

# Body fat changes in HIV patients on highly active antiretroviral therapy (HAART): a longitudinal DEXA study

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**Abstract.** – **OBJECTIVE:** We aimed to quantitatively evaluate body fat composition in a group of HIV patients treated with Highly Active Anti-retroviral Therapy (HAART) to ascertain both fat loss and fat distribution changes and to identify possible therapeutic and host related associated risk factors.

**PATIENTS AND METHODS:** A total of 180 patients with available total body DEXA scan were assigned to a) Group 1, with clinically evident body fat changes, (BFC) and b) Group 2, without BFC. Clinical and immunovirologic data were collected. We used Student *t*-test and  $\chi^2$  or Fisher exact test to compare the characteristics of the two groups. Paired *t*-test was used to compare basal and follow-up data. The relationships between variables were evaluated by calculating Pearson's correlation coefficient and its significance.

**RESULTS:** HAART duration was significantly ( $p<0.0001$ ) higher for patients in Group 1 than in Group 2, as well as PI ( $p<0.02$ ) and NRTI ( $p<0.002$ ) therapy duration. Current CD4 count and CD4 rise from nadir resulted significantly higher in Group 1 than in Group 2 ( $p<0.02$  and  $0.006$ , respectively). Whole Body Fat (WBF), Peripheral Fat (PF) and Leg (L) fat negatively correlated with PI and NRTI therapy duration, while Trunk Fat (TF)/PF positively correlated with PI and NNRTI duration. No significant correlation was found, instead, with NNRTI therapy duration. At 5-year follow-up, we registered a further increase in TF, Arms (A) and L fat, especially in PI-treated patients.

**CONCLUSIONS:** Body fat changes should always be considered when dealing with HIV-affected patients on HAART. The fat loss seemed

to involve mainly peripheral regions, while fat accumulation tendency occurred in the trunk.

*Key Words:*

HIV, Highly active anti-retroviral therapy (HAART), AIDS, DEXA, Body fat, Lipodystrophy.

## Introduction

The introduction of Highly Active Anti-Retroviral Therapy (HAART) has led to a dramatic decrease in both morbidity and mortality associated with HIV/AIDS<sup>1</sup> or virus-related cancers as Kaposi Sarcoma<sup>2</sup>. On the other hand, different long-term comorbidities such as diabetes mellitus, hypertriglyceridemia, hypercholesterolemia, metabolic syndrome, hypertension, endocrine disorders<sup>3</sup>, osteopenia<sup>4</sup>, neurocognitive disorders<sup>5</sup>, non-AIDS-defining cancers and lipodystrophy have been observed during therapy, despite virological control<sup>6-31</sup>. HIV-associated lipodystrophy syndrome (HALS) has been described as a pathological condition characterized by modifications in body fat distribution (lipoatrophy, lipohypertrophy) associated with metabolic disorders<sup>32</sup>. Body fat changes (BFC) are common in HIV-infected patients receiving HAART, ranging from 2 to 84% in subjects receiving protease inhibitors (PI) and from 0 to 4% in patients not receiving PI<sup>33</sup>. The large variability in the prevalence of BFC is mainly due to the lack of a standardized definition

to date and to the utilization of non-quantitative diagnostic procedures.

The pathogenetic mechanism underlying BFC in HIV patients receiving HAART is still unclear. Most important factors contributing to it seem to be represented by mitochondrial toxicity, insulin resistance and adipose tissue-derived cytokines, adipose gene expression derangements and proteasome dysfunction<sup>34</sup>.

The whole Protease Inhibitors (PI) seemed to be more involved in generating dyslipidemia (alteration in total cholesterol, low-density cholesterol, and triglycerides levels) than other HAART regimens<sup>35</sup>, while their contribution to lipohypertrophy (localized accumulation of adipose tissue) still remains ambiguous<sup>36,37</sup>. PI effect may be mediated by the inhibition of GLUT4 adipocyte-based insulin dependent transporter. In fact, GLUT4-deleted mice showed reduced subcutaneous fat, thus inducing insulin resistance and decreasing the adipogenesis<sup>34,38</sup>. Differently, nucleoside reverse transcriptase inhibitors (NRTI) seem to play a major role in the lipodystrophy (subcutaneous adipose loss) onset because of the inhibition of mitochondrial mtDNA polymerase- $\gamma$  that leads to a reduction in adipocyte mtDNA and cell dysfunction<sup>34,39</sup>. An increased secretion of TNF- $\alpha$ , which is an inducer of adipocyte apoptosis, has also been observed during HAART. Moreover, some studies have reported a dramatic polarization to TNF- $\alpha$  synthesis of both CD4 and CD8 cells in patients receiving HAART, particularly when lipodystrophy was present<sup>34,40</sup>. A history of low CD4 nadir or a rise in the CD4 count after therapy has been reported in association with lipodystrophy<sup>41,42</sup>. Finally, lipodystrophy in HIV-patients has been associated with many other cytokine level changes<sup>34</sup>. Among these: low plasma and adipose adiponectin's levels, which usually increase insulin sensitivity; higher levels of the interleukine-6 (IL-6), which is a pro-inflammatory and gluconeogenesis inductor leading to hyperglycemia and compensatory hyperinsulinemia; increased levels of visfatin, a visceral fat adipokine able to decrease plasma glycemia, lessen the adipose accumulation and fasten triglyceride synthesis from glucose.

In this study, we quantitatively evaluated body fat composition in a group of HIV patients treated with HAART, both at basal condition and in a long follow-up, to ascertain both fat loss and fat distribution changes and to identify possible therapeutic and host related associated risk factors.

## Patients and Methods

### Patients

This study was a longitudinal retrospective cohort study with a 5-year long follow-up time and designed to assess body fat changes in HIV-affected patients on HAART. Ethical Committee approval was obtained. Since it was a retrospective study, no specific written patient consent was needed because anonymity was ensured for all patients and data assessing followed the good standing clinical practice.

We consecutively enrolled 180 HIV-infected patients receiving HAART, 114 males and 66 females. Of these, 72 patients were classified as stage A, 60 were classified as stage B and 48 as stage C according to the Center for Disease Control and Prevention (CDC) classification system.

Patients were divided in order to be assigned to two different groups: a) Group 1, composed by 78 out of 180 patients with clinically evident body fat changes; b) Group 2, composed by the remaining 102 patients without any clinically evident body fat change. In order to be enrolled in Group 1, patients had to present at least one of the following clinical signs of fat distribution changes:

- Fat accumulation in cervical, supraclavicular, interscapular regions and in trunk, abdomen or breasts.
- Fat loss in the face, arms, legs, and glutei.

Patients were enrolled in Group 2 if they did not meet inclusion criteria for being included in Group 1.

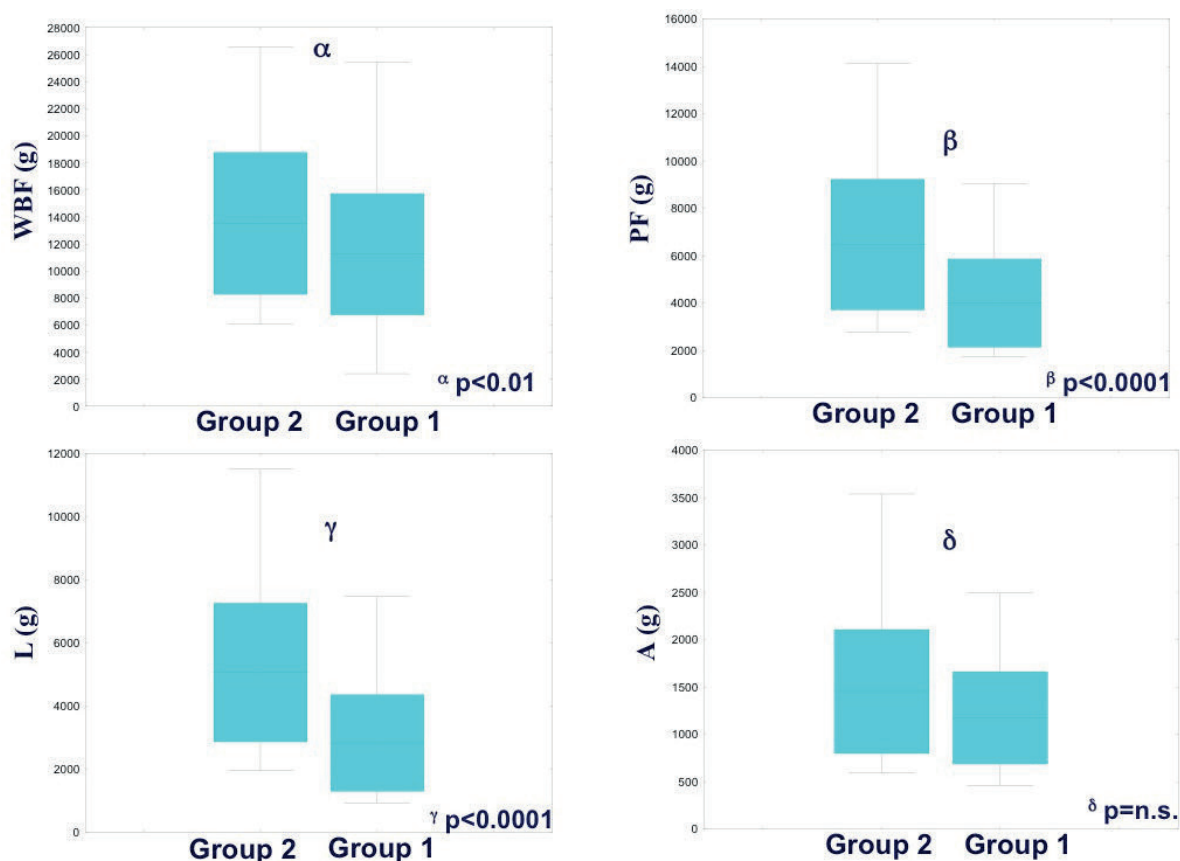
General exclusion criteria for being enrolled in any group were the following:

- A previous diagnosis of AIDS, wasting syndrome or AIDS dementia complex.
- Steroid or antineoplastic agents use in the 12 months before enrollment.
- Any active AIDS-defining event.

As regards Anti-Retroviral Therapy (ART) regimens, 86 patients had undergone to PI plus NRTI regimens, while 94 patients had taken both NNRTI and NRTI in their therapeutic protocol.

### Methods and Data Collection

In each patient, both at basal condition and during follow-up, we performed a fat mass (FM; g) measure by means of Dual Energy X-ray Absorptiometry (DEXA – Hologic QDR 4500A) in the following sites: whole body (WBF), trunk (TF), peripheral regions (PF), arms (A) and legs (L). Trunk/peripheral (TF/PF) ratio and to-



**Figure 1.** WBF, PF, L and A results in both Group 2 and Group 1 patients. Lines represent mean values, boxes SD and whiskers range.

tal weight (TW) were also obtained for every patient.

CD4 count by flow cytometry (FACSCalibur fluorimeter, Becton Dickinson, Erembodegem-Aalst, Belgium), together with HIV viral load by NucliSens NASBA (Organon Teknica, Boxtel, The Netherlands) were gathered.

Body mass index (BMI) was calculated as weight (kg) divided by height (m<sup>2</sup>), according to the World Health Organization (WHO) criteria<sup>43</sup>. Patients were interviewed about their ongoing ART regimens and, if women, about their menopausal condition. Age, CDC stage, CD4 cell nadir and rise from nadir, PI, NRTI, non-nucleoside reverse transcriptase inhibitors (NNRTI), and total HAART therapy duration (months) were registered from clinical records.

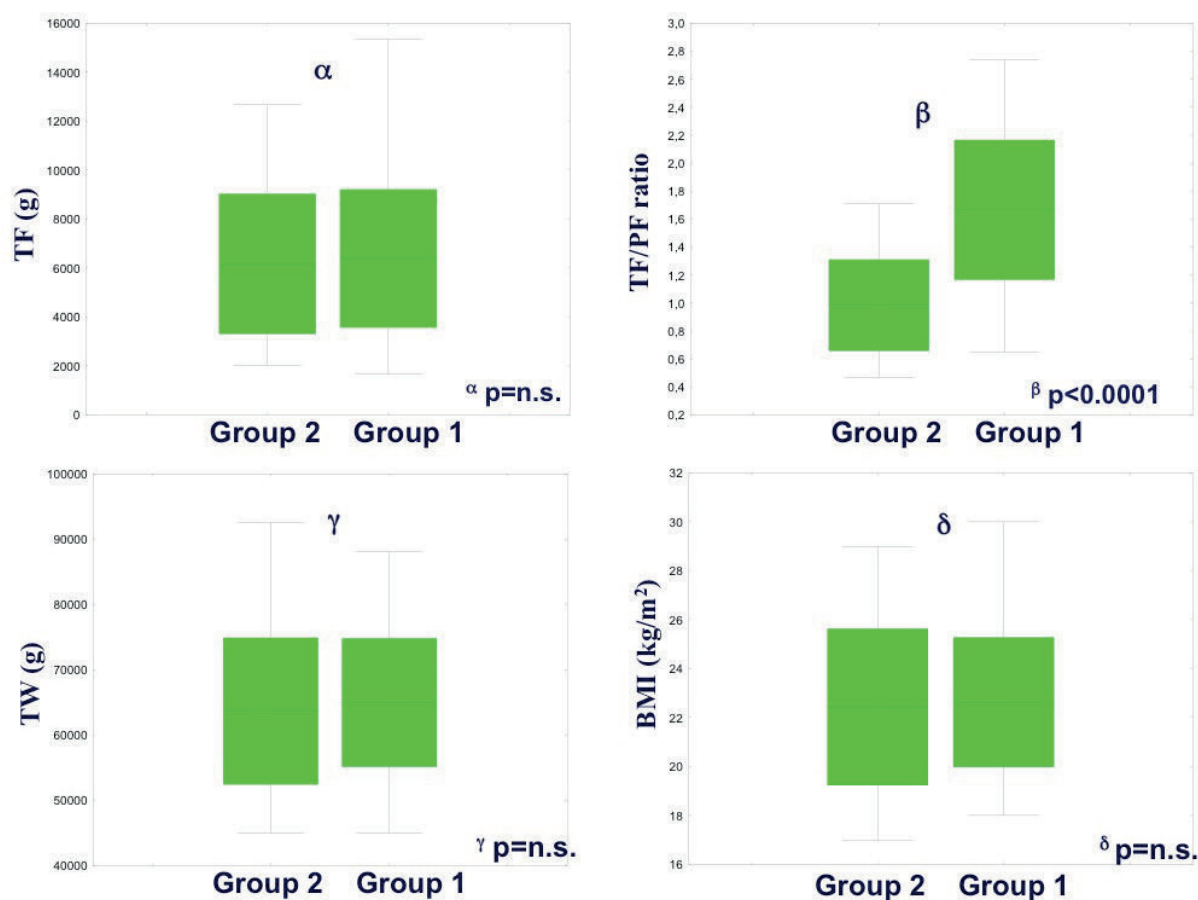
### Statistical Analysis

Student *t*-test for continuous variables and  $\chi^2$  or Fisher exact test for categorical variables were used to compare the characteristics of the

two groups: paired *t*-test to compare basal and follow-up data. The relationships between variables were evaluated by calculating Pearson's correlation coefficient and its significance. *p*-value <0.05 was considered as significant.

### Results

Data showed that, globally, HAART duration was significantly (*p*<0.0001) higher for patients in Group 1 than in Group 2, as well as PI (*p*<0.02) and NRTI (*p*<0.002) regimen based therapy duration. Current CD4 count and CD4 rise from nadir resulted significantly higher in Group 1 than in Group 2 (*p*<0.02 and 0.006, respectively). Nadir, NNRTI duration, and CDC stage, showed no significant differences. WBF negatively correlated with PI (*r*=-0.23, *p*<0.05) and NRTI therapy duration (*r*=-0.33, *p*<0.001). PF negatively correlated with PI (*r*=-0.34, *p*<0.001) and NRTI therapy duration (*r*=-0.37, *p*<0.001). L fat negatively correlated with PI (*r*=-0.35, *p*<0.001) and NRTI the-



**Figure 2.** TF, TF/PF ratio, BMI and TW results for Group 2 and Group 1 patients. Lines represent mean values, boxes SD and whiskers range.

rapy duration ( $r=-.39$ ,  $p<0.01$ ). Furthermore, TF/PF positively correlated with PI ( $r=0.28$ ,  $p<0.004$ ) and NRTI duration ( $r=0.30$ ,  $p<0.002$ ). No significant correlation was found, instead, with NNRTI therapy duration. At 5-year follow-up, we could monitor 84 patients (39 receiving PI and 45 receiving NNRTI), who continued the same therapy and remaining with stable disease. In these patients, TF further increased as well as A and L fat, especially in patients receiving PI, even though this increase was not statistically significant.

## Discussion

Consistently with previous data in literature<sup>33,44-48</sup>, this longitudinal study provided evidence that fat distribution changes can occur in HIV affected patients on HAART.

Fat loss mainly seemed to involve peripheral regions, while fat accumulation tendency was

maintained in the trunk. It should be pointed out though, that the difference between visceral and subcutaneous fat for the abdominal region cannot be usually detected by DEXA, thus undermining the evaluation of fat distribution within the trunk<sup>49</sup>. Conversely, the major part of the limb's adipose tissue is subcutaneous; therefore, leg fat DEXA measure reliably embodies the whole subcutaneous fat content in that region. Data gathered from this study also highlighted a significantly higher rise in CD4+ T cells count from nadir in Group 1 compared to the one in Group 2 patients. Regarding this finding, it could be speculated that the immune recovery plays a pro-inflammatory cytokine-mediated role, leading to a peripheral fat loss dysfunction. Central fat gain generally occurs equally in HIV-affected patients, independently from different HAART regimens<sup>48</sup>, and it usually does not go backward after switching the HAART regimen. For these reasons, fat gain might be seen as a product of therapy, which brings back to normal the levels of inflammation markers such as TNF- $\alpha$

(tumor necrosis factor alpha) that are known to generate wasting<sup>50</sup>. Interestingly, Lòpez-Dupla et al<sup>51</sup> described the correlation between low soluble tumor necrosis factor-like weak inducer of apoptosis (sTWEAK) concentrations and HALS, with sTWEAK emerging as a strong predictor of fat redistribution in HIV patients. In fact, in spite of the inflammatory potentiality of TWEAK, this marker resulted to possess an interfering activity with TNF $\alpha$  signaling. Therefore, its lower levels found in HALS-affected patients might corroborate our speculations about the pro-inflammatory cytokine-mediated role of the immune recovery. Furthermore, many other pro-inflammatory cytokines and adipocytokines altered levels have been demonstrated in HALS-affected patients<sup>34,52,53</sup>, such as higher interleukine-6 (IL-6) plasma levels<sup>54,55</sup>, lower adiponectin plasma and adipose tissue levels<sup>54</sup>, significantly higher plasma levels of visfatin<sup>56</sup> and plasminogen activator inhibitor type 1 (PAI-1)<sup>57</sup>. The longer exposure to PI and NRTI therapy, as well as the better immune recovery in Group 1 patients, could represent risk factors for fat loss, both conditions affecting adipocyte metabolism<sup>58</sup>. In our cohort, fat changes seemed to worsen over time. This possibility should be considered especially when dealing with HIV patients, in order to optimize treatment management in clinical practice. It might be advisable to perform a DEXA study for body fat composition assessment at least every 5 years during follow-up, with the purpose of registering and monitoring further body fat modifications over time.

## Conclusions

Body fat changes should always be considered when dealing with HIV-affected patients, especially among those with many years of ongoing HAART. Considering the well-established relationship between visceral adipose tissue accumulation and the increase cardiovascular risk<sup>59,60</sup>, a bigger effort in understanding the altered adipocyte metabolism affecting HIV patients might represent a valid motive for trying to stop, or at least delay, this mechanism, thus reducing the risk and prolonging the patients' life.

## Conflict of Interest

The authors declare that they had no financial interests or commercial associations during the course of this study.

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