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Changes in Lipid Profile and Fasting Blood Glucose in Protease Inhibitor Exposed HIV/AIDS Patients

Research Article

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Abstract

Background: The national second-line Anti retroviral Therapy (ART) programme was started in Kolkata, India in December 2008. It included a combination of Tenofovir, Lamivudine and Ritonavir-boosted Lopinavir ± Zidovudine. Dyslipidaemia and increased fasting blood sugar (FBS) often complicate protease inhibitor-containing ART. Thus a prospective study was designed to observe the above changes.

Methods: The data of 50 patients, on protease inhibitor for one year, were analyzed. Body Mass Index (BMI), grip strength (GS), Triceps skin fold (TSF), 24 hour dietary recall, serum triglyceride (TG), total cholesterol (TC), HDL, LDL, VLDL and FBS were estimated for all patients at baseline, 6 months and after one year.

Results: There was a significant increase in TG, TC and VLDL levels at 1 year as compared to baseline (p=0.013, 0.00 and 0.00 respectively) whereas LDL significantly increased at 6 months only (p=0.029). HDL decreased significantly at 6 months (p=0.019). TSF significantly decreased both at 6 and 12 months (p=0.00 and 0.00 respectively). The BMI and GS showed a significant increase at both 6 months (p=0.009, 0.000 respectively) and 1 year (p=0.002 and 0.00 respectively). Four patients with normal baseline FBG and one with impaired fasting glucose progressed to overt diabetes (FBG ≥ 124 mg/dl) at 12 months. No significant change was noted in energy and protein intake of patients.

Conclusion: There is an increased incidence of dyslipidaemia and unmasking of diabetes related to protease inhibitor in this cohort. There has been an improvement in nutritional status as shown by BMI and GS.

Keywords: Protease inhibitor; HIV/AIDS, Lipid profile; Fasting blood glucose

Introduction

The introduction of effective highly active antiretroviral therapy (HAART) in the mid-1990s led to a marked reduction in morbidity and mortality from human immunodeficiency virus (HIV) infection [1,2]. Effective HAART suppresses HIV RNA to undetectable levels, allowing immune recovery, measured by increases in $CD4^+$ T-cell counts, in the majority of patients. Metabolic effects of HIV infection such as hypertriglyceridemia are long recognised [3], and side effects of HAART such as dyslipidemia and insulin resistance were described

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very soon after its introduction [4]. Use of protease inhibitors (PI) has been associated with dyslipidemia which is more common and more severe [5,6]. These drugs have been associated with a syndrome of fat redistribution, insulin resistance, and hyperlipidemia. This is usually accompanied by some increases in total cholesterol and LDL-C which may be reverted according to some studies [7,5]. However, with some PI based therapies, HDL-C levels remain low [7,8], and hypertriglyceridemia may in fact worsen [8], giving rise to a distinctly atherogenic lipid profile [9]. In contrast, initiation of Non Nucleatide Reverse Transcriptase Inhibitor based HAART regimens has been shown to result in increases in HDL-C along with increases in total cholesterol, LDL-C and triglycerides (Ref) although the rise of triglyceride is usually not as high as those seen with some PIs [7]. Thismay lead to cardiological manifestations like increased rates of myocardial infarction arising as a result of dyslipidaemia in HIV-infected patients on antiretrovirals (ARV) [10,11,12] have been confirmed by studies such as the D:A:D study-a large, prospective, multi-cohort study that showed associations between exposure to antiretroviral therapy and an increased risk of myocardial infarction [13].

In Indian National ART guideline, launched on 1st April 2004, the initial first line Antiretroviral Therapy (ART) regimens comprised of combinations of Zidovudine/Stavudine, Lamivudine and Nevirapine/ Efavirenz and the secondline ART options included a combination of Tenofovir, Lamivudine and Ritonavir-boosted Lopinavir ± Zidovudine. The national second-line ART programme was started in School of Tropical Medicine, Kolkata from 1st December 2008. From July 2011 the second line regimen was changed and Lopinavir was replaced by Atazanavir and zidovudine was no longer used in the second line ART.

The initial second line ARV regimen comprised of a combination of Tenofovir, Lamivudine and Ritonavir-boosted Lopinavir ± Zidovudine. Patients with Hb% ≥ 9 gm/dl used to receive Zidovudine even if the drug was used in the first line ARV regimen. Dyslipidaemia and increased fasting blood sugar (FBS) often complicate protease inhibitor-containing ART. Thus a prospective study was designed to observe the above changes.

Methods

All patients starting 2nd line ART for the first time at Antiretroviral Therapy centre, School of Tropical Medicine, Kolkata till July 2011 were enrolled in the study and each patient was followed up for one year. The patients who were diabetic or had deranged lipid profile were excluded from the study. During this time their baseline, six months and one yearly anthropometric, Immunological, virologic and biochemical parameters were tested and recorded. The anthropometric parameters comprised of Body Mass Index (BMI), Grip Strength (GS) and Tricep Skin Fold (TSF), Immunological parameters included CD4 cell count done every 6 months following initition of ART. Viral load testing was done once before initiation of 2nd line and again after six months of treatment and in case the viral load was still detectable after six months it used to be repeated after one year of treatment. Biochemical parameters comprised of serum triglyceride, total cholesterol, High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL), Very Low Density Lipoprotein (VLDL) and Fasting Blood Sugar (FBS). Weight, height and MUAC were recorded using calibrated scale, stadiometer and standardized measuring tape respectively [14]. GS and TSF were measured with grip strength dynamometer from OG Gileen Company Limited, Japan and Harpenden Caliper respectively [15]. Information on dietary intake was collected by 24 hour recall method and dietary pattern was collected by food frequency questionnaire. 24 h dietary recall was taken with the help of 'katoris' (bowl), spoons, glasses which were standardized with commonly consumed recipes. Standardized models of different prepared food items like chapatti, paratha made by card board, dhokla, singara ladoo etc made by thermocol or cloth were prepared and used for accurate data collection. Depending on the Body Mass Index (BMI) each patient was classified into underweight (<18kg/m^2), normal weight (18-25kg/m^2) and overweight (>25kg/m^2) computed with the help of weight and height. Each participant was classified as having dyslipidemia if serum lipid levels were above (or, for HDL-c, below) the pre-specified threshold levels. These threshold levels were based on the cut-off values in Harrison et al. [16] as follows: hypercholesterolemia - serum TC levels ≥ 250 mg/ dl; low HDL-c - serum HDL-c levels <40 mg/ dl; high LDL-c - serum LDL-c levels ≥ 130 mg/dl. Hypertriglyceridemia was defined by serum fasting TG levels ≥150 mg/dl. Similarly diabetes was defined as FBS ≥ 124 mg/dl.

For statistical assessment, descriptive statistics regarding socio-demographic, epidemiological, clinical, and laboratory values were evaluated. In order to compare the parameters between baseline with 6 months and 1 year, Student's *t*-test or one-way analysis of variance for quantitative variables, with significant level placed at p-value ≤0.05 was used. All the tests were done using SPSS 16.

Results

Fifty patients were enrolled in the study. Among them 44 (88%) were men and 6 (12%) were women. The age ranged from 23 to 54 years, the median being 37 years. All the patients were from lower socio-economic background and were residing in the eastern states of West Bengal, Orissa and Bihar having similar socio demographic profile. The patients had failed first line treatments regimen (confirmed by virologic failure with plasma HIV RNA > 10,000 Copies/ml) as designated by National AIDS Control Organisation (NACO) and among them 3 patients had both immunological as well as clinical failure. In the present study Tenofovir, Lamivudine and Ritonavir-boosted Lopinavir was taken by 38 (76%) patients while 12 (24%) patients took Tenofovir, Lamivudine, Ritonavir-boosted Lopinavir and Zidovudine**.** The baseline characteristic have been summarised in Table 1.

The median values in Table 1 portray very high PVL since the patients starting protease inhibitor (PI) based regimen have already failed first line treatment. The rest of the base line characteristics are normal other than energy intake. It should be noted that the median energy intake of men and women taken together is much below the Recommended Daily Allowance (RDA) of even a sedentary woman which is 1875 kcal /day.

Hypertriglyiceridemia and Hypercholestrolemia were regularly noted at 6 months and 1 year of treatment with the percentage of the above represented in Figure 1. The trend of dyslipidaemia increased from 6 months to 1 year but the HDL improved from 6 months to one year, this change improved the TC: HDL ratio. After one year of treatment the range of Triglyceride was 110 to 386 mg/dl and that of total cholesterol was 214 to 465 mg/dl respectively.

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As shown in Table 2 there was a significant increase in TG, TC and VLDL levels at 1 year as compared to baseline (p=0.013, 0.00 and 0.00 respectively) whereas LDL significantly increased at 6 months only (p=0.029). HDL decreased significantly at 6 months (p=0.019). TSF significantly decreased both at 6 and 12 months (p=0.00 and 0.00 respectively) which is suggestive of lipodystrophy accompanied with increased BMI. The BMI and GS showed a significant increase both at 6 months (p=0.009, 0.000, respectively for BMI) and 1 year (p=0.002 and 0.00 respectively for GS). Four patients with normal baseline FBG and one with impaired fasting glucose progressed to overt diabetes (FBG ≥ 124 mg/dl) at 12 months. No significant change was noted in energy intake of patients.

Table 1: Baseline characteristics.

Characteristics	Value (median value)
Age (years)	37
CD4 (cells/μL)	84
PVL (copies/ μL)	250000
Clinical staging	2
BMI (Kg/m^2)	18.1
Grip strength (Kg force)	19
Tricep Skin fold (mm)	210
Triglyceride (mg/dl)	144
Total cholesterol (mg/dl)	147
HDLc (mg/dl)	31
LDLc (mg/dl)	70
VLDLc (mg/dl)	33.5
FBS (mg/dl)	93
Energy intake (Kcal/day)	1698

Source: Primary survey, 2011-12 Kolkata

Table 2: Comparison of study parameters with the corresponding baseline values.

Parameters	6 months	1 year
PVL	0.000**	
CD4	0.000**	0.000**
Clinical Staging	0.000**	0.000**
BMI (Kg/m^2)	0.009**	0.002**
Grip strength (Kg force)	0.001**	0.000**
Tricep Skin fold (mm)	0.000(-)**	0.000(-)**
Haemoglobin (gm %)	0.002**	0.000**
Albumin	0.304	0.303
Triglyceride(mg/dl)	0.067	0.008**
Total Cholesterol(mg/dl)	0.026*	0.008**
HDLc(mg/dl)	(-) 0.019*	(-) 0.091*
LDLc(mg/dl)	0.029*	0.370
VLDLc(mg/dl)	0.008**	0.000**
FBS(mg/dl)	0.100	0.242
Energy intake(Kcal/day)	0.528	0.073

Source: Primary survey, 2011-13 Kolkata;
* p<0.05
**p<0.01

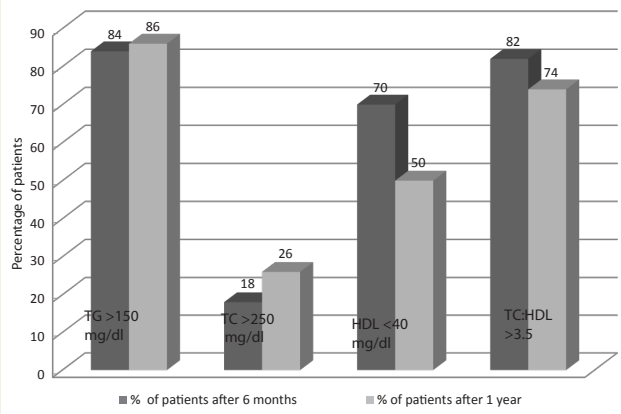

Figure 1: Distribution of the patients according to lipid profile changes over 1 year of second line treatment..

Discussions

The anthropometric results have shown an indication of lipodystrophy as there was steady decrease in tricep skin fold accompanied by an increase in grip strength and BMI. This suggests an increase in muscle mass but a decrease in fat around the triceps. Starting second line ART improved the nutritional status even though there was no significant increase in energy and protein intake. This may be due to lessening of the catabolic effect of HIV itself as shown by significant decreased PVL and improvement of immunologic status. The lipid profile was significantly deranged which is consistent with innumerable studies [6,8,17]. In most studies [6,8,17] the triglyceride and total cholesterol increased significantly with a decrease in the HDL level which is similar to our study. The exact procedure of derangement of lipid profile is not very clear but studies have suggested that HIV itself decreases HDL [18] at initial stage and increases TG and free fatty acid during AIDS [19]. Dual-PI therapy (ritonavir boosting) has been associated with the rapid development of hypertriglyceridemia. In the present study we have found an increase in HDL from 6 months to one year and hence there has been an improvement of TC: HDL ratio during the same time span. In a study by Churchill et al, hypertriglyceridemia occurred within 2 weeks of PI therapy among most patients. After 4th week the TG increased by 160% from the baseline and by 8th week there was significantly increased total cholesterol levels in addition [20]. In contrary to that, in the present study the TG was elevated significantly only at one year, this may be due to the lifestyle difference in developed and developing county.

In addition to dyslipidaemia, patients treated with PI therapy have been reported to develop insulin resistance and new-onset diabetes mellitus [21]. PIs tend to impair glucose sensing by cells. Peripheral insulin resistance and cell dysfunction together contribute to altered glucose homeostasis associated with PI [22]. In the present study it was observed that development of diabetes mellitus was not statistically significant but there were a few cases. However, long-term

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follow-up of the patients on boosted-PI will help in ascertaining the incidence of diabetes mellitus among them. This result is consistent with other documented studies [4,8]. Never the less it should be noted that in the present study insulin resistance was not tested due to resource limitation.

There is an increased incidence of dyslipidaemia and unmasking of diabetes related to protease inhibitor in this cohort. There has been an improvement in nutritional status as shown by BMI and GS. Effective control of virological and immunological parameters induced improved health parameters as reflected by improved BMI and GS. It should be noted that the virologic and immunological outcome outweighs the side effects induced by PI. Hence the use of PI based regimens continues to be an important part of HIV treatment in different countries. Nevertheless since HIV/AIDS is a chronic manageable disease now the quality of life is an important aspect. The side effects of PIs affect the quality of life of these patients. Hence this problem remains an important issue which needs to be managed and dealt with, since there is an increased use for PI in the treatment of HIV in the years to come in India. The National AIDS Control Organisation of India also changed lopinavir with Atazanavir in July 2011. Atazanavir is lipd-neutral and requires lesser dose of Ritonavir (100 mg/day) than Lopinavir (200 mg/day) for pharmacologic boosting with resultant lower incidence of dyslipidaemia. Nonetheless, regular monitoring of fasting lipid profile and blood glucose is crucial for patients on PI-based second line ART in the National Programme.

Our study has a few limitations, firstly since this is an operational research in a National Programme we could not use machines like DEXA for body composition and insulin resistance testing to observe metabolic disorder. These facilities have been used in many similar studies from different countries [8,23]. On the other hand it should be noted that when the patients who developed PI induced hypercholesterolemia and hypertriglyceridemia, went through both non-pharmacological and pharmacological interventions according to guidelines [16] during the study. Thus few patients controlled their lipid levels while receiving PI based regimen. This could not be avoided due to ethical issues, medical guidelines and the risk of cardio vascular diseases with high lipid levels [24]. The study was also limited by a small sample size as well as shorter follow-up period of one year.

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