

Metabolic changes in the patients on second-line highly active antiretroviral therapy (HAART): A prospective cohort study from north India

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ABSTRACT

Introduction: In India, there is a genetic predisposition to insulin resistance and cardiovascular risk, the impact of ART (antiretroviral therapy) on lipid profile and blood sugar may be significant. The study of potential implications of highly active antiretroviral therapy (HAART)-associated metabolic syndrome is critical to prevent cardiovascular diseases in the Indian population. **Aims:** This study was done to determine the prevalence of metabolic changes (dyslipidaemia, hyperglycemia and insulin resistance) among HIV patients on second-line ART. **Settings and Design:** A prospective cohort study. **Methods and Materials:** We enrolled 150 patients, who were started on second-line HAART. Patients were investigated for fasting blood sugar, lipid profile and insulin level at baseline and after 6 months. **Statistical Analysis:** The data were analysed using SPSS software (version 20; IBM Corp., Armonk, N.Y., USA). Student's *t*-test was used to compare numerical variables in the two groups. *P* value < 0.05 was considered as statistically significant. **Results:** There was a significant increase in serum cholesterol, LDL and triglyceride in patients with protease inhibitors (PIs) containing regimens. LDL levels were increased from 65 to 80 mg/dL (*P* = <0.003) after treatment. Triglycerides were increased from 138 to 152 mg/dL (*P* = <0.001). Median fasting blood sugar was increased from 85 to 96 mg/dL (*P* = <0.002). HOMA-IR was also significantly increased in the PI group (1.54 vs. 2.1, *P* <0.003). However, serum HDL did not change significantly. **Conclusions:** Appropriate drug selection with timely switching of ART is crucial to prevent metabolic complications in patients taking long-term PIs.

Keywords: Blood glucose, cardiovascular risk, HIV, metabolic syndrome, protease inhibitors

Introduction

The introduction of highly active antiretroviral therapy (HAART) has changed the course of HIV infection, increasing survival and improving the quality of life in HIV-infected individuals. However, it has been shown that a high proportion of patients treated with HAART regimens, especially those

including protease inhibitors (PIs), present metabolic disorders (dyslipidaemia, insulin resistance), as well as being at greater risk for cardiovascular disease.^[1] The study of potential implications of HAART-associated metabolic syndrome is critical to prevent cardiovascular diseases in the Indian population. A study from India by Theengh *et al.* showed a high frequency of metabolic syndrome among HIV-positive patients.^[2] Increased cardiovascular risk due to metabolic syndrome in HIV has been described by Triant *et al.*^[3] However, in a risk-prone Indian population, the additional burden associated with ART/HIV-induced metabolic syndrome needs to be evaluated.

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Aims and Objectives

To determine the prevalence of metabolic changes (dyslipidaemia, hyperglycemia and insulin resistance) among HIV-infected patients on second-line HIV therapy recommended by NACO (National AIDS Control Organisation).

Subjects and Methods

This prospective study was carried out at a tertiary care hospital among 150 patients who were started on PIs. Ethical approval was obtained from the Institutional Ethics Committee (Institute of Medical Sciences, BHU). All HIV infected patients, who had failed on first-line treatment and started on second-line HAART, formed the cases of the study and registered at ART centre.

Inclusion criteria

- HIV-infected individuals >18 years old
- HIV-infected individuals on second-line HIV therapy
- Willing to participate and sign an informed consent.

Exclusion criteria

- FBS >126 mg/dL or on antidiabetic drugs
- AIDS-defining events or severe illness within 1 month of evaluation
- Pregnancy
- Patient not giving consent for the study.

Eligible patients were included in the study after they were counselled regarding the study, its nature and the relevance. A total of 150 patients were enrolled who were started on PIs. Most of the subjects were male ($n = 96$) (64%) and the mean age of the subjects was $35 (\pm 7.33)$ years [Table 1]. The mean BMI of all the patients was $19.88 (\text{kg}/\text{m}^2)$, who was on second-line ART. The family history of diabetes was present in 9 patients. After the written informed consent was obtained, they were subjected to a detailed evaluation of history, clinical examination and investigations at the time of the first visit. (as per predesigned proforma). After the second-line ART was started, they were followed up to look for the metabolic changes in response to the treatment. The immunological and virological assessment was done at 6 months by CD 4 count and viral load. All the patients were subjected to investigations for fasting blood glucose, lipid profile and insulin resistance. Insulin resistance was calculated using the HOMA-IR

Table 1: Baseline characteristics of subjects (n=150)

Variable	Cases (n=150) (mean±SD)
Age (year)	35 (\pm 7.33)
Male sex - n (%)	96 (64%)
BMI (kg/m^2)	19.88 (\pm 1.9)
Family history of CVD (n)	9
Family history of diabetes (n)	9
Smokers (n)	15
Viral Load	2.67 \pm 2.42 (copies/mL)
CD 4 cell count	323 \pm 113.21 cells/ mm^3

equation.^[4] The homeostatic model assessment (HOMA) is a method to quantify insulin resistance and beta-cell function.

HOMA-IR - Fasting insulin x Fasting glucose/405

Glucose in mg/dL, Insulin in mIU/L. The venous sample was collected after 8 h of the overnight fast.

Statistical analysis

The data were analysed using SPSS software (version 20; IBM Corp., Armonk, N.Y., USA). The data was checked for the assumption of normality. A student's *t*-test was done to compare numerical variables in the two groups. *P* value < 0.05 was considered as statistically significant.

Results

There was a significant increase in serum cholesterol, LDL and triglyceride level in HIV-infected patients taking antiretroviral medication with protease inhibitor-containing regimens. Although as compared to similar previous studies we have not found any significant reduction in serum HDL. (median 35.3 to 34.2 mg/dL, *P* = NS), [Table 2]. In our study, we have also noticed that there was an increasing percentage of patients showing dyslipidaemia. Increase serum cholesterol (6 to 18%), increase triglyceride (from 36.66 to 63.33% *P* = 0.033), increase LDL level from 12 to 42.66% (*P* = 0.001). However, serum HDL did not change significantly after treatment with PI [Table 3, Figure 1]. Median fasting blood glucose was significantly increased after treatment with PIs (85 to 96 mg/dL *P* = <0.002). Fasting blood glucose was >140 mg/dl in 9 patients (in PIs treated group) after 6 months of ritonavir-based PI regimen. Fasting plasma insulin level was also increased in PI treated (8.2 to 10.9 mIU/L, *P* < 0.001) [Table 4].

Discussion

Our study showed a high prevalence of dyslipidaemia and insulin resistance among patients started on second-line ART. It has been

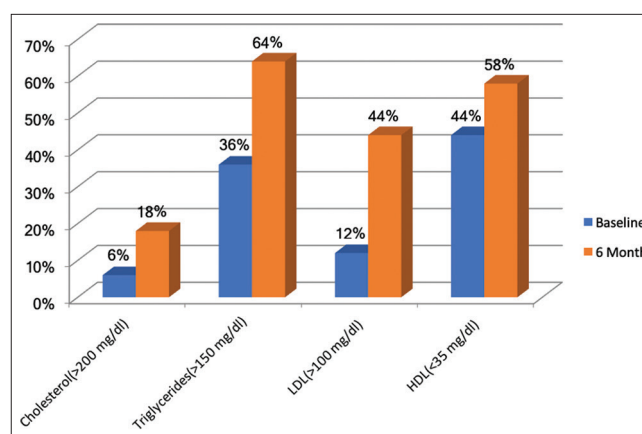


Figure 1: Prevalence of dyslipidaemia at baseline and after 6 months of PI therapy

Table 2: Changes in serum lipids from baseline (mg/dL) [median (interquartile range)]

	Cases (n=150)		P
	PIs (protease inhibitors) naïve	PIs Treated (after 6 months)	
Total cholesterol (mg/dL)	141.6 (80-235)	169.5 (100-261)	<.001
Triglyceride (mg/dL)	138.0 (58-440)	152.5 (59-549)	<.001
LDL (mg/dL)	65.5 (46-137)	80.3 (73-156)	<.003
HDL (mg/dL)	35.3 (26-45)	34.2 (29-42)	NS

Table 3: Percentages of patients with dyslipidaemia according to reference values

Hyperlipidaemia	PI naïve (baseline) n (%)	PI treated (after 6 month) n (%)	P
Cholesterol (> 200 mg/dL)	9 (6%)	27 (18%)	0.04
Triglycerides (> 150 mg/dL)	55 (36.66%)	95 (63.33%)	0.033
LDL cholesterol (>100 mg/dL)	18 (12%)	64 (42.66%)	0.001
HDL cholesterol (<35 mg/dL)	66 (44%)	86 (57.33%)	NS

Table 4: Baseline plasma glucose, insulin and HOMA IR [median (interquartile range)]

	Cases (n=150)		P
	PI naïve	PI treated (after 6 months)	
Fasting Blood Sugar mg/dL	85 (61-124)	96 (69-186)	<.002
Fasting Insulin (mIU/L)	8.2 (6.4-12.5)	10.9 (7-14.3)	<.001
HOMA-IR	1.54 (1.1-2.8)	2.1 (1.6-3.5)	<.003

shown that a high proportion of patients treated with HAART regimens, especially those including PIs, presents with metabolic disorders (dyslipidaemia, insulin resistance) as well as being at greater risk for cardiovascular disease. Indians as an ethnic group have a high prevalence of insulin resistance, type 2 diabetes and metabolic syndrome as compared to other western countries.^[5]

In India, there were a few studies on the metabolic effects of second-line ART treatment. The earlier similar study has been done in south India by Idiculla *et al.* but in their study, there were only three patients taking second-line PI-based regimens, the rest of them were on first-line ART.^[6] Patients receiving long-term PIs frequently develop dyslipidaemia, impaired blood glucose and insulin resistance^[7-10] but the development of secondary diabetes mellitus (DM) is relatively rare. In terms of a decrease in disease progression and improving survival, PIs are clearly effective, but as survival increases, more evident metabolic effects were observed. A study by Matoga *et al.* reported that ritonavir monotherapy frequently causes hyperlipidaemia.^[11] In our study, a ritonavir/atazanavir-based PI regimen was used. Whether the combination of PIs will increase the prevalence of dyslipidaemia is remains to be seen.

In this study, PI containing regimens found to have a dyslipidaemic effect, in particular, causing an increase in serum triglycerides, cholesterol and LDL concentration. The specific mechanism by which PIs causes dyslipidaemia is still unclear. One possible explanation is that PI inhibits cellular proteases which involve in lipid metabolism. It has been shown that

ritonavir can affect apoB lipoprotein degradation which can lead to the accumulation of triglycerides and VLDL.^[12] PIs also inhibits the SREBP-1 (sterol regulatory element-binding proteins) nuclear localisation in adipocytes, resulting in decrease adipocyte differentiation and reduce expression of peroxisome proliferator-activated receptor-gamma (PPAR γ) which further contributes to dyslipidaemia.

In our study, we found an increase in serum cholesterol from 141 to 169 mg/dL ($P = <.001$) in patients receiving a PI-based regimen. A similar study was done by Levy *et al.*,^[13] which showed a 20% rise in total cholesterol after 12 months of PIs. We have also found similar changes in triglyceride levels. Mean TG levels were increased from 138 to 152 mg/dL ($P = <0.001$). A similar Indian study by Idiculla *et al.* has reported higher TG levels (155 to 201 mg/dL).^[6] Ritonavir is possibly the most potent inducer of hyperlipidaemia among PIs. Hyperlipidaemia resulting from the use of PIs has been more commonly reported when PIs are boosted with low-dose ritonavir. We have not found any significant changes in HDL levels in patients on second-line ART. A study by Yone *et al.* revealed that PIs do not appear to deteriorate the lipid profile of HIV patients.^[14] The occurrence of lipid abnormalities was not significant in their report.

Insulin Resistance

In the PI-treated group, out of 150 patients, 9 patients had a fasting glucose level above 140 mg/dL. The baseline blood glucose level of each of these patients was in the normal range. Among 9 patients detected to be diabetic, 3 of them were on ritonavir/lopinavir-based therapy, later on, shifted to atazanavir. No other risk factors were observed in these patients. The prevalence of DM in people with HIV is relatively low, with studies reporting rates from 0.5% to 15%.^[15-19] Impaired glucose tolerance is considerably more common, affecting an estimated 15–25% of patients and research suggest that some degree of insulin resistance may occur in one-half of people taking PIs. A report by Fiseha *et al.* described the duration of ART is the most important risk factor for diabetes instead of HIV infection.^[18]

Some PIs may contribute to the inhibition of glucose transporter (glucose transporter type 4, GLUT4) with a reduction in insulin sensitivity resulting in decreased peripheral glucose uptake by adipocyte.^[19] Contrary to our report, Han *et al.* reported no significant association between PIs treatment and the development of impair glucose, diabetes in HIV patients.^[17]

Fargo *et al.*,^[20] reported a significant increase in median HOMA IR after 4 weeks of starting PIs. (1.9-fold change; 95% confidence interval, 1.73–2.05), which was similar to our study. However, another report by Guillen *et al.* did not find any significant association with insulin resistance and PIs.^[21] Though a number of a patient taking PIs were small in their study.

The choice of lipid-lowering agents should be limited to those agents with a low likelihood of interactions. Statins are primarily metabolized through cytochrome 3A4 and may lead to unfavourable drug interactions with PIs. The FDA has recommended the use of atorvastatin in the lowest possible doses with lopinavir/ritonavir. Pitavastatin has shown lesser drug interaction with PIs with no dose modification.^[22,23]

Conclusion

This study highlights the metabolic changes in patients on PIs. Despite the limitation of only 6 months of follow-up of patients in our study, we found a significant increase in dyslipidaemia and insulin resistance in patients on second-line ART. Larger population-based studies with long-term follow-up will be required to know more about the prevalence of metabolic disorders and cardiovascular risk in Indian patients taking HAART. The advent of PIs resulting in a significant decline in HIV related morbidity and mortality, however, an increase in the prevalence of metabolic complications is a serious cause for concern. Primary care physicians need to be aware of these metabolic changes in HIV patients taking long-term ART. We conclude, that aggressive screening for lipid profile and blood glucose is needed and appropriate drug selection with the timely switching of therapy is crucial to prevent metabolic complications in patients taking long-term PIs. Lipid-lowering therapy with statins and fibrates has been demonstrated to be successful but the safety and efficacy of these drugs must be assessed in HIV patients in further studies.

Declaration of study subjects consent

The authors certify that they have obtained all appropriate study subjects consent forms. In the form, the study subjects have given their consent for their images and other clinical information to be reported in the journal. The study subjects understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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