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Research Article

Effect of HAART (Highly Active Antiretroviral Therapy) on Hyperglycemia Among HIV-infected Patients

Enugurthy Ramana Chary[1] and Estari Mamidala[2]*

[1]*Dravidian University, Srinivasa Vanam, Agaram, Andhra Pradesh – 517425, India*
[2]*Department of Zoology, Kakatiya University, Warangal-506 009, Telangana State, India*

*Corresponding author:
E-mail: ramanachary200@gmail.com

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ABSTRACT

The effects of highly active antiretroviral therapy (HAART) on glucose and lipid metabolism in Adilabad distrct, Telangana State, for whom admission to antiretroviral therapy is increasing, remain mostly unknown. Therefore, the aim of this study was to measure antiretroviral treatment associated hyperglycemia and dyslipidemia among HIV-infected patients at HIV Care Centre, Rajeev Gandhi Institute of Medical Sciences (RIMS), Adilabad, Telangana State, India. A cross-sectional comparative study was conducted in HIV-infected adults at RIMS from September, 2015 to May, 2017. Equal number of HAART naïve and HAART initiated patients (n = 176 each) were incorporated in the study. Demographic data were collected using a well-structured questionnaire. Total cholesterol (TC), Triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and glucose were determined. Of 352 study subjects, 70.2% were females; mean age was 34.3 years; mean Body Mass Index (BMI) was 22.4(kg/m2). The prevalence of hyperglycemia, increased LDL-C hypercholesterolemia, hypertriglyceridemia and decreased HDL-C were 7.8%, 22%, 41.1%, 45.8% and 49.8% in HAART and 5.5%, 7%, 11%, 30% and 72% in non-HAART groups, respectively. First line anti-retrovirals were drugs containing 2 nucleoside backbones (from Zidovudine/Stavudine/Lamivudine/Tenofovir) with either Nevirapine or Efavirenz. There was statistically significant increase in serum lipid profile levels among HAART initiated patients than HAART naïve individuals (p =0.01 for TG and <0.001 for others). First-line HAART is connected with potentially atherogenic lipid profile levels in patients with HIV infection compared to untreated patients. This indicates glucose and lipid profile levels require being monitor regularly in HIV infected patients taking HAART.

1. Introduction

Highly active antiretroviral therapy (HAART) is the mainstay of treatment for those infected with HIV [1]. Since its introduction in 1996, mortality and morbidity rates in HIV-infected persons in countries with extensive access to HAART have plummeted. The main effect of HAART is to restrain viral replication, allowing the individual's immune system to recover and protecting from the development of AIDS and death [2]. In recent years, provision of HAART to those in need has become an increasingly significant and feasible global precedence [3]. However, the prospect of maintaining patients on long term HAART may be restricted by a heterogeneous collection of unexpected metabolic abnormalities, including dysregulation of glucose metabolism, dyslipidemia, and/or lipodystrophy [4,5]. Use of HAART has been linked to hyperglycemia, dyslipidemia and increased risk of cardiovascular disease (CVD) in HIV-infected patients in industrialized countries.

The effects of retroviral treatement on glucose and lipid metabolism in sub-Saharan Africans, for whom access to antiretroviral therapy is expanding, remain largely unknown [6]. This is specially a major gap that should be given high emphasis in a country like India where increased use of retroviral therapy is higher since 2005. Therefore, the aim of this study was to assess antiretroviral treatment associated hyperglycemia and dyslipidemia among HIV infected patients at HIV Care Center, Rajeev Gandhi Institute of Medical Sciences, Adilabad district, Telangana State, India.

Table-1. Study population characteristics of HAART status at RIMS, Adilabad, TS

Variable		HAART initiated (n=176)	Non-HAART (n=176)
		N (%)	N (%)
Gender	Female	111(68.3)	121(76.2)
	Male	65(31.7)	55(23.8)
Age group (years)	Mean ± SD	37.1(9.8)	33.4(10.2)
	18-29	35(19.8)	75(40.5)**
	30-39	86(48.4)	64(38.9)
	40-49	35(19.8)	22(12.7)
	≥50	20(11.9)	14(7.9)
BMI	Mean ± SD	21.9(3.2)	20.8(2.8)
	<18.5	16(7.1)	34(19)*
	18.5-24.9	127(77)	121(72.2)
	25-29.9	27(13.5)	18(7.9)
	≥30	6(2.4)	3(0.8)
CD4+ cells (cells/mm^3)	Mean ± SD	314.5 ± 152.5	413.6 ± 246.2
	<200	50(27)	41(19.8)**
	200-400	76(46)	60(33.3)
	>400	50(27)	75(46.8)
Duration of HIV infection (month)	Mean ± SD	29.5(17)	11.8(12.3)
	<6	0(0)	67(45.2)***
	6-12	34(17.5)	31(16.7)
	13-24	34(17.5)	37(21.4)
	25-41	72(46.8)	29(15.1)
	≥42	36(18.3)	12(1.6)
TB Co-infection	Present	46(16.7)	43(14.3)
	Not present	130(83.3)	133(85.7)

N, number; BMI, body mass index; HAART, highly active antiretroviral therapy; TB, tuberculosis; SD, standard deviation; *p-value =0.02; **p-value =0.004; ***p-value <0.0001.

2. Material and Methods

2.1 Study design, setting and period

A cross-sectional comparative study was conducted at voluntary counseling and testing (VCT) center of Burayu Health Center in collaboration with Ethiopian Health and Nutrition Research Institute (EHNRI) from September, 2011 to May, 2012. Two groups of study participants with age ≥18 years who were either on HAART for at least six months (HAART initiated group) and HAART naïve HIV patients (non-HAART groups) who visited the VCT center during the study period were included in the study. First-line HAART regimens used were nucleoside reverse transcriptase inhibitors (NRTIs) [lamivudine (3TC), zidovudine (AZT), stavudine (D4T) or Tenofovir (TDF)] and non-nucleoside reverse transcriptase inhibitors (NNRTIs) [nevirapine (NVP) or efavirenz (EFV)]. Patients with hyperglycemia or dyslipidemia at baseline (for HAART initiated patients) and pregnant women and nursing mother were excluded.

2.2 Data collection

Consecutive sampling technique was employed to include study participants. Two hundred fifty two (176 HAART initiated and 176 non-HAART) participants were enrolled. After having received a clear explanation of the objective, risk and confidentiality of the study, participants signed the informed consent and participated in the study. Demographic data regarding, age, gender, period with HIV infection, ART exposure in the previous six months and the ARV regimen were collected using questionnaire. Medical records were also used to confirm the information and baseline glucose and lipid profile levels. Height and weight were measured to calculate body mass index (BMI). Six to ten ml of blood sample was collected by venipuncture from 8–12 hours fasting individuals using vacuum tube and serum was separated within one hour of blood collection. The serum levels of glucose, TC, HDL-C, LDL-C and TG were measured using COBAS INTEGRA 400 random access full automated auto analyzer at EHNRI, clinical chemistry laboratory. Glucose was determined by Hexokinase (HK) method, TG and total TC were evaluated with enzymatic

colorimetric method and HDL-C and LDL-C were analyzed by homogenous enzymatic colorimetric method. CD4+ lymphocyte count was determined using flow cytometer (FACSCalibur, Becton Dickinson, CA, USA). Tuberculosis (TB) was diagnosed via microscopy from sputum sample and X-ray photography if smear negative TB encountered.

The cutoff points to categorize dyslipidemia was defined as TC ≥200 mg/dl, HDL-c <40 mg/dl, LDL-c ≥130 mg/dl, TG ≥150 mg/dl and hyperglycemia as glucose ≥110 mg/dl and were based on the United States National Cholesterol Education Program, Adult Treatment Panel (NCEP-ATP) III guideline [7].

2.3 Data analysis

Data were entered and analyzed using Statistical Package for Social Sciences (SPSS) window version 20 (IBM Statistics, USA). Chi-square, student-t-test and logistic regression tests were used to see the association between socio-demographic characteristics, duration with HIV, BMI and HAART regimens with serum glucose and lipid profile levels. P-Value <0.05 was considered to be statistically significant at 95% confidence interval (CI).

3. Results and Discussion

3.1 Socio demographic characteristics of study subjects:

A total of 352 HIV infected patients were enrolled in the study. Of these, 176 (50%) were initiated HAART (HAART group) and 176 (50%) were ART naive (non-HAART group). Majority of the study participants were females (72.2%). Of those HAART groups, 68.3% were females. In addition, among non-HAART groups, 76.2% were females. The overall mean age was 35.3 ± 10.2 years (range: 18 to 75 years). The total time from the serological diagnosis of HIV infection was 20.6 ± 17.3 months (Mean ± SD) and was longer in HAART group compared to non-HAART group (mean: 29.5 ± 17.1 versus 11.8 ± 12.3 months, p <0.0001). 27% HAART groups and 19.8% non-HAART groups had CD4+ cells <200 cells/mm^3. Of all the subjects, 15.5% had TB-HIV co infection during the study period 16.7% of the HAART and 14.3% non-HAART groups. (Table 1).

3.2 Characteristics of serum fasting glucose and lipid profile levels

Totally, 17 (6.7%) individuals had abnormally high fasting serum glucose level. There was no significant difference in serum glucose level between HAART initiated and non-HAART groups (P =0.45). However, there was higher serum lipid profile levels among HAART groups than HAART naïve individuals (p =0.01 for TG and <0.001 for others) (Table 2).

3.3 Serum fasting glucose/lipid profile level and HAART

Most of the HAART initiated patients (34.1%) were on ART for 13–24 months followed by those for 25–41 months (33.3%). The rest 22.2% and 10.3% were on ART for 6–12 months and above 3.5 years, respectively. Duration of HAART was not significantly associated with serum glucose/lipid profile levels.

A total of 4 nucleoside reverse transcriptase inhibitors [Lamivudine (3TC), Zidovudine (AZT), Stavudine (D4T) and Tenofovir (TDF)] and 2 non-nucleoside reverse transcriptase inhibitors [Nevirapine (NVP) and Efavirenz (EFV) with 5 combinations (D4T-3TC-NVP, AZT-3TC-EFV, D4T-3TC-EFV, AZT-3TC-NVP and TDF-3TC-EFV] were used to treat patients. Nevirapine and EFV based combinations were used by almost equivalent number of individuals [51.6% versus 48.4%,

Table-2. Serum lipid profile and glucose levels of study population by HAART status at RIMS, Adilabad, Telangana State

Parameters		HAART initiated (n=176)	Non-HAART (n=176)
		N (%)	N (%)
Glucose	Mean ± SD	97.1 ± 15.7	92.2 ± 16.9*
	≤110 mg/dl	141(92.1)	144(94.4)
	>110 mg/dl	35(7.9)	32(5.6)
Triglycerides	Mean ± SD	162.2 ± 92.7	131.5 ± 55.3**
	<150 mg/dl	92(53.2)	112(69)
	≥150 mg/dl	84(46.8)	64(31)*
Total cholesterol	Mean ± SD	194.3 ± 45.2	147.2 ± 37.7***
	<200 mg/dl	98(57.9)	137(88.9)
	≥200 mg/dl	78(42.1)	39(11.1)***
HDL-cholesterol	Mean ± SD	40.9 ± 12.9	32.6 ± 11.3***
	<40 mg/dl	89(50.8)	117(73)***
	≥40 mg/dl	87(49.2)	59(27)
LDL-cholesterol	Mean ± SD	107.2 ± 35	81.4 ± 29.3***
	<130 mg/dl	122(77)	142(92.9)
	≥130 mg/dl	54(23)	34(7.1)***

HAART, highly active antiretroviral therapy; HDL, high-density lipoprotein; LDL, low- density lipoprotein; SD, standard deviation; *p-value =0.01; **p-value =0.002; *** p-value <0.0001.

respectively]. In addition, D4T and AZT based ARVs were used by 37.3% and 53.2% individuals, respectively. AZT-3TC-NVP combinations of antiretrovirals were the most frequently used drugs among the HAART initiated study participants, [28.6%] while TDF-3TC-EFV combinations were relatively used by small number of patients, [9.5%] (Figure 1). No significant difference observed in glucose/lipid profile derangements between patients receiving AZT based combinations compared to those on D4T; and patients treated with EFV based combinations versus those treated with NVP (Table 3).

In this study, we addressed how with and without of HAART affects glucose and lipid profile levels in HIV individuals. Our results showed an improved incidance of hyperglycemia, hypercholesterolemia and hypertriglyceridemia in patients taking antiretroviral drugs than non-HAART study participants. The incidance of hyperglycemia (>110 mg/dl), low density lipoprotein cholesterol (LDL-C) hypercholesterolemia (≥130 mg/dl), total cholesterol (TC) hypercholesterolemia (≥200 mg/dl), hypertriglyceridemia (≥150 mg/dl) and high density lipoprotein cholesterol (HDL-C) hypocholesterolemia (<40 mg/dl) were 7.9%, 23%, 42.1%, 46.8% and 50.8% in HAART initiated and 5.6%, 7.1%, 11.1%, 31% and 73% in non-HAART groups, respectively.

In this study, we establish comparable percentage of ARV initiated individuals (7.9%) and non- HAART group (5.6%) who had an improved serum glucose level and HAART initiation was not associated (p =0.45). However, HAART group showed higher mean glucose level than non-HAART group (p =0.019). In agreement to this finding, a study in Brazil observed elevated glucose levels in 6.8% patients treated without PIs, 1.5% patients receiving PIs and 0.9% non-HAART persons despite the lower number cases limited their conclusions [8].

Among our study subjects, there was no relationship between serum glucose/lipid level and gender. However, based on the study from Thailand on 200 HAART treated patients for an average of 39.35 months, the occurance of

Table-3. Serum glucose and lipid profile levels distribution among different combinations of HAART taken by study participants at RIMS, Adilabad, Telangana State

Glucose/lipid profile		NVP versus EFV based combination of ARVs		P-value
		NVP (n=90)	EFV (n=86)	
		N (%)	N (%)	
Glucose	≤110	80(92.3)	69(91.8)	0.917
	>110	10(7.7)	17(8.2)	
Triglyceride	<150	50(56.9)	43(49.2)	0.384
	≥150	40(43.1)	43(50.8)	
Total cholesterol	<200	50(56.9)	49(59)	0.812
	≥200	40(43.1)	37(41)	
HDL-cholesterol	<40	40(43.1)	49(59)	0.074
	≥40	50(56.9)	37(41)	
LDL-cholesterol	<130	61(73.8)	62(80.3)	0.388
	≥130	29(26.2)	24(19.7)	
Glucose/lipid profile		**D4T versus AZT based combination of ARVs**		**P-value**
		D4T (n=67)	**AZT (n=87)**	
		N (%)	**N (%)**	
Glucose	≤110	50(85.1)	74(95.5)	0.053
	>110	14(14.9)	13(4.5)	
Triglyceride	<130	35(53.2)	45(52.2)	0.920
	≥130	32(46.8)	42(47.8)	
Total cholesterol	<200	38(59.6)	49(58.2)	0.884
	≥200	29(40.4)	38(41.8)	
HDL-cholesterol	<40	36(55.3)	43(49.3)	0.524
	≥40	31(44.7)	44(50.7)	
LDL-cholesterol	<130	47(78.7)	63(79.1)	0.961
	≥130	20(21.3)	24(20.9)	

AZT, Zidovudine; d4T, stavudine; EFV, efavirenz; NVP, nevirapine; p, significance level.

hyperlipidemia was elevated in men than women despite no difference in blood glucose level between the two. Among those reported patients, 6.5%, 10.5%, 34.0% and 35.5% developed improved LDL-C, diabetes mellitus, hypercholesterolemia and hypertriglyceridemia, respectively [9]. The inconsistency with our study may be due to our study subjects were not gender matched between the two groups.

Increased serum lipid profile level was connected with HAART initiation (p = 0.01 for TG and <0.0001 for others) in our study. Similar to our conclusion, a cross-sectional study from India showed significantly higher incidence of dyslipidemia in the first line treatment groups [10]. Moreover, according to a study from the same country, at baseline and at 12 months, TC was >200 mg/dl for 1% and 26% of patients; LDL-C level was >130 mg/ dl for 3% and 23%; HDL-C level was <40 mg/dl for 91% and 23% and blood glucose level was >110 mg/dl for 14% and 13%, respectively [11].

Inline to our finding, a long term analysis on plasma lipid concentration was done in patients starting first-line HAART in Netherlands and showed concentrations of TC, LDL-C and TG continued to increase with slight decrease in HDL-C [14]. Similarly, a study in Cameroon stated that, TC, LDL-C and HDL-C levels improved significantly (P <0.05) but TG remained unaltered with first line HAART for 3 months [15]. This might be due to short action period.

In this HAART initiated study participants, the mean serum HDL-C, LDL-C, TG and TC levels were 40.9, 107.2, 162.2 and 194.3 mg/dl, respectively. The result of another 1 year follow up study in Italy concluded elevated mean levels of serum HDL-C, 40.1 mg/dl; LDL-C, 165.2 mg/dl; TC, 258.7 mg/dl and TG, 306.4 mg/dl than ours. These mean differences might be perhaps due to population variation in India and Italy. They found decreased HDL-C level 9.4%, hypercholesterolemia 25%, increased LDL-C level 26.7% and hypertriglyceridemia 38.2% [16,17] in which almost comparable with our results.

With a combination of three drugs including NRTI, NNRTI and PIs, HAART is now used to control the replication of HIV and AIDS [8]. Even though, the national HAART guideline for adolescents and adults in India include PIs as second line regimens [18], only first line regimens, NRTI and NNRTI, were receiving by the study subjects at HIV Care Center, RIMS. Two nucleoside backbones (from AZT/D4T/3TC/TDF) with either NVP or EFV NNRTIs combinations were used. AZT-3TC-NVP combination was the most recurrently used drug in study participants (28.6%).

4. Conclusions

First-line HAART with regimens NRTIs and NNRTIs were linked with potentially atherogenic lipid profile levels compared to unprocessed HIV-infected patients in Indian setting. There were an improved prevalence of hyperglycemia, hypertriglyceridemia and hypercholesterolemia in HAART initiated patients than non-HAART HIV infected patients at RIMS HIV Care Centre. This might lead to metabolic difficulties mainly diabetes mellitus and dyslipidemia which potentially raise risk of cardiovascular diseases. From these results, serum fasting glucose and lipid profile levels needs to be check regularly in HIV-infected patients on or without HAART to rule out unwanted things that can be optimally managed. In addition, further studies on well-controlled cohort setting for the assessment of long-term effects of retroviral treatment on serum glucose and lipid profile level are suggested.

Competing Interests

The authors have declared that no competing interests exist.

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