DOI: 10.7860/JCDR/2013/4740.2743

Original Article

Infectious Diseases Section

The Development of Metabolic Risk Factors After the Initiation of the Second Line Anti- Retroviral Therapy

APOORVA MITTAL, BASAVAPRABHU ACHAPPA, DEEPAK MADI, MUKTA N CHOWTA, JOHN T RAMAPURAM, SATISH RAO, UNNIKRISHNAN B, SOUNDARYA MAHALINGAM

ABSTRACT

Background and objective: A Highly Active Anti-Retroviral Therapy (HAART) is accompanied with several metabolic effects like adipose redistribution and insulin resistance. In this study, we evaluated the association between a HAART and lipodystrophy.

Methods: A cross sectional study, whose subjects were Human Immunodeficiency Virus (HIV) infected patients, was conducted at a tertiary care hospital in south India. Among these, 27 were on protease inhibitors for at-least 6 months and 13 were drug naive patients. The assessments of lipodystrophy, fasting blood sugar and the fasting lipid profile were done and these parameters were compared in the two groups.

Results: The analysis of the data which was collected, showed an elevation in the total cholesterol levels in the individuals who were on the protease inhibitors versus the drug naive patients. There was a significant elevation in the Low Density Lipoprotein (LDL) cholesterol levels and a decrease in High Density Lipoprotein (HDL) cholesterol levels in the individuals who were on protease inhibitors. It was also observed that the HDL cholesterol levels decreased with an increase in the duration of the therapy. The LDL cholesterol levels increased with the duration of the therapy.

Conclusion: The human immunodeficiency virus infection is itself related to the metabolic complications which are aggravated on the use of second line anti retroviral therapy. Therefore, after initiating the treatment with protease inhibitors, a periodic evaluation of the serum lipid levels and the blood sugar profile should be done as a standard care.

Key Words: HAART, ART, HIV, Metabolic syndrome, Dyslipidaemia

INTRODUCTION

Highly Active Antiretroviral Therapy (HAART) has had a significant impact on the natural history of the human immunodeficiency virus infection, leading to a remarkable decrease in its morbidity and mortality, but it is accompanied by several metabolic effects [1]. The major anti-retroviral therapy related metabolic abnormalities are dyslipidaemia, morphological changes (fat accumulation), and dysregulation of the glucose metabolism [2]. An often encountered complication of the anti-retroviral therapy is the adipose redistribution syndrome, which is characterized by an altered distribution of the body fat, which is linked to the protease inhibitors (PIs) and the nucleoside reverse transcriptase inhibitors (NNRTIs) [3]. A localized accumulation of adipose tissue in the upper trunk, the anterior neck, the dorsocervical fat pad (Buffalo Hump), the abdomen and the breast has been well described for the patients who receive a potent combination of the anti-retroviral therapy [1]. It can also lead to Madlung's disease in which there is a fatty infiltration and bulging of the supraclavicular fat pad [3].

The entire class of PIs is associated with the dysregulation of glucose and the lipid metabolism due to a homology between HIV-1 protease and various human proteins. Insulin resistance, which can lead to Diabetes mellitus, is directly related to the use of some PIs and NNRTIs. Protease may have an early direct effect, which includes insulin resistance which is independent of the changes in the body composition. The inhibition of GLUT-4, which is the predominant transporter which is involved in the insulin stimulated glucose disposal, leads to insulin resistance and lipid metabolism deregulation [4].

The adverse metabolic effects of a potent anti-retroviral therapy are a major concern because they may stigmatise the patient and because the hyperlipidaemia and insulin resistance may increase the long term risk of cardiovascular diseases. Metabolic syndrome has been identified as a significant and a multifactorial risk factor for cardiovascular diseases by the U.S International Cholesterol Education Programme Adult Treatment Panel III. In recent times, due to the introduction of a HAART, the number of deaths which are caused by HIV has come down in large numbers, but studies have shown that a HAART increases the patient's risk of developing complications due to the metabolic syndrome and dying due to cardiovascular diseases than due to HIV itself [1].

There were very few studies which have addressed this issue in the Indian population. Hence, this study was planned with the objective of examining the metabolic risk factors which were associated with the initiation of second line anti- retroviral therapy.

MATERIALS AND METHODS

This cross sectional study was done at a tertiary care hospital in south India. The study population included the HIV positive patients who were diagnosed by the Integrated Counselling and Testing Centre (ICTC), who had been initiated on a second line anti-retroviral therapy and the treatment naïve HIV positive patients

were taken as the control group. The eligible patients should have been on an anti-retroviral therapy for a minimum of six months. The HIV positive patients who were diabetics or hypertensives even before the initiation of the antiretroviral therapy, were excluded from the study. The patients were enrolled in the study after obtaining their written informed consents. This study was approved by institutional ethics committee.

The relevant data was collected by using a pre tested semi questionnaire which was devised, based on a pilot study and on the discussion with experts who worked in this field. The questionnaire included: the demographic details, duration of the HIV infection, duration of the treatment and the ART regimen which was used and a history of smoking and alcohol consumption.

The clinical criteria for the metabolic syndrome like the mid arm circumference, was measured at the mid-point of the acromian process of the clavicle and at the olecranon process of the ulna. The assessment of lipodystrophy was done by measuring the waist circumference and the waist to hip ratio. The waist circumference was measured at the point's bare midriff after the patient exhaled, while standing without his/her shoes and with both his/her feet touching and the arms hanging freely. The measuring tape was of a material that could not be easily stretched. It was measured at the midpoint between the lowest rib and the iliac crest. The laboratory investigations which were done, included the fasting lipid profile and the fasting blood sugar.

STATISTICAL ANALYSIS

The collected data was analyzed by using SPSS, version 11.5. The Student't' test and ANOVA were used to compare the data between the different groups of patients. A 'p' value of less than 0.05 was considered as statistically significant.

RESULTS

A total of 40 patients were included in the study, among which 27 (67.5 %) were males and 13 (32.5) were females. Among these patients, 27 received PI and 13 were treatment naive patients. [Table/Fig-1] shows the comparison of the baseline characteristics among the patients who were on second line ART and the treatment naïve patients. There was no significant variation between the patients who were on 2nd line ART and the naive patients in terms of age, income, height, weight and the Body Mass Index (BMI).

Student't' test. Values were expressed as mean± SD

[Table/Fig-2] shows the comparison of the anthropometric measurements among the patients who were on second line ART and the treatment naive patients. There was no significant variation between the patients who were on 2nd line ART and the naive patients in terms of the mid arm circumference, the waist circumference and the waist to hip ratio.

Characteristics	2nd line ART (n=27)	Treatment naive patients (n=13)	P value
Age (years)	38.35±7.255	33.86±7.210	0.069
Monthly income (Rs)	8642.86±7498.413	4656.25±3170.561	0.192
Height (cms)	165.54±7.842	164.54±9.111	0.718
Weight (kg)	54.77±9.738	54.52±12.680	0.945
BMI(m2)	20.319±3.5983	20.321±4.0455	0.998

[Table/Fig-1]: Comparison of baseline characteristics between patients on second line ART and treatment naïve patients.

Student 't' test. The values were expressed as mean± SD

Characteristics	2nd line ART (n=27)	Treatment naive patient (n=13)	P value
Mid arm circumference (cm)	25.88±3.536	25.36±3.478	0.653
Waist circumference (cm)	76.58±8.528	74.57±11.168	0.529
Waist to hip ratio	0.8446±0.06719	0.8314±0.08254	0.588

[Table/Fig-2]: Comparison of anthropometric measurement among patients on second line ART and naive patients.

There was no significant difference among the patients who were on 2nd line ART and the treatment naive patients with regards to their fasting blood sugar. But a statistically significant difference was seen with respect to the total cholesterol and the LDL and HDL cholesterol (p=0.02, p=0.029, p=0.12 respectively, [Table/Fig-3]).

Student 't' test, Values were expressed as mean± SD

Characteristics	2nd line ART (n=27)	Naive Patient (n=13)	P value
Fasting Blood Sugar (mg/dl)	103.59 ±16.026	97.43±12.593	0.232
Total cholesterol (mg/dl)	172.65±47.609	141.36±7.702	0.020 *
LDL (mg/dl)	101.373±34.2136	79.307±16.6041	0.029 *
HDL (mg/dl)	29.71±14.631	40.43±5.515	0.012 *

[Table/Fig-3]: Comparison of blood sugar and lipid profile.

[Table/Fig-4] shows the comparison of the anthropometric and the metabolic parameters with the duration of the ART. Though there was no statistically significant relationship between the duration of the 2nd line ART and the anthropometric parameters, the fasting blood sugar and LDL cholesterol, an increasing trend was observed with these values with the duration of the ART. There was a significant association between the duration of the ART and the total cholesterol and HDL (p=0.05, p=0.025 respectively).

ANOVA* = significant

Parameters	Duration of ART			P value
	< 2 years	2-5 Years	> 5 years	
Mid arm circumference (cm)	24.94±3.094	25.57±3.435	26.38±3.754	0.787
Waist to hip ratio	0.819±0.747	0.871±0.569	0.849±0.065	0.051
Fasting Blood Sugar (mg/dl)	103.53±14.72	105.81±14.69	107.69±15.11	0.759
Total cholesterol (mg/dl)	169.82±46.248	186.09±37.490	207.92±42.958	0.05 *
LDL cholesterol (mg/dl)	102.182±39.324	113.696±29.012	127.385±22.660	0.104
HDL cholesterol (mg/dl)	29.05±15.717	21.57±15.413	14.02±22.16	0.025 *

[Table/Fig-4]: Comparison of anthropometric and metabolic parameters with duration of Anti Retro Viral Therapy (n=27).

DISCUSSION

The objective of the present study was to evaluate the development of the metabolic risk factors after initiating a second line anti-retroviral therapy. The introduction in the industrialized countries of the Highly Active Anti- Retroviral Therapy – a combination of three drugs which include either a protease inhibitor or a non-nucleoside reverse transcriptase inhibitor and two nucleoside analogues and reverse transcriptase inhibitors, led to a dramatic decline in the morbidity and mortality among the patients who were infected with the HIV infection.

It has been proven that the ART for HIV is accompanied with the occurrence of several metabolic effects [2]. Fat redistribution and metabolic anomalies have been reported increasingly in the HIV – infected patients who are treated with protease inhibitors. Hyperlipidaemia and insulin resistance are almost always associated with lipodystrophy [5]. In a study which was done by Erbelding EJ, it was seen that the reports of success with protease inhibitors were associated with metabolic risk factors like the loss of the peripheral subcutaneous fat, truncal obesity, hyperlipidaemia and frank Diabetes mellitus [6].

In a study which was done in Thailand, it was seen that the treatment with protease inhibitors was associated with elevations in the serum total cholesterol and the triglyceride levels [7]. In a study which was done by Calza L et al., in a cohort of 212 HIV positive patients who were started on a new protease based regimen, hypertriglyceridaemia (38.2%) and hypercholesterolaemia (25%) were observed [1]. A majority of the studies have shown that the use of protease inhibitors was associated with increased levels of total cholesterol, triglycerides, and low density lipoproteins [8-10]. Similarly, our study also showed significant elevations in the total cholesterol and LDL cholesterol with a second line ART. The elevation of total cholesterol showed an association with the duration of the therapy. The HDL cholesterol levels had significantly decreased in the patients who were on second line ART, which again showed a significant association with the duration of the therapy.

In our study, a total of 40 HIV positive adults were observed, out of which 27 were receiving PI and 13 are naive patients. An elevation in the total cholesterol level was observed in the patients who received PI (172.65 ±47.609 mg/dl) versus (141.36 ± 7.702 mg/dl) among the naive patients. It was observed that the HDL cholesterol levels decreased with an increase in the duration of the ART i.e. in the patients who received the ART for < 2 years [mean HDL (29.05±15.717 mg/dl)] as compared to the patients who received the ART for >5 years [mean HDL (14.02±22.16 mg/dl)]. Also, there is a significant increase in the LDL level, and with an increase in the duration of the ART, the LDL level increases, ranging from 102.182±39.324 in the individuals who are on PIs of less than 2 years, to 127.385±22.660 in the individuals who are on PIs for more than 5 years.

The protease related dyslipidaemia may be related to their interference with the key intracellular processes which regulate the glucose and lipid metabolism in the major insulin- responsive tissues. The lipid alterations may be the result of the increased production and the reduced catabolism of the very low density lipoproteins by the PIs. The PIs also increase the hepatic triglyceride (TG) synthesis by increasing the expression of the key enzymes which are involved in the biosynthesis of TG. Lipoprotein lipase normally binds to the LDL- receptor related protein type 1 in the capillary endothelium, which will be interfered with by the PIs, thus reducing the fat storage and increasing the free fatty acid plasma levels. The PIs also induce endoplasmic reticulum stress and the subsequent activation of the unfolded protein response by proteasome inhibition and a differential glucose transport blockade. This mechanism may also be involved in the PI induced dyslipidaemia [11].

To conclude, the patients who are on a second line anti-retroviral therapy, are prone to develop metabolic disorders, especially dyslipidaemia. The HIV infection is itself related to the metabolic complications which are aggravated by using a second line anti-retroviral therapy. The periodic evaluation of the lipid profile and the blood sugar levels should be done in these patients to recognize and to take appropriate action promptly for the metabolic complications.

Funding: ICMR STS 2011

REFERENCES

[1] Calza L, Manferdi R, Chiodo F. D yslipidemia associated with anti- retroviral therapy in HIV-infected patients. *JAC.* 2004; 53:10-14.
[2] Samaras K, Wand H, Law M, Enery S, Cooper D, Carr A. Prevalence of Syndrome in HIV – Infected Patients receiving HAART Using IDF and ATP III Criteria. *Diabetes Care.* 2007; 30:113-19.
[3] van der Valk M, Reiss P. Metabolic side effects of ART. *Ned Tijdschr Geneeskd.* 2008; 152:1260-64.
[4] Schambelan M, Benson CA, Carr A, Currier JS , Dube MP, Gerber JG et al. Management of metabolic complication associated with ART for HIV-1 infection: Recommendation of an internal AIDS society USA panel. *JAIDS.* 2002; 31: 259-71.
[5] Bernasconic E. Metabolic effects of Protease Inhibitor Therapy. *AIDS.* 1999; 9:254-69.
[6] Erbelding EJ. Metabolic complications of Protease Inhibitors: what have we learned so far? *Hopkins HIV Rep.*1999; 11:5- 15.
[7] Hiransuthikul N, Hiransuthikul P, Kanansook Y. Lipid profiles of Thai Adult HIV –infected patients receiving Protease Inhibitors. *Southeast Asian J Trop Med Public Health.* 2007; 38:69-77.
[8] Rhew D, Bernal M, Aguilar D, Iloeje U, Goetz MB. Association between Protease Inhibitor Use and Increased Cardio Vascular Risk in Patients Infected with HIV: A systemic review. *Clin Infect Dis.* 2003; 37:959-72.

[9] Périard D, Telenti A, Sudre P, Cheseaux JJ, Halfon P, Reymond MJ et al. Atherogenic Dyslipidemia In HIV Infected Individuals Treated with Protease Inhibitor. *Circulation.* 1999; 100:700-05.
[10] Ena J, Benito C, Llácer P, Pasquau F, Amador C. Abnormal body fat distribution and type of ART as predictors of cardiovascular disease risk in HIV- infected patients. *Med Clin(Barc).* 2004; 122:721-26.
[11] Estrada V, Portilla J. Dyslipidaemia related to antiretroviral therapy. *AIDS Rev.* 2011;13:49-56.

AUTHOR(S):
1. Mr. Apoorva Mittal
2. Dr. Basavaprabhu Achappa
3. Dr. Deepak Madi
4. Dr. Mukta N Chowta
5. Dr. John T Ramapuram
6. Dr. Satish Rao
7. Dr. Unnikrishnan B
8. Dr. Soundarya Mahalingam

PARTICULARS OF CONTRIBUTORS:
1. Final year MBBS Student,
2. Associate Professor, Department of General Medicine,
3. Assistant Professor, Department of General Medicine,
4. Professor, Department of Pharmacology,
5. Professor and Unit Chief, Department of General Medicine,
6. Associate Professor, Department of General Medicine,
7. Professor and HOD, Department of Community Medicine,
8. Associate Professor, Department of Paediatrics,
Kasturba Medical College, Mangalore (Affiliated to Manipal University), Karnataka, India.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Dr. Basavaprabhu Achappa,
Associate Professor, Department of General Medicine,
Kasturba Medical College, Attavar, Mangalore-575001
Phone: 09980170480
E-mail: bachu1504@gmail.com

FINANCIAL OR OTHER COMPETING INTERESTS:
None.

Date of Submission: **Jun 27, 2012**
Date of Peer Review: **Jul 27, 2012**
Date of Acceptance: **Nov 05, 2012**
Date of Publishing: **Feb 01, 2013**