Widespread use of anti-retroviral therapy elevated the prevalence of dyslipidemia in HIV-infected Chinese patients

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With the widespread use of high-efficiency antiretroviral therapy (HAART), the life expectancy of HIV-infected patients has been significantly extended. However, the metabolic complications among HIV-infected patients treated with HAART have become the most common problem in the world. It is very important to explore the incidence of dyslipidaemia and studies on the role of potential risk factors in HIV-infected Chinese patients treated with HAART are sparse. Therefore, we designed current study, to investigate the effects of therapeutic intervention and continuous information support on the lifestyle of HIV/AIDS patients with dyslipidaemia. Three hundred and six HIV/AIDS patients admitted to the AIDS clinic in Beijing from January 2016 to January 2017 were recruited and assigned into two groups: the treatment group (n=64) and the control group (n=64). The median age of the participants was 38.8±11.0 years (range 20–75 years). The prevalence of dyslipidemia in control and treatment group was (59/64) 92.2% and (53/64) 82.8%, respectively. In this study, low HDL-cholesterol (HDLC) led to abnormalities 47/64 (73.3%) in the control group and 35/64 (54.7%) in HAART-treatment group. Additionally, HAART group showed higher triglyceride, total cholesterol, and low-density lipoprotein (246.1±171.8, 1.73±1.61 mmol/L, 4.46±1.1 mmol/L, 2.54±0.74 mmol/L). In multivariate analysis, gender, marital status, high BMI, dietary habits and physical activity were potential risk factors for dyslipidemia in HIV-infected Chinese patients. In this study, we reported high prevalence dyslipidemiain two HIV infected groups. We suggest that the appropriate diagnosis should be performed for analyzing the metabolic complications in HIV-infected Chinese patients. Further studies are very important to understand the role of potential risk factors in metabolic complications.

Keywords: Metabolic Complications; Lipid; Dyslipidaemia; HIV; HAART

INTRODUCTION

AIDS is an infectious disease characterized by immunodeficiency caused by human immunodeficiency virus (HIV) (Brooks, Buchacz, Gebo, Mermin, 2012). The HIV/AIDS epidemic continues to pose a humanitarian crisis to the world's most disadvantaged communities. Today, 36.9 million people are infected with HIV, 70% of who reside in sub-Saharan Africa.

Antiretroviral therapy (ART) confers those adherents to the lifelong drug regimen near normal life expectancy. According to statistics from China CDC, as of 2015, there were about 580,000 HIV/AIDS patients in China. The main treatment for AIDS is high-efficiency antiretroviral therapy (HAART). Daily HAART treatment can significantly inhibit HIV replication and reduce viral invasion, thus greatly prolonging the lifespan of HIV/AIDS patients (Grinsztejn *et al.*, 2013;Lynch, Clark, Zhanel, (2013). However, long-term HAART treatment also brings a series of metabolic abnormalities to HIV/AIDS patients. Hyperlipidemia is one of the most common manifestations, as well as one of the important

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risk factors for secondary disease in HIV/AIDS patients according to study findings. Therefore, attention to abnormal lipid metabolism in HIV/AIDS patients is of immense significance to improve the quality of life of this particular population.

There are different studies documented on the metabolic complication (hyperlipidemia) in HIV/AIDS patients treated with HAART in the world (Dave *et al.*, 2011; Oh *et al.*, 2017), most of which have been reported in developed countries and areas such the US and Europe (Dave *et al.*, 2011). These data cannot be extrapolated to developing countries like China, which bear the major HIV burden. While HAAT-instigated CD4 counts are increasing, wealthy patients initiate HAART at the complex phase of HIV infection. In developing countries, antiretroviral drugs are correlated with elevated menace of dyslipidaemia, such as stavudine (d4T) andzidovudine, and are still extensively prescribed. Differences in potential risk factor such genetic background, age, education, diet, and living habits may also involve in lipid responses to HAART. Therefore, it is very important to explore the effects of HAART treatment on metabolic complications and highlight its potential risk factors.

To date, different research groups have explored the metabolic complications in HIV-infected patients in China, but such investigations were limited to specific areas. In addition, these studies did not comprehensively analyze potential risk factors. Therefore, we designed this study to investigate the prevalence of metabolic complications in HIV-infected Chinese patients and highlight the role of potential risk factors for the occurrence of metabolic complications in HIV-infected Chinese patients.

METHODS

Participants

In this study, a total of 128 HIV/AIDS patients with dyslipidemia were recruited in the three AIDS clinics in Beijing. The standard of AIDS diagnosis refers to the "AIDS treatment guidelines" formulated in 2006; the diagnostic criteria for hyperlipidemia refer to the "Guidelines for the Prevention and Treatment of Chinese Adult Blood Lipids"; the average age of participants is 38.7 years. All participants were randomly divided into three groups: 1). Treatment lifestyle combined with continuous information support group, 2). Therapeutic lifestyle adjustment group, and 3). Regular group. A participant was qualified for the study if he/she: (1) was above the age of 18 years, (2) was under ART treatment, (3) had a dyslipidic edge state (one or more of the following): (i) Total cholesterol (TC) ≥ 5.2 (200) and <6.2 (240), (ii) LDL-C ≥ 3.4 (130) and <4.1 (160), (iii) Triglycerides (TG) ≥ 1.7 (150) and <2.3 (200), (4) voluntarily agreed to sign the patient's informed consent and guaranteed follow-ups, (5) was a permanent resident of local area during the experiment. Similarly, a participant was disqualified if (1) he / she has been currently diagnosed with opportunistic infections (specified by the National AIDS Treatment Guidelines) or AIDS-related malignant tumors at the time of enrollment; or opportunistic infections occurred within 3 months before the enrollment, and the condition remained unstable for 2 weeks before the enrollment, (2) he/she had a history of diabetes and hypertension, (3) overweight (BMI>24), (4) has not received lipid-lowering drug treatment for nearly 1 week.

Ethical statement

The experimental protocol was permitted by local Institutional Review Board of concerned hospitals. All participants agreed and provided their consent.

Data collection

A questionnaire was typically developed for this study. Participants attended the study visit after fasting overnight. All participants were interviewed by a trained interviewer in local dialect of Chinese by using a standardized questionnaire to elicit information on the alcohol consumption, smoking, and current medication. We also collected details about HAART, CD4 counts, HIV viral load and opportunistic infections. Additionally, a trained nurse also measured participants' weight, height, waist-hip ratio (WHR) and waist circumference.

Biochemical analysis

All samples were collected and centrifuged to isolate serum and serum was stored at -80 °C until further analysis. Triglycerides and Total cholesterol (TC) were calculated by enzymatic colorimetry on a Cobas 6000 autoanalyzer (Roche, Switzerland). At the same time, HDL cholesterol (HDLC) was calculated through the widely used direct method (Roche HDLC3 assay,

Switzerland). LDL cholesterol (LDLC) was measured using the Friedewald formula.

Classification of dyslipidemia

In this study, we used the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP-III) protocol to classify lipid abnormalities (Jama. 2001; 285(19):2486–97). We considered TC, LDLC and triglycerides of > 5.2 mmol/L, >2.5 mmol/L and > 1.7 mmol/L, respectively, as elevated and HDLC of < 1.0 mmol/L as low, irrespective of gender. Participants with at least one abnormal lipid parameter were classified as dyslipidemia.

Statistical analysis

In this study, we expressed continuous variables as mean or median (quartile range) and we used Student's t-test to compare normal distributions. We used the Mann-Whitney U test to perform a skewed distribution of continuous variables. However, χ_2 test was used to compare categorical variables. Firstly, we performed univariate analysis; only variables with a *P* value of less than 0.05 in the univariate analysis were included in the logistic regression model for multivariate analysis. IBM SPSS Statistics 20.0 was used for all the statistical analysis. P <0.05 was considered to indicate statistical significance.

RESULTS

Demographic variables

All participants were recruited from three HIV clinics in Beijing, China (Table I). The median age of the participants was 38.8±11.0 years (range 20–75 years) (mean=38 years, SD=11.0 years). 90% of the totals were men and 10% of the totals were women. In addition, 51% of the participants came from rural areas, and 49% were from urban areas, of which, 7% attended primary school, 20% middle school, 20% secondary school and 53% received university level education. 64% of the participants were drinkers and 38% were smokers. Obesity (BMI_30 kg/m^2) was more common than underweight and was found in 44/128 (34%) participants. A summary of the participants' characteristics is shown in Table I.

TABLE I - Demographic characteristics of participants'

Variables	Participants	Percentage
Grouping		
Control	64	50
Treatment group	64	50
Gender		
Men	115	89.8
Women	13	10.2
Nation		
Han Chinese	120	93.7
Other Minority	8	6.3
Body Mass index(BMI)		
Underweight <18	6	4.7
Normal weight 18-24	78	60.9
Overweight 24-28	33	25.8
Obesity >28	10	7.8
Education		
Primary	10	7.8
Middle	26	20.3
Secondary	25	19.5
Bachelor	67	52.3
Employment status		
Unemployed	19	14.8
Self-employed	39	30.5
Private employed	70	54.7

(continuing)

TABLE I - Demographic characteristics of participants'

Variables	Participants	Percentage
Job category		
Labor	24	18.7
Managerial	104	81.3
Marital status		
Single	83	64.8
Married	45	35.2
Income		
Low income	43	33.6
Middle income	76	59.4
High income	9	7.0
Do you smoke		
No	85	66.4
Yes	43	33.6
Do you drink		
No	56	43.7
Regular	72	56.3

Lipids Analysis

In this study, the baseline lipid values have been shown in Table II. We classified(59/64) 92.2% and (52/64) 81.2% of the control group and HAART treatment group participants diagnosed with dyslipidemia by using the definition given in the Methods section. In this study, low HDLC (<1.0 mmol/L) was one of the largest lipid abnormalities, found in 68.7% (44/64) and 46.9% (30/64) of the control group and HAART treatment group, respectively. Hypertriglyceridemia of >5.0 mmol/L was detected in 1.5% (1/64) of the control group and 6.2% (4/64) of the treatment group, whereas

hypercholesterolemia of >10 mmol/L was found in 3.1% (2/64) of the control group and 1.1% (1/64)of the treatment group. LDL hypercholesterolaemia of > 4.9 mmol/L was found in 1.6% (1/64) of the control group and 4.6% (3/64) of the treatment group. Severe hypercholesterolaemia, (TC > 7.5 mmol/L), was detected in 0% (0/64) of the control group and 16% (10/64) of the treatment group, respectively.

TABLE II - Baseline lipid values in control and treatment group

Variable	Control n=64	Treatment group n=64
Total cholesterol (mmol/L)*	4.1 (3.6,4.4)	4.36(3.81-4.97)
Triglycerides (mmol/L)*	1.1(0.85,1.25)	1.28(0.86-2.05
HDLC (mmol/L)*	0.90(0.75,1.05)	1.06(0.91-1.23)
LDLC (mmol/L)*	2.32(1.93,2.81)	2.5(2.04-2.93)
CD4 count	237(113-346.75)	407(276-498)

Potential risk factors

To investigate the potential risk factors for dyslipidemia in Chinese HIV-infected patients, we performed univariate (Table III) and multivariate analysis (Table IV). We found that men were more prone to dyslipidemia ((P=0.047, OR=0.162). Similarly, married participants were more prone to dyslipidemia ((P=0.045, OR=2.263). Aged participants significantly suffered more dyslipidemia {(<30 years' old P=0.019), (30-39 years' old P=0.010, OR=33.705), (40-49 years' old, P=0.060, OR=41.996)}. But in the case of BMI, participants with higher BMI were more prone to dyslipidemia {((BMI<18, P=0.013), overweight (BMI=24-28, P=0.003, OR=155.331), obesity (BMI>28, P=0.059, OR=29.434)). We also investigated the effect of eating habits on dyslipidemia, and we found that participants with lower comprehensive score were more likely to have dyslipidemia (P=0.032, OR=0.044). When we compared the dietary habit with

gender, we found that women's blood lipid levels were more relevant to diet as compared to men (P=0.020, OR=21.344) (Table IV).

TABLE III - Univariate analysis of potential risk factor for metabolic abnormalities

Variables	P*
Education	0.022
employment status	0.055,0.026
Dietary habits	**0.029**
marital status	<0.001
Antiviral treatment drug category	0.035
generation	0.004,0.001
BMI index	<0.001,0.054
Course/month	0.018,0.002
Antiviral time	0.016

TABLE IV - Multiple logistic regression analysis of potential risk factor for metabolic abnormalities

Variable s	P*	OR
Gender	0.047	0.162
marital status	0.045	2.263
Age group	0.019	
Age group(1)	0.010	33.705
Age group(2)	0.060	41.996
BMi group 1	0.013	
BMI group 2	0.003	155.331

(continuing)

TABLE IV - Multiple logistic regression analysis of potential risk factor for metabolic abnormalities

Variable s	P*	OR
Dietary habits group(1)	0.032	0.044
Gender by eating habits comprehensive score group(1)	0.020	21.344
BMI index (2) by physical activity level (1)	0.034	0.045
BMI index (2) by physical activity level (2)	0.005	0.015
BMI Grading (3) by Physical Activity Level (2)	0.045	0.032

DISCUSSION

Due to the widespread use of HAART treatment, the life expectancy of HIV-infected patients is continually increasing, but metabolic complications caused much concern in those cases. In this study, firstly, we assessed the prevalence of metabolic complications in HIV-infected Chinese patients, and further we explored the possible role of potential risk factors for the occurrence of metabolic complications in HIV-infected Chinese patients.

In this study, prevalence of dyslipidaemia was very high in both control and treatment groups, with low HDLC as the most common abnormality. Additionally, we found elevated HDLC levels in HAART participants. In this study, we defined triglycerides >5.0 mmol/L or dyslipidaemia, as LDLC >4.9 mmol/l. In this study, we observed very high prevalence of dysglycaemia in HAART treatment group than the control group. Our observations are completely in line with previously reported data (Dave *et al.*, 2011). Additionally, linkage between lipid abnormalities and HIV has already been documented (Dave *et al.*, 2016; Grunfeld *et al.*, 1989; Grunfeld *et al.*, 1991). In many studies that have already been reported, HIV disease is linked with decreased concentrations of TC, LDLC, and HDLC, whereas hypertriglyceridaemia has a positive correlation with lipid abnormalities and the degree of immune-suppression. Chronic infection occurred due

to continued acute phase reaction, which is usually associated with elevated triglycerides due to the decline in lipoprotein lipase activity. It has been suggested that the boost in triglyceride-rich lipoproteins potentially promotes the substitution of triglycerides into HDL by hepatic lipase after lipolysis, accounting for lower HDLC concentration (van der Voort *et al.*, 2003;van der Westhuyzen, de Beer, Webb, 2007). In this study, we found high lipid abnormalities are consistent with the previously reported observation (Jantarapakde *et al.*, 2014; Muhammad, Sani, Okeahialam, 2013; Oka *et al.*, 2012). It has already been highlighted that immunosuppression increased with the decrease of CD4 counts, which is linked with an increase in triglycerides. Additionally, the risk of obesity increased with the increase of waist-hip ratio (WHR), which is also linked with higher triglycerides figures. Another important observation of the current study was low HDLC in the control group, which is completely consistent with previously reported studies (Asiki *et al.*, 2015; Bekolo, Nguena, Ewane, *et al.*, Kollo, 2014; Kuti *et al.*, 2015; Seedat, Mayet, Latiff, Joubert, 1992). Many new treatment trends have been adopted over the last decade. Therefore, the characteristics of HIV-infected patients have been distorted. When, we compared the metabolic complication between control and treatment groups by using antiretroviral drugs (HAART), median HDL-cholesterol, total cholesterol, and triglyceride levels elevated in the treatment group. Additionally, the prevalence of dyslipidemia and lipodystrophy also significantly elevated in the treatment group. Our study observations are completely consistent with previous study findings (Jantarapakde *et al.*, 2014). Jantarapakde, a Thailand based scientist has reported significantly higher prevalence of lipodystrophy in HIV patients treated with HART. Similarly, the mean of HDL-cholesterol, total cholesterol and triglyceride levels also increased in other investigations (Gupta, Biswas, Sharma, 2011; Wu *et al.*, 2012). In view of abovementioned facts, we can suggest that antiretroviral therapy may influence the incidence of metabolic complications.

In this study, we performed univariate and multivariate analysis to explore the role of potential risk factors in the prevalence of metabolic complication. We found that gender, BMI, marital status, age, dietary habits and physical activity levels were significant risk factors for dyslipidemia. It has already been reported by Ishikawa-Takata*et al.* that BMI was associated with the prevalence of dyslipidemia in Japanese than Caucasian,

despite of a low BMI. These observations are supported by data (Ishikawa-Takata, Ohta, Moritaki, *et al.*, 2002. Other investigations have reported the correlation between PI exposure and metabolic complications (Gazzaruso *et al.*, 2002; Samaras *et al.*, 2007).But in this study, multivariate analysis showed non-significant differences. Moreover, dyslipidemia may be correlated with lipodystrophy in HIV-infected patients, thus inducing fact accretion (Wohl *et al.*, 2008).

Our study has several important strengths and limitations. To the best of our knowledge, here for the first time, we have reported in detail the metabolic effects of HART on Chinese HIV infected patients. All participants took part in an inclusive and complete metabolic evaluation at the time of recruitment. Additionally, in this study, we have explored the effects of potential risk factors on hypolipidemia. Small number of participants is the only limitation of the current study.

In conclusion, we found that participants in HART treatment group had higher triglycerides, TC, LDLC and HDLC than those in the control group. HART is significantly associated with an increase in dyslipidemia. Based on these findings, we suggest that there exists a correlation between smoking and another risk factor such as age, smoking, BMI, gender, marital status and dietary habits. We will attempt to explain the correlations of potential risk factors in our future study. Thus, based on our observations, car should be taken during the treatment of HIV infected patients. Therefore, we suggest the importance of discovering a new drug and it is mandatory for the treatment of HIV infected patients. Furthermore, considering the future large scale, multi-ethnic population-based study must be conducted to obtain comprehensive information on the prevalence of metabolic complication in various HIV infected Chinese patients.

DECLARATIONS

Availability of data and materials

The datasets generated or analyzed during the current study are available from the corresponding authors upon reasonable request.

Competing interests

The authors declare that they have no competing interests.

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