Metabolic syndrome and cardiovascular disease risk assessment among human immunodeficiency virus-infected individuals on antiretroviral therapy

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Abstract

Background: The association of cardiovascular risk with first-line antiretroviral therapy (ART) in Indians has been a matter of concern with the background of a high risk in South Asians. **Aims:** This study aimed to compare metabolic syndrome and its components, dyslipidemia, insulin resistance, and cardiovascular risk among patients on first-line ART (Group 1) with age-matched, ART-naïve human immunodeficiency virus (HIV)-infected patients (Group 2) and normal controls (Group 3). **Methods:** Patients attending a tertiary care center in Mysore were enrolled in the study after obtaining informed consent and controls were chosen from relatives of patients. **Results:** The total number of patients enrolled in the study was 217 (males 111; females 106), and the mean age of these patients was 34.1 ± 7.4 years. The number of patients in Group 1 (HIV+, ART experienced) was 76; in Group 2 (HIV+, ART naïve) was 71, and in Group 3 (HIV−) was 70. There was no statistically significant difference in the prevalence of metabolic syndrome between the three groups. On comparing the components of metabolic syndrome, serum triglycerides (mg/dl) were significantly higher in the ART group (Group 1: 149.5 [interquartile range (IQR): 84–187], Group 2: 108 [IQR: 74–152], and Group 3: 141.5 [IQR: 89–192]; $P = 0.014$) and serum high-density lipoprotein cholesterol was higher in HIV-uninfected individuals (Group 1: 37.5 ± 11.83, Group 2: 31.5 ± 12.23, and Group 3: 40.1 ± 12.09; $P = 0.0002$). There was no association between metabolic syndrome, duration of HIV, and type of first-line ART. Total and low-density lipoprotein (LDL) cholesterol were significantly higher in the ART group. Homeostatic model assessment and Framingham scores did not reveal any significant difference across the three groups. **Conclusion:** HIV-infected individuals on ART had higher levels of triglycerides, LDL, and total cholesterol, but no increased cardiovascular risk compared to other groups.

Key words: Antiretroviral therapy, cardiovascular risk, metabolic syndrome

INTRODUCTION

Globally, cardiovascular disease accounts for approximately 30% of deaths every year, which is higher than the combined rates of all other noninfectious diseases, and India is a major contributor toward this alarming statistic.[1] While the Asian Indian phenotype is implicated in the pathogenesis of cardiovascular disease, urbanization and changes in lifestyle have also played significant roles in the evolution of this risk.[2] The role of

human immunodeficiency virus (HIV) and its therapy in the development of insulin resistance (IR), dyslipidemia, and consequent cardiovascular risk is multifactorial and has been recognized for some time now.[3] While most studies point to an increased risk of metabolic derangements with the use of protease inhibitors, nonnucleoside reverse transcriptase inhibitors (NRTIs), especially stavudine and zidovudine, have been reported to confer an increased risk.[4-6] Crippling of mitochondrial function is considered to be the main pathogenetic factor causing metabolic abnormalities with NRTIs use.[7] However, the D: A: D study, an international collaborative study which followed up over 30,000 HIV-infected individuals, reported no association between the use of tenofovir, zalcitabine, zidovudine, stavudine, or lamivudine and cardiovascular disease risk.[8]

In India with over 2 million patients infected with HIV, the backbone of first-line antiretroviral therapy (ART) is mainly NRTI drugs in the form of zidovudine or tenofovir (stavudine is currently phased out) along with lamivudine and a non-NRTI.[9,10] The association of risk factors for cardiovascular disease in patients with HIV on ART has been investigated in some parts of India.[11-14] These studies have been on small numbers of patients and have published reports from no increase to varying prevalence of risk factors in patients on ART. "Metabolic syndrome," a cluster of increasingly common conditions such as increased blood pressure, high blood glucose, excess body fat around the waist, and abnormal cholesterol or triglyceride levels, can increase the risk of heart disease, stroke, and diabetes, particularly in those chronically infected with HIV. Hence, the present study was planned to compare cardiovascular risk factors and metabolic syndrome (which confers increased cardiovascular risk), in patients on first-line ART in comparison with ART-naïve patients and HIV-uninfected individuals.

METHODS

Study setting
The study was conducted at Krishna Rajendra Hospital, Mysore, Karnataka, from September 2011 to August 2013. This is a public HIV clinic in a state-owned tertiary-level hospital. Ethical approval for conducting the study was obtained from the Institutional Review Board.

Study participants
Two groups of participants were chosen from adult patients and attending the above hospital; Group 1 included HIV-infected patients who have been on first-line ART for at least 1 year; Group 2 included HIV-infected individuals who were not on ART, matched with Group 1 for age and time since diagnosis; and Group 3 included HIV-negative individuals who were matched with Group 1 for age (chosen from individuals accompanying the patients and those working in the hospital). Patients were excluded if they were diagnosed with any of the following conditions prior to diagnosis of HIV infection; diabetes mellitus, hypertension, dyslipidemia, coronary artery disease, malignancy, or chronic renal failure. In addition, patients who had <95% adherence to ART medication were excluded from Group 1.

Study procedure
Individuals who met recruitment criteria and were willing to participate in the study were enrolled after obtaining written informed consent. A full clinical examination including anthropometric measurements (height, weight, and waist circumference) was performed for each patient. Following this, venous blood samples were collected, and fasting blood glucose, lipid profile, and fasting insulin were assayed in the standard laboratory attached to the institution.

Definitions
Metabolic syndrome was defined according to the National Cholesterol Education Program–Adult Treatment Plan III (NCEP ATP III) 2001 criteria as follows: the presence of three or more of the following criteria: (i) Waist circumference ≥90 cm in men and ≥80 cm in women, (ii) serum triglycerides ≥150 mg/dl, (iii) high-density lipoprotein (HDL) cholesterol ≤40 mg/dl in men and ≤50 mg/dl in women, (iv) blood pressure ≥130/85 mm Hg, and (v) fasting glucose ≥100 mg/dl.[15]

IR was calculated using the homeostatic model assessment of IR (HOMA-IR): (Fasting insulin level [micro IU] multiplied by fasting glucose [mmol/L]) divided by 22.5.[16]

Cardiovascular risk: The absolute risk of developing cardiovascular disease was calculated for each individual using the Framingham Risk Score.[17]

Sample size
Based on a previous study done in a tertiary referral center which reported a prevalence of metabolic syndrome of 43% in ART-treated patients and 10% in ART-naïve patients, a sample size of 72 was taken

in each group, with a power of 90% and alpha error of 0.5.[18]

Statistical analysis

Data were analyzed using SPSS software for windows version 17.0 Chicago: SPSS Inc. Frequencies, measures of central tendency, and deviation were used to describe the continuous variables. Further, associations between demographic variables and cardiovascular risk factors were derived using Chi-square test, Student's *t*-test, Mann–Whitney U-test, or Kruskal–Wallis test as appropriate.

RESULTS

The total number of patients enrolled in the study was 217 (males 111; females 106). The mean age of these patients was 34.1 ± 7.4 years. The distribution of demographic characteristics in each group is shown in Table 1. The number of patients in Group 1 (HIV+, ART experienced) was 76; in Group 2 (HIV+, ART naïve) was 71, and in Group 3 (HIV−) was 70. The median duration of HIV (since HIV diagnosis) for Groups 1 and 2 combined was 47.1 (interquartile range [IQR]: 31.5–68), in Group 1, 48.2 (IQR: 31.5–70.4) and in Group 2, 46.8 (IQR: 29.5–68) months. In Group 1, the median duration of current ART was

33.2 (IQR: 16.1–49.2) months. The current ART regimens were zidovudine (48)-, stavudine (26)-, and tenofovir (2)-based combinations with lamivudine and either efavirenz or nevirapine.

Table 2 summarizes the individual components of metabolic syndrome (waist circumference, triglycerides, HDL cholesterol, fasting glucose, and blood pressure), fasting insulin, IR, total cholesterol, low-density lipoprotein (LDL) cholesterol, metabolic syndrome, and Framingham Risk Score in the whole group and in each subgroup. On comparing these variables, serum triglycerides (mg/dl) were significantly higher in the ART group (Group 1: 149.5 [IQR: 84–187], Group 2: 108 [IQR: 74-152], Group 3: 141.5 [IQR: 89–192]) and serum HDL cholesterol was highest in HIV-uninfected individuals [Table 2]. The most frequent positive criteria in all the groups were high triglycerides and low HDL [Table 3].

The number of patients with one, two, three, or more components of metabolic syndrome is shown in Table 4. The number of patients with two positive components was highest in Group 1. The prevalence of metabolic syndrome in Groups 1, 2, and 3 was 17 (22.4%), 12 (16.9%), and 14 (20.0%), respectively, with no statistical difference between the groups.

Table 1: Patient characteristics

Variable	Overall	HIV+ ART experienced Group 1 (*n*=76)	HIV+ ART naïve Group 2 (*n*=71)	HIV negative Group 3 (*n*=70)
Sex, *n* (%)				
Male	115 (51.2)	37 (48.7)	27 (38.0)	47 (67.1)
Female	106 (48.8)	39 (51.3)	44 (62.0)	23 (32.9)
Age, mean±SD (years)				
Mean	34.1±7.47	35.9±6.93	34.2±7.60	32.2±7.52
BMI, mean±SD (kg/m²)	21.3±3.86	21.2±3.51	21.0±3.86	21.8±4.22

SD=Standard deviation; HIV=Human immunodeficiency virus; ART=Antiretroviral therapy; BMI=Body mass index

Table 2: Metabolic syndrome, insulin resistance, and cardiovascular risk

Variable	Overall	HIV+ ART experienced Group 1	HIV+ ART naïve Group 2	HIV negative Group 3	*P*
Waist circumference (cm)	76.8±10.63	77.9±10.01	75.9±10.39	76.7±11.56	0.531
Triglycerides, median (IQR) (mg/dl)	133 (84-187)	149.5 (84-215)	108 (74-152)	141.5 (89-198)	0.014*
HDL, mean±SD (mg/dl)	36.3±12.51	37.5±11.83	31.5±12.23	40.1±12.09	0.0002*
Fasting glucose, mean±SD (mg/dl)	76.0±15.78	75.3±16.62	76.9±16.97	75.9±13.65	0.815
SBP, mean±SD (mmHg)	117.6±15.56	117.9±15.68	116.1±14.07	118±16.92	0.578
DBP, mean±SD (mmHg)	70.7±10.05	71.1±9.32	70.1±8.76	70.9±11.96	0.837
Fasting insulin, median (IQR)	5.5 (3.4-8.6)	6.6 (3.8-10.3)	5.2 (3.5-7.0)	4.7 (3.0-8.7)	0.074
Insulin resistance (HOMA), median (IQR)	1.0 (0.6-1.6)	1.2 (0.6-01.9)	1.0 (0.6-1.4)	0.9 (0.6-1.6)	0.219
Total cholesterol, mean±SD (mg/dl)	177.6±51.73	189.9±49.07	155.5±45.27	186.6±54.18	<0.001*
LDL cholesterol, mean±SD (mg/dl)	110.4±38.18	117.3±35.83	98.1±34.51	115.3±41.6	0.004*
Metabolic syndrome (number of individuals)	43	17	12	14	0.703
Framingham Risk Score	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	0.0 (0.0-1.0)	-

SD=Standard deviation; IQR=Interquartile range; HDL=High-density lipoprotein; HOMA=Homeostatic model assessment; LDL=Low-density lipoprotein; HIV=Human immunodeficiency virus; ART=Antiretroviral therapy; DBP=Diastolic blood pressure; SBP=Systolic blood pressure

Table 3: Comparison of metabolic syndrome criteria

Variable	Group 1, *n* (%)	Group 2, *n* (%)	Group 3, *n* (%)	*P*
Serum triglycerides ≥150 mg/dl	38 (50.00)	19 (73.24)	31 (55.71)	0.012
HDL cholesterol ≤40/≤50 mg/dl	54 (71.05)	62 (87.32)	42 (60.00)	0.001
SBP ≥130 mmHg	11 (14.47)	12 (16.90)	13 (18.57)	0.79
DBP ≥85 mmHg	5 (6.67)	4 (5.63)	8 (11.43)	0.39
≥ waist circumference 80/90≥ cm	17 (22.37)	20 (28.17)	16 (22.86)	0.66

HDL=High-density lipoprotein; DBP=Diastolic blood pressure; SBP=Systolic blood pressure

Table 4: Frequency of metabolic syndrome criteria in each group

	Group 1 (*n*=76), *n* (%)	Group 2 (*n*=71), *n* (%)	Group 3 (*n*=70), *n* (%)	Total (*n*=217)
None of the conditions positive	9 (11.84)	4 (5.63)	12 (17.14)	25
One condition positive	26 (34.21)	32 (45.07)	25 (35.71)	83
Two conditions positive	24 (31.58)	23 (32.39)	19 (27.14)	66
Three conditions positive	16 (21.05)	7 (9.86)	8 (11.43)	31
Four conditions positive	1 (1.32)	5 (7.04)	6 (8.57)	12
Total	76	71	70	217

There was no association between metabolic syndrome and duration of HIV, CD4 counts, or type or duration of ART. There was no statistical difference in the prevalence of dyslipidemia (any one of the NCEP–ATP III criteria) between groups (Group 1: 63, Group 2: 60, and Group 3: 50). Similarly, there was no association between the presence of dyslipidemia (NCEP–ATP III criteria) and duration or the type of first-line regimen. The number of patients with dysglycemia (fasting blood glucose ≥100 mg/dl) was 2, 4, and 5 in Groups 1, 2, and 3, respectively.

Fasting insulin, IR HOMA, total cholesterol and LDL cholesterol, and Framingham Risk Scores are compared between the groups [Table 2]. The total and LDL cholesterol were significantly higher in the ART group. The median Framingham Risk Score for cardiovascular risk was 0 in all the groups. However, on comparing the scores in those above 45 years of age, it was 6% in Group 2 (ART treated) and in controls and 4% in the ART-naïve group.

DISCUSSION

This study, conducted to assess the influence of currently used first-line ART on cardiovascular disease risk, showed that the prevalence of metabolic syndrome did not significantly differ between ART-treated, ART-naïve, and normal controls. On comparing the components of metabolic syndrome, triglycerides were significantly higher in ART-treated patients, while HDL cholesterol was highest in normal controls. There was no difference in the prevalence of metabolic syndrome between those on ART, ART-naïve patients, and normal controls. Two-condition positivity for metabolic syndrome components was highest in Group 1. Dyslipidemia as defined by ATP III was also most frequent in Group 1. This was not found to be associated with the type of ART or duration of HIV. Cardiovascular risk scores were also similar across groups. The patients on ART had significantly higher levels of total and LDL cholesterols and high triglycerides in comparison to the other two groups.

Two major studies on metabolic syndrome in patients infected with HIV reported prevalence rates of 14%–17%, which are similar to the general population.[5,19] Metabolic syndrome was diagnosed in 121 of 788 patients with HIV in the earlier of these studies published from Spain. Of these, 116 patients were on ART, and stavudine and lopinavir/ritonavir therapies were found to be associated with an increased prevalence of metabolic syndrome.[5] In the other cross-sectional study conducted in 32 centers worldwide, metabolic syndrome was noted to be more common in patients on protease inhibitors. In India, 18% prevalence was noted in a Mumbai cohort of 660 patients.[20] The prevalence rates in patients on stavudine (28.4%) and protease inhibitors (40%) were higher than the overall prevalence. In a recent cross-sectional study from Lucknow, the prevalence of metabolic syndrome by NCEP–ATP III criteria was 20% with no statistically significant difference between those on and not on ART.[14] In our study, the prevalence rates were similar (22%), and there was no significant difference between the groups. IR, the core pathogenetic factor of metabolic syndrome, was also similar across groups. It is also noteworthy that, in the pilot study where the prevalence rates of metabolic syndrome were as high as 43%, enrolled older patients who were exposed to longer duration of ART.[18]

When components of metabolic syndrome were analyzed, high triglycerides and low HDL were most frequently observed in all the groups. This observation of higher triglycerides and low HDL concurs with previous studies from India and abroad.[5,11,14,19] The major discordance in the components of metabolic syndrome in the comparison with the Lucknow study is in the prevalence of dysglycemia.[14] Our patients had very low prevalence rates of 2.67 and 5.7, respectively, in ART-treated and ART-naïve groups which was 27.7% and 30.4%, respectively, in their study. The study from Vellore, which is similar to the present study, also reported 34% prevalence of abnormal glycemic status.[11] It is to be noted that the study from Vellore had performed oral glucose tolerance test and assessed postload glucose levels also. The duration of ART may also be contributory to higher dysglycemia as it is higher in the Vellore study and not mentioned in the study from Lucknow. The Vellore study has also observed that dysglycemia was more prevalent in those on ART for more than 2 years. It is also of interest that waist circumference was not increased in any of the patients in the Lucknow study. In our study, though mean waist circumference measurements were less than the cutoffs for metabolic syndrome, there was a 24.4% prevalence of this criterion in the whole cohort. The Vellore study results on waist circumference are similar to our reports.

Bajaj *et al.* from Lucknow had reported that 18.6% had at least two conditions, while 35.8% of patients had two or more conditions in the Spanish study.[14,19] Our study was comparable to the Spanish study with 31.5% of patients having two conditions positive when combining Groups 1 and 2. About 31% of ART-treated patients (Group 1) had two or more criteria recorded. The ART-naïve group had 32% of two-condition positivity, while controls had 27% with this. While Bajaj *et al.* reported only 21% of ART-treated patients in this category, which is lower than in our study. This may be due to the higher prevalence of dyslipidemia in our study group. It is also to be noted that the mean waist circumference is below the cutoff for metabolic syndrome in all the patients in this study, and if waist circumferences increase, the prevalence of metabolic syndrome will also increase.

Dyslipidemia has been described in patients with HIV in both ART-naïve and ART-treated groups. Although protease inhibitor-based regimens are usually implicated in HIV-associated dyslipidemia, NRTIs are also known to cause mitochondrial DNA depletion, enzyme deficiencies, and adipocyte apoptosis with resultant lipid abnormalities.[21] In a retrospective analysis of data from 495 patients

from Brazil, zidovudine and tenofovir were not associated with dyslipidemia, though treatment with ART raised all components of lipid profile.[22] However, a cross-sectional study from Cameroon reported an increased prevalence of atherogenic dyslipidemia in first-line ART-treated patients.[23] This study compared 138 patients on ART for a mean duration of 13.1 months with 138 patients who were ART naïve. Total and LDL cholesterol were higher in ART-treated patients. The mean values were 196, 133, and 134 mg/dl for total cholesterol, LDL cholesterol, and triglycerides, respectively. In our study, though total cholesterol, LDL cholesterol, and triglycerides are higher in ART-naïve patients and normal controls, the mean values remain within acceptable levels. Despite the increase in HDL cholesterol, they were still lower than the levels suggested by the NCEP–ATP III guidelines.[24] In the study from Vellore, the lipid profile was similar to that observed in our study with higher cholesterol (195 vs. 189 mg/dl) and triglyceride (268 vs. 149 mg/dl) levels in the ART-treated group, while the LDL cholesterol levels were similar (110 vs. 106 mg/dl).[11] The higher proportion of stavudine-treated patients may account for these differences. Another study from Haryana which compared lipid levels in patients on ART found that the total cholesterol, LDL cholesterol, and triglycerides were lower at 6 months of therapy.[12]

Despite the increased prevalence of atherogenic lipidotype, when cardiovascular risk is analyzed using Framingham Risk Scores, it remained at <1% across all groups. On subgroup analysis of those aged over 45 years to nullify the protective effect of age, the risk scores increased to 6% in Groups 1 and 3 and 4% in Group 2, though there was no statistically significant difference between the groups. Framingham Risk Score comparison from Zimbabwe in patients treated with tenofovir- and zidovudine-based regimens also did not show any difference between ART-naïve and ART-treated groups.[25] In this study, 84.8% of patients had Framingham Risk Scores <1%.

Our study is limited by the cross-sectional design used. True cardiovascular risk is best assessed over time, and this assessment was not possible in our study design. As some patients may have been exposed to different regimens at different times, the risk conferred by each drug/regimen could not be accurately calculated. The other drawback is that the D. A. D. risk score which has higher accuracy in predicting cardiovascular risk in HIV-infected patients could not be applied to this study due to lack of data on required parameters. Despite our best

efforts, there was an increase in the proportion of women in the HIV-negative group, which may have lowered the prevalence rates of risk factors in this group. The three-group age-matched design which enabled comparison of the ART exposure among HIV-infected individuals, along with HIV-uninfected individuals, is a major strength of this study. Achieving adequate sample size also adds to the power of results.

CONCLUSION

HIV-infected individuals on ART had higher levels of triglycerides, LDL, and total cholesterol. However, they did not exhibit an increased cardiovascular risk in comparison to ART-naïve or HIV-uninfected individuals. While this is encouraging toward early initiation of ART, longitudinal observational studies are required to assess the true cardiovascular risk in HIV-positive individuals in India.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Global Atlas on Cardiovascular Disease Prevention and Control. Available from: http://www.world-heart-federation.org/fileadmin/user_upload/images/CVD_Health/Global_CVD_Atlas.pdf. [Cited on 2017 May 17].
2. Gupta M, Singh N, Verma S. South Asians and cardiovascular risk: What clinicians should know. Circulation 2006;113:e924-9.
3. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. N Engl J Med 2005;352:48-62.
4. Leow MK, Addy CL, Mantzoros CS. Clinical review 159: Human immunodeficiency virus/highly active antiretroviral therapy-associated metabolic syndrome: Clinical presentation, pathophysiology, and therapeutic strategies. J Clin Endocrinol Metab 2003;88:1961-76.
5. Samaras K, Wand H, Law M, Emery S, Cooper D, Carr A. Prevalence of metabolic syndrome in HIV-infected patients receiving highly active antiretroviral therapy using International Diabetes Foundation and Adult Treatment Panel III criteria: Associations with insulin resistance, disturbed body fat compartmentalization, elevated C-reactive protein, and [corrected] hypoadiponectinemia. Diabetes Care 2007;30:113-9.
6. De Wit S, Sabin CA, Weber R, Worm SW, Reiss P, Cazanave C, *et al.* Incidence and risk factors for new-onset diabetes in HIV-infected patients: The Data Collection on Adverse Events of Anti-HIV Drugs (D: A: D) study. Diabetes Care 2008;31:1224-9.
7. Kakuda TN. Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity. Clin Ther 2000;22:685-708.
8. Worm SW, Sabin C, Weber R, Reiss P, El-Sadr W, Dabis F, *et al.* Risk of myocardial infarction in patients with HIV infection exposed to specific individual antiretroviral drugs from the 3 major drug classes: The data collection on adverse events of anti-HIV drugs (D: A: D)
study. J Infect Dis 2010;201:318-30.
9. Antiretroviral therapy Guidelines for HIV-Infected Adults and Adolescents; May, 2103. Available from: http://www.naco.gov.in/sites/default/files/AntiretroviralTherapyGuidelinesfor HIV-InfectedAdultsandAdolescents.pdf. [Cited on 2017 May 24].
10. Part-B National AIDS Control Organization. Available from: http://www.naco.gov.in/sites/default/files/annual_report_NACO_2014-15_0.pdf. [Cited on 2017 May 24].
11. Carey RA, Rupali P, Abraham OC, Kattula D. Does first line antiretroviral therapy increase the prevalence of cardiovascular risk factors in Indian patients?: A cross sectional study. J Postgrad Med 2013;59:258-62.
12. Singh J, Verma M, Ghalaut PS, Verma R, Soni A, Ghalaut VS. Alteration in lipid profile in treatment-naive HIV-infected patients and changes following HAART initiation in Haryana. J Endocrinol Metabol 2014;4:25-31.
13. Mittal M, Dandu H, Verma SP, Gutch M, Tripathi AK. National PMTCT Task Team. Vol. 1. Nigeria: Medknow Publications and Media Pvt., Ltd.; 2013. p. 20.
14. Bajaj S, Tyagi SK, Bhargava A. Metabolic syndrome in human immunodeficiency virus positive patients. Indian J Endocrinol Metab 2013;17:117-20.
15. Grundy SM, Cleeman JI, Daniels SR, Donato KA, Eckel RH, Franklin BA, *et al.* Diagnosis and management of the metabolic syndrome: An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112:2735-52.
16. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, *et al.* Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: Studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care 2000;23:57-63.
17. Assessing Cardiovascular Risk: Systematic Evidence Review from the Risk Assessment Work Group – NHLBI, NIH. Available from: https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/risk-assessment/. [Cited on 2017 May 24].
18. Idiculla J, Ravindra'n GD, D'Souza J, Singh G, Furruqh S. Diabetes mellitus, insulin resistance, and metabolic syndrome in HIV-positive patients in South India. Int J Gen Med 2011;4:73-8.
19. Jericó C, Knobel H, Montero M, Ordoñez-Llanos J, Guelar A, Gimeno JL, *et al.* Metabolic syndrome among HIV-infected patients: Prevalence, characteristics, and related factors. Diabetes Care 2005;28:132-7.
20. Abstract View. Available from: http://www.library.iasociety.org/AbstractView.aspx?confID=2006&abstractId=14111. [Cited on 2017 May 24].
21. Côté HC. Mechanisms of antiretroviral therapy-induced mitochondrial dysfunction. Curr Opin HIV AIDS 2007;2:253-60.
22. Pinto Neto LF, das Neves MB, Ribeiro-Rodrigues R, Page K, Miranda AE. Dyslipidemia and fasting glucose impairment among HIV patients three years after the first antiretroviral regimen in a Brazilian AIDS outpatient clinic. Braz J Infect Dis 2013;17:438-43.
23. Pefura Yone EW, Betyoumin AF, Kengne AP, Kaze Folefack FJ, Ngogang J. First-line antiretroviral therapy and dyslipidemia in people living with HIV-1 in Cameroon: A cross-sectional study. AIDS Res Ther 2011;8:33.
24. ATP III At-A-Glance: Quick Desk Reference – NHLBI, NIH. Available from: https://www.nhlbi.nih.gov/health-pro/guidelines/current/cholesterol-guidelines/quick-desk-reference-html. [Cited on 2017 May 24].
25. Zhou DT, Kodogo V, Chokuona KF, Gomo E, Oektedalen O, Stray-Pedersen B. Dyslipidemia and cardiovascular disease risk profiles of patients attending an HIV treatment clinic in Harare, Zimbabwe. HIV AIDS (Auckl) 2015;7:145-55.