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Metabolic syndrome among HIV-infected Taiwanese patients in the era of highly active antiretroviral therapy: prevalence and associated factors

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Objectives: Metabolic complications related to antiretroviral therapy are rarely investigated among HIV-infected patients in Asian countries. We investigated the prevalence of and factors associated with metabolic syndrome among HIV-infected patients who are ethnic Chinese in the era of highly active antiretroviral therapy (HAART).

Methods: A cross-sectional survey was performed to collect information on the demographic and clinical characteristics and antiretroviral therapy prescribed in 877 HIV-infected patients at a university hospital in Taiwan from May 2008 to April 2009. The modified Adult Treatment Panel III criteria were used to define metabolic syndrome after adjusting for the waist circumference criteria for Asians.

Results: Of the 877 patients, 75.3% were male homosexuals, 80.7% were receiving HAART and 88.7% had CD4 counts ≥200 cells/mm^3. Metabolic syndrome was diagnosed in 210 patients (26.2%). After adjusting for age, gender, smoking status, family history of diabetes mellitus, cardiovascular disease and hypertension, and baseline CD4 and plasma HIV RNA load, use of protease inhibitors (PIs) was significantly associated with the presence of metabolic syndrome (OR 1.63; 95% CI 1.10–2.43). In addition, exposure to PI for ≥3 years, to HAART for ≥6 years and to nucleoside reverse transcriptase inhibitor(s) for ≥6 years was significantly associated with the presence of metabolic syndrome with an adjusted OR of 1.96 (95% CI 1.13–3.42), 1.78 (95% CI 1.03–3.07), and 1.91 (95% CI 1.11–3.30), respectively.

Conclusions: Approximately one-fourth of HIV-infected Taiwanese patients developed metabolic syndrome in the HAART era. Receipt of HAART and prolonged exposure to PI and nucleoside reverse transcriptase inhibitor(s) were associated with metabolic syndrome.

Keywords: hyperlipidaemia, protease inhibitors, nucleoside reverse transcriptase inhibitors, non-nucleoside reverse-transcriptase inhibitors, survey

Introduction

With the introduction of highly active antiretroviral therapy (HAART), HIV-related morbidity and mortality have declined and survival and life quality have improved significantly in HIV-infected patients with access to HAART.[1,2] HAART has transformed a previously universally fatal disease to a chronic, manageable infectious disease that requires life-long treatment. However, long-term toxicities are emerging after prolonged exposure to antiretroviral therapy, these have become challenges to the successful management of HIV infection. Those long-term toxicities are mainly metabolic complications that include osteoporosis, lipodystrophy, dyslipidaemia, hyperglycaemia, hypertension and cardiovascular disease.[3–13] These complications may be associated with increased risk of coronary artery disease. The Data Collection on Adverse Events of Anti-HIV

Drugs (DAD) study has shown that, at least for up to 6 years of exposure, there is a relative increase of 26% in the incidence of myocardial infarction per year of exposure to combination antiretroviral treatment.[14]

Metabolic syndrome is an aggregation of central obesity and metabolic abnormalities that confers an increased risk of cardiovascular disease and type 2 diabetes.[10,15] According to previous studies, the prevalence of metabolic syndrome among HIV-infected patients ranges from 17.0% to 45.4%.[16–25] The differences in prevalence of metabolic syndrome among the published studies may be explained by the different study populations and criteria used and different populations studied.[16–20] While the relationship between metabolic syndrome and HAART is well known,[20] the relationship between each individual antiretroviral agent with metabolic syndrome remains difficult to clearly define because at least two classes of antiretroviral agents are concurrently initiated. However, the use of protease inhibitors (PIs) has been reported to be associated with metabolic syndrome.[16,17,25] Of all nucleoside reverse transcriptase inhibitors (NRTIs), stavudine is the most commonly cited antiretroviral agent that is associated with metabolic syndrome.[16,19]

Hyperlipidaemia, especially hypertriglyceridaemia, is common in HIV-infected patients on long-term HAART, especially those with exposure to ritonavir-boosted PI-containing antiretroviral therapy. Riddler *et al.*[9] found that use of HAART for 6–12 months or longer leads to significant increases in triglyceride (TG) levels. Tien *et al.*[10] also found that the risk of type 2 diabetes and cardiovascular disease increased in HIV-infected patients who had received HAART for ≥6 months.

The introduction of HAART into many Asian countries has been slower than in many Western countries. Currently there are very limited studies published in the literature investigating the association between HAART and metabolic syndrome outside of clinical trial settings in this region. In the present study we aimed to assess the prevalence of metabolic syndrome in HIV-infected patients at a major hospital designated for HIV care in Taiwan and to evaluate the association between the use of three main drug classes [PIs, NRTIs and non-nucleoside reverse transcriptase inhibitor (NNRTIs)] and the cumulative durations of their use with the development of metabolic syndrome.

Materials and methods

Study design

This was a cross-sectional study that enrolled HIV-infected subjects who were aged ≥18 years and sought HIV care at the HIV clinic of the National Taiwan University Hospital from 1 May 2008 to 30 April 2009. Participants completed a questionnaire interview performed by the investigators. The content of questionnaires (available as Supplementary data at *JAC* Online) included smoking status (never, past or current), self-reported family history of diabetes mellitus, cardiovascular disease, hypertension and stroke, and current use of medications for hypertension, dyslipidaemia or diabetes. Pregnant women were excluded. Medical records of participants who completed the questionnaire interview were retrospectively reviewed. Variables that were collected included previous and current antiretroviral regimens, the cumulative duration of antiretroviral agents and the route of HIV transmission (injecting drug use, homosexual or heterosexual contact, others and unknown). The study was approved by the Research Ethics Committee of the hospital and participants gave written informed consent.

Clinical measurements

Systolic and diastolic blood pressures were assessed after the subjects were seated and rested for at least 5 min. Height was determined without shoes by the same machine. Weight was measured by a digital scale, and patients were fully dressed, but without shoes or heavy clothing. Waist circumference was measured in accordance with the standard protocol of the Bureau of Health Promotion, Department of Health, Taiwan.[26] Body mass index (BMI) was calculated as weight in kilograms (kg) divided by the square of the height in metres (m).

Framingham equation assessment

The 10 year cardiovascular disease risk was assessed in all patients using the Framingham equation.[27] The variables that are included in that equation include age, gender, total cholesterol, high-density lipoprotein-cholesterol (HDL-C), systolic blood pressure and smoking status. We categorized individuals on the basis of two levels of 10 year cardiovascular disease risk: ≥10% and ≥20%.

Laboratory investigations

Total cholesterol, TG, glucose, HDL-C and low-density lipoprotein-cholesterol (LDL-C) levels of blood specimens were determined after an 8 hour fast. The data of most recent plasma HIV RNA load and CD4 cell count (within 6 months of survey) were collected using a standardized case record form. CD4 cell count was determined by flow cytometry and plasma HIV RNA load was determined by Roche real-time PCR (limit of detection, 40 copies/mL).

Definitions of metabolic syndrome and HAART

According to the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III guidelines (2005),[28] metabolic syndrome was defined as having three or more of the following criteria: (i) waist measurement ≥80 cm for women and ≥90 cm for men; (ii) TG level of ≥150 mg/dL or drug treatment for elevated TG level; (iii) HDL-C of <50 mg/dL for women and <40 mg/dL for men or drug treatment for reduced HDL-C; (iv) elevated blood pressure (systolic ≥130 mmHg or diastolic ≥85 mmHg, using the average of two seated measurements) or antihypertensive drug treatment; and (v) fasting glucose ≥100 mg/dL or currently using anti-diabetic medications.

HAART, which was introduced in Taiwan in 1997, was defined as the use of at least three agents from at least two classes of antiretroviral agents according to the local treatment guidelines for adults with HIV infection. The most commonly prescribed antiretroviral combinations in antiretroviral-naive patients were two NRTIs plus one NNRTI and two NRTIs plus ritonavir-boosted PI or unboosted PI, while three NRTIs or combinations of three classes were only infrequently prescribed. Enfuvirtide, tenofovir, etravirine, darunavir, tipranavir and raltegravir were prescribed only in patients with virological failure and documentation of genotypic resistance to the first-line agents according to local treatment guidelines.

Statistical analysis

Categorical variables were analysed using the χ^2 test. Continuous variables were compared using Student's *t*-test. Baseline and treatment characteristics were compared between patients with and without metabolic syndrome. Significant variables in univariate analysis were

entered into a multiple logistic regression adjusted for the following potential confounding variables: sex, age, BMI, smoking status, diabetes, cardiovascular disease and hypertension. For each drug class we separately analysed the effect of the duration of treatment by logistic regression in order to calculate the OR and 95% CI for metabolic syndrome. With regards to the duration of antiretroviral therapy, we defined several cut-off points: <12 months, 12–35 months, 36–71 months and ≥72 months. Plasma HIV RNA loads were log-transformed. A P value <0.05 was considered statistically significant. All P values were two-tailed. Analyses were performed using SAS software (version 9.1).

Results

During the 12 month study period, 1333 HIV-infected adult patients sought HIV care at this hospital; 877 (65.8%) were enrolled in our study. Compared with the 456 patients that were not enrolled, no statistically significant differences were found in baseline demographic and clinical characteristics (data not shown). In those patients, 803 (91.6%) had complete laboratory data available for diagnosis of metabolic syndrome and their clinical characteristics are shown in Table 1, and 795

Table 1. Clinical characteristics of HIV-infected patients with metabolic syndrome and those without metabolic syndrome

Variable	All patients, $N=803$	No metabolic syndrome, $N=593$	Metabolic syndrome, $N=210$	P
Age (years), mean (SD)	803	36.8 (10.6)	44.5 (9.7)	<0.0001
Male, *n* (%)	762 (94.9)	571 (96.3)	191 (91.4)	0.003
Smoking				0.55
never	317 (39.8)	240 (40.5)	82 (39.1)	
past	213 (26.7)	162 (27.3)	52 (24.8)	
current	267 (33.5)	191 (32.2)	76 (36.2)	
Risk behaviour, *n* (%)				<0.0001
MSM	604 (75.2)	481 (81.1)	123 (58.6)	
heterosexual	149 (18.6)	86 (14.5)	63 (30.0)	
IDU	39 (4.9)	22 (3.7)	17 (8.1)	
other	11 (1.4)	4 (0.7)	7 (3.3)	
Baseline CD4 count (cells/mm^3), mean	(772 with data)			0.14
<200	393 (50.9)	282 (48.9)	111 (56.9)	
200–499	278 (36.0)	218 (37.8)	60 (30.8)	
≥500	10 (13.1)	77 (13.3)	24 (12.3)	
Family history of diabetes, *n* (%)	195 (24.3)	129 (21.8)	66 (31.4)	0.005
Family history of coronary heart disease, *n* (%)	126 (15.7)	81 (13.7)	45 (21.4)	0.008
Family history of hypertension, *n* (%)	362 (45.1)	248 (41.9)	114 (54.3)	0.002
Waist circumference (cm), mean (SD)	796 (99.1)	78.8 (6.8)	87.5 (9.1)	<0.0001
BMI (kg/m^2), mean (SD)	791 (98.6)	21.7 (2.6)	24.5 (3.6)	<0.0001
Systolic blood pressure (mmHg), mean (SD)		116.9 (13.8)	129.7 (16.1)	<0.0001
Diastolic blood pressure (mmHg), mean (SD)		74.2 (10.0)	82.5 (10.4)	<0.0001
TG (mg/dL), mean (SD)		149.5 (116.7)	320.6 (270.2)	<0.0001
Total cholesterol (mg/dL), mean (SD)		182.4 (40.6)	190.9 (45.5)	0.012
HDL-C (mg/dL), mean (SD)		44.2 (11.3)	36.9 (8.0)	<0.0001
LDL-C (mg/dL), mean (SD)		102.3 (31.3)	94.4 (33.7)	0.004
Fasting glucose (mg/dL), mean (SD)		91.4 (15.1)	109.2 (38.4)	<0.0001
PVL ($\log_{10}$ copies/mL), mean (SD)		2.5 (1.3)	2.2 (1.1)	0.0002
CD4 (cells/mm^3), mean (SD)		439.9 (224.6)	500.6 (265.9)	0.003
10 year risk ≥10%, *n* (%)		91 (15.7)	71 (36.4)	<0.0001
10 year risk ≥20%, *n* (%)		21 (3.6)	22 (11.2)	<0.0001
PI, *n* (%)	464 (57.8)	314 (53.1)	150.0 (71.4)	<0.0001
NRTI, *n* (%)	656 (81.7)	469 (79.1)	187.0 (89.1)	0.001
NNRTI, *n* (%)	410 (51.1)	287 (48.4)	123 (58.6)	0.011
Duration of HAART (months), mean (SD)		41.5 (36.9)	62.5 (44.5)	<0.0001
duration of PI (months), mean (SD)		25.1 (27.7)	35.5 (34.5)	0.002
duration of NRTI (months), mean (SD)		41.4 (36.6)	62 (44.2)	<0.0001
duration of NNRTI (months), mean (SD)		39.7 (32.1)	49.1 (33.8)	0.01

MSM, men who have sex with men; PVL, plasma viral load; IDU, intravenous drug use.
The 10 year cardiovascular disease risk was assessed in all patients using the Framingham equation.[27]

(90.6%) had complete data for assessment of cardiovascular risk with the use of the Framingham equation. There were no differences in variables between the 803 patients with complete laboratory data and the 74 without (data not shown).\

The data for fasting glucose, TG, total cholesterol, HDL-C and LDL-C are shown in Table 1. Of the patients with available data, 20.4% (159/778) had glucose levels ≥100 mg/dL, 47.2% (402/851) had TG levels ≥150 mg/dL, 22.7% (193/851) had TG levels ≥250 mg/dL and 9.2% (78/848) had total cholesterol levels ≥240 mg/dL. Of the 877 patients, 31 (3.5%) were taking oral hypoglycaemic agents or receiving insulin replacement for control of diabetes, 73 (8.3%) were taking lipid-lowering agents and 67 (7.6%) were taking anti-hypertensives. According to the criteria of the Bureau of Health Promotion, Department of Health, Taiwan, 227/866 (26.2%) were classified as overweight with a BMI >24.

According to NCEP ATP III, 210/803 patients (26.2%) fulfilled the criteria of metabolic syndrome (Table 1). Patients with metabolic syndrome were more likely to have higher levels of TG, total cholesterol, systolic and diastolic blood pressures, BMI and CD4 counts, were of older age, and were more likely to have a family history of diabetes, hypertension and cardiovascular disease compared with patients without metabolic syndrome ($P<0.05$ for all comparisons) (Table 1). Furthermore, a significantly higher proportion of patients with metabolic syndrome had a 10 year cardiovascular disease risk ≥10% and ≥20% than those without metabolic syndrome, as assessed by the Framingham equation (Table 1) ($P<0.05$ for the two comparisons).

The distributions of treatment-related factors in patients with and without metabolic syndrome are shown in Table 1. Compared with patients without metabolic syndrome, patients with metabolic syndrome were more likely to have received HAART, PI, NRTI and NNRTI. Furthermore, the duration of exposure to each class of antiretroviral agent in the patients with metabolic syndrome was significantly longer than that in the patients without metabolic syndrome. The antiretroviral agents ever prescribed to patients are shown in Table 2. In multiple logistic regression after adjustments made for age, gender, smoking status and family history of diabetes, cardiovascular disease and hypertension, use of PI (OR 1.77; 95% CI 1.08–2.91) was the strongest contributor to metabolic syndrome (Table 3), while the use of NRTI or NNRTI was not statistically significant in all of the four different models of multiple logistic regression analysis (Table 3).

The relationships between exposure to antiretroviral agents and levels of TG, total cholesterol and fasting glucose are shown in Figure 1. The levels of TG and total cholesterol and the proportions of patients with TG >250 mg/dL and total cholesterol >240 mg/dL increased with the duration of exposure to each class of antiretroviral agent and HAART (Figure 1).

Compared with the patients who had received PI for less than 12 months, the patients who had received PI for ≥72 months were more likely to have TG levels >250 mg/dL ($P<0.0001$). A duration of NRTI use for ≥72 months ($P<0.0001$) was associated with TG levels >250 mg/dL and total cholesterol >240 mg/dL ($P<0.0001$). The use of NRTI and NNRTI was each independently associated with increased HDL-C levels ($P<0.05$) (Table 4) (Figure 1).

In multiple logistic regression analysis after adjustments for age, gender, smoking status and family history of diabetes, cardiovascular disease and hypertension, a duration of HAART for ≥72 months (OR 1.96; 95% CI 1.13–3.42; *P* for trend 0.0006) was the factor most strongly associated with metabolic syndrome. Similarly, exposure to PI for 36–71 months (OR 1.78; 95% CI 1.03–3.07; *P* for trend 0.02) and to NRTI for ≥72 months (OR 1.91; 95% CI 1.11–3.30; *P* for trend 0.0008) was statistically significantly associated with metabolic syndrome. However, a treatment duration of NNRTI for ≥72 months was of borderline statistical significance in association with metabolic syndrome in multiple logistic regression analysis (OR 1.52; 95% CI 0.92–2.50; *P* for trend 0.06) (Table 5).

Table 2. Type and frequency of antiretroviral therapy ever prescribed to patients

Drug class and drug	Patients
PI	
indinavir	122
saquinavir	82
nelfinavir	32
ritonavir	129
lopinavir/ritonavir	251
atazanavir	254
darunavir	3
tipranavir	3
NRTI	
stavudine	229
zidovudine	97
lamivudine	321
deoxycytidine	30
didanosine	157
abacavir	146
zidovudine/lamivudine	481
abacavir/lamivudine	353
tenofovir/emtricitabine	9
NNRTI	
nevirapine	93
efavirenz	401

Table 3. Association between metabolic syndrome and different antiretroviral classes in multivariate analysis for selected variables

	PI, OR (95% CI)	NRTI, OR (95% CI)	NNRTI, OR (95% CI)
Model 1	2.02 (1.29, 3.15)	0.77 (0.39, 1.52)	1.31 (0.88, 1.96)
Model 2	2.06 (1.32, 3.23)	0.73 (0.37, 1.45)	1.37 (0.91, 2.04)
Model 3	2.06 (1.32, 3.23)	0.73 (0.37, 1.45)	1.37 (0.92, 2.05)
Model 4	1.77 (1.08, 2.91)	0.91 (0.42, 1.95)	1.26 (0.79, 2.00)

Model 1: adjusted for age and gender.
Model 2: adjusted for age, gender and smoking.
Model 3: adjusted for age, gender, smoking and family history.
Model 4: adjusted for age, gender, smoking, family history, baseline PVL and CD4.

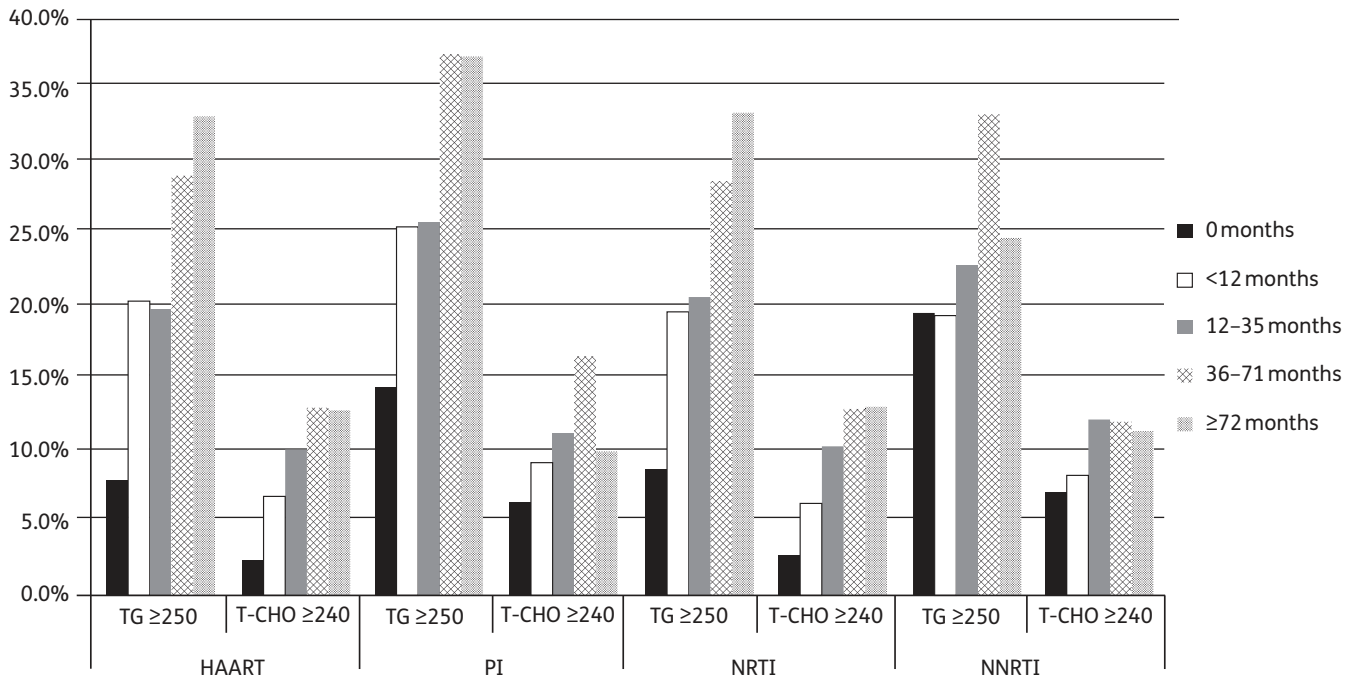

Figure 1. Proportions of participants with hyperlipidaemia [TG level ≥250 mg/dL and total cholesterol (T-CHO) ≥240 mg/dL] after different durations of exposure to the three classes of antiretroviral agents.

Discussion

In this study, we describe the prevalence of and analyse the factors associated with metabolic syndrome among HIV-infected patients who are ethnic Chinese in the era of HAART. We found that 26.2% of HIV-infected Taiwanese patients with prolonged exposure to antiretroviral therapy had metabolic syndrome. Similar to what has been observed in HIV-infected patients with access to HAART in many Western countries, we also found that receipt of HAART and prolonged exposure to PI and NRTI are associated with an increased prevalence of metabolic syndrome.

The prevalence of metabolic syndrome in our subjects who are ethnic Chinese falls within the range of the prevalence reported in the literature (17.0%–45.4%).[16–25] The wide range of prevalence of metabolic syndrome could be attributed to the use of different criteria, different exposure durations of antiretroviral therapy among the subjects and different study populations and ethnicities. For example, in a cross-sectional study of 710 HIV-infected patients with a mean age of 41.9 years who had received antiretroviral therapy for ≥72 months in Spain,[16] the overall prevalence of metabolic syndrome was 17.0%, with the use of ATP III (2001) criteria[27] to define metabolic syndrome. In another cross-sectional study of 1725 HIV-infected female patients with a mean age of 40 years in the USA,[19] using ATP III (2001) criteria,[27] the prevalence of metabolic syndrome was 33.0%.

The prevalence of metabolic syndrome among HIV-infected patients may be similar to or different from that in the general population, depending on the populations studied.[18,19,25,29] In the Taiwanese survey on the prevalence of hyperglycaemia, hyperlipidaemia and hypertension (TwSHHH) among the general population, which was conducted in 2001,[30] the age-standardized prevalence of metabolic syndrome was 15.7%. In our study of HIV-infected patients, in whom the majority received HAART, the prevalence of metabolic syndrome would be 26.4% if we used the same age standardization, which indicates that the prevalence of metabolic syndrome is significantly increased in HIV-infected patients with exposure to HAART compared with the HIV-seronegative population or the population of unknown HIV serologic status in Taiwan.

While exposure to HAART contributes to the development of metabolic syndrome,[20] the relationship between each individual antiretroviral agent and metabolic syndrome is less clear because antiretroviral agents have been sequentially introduced into clinical use over the past 25 years, and the combination of at least two classes of antiretroviral agents is indicated in order to achieve long-term virological suppression and reduce the risk of emergence of resistance mutations. Furthermore, switching of antiretroviral therapy due to drug–drug interactions, adverse effects, treatment failures and co-morbidities is common.[31] In our study, we found that PI use was independently associated with metabolic syndrome because PI use results in increases in TG, total cholesterol and fasting glucose levels, as well as a decrease in HDL-C level,[3,8,20,32–35] which is consistent with previous studies that demonstrated an association between metabolic syndrome and both current and previous PI exposure.[17,21,24] While exposure to lopinavir/ritonavir has been reported to be associated with metabolic syndrome,[16,25] the study by Sobieszczyk *et al.*[19] and ours were unable to demonstrate such an association, probably because of the small number of patients ($n=251$) receiving lopinavir/ritonavir in our study, or because patients who developed metabolic syndrome while receiving lopinavir/ritonavir were switched to other

Table 4. Levels of TG, total cholesterol, HDL-C and fasting glucose in 877 HIV-infected participants by durations of HAART, PI, NRTI and NNRTI

HAART	0 months, *N*=185	<12 months, *N*=149	12–35 months, *N*=180	36–71 months, *N*=181	≥72 months, *N*=182	*P*
TG (mg/dL), mean (SD)	132.3 (82.0)	181.7 (133.5)	191.4 (218.5)	228.9 (228.7)	230.6 (185.3)	<0.0001
Total cholesterol (mg/dL), mean (SD)	167.3 (32.2)	182.5 (40.3)	186.3 (46.5)	194.4 (48.2)	192.3 (37.8)	<0.0001
HDL-C (mg/dL), mean (SD)	39.4 (10.9)	42.7 (11.1)	42.2 (9.9)	44.1 (11.9)	42.7 (10.5)	0.002
Fasting glucose (mg/dL), mean (SD)	89.3 (9.4)	96.4 (35.8)	96.2 (25.3)	97.0 (18.6)	101.0 (26.5)	0.0006
PI	0 months, *N*=408	<12 months, *N*=166	12–35 months, *N*=170	36–71 months, *N*=93	≥72 months, *N*=40	*P*
TG (mg/dL), mean (SD)	160.8 (136.2)	207.1 (229.3)	206.6 (203.8)	261.4 (178.7)	259.1 (224.9)	<0.0001
Total cholesterol (mg/dL), mean (SD)	180 (39.5)	185.2 (41.9)	190.1 (48.5)	198 (40.6)	178.3 (43.6)	0.0016
HDL-C (mg/dL), mean (SD)	42.6 (12.0)	42.7 (10.6)	41.5 (9.8)	42.6 (8.6)	39.1 (11.4)	0.31
Fasting glucose (mg/dL), mean (SD)	93.2 (15.4)	97.2 (35.4)	98.6 (29.0)	100.1 (23.4)	100.1 (25.3)	0.04
NRTI	0 month, *N*=192	<12 months, *N*=148	12–35 months, *N*=179	36–71 months, *N*=181	≥72 months, *N*=177	*P*
TG (mg/dL), mean (SD)	135.8 (91.0)	181.7 (133.4)	192.4 (219.1)	227.0 (229.3)	231.4 (183.6)	<0.0001
Total cholesterol (mg/dL), mean (SD)	168.7 (33.5)	181.1 (39.5)	186.8 (46.4)	194.1 (48.1)	192.7 (38.1)	<0.0001
HDL-C (mg/dL), mean (SD)	39.5 (10.8)	42.5 (11.1)	42.3 (9.9)	44.3 (12.0)	42.5 (10.5)	0.002
Fasting glucose (mg/dL), mean (SD)	90.2 (11.3)	96.6 (35.9)	96.3 (25.3)	96.4 (17.9)	101.0 (26.8)	0.002
NNRTI	0 month, *N*=466	<12 months, *N*=97	12–35 months, *N*=101	36–71 months, *N*=108	≥72 months, *N*=105	*P*
TG (mg/dL), mean (SD)	180.0 (160.6)	208.3 (290.9)	191.0 (136.1)	236.4 (212.7)	200.4 (149.3)	0.06
Total cholesterol (mg/dL), mean (SD)	179.3 (41.6)	179.5 (51.0)	193.1 (37.6)	195.1 (45.6)	195.2 (33.6)	<0.0001
HDL-C (mg/dL), mean (SD)	40.9 (10.2)	42.1 (12.3)	44.8 (11.0)	43.6 (12.4)	44.6 (10.3)	0.001
Fasting glucose (mg/dL), mean (SD)	94.1 (25.2)	94.5 (18.3)	98.2 (24.9)	99.5 (29.6)	99.7 (19.7)	0.11

Table 5. Associations between metabolic syndrome and exposure durations for three classes of antiretroviral agents in logistic regression

	0 months, reference	<12 months OR (95% CI)	12–35 months OR (95% CI)	36–71 months OR (95% CI)	≥72 months OR (95% CI)	*P* for trend
HAART duration	1	0.79 (0.42, 1.51)	1.20 (0.67, 2.15)	1.59 (0.91, 2.79)	1.96 (1.13, 3.42)	0.0006
PI duration	1	1.25 (0.78, 2.00)	1.47 (0.89, 2.31)	1.78 (1.03, 3.07)	1.98 (0.96, 4.06)	0.02
NRTI duration	1	0.76 (0.40, 1.43)	1.18 (0.67, 2.09)	1.43 (0.82, 2.49)	1.91 (1.11, 3.30)	0.0008
NNRTI duration	1	0.77 (0.43, 1.39)	1.37 (0.80, 2.34)	1.17 (0.70, 1.98)	1.52 (0.92, 2.50)	0.06

antiretroviral combinations or put on lipid-lowering agents when this survey was conducted.

Of the nucleoside analogues, stavudine was associated with metabolic syndrome in our study ($P<0.0001$, data not shown), after adjustment for age and gender, which is in agreement with other studies.[16,19] Gallant *et al*.[36] also found that the use of stavudine and PI contributed to hypertriglyceridaemia. Many studies have shown that the use of NRTI is associated with increases in TG, total cholesterol and HDL-C.[9,37–40] NRTI may cause mitochondrial toxicity by inhibiting mitochondrial DNA polymerase–γ in fat and other tissues, which interferes with respiratory chain complexes, leading to lipodystrophy and hyperlipidaemia.[41–44] In contrast to NRTI, our study failed to link NNRTI to metabolic syndrome in the multiple logistic regression. This finding is consistent with those of other studies.[17–20,24,35] The possible explanation may be that NNRTI-containing regimens are less likely to cause metabolic abnormalities than PI-containing regimens.[20,21,45,46] While exposure to efavirenz plus two NRTIs is more likely to cause increases in TG, total cholesterol and HDL-C levels compared with exposure to nevirapine-containing regimens,[47] patients who switched from a PI to an NNRTI usually achieved decreases in mean total cholesterol and TG levels 6 months later.[48]

The prevalence of metabolic syndrome increases with duration of exposure to HAART, and thus the prevalence of hyperlipidaemia, hyperglycaemia (Table 3) and hypertension.[3,5,8,9,29,32] In our study, a high proportion of HIV-infected patients smoked (60.2%) and were ≥40 years of age (41.4%), further increasing their risk of cardiovascular disease. By estimating the cardiovascular risk with the use of the Framingham equation, we found that 21.3% (169/795) of the subjects had a 10 year cardiovascular disease risk ≥10% and 5.7% (45/795) of the subjects had a 10 year cardiovascular disease risk ≥20%. Furthermore, the OR for a 10 year risk ≥20% was 3.59 (95% CI 1.94–6.67) in the patients receiving HAART compared with those not receiving HAART (data not shown). Therefore an increased risk of cardiovascular disease is not unexpected in HIV-infected patients compared with the HIV-uninfected general population,[33] which has become a challenge to the long-term successful management of HIV infection in patients who enjoy recovery of immune function after receiving HAART.

Our study has several limitations. First, similar to all published studies on the prevalence of metabolic syndrome, the cross-sectional study design precludes us from examining exactly the role of each class of antiretroviral agent in the development of metabolic syndrome. Second, the hospital where the study was conducted is a major referral hospital for HIV care in greater Taipei. Over the past decade, 7402 patients who were newly diagnosed with HIV infections in greater Taipei according to statistics of Taiwan Centers for Disease Control (CDC), 5521 (74.6%) being sexually transmitted, were reported to the Taiwan CDC. Of these, 3555 (48.0%) sought HIV care at this hospital. While the proportion of our adult patients (55.1%; 1777/3223) who were started on HAART was similar to that of all HIV-infected patients in Taiwan according to the Taiwan CDC (55%) (C.-H. Yang, Taiwan CDC, personal communication), a previous history of antiretroviral treatment may not be complete in many patients who were referred from other hospitals. Therefore the effects of antiretroviral drugs on metabolic syndrome may have been underestimated or overestimated in our study and our findings may not be generalizable to the entire population of HIV-infected adults in Taiwan. Third, 75.2% of the subjects enrolled in this study were male homosexuals, and only a small number of them were injecting drug users (IDUs; 3.9%), which is different from the epidemiology of the 17282 cases of HIV infections reported to the Taiwan CDC as of April 2009 in which 39.27% were male homosexuals. However, IDUs were either incarcerated or lost to follow-up after release from correctional facilities or prisons, and it was estimated that <5% of IDUs continued to receive HAART. Although the distribution and trends of risks for HIV transmission in our cohort over the past decade were similar to those of all HIV-infected patients who were not IDUs in Taiwan, the findings of our study may not be generalizable to other HIV care facilities with a higher proportion of IDUs in Taiwan. Fourth, information on potential confounding factors that may influence metabolic syndrome, such as alcoholic intake, dietary habit and physical activity, were not collected during the study period. The reported prevalences of metabolic syndrome in different studies among different ethnic groups range widely, from 17.0% to 45.4%;[16–25] therefore, not only antiretroviral therapy, but alcohol intake, dietary habit and physical activity, may play a role.

In conclusion, our study demonstrates a high prevalence of metabolic syndrome among HIV-infected patients who are ethnic Chinese. In this study, we found that the duration of exposure to drug classes or combinations carries an increased risk of metabolic syndrome. Behavioural and medical interventions are needed to reduce modifiable risk factors for cardiovascular diseases, such as smoking, hyperlipidaemia, hypertension and hyperglycaemia.

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Transparency declarations

All the authors have no financial conflicts of interest to declare and the funder has not played any decision-making role in the research.

Supplementary data

The two questionnaires (one for men and one for women) are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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