

Lipodystrophy and Quality of Life of HIV-Infected Persons

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Abstract

Morphological changes induced by HIV-related lipodystrophy profoundly affect body image and influence health-related quality of life. Measurements of health-related quality of life in patients with lipodystrophy are complex due to a lack of consensus on the definition of lipodystrophy, a lack of appropriate methods to capture the impact of body fat changes, and the subjective perception of those changes by patients. This review describes the different tools that have been used to assess quality of life in patients with lipodystrophy, and critically analyzes published papers on health-related quality of life.

With regard to facial lipoatrophy, the most stigmatizing condition of lipodystrophy, we have analyzed the impact of reconstructive plastic surgery on patient-related outcomes and health-related quality of life.

A better knowledge of the associations between lipodystrophy and health-related quality of life will allow us to understand the burden of long-term toxicities of antiretroviral therapies as well as to identify novel patient-related endpoints useful in assessing the efficacy of lipodystrophy treating programs.

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Key words

Lipodystrophy; Body changes. Health-related quality of life. Body image. Lipodystrophy case definition.

Introduction

Recently published recommendations on HIV management are relatively standardized and all agree that lipid and glucose homeostasis abnormalities and fat distribution assume a central role in guiding choices for antiretroviral therapy^{1,2}. In this regard, the European

AIDS Clinical Society (EACS) published the first guidelines on the prevention and management of metabolic disease, emphasizing the physicians' growing awareness of the increased cardiovascular risk and drug-induced metabolic abnormalities in HIV-infected patients³.

Clinical experience suggests that lipodystrophy can have a profound influence on health-related quality of life (HRQoL), producing erosion of self-esteem and decreasing the social functioning of patients experiencing this condition. Unfortunately, there is neither consensus on the definition of lipodystrophy nor agreement on the best method for measuring its consequences. What is needed is to break down the hierarchical structure in considering endpoints of lipodystrophy. Metabolic and cardiovascular endpoints need to be displayed at the same level of patient-related outcomes in a composite evaluation of HRQoL.

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Only patients can report their perceptions and physicians need to get this information in order to prescribe and evaluate specific medical interventions. The objective of this article is to review studies that analyzed the impact of lipodystrophy on HRQoL as well as lipodystrophy treatment strategies that have been evaluated with patient-related outcomes.

Search strategies and selected criteria

Data from this review were identified by searches of MEDLINE, references from relevant articles, and abstract books of the first nine International Workshops on Adverse Drug Reactions and Lipodystrophy. Search terms were “lipodystrophy”, “HIV”, “quality of life”, “body image”, “psychosocial”, and “depression”. Only studies reported in the English language were included. The aim of this report is to provide an update on the knowledge of the impact of lipodystrophy on quality of life (QoL).

Impact of body image on health-related quality of life

Lipodystrophy in HIV-infected patients includes morphologic changes and metabolic alterations⁴⁻⁷. The main clinical features of lipodystrophy are peripheral fat loss (lipoatrophy) of the face, limbs, and buttocks and central fat accumulation of the abdomen, breasts, and dorso-cervical spine. Both lipoatrophy and fat accumulation may be present simultaneously in the same individual. It is intuitive that facial lipoatrophy is the most stigmatizing feature of HIV-related lipodystrophy, as the face cannot be masked by clothes and usually it is perceived as the expression of our health.

One way to assess the psychological consequences of lipodystrophy is by examining body image perception. Body image is a multidimensional concept referring to the psychological experiences of one's appearance and functioning⁸⁻¹⁰. Body image includes both perceptions and attitudes, together with accuracy or distortion of perceived body dimensions, thoughts, beliefs, actions, feelings, emotions, and satisfaction concerning one's body^{11,12}. Body image is also related to aesthetics, fitness and health/illness domains.

Assuming Testa's hypothesis of HRQoL as an association of physical, psychological and social health domains¹³, we can argue that the body image concept is a subset of QoL. In particular, somatic domains of

body image refer to the physical experience of HRQoL, while aesthetic domains refer to both psychological and social experience of HRQoL. Figure 1 depicts the conceptualization of this hypothesis.

Two kinds of body image alterations are described in the literature: the first refers to body size distortion, and the second to body dissatisfaction¹². The great majority of research has been done in female populations. Currently, female body image is related to socio-cultural stereotypes of beauty, idealized by thinness. Body image has been explored in individuals with eating disorders, and there are extensive data in young women affected by anorexia and bulimic disorders¹⁴. In the recent literature three different tools have been used to assess body image in patients with lipodystrophy. These tools relate both to body aesthetic dissatisfaction and to the interference of body changes with habits and social relations.

The Adult AIDS Clinical Trials Group (ACTG) Assessment of Body Change and Distress (ABCD) is a patient-administered questionnaire that includes 22 items. The first question (ABCD7) asks about body image satisfaction (the lower the score, the higher the body aesthetic satisfaction), and the remaining 21 items allow to calculate a global value (ABCD8), describing body change interference with habits, social life and attitudinal aspects of body image (the higher the score, the lower the interference of body changes with habits and social life). This questionnaire has been validated in the Italian language¹⁵.

The Body Image Quality of Life Inventory (BIQLI) is a questionnaire that uses a seven-point response format, ranging from very negative (-3) to very positive (+3) effects of body image on 19 life domains^{10,16}. The 19-item BIQLI is internally consistent and has been demonstrated to converge significantly with multiple measures of body image evaluation as well as with body mass. The BIQLI is valuable for quantifying how a person's body image experiences affect a broad range of life domains, including sense of self, social functioning, sexuality, emotional well-being, eating, exercise, grooming, etc. The BIQLI is scored as an average numeric value of the 19 items, with a more negative score reflecting a more negative body image.

The Situational Inventory of Body Image Dysphoria (SIBID) is an assessment of the frequency of negative body image emotions across specific situational contexts. This inventory asks respondents how often they experience body image dysphoria or distress (according to a numeric range of 0 = never to 4 = always) in

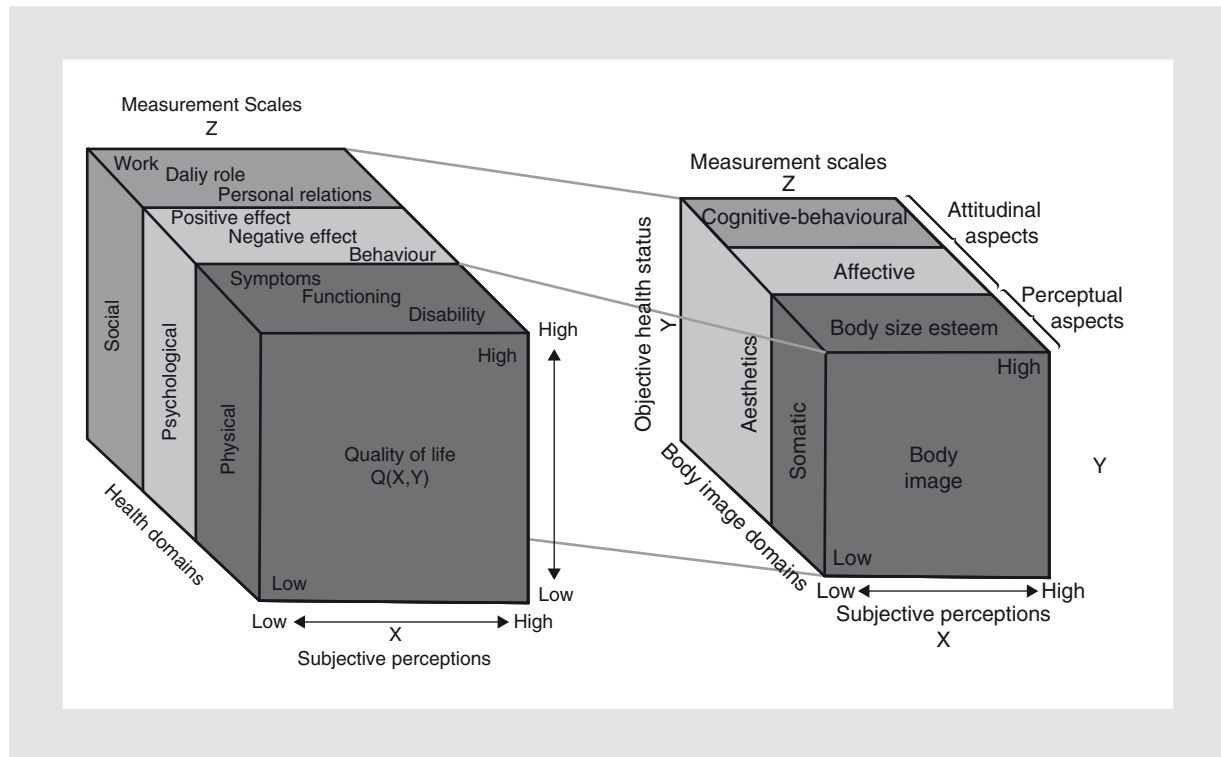


Figure 1. Conceptualization of body image domains as a subset of quality of life domains: somatic domains of body image refer to physical experience of health-related quality of life, while aesthetic domain refers to both psychological and social experience of health-related quality of life.

each of 48 identified situations in both social and nonsocial contexts related to such activities as exercising, grooming, eating, intimacy, and appearance alterations. Research has confirmed that this is an internally consistent, stable, convergent, valid measure of body image affect that is responsive to body image therapy. Recently, a 20-item short form of the SIBID has been validated and found to correlate highly ($p > 0.95$) with the original longer version¹⁰. The SIBID-S is scored as the numeric mean of its 20 items, where a higher score is associated with increased body image dysphoria.

Assessment of health-related quality of life in patients with lipodystrophy

Lipodystrophy may lead to the forced disclosure of an HIV diagnosis or increase the fear of adverse events related to antiretroviral treatment¹⁷⁻¹⁹. A recent paper found that 85% of patients with lipodystrophy reported that changes have been noticed by family, friends, or work colleagues^{18,19}. Disfigurement may cause stigma,

erosion of self-esteem, and a decrease of desirability or attractiveness; it may also influence social relations, and lead to anxiety and depression²⁰.

Few studies have addressed QoL issues in HIV-infected patients with lipodystrophy, and its impact has not been definitively established (Table 1). No differences in QoL have been found between Spanish people with or without lipodystrophy²¹, using a QoL questionnaire not previously validated in patients with HIV infection. Even though the sample size was small, men scored lower on negative mood and homosexual men scored lower on psychological functioning. Applying a different questionnaire on a subsample of this study, Blanch, et al. found that changes in the breast, the face, or the legs were significantly associated with a greater impairment of psychosocial functioning²². In the multivariate analysis, only changes in the breast remained significant. Once again, however, the authors did not use standardized questionnaires for measuring QoL in HIV-infected people. More recently, the total lipodystrophy score has been found not to be correlated with any domain of the Medical Outcomes Study (MOS) HIV Health Survey or HIV/AIDS targeted (HAT)-QoL subscales, except for

Table 1. Studies on lipodystrophy impact on health-related quality of life

Study	Patients (n)	Methods	LD assessment	Results	Comments
Blanch J, et al. ²¹ 2002	84	PLC (Profil der Lebensqualität Chroniskranker)	Lipodystrophy severity scale, LDCD (Carr-modified)	LD not correlated to QoL. In MSM and psychiatric pts greater impact of LD on QoL (Mental Health domains)	Questionnaire not previously validated in HIV pts
Blanch J, et al. ²² 2004	84	Dermatology Life Quality Index modified	Lipodystrophy severity scale, LDCD (Carr-modified)	Legs, face and breast alterations are correlated to a worse mental health, but in multivariate only breast was	Questionnaire not previously validated in HIV pts
Santos C, et al. AIDS 2005	457	Interview	Patient-assessed	LD has a negative impact on the quality of relationships	
Burgoyne R, et al. ²³ 2005	77	MOS-HIV HAT-QoL HOPES	Lipodystrophy severity scale, LDCD (Carr-modified)	Correlation between LD and some domains of QoL (physical, body pain, medication worries, body image), not with depression	
Marin A, et al. ²⁶ 2006	128 (plus controls)	MOS-HIV and BDI	Patient-assessed with validation of a new questionnaire	LD correlates to QoL and depression	Not all Chronbach values are satisfactory
Reynolds N, et al. AIDS Care 2006	58	Focus groups plus interviews	–	LD has a great negative impact on QoL and adherence	
Steel J, et al. ²⁷ 2006	37 (plus controls)	SF-36 and CES-D	Physician	No significant difference between HIV ⁺ without LD and HIV ⁻	
Guaraldi G, et al. ²⁵ 2008	401	MOS-HIV	Patient and physician assessed (HOPS) and LDCD	Strong correlation between severity of LD and mental health domains of QoL	

LD: lipodystrophy; LDCD: lipodystrophy case definition; QoL: quality of life; MSM: men who have sex with men; MOS: Medical Outcomes Study; HAT: HIV/AIDS targeted; BDI: Beck Depression Inventory; SF-36: Short Form 36; CES-D: Center for Epidemiological Studies-Depression.

physical function areas, while the lipodystrophy score was strongly correlated with the patient-perceived body image score²³. Unfortunately, the sample size of the study was too small (77 patients) to draw definitive conclusions.

A recent analysis of factors correlated with a lower QoL in the HAART era in a large cohort did not include lipodystrophy as a possible predictor of both physical and mental health²⁴. A dramatic association has been found only between lipodystrophy severity and dissatisfaction with body image^{17,23}. Correlations between lipodystrophy and QoL have been obscured by the

lack of specificity of the applied instrument and by the small sample size of the studies. In a cross-sectional study of 401 patients evaluated for lipodystrophy at the Modena Metabolic Clinic in Northern Italy, HRQoL was strongly correlated with lipodystrophy severity using a patient-based score²⁵. The key interpretation of our study is that the impact of lipodystrophy on QoL can be identified only in patients with a perceived body image alteration of a moderate to severe entity, notwithstanding physician-based definition of lipodystrophy. Table 1 summarizes the main studies on lipodystrophy and QoL.

In patients with HIV-related lipodystrophy (assessed by patients and confirmed by physicians), Marin, et al. have recently validated a new questionnaire consisting of 35 items divided into six subclasses, which include different social and psychological aspects: body image perception (five items), depression (eight items), anxiety (three items), social distress and anxiety (ten items), social support (five items), and QoL (four items). All the subscale scores except QoL discriminated between HIV-infected patients with lipodystrophy and the control groups (HIV-infected on therapy without lipodystrophy, HIV-infected but treatment-naive, and HIV uninfected; $p < 0.01$). All subscale scores except QoL strongly and significantly correlated with the severity of lipodystrophy, with correlation coefficients ranging from 0.3 to 0.6 ($p < 0.01$, Pearson's test). These results remained unchanged after adjusting by demographic or clinical factors, and there was no association between nadir CD4 count, HIV RNA level, or AIDS diagnosis and any of the subclass scores. Notably, there was a close correlation between different subclasses in patients with lipodystrophy, especially between body image perception and social distress subclasses. The questionnaire was unable to find differences in QoL, considering only the presence of lipodystrophy. The authors justify this result for the complexity of the concept of QoL itself, that is it is not affected just by lipodystrophy in patients with HIV infection²⁶.

According to Steel, et al., lipodystrophy does not negatively affect HRQoL or depression above and beyond the diagnosis of HIV infection itself. In this study, 37 HIV-seropositive men who have sex with men, and who met the criteria for lipodystrophy, have been longitudinally compared, over a two-year follow-up, to 92 HIV-seropositive men without lipodystrophy and to 88 HIV-seronegative men on measures of HRQoL and depression. A series of questionnaires, which included the Medical Outcomes Study Short-Form 36 (SF-36) and the Center for Epidemiological Studies-Depression (CES-D), have been administered to assess HRQoL and depression, respectively. Neither the mental nor the physical components of the SF-36 have shown any significant differences between patients with lipodystrophy versus HIV-seropositive patients without lipodystrophy. Similarly, lipodystrophy status was not significantly associated with either continuous depression scores or the presence of clinical depression. Consistent with previous results, however, HIV-infected men without lipodystro-

phy (compared to HIV-seronegative men) reported higher scores on both components of the SF-36 scales and both categorizations of the CES-D²⁷.

People experiencing lipodystrophy report a very significant decrease in sexual activity²⁸. In a study of 357 HIV-infected men evaluating erectile dysfunction, desire, orgasm, intercourse satisfaction, and overall satisfaction in relation to body image, QoL and hypogonadism (assessed with plasma free and total testosterone), we were able to depict that sexual function domains were associated with body image and mental health and not with HAART or hypogonadism. Prevalence of erectile dysfunction was substantially high, being up to 40% in this HIV-infected cohort²⁹.

It is curious that body image may also interfere with immune-virologic outcomes. Since the very beginning of lipodystrophy syndrome, it has been noted that greater adherence was related to a higher probability of having lipodystrophy; however, the strength of this relationship diminished over time. This effect could be related to decreased adherence in patients developing lipodystrophy³⁰. In fact, baseline self-perceived adipose tissue alterations were independently related to subsequent nonadherence and to development of drug resistance³¹. Nowadays, where new drugs with lower pill burden and simpler drug schedules are available, lipodystrophy is unlikely to act as an independent predictor of future nonadherence, but could have an impact in the context of a multiplicity of factors, either increasing or decreasing the probability of nonadherence in a complex system interplay. Table 2 reports the main studies on lipodystrophy and adherence.

Patient-related outcomes to evaluate lipodystrophy treatments

Lipodystrophy cannot be hidden but, as the EACS guidelines suggest, it can be prevented and treated. With regard to the most stigmatizing condition of lipodystrophy, facial lipoatrophy, the only clinically appreciable intervention is plastic surgery. Surgeons can perform autologous fat transfer from a subcutaneous abdominal graft, or injections of absorbable or nonabsorbable fillers into the lipoatrophic areas of the face. It is surprising how very few studies have assessed the safety, efficacy, and durability of these interventions, and only two studies have compared different surgical approaches^{32,33}.

Table 2. Studies on lipodystrophy impact on adherence to antiretroviral therapy

Author	Study typology	Patients (n)	LD assessment	AD assessment	AD rate	Results
Duran S, AIDS 2001	Cohort study (experienced to PIs) M0-M20	277 EU pts (APROCO)	Self-administered questionnaire 50.5% "change in body shape"	ACTG questionnaire (5 questions) 4 day period No QD regimens	M0 = 100% AD M20 = 70% AD	Self-reported lipodystrophy symptoms were independently associated with adherence failure.
Ammassari A, et al. ³¹ 2002	Cohort study	207 EU pts (AD-ICoNA Lipo-ICONA)	Self-administered questionnaire 15% perceived and 25% physician-assessed	"Cattolica University" questionnaire (16 items) Evaluate 3 day period	35% AD	Self-perceived ATA at baseline independently related to subsequent non-adherence, but clinically diagnosed ATA was not. Better adherence associated with a higher risk of subsequent occurrence of ATA - Onset of morphologic alterations can reduce adherence to ART.
Paton N, et al. ¹⁷ 2002	Cross-sectional (advanced)	410 Asian patients in Singapore	Self-administered questionnaire For LD 86% LD	Simple question: "Would you like to stop therapy due to LD"	Not specified	Self-reported lipodystrophy did not appear to have a major psychological impact.
Guaraldi G, et al. ³⁰ 2003	Cross-sectional multicenter study	175 EU pts (GRAAL)	Self-administered questionnaire 47% LD	"Cattolica" questionnaire (16 items) 3 day period	77 AD	Higher the adherence, higher the occurrence of LD. Longer time on HAART and self-reported adherence are correlated to morphologic alterations.
Corless I, AIDS Patient Care STDS 2005	Cross-sectional, descriptive design	165 (3 outpatients US setting)	Open-ended questions	Morisky Medication Adherence Scale	Moderate AD (MMAS = 1.4)	Type of lipodystrophy symptoms did not affect adherence. Time since initial diagnosis was not related to adherence. Quality of life however, was significantly related to adherence.
Santos C, et al, AIDS 2005	Cross-sectional, descriptive design	457 in Brazil	Self-administered questionnaire 64% LD	No formal questionnaire for AD	Not specified	Subjects who admitted 'skipping doses' were more likely to perceive peripheral fat loss. We cannot rule out the possibility that this lack of adherence may have followed the perception of body changes, as a reaction aimed at stopping the progression of these disturbances. As a result of its cross-sectional design, the present study does not allow us to evaluate the temporal framework of this association.

(continue)

Table 2. Studies on lipodystrophy impact on adherence to antiretroviral therapy (continued)

Author	Study typology	Patients (n)	LD assessment	AD assessment	AD rate	Results
Collins E, AIDS Behav 2006	Cross-sectional	77 pts Canada	Self-administered questionnaire 100% LD (different range of severity) 83% moderate/severe LD	PMAQ7 PMAQ10	81% AD (56% with VL BLD)	Body fat redistribution was not related to antiretroviral adherence. Lipodystrophy severity rating contributed to no more than 1% of the variance in AD rating and produced no greater likelihood of suboptimal adherence.
Guaraldi G, et al.	Prospective study	218 EU pts	Self-administered questionnaire 89.8% LD	"Cattolica" questionnaire (16 items) Evaluate 3 day period	"Cattolica" questionnaire (16 items) Evaluate 3 day period Baseline 80.7 LD FU 86% LD	LD determinants on adherence: it is not based on "time on lipodystrophy" but on patient perception of "body image alteration". Adherence is the net result of the "complex system" interaction of its determinants.

In our experience, we evaluated the short-term toxicity of autologous fat transfer represented by four cases of disfiguring facial fat graft hypertrophy occurring at the same time of recurrent fat growth in the harvest site (the so-called Hamster syndrome)³⁴. Besides this side effect, which has led us to exclude fat hypertrophy sites as a graft, a higher proportion of mild edema and pain has been observed in all individuals undergoing autologous fat transplant in comparison to those undergoing injections of facial fillers. We have compared polyacrylamide (Aquamid®) (Fig. 2) to polylactic acid (Sculptra®) injections. We have observed that 30-50% of individuals undergoing polylactic acid injections have developed palpable intradermal skin nodules, compared to 0% of those undergoing polyacrylamide. Most of the authors agree that permanent fillers should be preferred to absorbable fillers in patients with severe facial lipoatrophy, while absorbable fillers should be used in patients with mild to moderate facial lipoatrophy.

Some studies have utilized picture comparisons and ultrasound assessment of cheek thickness as aesthetic outcomes. As previously said, it is necessary to consider patient-related outcomes such as the assessment of body image, aesthetic perception, depression, and QoL. Long-term psychometric outcomes of plastic surgery for the treatment of facial lipoatrophy have been described by Orlando, et al. in an observational, prospective, nonrandomized study of 299 participants (70.8% male)³⁵. Fifty-four (18.1%) have undergone lipofilling, 24 (8%) after an initial lipofilling have needed polylactic acid injections to correct cheek asymmetry, 91 (30.4%) have received only polylactic acid infiltrations, and 130 (43.5%) only polyacrylamide infiltrations. At 48 weeks after end of surgery, participants have shown an improvement of face satisfaction (by a Visual Analog Scale from 2.9 ± 2.1 to 6.2 ± 2.1 ; $p < 0.0001$), of body image satisfaction (ABCD question 7 from 3.8 ± 1 to 3.1 ± 1 ; $p < 0.0001$, and ABCD question 8 from 70.7 ± 16.7 to 77.2 ± 17.2 ; $p < 0.0001$), as well as improvement of objective outcome as the augmentation of both cheeks' thickness (right cheek from 4.3 ± 1.9 mm to 9.5 ± 3 mm; $p < 0.0001$; left cheek from 4.4 ± 2 mm to 9.6 ± 3.1 mm; $p < 0.0001$). Notwithstanding that surgery has been limited to the face, all patients have reported body image improvement, even though the ABCD questionnaire had no specific questions or items referring to facial lipoatrophy. Apparently, facial surgery has resulted in an improvement of whole body aesthetic satisfaction and psycho-social life (social and sexual life, health perception, habits, affections,



Figure 2 . Pre- and post-picture comparison of a patient undergoing 10 ml polyacrylamide injections.

relationships). This positive effect was evident in the overall sample and in the polyactic acid and polyacrylamide groups, while it has reached no statistical significance in the lipofilling group.

One of the most striking impacts of surgery was on depression as assessed by the Beck Depression Inventory (BDI)³⁶. This is a self-administered, 21-item scale measuring supposed manifestations of depression. It includes factors reflecting negative attitudes towards self, performance impairment, and somatic disturbances, as well as a general factor of depression³⁷. The BDI takes approximately 10 minutes to complete. The higher the score, the greater the state of depression. Total possible scores range from 0 to 63. Mild depression was defined as a value between 9-17, moderate depression between 18-29, and a severe depression for values greater than 30. At follow-up, the change in BDI revealed a significant improvement in the depression score for the overall cohort from 11.4 ± 8.3 (corresponding to mild depression) to 9.4 ± 7.8 (almost absent of depression); $p = 0.001$. Nevertheless, analyzing the score by a single surgery group the change was significant in the polyactic acid and polyacrylamide groups only (lipofilling score changed from 10 ± 8.3 to 10.4 ± 8.7 , $p = ns$; lipofilling plus polyactic acid score changed from 15.6 ± 10.5 to 12.7 ± 12.1 , $p = ns$; polyactic acid score changed from 10.7 ± 7.4 to 8 ± 6.5 , $p = 0.001$; poly-

acrylamide score changed from 11.8 ± 8.5 to 9.6 ± 8.1 , $p = 0.014$) (Fig. 3)

Loutfy, et al. have evaluated the safety and efficacy of polyalkylimide gel (PAIG) in the treatment of HIV-associated facial lipoatrophy in a randomized, open-label, single-centre study. Thirty-one HIV-infected individuals (median age 48 years, 97% male) with facial lipoatrophy (based on physician assessment) have been randomly assigned to immediate (weeks 0 and 6) or delayed (weeks 12 and 18) PAIG injections administered into the subcutaneous plane. Overall, the median volume of product injected bilaterally has been 16.0 ml. Adverse events, including swelling, redness, bruising, and pain, were mild and resolved after a median of three days. Outcome measures have included a change in facial lipoatrophy severity scores (five-point scale), adverse events, photographic assessment, and changes in QoL, depression, and anxiety using validated surveys. Compared with patients randomly assigned to delayed treatment, patients in the immediate therapy group had significantly lower physician-rated facial lipoatrophy scores (0 vs. 2; $p < 0.0001$), improved QoL ($p = 0.01$), and lower anxiety ($p = 0.02$) at week 12. At week 48, median physician and patient facial lipoatrophy scores were 0 and 1, respectively, for the entire cohort, and were not significantly different between the groups. Significant improvements in patient anxiety ($p = 0.001$)

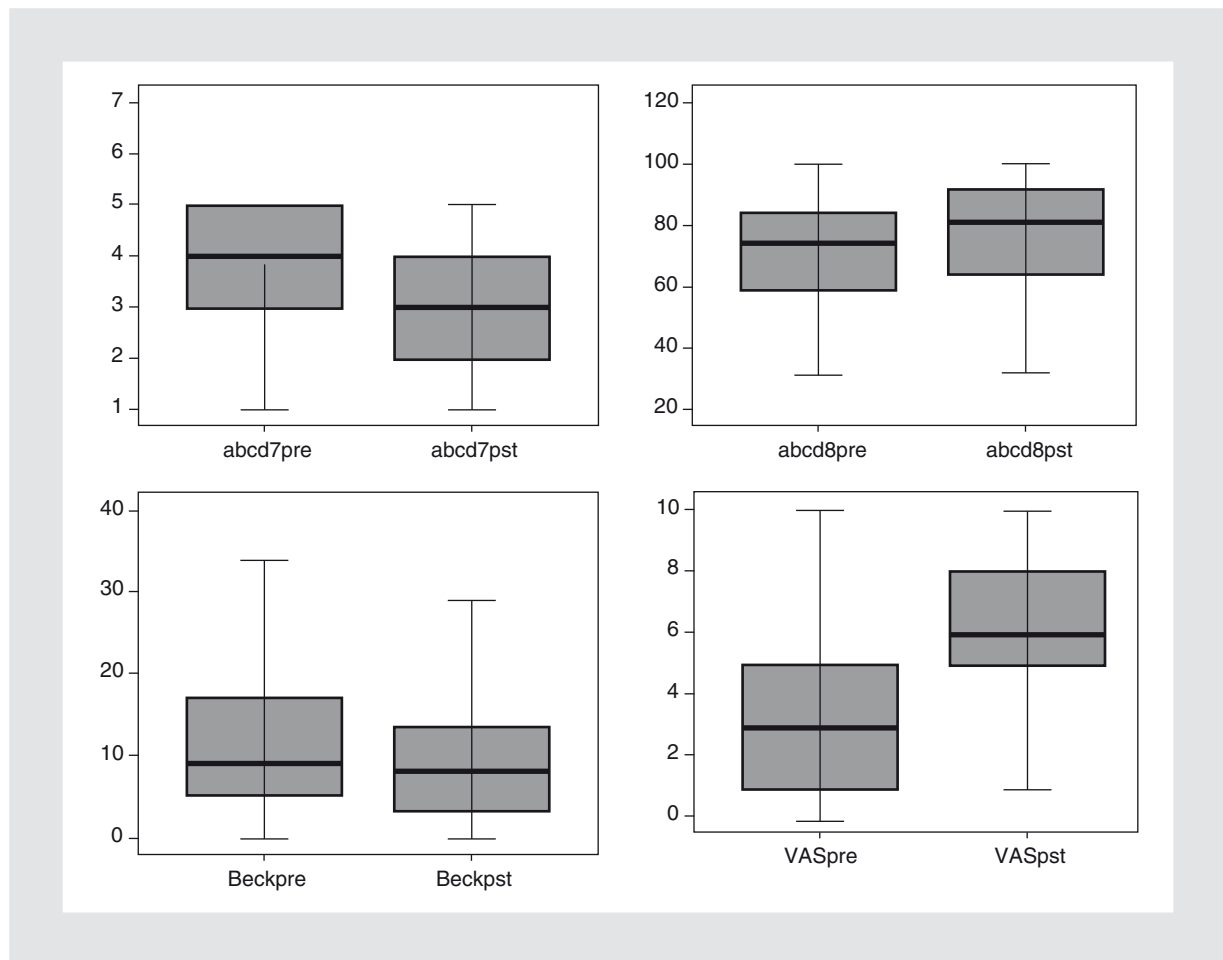


Figure 3. Evaluation of body image perception (ABCD7 & ABCD8), depression (Beck Depression Inventory) and facial aesthetic satisfaction (Visual Analog Scale), as subjective variables 48 weeks after the end of surgery compared to baseline. All the differences are statistically significant.

and depression ($p = 0.01$) were observed from baseline to week 48³⁸.

Conclusions

Lipodystrophy constitutes a major cause of concern for a growing proportion of patients infected with HIV who are compelled to receive long-term antiretroviral therapy. This problem may dramatically diminish the effectiveness of current antiretroviral regimens. We need to assess the impact that lipodystrophy may have on the everyday life of patients infected with HIV. A better knowledge of the associations between lipodystrophy and HRQoL allows us to understand the burden of long-term toxicities of antiretrovirals as well as to identify novel patient-related endpoints useful in assessing the efficacy of programs treating lipodystrophy.

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