LIPID PROFILES OF THAI ADULT HIV-INFECTED PATIENTS RECEIVING PROTEASE INHIBITORS

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Abstract. Dyslipidemia is a common metabolic complication among HIV-infected patients who receive protease inhibitor (PI)-based antiretroviral therapy (ART). In order to assess the prevalence of lipid abnormalities and related factors, a cross-sectional analytic study of the lipid profiles of 170 Thai adult HIV-infected patients receiving PI-containing HAART who attended the HIV-clinic, King Chulalongkorn Memorial Hospital, Bangkok, Thailand between January and August 2005 was conducted. Studied subjects had a median age of 40 years with a median duration of taking PIs of 22.1 months. The mean serum total cholesterol (TC), high density lipoprotein cholesterol (HDL-c), low density lipoprotein cholesterol (LDL-c), and triglyceride (TG) levels were 259.7, 43.7, 135.2, and 506.8 mg/dl, respectively, and the mean TC:HDL-c ratio = 6.4. According to the US National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines, high TC, low HDL-c, high TC:HDL-c ratio, high LDL-c, and high TG were found in 52.4, 36.5, 18.8, 44.1, and 42.9%, respectively. Seventy-five subjects (44.1%) were taking lipid-lowering drugs. Only 54 subjects (31.8%) had baseline serum lipid profiles tested before beginning PI. There was statistically significant association between group of PI with serum TC and TG. Subjects taking double boosted and single boosted PI had significantly higher serum TC and TG levels than unboosted PI. Males had significantly higher serum TG levels, while females had significantly higher serum HDL-c levels. Age was significantly associated with serum TC, LDL-c levels, and TC:HDL-c ratios. Serum TC and LDL-c levels were also significantly higher in subjects taking efavirenz.

INTRODUCTION

Dyslipidemia is a common problem affecting HIV-infected patients who receive antiretroviral therapy (ART) (Dube *et al,* 2003). Although, abnormalities of lipid metabolism were described before the advent of highly active antiretroviral therapy (HAART), use of protease inhibitors (PI) has been associated with dyslipidemia which is more common and more severe (Feingold *et al,* 1993; Carr *et al,* 1998; Henry *et al,* 1998; Periad *et al,* 1999; Penzak and Chuck, 2000). These drugs have been associated with a syndrome of fat redistribution, insulin resistance, and hyperlipidemia. A study of 133 PI recipients at an HIV clinic in the United States found that 47% had lipid abnormalities that met the 1994 National Cholesterol Education Program (NCEP) intervention criteria (National Cholesterol Education Program, 1994). In a Swiss Cohort study, hypercholesterolemia and hypertriglyceridemia were 1.7-2.3 times more common among individuals receiving HAART that contained a PI (Fellay *et al,* 2001). Elevations in serum total cholesterol (TC) and triglyceride (TG) levels, along with dyslipidemia that typically occurs in patients with HIV infection, may predispose

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patients to complications such as premature atherosclerosis, particularly coronary heart disease, and pancreatitis (Penzak and Chuck, 2002; Dube *et al,* 2003). The Data Collection on Adverse Events of Anti-HIV Drugs Study reported a 26% increase in the risk of myocardial infarction per year of exposure to PI-containing ART among HIV-infected patients (Penzak and Chuck, 2002; Calza *et al,* 2004).

In Thailand, PI have been used for the treatment of HIV infection since 1996. However, there have been few studies addressing the frequency and determinants of dyslipidemia among HIV-infected patients taking PIs. In order to assess the prevalence of lipid abnormalities and related factors in this group, we conducted a study of lipid profiles among Thai adult HIV-infected patients receiving PI-containing HAART.

MATERIALS AND METHODS

Studied subjects were selected from adult HIV-infected clients who attended the HIV-clinic, King Chulalongkorn Memorial Hospital, Bangkok, Thailand between January and August 2005. King Chulalongkorn Memorial Hospital is a 2,000-bed public university hospital, which serves mainly the lower and middle class population of Bangkok. Inclusion criteria were age ≥15 years and having taken PI-containing ART for at least 6 months. Exclusion criteria included a previous diagnosis of diabetes mellitus, hypothyroidism, nephrotic syndrome, chronic or acute renal failure, chronic or acute pancreatitis, Cushing syndrome, alcoholism, or concomitant therapy with corticosteroid, diuretics, or thyroid preparations. On enrollment, the following baseline data were collected: sociodemographic characteristics, medical history, history of possible route of HIV acquisition, history of current and prior ART, duration of taking current and previous PI (for PI-experienced individuals), plasma HIV RNA level, CD4+ lymphocyte count and a history of other concomitant medications, including lipid lowering drugs. We retrospectively collected data of serum TC, TG, high-density lipoprotein cholesterol (HDL-c), and low-density lipoprotein cholesterol (LDL-c) levels both before and while taking PI. In cases where serum lipid profiles were done more than one month prior to enrollment, repeated blood testing with overnight fasting serum lipid profiles were done as close to the enrollment date as possible.

Fasting serum total cholesterol and triglyceride levels were measured by enzymatic colorimetric test. For serum total cholesterol, the measurement was based on the determination of $\triangle^4$ – cholesterone after enzymatic cleavage of the cholesterol ester by cholesterase, conversion of cholesterol by cholesterol oxidase, and subsequent measurement by Trinder reaction of hydrogen peroxide formed (Roche Diagnostics, Bangkok,– Thailand). For measuring serum triglycerides, the method was based on the work by Wahlefeld using a lipoprotein lipase from microorganisms for the rapid and complete hydrolysis of triglycerides to glycerol followed by oxidation to dihydroxyacetone phosphate and hydrogen peroxide. The hydrogen peroxide produced then reacts with 4-aminophenazone and 4-chloroquenol under the catalytic action of peroxidase to form a red dyestuff (Trinder endpoint reaction) (Roche Diagnostics, Bangkok, Thailand). Direct measurement of HDL-c and LDL-c were done by homogeneous enzymatic colorimetric test using PEG-modified enzymes and dextran sulfate. When cholesterol esterase and oxidase enzymes are modified by PEG, they showed selective catalytic activities toward lipoprotein fractions, with the reactivity increasing in order: LDL<VLDL ≅ chylomicrons < HDL.

Each participant was classified as having dyslipidemia if serum lipid levels were above (or, for HDL-c, below) the pre-specified threshold levels. These threshold levels were based on the cutoff values recom-

mended by the US National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) Guidelines (Executive Summary of The Third Report of The National Cholesterol Education Program, 2001), as follows: hypercholesterolemia, serum TC levels ≥240 mg/dl; low HDL-c, serum HDL-c levels <40 mg/dl; high TC:HDL-c ratio, serum TC:HDL-c ratio ≥4.5; high LDL-c, serum LDL-c levels ≥160 mg/dl. Hypertriglyceridemia was defined by serum fasting TG levels ≥200 mg/dl.

Patients with newly diagnosed dyslipidemia were counseled about risk for developing complications from dyslipidemia and the benefit of adjusting serum lipids by diet modification and exercise. Individuals, for whom lipid-lowering agents were indicated, were referred to an endocrinologist for proper treatment. Patients who were taking lipid-lowering drugs were given counseling and informed of their serum lipid levels and the importance of adherence and follow-up with their physicians.

For statistical assessment, descriptive statistics regarding sociodemographic, epidemiological, clinical, and laboratory values were evaluated. In order to examine the association between the independent variables and lipid profiles, univariate analysis was carried out by Student's *t*-test or one-way analysis of variance for quantitative variables, and chi-square test, or Fisher exact test for qualitative variables, with significant level placed at p-value ≤0.05. Multivariate analysis was conducted using a linear regression. Independent variables that were significantly associated with serum lipid profiles on univariate analysis at a p-value ≤0.05 and variables that were biomedically associated with the outcome were included in the multivariate models. A forward regression approach was used to select variables entered into the full model. Variables were retained in the linear regression model with significant values ≤0.05.

RESULTS

A total of 182 patients were enrolled in the study and 12 (6.6%) were excluded from the final evaluation due to the presence of diabetes mellitus before taking PIs (6), concurrent treatment with corticosteroids (2), thyroid hormone (2), or thiazide diuretics (2).

Sociodemographic, epidemiological, clinical, and laboratory characteristics of the 170 evaluable subjects are summarized in Table 1. The median age was 40 years and 127 subjects (74.7%) were male. One hundred and

Table 1
Baseline characteristics of 170 HIV-infected patients receiving PI-containing HAART.

Characteristic	Value
Age, median (IQR), years	40 (36-4)
Male (%)	127 (74.7)
Route of HIV transmission	
Heterosexual	154 (90.6)
Homosexual	14 (8.2)
Inravenous drug use	2 (1.2)
Patients naive to all ARV (%)	13 (7.6)
Patients naive to PI (%)	140 (82.4)
Duration of exposure to current PI at the time of recent lipid profile testing, median (IQR), month	22.1 (11.7-40.3)
CD4 +T lymphocyte count at time of enrollment, median (IQR) cells/mm^3	372 (260-560)
HIV RNA load <400 copies/ml at time of enrollment (%)	151 (88.8)

ARV=antiretroviral drug; HIV=human immunodeficiency virus; IQR=interquartile range

Table 2
Type of antiretroviral drugs being taken among 170 subjects.

Type of antiretroviral drugs taken	Number (%)
PIs	170 (100)
Single boosted PI	122 (71.8)
Indinavir/ritonavir	83
Lopinavir/ritonavir	28
Saquinavir/ritonavir	7
Unboosted PI	32 (18.8)
Nelfinavir	24
Indinavir	5
Ritonavir	2
Saquinavir	1
Double boosted PI	16 (9.4)
Indinavir+Lopinavir/ritonavir	9
Saquinavir+Lopinavir/ritonavir	6
Saquinavir+Indinavir/ritonavir	1
NRTIs	133 (78.2)
Lamivudine	99
Didanosine	53
Stavudine	52
Zidovudine	32
Abacavir	7
NNRTIs	41 (24.1)
Efavirenz	32
Nevirapine	9

NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor

fifty-four (90.6%) were heterosexual. Most subjects (82.4%) were naive to PIs and 7.6% were naive to all ART. The median duration of current PI-containing ART was 22.1 months. At the time of enrollment, the median CD4+ lymphocyte count was 372 cells/mm^3 and 151 of 170 subjects (88.8%) had plasma HIV-RNA less than 400 copies/mm^3 . We found that 122 (71.8%), 32 (18.8%), and 16 (9.4%) were taking single boosted PI, unboosted PI, and double boosted PI, respectively. The types of PIs are shown in Table 2.

All serum lipid profiles were normally distributed. The mean serum lipid profiles of the participants at the time of enrollment were as follows: TC = 235.5 mg/dl (SD = 54.1), HDL-c = 44.3 mg/dl (SD = 11.5) , TC:HDL-c ratio = 5.7 (SD = 1.9), LDL-c = 129.1 mg/dl (SD = 46.2), and TG = 326.9 mg/dl (SD = 331.32). According to the cutoff values for high risk for coronary artery disease recommended in the US NCEP-ATP III guidelines, high TC, high LDL-c, high TG, low HDL-c, and high TC:HDL-c ratio, were found in 52.4, 44.1, 42.9, 36.5, and 18.8%, respectively.

Only 54 of 170 (31.8%) had baseline serum lipid profiles before beginning PI-containing ART. Of these subjects, high TC, high LDL-c, high TG, low HDL-c, high TC: HDL-c ratio, were found in 27.8, 49.0, 31.5, 68, and 17.6%, respectively. Compared with the lipid profiles before beginning PI, there were statistically significant increases in mean serum TC, LDL-c, TG and TC:HDL-c ratio. For serum HDL-c, there was a slight increase in mean HDL-c after taking PI but the difference was not statistically significant (Table 3).

On univariate analysis, serum TC and TG were significantly associated with the group of PI. The highest serum TC and TG levels were seen in subjects receiving double boosted PI, followed by single boosted PI and unboosted PI, respectively (Table 4). Because there was small numbers of subjects in several subgroups of PI, we did not find on association between the type of PI and serum lipid profiles. Regarding other variables, serum TC was significantly associated with age and history of previous treatment with PI. Serum TG was significantly associated with gender and history of previous treatment with PI. Serum HDL-c was significantly associated with gender while TC:HDL-c ratio and serum LDL-c were significantly associated with age.

On multivariate analysis, we put group of PI, age, gender, duration of taking PI, CD4 count at time of enrollment, HIV-RNA <400 copies/ml, whether subject was taking stavudine, and whether subject was taking efavirenz into the regression model. The re-

Table 3
Serum lipid profiles before and after taking PI among 54 HIV-infected subjects.

Serum lipid profiles	Before taking PI	After taking PI	Difference between after *vs* before taking PI	95% CI of difference	p-value
TC, mg/dl	213.2	260.6	47.4	26.0 -68.8	<0.001
TG, mg/dl	278.1	462.2	184.1	58.4 -309.8	0.005
HDL-c, mg/dl	41.8	45.1	3.3	-68.62	0.066
TC:HDL-c ratio	5.4	6.1	0.7	0.1 -1.3	0.024
LDL-c, mg/dl	119.3	144.8	25.5	5.4 -45.5	0.014

HDL-c=high-density lipoprotein cholesterol; LDL-c=low density lipoprotein cholesterol; PI=protease inhibitor; TC=total cholesterol; TG=triglyceride

Table 4
Mean serum lipid profiles (standard deviation) in 170 subjects according to group and type of PI.

Group and type of PI	N	TC	TG	HDL-c	TC:HDL-c	LDL-c
Unboosted PI	32	236.9 (57.5)	280.4 (189.2)	43.9 (11.6)	5.7 (1.6)	134.3 (55.6)
Single boosted PI	122	262.2 (95.9)	507.6 (226.6)	43.3 (12.3)	6.3 (2.2)	127.4 (57.6)
Double boosted PI	16	292.9 (96.3)	1,005.1 (869.5)	45.7 (10.8)	6.8 (2.6)	147.5 (98.0)
p-value	170	0.047	0.001	0.760	0.103	0.728

TC = Total cholesterol; TG = Triglyceride; HDL-c = High density lipoprotein cholesterol; LDL-c = Low density lipoprotein cholesterol

sults showed that group of PI, age, gender, and whether subject was taking efavirenz were significant predictors of serum lipid profiles in the model (Table 5). We found a significant association between group of PI and serum TC and TG. Subjects taking double boosted and single boosted PI had significantly higher serum TC and TG levels than unboosted PI. Other lipid profiles were not associated with group of PI. Males had significantly higher serum TG levels while females had significantly higher serum HDL-c levels. Age was significantly associated with serum TC levels, TC:HDL-c ratio, and LDL-c levels. We also found that serum TC and LDL-c levels were significantly higher in subjects taking efavirenz.

Seventy-five subjects (44.1%) were taking lipid-lowering drugs at the time of enrollment. Most (81.3%) had taken a single drug, the most common was gemfibrozil (52.0%). Fourteen subjects (18.7%) had taken a combination of a fibrate and a statin. The type of hypolipemic drugs is shown in Table 6. Four subjects (5.3%) were taking simvastatin concomitantly with PI. We found that 43.8, 42.6, and 56.3% of subjects in the unboosted PI, single boosted PI, and double boosted PI groups, respectively, were taking lipid-lowering drugs, the difference was not statistically significant (p-value >0.05).

DISCUSSION

In our study, dyslipidemia was common in HIV-infected patients receiving a PI-containing ART. Hypertriglyceridemia was the most prevalent and found in nearly three-fourths of patients. Hypercholesterolemia was the second most common dyslipidemia affecting more than half of studied subjects. These findings are consistent with previous studies which showed that the prevalence of dyslipidemia in patients receiving PI-containing ART ranged

Table 5
Factors associated with serum lipid profiles in 170 subjects taking PI by multiple linear regression.

Lipid profile	Boosted PI		Double boosted PI		Age		Sex		Efavirenz	
	β	p-value	β	p-value	β	p-value	β	p-value	β	p-value
TC	12.90	0.044	57.96	0.002	1.98	0.006	7.79	0.584	51.51	<0.001
TG	197.97	0.032	555.09	<0.001	7.27	0.112	-165.37	0.034	9.66	0.916
HDL-c	-1.82	0.515	-0.80	0.853	-0.215	0.116	6.50	0.006	5.01	0.060
TC/HDL-c	0.87	0.159	1.89	0.059	0.10	0.001	-0.636	0.228	0.93	0.133
LDL-c	6.57	0.753	8.59	0.788	3.59	0.001	18.04	0.307	68.75	0.001

β=coefficients determine the change in each parameter compared to the reference group or per unit change, *ie*, boosted PI compared to unboosted PI=double boosted PI compared to unboosted PI; sex=compared female to male; age=change per 1 year increase in age; efavirenz compared to non-efavirenz containing antiretroviral regimens.

Table 6
Type of current lipid-lowering drugs administered among 75 subjects.

Hypolipemic drug	Number (%)
Single drug	61 (81.3)
Gemfibrozil	39 (52.0)
Fenofibrate	19 (25.3)
Simvastatin	2 (2.7)
Bezafibrate	1 (1.3)
Combined drug	14 (18.7)
Atorvastatin + Fenofibrate	4 (5.3)
Atorvastatin + Gemfibrozil	4 (5.3)
Pravastatin + Fenofibrate	2 (2.7)
Pravastatin + Gemfibrozil	2 (2.7)
Simvastatin + Gemfibrozil	2 (2.7)

from 28-80%, of which the majority were hypertriglyceridemia (40-90%) and hypercholesterolemia (10-50%) (Behren *et al,* 1999; Carr *et al,* 1999; Roberts *et al,* 1999; Vigouroux *et al,* 1999; Tsiodras *et al,* 2000).

Of subjects with available baseline serum lipid profiles before receiving PIs, we demonstrated significant increases in serum TG, TC, LDL levels and TC/HDL ratio. The increase in serum TG levels was more pronounced than the other lipid abnormalities. We also found a high prevalence of pretreatment baseline dyslipidemia among HIV-infected subjects. Several studies showed that dyslipidemia is common in HIV-infected patients even before receiving HAART (Grunfeld *et al,* 1991; Feingold *et al,* 1993; Shor-Posner *et al,* 1993; Dube *et al,* 2003). Elevated serum TG (Grunfeld *et al,* 1991) and decreased serum TC (Shor-Posner *et al,* 2003) are associated with advanced HIV disease. They also have lower levels of serum HDL-c and LDL-c, decreased TG clearance and a predominance of small dense LDL particles. However, because most of our subjects were ART-experienced, other antiretroviral drugs, including NRTIs, particularly stavudine, and/or NNRTIs might have contributed to the high prevalence of baseline dyslipidemia. Only one-third of our subjects had baseline lipid profile testing before starting PIs. This emphasizes the importance of educating physicians to test patients' baseline serum lipid profiles before administration of ART, particularly PIs.

Our results suggest that PI is associated with elevations in serum TC and TG levels. TC and TG levels were significantly higher in subjects receiving boosted PI and the double boosted PI group had significantly higher serum TC and TG levels than single boosted PI.

A number of studies have reported differences in serum lipid profiles among HIV-infected patients receiving different PI and suggest that RTV, whether given alone or as boosted PI, may induce more severe dyslipidemia than others (Sullivan and Nelson, 1997; Sullivan *et al*, 1998; Periad *et al,* 1999; Thiebaut *et al,* 2000). The results of our study confirmed these findings in regard to serum TC and TG in patients who took RTV-boosted or double boosted PI. Age also had a significantly positive association with serum TC, LDL-c levels, and TC/LHDL-c ratio. Males had significantly higher serum TG and lower serum HDL-c levels than females. These were consistent with several previous studies (Penzak and Chuck, 2000; Tsiodras *et al,* 2000; Mooser and Carr, 2001; Calza *et al,* 2003). In our study, EFV was another significant determinants of higher serum TC and LDL-c levels. EFV given with NRTI has been shown to raise serum TC and LDL-c levels within 4-8 weeks of therapy and subjects who received both EFV and PI, particularly IDV, experienced the greatest increase in serum TC levels (Tashima *et al,* 1999; Gerber *et al,* 2005; Young *et al,* 2005). Therefore, in patients receiving both EFV and PI, continuous monitoring of lipid profiles is suggested. Nearly half our subjects had taken lipid-lowering drugs at the time of enrollment. Currently, statins are considered first-line agents for the treatment of hypercholesterolemia (Dube *et al,* 2003). However, they are variously metabolized by cytochrome P450 3A4 and have significant interactions with PI, which may lead to elevated plasma levels of statins and increased risk for rhabdomyolysis and liver toxicity (Vickers *et al,* 1990; Vyas *et al,* 1990; Smith *et al,* 1991; Lennernas and Fager, 1997; Prueksaritanont *et al,* 1997; Fichtenbaum and Gerber, 2002; Hare *et al,* 2002; Williams and Feely, 2002; Lennernas, 2003). Therefore, pravastatin or fluvastatin, which are not significantly metabolized by CYP 3A4, are recommended as first-line therapy for hypercholesterolemia in PI-treated patients. Simvastatin and lovastatin should be avoided and atorvastatin should be used with caution (Dube *et al,* 2002). For hypertriglyceridemia, fibrates are considered the cornerstone of drug therapy and do not show clinically significant drug-drug interaction with PI (Calza *et al,* 2003). However, concomitant use of fibrates and statins may increase the risk of rhabdomyolysis and should be avoided (Calza *et al,* 2002; Mastroianni *et al,* 2002). In our study, 15-20% of subjects had been given simvastatin, atorvastatin or a combination of fibrates and statins concomitantly with PI. Therefore, the issue of drug-drug interactions must be further emphasized to physicians who provide care for HIV-infected patients.

Our study had some limitations. First, the analysis is based on data collected cross-sectionally and retrospectively. Treatment allocation is not random, as a consequence, subjects in various treatment groups of PI may differ in several factors apart from PI. Though we used multivariate analysis to adjust for the known confounding variables, we could not control the effect from other unknown variables, for example, patient behavior modification to control dyslipidemia after knowing their serum lipid profiles and compliance to PI which might affect the serum lipid profiles. Second, though we reported the associations between PI and serum lipid profiles, the cross-sectional nature of the present study may prevent us from establishing a causal association between PI and dyslipidemia. In particular, because the information on pretreatment serum lipid levels is unavailable for the majority of patients, we were unable to exclude the possibility that dyslipidemia occurred before exposure to PI. Third, though we emphasized collecting the blood for lipid profile testing after an overnight fast, some values of lipid profile were collected retrospectively, so not all blood samples were obtained after an overnight fast.

In summary, we report the high prevalence

of dyslipidemia, particularly hypertriglyceridemia and hypercholesterolemia, in HIV-infected patients receiving PI-containing ART. Group of PI, age, gender, and EFV were significantly associated with serum lipid profiles. The majority of HIV-infected patients are administered PI without pretreatment lipid profile testing. Administration of simvastatin for the treatment of dyslipidemia in patients receiving PIs is still encountered. Therefore, the importance of baseline and subsequent serum lipid profile testing in patients receiving PIs and drug-drug interaction should be emphasized to physicians who provide care for HIV-infected patients.

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REFERENCES

Behrens G, Dejam A, Schmidt H, *et al*. Impaired glucose tolerance, beta cell function and lipid metabolism in HIV patients under treatment with protease inhibitors. *AIDS* 1999; 13: F63-70.

Calza L, Manfredi R, Chiodo F. Dyslipidaemia associated with antiretroviral therapy in HIV-infected patients. *J Antimicrob Chemother* 2004; 53: 10-4.

Calza L, Manfredi R, Chiodo F. Statins and fibrates for the treatment of hyperlipidaemia in HIV-infected patients receiving HAART. *AIDS* 2003; 17: 851-9.

Calza L, Manfredi R, Chiodo F. Use of fibrates in the management of hyperlipidemia in HIV-infected patients receiving HAART. *Infection* 2002; 30: 26-31.

Carr A, Samaras K, Chisholm D, Cooper D. Pathogenesis of HIV-1-protease inhibitor-associated peripheral lipodystrophy, hyperlipidaemia, and insulin resistance. *Lancet* 1998; 351:1881-3.

Carr A, Samaras K, Thorisdottir A, Kaufmann G, Chisholm D, Cooper D. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet* 1999; 353: 2093-9.

Dube M, Stein J, Aberg J, *et al*. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy: recommendations of the HIV Medical Association of the Infectious Disease Society of America and the Adult AIDS Clinical Trials Group. *Clin Infect Dis* 2003; 37: 613-27.

Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001; 285: 2486-97.

Feingold K, Krauss R, Pang M, Doerrler W, Jensen P, Grunfeld C. The hypertriglyceridemia of acquired immunodeficiency syndrome is associated with an increased prevalence of low density lipoprotein subclass pattern B. *J Clin Endocrinol Metab* 1993; 76: 1423-7.

Fellay K, Ledergerber B, *et al*. Prevalence of adverse events associated with potent antiretroviral treatment: Swiss HIV Cohort Study. *Lancet* 2001; 358: 1322-7.

Fichtenbaum CJ, Gerber JG. Interactions between antiretroviral drugs and drugs used for the therapy of the metabolic complications encountered during HIV infection. *Clin Pharmacokinet* 2002; 41: 1195-211.

Gerber JG, Rosenkranz S, Fichtenbaum C, *et al*. Effect of efavirenz on the pharmacokinetics of simvastatin, atorvastatin, and pravastatin: results of AIDS Clinical Trials Group 5108 Study. *J Acquir Immune Defic Syndr* 2005; 39: 307-12.

Grunfeld C, Kotler DP, Shigenaga JK, *et al*. Circulating Interferon-alpha levels and hypertriglyceridemia in the acquired immunodeficiency syndrome. *Am J Med* 1991; 90: 154-62.

Hare CB, Vu MP, Grunfeld C, Lampiris H. Simvastatin-nelfinavir interaction implicated in rhabdomyolysis and death. *Clin Infect Dis* 2002; 35: e111-2.

Henry K, Melroe H, Huebsch J, *et al*. Severe premature coronary artery disease with protease in-

hibitors. *Lancet* 1998; 351: 1328.

Lennernas H. Clinical pharmacokinetics of atorvastatin. *Clin Pharmacokinet* 2003; 42: 1141-60.

Lennernas H, Fager G. Pharmacodynamics and pharmacokinetics of the HMG-CoA reductase inhibitors. Similarities and differences. *Clin Pharmacokinet* 1997; 32: 403-25.

Mastroianni C, d'Ettorre G, Forcina G, *et al*. Rhabdomyolysis after cerivastatin-gemfibrozil therapy in an HIV-infected patient with protease inhibitor-related hyperlipidemia. *AIDS* 2001; 15: 820-1.

Mooser V, Carr A. Antiretroviral therapy-associated hyperlipidaemia in HIV disease. *Curr Opin Lipidol* 2001; 12:313-9.

National Cholesterol Education Program. Second Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel II). *Circulation* 1994; 89: 1333-445.

Penzak S, Chuck S. Hyperlipidemia associated with HIV protease inhibitor use: pathophysiology, prevalence, risk factors and treatment. *Scand J Infect Dis* 2000; 32: 111-23.

Penzak S, Chuck S. Management of protease inhibitor-associated hyperlipidemia. *Am J Cardiovasc Drugs* 2002; 2: 91-106.

Periard D, Telenti A, Sudre P, *et al*. Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors. The Swiss HIV Cohort Study. *Circulation* 1999; 100: 700-5.

Prueksaritanont T, Gorham L, Ma B, *et al*. *In vitro* metabolism of simvastatin in humans [SBT]identification of metabolizing enzymes and effect of the drug on hepatic P450s. *Drug Metab Dispos* 1997; 25: 1191-9.

Roberts A, Muesing R, Parenti D, *et al*. Alterations in serum levels of lipids and lipoproteins with indinavir therapy for human immunodeficiency virus-infected patients. *Clin Infect Dis* 1999; 29: 441-3.

Shor-Posner G, Basit A, Lu Y, *et al*. Hypocholesterolemia is associated with immune dysfunction in early human immunodeficiency virus-1 infection. *Am J Med* 1993; 94: 515-9.

Smith P, Eydelloth R, Grossman S, *et al*. HMG-CoA reductase inhibitor-induced myopathy in the rat: cyclosporine A interaction and mechanism studies. *J Pharmacol Exp Ther* 1991; 257: 1225-35.

Sullivan A, Feher M, Nelson M, Gazzard B. Marked hypertriglyceridaemia associated with ritonavir therapy. *AIDS* 1998; 12: 1393-4.

Sullivan A, Nelson M. Marked hyperlipidaemia on ritonavir therapy. *AIDS* 1997; 11: 938-9.

Tashima K, Stryker R, Skiest D, *et al*. Lipid profiles and clinical lipodystrophy in study 006 patients [Abstract 1304]. Washington, DC: 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1999.

Thiebaut R, Dabis F, Malvy D, Jacqmin-Gadda H, Mercie P, Valentin VD. Serum triglycerides, HIV infection, and highly active antiretroviral therapy, Aquitaine Cohort, France, 1996 to 1998. Groupe d'Epidemiologie Clinique du Sida en Aquitaine (GECSA). *J Acquir Immune Defic Syndr* 2000; 23: 261-5.

Tsiodras S, Mantzoros C, Hammer S, Samore M. Effects of protease inhibitors on hyperglycemia, hyperlipidemia, and lipodystrophy: a 5-year cohort study. *Arch Intern Med* 2000; 160: 2050-6.

Vickers S, Duncan CA, Vyas KP, *et al*. *In vitro* and *in vivo* biotransformation of simvastatin, an inhibitor of HMG CoA reductase. *Drug Metab Dispos* 1990; 18: 476-83.

Vigouroux C, Gharakhanian S, Salhi Y, *et al*. Diabetes, insulin resistance and dyslipidaemia in lipodystrophic HIV-infected patients on highly active antiretroviral therapy (HAART). *Diabetes Metab* 1999; 25: 225-32.

Vyas K, Kari P, Pitzenberger S. Regioselectivity and stereoselectivity in the metabolism of HMG-CoA reductase inhibitors. *Biochem Biophys Res Commun* 1990; 166: 1155-62.

Williams D, Feely J. Pharmacokinetic-pharmacodynamic drug interactions with HMG-CoA reductase inhibitors. *Clin Pharmacokinet* 2002; 41: 343-70.

Young J, Weber R, Rickenbach M, *et al*. Lipid profiles for antiretroviral-naive patients starting PI- and NNRTI-based therapy in the Swiss HIV cohort study. *Antivir Ther* 2005; 10: 585-91.