Asian Journal of Pharmaceutical and Health Sciences
www.ajphs.com

Assessment of lipid profile in HIV-TB co-infected patients on drug therapy

Pallab Basu[1]*, Sanjoy Kunti[1], Soma Gupta[2], Swati Bera[3], Gairik Sengupta[4]

1 Assistant Professor, Dept. of Biochemistry, College of Medicine & Sagore Dutta Hospital, Kolkata
2 Professor, Dept. of Biochemistry, College of Medicine & Sagore Dutta Hospital, Kolkata
3 Associate Professor, Dept. of Biochemistry, R. G. Kar Medical College & Hospital
4 Assistant Professor, Dept. of Pharmacology, College of Medicine & Sagore Dutta Hospital, Kolkata.

ARTICLE HISTORY

Received: 12.07.2013

Accepted: 08.08.2013

Available online: 10.11.2013

Keywords:

HIV-TB co-infection, Hypertriglyceridemia, Hypercholesterolemia, Dyslipidemia.

*Corresponding author:

Email : basu_pallab@yahoo.co.in
Tel : +91-9433232481

ABSTRACT

To assess the lipid profile in HIV and TB co-infected patients receiving drugs and to correlate any variations between the lipid parameters and the CD4 cell counts and to establish relationship between the variables. Fasting blood samples were collected from 33 HIV and TB co-infected patients on combined anti-tubercular and anti-retroviral therapy and 33 healthy controls. Lipid profiles were analysed by enzymatic kit methods and CD4 count were estimated in flow cytometer (BDFACS). Statistical analysis was done by statcalc software.

High mean Serum total cholesterol, triglycerides, LDL and VLDL cholesterol, and low HDL cholesterol levels were seen among patients with CD4 cells less than 200/ cmm. Whereas high mean serum total cholesterol and LDL cholesterol, low HDL cholesterol and normal triglyceride levels were seen in comparison to control in patients with CD4 cell count more than 200 cells/ cmm. Neither any correlation was established between CD4 cell count and lipid parameters nor between lipid parameters and duration of drug therapy. Severe dyslipidemia is an associated complication in later stage of HIV-TB co-infected patients on combined therapy. Multiple host factors as well as anti-retroviral drugs precipitate dyslipidemia. In early stage of the disease serum triglycerides and VLDL cholesterol levels remain normal. Follow up of the patients should be undertaken for dyslipidemia related complications in all HIV-TB co-infected patients irrespective of their stages.

INTRODUCTION

In India Presently there are about 3.7 million people are suffering from Human Immuno Deficiency Virus (HIV). [1] About 1.85 million new cases of tuberculosis (TB) occurs annually in India a greater number than in any other country. [1] Different reports from referral Institutions in India have suggested that HIV prevalence is high among TB patients. [2 9] About 5% of new tuberculosis cases in India occur in people with HIV co-infection. HIV infected patients are often subjected to alterations in different biochemical parameters like thyroid profile, LFT (Liver Function Test), lipid profile, renal profile etc. Many previous works have reported hypocholesterolemia in early stage and hypertriglyceridemia and low High Density Lipoprotein Cholesterol (HDL-C) in later stage of HIV positive patients with low CD4 cell counts. [10, 11, 12] But when the patients are treated with protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI) then the lipid profile presents differently like increased total cholesterol, triglycerides, LDL lipoproteins and decreased HDL cholesterol. [13] Dyslipidemia and risk of developing cardiovascular complications have been linked with HIV patients treated with anti-retroviral drugs. [14, 15] Several studies have shown that

Abbreviation: - HIV = Human Immuno Deficiency Virus, NRTI = Nucleoside Reverse Transcriptase Inhibitor, NNRTI = Non-Nucleoside Reverse Transcriptase Inhibitor, PI = Protease Inhibitor, HAART = Highly Active Antiretroviral Therapy, LDL-C = Low Density Lipoprotein Cholesterol, VLDL-C = Very Low Density Lipoprotein Cholesterol, HDL-C = High Density Lipoprotein Cholesterol, TC = Total cholesterol, TG = Triglyceride, TB = Tuberculosis, CAT I and II = Category I and II.

stavudine and zidovudine increase serum total cholesterol, triglycerides and LDL cholesterol levels and decrease HDL-C levels and cause lipodystrophy whereas Nevirapine (NNRTI) therapy causes minimal changes in lipid profile with rise in HDL cholesterol, Total cholesterol TC and no change or decline in Triglyceride (TG) level and switching from PI to nevirapine causes reduction in TC, TG levels and waist-hip ratio. [16 24, 25, 26, 27] Some studies have reported that increase in HDL-C might protect against development of coronary vascular diseases. [28] But as per Martindale drug reference lamivudine, Stavudine, Zidovudine and Nevirapine all they cause hypertryglyceridemia, hypercholesterolemia, insulin resistance and hyperglycemia. [29] There are very few studies done in India on lipid profiles of HIV-TB co-infected patients receiving ATD (anti-tubercular drug) and HAART (Human anti-retroviral therapy) simultaneously. This study tends to work out any changes in the lipid profile of such patients when on ATDs as per DOTS Category I and II (CAT I or II) and Highly Active Antiretroviral Therapy (HAART) as a combination of 2 NRTI and 1 NNRTI (it is a well-studied and effective antiretroviral combination). [30] Besides how lipid profile is affected when so called lipid friendly Nevirapine was combined with NRTI was also observed here. None of our patients received PI.

MATERIALS AND METHOD

Fasting blood samples were collected from 33 (non-icteric and non-diabetic) patients having HIV-TB co-infections on combined therapy of anti-tubercular drugs (like Isoniazid, Rifampicin, Pyrazinamide, Ethambutol and Streptomycin in different combinations according to categories of DOTS) and human anti-retroviral drugs (like Stavudine, Zidovudine, Lamivudine and Nevirapine in different three drugs combinations of 2 NRTI and 1 NNRTI). Also fasting blood samples were collected from 33 healthy controls. CD4+ counts and lipid parameters were estimated in those samples. We have excluded patients who were not on combined anti-tubercular and anti-retroviral therapy. Serum total cholesterol (TC), triglycerides (TG), HDL-cholesterol (HDL-C) were analysed by enzymatic kit methods in semi-autoanalyser, LDL cholesterol (LDL-C) levels were determined from the formula (Friedewald formula) :LDL-C = TC (TG/5 + HDL-C), serum VLDL-C levels were calculated as TG/5 and CD4 count were estimated in flow cytometer (BDFACS). Statistical analysis was done by statcalc software.

The result shows dyslipidemia among all the patients suffering from HIV and TB co-infection. But it is more significant among patients having CD4 count less than 200 cells / cmm. Patients having CD4 count less than 200 cells / cmm and on both HAART and ATD therapy for some duration have significant hypercholesterolemia, hypertriglyceridemia, high VLDL and LDL cholesterol levels and low HDL cholesterol level. Whereas patients receiving combined anti-tubercular and anti-retroviral drugs with CD4 counts more than 200 cells / cmm present with better lipid profiles. Their mean triglycerides and VLDL cholesterol levels were within normal limits, mean serum cholesterol level was high in comparison to controls but less than 200 mg/dl and mean HDL cholesterol level was low but more than 40 mg/dl.Neither any correlation could be established between mean CD4 cell count and lipid profile parameters nor between duration of drug therapy and lipid profiles.

DISCUSSION

Pathogenesis of dyslipidemia is multifactorial. It is the interactive products of viral load, host factors and drug therapy.

Table 1: Comparison of different parameters between cases and controls

Parameters	Cases (N = 18) (CD4 > 200/cmm)	Cases (N = 15) (CD4<200/cmm)	Controls (N = 33)
CD4 Count	503.27 ± 186.17 ($p < 0.001$)	83.33 ± 39.4 ($p < 0.001$)	1040.51 ± 189.89
Total Cholesterol	189.38 ± 50.48 ($p< 0.03$)	297.7 ± 42.02 ($p < 0.002$)	157.06 ± 43.05
Triglycerides	109 ± 29.13 ($p< 0.6$)	306.73 ± 189.07 ($p< 0.003$)	115.45 ± 49.47
HDL Cholesterol	41.05 ± 5.82 ($p < 0.001$)	34 ± 5.59 ($p < 0.001$)	47.89 ± 4.80
LDL Cholesterol	126.53 ± 50.53 ($p < 0.001$)	206.56 ± 35.09 ($p < 0.001$)	81.27 ± 34.46
VLDL Cholesterol	21.8 ± 5.8 ($p< 0.58$)	57.1 ± 20.73 ($p < 0.001$)	23 ± 9.9

Table 2: Correlation of lipid profile with CD4 count (when CD4 > 200 / cmm)

Parameters	Correlation Co-efficient	Significance
Total Cholesterol	- 0.213	< 0.395
Triglyceride	- 0.139	< 0.581
HDL cholesterol	0.214	< 0.394
LDL cholesterol	- 0.222	< 0.377
VLDL cholesterol	- 0.139	< 0.581

Table 3: Correlation of lipid profile with CD4 count (CD4 < 200 / cmm)

Parameters	Correlation Co-efficient	Significance
Total Cholesterol	- 0.337	< 0.220
Triglyceride	- 0.329	<0.232
HDL cholesterol	0.26	< 0.351
LDL cholesterol	- 0.259	< 0.352
VLDL cholesterol	- 0.439	< 0.101

Table 4: Correlation of lipid profile with duration of HAART (when CD4>200/mm3)

Parameters	Correlation Co-efficient	Significance
Total Cholesterol	0.281	< 0.259
Triglyceride	0.244	< 0.329
HDL cholesterol	- 0.182	< 0.469
	0.273	< 0.272
VLDL cholesterol	0.244	< 0.329

Table 5: Correlation of lipid profile with duration of HAART (when CD4<200/cmm)

Parameters	Correlation Co-efficient	Significance
Total Cholesterol	0.206	< 0.461
Triglyceride	0.21	< 0.452
HDL cholesterol	0.144	< 0.608
LDL cholesterol	- 0.025	< 0.929
VLDL cholesterol	0.436	< 0.104

[24, 31] In untreated patients HIV infection itself causes dyslipidemia by declining serum TC, HDL-C, LDL-C and increasing TG levels with higher circulating HIV RNAs and longer period of infection. [11, 32, 33, 34, 35, 36] PIs have the highest incidence of causing dyslipidemia. But the patients in our study received either zidovudine (NRTI) or stavudine (NRTI) and nevirapine (NNRTI), lamivudine (NRTI) in combinations. The etiopathogenic role of NRTI causing dyslipidemia has been related to mitochondrial toxicity though controversial. [37, 38] Virus itself activates cytokines leading to dyslipidemia. Increased Interferon A level can cause hypertriglyceridemia. [11] Lipid parameters are also influenced by the opportunistic infections with the progress of diseases. [39] Apolipoprotein CIII and E polymorphism may play contributory role in different lipid parameters in different patients. [40, 41, 42] But finally several studies said that dyslipidemia is more prevalent in patient on anti-retroviral therapy than those who are not. [43, 44] Again the pattern of lipid profile changes and severity of dyslipidemia differs from one group of anti-retroviral agents to another group. [45] Gillard et al demonstrated in their study that lipoproteins from HIV patients on HAART are larger and more neutral lipid-rich, and their HDL are less stable and less receptor-competent. Plasma lipolytic activities or hepatic cholesteryl ester uptake are impaired in them. These findings may predict atherosclerosis of carotid artery. [46] Long term anti-retroviral therapy can lead to the development of metabolic syndrome characterised by insulin resistance, fat redistribution, hyperglycemia and hyperlipidemia (elevation in serum cholesterol and triglycerides) and known as the HIV lipodystrophy syndrome. [47, 48, 49, 50] It occurs with all kinds of drug combinations in 10 40% of treated patients. Among NRTIs stavudine has substantial mitochondrial toxicity and symptomatic manifestations. American Heart Association has recommended management of hyperlipidemia to reduce the risk of developing myocardial infarction and other cardiovascular risks from lipodystrophy and lipoatrophy. [47, 49, 50, 25] Our study includes data on 33 HIV-TB co-infected patients on combined anti-tubercular and anti-retroviral therapy and 33 healthy controls. All the patients of this study presented with hypertriglyceridemia, hypercholesterolemia, high VLDL-C and low HDL-C when mean CD4 count was less than 200 cell/ cmm. But no correlation could be established between CD4 counts and lipid parameters. Which means development of dyslipidemia was not proportional to the viral load rather it was multifactorial. No significant correlations could also be established between duration of drug therapy and lipid profiles. So, in addition to dyslipidemia contributed by NRTI and NNRTI combined therapy, other factors like sex, race, viral load, apolipoprotein polymorphism, activated cytokines, opportunistic infections, dietary habits, life style, insulin resistance, glucose intolerance, redistribution of lipids, lipodystrophy and many other host factors play major role in developing dyslipidemia than drugs or virus alone. [51, 52, 53, 54, 55, 56] Van Leth et al claimed that NNRTI causes elevation of HDL-C and TC levels. [21] Tungsiripat et al mentioned in his article that stavudine can cause elevation of TC, LDL-C and triglyceride levels or as per Saint-Marc T et al, can increase only triglyceride level. [53, 17] Khiangte et al in his study showed that patients on HAART had significantly high TC, HDL-C and TG levels than HIV positive patients without HAART. [57] In a study by Obirikorang et al significantly increased triglycerides was demonstrated in HIV positive patients in comparison to control. They also showed that there was no statistically significant correlation between mean HDL-C level and mean CD4 count when CD4 count was more than 200 cells / cmm. [58] Rather there were low TC, HDL-C and LDL-C. Another study by Nguema□m et al also showed hypertriglyceridemia in HIV positive patients but mean total cholesterol level was low in them. [59] Study conducted by Adewole et al demonstrated low serum HDL-C and high LDL-C levels in HIV positive patients on anti-retroviral therapy. [60] Kumar et al had 47 HIV positive cases and 44 controls. High triglycerides and high LDL-C were their findings among HIV positive patients whereas there was no change in the value of TC and HDL-C. The rise in triglycerides and LDL-C levels had significant positive correlation with CD4 cell count in their study. [39] In our study patients with CD4 count more than 200 cells/ cmm had mean serum triglyceride level was normal, mean serum TC, LDL-C levels were high and HDL-C level was low. That means dyslipidemia is more severe in late stage of disease than in early phase. Hypertriglyceridemia, hypercholesterolemia and low HDL-C levels are more significant in late stage of the disease with variations from patient to patient. Grunfeld et al found that hypertriglyceridemia worsens with the progress of the disease. [61] Galli et al reported 10% hypercholesterolemia and 23% hypertriglyceridemia in patients on two NRTI therapies. [18] Though few studies have showed hypocholesterolemia, our study clearly demonstrates hypercholesterolemia. So always the patients on HAART should undergo serum lipid profile estimations. There is several risk factors exists in relation to dyslipidemia. This dyslipidemia occurs with or without metabolic syndrome. Klein et al, FriisMollar et al reported in their studies that HIV-infected patients have higher incidence of myocardial infarction and other cardiovascular diseases. [14, 15]

CONCLUSION

Severe dyslipidemia is an associated complication in later stages of HIV-TB co-infected patients on combined therapy of anti-tubercular and anti-retroviral drugs. Multiple host factors as well as anti-retroviral drugs precipitate dyslipidemia. In early stage of the disease serum triglycerides and VLDL cholesterol levels remain normal. Though nevirapine was described as lipid friendly, when it was combined with zidovudine-lamivudine or stavudine-lamivudine, then prominent dyslipidemia occured in the later stage of the disease and HDL-C remains low in all stages. Serum lipid profile should be estimated for dyslipidemia and long term follow up investigations for complications should be undertaken in all HIV-TB co-infected patients irrespective of their stages. Dyslipidemia so diagnosed should be treated accordingly to prevent development of related complications.

REFERENCES

1. WHO Global TB Control: Surveillance, Planning, Financing 2007. WHO/ HTM/ TB/ 2007. 376.
2. Shah I, Katira B (2007) Seroprevalence of HIV infection in

hospitalized paediatric patients at a tertiary care centre in western India. HIV Med 8: 265266.

3. Piramanayagam P, Tahir M, Sharma SK, Smith-rohrberg D, Biswas A, et al. (2007) Persistently high HIV seroprevalence among adult tuberculosis patients at a tertiary care centre in Delhi. Indian J Med Res 125: 163167.
4. Hussain T, Sinha S, Talan S, Verma S, Yadav VS, et al. (2007) Seroprevalence of HIV infection among paediatric tuberculosis patients in Agra, India: a hospital-based study. Tuberculosis (Edinb) 87: 711.
5. Dey SK, Datta PK, Chakraborty MS, Niyogi DK (2003) Epidemiology of HIV infection among tuberculosis patients in Calcutta. Indian J Public Health 47: 3738, 30.
6. Sharma SK, Aggarwal G, Seth P, Saha PK (2003) Increasing HIV seropositivity among adult tuberculosis patients in Delhi. Indian J Med Res 117: 239242.
7. Hussain T, Sinha S, Kulshreshtha KK, Yadav VS, Sharma P, et al. (2006) Seroprevalence of HIV infection among tuberculosis patients in Agra, India hospital-based study. Tuberculosis (Edinb) 86: 5459.
8. Mehrotra R, Chaudhary MK, Singh M (2006) HIV seroprevalence in patients with tuberculosis in Allahabad, North India. Indian J PatholMicrobiol 49: 302306.
9. Ramachandran R, Datta M, Subramani R, Baskaran G, Paramasivan CN, et al. (2003) Seroprevalence of human immunodeficiency virus (HIV) infection among tuberculosis patients in Tamil Nadu. Indian J Med Res 118: 147151.
10. Constans J, Pellegrin JL, Peuchant E. Et al. Plasma lipids in HIV-infected patients: a prospective study in 95 patients. Eur J Clin Invest 1994; 24:416-20.
11. Grunfeld C, Pang M, Doerrler W, Shigenaga JK, Jensen P, Feingold KR. Lipids, lipoproteins, triglyceride clearance and cytokines in human immunodeficiency virus infection and the acquired immunodeficiency syndrome. J ClinEndocrinolMetab 1992; 74: 1045 52.
12. Zangerle R, Sarcletti M, Gallati H, Reibnegger G, Wachter H, Fuchs D. Decreased plasma concentrations of HDL cholesterol in HIV-infected individuals are associated with immune activation. J Acquir Immune DeficSyndr 1994; 7: 1149 56.
13. Garg A. Lipodystrophies. Am J Med 2000; 108: 143 52.
14. Klein D, Hurley L, Quesenberry C. Hospitalisation for CHD and MI among Northern California HIV+ & HIV-Med: additional follow-up and changes in practice. 12 th Conference on Retroviruses & Opportunistic infections. Boston, MA, February 22 25, 2005.
15. Friis Moller N, Sabin CA, Weber R, et al. Combination of antiretroviral therapy and risk of Myocardial Infarction N Engl J Med 2003; 349: 1995 2003.
16. Boufassa F, Dulioust A, Las Caux AS, et al. Lipodystrophy in 685 HIV-1-treated patients: influence of antiretroviral treatment and Immunovirological response. HIV Clin Trials 2001; 2: 339 45.
17. Saint-Marc T, Partisani M, Poizot Martin I, et al. A Syndrome of Peripheral Fat Wasting (lipodystrophy) in patients receiving long term nucleoside analogue therapy. AIDS 1999; 13: 1659 67.
18. Galli M, Ridolfo AL, Adorni F, et al. Body habitus changes and metabolic alterations in protease inhibitor naive HIV-1 infected patients treated with two nucleoside reverse transcriptase inhibitors. J Acquir Immune DeficSyndr 2002; 29: 21 31.
19. Bogner JR, Vielhauer V, Beckmann RA, et al. Stavudine versus Zidovudine and the development of lipodystrophy. J Acquir Immune DeficSyndr 2001; 27: 237 44.
20. Van der Valk M, Gisolf EH, Reiss P et al. Increased risk of lipodystrophy when nucleoside analogue reverse transcriptase inhibitors are included with protease inhibitors in the treatment of HIV-1 infection. AIDS 2001; 15: 847 55.
21. Van Leth F, Phanuphak P, Stores E, et al. Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral therapy-naive patient infected with HIV-1. Plos Med 2004: e 19.
22. Young J, Weber R, Rickenbach M, Furrer H, Bernasconi E, Hirschel B, et al. Lipid profiles for antiretroviral naive patients starting on PI and NNRTI-based therapy in the Swiss HIV cohort study. AntivirTher 2005; 10: 585 591.
23. Martinez E, Conget I, Lozano L, Casamitjana R, Gatell JM. Reversion of metabolic abnormalities after switching from HIV-1 pretease inhibitors to nevirapine. AIDS 1999; 13: 805 10.
24. Green ML. Evaluation and Management of Dyslipidemia in Patients with HIV infection. J Gen Inten Med 2002; 17: 797 810.
25. Souza SJ, Luzia LA, Santos SS, Rondó PH. Lipid profile of HIV-infected patients in relation to antiretroviral therapy: a review. Rev Assoc Med Bras 2013 Mar-Apr; 59(2): 186-98. doi: 10.1016/j.ramb.2012.11.003.
26. Matthews GV, Moyle GJ, Mandalia S, Bower M, Nelson M, Gazzard BG. Absence of association between individual thymidine analogues or non-nucleoside analogues and lipid abnormalities in HIV-1 infected persons on initial therapy. J Acquir Immune Defic Syndr 2000; 24 (4): 310 15.
27. Petit JM, Duong M, Masson D, et al. Serum adiponectin and metabolic parameters in HIV-1-infected patients after substitution of nevirapine for protease inhibitor. Eur J Clin Invest 2004; 34: 569 75.
28. Van der Valk M, Kastelein JJ, Murphy RL et al. Nevirapine containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. AIDS 2001; 15 (18): 2407 14.
29. Sweetman SC. Lamivudine, Nevirapine, Stavudine, Zidovudine. In Martindale The Complete Drug Reference. Sweetman SC, ed. Pharmaceutical Press, London, 2011, pp 987 1010.
30. Panel on Antiretroviral Guidelines for adult and Adolescents. Guidelines for the use of Antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. November 3, 2008; 1 139. Available at http: // www.aidsinfo.nih.gov/contentFiles/ AdultandAdolescentGL. Pdf.

31. Mooser V, Carr A. Antiretroviral therapy associated hyperlipidemia in HIV disease. CurrOpinLipidol 2001; 12: 313 19.

32. Grunfeld C, Kotler DP, Hamadeh R, et al. Hypertriglyceridemia in the acquired immunodeficiency syndrome. Am J Med 1989; 86: 27 31.

33. Shor-Posner G, Basil A, Lu Y, et al. Hypocholesterolemia is associated with immune dysfunction in early human immune deficiency virus-1 infection. Am J Med 1993; 94: 515 19.

34. Anastos K, Lu D, Shi Q, et al. Association of serum lipid levels with HIV serostatus, specific antiretroviral agents and treatment regimens. J Acquir Immune Defic Syndr 2007; 34 42.

35. El-Sadr WM, Mullin CM, Carr A, et al. Effects of HIV disease on lipids, glucose and insulin levels: results from a large antiretroviral naïve cohort. HIV Med 2005; 6: 114 21.

36. Rose H, Woolley I, Hoy J, et al. HIV infection and high density lipoprotein: the effect of the disease vs the effects of treatment. Metabolism 2006; 55: 90 5.

37. Zaera MG, Miro O, Pedrol E, et al. Mitochondrial involvement in antiretroviral therapy-related lipodystrophy. AIDS 2001; 15: 1643 51.

38. Moyle G. Mitochondrial toxicity hypothesis for lipoatrophy: a refutation. AIDS 2001; 15: 413 15.

39. Kumar A, Sathian B. Assessment of lipid profile in patients with human immune-deficiency virus (HIV/ AIDS) without antiretroviral therapy. Asian Pacific Journal of Tropical Disease 2011: 24 27.

40. Behrens G, Schmidt HH, Stoll M, Schmidt RE. Apo E genotype and Protease-inhibitor-associated hyperlipidemia. Lancet 1999; 354: 76.

41. Grunfeld C, Doerrler W, Pang M, Jensen P, Weisgraber KH, Feingold KR. Abnormalities of apolipoprotein E in the acquired immune-deficiency syndrome. J ClinEndocrinolMetab 1997; 82: 3734 40.

42. Fauvel J, Bonnet E, Ruidavets JB, et al. An interaction between apo C-III variants and protease inhibitors contribute to high triglycerides/ low HDL levels in treated HIV patients. AIDS 2001; 15: 2397 406.

43. Sullivan AK, Nelson MR. Marked Hyperlipidemia on ritonavir therapy. AIDS 1997; 938 39.

44. Segerer S, Bogner JR, Walli R, Loch O, Goebel FD. Hyperlipidemia under treatment with proteinase inhibitors infection 1999; 27: 77 81.

45. Fontas E, Van Leth F, Sabin CA, et al. Lipid profiles in HIV-infected patients receiving combination antiretroviral therapy: are different antiretroviral drugs associated with different lipid profiles? J Infect Dis 2004; 189: 1056 74.

46. Gillard BK, Raya JL, Ruiz-Esponda R, Iyer D, Coraza I, Balasubramanyam A, Pownall HJ. Impaired Lipoprotein Processing in HIV Patients on Antiretroviral Therapy: Aberrant High-Density Lipoprotein Lipids, Stability, and Function. Arterioscler Thromb Vasc Biol 2013 Jul; 33(7): 1714-21. doi: 10.1161/ATVBAHA.113.301538. Epub 2013 May 2.

47. Fauci AS, Lane HC. Human Immunodeficiency Virus Disease: AIDS and related disorders. In HARRISON'S PRINCIPLES OF INTERNAL MEDICINE, Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. 18th e, 2012, New York, The McGraw-Hill Companies, Inc., p 1554, p 1574.

48. Sweetman SC. Lamivudine, Nevirapine, Stavudine, Zidovudine. In Martindale The Complete Drug Reference. Sweetman SC, ed. Pharmaceutical Press, London, 2011, pp 987 1010.

49. Flexner C. Antiretroviral Agents and Treatment of HIV Infection. In Goodman & Gilman's The Pharmacological Basis of Therapeutics. Brunton LL, Chabner BA, Knollmann BC, eds. 12th e, New York, The McGraw-Hill Companies, Inc., 2011, p1628, p1634.

50. . Safrin S. Antiviral agents. In Basic & Clinical Pharmacology. Katzung BG, Masters SB, Trevor AJ, eds. 12th e, New York, The McGraw-Hill Companies, Inc., 2012, p 871.

51. Kumar P, Rodriguez-French A, Thompson M. Prospective Study of Hyperlipidemia in ART-naïve subjects taking Combivir/ Abacavir (COM/ ABC), COM/ Nelfinavir (NFV), or Stavudine (d4t)/ Lamivudine (3TC)/ NFV (ESS40002) [abstract No. 33]. 9th Conference on Retroviruses and Opportunistic Infections. Seatle, WA, February 24 28, 2002.

52. Kumar P, Willimas V, Taslima K, et al. Determinants of hyperlipide3mia in ARV-naïve subjects treated with trizivir (TZV), Combivir (COM)/ nelfinavir (NFV), or stavudine (d4t)/ lamivudine (3TC)/ NFV [abstract 713]. 11th Conference on Retroviruses and Opportunistic Infections. San Francisco, CA, February 8 11, 2004.

53. Tungsiripat M, Aberg JA. Dyslipidemia in HIV Patients. Cleveland Clinic Journal of Medicine 2005; 72 (12): 1113 1120.

54. Heath KV, Hogg RS, Chan KJ, et al. Lipodystrophy-associated morphological, cholesterol and triglyceride abnormalities in a population-based HIV/AIDS treatment database. AIDS 2001; 15: 231 9.

55. Kosmiski LA, Kuritzkes DR, Lichtenstein KA, et al. Fat distribution and metabolic changes are strongly correlated and energy expenditure is increased in the HIV lipodystrophy syndrome. AIDS 2001; 15: 1993 2000.

56. Hadigan C, Meigs JB, Corcoran C, et al. Metabolic abnormalities and cardiovascular disease risk factors in adult with human immunodeficiency virus infection and lipodystrophy. Clin-Infect Dis 2001; 32: 130 9.

57. Khiangte L, Vidyabati RK, Singh MK, Bilasini DS, Rajan ST, Gyaneswar SW. Study of Serum Lipid Profile in human immune-deficiency virus (HIV) infected patients. J Indian Acad Clin Med 2007; 8: 307 11.

58. Obirikorang C, Yeboah F, Quaye L. Serum lipid profiling in highly active antiretroviral therapy naïve HIV positive patients in Ghana; any potential risk? Webmedcentral 2010; 1 (10): WMC001558.

59. Naguemainn NF, Mbuagbaw J, Nkoa T, Alemnji G, Tetol G, Fanhil TC, et al. Serum lipid profile in highly active

antiretroviral therapy naïve HIV infected patients in Cameroon: a case control study. HIV Medicine 2010; 11 (6): 353 359.

60. Adewole OO, Eze S, Betiku Ye, Anteyi E, Wada I, Ajuwon Z, et al. Lipid profile in HIV/ AIDS patients in Nigeria. Afr Health Sci 2010; 10 (2): 144 149.

61. Grunfeld C, Kotler DP, Shigenaga JK, et al. Circulating interferon alpha levels and hypertriglyceridemia in the acquired immunodeficiency syndrome. Am J Med 1991; 90: 154 162.