Impact of Switching from Human Immunodeficiency Virus Type 1 Protease Inhibitors to Efavirenz in Successfully Treated Adults with Lipodystrophy

Esteban Martínez,1 Miguel Angel García-Viejo,1 José Luis Blanco,1 Luis Bianchi,2 Elisabet Buira,1 Ignacio Conget,3 Roser Casamitjana,4 Josep Mallolas,1 and José M. Gatell1

We prospectively followed 20 consecutive patients with human immunodeficiency virus type 1 (HIV-1) with viral loads of <200 RNA copies/mL. These patients had been treated with 2 nucleoside reverse transcriptase inhibitors and ≥1 HIV-1 protease inhibitor for ≥3 months; they developed body changes consistent with lipodystrophy and requested they be switched from protease inhibitor to efavirenz. At baseline and every 3 months, we assessed the following: body mass index, waist-to-hip ratio, regional fat thickness (assessed by sonography), fasting total and high-density lipoprotein cholesterol, triglycerides, glucose, insulin, CD4+ cells, and viral load. At baseline, hypertriglyceridemia (>200 mg/dL) was present in 17 (85%) patients, hypercholesterolemia (>200 mg/dL) in 14 (70%), and impaired fasting glucose (>110 mg/dL) in 8 (40%); CD4+ T cells were cells/L (range, cells/L). HIV-1 RNA had been at <200 copies/mL for a median of 14 months (range, 3–24 months). Six months after switching to efavirenz, there was a reduction in triglyceride levels (a decrease of 31%; P < 0.03) and fasting insulin resistance index (a decrease of 28%; P < 0.03), but total and high-density lipoprotein cholesterol and glucose did not change. Waist-to-hip ratio decreased from 0.92 to 0.87 (P < 0.06). Subcutaneous fat thickness did not change. CD4+ cells remained stable (363 × 10⁴ cells/L; range, 102–741 × 10⁴ cells/L; P = 0.65). Nineteen patients (95%) had HIV-1 RNA levels that remained at <200 copies/mL. Although CD4+ response and viral suppression remained preserved after 6 months of switching from protease inhibitor to efavirenz, the benefits of this approach on the evolution of lipodystrophy were limited, and our findings do not support its routine recommendation to treat lipodystrophy.
and immunological responses that could have been expected with PI therapy.

Efavirenz, a nonnucleoside reverse transcriptase inhibitor (NNRTI), was made available for clinical use later than nevirapine. Combination therapy with efavirenz plus 2 nucleoside reverse transcriptase inhibitors (NRTIs) has been shown to be at least as potent for viral suppression as the standard combination therapy, which includes a PI plus 2 NRTIs [12]. A retrospective analysis [13] showed no cases of lipodystrophy among patients who received efavirenz, azidothymidine, and lamivudine, as compared with ~2% incidence among the group of patients who received indinavir, azidothymidine, and lamivudine and the group who received indinavir and efavirenz. However, the findings of this study that concern lipodystrophy should be considered with caution because lipodystrophy was not predefined as an end point. Increases in total cholesterol have been observed in patients treated with HAART that includes efavirenz, although they have been tentatively attributed to increases in high-density lipoprotein (HDL) cholesterol [14]. Controversial results concerning the evolution of lipodystrophy have been described in 3 studies that examined the substitution of PI with efavirenz therapy in HIV-1–infected people with lipodystrophy who were receiving HAART [15–17]. In the most comprehensive study [15], glucose tolerance improved and visceral fat decreased, whereas blood lipids increased in relation to baseline after 6 months of follow-up. In the second study [16], no changes in metabolic abnormalities or body changes were observed after 3 months of follow-up. Conversely, in the third study [17], partial or complete resolution of PI-associated lipodystrophy was reported in most of the patients after 3–6 months of follow-up.

We assessed the effects of switching from PI to efavirenz therapy in HIV-1–infected adults with lipodystrophy and a plasma viral load <200 copies/mL. We assessed patients’ responses by measuring metabolic abnormalities, fat redistribution, CD4+ cell counts, and viral load, and compared our findings with those of a previous study of nevirapine therapy [9].

Patients and Methods

Patients. Twenty consecutive HIV-1–infected adults were enrolled in this study. They spontaneously complained of body changes due to fat redistribution. Body changes in every patient were confirmed by the doctors taking care of the patients; descriptions of body changes were standardized by use of a questionnaire, which included a qualitative assessment of the perception by the patient of 1 or more of the following possibilities: “buffalo hump,” breast enlargement, increased abdominal girth, and fat loss in arms, legs, buttocks, and face. Patients had received antiretroviral therapy before enrollment consisting of 2 NRTIs and at least 1 PI. All patients agreed to switch from PI therapy to efavirenz because of concerns attributable to metabolic abnormalities and body changes despite sustained viral suppression (<200 HIV-1 RNA copies/mL) for at least the previous 3 months. We chose to prescribe efavirenz because all the patients were naive for NNRTIs and for all of them triple therapy with 2 NRTIs and efavirenz had shown similar efficacy to standard triple therapy that included 2 NRTIs and 1 PI [12]. The rest of the patients’ antiretroviral therapy regimen was left unchanged. Patients were not recommended to modify their daily activities. No specific dietary restrictions were given.

Study design. Data on fasting serum lipids and glucose before PI withdrawal were obtained from the patients’ medical files before they enrolled in the study and prospectively assessed thereafter. At the time of study enrollment and every 3 months thereafter, we performed physical examinations on all the patients; the examinations included measurements of weight, height, waist, and hip circumferences, and regional visceral and subcutaneous fat (assessed by means of sonography). We also performed laboratory tests, including assessments of metabolic parameters, CD4+ T lymphocyte counts, and plasma HIV-1 RNA levels. For the purpose of this study, the following 6 time points were considered: (1) the onset of antiretroviral therapy; (2) the commencement of PI therapy; (3) the patient’s perception of body changes; (4) the withdrawal of PI therapy and the commencement of efavirenz (baseline); (5) 3 months after PI withdrawal; and (6) 6 months after PI withdrawal. Those patients who started a PI with their initial antiretroviral therapy were counted from time 2 on. The stage of HIV-1 infection was defined according to the 1993 Centers for Disease Control classification [18]. All patients were recruited from the AIDS Unit at the Hospital Clinic of Barcelona, Spain.

Laboratory determinations. Venous blood samples were drawn after the patient had fasted for 12 h overnight. Plasma glucose was measured by the glucose hexokinase method. Cholesterol and triglycerides were measured by automated enzymatic methods (Bayer Diagnostics, Tarrytown, NY). Total cholesterol and triglyceride concentrations were determined in the supernatant fraction containing very low density lipoprotein. HDL cholesterol was determined in the infranate by precipitation of apolipoprotein B–containing lipoproteins with phosphotungstate and magnesium. Insulin was measured by monoclonal immunoradiometric assay (IRMA, Med-Genix Diagnostics, Fleunes, Belgium).

Triglyceride levels were classified as follows: normal, <200 mg/dL; borderline-high, 200–400 mg/dL; and high, >400 mg/dL [19]. Cholesterol levels were classified as follows: normal, <200 mg/dL; borderline-high, 200–239 mg/dL; and high, ≥240 mg/dL [19]. For glucose, the following ranges were classified: normal, <110 mg/dL; impaired fasting, ≥110–126 mg/dL; and diabetes, ≥126 mg/dL [20]. Fasting insulin resistance index (FIRI) was calculated as previously described [21]. Briefly, FIRI consists of the product of plasma insulin and glucose normalized to an expected glucose of 5 mmol/L and insulin of 5 mU/L. The normal range of FIRI values has not been established.

The number of CD4+ T lymphocyte cells was measured by flow cytometry. Plasma HIV-1 RNA was measured by both the standard method (lower limit of detection, 200 copies/mL) and the ultrasensitive method, modified as previously described [22] (lower limit of detection, 5 copies/mL), polymerase chain reaction (PCR) assays (Amplicor HIV Monitor, Roche Diagnostic Systems, Branchburg, NJ). The modified ultrasensitive PCR assay was performed at the end of the study on plasma samples taken from the patients at times 4 and 6 described above. Samples from patients whose standard PCR assay at those times had been below the limit of detection
Subcutaneous fat thickness was always measured by the same radiologist, who was blinded to the laboratory and the other anthropometric data, by sonography with one of the following pieces of equipment: Toshiba Power Vision (7.5–10-MHz linear transducer; 3.7–4.2-MHz convex and sectorial transducer) or Toshiba SSH-140A (8-MHz linear transducer; 3.75-MHz convex and sectorial transducer). Subcutaneous fat thickness was measured with high-frequency transducers (7.5–8 MHz) at 3 reference skin points: periumbilical (~5 cm to the left of the umbilicus), brachial (~10 cm above the right elbow), and malar (on the right malar bone). The measurements of subcutaneous fat thickness were always performed without applying pressure to the underlying skin. Intra-abdominal fat thickness was calculated at the level of the minor omentum by measuring the distance between the pole of the left hepatic lobe and the anterior wall of the aorta on transversal and longitudinal sections with 3.75-MHz transducers.

Statistical analysis. The values of HIV-1 RNA copies/mL were log transformed for comparisons. Differences in means of normally distributed variables were compared with the t test; abnormally distributed variables were compared with the Wilcoxon rank test. Differences in proportions were tested by the χ² test with continuity correction. Statistical significance was assumed at P < .05.

Results

Population characteristics. There were 11 men and 9 women in the study group. The median age at baseline was 40 years (25%–75% interquartile range [IQR], 33–50). Seven patients (35%) met criteria for AIDS. The PI therapy that was withdrawn was indinavir for 13 patients, ritonavir for 4 patients, nelfinavir for 1 patient, and ritonavir and hard-gel saquinavir for 2 patients. The combinations of NRTI inhibitors that were maintained on switching to efavirenz were as follows: stavudine and lamivudine (16 patients; 80%), stavudine and didanosine (3 patients; 15%), and azidothymidine and lamivudine (1 patient; 5%).

Eight patients (40%) had a PI-containing regimen as their initial antiretroviral therapy. In the remaining 12 patients, there was a median of 38.5 months (IQR, 21.5–60.5) between the commencement of antiretroviral therapy and the introduction of PI therapy. There was a median of 17.5 months (IQR, 14.5–23) from the commencement of PI therapy to the awareness of body changes. None of the patients had been taking concurrent therapies affecting carbohydrate or lipid metabolism before the awareness of body changes.

Median metabolic laboratory parameters at the time of the awareness of body changes were as follows: triglycerides 282 mg/dL (IQR, 209.5–384), cholesterol 208.5 mg/dL (IQR, 187.5–257.5), glucose 93.5 mg/dL (IQR, 83–108), insulin 18.3 mU/L (IQR, 14.9–24.2), and FINS 0.152 mmol/mL (IQR, 0.119–0.269). On detection of body changes, all patients had <200 HIV-1 RNA copies/mL. HIV-1 RNA had been <200 copies/mL a median of 14 months (range, 3–24 months) before the withdrawal of PI therapy and the commencement of efavirenz.

Median CD4⁺ T lymphocyte counts on perception of body changes were 319 × 10⁶ cells/L (IQR, 253–534). The median values of BMI were 23.4 (IQR, 22.1–25.0) in men and 20.9 (IQR, 20.1–22.5) in women; median WHRs were 0.90 (IQR, 0.89–0.93) in men and 0.91 (IQR, 0.86–0.94) in women.

Body changes included ≥1 of the following: ”buffalo hump” (n = 2), breast enlargement (n = 8), abdominal obesity (n = 19), and fat loss in arms (n = 19), legs (n = 20), buttocks (n = 18), and face (n = 20). Table 1 shows the combinations of body changes reported by the patients and confirmed by the doctors. Nineteen patients (95%) reported mixed changes of both fat accumulation and fat depletion.

Evolution of laboratory parameters. Plasma viral load at times 1 and 2 was available only for 3 and 16 patients, respectively. The other laboratory parameters (except for HDL cholesterol and insulin, which were only measured from time 4) were available for all patients and for all the times considered. The means and 95% CIs for triglycerides, total and HDL cholesterol, glucose, FINS, CD4⁺ T lymphocytes, and HIV-1 RNA log copies/mL at every time point of the study are shown in figure 1. The values of triglycerides (P = .03, paired t test) and FINS (P = .03, paired t test) significantly decreased from baseline to month 6 after switching therapy. The rest of the laboratory values (total and HDL cholesterol, glucose, CD4⁺ T

<table>
<thead>
<tr>
<th>Body change</th>
<th>Patients</th>
<th>Women</th>
</tr>
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<tbody>
<tr>
<td>Abdominal obesity and subcutaneous fat loss</td>
<td>10</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Abdominal obesity, breast enlargement, and subcutaneous fat loss</td>
<td>7</td>
<td>7 (100)</td>
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<tr>
<td>Abdominal obesity, breast enlargement, buffalo hump, and subcutaneous fat loss</td>
<td>1</td>
<td>1 (100)</td>
</tr>
<tr>
<td>Abdominal obesity, buffalo hump plus subcutaneous fat loss</td>
<td>1</td>
<td>1 (100)</td>
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<tr>
<td>Subcutaneous fat loss</td>
<td>1</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Total</td>
<td>20</td>
<td>9 (45)</td>
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NOTE. Data are no. or no. (%).
BMI than women at baseline (23.3 kg/m² vs. 21.2 kg/m², respectively; \( P = .01 \), Wilcoxon rank test), 3 months (23.2 kg/m² vs. 20.7 kg/m², respectively; \( P = .009 \), Wilcoxon rank test), and 6 months after switching (23.0 kg/m² vs. 20.5 kg/m², respectively; \( P = .008 \), Wilcoxon rank test). None of the men or women had a BMI of \( \geq 27 \) at any time when this parameter was measured.

WHRs did not show differences among men and women at baseline (0.90 vs. 0.93, respectively; \( P = .39 \), Wilcoxon rank test), 3 months (0.89 vs. 0.90, respectively; \( P = .99 \), Wilcoxon rank test), and 6 months after switching (0.88 vs. 0.86, respectively; \( P = .45 \), Wilcoxon rank test). Among the 11 men included in the study, a WHR of \( \geq 0.9 \) was present in 6 (55%) at baseline, 4 (36%) at month 3, and 2 (18%) at month 6. Among the 9 women included in the study, a WHR of \( \geq 0.8 \) was present in 9 (100%) at baseline, 9 (100%) at month 3, and 7 (78%) at month 6.

Figure 2 shows the mean and 95% CI of waist and hip circumference, WHR, and BMI at baseline and at months 3 and 6. On comparing anthropometric parameters at baseline and at month 6, no differences were seen in weight (63.6 kg vs. 62.4 kg, respectively; \( P = .70 \), Wilcoxon rank test), height (1.68 vs. 1.68 m, respectively; \( P = .89 \), Wilcoxon rank test), hip circumference (93.4 vs. 93.4 cm, respectively; \( P = .99 \), Wilcoxon rank test), and BMI (22.4 vs. 21.9 m/kg², respectively; \( P = .45 \), Wilcoxon rank test). Waist circumference (85.3 vs. 81.5 cm, respectively; \( P = .06 \), Wilcoxon rank test) and WHR (0.92 vs. 0.87, respectively; \( P = .06 \), Wilcoxon rank test) showed trends towards significance. On comparing the echographic measurements of regional fat thickness at baseline and at month 6, no differences were seen in subcutaneous abdominal fat (15.1 vs. 14.7 cm, respectively; \( P = .84 \), Wilcoxon rank test), subcutaneous brachial fat (3.3 vs. 3.5 mm, respectively; \( P = .46 \), Wilcoxon rank test), and subcutaneous malar fat (4.1 vs. 4.3 mm, respectively; \( P = .56 \), Wilcoxon rank test). Intra-abdominal fat variation showed a trend toward significance (20.8 vs. 19.2 mm, respectively; \( P = .16 \), Wilcoxon rank test). Overall, the evolution of anthropometric measurements, including regional fat thickness, between baseline and month 6 was similar in both women and men.

**Clinical evolution.** Eleven patients (55%) reported a subjective improvement of body changes 6 months after switching from PI to efavirenz therapy. Subjective perception of improvement in those patients was not restricted to any particular body change. However, we could confirm that patients who noticed improvement in body changes had greater decreases in WHR (\(-0.06 \) vs. \(-0.02 \), \( P = .02 \), Wilcoxon rank test), subcutaneous abdominal fat (\(-1.4 \) mm vs. \(+0.8 \) mm, \( P = .02 \), Wilcoxon rank test), and especially intra-abdominal fat (\(-3.00 \) mm vs. \(-0.08 \) mm, \( P = .0001 \), Wilcoxon rank test). These patients also tended to have higher reductions in waist circumference (\(-4.6 \) cm vs. \(-2.7 \) cm, \( P = .1 \), Wilcoxon rank test) and BMI (\(-0.69 \) kg/m² vs. \(-0.28 \) kg/m², \( P = .12 \), Wilcoxon rank test) and higher in-
creases in hip circumference (+0.9 cm vs. −1.1 cm, \( P = .11 \), Wilcoxon rank test). No significant differences were seen between the patients who had a subjective perception of improvement and the patients who did not have this perception, either with respect to changes in subcutaneous brachial fat (+0.38 vs. −0.01 mm, respectively; \( P = .21 \), Wilcoxon rank test) or with respect to changes in and malar fat (+0.29 mm vs. +0.15 mm, respectively; \( P = .53 \), Wilcoxon rank test).

More women had a subjective perception of improvement (\( n = 7 \); 78%) than men (\( n = 4 \); 36%) (\( P = .16 \), \( \chi^2 \) test with continuity correction). All the patients who received azidothymidine/lamivudine therapy (\( n = 1 \)) and stavudine/didanosine therapy (\( n = 3 \)) reported subjective perceptions of improvement in body changes, whereas only 7 (44%) of the 16 who received stavudine/lamivudine did so.

We analyzed the influence of baseline laboratory and anthropometric data on the subjective perception of improvement of body changes after 6 months of switching from PI to efavirenz therapy. Baseline height (1.65 ± 0.07 m vs. 1.72 ± 0.06 m, \( P = .05 \), Wilcoxon rank test), weight (59.6 ± 8.6 kg vs. 68.5 ± 8.7 kg, \( P = .03 \), Wilcoxon rank test), and total cholesterol (256 ± 66 vs. 200 ± 40, \( P = .03 \), Wilcoxon rank test) were significantly lower in those patients who later recognized subjective improvement than in those who did not.

Five patients (25%) experienced minor efavirenz-associated neuropsychological side effects consisting of insomnia (\( n = 1 \)), intense and frequent dreams (\( n = 3 \)), and dizziness (\( n = 1 \)); these adverse effects were relatively well tolerated, and they disappeared after the first month of efavirenz therapy. Three patients (15%) had severe adverse effects associated with the introduction of efavirenz and needed to discontinue it. One patient experienced intense dizziness from the first dose of efavirenz. The remaining 2 patients showed bizarre symptoms consisting of motor slowness and incoordination; they were normally alert but had a strange and unpleasant feeling of lack of control. Severe adverse effects leading to drug discontinuation disappeared completely a few days after nevirapine was replaced with efavirenz. It should be noted that the only patient whose viral load rose above 200 copies/mL in month 6 (555 copies/mL) had previously needed to discontinue efavirenz. Overall results did not change when those 3 subjects intolerant to efavirenz who were switched to nevirapine were excluded from the analysis. As expected, no adverse effects attributable to NRTI were observed.

**Discussion**

The results of this observational study show that some metabolic abnormalities, such as hypertriglyceridemia and insulin resistance, may significantly improve after 6 months of switching from PI to efavirenz therapy. The improvement in those metabolic parameters was associated with a trend toward decreased abdominal obesity, as measured by WHR and by sonography. Other metabolic parameters, such as hypercholesterolemia, and other body changes, such as fat loss in the face and the extremities, did not change. Virological suppression was well maintained in almost all the patients after 6 months of switching to efavirenz.

One randomized [11] and 2 observational [9, 10] studies in which PIs were replaced by nevirapine also showed an improvement in metabolic parameters and a maintenance of viral suppression in most of the patients after 6–12 months. Improvement of body fat changes was seen only in the observational studies [9, 10], but patients did not recover their previous body shapes. Most of the studies of lipodystrophy in which PI therapy was replaced by NNRTI (nevirapine or efavirenz) were observational studies, with a relatively small number of patients and a relatively short study duration. Moreover, in every study, metabolic and anthropometric parameters at baseline may not be comparable, and the methods used to measure the evolution
of those parameters are different. This could help to explain some of the differences found in these studies. Nevertheless, there seems to be a clear consensus among most of the studies that at least some metabolic abnormalities partially improve in patients treated with PIs who develop lipodystrophy and switch from PI to NNRTI therapy.

It is less clear what clinical impact switching from PIs to nevirapine or efavirenz has on body fat redistribution. We have seen a trend toward improvements in WHR, both in a previous study of nevirapine therapy [9] and in the present study, in which 11 patients (55%) who reported a subjective improvement not only had a reduced WHR, but also showed a significant decrease in intra-abdominal fat. However, the improvement in abdominal obesity was not uniform in these patients, and other studies with nevirapine or efavirenz have reported conflicting results on this issue. No improvement at all was observed in our patients with respect to loss of fat from the extremities and face. Although patients were not specifically recommended to modify their daily activities or their diet, we cannot completely exclude the possibility that these variables had some influence on the final outcome, because the effects of these variables were not assessed.

We do not now know the etiology of lipodystrophy, nor do we know whether lipodystrophy can be completely reversed. Central obesity may revert, at least partially, after switching from PI to NNRTI therapy, as shown in the present study and in other studies [9, 10]. Physical training [25] and therapy with metformin [26] or recombinant growth hormone [27] have also been reported to improve central obesity without discontinuation of PI therapy. Conversely, the reversibility of subcutaneous fat loss in HIV-1–infected patients with lipodystrophy has been less obvious. Two recent studies that included a small number of patients reported the possibility of ameliorating subcutaneous fat loss after discontinuation of stavudine therapy irrespective of the continuation of PI therapy [28, 29]. Recently, the findings of a group of investigators who reported apoptosis in the subcutaneous fat tissue of patients with subcutaneous fat loss [30] were disappointing. The results suggested that subcutaneous fat loss may not be completely reversible.

There are no data on normal regional fat distribution in the general population. Therefore, when assessing the evolution of body fat changes, each patient must be his or her own control. To our knowledge, this is the first study to use sonography to measure the evolution of fat distribution in HIV-1–infected patients with lipodystrophy. Several methods have been used to measure body composition in HIV-1–infected subjects with lipodystrophy. Bioelectrical impedance analysis documents total body lean mass, from which total body fat may be assessed; however, this method is not able to detect the regional distribution of body fat. Dual-energy x-ray absorptiometry [5], CT scans [3], and MRI scans [31] have been used to quantify fat distribution in selected body regions. However, dual-energy x-ray absorptiometry does not reliably distinguish between subcutaneous and intra-abdominal fat, CT has the disadvantage of radiation exposure, and MRI requires lengthy scanning times (45 min for a limited body region). Moreover, all these techniques may be too expensive to add to routine clinical practice. Sonography has been shown to be a valid method for the measurement of fat distribution in the subcutaneous compartment in the general population [32]. It has also been used for the evaluation of intra-abdominal fat [33], although it has some limits: the presence of air in the gastrointestinal lumen can interfere with measurement, and the accuracy of the procedure depends greatly on the skill of the operator. In contrast, sonography has potential advantages for the measurement of regional fat distribution in HIV-1–infected patients with lipodystrophy: it is simple to use, rapid, readily available, harmless, well accepted by patients, and low cost as compared with the other techniques mentioned above.
The results of this study further support the conclusion that reasonably safe viral control can be maintained, at least in the short term, if triple regimens that contain NNRTIs and PIs are replaced with regimens that do not contain PIs [34, 35]. It should be noted, however, that our study was limited to a period of 6 months and that viral load was only measured in the plasma compartment. It should also be realized that switching to efavirenz may cause severe adverse effects in some patients. Pathophysiological basis and risk factors for efavirenz-associated neuropsychological adverse events are unknown. The high incidence of severe adverse effects that we observed in this study may not reflect the true incidence of these effects in the general population of HIV-1–infected patients treated with efavirenz [14]. Replacement of PIs with NNRTIs in the treatment of lipodystrophy may be useful for selected patients; however, new adverse effects may develop, and it is not certain that NNRTI regimens will have long-term potency similar to PI therapy; in addition, lipodystrophy is not completely reversible in the middle term. These are strong arguments against generalizing the replacement of PIs with NNRTIs into routine clinical treatment of lipodystrophy.

In summary, 6 months after switching from PI to efavirenz therapy, some metabolic abnormalities associated with potent antiretroviral regimens that include PI, such as hypertriglyceridemia and insulin resistance, as so may certain body fat changes, such as abdominal obesity, may improve, whereas CD4+ response and viral suppression are preserved. However, the benefits of switching drug regimens on the basis of developing lipodystrophy were very limited and of questionable clinical importance. The results of this study do not support the recommendation that PIs be replaced with efavirenz to treat lipodystrophy.

References