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Effect of adiponectin-encoding gene *ADIPOQ* single nucleotide polymorphisms +45 and +276 on serum lipid levels after antiretroviral therapy in Japanese patients with HIV-1-infection

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Abstract

Objectives: To investigate the association between single nucleotide polymorphisms (SNPs) in the adiponectin-encoding gene *ADIPOQ* and changes in serum lipid levels in HIV-1-infected patients after antiretroviral therapy (ART).

Methods: ART-naïve HIV-1-infected patients were recruited to this prospective analysis. SNP +45 and SNP +276 genotype was determined by direct sequencing. Multivariate linear regression analysis was performed to analyse the effects of genotype, and predisposing conditions on serum total cholesterol and triglyceride in the 4 months before and after ART initiation.

Results: The study enrolled 78 patients with HIV-1-infection (73 male, five female; age range 22–67 years). HIV-1 viral load $\geq$5 $\log_{10}$ copies/ml, baseline total cholesterol $\geq$160 mg/dl, and $CD4^+$ lymphocyte count $<$200/μl were associated with increased serum total cholesterol levels after ART initiation. Protease inhibitor treatment and body mass index $\geq$25 kg/m^2 were associated with increased triglyceride levels after ART initiation. There were no significant associations between SNP +45 or SNP +276 genotype and serum total cholesterol or triglyceride levels.

Conclusions: SNP +45 and SNP +276 genotype is not associated with changes in serum total cholesterol or triglyceride levels after ART initiation.

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Introduction

Antiretroviral therapy (ART) has dramatically improved the prognosis of people infected with human immunodeficiency virus 1 (HIV-1), with the typical life expectancy of a 20-year-old person being >45 years.[1] The adipocytokine adiponectin plays a key role in serum lipid metabolism; low levels of adiponectin are associated with abnormally high serum lipid concentrations.[2] ART-naïve HIV-1 infected patients have lower serum adiponectin levels than noninfected individuals,[3] and ART is known to further lower adiponectin levels, resulting in dyslipidaemia.[4] The prolonged survival of ART-treated patients raises concerns regarding cardiovascular and cerebrovascular diseases originating from lipid disorders, and good management of serum lipid levels is therefore critical in these patients.[5,6] In humans, adiponectin is encoded by *ADIPOQ* (GenBank: Q15848), single-nucleotide polymorphisms (SNPs) of which have been reported to affect serum adiponectin levels in non-HIV-infected individuals.[7,8] These SNPs include SNP +45 T>G (rs2241766) and SNP +276 G>T (rs1501299). The G alleles of both SNP +45 and SNP +276 are associated with increased risk of type 2 diabetes In addition, the SNP +276 G/G genotype is associated with lower serum adiponectin levels than the SNP +276 G/T or T/T genotypes in obese non-HIV-1 infected Japanese subjects.[9] It is possible that *ADIPOQ* SNPs are responsible for changes in serum total cholesterol and triglyceride levels after initiation of ART.

The aim of the present prospective analysis of serum total cholesterol and triglyceride levels in ART-naïve HIV-1-infected Japanese patients was to investigate the effects of SNP +45 and SNP +276 genotype on serum lipid levels after ART initiation.

Patients and methods

Study population

The study recruited ART-naïve HIV-1-infected Japanese patients who began ART treatment between May 2005 and December 2011 at Yokohama City University Hospital, Yokohama, Japan. Exclusion criteria were: statin or fibrate drug treatment to control serum lipid levels prior to ART initiation; steroid therapy for AIDS; active hepatitis B virus (HBV) infection (HBs antigen positive/HBs antibody negative; active hepatitis decreases serum adiponectin level[10]); severe renal (serum creatinine ≥2.0 mg/dl) or liver dysfunction (Child–Pugh Class B or C). Patients with a history of (or inactive) HBV infection (HBs antigen negative/HBs antibody positive) were included in the study. Data regarding predisposing conditions, sex, age, body mass index (BMI), AIDS status, coinfection with HBV or hepatitis C virus (HCV), and SNP +45 and SNP +276 genotype were determined immediately prior to ART initiation, using standard methods.

All patients were prescribed standard regimens of ART therapy with protease inhibitors (PI; darunavir, atazanavir, lopinavir or fosamprenavir), non-nucleoside reverse transcriptase inhibitors (NNRTI; efavirenz) or integrase inhibitors (INSTI; raltegravir), and received standard care for HIV-1 infection in our institution. $CD4^+$ lymphocyte count, viral load, fasting total cholesterol and triglyceride levels, complete

blood cell count, liver enzymes, renal function and urinary tests were evaluated once per month for 4 months before and 4 months after ART initiation, using standard methods. Data from each 4-month period were pooled; the mean value was used to provide ''before ART'' (baseline) and ''after ART'' values.

The study was conducted with the approval of Yokohama City University Ethical Board. Written informed consent was obtained from all patients.

Genotyping

Whole-blood DNA was extracted using a DNA Extractor WB kit (Wako, Osaka, Japan), according to the manufacturer's instructions. Nested polymerase chain reaction (PCR) amplification was performed using KOD plus-and-buffer (Toyobo, Tokyo, Japan), according to the manufacturer's instructions. Primers were designed using Primer3 (http://frodo.wi.it.edu/). Primer sequences for the first round of PCR were: forward 5′-CAT AAT CTT GGT GAG GAA AGG AGA CTA C-3′, and reverse 5′-GAG TAG ACT TTC TTG TAG TAA CCA CCA AC-3′ (903 base pair [bp] product). Nested PCR primer sequences were: forward 5′-CTG AGA TGG ACG GAG TCC TTT GTA GGT C-3′, and reverse 5′-TGG TTA TAG AGG CAC CAT CTA CAC TCA TC-3′ (500 bp final product). Cycling conditions were an initial denaturation step at 94°C for 2 min, followed by 35 cycles of denaturation at 96°C for 15 s, annealing at 53°C for 30 s, and extension at 68°C for 30s. The 500 bp products were directly sequenced using an Applied Biosystems 3730*xl* DNA Analyzer and BigDye® Terminator v3.1 Cycle Sequencing Kit (Applied Biosystems, Foster City, CA, USA), according to the manufacturer's instructions. SNP genotypes were assigned according to analysis of the sequencing signals.

Statistical analyses

As this was an exploratory observational study, we did not conduct a power calculation. Continuous data were presented as mean ± SD or 95% confidence intervals (CI); categorical data were presented as *n* (%). HIV-1 viral load data were $\log_{10}$-transformed. Categorical data included sex, age (< or ≥50 years), BMI (< or ≥25 kg/m^2), AIDS status, $CD4^+$ lymphocyte count (< or ≥200/μl), HIV-1 viral load (< or ≥5 $\log_{10}$ copies/ml), HBV coinfection, HCV coinfection, baseline total cholesterol (< or ≥160 mg/dl), baseline triglyceride (< or ≥160 mg/dl). Data were analysed using two-tailed Mann–Whitney *U*-test and Kruskal–Wallis test for comparisons of continuous variables between two or three groups.

In linkage disequilibrium (LD) analysis, SNP +45 and SNP +276 haplotypes were inferred for each subject using a maximum likelihood estimation, based on an expectation–maximization (EM) algorithm.[11]

Multivariate linear regression analysis was performed to investigate predictors of serum total cholesterol after ART initiation, with adjustments for HIV-1 viral load, baseline total cholesterol and baseline $CD4^+$ lymphocyte count. In multivariate linear regression analysis to investigate predictors of triglyceride levels after ART initiation, adjustments were made for the ART base drug (the reference group was the patients receiving INSTIs, as these agents have fewer effects on serum lipid levels than PIs or NNRTIs[12]), BMI and baseline triglyceride level. In multivariate linear regression analysis of SNP +45 and SNP +276 genotypes, the Akaike information criterion (details not shown) determined that a codominant model (where the three genotypes are separated) was the best fit, compared with a dominant, recessive and a log-additive model. Homozygous carriers of the major allele were used as the reference group for multivariate analyses.

Statistical analyses were performed using SPSS® version 21 (SPSS Inc., Chicago, IL, USA) for Windows®, and Prism 5 (GraphPad Software, San Diego, CA, USA). *P*-values < 0.05 were considered statistically significant.

Results

The study enrolled 78 patients with HIV-1-infection (73 male and five female; mean age 43.1 ± 11.0 years; age range 22–67 years. Demographic and clinical characteristics of the study population are shown in Table 1. A total of 32 participants were diagnosed with AIDS (pneumocystis pneumonia, $n = 18$; tuberculosis, $n = 7$; Kaposi's sarcoma, $n = 4$; toxoplasmosis, $n = 2$; cytomegalovirus infection, $n = 1$). The base ART drug was a PI in 36 patients (darunavir, $n = 14$; atazanavir, $n = 9$; lopinavir, $n = 8$; fosamprenavir, $n = 5$), 24 patients received the NNRTI efavirenz and 18 received the INSTI raltegravir. Patients also received two ART backbone nucleoside reverse-transcriptase inhibitor drugs (tenofovir + emtricitabine, $n = 66$; abacavir + lamivudine, $n = 12$). Serum total cholesterol and serum triglyceride levels were significantly higher after initiation of ART compared with baseline ($P < 0.001$ and $P = 0.001$, respectively).

Data regarding SNP +45 and SNP +276 genotype prevalence are shown in Table 1. The minor allele frequencies of SNP +45 and SNP +276 were 0.429 and 0.25, respectively. Using an EM algorithm, the haplotype frequencies for SNP +45 and SNP +276 were estimated to be 0.333 for T–G, 0.238 for T–T, 0.417 for G–G and 0.012 for G–T. There was a high level of linkage disequilibrium between SNP +45 and SNP +276 ($D' = 0.886$), but the correlation between SNP +45 and SNP +276 was weak ($r^2 = 0.197$), indicating possible disequilibrium lying between SNP +45 and +276. It was considered difficult to perform the analysis based on haplotype instead of genotype, therefore independent statistical analyses were performed for each SNP +45 and SNP +276 genotype.

Table 1. Demographic and clinical characteristics of Japanese patients with HIV-1 infection included in a study to investigate the effect of the single-nucleotide polymorphisms (SNP) + 45 and +276 in the adiponectin-encoding gene *ADIPOQ* on serum lipid levels following the initiation of antiretroviral (ART) therapy ($n = 78$).

Characteristic	Value
Sex, male/female	73 (93.6)/5 (6.4)
Age, years	43.1 ± 11.0
BMI, kg/m^2	22.3 ± 3.2
AIDS positive prior to ART	32 (41.0)
Baseline CD4$^+$ lymphocytes/μl	166.2 ± 155.9
Baseline HIV-1 viral load, $\log_{10}$ copies/ml	4.85 ± 0.7
HBV coinfection	24 (30.8)
HCV coinfection	4 (5.1)
Base ART drug	
INSTI	18 (23.0)
PI	36 (46.2)
NNRTI	24 (30.8)
SNP +45 genotype	
T/T	22 (28.2)
T/G	45 (57.7)
G/G	11 (14.1)
SNP +276 genotype	
G/G	43 (55.2)
G/T	31 (39.7)
T/T	4 (5.1)
Total cholesterol, mg/dl	
Before ART	154.9 ± 35.3
After ART	176.2 ± 33.7**
Triglyceride, mg/dl	
Before ART	148.9 ± 58.7
After ART	191.0 ± 90.5***

Data presented as *n* (%) or mean ± SD.
BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; INSTI, integrase inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.
**$P < 0.01$, ***$P < 0.001$ vs before ART; two-tailed Mann–Whitney *U*-test and Kruskal–Wallis test.

Data regarding serum total cholesterol and triglyceride levels before and after ART initiation are presented in Table 2. Before initiation of ART, total cholesterol levels were significantly higher in patients without AIDS than in those with AIDS ($P = 0.03$), and in patients with high $CD4^+$ lymphocyte counts ($\geq$200/μl) compared with those with low $CD4^+$ lymphocyte count ($P < 0.05$). After ART initiation, total cholesterol levels were significantly higher in patients with AIDS than in those without ($P = 0.03$), in patients with high HIV-1 viral loads ($\geq$5 $\log_{10}$ copies/ml) than those with low HIV-1 viral loads ($P = 0.002$), and in patients with high baseline total cholesterol ($\geq$160 mg/dl) compared with those with low baseline total cholesterol ($P < 0.001$; Table 2). There were no significant between-group differences in serum triglyceride levels before ART initiation. After ART initiation, serum triglyceride levels were significantly higher in patients with high BMI ($\geq$25) than those with low BMI ($P = 0.04$), patients treated with PI compared with INSTI or NNRTI ($P = 0.02$), and in patients with high baseline triglyceride levels ($\geq$160 mg/dl) compared with those with low baseline triglyceride levels ($P < 0.05$).

Multivariate linear regression analysis found that high viral load (unstandardized coefficient [B] 21.315; 95% CI 8.421, 34.210), high baseline total cholesterol level (B 37.970; 95% CI 24.349, 51.591) and low $CD4^+$ lymphocyte count (B 19.918; 95% CI 6.299, 33.537) were significantly associated with an increase in mean serum total cholesterol level after ART (Table 3). Use of PI as a base ART drug (B 75.418; 95% CI 25.568, 125.268) and high BMI (B 60.026; 95% CI 11.930, 108.122) were significantly associated with an increase in the mean serum triglyceride level after ART (Table 4). There were no significant associations between SNP +45 or SNP +276 genotype and changes in serum total cholesterol or triglyceride levels after ART initiation.

Discussion

The present study found no association between two major *ADIPOQ* SNPs (+45 and +276) and serum total cholesterol or triglyceride levels before or after initiation of ART. Our finding that AIDS and low $CD4^+$ lymphocyte count is associated with a low serum total cholesterol level before ART is consistent with a report that untreated HIV-1-infected patients had low levels of serum total cholesterol.[13] ART initiation is an important event for HIV-1-infected patients because it can markedly increase patients' serum lipid levels.[2,7] After ART initiation, high HIV-1 viral load, high baseline total cholesterol level and low $CD4^+$ lymphocyte count were positively correlated with serum total cholesterol level in the present study. Serum triglyceride levels were significantly higher in patients treated with PIs than in those treated with INSTIs in the present study. This is consistent with the findings of others that ART with boosted PIs results in a greater decrease in serum adiponectin levels (and therefore increased triglyceride levels) than INSTIs, in both humans and mice.[14,15] Patients with high baseline total cholesterol levels were more likely to develop high serum total cholesterol levels after ART than those with low total cholesterol levels, in the present study. In addition, those with a high BMI ($\geq$25) were found to have a higher mean serum triglyceride level than those with a low BMI. It is widely accepted that patients with a high lipid profile and high body weight are at greater risk of developing dyslipidaemia than those with a low lipid profile and low body weight.[5] Lipodystrophy (which is the abnormal production, use and storage of adipose tissue) is a known major adverse effect of long-term PI therapy that is strongly associated with low serum adiponectin and dyslipidaemia.[16] However, because the observation period in the present study was limited only to the 4 months immediately after ART initiation, we were unable to

Table 2. Serum total cholesterol and triglyceride levels before and after initiation of antiretroviral therapy (ART) in Japanese patients with HIV-1 infection ($n = 78$).

		Serum TC, mg/dl		Serum triglyceride, mg/dl	
Parameter	*N*	Before ART	After ART	Before ART	After ART
Sex					
Male	73	154.5 ± 35.6	174.6 ± 32.8	148.5 ± 60.6	193.2 ± 92.8
Female	5	161.3 ± 34.2	206.2 ± 38.3	154.5 ± 16.0	159.1 ± 37.0
Age, years					
<50	56	154.2 ± 31.5	173.1 ± 32.9	149.9 ± 58.5	179.7 ± 85.2
≥50	22	156.7 ± 44.5	184.0 ± 35.0	146.3 ± 60.6	219.5 ± 99.1
BMI, kg/m^2					
<25	61	154.9 ± 37.6	176.4 ± 36.0	144.8 ± 59.6	178.0 ± 80.3*
≥25	17	155.1 ± 26.6	175.2 ± 24.3	163.6 ± 54.4	237.4 ± 111.0
AIDS status					
Negative	46	157.9 ± 26.8*	170.0 ± 32.1*	142.6 ± 57.2	174.9 ± 72.3
Positive	32	150.6 ± 45.0	185.0 ± 34.4	158.0 ± 60.5	214.1 ± 108.7
CD4$^+$ lymphocytes/μl					
≥200	28	161.0 ± 28.1*	166.7 ± 30.3	140.1 ± 64.7	171.1 ± 75.9
<200	50	151.5 ± 38.7	181.4 ± 34.6	153.9 ± 55.2	202.1 ± 96.7
HIV-1 viral load, $\log_{10}$ copies/ml					
<5	47	151.3 ± 27.9	166.9 ± 30.1**	145.7 ± 56.1	189.9 ± 90.3
≥5	31	160.4 ± 44.3	190.2 ± 34.4	153.8 ± 63.1	192.6 ± 92.3
HBV coinfection					
Negative	54	150.7 ± 34.6	178.4 ± 34.2	152.1 ± 59.4	195.3 ± 82.4
Positive	24	164.4 ± 35.9	171.0 ± 32.5	141.6 ± 57.5	181.3 ± 107.9
HCV coinfection					
Negative	74	154.7 ± 36.2	175.7 ± 33.8	147.8 ± 58.6	185.2 ± 78.1
Positive	4	159.8 ± 13.6	184.0 ± 35.6	168.7 ± 66.6	298.1 ± 214.1
Base ART drug					
INSTI	18	161.1 ± 35.2	167.2 ± 21.5	152.1 ± 69.8	151.8 ± 64.4*
PI	36	160.4 ± 38.2	181.0 ± 37.9	143.6 ± 56.7	220.3 ± 100.7
NNRTI	24	142.1 ± 28.3	175.7 ± 34.2	154.5 ± 54.4	176.3 ± 78.5
SNP +45 genotype					
T/T	22	160.0 ± 34.2	177.7 ± 30.5	134.8 ± 65.1	177.8 ± 68.7
T/G	45	152.0 ± 36.6	175.5 ± 35.4	155.7 ± 56.6	193.7 ± 99.4
G/G	11	156.7 ± 34.1	175.8 ± 35.3	149.3 ± 53.5	206.0 ± 95.3
SNP +276 genotype					
G/G	43	153.8 ± 36.8	176.7 ± 36.5	143.9 ± 49.4	192.1 ± 82.9
G/T	31	157.0 ± 34.2	175.4 ± 31.5	149.9 ± 57.7	189.8 ± 104.2
T/T	4	151.1 ± 37.0	176.3 ± 23.4	195.5 ± 132.7	188.1 ± 73.4
Baseline TC, mg/dl					
<160	51	–	165.4 ± 29.1***	–	188.1 ± 86.3
≥160	27	–	196.4 ± 32.8	–	196.4 ± 99.4
Baseline triglyceride, mg/dl					
<160	50	–	177.2 ± 33.7	–	180.9 ± 92.8*
≥160	28	–	174.2 ± 34.1	–	209.0 ± 84.9

Data presented as mean ± SD.

TC, total cholesterol; BMI, body mass index; HBV, hepatitis B virus; HCV, hepatitis C virus; INSTI, integrase inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ within group; two-tailed Mann–Whitney *U* test and Kruskal–Wallis test.

Table 3. Multivariate linear regression analysis of the association between serum total cholesterol and genetic and clinical parameters in Japanese patients with HIV-1 infection ($n = 78$).

Parameter	Unstandardized coefficient (B)	95% confidence intervals
SNP + 45 genotype		
T/T	Reference	–
T/G	−4.173	−19.451, 11.104
G/G	1.169	−20.369, 22.707
SNP + 276 genotype		
G/G	Reference	–
G/T	5.157	−8.503, 18.818
T/T	4.465	−26.151, 35.081
HIV-1 viral load, log_{10} copies/ml		
<5	Reference	–
≥5	21.315	8.421, 34.210
Baseline TC, mg/dl		
<160	Reference	–
≥160	37.970	24.349, 51.591
$CD4^+$ lymphocytes/μl		
≥200	Reference	–
<200	19.918	6.299, 33.537

TC, total cholesterol.

Table 4. Multivariate linear regression analysis of the association between serum triglyceride and genetic and clinical parameters in Japanese patients with HIV-1 infection ($n = 78$).

Parameter	Unstandardized coefficient (B)	95% confidence intervals
SNP + 45 genotype		
T/T	Reference	–
T/G	16.591	−33.550, 66.731
G/G	25.099	−43.960, 94.159
SNP + 276 genotype		
G/G	Reference	–
G/T	−1.8140	−45.252, 41.623
T/T	10.178	−88.828, 109.184
Base ART drug		
INSTI	Reference	–
PI	75.418	25.568, 125.268
NNRTI	28.712	−25.823, 83.247
Body mass index, kg/m^2		
<25	Reference	–
≥25	60.026	11.930, 108.122
Baseline triglyceride, mg/dl		
<160	Reference	–
≥160	27.535	−15.789, 70.859

Abbreviations: INSTI, integrase inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor.

assess the association between PI use and lipodystrophy. HBV coinfection has been shown to lower serum adiponectin levels but does not affect serum total cholesterol and triglyceride levels.[10,17] In the present study, neither HBV nor HCV coinfection status was associated with a change in serum total cholesterol or triglyceride levels. A study in a HCV–HIV coinfected population suggested that participants harbouring the SNP +45 G allele (G/G or G/T) have lower serum total cholesterol levels than those harbouring T/T,[18] but we were unable to confirm these results due to the low number (five) of HCV–HIV coinfected patients enrolled in our study.

Several studies have indicated that SNP +45 and SNP +276 affect serum adiponectin levels in non-HIV-1-infected subjects. The major G allele of SNP +276 was associated with lower serum adiponectin levels in a study from Spain,[19] and reports from Korea[20] and Finland,[21] and studies conducted in Italian Caucasian[7] and African American[22] populations, have shown that the minor T allele is associated with high serum adiponectin levels. A study in an obese subgroup of a non-HIV-1-infected Japanese population indicated that the greater the number of G alleles a subject has in the SNP +276 location, the lower their serum adiponectin levels; in addition, this study found that the SNP +276 T allele prevents an increase in serum triglyceride levels.[9] We were unable to confirm these results in the present study because we enrolled only HIV-1-infected and ART-naïve Japanese subjects.

Few studies have investigated the associations between *ADIPOQ* SNPs and serum lipid levels in HIV-1-infected patients. Caucasian HIV-1-infected patients with the SNP +276 G/T genotype are at greater risk of developing high triglyceride levels than those with the homozygous major allele SNP +276 G/G.[23] The role that SNP +45 plays in non-HIV-1-infected subjects or in HIV-1-infected people who have undergone ART remains unclear. A report from a non-HIV-1-infected Japanese population suggested that patients harbouring the major G allele are at increased risk of developing type 2 diabetes, but the authors concluded that there was no association between SNP +45 and serum adiponectin levels.[9] No SNP +45 genotype had a significant effect on serum total cholesterol or triglyceride levels in the present study. The serum triglyceride level after ART initiation was higher in those with the SNP +45 G/G genotype than in those with SNP +45 G/T or T/T, but this finding was not statistically significant.

The present study had several limitations. The study population included only five female participants, therefore it was impossible to evaluate the association between sex and serum lipid levels. This limitation is in part due to the low prevalence of HIV-1 infection in Japan and the fact that most HIV-1-infected persons in Japan are homosexual men.[24] The American Heart Association has suggested that sex may affect fat accumulation, but the association between sex and dyslipidaemia in HIV-1-infected patients remains unclear.[5] Our limited study population also made it difficult to analyse the effects of other *ADIPOQ* SNPs such as SNP −11379 and SNP −11365, which are known to affect serum adiponectin levels in HIV-1-infected patients.[25] It has been reported that six major haplotypes containing −11379, −11365, +45 and +276 have linkage disequilibrium in non-HIV-1-infected Italian subjects.[7] Further, larger-scale studies will allow a more detailed examination of the influence of these SNPs in Japanese HIV-1-infected patients. Although low serum adiponectin levels are known to be associated with lipodystrophy caused by long term ART,[23,26] serum adiponectin levels are not widely measured in daily outpatient care in Japan. We therefore chose to examine the association between SNP genotype and serum lipid level based only on data that are commonly

collected in daily care. Finally, because our observation period covered only the 4 months before and after ART initiation, long-term observational studies are needed to further clarify the association between SNP genotype, serum lipid level and individual differences in patients.

Declaration of conflicting interest

The authors declare that there are no conflicts of interest.

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