

# Effects of Protease Inhibitors on Hyperglycemia, Hyperlipidemia, and Lipodystrophy

## A 5-Year Cohort Study

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**Background:** Although human immunodeficiency virus (HIV)-related morbidity and mortality rates in patients with advanced HIV infection who are treated with combination antiretroviral drugs have declined, significant metabolic adverse effects associated with these regimens have been increasingly recognized. However, since data from patients studied before and after initiation of protease inhibitor (PI) therapy are scant, the true effect of PIs on these metabolic changes remains unknown.

**Objectives:** To examine temporal trends in serum glucose and lipid levels after initiation of PI therapy, to assess whether changes are independent of virological response and improvement in disease severity, and to determine risk factors associated with the development of hyperglycemia, hyperlipidemia, and lipodystrophy.

**Methods:** A 5-year historical cohort analysis in a population of 221 HIV-infected patients observed in the Infectious Diseases Clinic of a tertiary care center from October 1, 1993, through July 31, 1998. Clinical and laboratory data were retrieved from medical records and a computerized database. The main outcome measure was the incidence of hyperglycemia, hypercholesterolemia, hypertriglyceridemia, and lipodystrophy. Adjusted incidence rate ratios (IRRs) were estimated by means of Poisson regression. In addition, mixed regression analyses were performed to examine effects of PIs on serum lipid and glucose levels, modeled as continuous outcomes.

**Results:** The cumulative incidence of new-onset hyperglycemia, hypercholesterolemia, hypertriglyceridemia, and lipodystrophy was 5%, 24%, 19%, and 13%, respectively. Most of these events occurred after initiation of PI therapy. Protease inhibitors were independently associated with hyperglycemia (adjusted IRR, 5.0; 95% confidence interval [CI], 1.3-19.4), hypercholesterolemia (adjusted IRR, 2.8; 95% CI, 1.5-5.2), hypertriglyceridemia (adjusted IRR, 6.1; 95% CI, 3.1-11.7), and lipodystrophy (adjusted IRR, 5.1; 95% CI, 1.9-13.9). Anabolic steroids and psychotropic medications were also associated with lipodystrophy. Inclusion of potential intermediate variables (eg, virological suppression and increase in body weight) did not reduce the magnitude of the association with PIs. The association between hypertriglyceridemia and ritonavir was stronger than for other PIs (Wald test,  $P=.02$ ). In contrast, the incidence of hyperglycemia, hypercholesterolemia, and lipodystrophy did not vary significantly across different PIs. Longitudinal mixed models confirmed that serum lipid levels were more substantially affected by antiretroviral therapy, particularly PIs, than serum glucose levels. Similarly, controlling for surrogate markers did not abolish the strong association between PIs and increase in serum lipid levels.

**Conclusion:** We found an independent association between PI use and hyperglycemia, hyperlipidemia, and lipodystrophy that is not explained by the antiviral and therapeutic effect of PIs.

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**T**REATMENT OF human immunodeficiency virus type 1 (HIV-1) infection has evolved dramatically during the past 3 years. Combination therapy with protease inhibitors (PIs) leads to profound and sustained suppression of HIV-1 replication,<sup>1,2</sup> which in turn has resulted in declining HIV-related morbidity and mortality rates in patients with advanced HIV infection.<sup>3</sup> However, exposure to these agents recently has been associated with the development of

significant metabolic adverse effects such as hyperlipidemia, peripheral fat wasting, central adiposity, hyperglycemia, insulin resistance, and new-onset diabetes.<sup>4</sup> This spectrum of changes is now thought to be part of a new syndrome associated predominantly with PI use.<sup>5-8</sup> A recent cohort study, which followed up patients already treated with PIs for 21 months, revealed that hyperlipidemia and impaired glucose tolerance were common in PI-treated patients.<sup>6</sup> Nonetheless, there has been no systematic evaluation of

## PATIENTS AND METHODS

### STUDY PATIENTS

The 221 adult patients who fulfilled the following criteria were included in the study: laboratory documentation of HIV-1 infection, minimum of 6 months of follow-up, measurement of serum glucose levels at least twice during the follow-up period, and survival until November 1997 (initiation of data extraction). The primary rationale for these criteria was to ensure adequate follow-up and the availability of at least 2 data points for analysis. Although PI therapy was introduced in 1995, the study period encompassed 58 months to include a sufficient observation period before the use of PIs. Study entry was defined as October 1993 for patients who initiated routine care at Beth Israel Deaconess Medical Center before October 1, 1993. For patients who initiated routine care on or after October 1, 1993, study entry was defined as the month and year of the first visit. The end of follow-up was defined as the month and year of the last clinic visit before July 31, 1998.

### DATA COLLECTION

The following data elements were extracted from outpatient and inpatient medical records: age, sex, comorbidities or underlying diseases, family history, social history, alcohol and illicit drug use, results of serologic examination for hepatitis infection, vital signs, weight, height, and causes of inpatient admissions. These data had been systematically entered into medical records as part of structured visit notes. Dates of initiation and discontinuation of therapy with all prescribed medications were recorded. Particular attention was paid to antiretroviral therapy, medications potentially contributing to glucose intolerance or other metabolic disturbances (ie, megestrol acetate, pentamidine, didanosine, anabolic hormones, and synthetic steroids), and medications with known drug-drug interactions with PIs.

Inpatient and outpatient laboratory data were extracted from an electronic database maintained by the medical center and included the following items: levels of serum glucose, cholesterol, triglycerides, uric acid, alanine aminotransferase, aspartate aminotransferase, serum amylase, lipase, and plasma HIV RNA and CD4 cell count.

A single certified clinical laboratory performed all chemistry laboratory measurements under standardized conditions. For the purposes of the statistical analysis, results of serum glucose and lipid measurements were not differentiated on the basis of the time of blood draw or state of fasting. Results of most glucose tests were categorized as random. Baseline serum glucose and lipid levels were defined as the first laboratory test results after study entry.

### STATISTICAL ANALYSIS

#### Definitions of Outcomes

Two types of outcomes were examined: continuous and discrete. Continuous outcomes represented the serial measurements of glucose, cholesterol, and triglyceride levels in individual patients. Discrete outcomes were defined with the use of prespecified criteria. Since most glucose measurements were collected randomly, hyperglycemia was defined as 2 or more serum glucose values greater than 7.8

mmol/L (140 mg/dL) obtained during follow-up.<sup>9</sup> Diabetes was defined as a single random serum glucose value greater than 11.1 mmol/L (200 mg/dL).<sup>9</sup> Hypercholesterolemia and hypertriglyceridemia were defined as 1 or more serum cholesterol level above 6.2 mmol/L (240 mg/dL) and 1 or more serum triglyceride level above 5.6 mmol/L (500 mg/dL), respectively.<sup>10</sup> Development of lipodystrophy was defined as any significant change in the physical habitus or fat distribution noted by the patient or the clinician and documented in the chart. Lipodystrophy was characterized by at least 1 of the following: truncal obesity (central abdominal fat accumulation), focal fatty deposits, and peripheral fat wasting or atrophy (face, arms, buttocks, or legs). The study was reviewed and approved by the Institutional Review Board of Beth Israel Deaconess Medical Center.

### Analysis

Risk factors for hyperglycemia, hyperlipidemia, and lipodystrophy were assessed by means of Poisson regression to calculate crude and adjusted incidence rate ratios (IRRs). Kaplan-Meier curves were also constructed. Robust SEs were specified in the Poisson models. Continuous exposure variables were stratified into levels by means of predefined cut-off points. Only the first episode of hyperlipidemia and hyperglycemia during follow-up was included for analysis of these discrete outcomes. The primary exposure of interest was use of PIs. Protease inhibitors initially were tested as a single medication category, and then effects of potential confounders such as age, sex, obesity, medication use, amylase and lipase levels, and hepatitis C positivity (known association with glucose intolerance)<sup>11,12</sup> were examined. Interactions were tested by means of appropriate multiplicative terms. The effects of possible intermediate variables (eg, virological suppression, weight change) or confounders (eg, baseline CD4 cell count) were specifically examined. Variables that had substantial confounding effect (ie, >15% change in PI effect) or were significantly associated with the outcome were included in the final multivariable models. The effects of individual PIs were also compared in these models. Goodness-of-fit was tested by means of the  $\chi^2$  statistic.

Mixed regression models were fit to the serial measurements of cholesterol, triglyceride, and glucose levels. This is the appropriate statistical method for analysis of longitudinal data from individual subjects. We used PROC MIXED in SAS 7.0 (SAS Institute Inc, Cary, NC). The outcomes (glucose, triglyceride, and cholesterol levels) were log transformed to improve normality. Random effects were specified for intercept and 2-slope (linear trend) terms, one of which was the month after starting PI therapy and the other the month after starting combination NRTI therapy. Within-subject variance was fit with an autoregressive correlation structure. Fixed variables included the baseline laboratory test result, baseline CD4 cell count, PI therapy, combination NRTI therapy, month after starting PI therapy, and month after starting combination NRTI therapy. Models were constructed with and without surrogate markers such as change in weight, CD4 cell count, and change in HIV RNA to examine the hypothesis that these were intermediate variables that mediated the effect of PIs on the metabolic outcomes.

Statistical packages Stata 5.0 (Stata Corporation, College Station, Tex) and SAS 7.0 (SAS Institute Inc) were used for statistical analyses.

**Table 1. Characteristics of the Study Cohort\***

Characteristic	Finding
Demographic, mean (SE)	
Age, y	36.8 (0.5)
Baseline weight, kg	74.3 (1.0)
Height, cm	173 (1.5)
Baseline systolic blood pressure, mm Hg	124 (0.9)
Baseline diastolic blood pressure, mm Hg	78.7 (0.7)
Comorbidities, No. (%)	
Medical history of diabetes	8 (4)
History of hypertension	22 (10)
Tobacco history	134 (61)
History of alcohol use	169 (76)
History of illicit intravenous drug use	54 (24)
History of recreational drug use	115 (52)
Family history of diabetes	44 (20)
Family history of coronary artery disease	43 (19)
Positive hepatitis C serologic findings	44 (20)
Positive hepatitis B surface antigen	11 (5)
Positive hepatitis B surface antibodies	79 (36)
Positive hepatitis A serologic findings	22 (10)
Laboratory values at baseline, mean (SE)	
Glucose, mmol/L	5.6 (0.1)†
Cholesterol, mmol/L	4.4 (0.03)‡
Triglycerides, mmol/L	2.8 (0.1)§
Uric acid, $\mu\text{mol/L}$	350.9 (5.9)
AST, U/L	56.2 (1.4)
ALT, U/L	77.4 (3.8)
Amylase, U/L	79.2 (1.5)
CD4 cell count, $\times 10^9/\text{L}$	0.33 (0.003)
HIV RNA levels, log	4.25 (1)
Medication use, No. at baseline/ever	
Aerosolized pentamidine	7/31
Zidovudine	113/195
Stavudine	12/163
Zalcitabine	21/64
Didanosine	34/119
Insulin	4/6
Indinavir	0/115
Lamivudine	12/202
Megestrol acetate	3/35
Nelfinavir	0/81
Oral hypoglycemics	1/7
Pentamidine (intravenous)	1/8
Prednisone	6/28
Ritonavir	1/70
Saquinavir	0/102
Steroid cream	5/49
Steroids (anabolic)	2/58
Amprnavir	0/5

\*The study cohort included 221 patients (171 male [77%]). AST indicates aspartate aminotransferase; ALT, alanine aminotransferase; and HIV, human immunodeficiency virus.

†To obtain milligrams per deciliter, divide by 0.0555.

‡To obtain milligrams per deciliter, divide by 0.0259.

§To obtain milligrams per deciliter, divide by 0.01129.

||To obtain milligrams per deciliter, divide by 59.48.

¶To obtain cells per cubic millimeter, divide by 0.001.

PI-treated, HIV-infected patients before and after initiation of PI therapy. Previous studies have not performed mutual adjustment for potential cofounders, including other medication use such as nucleoside reverse-transcriptase inhibitor (NRTI) therapy, body weight changes, or improvement of the underlying HIV status. In addition, it is still unclear whether the components of the metabolic syndrome (glycemia, hypercholesterol-

emia, hypertriglyceridemia, and body habitus changes) represent an idiosyncratic reaction to PIs manifesting immediately after initiation of therapy or a long-term, progressive pharmacological consequence that evolves over time.

To examine temporal trends in glucose and lipid levels before and after initiation of PI therapy, we performed a historical cohort analysis of a population of 221 HIV-infected patients followed up in the Infectious Diseases Clinic of the Beth Israel Deaconess Medical Center, Boston, Mass, from October 1, 1993, through July 31, 1998. We assessed metabolic variables longitudinally before and after initiation of PI treatment, and we determined whether the observed metabolic alterations are independent of baseline metabolic alterations; changes in viral load, CD4 cell counts, or body weight; or other potential confounders.

## RESULTS

### DESCRIPTION OF THE COHORT

The clinical characteristics of the patients are depicted in **Table 1**. The study cohort consisted of 221 patients, of whom 171 (77%) were male. Fifty-four patients (24%) had a history of intravenous drug use. Mean time of follow-up was 45 months (SD, 12.9 months). A total of 176 patients received PIs, contributing 405 patient-years of follow-up before initiation of PI therapy and 298 patient-years of follow-up after initiation of PI therapy (**Table 2**). The 45 patients not exposed to PIs contributed 155 patient-years of follow-up time.

### HYPERCHOLESTEROLEMIA AND HYPERTRIGLYCERIDEMIA

Serum lipid levels (cholesterol and/or triglyceride) were measured a mean of 2.4 times per year per patient. The number of triglyceride and cholesterol level measurements obtained per year was stable through the course of the study. The average interval from study entry to the first recorded lipid and glucose levels was 4 months (interquartile range, 1-13 months).

Seven patients had baseline hypercholesterolemia and 9 patients had baseline hypertriglyceridemia. Six patients who had less than 2 cholesterol or triglyceride level measurements obtained during follow-up were excluded from the risk factor analysis for hyperlipidemia. Fifty patients had new onset of hypercholesterolemia during follow-up and 42 patients had new-onset hypertriglyceridemia (Table 2).

Protease inhibitor therapy was associated with a 2.8-fold higher incidence rate of hypercholesterolemia and 6-fold higher incidence rate of hypertriglyceridemia (adjusted in multivariable models, **Table 3**). For hypercholesterolemia, the effects of different PIs were similar. In contrast, the association between PI use and hypertriglyceridemia was significantly stronger for ritonavir than for the other PIs. Among the 176 patients who started PI therapy, ritonavir was associated with a 2.6-fold higher rate of development of hypertriglyceridemia ( $P=.02$ ), compared with other PIs.

**Table 2. Incidence Rates for Each of the Outcomes\***

Outcomes (No. of Cases)	Never Received PIs (n = 45)	Received PIs (n = 176)	
		Before PI Therapy	After PI Therapy Started
Total PY of follow-up	155	405	298
Hyperglycemia (n = 11)	1 (0.65)	2 (0.49)	8 (2.68)
Hypercholesterolemia (n = 50)	5 (3.23)	15 (3.70)	30 (10.07)
Hypertriglyceridemia (n = 42)	1 (0.65)	10 (2.47)	31 (10.40)
Lipodystrophy (n = 29)	4 (2.58)	1 (0.25)	24 (8.05)

\*PI indicates protease inhibitor; PY, person-years; and IR, incidence rate. Data are given as number of cases (IR) per 100 PY, after excluding baseline abnormal values.

**Table 3. Multivariate Poisson Regression Models for the Outcomes\***

Outcome	Risk Factor	IRR (95% CI)	P
Hyperglycemia	Age >40 y	4 (1.1-14.1)	.03
	Protease inhibitor use	5 (1.3-19.4)	.02
	Pentamidine	16.8 (3.2-87.7)	.001
Hypercholesterolemia	Baseline cholesterol >5.2 mmol/L†	3.8 (2.1-7.2)	<.001
	Age >40 y	1.9 (1.1-3.4)	.03
	Protease inhibitor use	2.8 (1.5-5.2)	.001
Hypertriglyceridemia	Non-protease inhibitor combination regimens	2.5 (1.2-5.2)	.02
	Baseline triglyceride level >3.4 mmol/L‡	2.9 (1.4-6.3)	.006
	Baseline hyperglycemia	3.4 (1.1-11)	.04
	Protease inhibitor use	6.1 (3.1-11.7)	<.001
Lipodystrophy	Age >40 y	3.5 (1.7-7.6)	.001
	Protease inhibitor use	5.1 (1.9-13.9)	.001
	Anabolic steroids	3.5 (1.6-7.8)	.002
	Psychotropic medications	2.9 (1.2-7.0)	.02
	Hyperlipidemia	2.3 (1.1-4.9)	.03

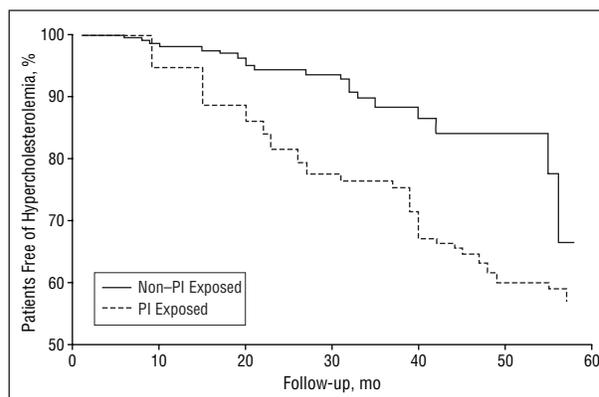
\*IRR indicates incidence rate ratios; CI, confidence interval. Models shown here include baseline covariates and medication exposures. Adjustment was performed for weight changes and CD4 cell counts.

†To obtain milligrams per deciliter, divide by 0.0259.

‡To obtain milligrams per deciliter, divide by 0.01129.

Elevations of cholesterol level were sustained, defined by 3 consecutive cholesterol levels of greater than 6.2 mmol/L (240 mg/dL) in 37 (74%) of the 50 patients with new onset of hypercholesterolemia. Elevations of serum triglyceride levels were sustained (3 consecutive levels >5.6 mmol/L [ $>500$  mg/dL]) in 25 patients (60%). No pancreatitis or other acute untoward effects of hypertriglyceridemia developed in any of these patients. Therapy with individual PI agents was modified or discontinued within 4 months of onset of hypertriglyceridemia in 10 patients.

Plasma HIV RNA levels and body weight were not predictors of hyperlipidemia or confounders of the association between PIs and elevated serum lipid levels. For hypercholesterolemia, the IRR associated with PIs, adjusted for maximum reduction in HIV RNA and change in weight, was still 2.8. For hypertriglyceridemia, the IRR associated with PIs, adjusted for maximum reduction in HIV RNA and change in weight, was still 6.2. Kaplan-Meier curves for the occurrence of hypercholesterolemia and hypertriglyceridemia are depicted in **Figure 1** and **Figure 2**. The risk of hyperlipidemia per unit of time (hazard rate) demonstrated a modest increasing trend during follow-up. The steep drop in the Kaplan-Meier curve for hypercholesterolemia in patients not receiving PIs late during follow-up reflected the occurrence of hypercho-

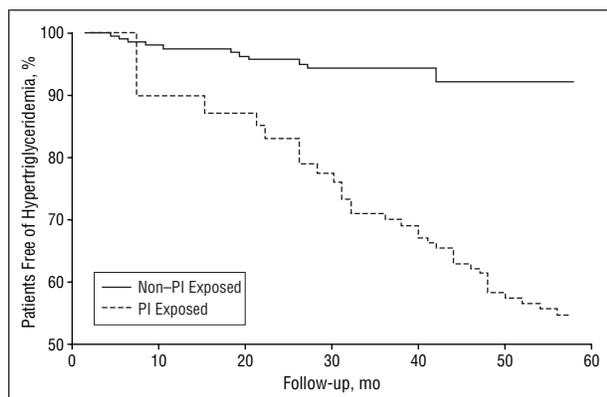


**Figure 1.** Kaplan-Meier curves for the occurrence of hypercholesterolemia in protease inhibitor (PI)-exposed vs -nonexposed patients. The graphic representation shows the proportion of patients in whom hypercholesterolemia does not develop.

lesterolemia in 2 of these patients when fewer than 15 remained under observation.

## HYPERGLYCEMIA

Serum glucose levels were measured a mean of 2.8 times per year in each patient. The number of glucose deter-



**Figure 2.** Kaplan-Meier curves for the occurrence of hypertriglyceridemia on protease inhibitor (PI)-exposed vs -nonexposed patients. The graphic representation shows the proportion of patients in whom hypertriglyceridemia does not develop.

minations per year increased from 2.4 in 1994 to 3.2 in 1997. Twenty-five patients (11%) had serum glucose levels above 7.8 mmol/L (140 mg/dL) on 2 or more occasions. Fourteen of these patients had a preexisting diagnosis of diabetes mellitus (n=8) or a baseline serum glucose level above 7.8 mmol/L (140 mg/dL). Thus 11 (5%) of 207 patients had new-onset hyperglycemia during follow-up. One patient in whom hyperglycemia developed never received PIs (Table 2). In the other 10 patients, the onset of hyperglycemia occurred after initiation of PI therapy in 8 and before initiation of PI therapy in 2. Five of these 11 patients had glucose levels of greater than 11.1 mmol/L (200 mg/dL), meeting criteria for the diagnosis of diabetes.

Protease inhibitor therapy was associated with a 5-fold increase in the incidence rate of hyperglycemia (adjusted IRR, 5.0; 95% confidence interval [CI], 1.3-19.4). Increased age and pentamidine use were other risk factors for hyperglycemia (Table 3). Effects on hyperglycemia did not vary among individual PIs. Transient elevations in glucose level were not uncommon: 27 other patients had a single glucose measure above 7.8 mmol/L (140 mg/dL) during follow-up.

Three of 11 patients with new-onset hyperglycemia were treated with oral hypoglycemic agents or insulin. None of the patients were hospitalized as a result of hyperglycemia. One patient had evidence of pancreatitis during the hyperglycemic episodes. The IRR for the development of hyperglycemia associated with PI treatment was 4.9 when adjusting for HIV RNA levels and weight, compared with 5.0 in models that did not include HIV RNA and weight.

### LIPODYSTROPHY

Lipodystrophy developed in 29 patients. Most patients with lipodystrophy exhibited truncal obesity. Lipodystrophy developed in 5 patients who were not receiving PIs and in the other 24 patients after initiation of PI therapy. Use of PIs was associated with a 5.1-fold increase in rate of development of lipodystrophy (adjusted IRR, 5.1; 95% CI, 1.9-13.9). Age, use of anabolic steroids, and use of psychotropic medications (includ-

**Table 4. Regression Models for Serum Triglyceride and Cholesterol Levels\***

Independent Variable	Triglycerides		Cholesterol	
	Exponentiated Coefficient	P	Exponentiated Coefficient	P
High baseline level†	1.987	<.001	1.379	<.001
PI therapy	1.103	.007	1.060	.02
Combination NRTI therapy (≥2 drugs)	1.015	.71	1.003	.83
Linear trend PI (month receiving therapy)	1.005	.18	1.005	<.001
Linear trend NRTI (month receiving therapy)	1.003	.24	1.003	<.001

\*PI indicates protease inhibitor; NRTI, nucleoside reverse transcriptase inhibitor. The exponentiated coefficient represents the fold change in cholesterol or triglyceride level associated with the independent variable. For continuous independent variables such as month receiving therapy, it represents the estimated change per unit or month. Adjustment for CD4 count and change in weight was performed.

†Indicates cholesterol level of greater than 5.2 mmol/L (200 mg/dL) or triglyceride level of greater than 3.4 mmol/L (300 mg/dL).

ing antidepressants and benzodiazepines) were associated with lipodystrophy (Table 3).

### LONGITUDINAL MODELS

We constructed longitudinal mixed models to further compare the effect of PIs and NRTIs on serum lipid and glucose levels and to broaden the focus beyond the group of patients with results in the abnormal range. Terms for baseline laboratory results were included, as were changes in CD4 cell count and weight. Serum glucose levels were not associated with PIs or with combination NRTIs (data not shown). Serum triglyceride levels demonstrated a statistically significant association with PIs but not with combination NRTIs (Table 4). Protease inhibitor therapy also was associated with increased cholesterol levels, but in contrast to triglyceride levels, the linear trend terms for PIs and combination NRTIs were statistically significant as well. Cholesterol level increased by an average of 0.47% per month of PI therapy and 0.29% per month of combination NRTI therapy. The effects of PI therapy on triglyceride and cholesterol levels were independent of changes in weight and CD4 cell count. Thus, models that did not include these terms yielded effect estimates for PI therapy that were similar to the estimates from models that included these terms. Likewise, there was no evidence of confounding by change in HIV RNA concentration. The mixed regression models strongly supported the observation that ritonavir had a greater effect on triglycerides than did other PIs. In a mixed model comparing the effect of individual PIs among patients treated with at least 1 PI, the effect of ritonavir ( $\beta$  coefficient, .36;  $P < .001$ ) was substantially higher than that of other PIs ( $\beta$  coefficient range, -.06 to .06;  $P = .34-.70$ ).

### COMMENT

The introduction of newer combinations of antiretroviral drugs, particularly PIs, has had an enormous posi-

tive impact on morbidity and survival in HIV-infected individuals in developed countries.<sup>3</sup> As a consequence, the long-term implications and health problems associated with the use of the newer regimens have gained in importance.

Previous studies of patients already receiving PIs demonstrated an association between PI use and metabolic abnormalities like hyperglycemia, hyperlipidemia, and lipodystrophy.<sup>6,13-19</sup>

However, there are a number of intrinsic obstacles to studying the pathophysiology and clinical manifestations and to understanding the long-term effects of PIs on glucose and lipid metabolism. One difficulty is in determining whether observed metabolic changes are attributable to direct actions of PIs or are secondary effects related to virological suppression, increased weight, or other factors. Another problem is the need to control for confounding effects of other medications and to account statistically for the interrelationships between different physiological variables. We conducted a historical cohort study on HIV-infected patients before and after introduction of PI therapy that encompassed the spectrum of laboratory and clinical variables associated with alterations in glucose and lipid metabolism.

Our major findings are as follows: (1) Protease inhibitors as a class of medication were independently associated with elevations in glucose, cholesterol, and triglyceride levels. The PI effects were not abolished by controlling for virological suppression, CD4 cell count, and increase in weight. Thus, to the extent that these variables are adequate surrogate markers for disease progression or therapeutic response, the development of the metabolic syndrome appears not to be related to improvement in HIV status. (2) The effects of PIs on triglyceride and cholesterol levels are much more frequent and substantial than changes in glucose levels. Different PIs appear to have varying effects on triglycerides, since the association between serum triglyceride levels and ritonavir use was stronger than that for other PIs. (3) Protease inhibitors may not be the only class of antiviral medication associated with hyperlipidemia. Combination NRTI therapy was associated with hypercholesterolemia and a statistically significant linear, temporal increase in serum cholesterol levels. However, the effect of NRTIs on cholesterol level was weaker than the effect of PIs. (4) Although lipodystrophy was strongly associated with PI use, it was also associated with the use of other classes of drugs such as anabolic steroids and psychotropic medications.

These results provide new information and extend previous observations on this subject. Initial case reports of the development of diabetes mellitus in patients receiving PIs resulted in the issuance of a Food and Drug Administration advisory in May 1997.<sup>4</sup> Subsequent reports typically of cross-sectional design attempted to confirm this association.<sup>13</sup> In a large, randomized, controlled trial that was not designed to look for hyperglycemia, there was no difference in the incidence of diabetes between the groups exposed and not exposed to PIs after 1 year of follow-up,<sup>1</sup> which is consistent with the low incidence of diabetes in our study. Our findings are in concordance with a recently pub-

lished cohort study of metabolic complications in patients with HIV-1 treated with PIs,<sup>6</sup> which showed presence of diabetes mellitus in 7% of PI recipients. From the studies reported so far, it appears that diabetes mellitus develops in a relatively small fraction of patients.

Other studies have also demonstrated high rates of hyperlipidemia associated with PI use, ranging from 12.9% to 80% for hypertriglyceridemia and from 8% to 42% for hypercholesterolemia.<sup>14-18</sup> Whether this will translate into higher rates of coronary artery disease is not yet clear. However, "premature" myocardial infarction has been reported in patients with HIV infection,<sup>20</sup> raising the concern that HIV-infected patients may exhibit an increased incidence of cardiovascular disease similar to that of patients with syndrome X.<sup>21</sup> An increased risk for coronary artery disease with total serum cholesterol levels in the high-normal range is well established, as well as a progressively increased risk with even higher cholesterol levels,<sup>22-25</sup> and has led to consensus statements that strategies for cholesterol reduction are warranted.<sup>26,27</sup>

Previous studies have reported variable rates of PI-induced lipodystrophy. One of the largest studies, which used a specifically designed questionnaire, reported an 83% prevalence rate of lipodystrophy.<sup>6</sup> However, severe lipodystrophy was only seen in 11% of the patients, which is very close to the 13% rate reported by patients and/or their physicians in our study. Similar lower prevalence rates have been seen by previously published studies.<sup>7,8</sup> A long-anticipated uniform definition of lipodystrophy<sup>6</sup> resulting in the introduction of objective criteria in everyday clinical practice would define more precisely patients affected by the syndrome. Importantly, the development of lipodystrophy in our study was not only associated with PI use but with other frequently used medications such as anabolic steroids and psychotropic medications. Interactions of these medications in the development of the syndrome warrant further study. Moreover, the hypothesized link between improvement in HIV status and body fat redistribution needs to be further explored.<sup>19</sup>

A limitation of our study was that serum lipid and glucose levels were obtained at the discretion of clinicians caring for the patients and usually were not obtained in a fasting state. A higher frequency of testing might have detected additional cases of diabetes mellitus and hyperlipidemia. Conversely, underrecognition of lipodystrophy at baseline may have led to an overestimate of incident events. Prospective studies are more likely to avoid some of these problems in measurement of exposures and outcomes.

The mechanism by which PIs cause diabetes and other metabolic effects as well as body habitus changes remains to be fully elucidated. Features of the syndrome are shared by patients with the metabolic profile of syndrome X, and this has led recently to the hypothesis that insulin resistance underlies this syndrome.<sup>5</sup> With regard to the cause of the lipodystrophy, it has been speculated that interference of PIs with apoptosis and impaired differentiation of peripheral adipocytes but relative sparing of intra-abdominal adipocytes is the underlying mechanism.<sup>28</sup> The occurrence of hyperlipidemia as the primary metabolic change may contribute to

a certain degree to the development of hyperglycemia at a later stage (Randle hypothesis).<sup>29</sup>

## CONCLUSIONS

Our study reports an independent association between PI use and hyperlipidemia, hyperglycemia, and lipodystrophy, on the basis of a 5-year cohort study that encompassed the pre-PI and post-PI therapeutic eras. Although these metabolic changes were occasionally observed in patients not exposed to PIs, they were much more frequent after initiation of PI therapy. Although it appears that the metabolic effects are not serious enough to warrant discontinuation of PI therapy, this decision should be left with the patients and their primary health care providers. Future studies of PI-treated patients are warranted to further address the clinical implications of these metabolic effects and examine their pathogenesis.

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