Long-Term Metabolic Consequences of Switching from Protease Inhibitors to Efavirenz in Therapy for Human Immunodeficiency Virus–Infected Patients with Lipoatrophy

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The roles of nucleoside analogues and protease inhibitors (PIs) in the development of metabolic complications and fat-distribution abnormalities associated with highly active antiretroviral therapy (HAART) are not well known. We performed an observational study in which efavirenz was substituted for a PI for 41 patients receiving HAART who had prolonged virus suppression, clinical signs of severe lipoatrophy, hyperlipidemia, and insulin resistance. Clinical follow-up was performed for 1 year. Virus suppression was maintained in most of the patients, and a significant increase in $CD4^+$ lymphocyte count was observed, but no change in lipid profile or insulin resistance was observed. Abdominal fat content did not change, and subcutaneous fat depletion was even more pronounced >1 year after the switch. We conclude that, for PI-treated patients who present with lipoatrophy, hyperlipidemia, and insulin resistance, substituting efavirenz for PIs can maintain virus suppression and immunologic response to HAART, but it does not improve the lipid profile or resolve insulin resistance or lipoatrophy.

Lipid disorders, derangements of glucose homeostasis, and fat-distribution abnormalities are observed in a significant proportion of HIV-infected patients receiving highly active antiretroviral therapy (HAART) [1]. Initial studies assumed that protease inhibitors (PIs) had a unique etiologic role, but conclusive reports about lipodystrophy syndrome (LDS) in patients treated only with nucleoside analogues (NAs) have led researchers to implicate NAs in the pathogenesis of these complications of HAART [2]. A synergistic toxic effect of the drugs used in HAART is probably a main causative factor in these complications. However, the mechanism(s) by which the drugs used in HAART can induce these metabolic and adipose-tissue abnormalities is largely unknown. However, PIs are believe to have a main role in the pathogenesis of some aspects of metabolic disturbances of LDS (in particular, glucose hemostasis), on the basis of in vitro studies that have shown that insulin-mediated glucose transport is reduced by PIs [3, 4]. Moreover, increased incidences of glucose intolerance, insulin resistance, and overt diabetes mellitus have been related to PI-containing HAART [5]. In patients who present with significant glycemic disturbances, substituting different antiretroviral agents for PIs can be considered.

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Table 1. Clinical characteristics of and therapy data for 28 patients who completed 1 year of follow-up in a study in which the protease inhibitor component of therapy was switched to efavirenz.

Variable	Value
No. of patients	28[a]
Sex, no. (%) of patients	
Male	24 (85.7)
Female	4 (14.3)
Age, mean years ± SD (range)	44.7 ± 11.2 (30–72)
Route of HIV acquisition, % of patients	
Sex	71.4
Parenteral	28.6
Centers for Disease Control and Prevention HIV stage,[b] % of patients	
A	46.4
B	25
C	28.5
$CD4^+$ lymphocyte count, mean cells/mm^3 ± SD	483 ± 279
$CD8^+$ lymphocyte count, mean cells/mm^3 ± SD	1213 ± 633
Body mass index, mean kg/m^2 ± SD	23.75 ± 2.62
Waist-to-hip ratio, mean cm ± SD	0.95 ± 0.09
Duration of therapy, mean months ± SD (range)	
Protease inhibitor	20.7 ± 7.8 (6–35)
Zidovudine	30.1 ± 24.6 (0–91)
Lamivudine	17.3 ± 9.6 (0–37)
Stavudine	15.2 ± 9.8 (0–33)
Zalcitabine	8.7 ± 11 (0–62)
Didanosine	7.1 ± 12 (0–38)

[a] No. of patients at 1 year, from 41 initially enrolled.
[b] From [8].

Published studies of PI switching have mostly been uncontrolled and have included relatively small numbers of patients and limited periods of follow-up. The main reasons for substitution in these studies have been changes in body shape, metabolic disturbances, or other PI-related toxicities. Patients with different fat-distribution abnormalities have been included in some studies, although the lack of an accepted definition of LDS casts uncertainty on the interpretation of the results. In most of the published reports [6, 7], an incomplete resolution of metabolic disturbances has been observed, with only partial improvements in insulin resistance and/or inconsistent changes of lipid profile and fat-distribution abnormalities.

Therefore, the purpose of our study was to assess the long-term (i.e., 1-year) effects of switching from a PI to efavirenz in a therapeutic regimen in a cohort of 41 patients with LDS who showed a predominant lipoatrophic phenotype of fat maldistribution and features of the insulin-resistance syndrome.

SUBJECTS AND METHODS

Patients. Forty-one HIV-infected patients who were receiving antiretroviral treatment that included ⩾1 PI and who developed LDS were initially included in the study; all patients presented with a clinically stable condition, as defined by the absence of any HIV-related symptoms; virus suppression, as indicated by undetectable HIV type 1 (HIV-1) load (i.e., <400 copies/mL); and a $CD4^+$ lymphocyte count of >150 cells/mm^3 in 2 consecutive determinations during the preceding 6 months. All patients presented with clinical signs of LDS with a lipoatrophic phenotype. The main clinical characteristics of the patients are shown in table 1.

Control subjects. Both healthy subjects and HIV-infected, treatment-naive patients were used as control subjects. HIV-infected control patients consisted of 13 male, treatment-naive patients with a mean age of 35.5 years (range, 24–46 years), mean body mass index (BMI) of 24.7 kg/m^2 (range, 21–27 kg/

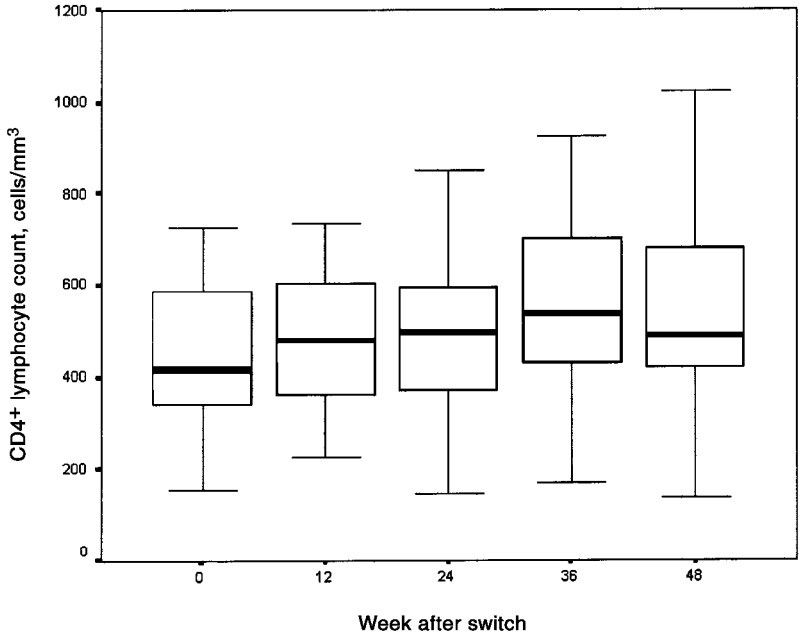

Figure 1. Changes in $CD4^+$ lymphocyte count 1 year after a change in antiretroviral therapy from a PI to efavirenz. Plot box includes median value *(thin line),* interquartile range, and SD.

m^2), mean $CD4^+$ lymphocyte count of 393 cells/mm^3 (range, 30–1107 cells/mm^3), and mean HIV-1 load of 133,225 copies/mL (range, 3000–547,000 copies/mL). Age- and BMI-matched healthy male subjects without HIV infection served as the HIV-uninfected control group ($n = 381$).

Definitions of LDS and lipoatrophy. Fat loss, normal weight, and absence of lipoaccumulation were required for inclusion into the study. Lipoatrophy was diagnosed when unquestionable loss of fat on certain areas (face, Bichat pad, extremities, or buttocks) was clinically present. In all cases, the lipoatrophy reported by the patient was confirmed by the physician in charge of clinical examination. A BMI of 20–27 kg/m^2 was considered to be normal. Fat accumulation was excluded on physical examination and by the anthropometric criterion of a waist-to-hip ratio of <1.

Study protocol and long-term follow-up. For all case patients, detailed information about their antiretroviral treatment was obtained and the accumulated time of receipt of each drug was calculated. Appropriate informed consent was obtained from all subjects, and clinical research was conducted in accordance with the guidelines for human experimentation specified by the US Department of Health and Human Services and local Ethics and Research Committee (Hospital Clínico San Carlos, Madrid).

At the initial study visit, a thorough clinical examination was performed, and anthropometric measurements were determined. Case patients were asked to stop PI therapy and, on the same day, to start therapy with efavirenz at a dosage of 600 mg once daily, without any change in the NA combination. Blood determinations and anthropometric measurements were performed every 3 months thereafter for all subjects. CT was repeated at the sixth and 12th months after the start of efavirenz therapy. Only patients who presented with hyperlipidemia received dietary advice about a healthy, low-fat diet; the outline's recommendations consisted of a reduction of total dietary fat to <30% of daily calories and a reduction in both saturated fatty acids and cholesterol content. Exercise recommendations were also provided. No lipid-lowering drugs were used. Alcohol intake was assessed, and only reduced alcohol intake (<3 typical drinks or ~30 g of alcohol per day) was allowed. No variation in antiretroviral regimen was allowed during the study period unless the patient's HIV load became elevated; in that event, the patient was withdrawn from the study.

Laboratory studies. Approximately 20 mL of blood was obtained from all patients after an ~10-h overnight fasting period; the blood sample was obtained from an antecubital vein, without compression, between 8:30 A.M. and 9:00 A.M. Blood samples were collected in EDTA-coated tubes and immediately centrifuged at room temperature. The removed plasma was appropriately aliquoted for determination of glucose, cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride (TG) levels. The plasma glucose level was determined in duplicate by a glucose-oxidase method adapted to an autoanalyzer. Total cholesterol, TG, and HDL cholesterol levels were determined by enzymatic methods, using commercial kits (Boehringer Mannheim). Low-density lipoprotein cho-

Table 2. Findings of biochemical studies during the study period for 28 patients who completed 1 year of follow-up in a study in which the protease inhibitor component of therapy was switched to efavirenz.

Characteristic	Study entry	Week of study			
		12	24	32	48
Body mass index, kg/m^2	23.7 ± 2.4	23.7 ± 2.3	23.9 ± 2.3	24.2 ± 2.1	23.8 ± 2.2
Waist-to-hip ratio, cm	0.96 ± 0.08	0.95 ± 0.07	0.95 ± 0.04	0.97 ± 0.06	0.98 ± 0.05
TAT level, cm^2	238.5 ± 121.9	—	241.9 ± 99	—	218.9 ± 106
VAT level, cm^2	132.25 ± 96	—	131.7 ± 61.4	—	125.7 ± 72.2
Ratio of VAT to TAT, cm^2	0.55 ± 0.18	—	0.54 ± 0.15	—	0.57 ± 0.18
SAT level, cm^2	27.48 ± 25.2	—	32 ± 25.3	—	21.93 ± 18.5
Fasting glucose level, mg/dL	93.8 ± 12.2	95.9 ± 10.9	96.5 ± 8.8	94.3 ± 10.6	99 ± 9.3
Fasting insulin level, μU/mL	13.24 ± 6.5	15.85 ± 10.4	13.3 ± 7.5	13.48 ± 9	15.3 ± 8.6
Fasting proinsulin level, μU/mL	11.7 ± 9.8	11.7 ± 7.9	16.8 ± 16.2	9.69 ± 7.5	14.2 ± 11.7
2-h OGTT glucose level, mg/dL	105.3 ± 36.1	108.8 ± 33.1	109.9 ± 46.5	94.3 ± 10.6	112.5 ± 39.9
2-h OGTT insulin level, μU/mL	72.8 ± 89.1	62.7 ± 57.4	57.25 ± 57	50.4 ± 57.7	69.5 ± 74
2-h OGTT proinsulin level, μU/mL	45 ± 60.6	36.9 ± 26.7	51.17 ± 63.3	41.2 ± 61	52.1 ± 42.1
Leptin level, μU/mL	3.24 ± 2.2	3.21 ± 2.1	3.37 ± 2.8	3.68 ± 2.8	4.91 ± 2.2
Total cholesterol level, mg/dL	230.7 ± 46.3	218.2 ± 45.5	237.4 ± 46.9	236.6 ± 51.3	228 ± 43.6
HDL cholesterol level, mg/dL	47 ± 11.7	55.5 ± 18.4	53.8 ± 16.7	51.6 ± 16.9	49.4 ± 9.5
LDL cholesterol level, mg/dL	122.4 ± 45.1	119.8 ± 41.1	127.9 ± 48.2	138.3 ± 48.3	127.7 ± 39.3
Triglyceride level, mg/dL	346.2 ± 290.4	230.6 ± 127.3	260.3 ± 173.7	237.6 ± 129.5	311 ± 199

NOTE. Data are mean values ± SD. HDL, high-density lipoprotein; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; SAT, subcutaneous adipose tissue; TAT, total adipose tissue; VAT, visceral adipose tissue.

lesterol levels were calculated by the Friedewald method for patients with TG levels of >400 mg/dL. The $CD4^+$ lymphocyte count was calculated by standard flow cytometry, and the HIV-1 load was determined using standard PCR (Amplicor; Roche), with lower limits of detection of 400 copies/mL (Ampicor; Roche) or 50 copies/mL (Ultrasensitive HIV-1 Monitor Test; Roche).

Special tests. The oral glucose–tolerance test was performed with use of 75 g of glucose under standard conditions, in accordance with World Health Organization recommendations [9]. Blood samples were obtained after 1 h and 2 h for determination of glucose, insulin, and proinsulin plasma levels. Results were interpreted according to the criteria recommended by the American Diabetes Association in 1999 [10].

Plasma insulin concentrations were determined using RIA (Human Insulin Specific RIA kit; Linco Research). The limits of detection for the test were 2 μU/mL to 100 μL. The intra- and interassay coefficients of variation were <1% and 0.67%–7.43%, respectively.

Plasma proinsulin levels were determined using RIA (Linco Research). The limits of detection for the test were 2 p*M*/L to 200 μL. The intra- and interassay coefficients of variation were 0.52%–10.3% and 0.3%–11.8%, respectively. The cross-reactivity with insulin was <1%.

Insulin resistance was calculated, using the homeostasis model assessment (HOMA) method, from fasting glucose and insulin concentrations, according to the formula [insulin (in μU/mL) × glucose (in m*M*/L)/22.5] [11].

Leptin levels were determined using a highly sensitive RIA (Linco Research, Inc.) with limits of detection of 0.5 ng/mL to 100 μL. The intra- and interassay coefficients of variation were 3%–7% and 2%–6%, respectively.

Fat CT measurements. Abdominal and subcutaneous thigh adipose-tissue content was measured by CT at L4 and midthigh levels. Two CT slices separated by 1 cm were done at the L4 level and at midthigh, and fat volume was calculated using computer-assisted software (Advantage Windows, version 3.1; General Electric Medical Systems) that added together the pixels of the 2 slices with CT values between −50 and −150 Hounsfield units. Total abdominal, visceral, and subcutaneous adipose-tissue levels were determined by use of this method, as described elsewhere [12].

Statistical analysis. The results of investigations of and laboratory measurements for the case patients were compared with those of HIV-uninfected healthy control subjects and HIV-infected, treatment-naive patients. All statistical analyses were performed by use of SPSS software, version 9.01. The χ^2 and Fisher's exact test were used for comparison between qualitative variables; Student's *t* test was used for comparison between quantitative data for variables with normal distribution. Wilcoxon's signed-rank test was applied for variables without normal distribution. Changes in variables with time (at baseline

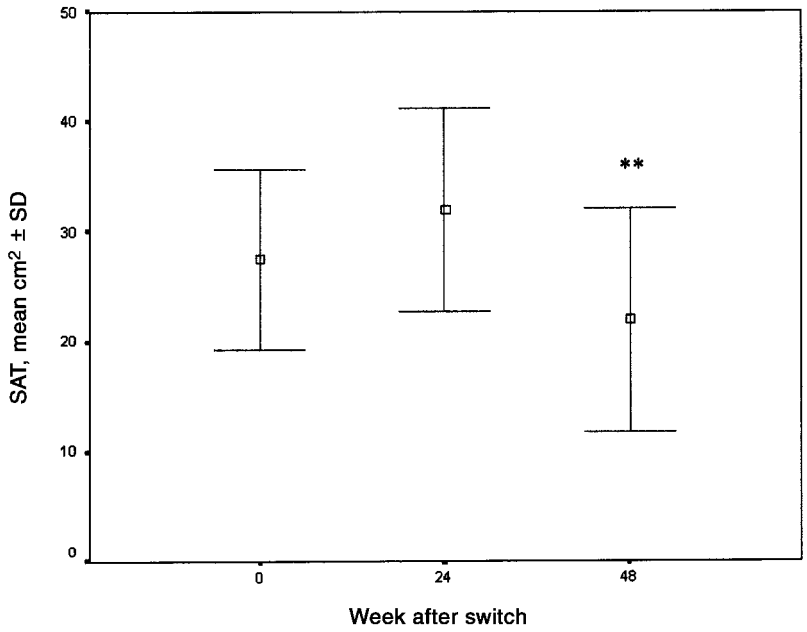

Figure 2. Changes in subcutaneous adipose-tissue (SAT) content, as measured by midthigh CT, 1 year after a change in antiretroviral therapy from a PI to efavirenz. *$P < .05$, for values at study entry vs. 48 weeks after the switch.

and 1 year after the switch) were analyzed by a repeated-measures analysis of variance (RMMANOVA) with a covariate polynomial contrast. Bonferroni's test was used for multiple contrast. A nonparametric test was used for comparing insulin plasma levels between treatment-naive, HIV-infected patients and case patients and before and after the case patients switched regimens. Associations between variables were determined by use of Pearson's correlation coefficients. Results are expressed as mean values ± SD.

RESULTS

Of the 41 patients initially included in the study, 28 (68.2%) were suitable for full evaluation after 1 year of efavirenz therapy; 13 patients did not complete the whole study period and were not included in the final analysis. These patients dropped out of the study because of a personal decision or loss of contact (8 patients [19.5%]), intolerance to efavirenz (in all cases related to CNS toxicity; 4 patients [9.7%]), or incomplete virus suppression (1 patient [2.4%]).

As shown in figure 1, a significant increase in the mean $CD4^+$ lymphocyte count was observed, from 483 cells/mm^3 to 577 cells/mm^3 1 year after the switch (+94 cells; $P = .01$, by RMMANOVA), with no significant variation in mean $CD8^+$ lymphocyte count. In all 28 patients, the HIV load remained undetectable (i.e., <50 copies/mL).

All results of biochemical testing and anthropometric determinations are shown in table 2. Neither BMI (23.75 ± 2.6 kg/m^2 before the switch vs. 23.81 ± 2.2 kg/m^2 1 year after the switch) nor waist-to-hip ratio (0.95 before the switch vs. 0.98 one year after the switch) changed significantly throughout the study period.

Neither total abdominal nor visceral adipose-tissue findings had changed 1 year after study entry. The ratio of visceral fat tissue to total abdominal fat tissue showed a nonsignificant tendency to increase (0.53 ± 0.17 vs. 0.57 ± 0.18 cm; $P = .052$). The level of thigh fat decreased significantly during the study period, from 35.9 ± 31.2 to 21.9 ± 18.5 cm^2 ($P = .001$, by RMMANOVA; figure 2).

Plasma leptin levels increased significantly during the study period, from 2.85 ± 1.58 to 4.91 ± 2.2 ng/mL ($P < .05$) at 1 year after the switch. No significant relationship has been found between subcutaneous or abdominal fat stores and leptin values or $CD4^+/CD8^+$ changes, respectively.

No significant changes were observed in the lipid profile. No differences were observed 1 year after the switch from a PI to efavirenz in patients with total cholesterol levels of >200 mg/dL or in the 15 patients who presented with plasma TG levels of >200 mg/dL at study entry (445 ± 327 before vs. 434.2 ± 192 mg/dL after the switch).

Similarly, at 1 year after the switch, there were no significant changes from baseline in glucose, insulin, and proinsulin plasma levels, both in fasting and 1-h and 2-h postglucose load ($P = .25$). Fasting plasma insulin levels in treatment-naive patients (10.8 ± 3.8 μU/mL) were lower than in those with LDS, both before (13.2 ± 6.5 μU/mL) and 1 year after therapy was switched (15.3 ± 8.6 μU/mL; $P < .05$ for both comparisons; figure 3). A total of 12.5% of HIV-infected, treatment-naive

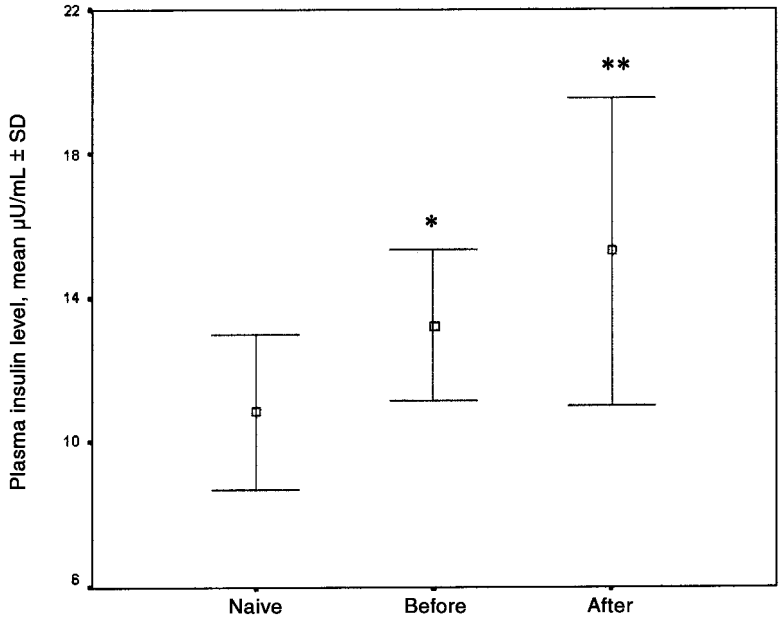

Figure 3. Fasting plasma insulin values for HIV-infected, treatment-naive patients, lipoatrophic patients receiving protease inhibitor–containing regimens of highly active antiretroviral therapy before therapy was switched to a nonnucleoside reverse-transcriptase inhibitor and 1 year after therapy was switched to efavirenz. $^{*}P$ = NS, for case patients before vs. after the therapy switch; $^{**}P < .05$, for treatment-naive patients vs. lipoatrophic patients before the switch.

patients were in the 75th percentile of fasting insulin levels for healthy controls (>15.38 μU/mL), versus 39% of patients with LDS before and 30% of patients with LDS 1 year after the PI was switched to efavirenz. Insulin resistance, as measured by HOMA, did not change during the study period (3.08 vs. 3.89; P = NS).

DISCUSSION

Complete virus suppression was maintained in the majority of patients after they had a regimen switch from a PI to efavirenz, and there was a sustained increase in $CD4^+$ lymphocyte counts throughout the 1-year period of follow-up. These results are in agreement with the results of both randomized [13] and observational studies [14] that have confirmed that, when sustained virus suppression is achieved with a PI-based regimen, switching to a nonnucleoside reverse-transcriptase inhibitor–based regimen is a safe strategy. PI-substitution studies have been performed with both nonnucleoside reverse-transcriptase inhibitors (efavirenz and nevirapine) and NAs (abacavir). Substitution of abacavir for a PI has been shown to reduce cholesterol and TG levels [15]. In general, substitution of nevirapine for a PI results in a reduction in TG levels and variable cholesterol modification levels during periods of up to 1 year [16, 17]. However, substitution of efavirenz for a PI does not necessarily modify the lipid profile in the short term, and an increase in TG levels and in both total and HDL cholesterol levels has been occasionally observed [18]. There are few published long-term studies of the effect of efavirenz on lipids [19], so our study can be considered one of the first to be reported.

One of the most interesting findings of our study was that, despite the beneficial effects of switching therapy with regard to both virus suppression and $CD4^+$ lymphocyte count, no noticeable changes in either the fat maldistribution pattern at baseline or in insulin resistance occurred 1 year after the switch. Given that lipodistrophy may take >1 year to appear, it can be hypothesized that a longer period may be required for a firmer verification of significant changes in fat redistribution. However, we have shown that fat loss was even more pronounced >1 year after the switch. Therefore, it would be unlikely—but possible—that improvement would occur after that period of time.

The absence of changes in lipid profiles are in agreement with the aforementioned direct effect of efavirenz on lipids. Subcutaneous adipose-tissue loss has been attributed to NA-related toxicity because of mitochondrial DNA–polymerase inhibition, which results in reduced energy production and cellular damage [20]. In our study, the NA component of therapy was not modified, so it can be argued that the same etiologic factor could have been present during the whole study period. An even more pronounced subcutaneous fat loss was observed in our patients, which suggests an evolving phenomenon.

Plasma leptin levels increased 1 year after the switch. Because no significant increase in fat deposits has been detected in any

compartment studied, no clear explanation can be provided for this particular issue. Also, it must be mentioned that the absence of data about total body fat is a limitation of the study and jeopardizes the interpretation of the leptin results.

No clear explanation exists for the absence of change in insulin sensitivity after PI therapy was stopped, because insulin resistance has been a complication attributed mainly to PI therapy [21]. Moreover, insulin resistance has been detected even in the absence of any measurable change in body composition in PI-treated patients [22]. Whether fat distribution abnormalities and metabolic disturbances, such as insulin resistance, are different aspects of the same problem, or whether they represent unrelated adverse effects of antiretroviral therapy, is not yet known. CT and MRI studies of HIV-infected patients with LDS have revealed a preferential visceral accumulation of fat [23]. In the general population, visceral adiposity is related to insulin resistance and hypertriglyceridemia [24], and, in animal models, surgical removal of visceral fat can reverse insulin resistance [25]. Furthermore, in patients with lipoatrophic diabetes, a genetic form of generalized absence of adipose tissue and insulin resistance, troglitazone treatment decreases insulin resistance in parallel with the decrease in visceral adipose-tissue content and the increase in subcutaneous fat [26].

We believe that the lack of change in insulin resistance and its metabolic disturbances after PI therapy is stopped is due, at least partially, to the persisting fat maldistribution. Therefore, one could expect that reversing fat loss so that stores return to normal or near-normal status will also reverse insulin resistance. Therefore, there is a potential role for insulin-sensitizing agents, such as metformin; also, the peroxisome proliferator–activated receptor–γ agonists thiazolidindiones could be an option for that purpose, as already has been suggested by a recent report [27].

In summary, we have shown in our study that, in HIV-infected patients with LDS, substitution of efavirenz for a PI adequately maintains virus suppression and improves the $CD4^+$ lymphocyte count; however, after 1 year, it does not significantly change the evolution of insulin resistance, of glucose homeostasis, or of the lipid profile. Furthermore, adipose-tissue distribution abnormalities, as measured by CT, had not changed 1 year after the switch; a persistent visceral abdominal accumulation and even a significant worsening of loss of peripheral fat were observed.

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