several changes over time have been noted in the DAD cohort, including a decrease in PI use (2000:47.4%, 2003: 40.1%), an increase in NNRTI use (2000:32.6%, 2003: 38.5%), an increase in patient receiving lipid-lowering therapy (2000: 4.0%, 2003: 8.1%), and an increasing proportion of ex-smokers (2000: 15.7%, 2003: 24.9%). Such trends have also been recorded in other studies, and suggest that physician awareness of cardiovascular risk is increasing [62, 70, 71]. In a large cohort study from California, the use of d4T decreased, and the use of ATV and lipid-lowering therapy increased during the study period (1996-2004) [62]. More widespread use of lipid-lowering therapy in the most recent years and a tendency to use PIs more sparingly has also been noted in a study from Tennesse [72]. In the French Aquitaine Cohort of HAART-treated patients, a decrease in the prevalence of smoking, decreased PI use and an increase in the use of lipid-lowering medication was noted between 2000 and 2004, along with a significant decrease in the intimal media thickness [71]. Although the effect on cardiac outcomes remains to be confirmed, each of these studies suggests

the feasibility and potential efficacy of interventions aimed at cardiovascular prevention in HIV-infected patients.

EFFECTS OF SWITCHING ANTIVIRAL THERAPIES

The association of increased serum lipid levels with certain antiretroviral therapies had led to exchanging the potentially offending component for another drug. This switching strategy has the potential advantage of avoiding pharmacologic intervention for elevations in lipid levels. However, because of the multifactorial nature of dyslipidemia in HIV infection, abnormalities may not resolve simply by switching drugs. Switching from a PI to nevirapine or abacavir has generally resulted in an improvement in total cholesterol and triglyceride levels [73-81], whereas switching to efavirenz has produced less consistent results (82). These trials have generally demonstrated persistent viral suppression for 6-12 months after switching regimens.

In patients with a favourable treatment history (i.e., no previous receipt of an NRTI-based regimen that was less than fully suppressive and no history of virologic rebound occurring while receiving treatment), switching from a potentially lipid level increasing PI to nevirapine or

abacavir may be preferable to a pharmacologic intervention with a lipid-lowering drug . In practice, however, many patients will have already received NNRTI therapy or are extensively NRTI experienced. Studies comparing the effects of treatment switching to those of adding lipid-lowering agents to ongoing successful therapy have not been reported. Clinicians will need to weigh the risks of new treatment-related toxicities and the possibility of virologic relapse when switching antiretroviral drugs to the risks of potential drug interactions and new treatment-related toxicities from lipid-lowering agents that are added to existing regimens.

COMPLICATIONS OF HYPERTRIGLYCERIDAEMIA IN HIV – INFECTED PERSONS

Extremely high TG levels (>1000 mg/dl) are usually associated with fasting chylomicronemia and cause the 'Chylomicronemia syndrome', which includes Acute Pancreatitis, abdominal pain with normal pancreatic enzymes, memory loss, lipemia retinalis, and eruptive xanthomata [83] . In addition, non-alcoholic steatohepatitis is also reported.

Some patients suffer significant psychological morbidity related to their body habitus change.

RESULTS AND OBSRVATION

AGE DISTRIBUTION

Table No. 1 : Shows age distribution in Group 1 (n-50)

Age	Dyslipidaemia	No Dyslipidaemia
< 30	14 (60.9%)	9 (39.1%)
30 – 40	15 (65.2%)	8 (34.8%)
> 40	4 (100.0%)	-
Mean ± SD	**32±6**	

Chisquare Test P = 0.31

Table No. 2: Shows age distribution in Group 2 (n=50

Age	Dyslipidaemia	No Dyslipidaemia
< 30	4 (100.0%)	-
30 – 40	27 (84.4%)	5 (15.6%)
> 40	12 (85.7%)	2 (14.3%)
Mean ± SD	**38±8**	

Chisquare Test P = 0.70

Majority of the patients in our study were between 30 and 40 years of age. Of the 23 patients, who were in the age group of 30 – 40 among Group 1, 15(65.2%) had dyslipidaemia and, of the 32 patients, who were in the age group of 30-40 among Group 2, 27(84.4%) had lipid profile abnormaities.

SEX DISTRIBUTION

Table No. 3: Shows sex distribution in Group - 1

Gender	**Dyslipidaemia**	**No Dyslipidaemia**
Male	16 (64%)	9 (36%)
Female	17 (68%)	8 (32%)
Total	**33 (66%)**	**17 (34%)**

Table No. 4: Shows sex distribution in Group 2

Gender	**Dyslipidaemia**	**No Dyslipidaemia**
Male	29 (85.3%	5 (14.7%)
Female	14 (87.5%)	2 (12.5%)
Total	**43 (86%)**	**7 (14%)**

In our study the prevalence of dyslipidaemia was found to be more among females than males in both the groups

CD_4 DISTRIBUTION

Table No. 5:

CD_4 Count	**Group 1**	**Group 2**
Mean	508.70	357.64
Range	257-1208	17.882

The CD_4 count of patients among Group 1 ranged from 257 to 1208 with the mean of 508.70 and among Group 22 ranged from 17 to 882 with the mean of 357.64.

TOTAL CHOLESTEROL (TC)

Table No. 6

TOTAL CHOLESTEROL	**Group 1**
Normal	40 (80.0%)
Borderline High	9 (18.0%)
High	1 (2.0%)
Mean ± SD	**176 ± 27**

Table No. 7

TOTAL CHOLESTEROL	**Group 2**
Normal	36 (72.0%)
Borderline High	8 (16.0%)
High	6 (12.0%)
Mean ± SD	**180 ± 55**

Majority of patients among group 1 and 2 found to have normal T.C. levels. Only 20% of patients among Group 1 and 28% of patients among Group 2 were found to have high T.C. levels.

The mean total cholesterol level among Group 1 was 176 ± 27 and among Group – 2 was 180 ± 55. The alterations in T.Cholesterol Level was not statistically significant in both the groups. (P = 0.15)

HDL CHOLESTEROL (HDL-C)

Table No. 8

HDL CHOLESTEROL	**Group 1**
Low	7 (14.0)
Normal	42 (81.0%)
Negative Risk Factor	1 (2.0%)
Mean ± SD	**41 ± 3**

Table No. 9

HDL CHOLESTEROL	**Group 2**
Low	8 (16.0%)
Normal	42 (84.0%)
Negative Risk Factor	-
Mean ± SD	**43±5**

Majority of patients among Group 1 and 2 found to have normal HDL-Cholesterol level. Only 14.0% of patients among Group 1 and 16.0% of patients among Group 2 were found to have Low HDL-C levels. Surprisingly, one patient among Group 1 was found to have HDL-C level of 60 which is considered as a negative risk factor for future cardiac events.

The mean HDL – C level among Group 1 was 41±3 and among Group 2 was 43±5. The alteration in HDL – L levels were not statistically significant in both the groups (P=0.59)

TRIGLYCERIDES

(p = 0.00)

Table No. 10

TRIGLYCERIDES	**Group 1**
Normal	19 (38.0%)
Borderline High	21 (42.0%)
High	10 (20.0%)
Very High	-
Mean ± SD	**180 ±69**

Table No. 11

TRIGLYCERIDES	**Group 2**
Normal	9 (18.0%)
Borderline High	11 (22.0%)
High	26 (52.0%)
Very High	4 (8.0%)
Mean ± SD	**281±202**

About 62.0% of patients among Group 1 and 82.0% of patients among Group 2 found to have high Triglyceride levels.

The mean Triglycerides level among Group 1 was 180±69 and among Group 2 was 281±202. Around 8.0% of patients among Group 2 found to have very high TG Levels.

The alteration in Triglyceride levels were statistically significant in both the groups (P=0.00)

DYSLIPIDAEMIA

(p = 0.03)

Table No. 12

DYSLIPIDAEMIA	Group 1	Group 2
Yes	33 (66.0%)	43(86.0%)
No	17 (34.0%)	7(19.0%)

66% of patients among Group 1 found to have altered lipid profile whereas among Group 2, 86.0% of patients found to have altered lipid profile confirming the relationship of HAART with dyslipidaemia.

WHO STAGEWISE DISTRIBUTION OF PATIENTS

Table No. 13

STAGE	Group 1	Group 2
I	34 (68.0%	14 (28.0%)
II	16 (32.0%)	14 (28.0%)
III		12 (24.0%)
IV		10 (20.0%)
Total	50	50

All the patients among Group 1 were in Stage I & II and many of the patients (56.0%) among Group 2 were in Stage I & II and 24.0% in Stage III & 20% in Stage IV.

CORRELATION OF WHO STAGING AND DYSLIPIDAEMIA

Table No. 14

P = 0.76

STAGE	Group – 1	
	Dyslipidaemia	No Dyslipidaemia
I	23 (67.6%)	11 (32.4%)
II	10 (62.5%)	6 (37.5%)
III		
IV		

ChI-square Test

Table No. 15

P = 0.61

STAGE	Group – 2	
	Dyslipidaemia	No Dyslipidaemia
I	13 (92.9%)	1 (7.1%)
II	11 (78.6%)	3 (21.4%)
III	11 (91.7%)	1 (8.3%)
IV	8 (80.0%)	2 (20.0%)

ChI-square Test

Majority of patients in Stage I & II in both the groups were found to have more alterations in lipid profile. There was no statistically significant correlation of WHO staging with dyslipidaemia.

CORRELATION OF CD_4 AND DYSLIPIDAEMIA

Table No. 16

DYSLIPIDAEMIA	MEDIAN	RANGE
Yes	404	17,1208
No	445	42,961

Mann – Whitney Test

There was no statistically significant correlation of CD_4 counts with dyslipidaemia.

DISCUSSION

AGE

The mean age of patients in Group 1 was 32±6 and the mean age in Group 2 was 38±8. There was no statistical significance found between Age and dyslipidaemia in both the groups.

SEX DISTRIBUTION

In our study the prevalence of dyslipidaemia was found to be more among females than males in both the groups. But there was no statistically significant correlation found between gender and dyslipidaemia.

There are no studies available to suggest the correlation of Age / Gender with dyslipidaemia in HIV – infected patients.

TOTAL CHOLESTEROL

Majority of patients in our study were found to have normal T.Cholesterol levels in both the groups. Only 20% of patients in Group 1 and 28% of patients in Group 2 were documented to have high T.Cholesterol levels.

In our study, only 12.0% of patients among Group 2 were found to have T.Cholesterol level > 250mg% whereas in DAD study, the prevalence of T.Cholesterol > 240mg/dl among persons treated with HAART that include a NNRTI was 27% [5, 6].

	Present Study	**DAD Study**
Prevalence of T.Cholesterol >250mg/dl	12.0%	27.0%

In a another prospective, but uncontrolled study, Galli et al, followed 335 PI naïve patients taking 2NRTI's for a period of 748 days, 10% of patients developed T.Cholesterol level > 250mg/dl [24].

	Present Study	**Galli et al**
Prevalence of T.Cholesterol >250mg/dl	12.0%	10%

HDL CHOLESTEROL

Majority of patients in our study were found to have normal HDL-C levels only 14% of patients among Group 1 and 16% among Group 2 were documented to have HDL-C <40mg/dl.

Hypertriglyceridaemia in association with Low HDL-C was commonly observed in HIV infected patients before the HAART [1, 37-40].

In our study also, 14% of patients found to have HDL-C <40mg/dl in Group 1.

In our study, 16.0% of patients among Group 2 were found to have HDL-C <40mg/dl where as in DAD study, the prevalence of HDL-C <35mg/dl among persons treated with HAART that included a NNRTI was 27.1% [5,6].

	Present Study	**DAD Study**
Prevalence of HDL-C < 40mg/dl	16%	
Prevalence of HDL-C < 35mg/dl		27.1%

TRIGLYCERIDES

Majority of patients in our study were found to have high Triglyceride levels in both the groups (62% among Group 1 & 82% among Group 2)

In our study, the prevalence of Triglycerides > 200mg/dl were 20.0% among Group 1 and 60.0% among Group 2 whereas Galli et al, observed that the prevalence of TG> 200mg/dl was 23% in patients taking 2 NRTI's [24].

	Present Study	**Galli et al**
Prevalence of Triglycerides >200mg/dl in HIV infected patients on HAART (excluding PI)	60%	23%

Hypertriglyceridaemia in association with Low HDL-C was commonly observed in HIV – infected persons before the HAART. In our study also, 20% [1, 37-40] of patients among Group 1 found to have elevated TG level >200mg/dl before starting HAART.

Both hypertriglyceridaemia and hypocholesterolemia are associated with progressive HIV disease. These abnormalities may be a non specific

response to chronic infection as indicated by the well-documented relationship between Triglycerides concentration and levels of inflammatory cytokines. [38, 40, 42].

DYSLIPIDAEMIA

In our study 66% of patients among Group 1 and 86% of patients among Group 2 were found to have altered lipid profile in the form of elevated TG, Low HDL-C and elevated T.Cholesterol alone or combination of these abnormalities.

Hypertriglyceridaemia was the most common lipid profile abnormality detected in our study.

There was no major or significant alterations in T.Chol & HDL-C levels observed in both the groups, whereas Triglyceride level, was significantly altered in both the groups, more with Group 2.

In our study, Dyslipidaemia was defined as alteration in any one of the three parameters namely T-Cholesterol, Triglyceride and HDL-c alone or combination of these abnormalities.

The prevalence of Dyslipidaemia among Group 2 was significantly more than that of Group1 indicating the role of HAART on lipid profile alterations.

In our study, all the 50 patients in Group 2 were on 2 NRTI's (Satvudine) and Lamivudine) and 1 NNRTI (Nevirapine) Thereore, a significant lipid profile abnormalities can also occur in PI-naïve HAART regimens.

Many studies have documented the role of protease inhibitors in lipid profile alterations. It was evident from our study that significant alterations in lipid profile can occur in PI-naïve patients on NNRTI's, NRTI's or combination of both.

CORRELATION OF WHO STAGE AND CD_4 COUNT WITH DYSLIPIDAEMIA

In our study, there was no statistical significance observed between CD_4 count, WHO stage and dyslipidaemia.

A well conducted analysis did not find associations of dyslipidaemia with indicators of HIV infection status such an CD4 lymphocyte count or HIV viral load [12, 24].

CONCLUSION

- Hypertriglyceridaemia was the most common lipid profile abnormality in HIV-infected patients before HAART and after HAART. There is no significant alteration in T.Chol and HDL-C levels as such in both the groups.
- The prevalence of Dyslipidaemia in HIV positive patients before starting HAART (Group 1) was 66.0%
- The prevalence of Dyslipidaemia in HIV positive patients on HAART (which includes stavudine, Lamivudine and nevirapine) for atleast 1 year was 86.0% which confirms the effect of HAART on lipid profile.
- There was no significant correlation of WHO stage, CD_4 count with the alteration of lipid profile in both the groups.
- Significant alteration in lipid profile can occur in PI-naïve patients on NRTI's, NNRTI's or combination of both.

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MASTER CHART

S.NO.	NAME	AGE	SEX	CD4	WHO STAGE	TC	TGL	HDL	GROUP
1	Narayanan	40	M	388	II	138	94	42	2
2	Kavitha	42	F	368	II	226	211	40	2
3	Parthasarathy	42	M	275	IV	176	112	50	2
4	Moorthy	38	M	155	I	254	316	33	2
5	Vijaya	43	F	142	III	159	269	42	2
6	Joseph	33	M	42	III	115	76	58	2
7	Mani	36	M	52	III	199	151	41	2
8	Renganathan	63	M	162	III	251	441	36	2
9	Shankar	34	M	17	II	212	412	35	2
10	Venkatesan	36	M	138	IV	136	182	46	2
11	Kutty	35	M	268	IV	217	287	38	2
12	Lakshmi Sundari	47	F	325	II	186	350	36	2
13	S.Kumar	33	M	433	II	194	100	45	2
14	Gnanasekaran	42	M	233	III	126	249	242	2
15	Sairabanu	38	F	288	III	150	517	47	2
16	Gopalakrishnan	45	F	493	II	183	121	51	2
17	Manickam	42	M	882	I	279	456	40	2
18	Anbarasi	27	F	837	II	252	185	41	2
19	Baby	30	F	423	I	214	125	44	2
20	Parthasarathy	34	M	690	I	209	209	43	2
21	Murugesan	61	M	209	I	165	320	50	2

22	Shankar	52	M	517	II	439	1365	44	2
23	Sivakolunthu	56	M	570	II	167	355	46	2
24	Ramesh	30	M	588	I	140	187	50	2
25	Violet	44	F	303	IV	175	298	42	2
26	Arumugam	39	M	795	I	131	167	50	2
27	Sridhar	36	M	384	II	150	313	49	2
28	Malligarani	34	F	254	I	183	553	48	2
29	Anbarasan	36	M	420	I	136	210	45	2
30	Rajamanickam	40	M	556	I	140	162	40	2
31	Vijaya	34	F	384	II	150	313	49	2
32	Ponnurangam	44	M	254	I	183	553	48	2
33	Ramasamy	38	M	420	I	136	210	45	2
34	Dhanalakshmi	32	F	556	I	140	162	40	2
35	Mani	36	M	448	III	132	350	38	2
36	Dhanasekar	38	M	119	IV	164	160	44	2
37	Dhanabalan	36	M	113	IV	175	458	40	2
38	Devakumar	32	M	289	III	210	240	42	2
39	Neetha	38	F	86	II	180	186	50	2
40	Chinnathai	27	F	446	III	120	382	42	2
41	Latha	30	F	443	I	142	120	40	2
42	Krishnamoorthy	30	M	295	II	110	268	41	2
43	Sagayaraj	37	M	289	II	198	160	42	2
44	Sugumaran	41	M	76	IV	246	129	42	2
45	Venkatesan	34	M	171	IV	202	492	38	2
46	Shanthi	28	F	297	III	182	152	46	2

47	Manickam	32	M	318	IV	138	110	40	2
48	Vasantha Kumari	26	F	398	IV	168	312	42	2
49	Babu	38	M	646	III	212	284	41	2
50	Gunasekar	34	M	627	III	126	212	39	2
51	Tamilselvi	32	F	480	I	160	130	44	1
52	Kumar	40	M	366	II	196	152	40	1
53	Anandan	36	M	420	I	150	140	42	1
54	Devendran	32	M	588	II	126	160	46	1
55	Srinivasan	35	M	257	II	184	148	40	1
56	Vijayalakshmi	29	F	985	I	202	158	38	1
57	Janarthanan	26	M	260	II	166	202	42	1
58	Viji	35	F	580	I	192	210	40	1
59	Rajasekar	41	M	299	II	206	160	41	1
60	Mercy .P	29	F	726	I	240	198	42	1
61	Lakshmi Sundari	23	F	625	I	160	130	44	1
62	Manikandan	27	M	427	I	196	152	40	1
63	S. Santhanavairavan	26	M	726	I	156	140	42	1
64	K.Balaji	34	M	444	I	192	260	40	1
65	M. Manivannan	36	M	437	I	196	210	42	1
66	Kasthuri	27	F	400	I	210	140	38	1
67	S. Amudha	35	F	280	II	202	290	42	1
68	Mala	30	F	461	I	200	202	40	1
69	P. Balamani	40	M	447	II	196	142	42	1
70	Saranya .K	25	F	306	I	182	168	42	1
71	Devaki	39	F	564	I	220	192	38	1

72	Ravi	44	M	305	II	186	190	44	1
73	Pushparaj	35	M	825	I	202	140	40	1
74	Mayakrishnan	34	M	584	I	160	138	42	1
75	K.Rekha	23	F	498	I	142	156	42	1
76	Basheera	24	F	352	I	148	162	40	1
77	Perumal	39	M	543	I	168	159	41	1
78	S.Kumar	28	M	987	I	174	170	38	1
79	V.Kasthuri	31	F	627	I	130	316	40	1
80	Pencilliah	27	M	598	I	190	126	42	1
81	Monica	27	F	747	I	120	130	42	1
82	M.Mani	29	M	365	II	138	142	44	1
83	G.Kumar	40	M	407	II	178	152	40	1
84	Sathya	30	F	350	II	182	148	42	1
85	Jayadha	30	F	468	I	198	122	42	1
86	B.Usha	36	F	363	II	140	190	40	1
87	Shankari	30	F	365	II	162	124	42	1
88	T.Sumathy	29	F	961	I	156	136	40	1
89	P.Srinivasan	28	M	436	I	182	130	42	1
90	Damodharan	26	M	498	II	198	148	41	1
91	K.Nagalingam	36	M	555	I	138	412	38	1
92	D.Shanmugam	26	M	366	II	154	152	40	1
93	A.Mani	42	M	476	I	188	162	42	1
94	Narayani	45	F	377	II	202	180	40	1
95	T.Amulu	20	F	461	I	149	420	38	1
96	Prema .K	28	F	519	I	169	148	40	1

97	R.Rajeswari	22	F	1208	I	180	162	40	1
98	Ramu	28	M	653	I	136	382	39	1
99	Vimala	36	F	441	I	210	156	40	1
100	Geetha	29	F	522	I	192	172	42	1

PROFORMA

Name : Age: Sex:

Address : Occupation :

Hospital No.

Duration of Illness :
(Since Diagnosis)

Past History:

DM / COPD / Drug intake etc..

Personal History:

Smoking / Alcohol intake / Drug abuse

Treatment History :

HAART Therapy duration :

Drug combination

GENERAL PHYSICAL EXAMINATION

Weight : BMI :

Height :

P I CL PE LN

Oral Candidiasis

Herpes Zoster

Vital Signs

Pulse :

BP :

Temperature :

Respiratory Rate :

System Examination

CVS :

Rs :

Abdomen :

CNS :

Investigation

Hemogram : TC DC HB PCV

Platelets ESR

RFT: Sugar Urea Creatinine

LFT: Bilirubin SGOT SGPT SAP

T.Protein Albumin

Urine Routine

ECG :

CXR :

ELISA for HIV :

CD4 Counts :

Lipid Profile

TC TGL HDL