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Disorders of Body Fat Distribution in HIV-1-Infected Patients

Santiago Moreno[1], Celia Miralles[2], Eugenia Negredo[3], Pere Domingo[4], Vicente Estrada[5], Felix Gutiérrez[6], Fernando Lozano[7] and Esteban Martínez[8]

[1]Hospital Ramón y Cajal, Madrid, Spain; [2]Complejo Hospitalario Xeral de Vigo, Pontevedra, Spain; [3]Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; [4]Hospital de la Santa Creu i San Pau, Barcelona, Spain; [5]Hospital Clínico Universitario, Madrid, Spain; [6]Hospital General Universitario de Elche, Alicante, Spain; [7]Hospital Universitario de Valme, Seville, Spain; [8]Hospital Clínic - Institut d'Investigaciones Biomèdiques August Pi i Sunyer, University of Barcelona, Barcelona, Spain

Abstract

Body fat disorders are a common and relevant problem in HIV-1-infected patients that can be associated with metabolic alterations. Many controversies in their definition, pathogenesis, measurement, and management remain unclear. Several factors including HIV-1 infection itself and antiretroviral therapy have been associated with the development of these alterations. Most studies show that the action of drugs on the pathogenesis of lipoatrophy is undeniable. However, they also show that there are considerable differences not only between the different families of antiretroviral drugs, but also between the individual members of these families. The diagnosis of lipodystrophy is limited by the absence of an agreed definition and a reference for normality. Accurate diagnosis, especially in mild-moderate cases, is difficult, almost always subjective, not standardized, and cannot be carried out by a single method. In general, subjective evaluation by the physician and patient, together with simple techniques such as anthropometry, can provide highly valuable information, especially when used over time. Although there is no known therapy to completely reverse lipodystrophy once it becomes established, there is evidence that lipoatrophy can be partially improved by replacing thymidine analogs in certain cases. In addition, reparative surgery may prove useful in moderate or severe cases. Neither the interruption of antiretroviral therapy nor the use of metformin, glitazones or growth hormone analogs can be recommended due to their limited efficacy or associated complications. **(AIDS Rev. 2009;11:126-34)**

Corresponding author: Esteban Martínez, esteban@fundsoriano.es

Key words

Lipoatrophy. Lipohypertrophy. HIV-1 infection. Antiretroviral therapy.

Introduction

Body fat disorders are a common and relevant problem in HIV-1-infected patients. Their clinical presentation involves fat loss (lipoatrophy) and/or fat gain (lipohypertrophy) in different parts of the body. Lipoatrophy is usually observed on the face, buttocks, and limbs, and lipohypertrophy generally presents as an accumulation of abdominal visceral, dorsocervical, mammary, and/or suprapubic fat.

Correspondence to:
Esteban Martínez
Unidad de Enfermedades Infecciosas
Hospital Clínic, Universidad de Barcelona
Villarroel 170
08036 Barcelona, España
E-mail: esteban@fundsoriano.es

Disorders in the distribution of body fat associated with HIV-1 infection must be differentiated from wasting syndrome and from the body changes associated with aging. Wasting syndrome is characterized by a generalized loss of body fat and lean mass. Aging may involve a reduction in lean mass, and a redistribution of body fat with an increase in the trunk and a reduction in the lower limbs[1].

Anthropomorphic changes in HIV infection can be associated with various metabolic alterations, especially dyslipidemia and insulin resistance, which are covered by the term "lipodystrophy syndrome." However, these conceptually different processes can appear as clinically independent forms[2].

These disorders are important because of the effect of esthetic changes on a patient's quality of life; the psychological repercussions may affect the patient's working and social life and compromise adherence to therapy[3]. However, the long-term consequences of cardiovascular risk stemming from metabolic disorders must also be taken into account[4].

Table 1. Classification of body fat distribution disorders associated with HIV-1 infection

Body fat distribution disorders classification	
1. Fat loss (lipoatrophy)	Face Buttocks Arms Legs
2. Fat accumulation (lipohypertrophy)	Abdominal obesity Mammary hypertrophy Accumulation of fat on the dorsal region of the neck Accumulation of fat on the anterior region of the neck Accumulation of fat on the side of the neck Accumulation of fat on the suprapubic region Localized or generalized lipoma
3. Mixed Alterations	

Definition

Disorders of body fat distribution are difficult to define and measure owing to the absence of "normality" references in the general population, variability in clinical presentation, and the lack of standardized, reproducible, and affordable methods of measuring regional fat. The current definition and classification are based on the findings of a detailed physical examination by the physician and the patient's self-assessment. In some cases, anthropometric measurements and/or imaging may prove useful for follow-up.

Several attempts have been made to agree on an objective case definition. A definition based on the following has been put forward: demographic variables (sex, age), variables related to HIV-1 infection (duration and stage of infection), anthropometric variables (waist-hip index), biochemical variables (anion gap, HDL cholesterol), and measurements by computed tomography (CT) (ratio of visceral fat to subcutaneous fat) and dual-energy x-ray absorptiometry (DXA) (ratio of trunk fat to leg fat)[5]. This case definition is 80% accurate and more sensitive than the usual clinical evaluation, both for diagnosis and for assessment of the intensity of distribution disorders[6].

In addition to being complex and requiring variables from CT and DXA, this classification groups lipoatrophy and lipohypertrophy under the common term "lipodystrophy." Today, we know that the pathogenesis of each process is different. In fact, there is consensus on classifying body fat disorders into two clearly differentiated clinical syndromes, i.e. fat loss or lipoatrophy, and fat accumulation or lipohypertrophy[2] (Table 1), although some patients can present mixed conditions.

It may be useful to grade the intensity of clinical disorders using a severity scale. The most well known is the Lipodystrophy Severity Grading Scale (LSGS) used in the HOPS (HIV Outpatient Study)[7] cohort, which, after observer- and patient-based evaluation of the different areas, classifies lipodystrophy as mild, moderate, or severe. In order to clinically evaluate facial lipoatrophy, Fontdevila, et al. have proposed a grade classification based on the relief of facial bone and muscle structures[8]. Starting from a normal situation in which the skin in the malar region protrudes slightly from the orbit to the nasogenial fold, grade I involves a flattening of malar relief, grade II includes malar depression, and grade III is characterized by skeletization of the face with exposure of facial muscle, especially the major zygomatic muscle. This classification has been validated using CT, and has shown significant agreement between different assessors on each of its grades[9].

Pathogenesis

Lipoatrophy and lipohypertrophy have common risk factors[2] and at least three are involved in their pathogenesis: the patient, HIV-1 infection, and antiretroviral drugs.

The patient-related factors that have been associated with the onset of lipoatrophy and lipohypertrophy are similar, if not identical, and include age, sex, baseline body mass index (BMI), and ethnic group[2]. Furthermore, mutations in the tumor necrosis factor (TNF) alpha-promoting gene and in the interleukin 1 (IL) beta-promoting gene have been reported to affect the incidence of lipoatrophic changes[10,11]. However, the association of these mutations with the presence of lipoatrophy has not been reproduced in the literature.

We have no direct evidence of the involvement of viral factors in the pathogenesis of lipohypertrophy, although its onset is similar to that of lipoatrophy in aspects of HIV-1 infection such as CD4 levels, previous diagnosis of AIDS, and the number of copies of HIV-1 RNA[2]. As for the action of the virus on subcutaneous fat, reports on treatment-naive patients tell us that infection *per se* can increase expression of anti-adipogenic and proinflammatory genes and reduce the expression of pro-adipogenic genes and genes coding for "trophic" adipocytokines (adiponectin and leptin)[12].

Most research into the pathogenesis of lipoatrophy and, to a lesser extent, lipohypertrophy is based on *in vitro* or *ex vivo* studies with patient fat samples. All these studies show that the action of drugs on the pathogenesis of lipoatrophy is undeniable. However, they also show that there are considerable differences not only between the different families of antiretroviral drugs, but also between the individual members of these families. Nucleoside reverse transcriptase inhibitors (NRTI), especially thymidine analogs, have been shown to act as mitochondrial toxins due to their ability to inhibit DNA polymerase gamma, which is essential for the replication and repair of mitochondrial DNA[13]. In addition, NRTI have a negative effect on adipogenesis, insulin sensitivity, and secretion of adipocytokines[14,15]. In general, the same occurs with protease inhibitors (PI), although with some differences: their effect is more intense on adipocyte differentiation and less marked on mitochondrial function[16]. Furthermore, with the important exception of atazanavir, PI have an effect on insulin sensitivity in which GLUT4 glucose transporter channel inhibition plays a role[16]. The confluence of the toxicity mechanisms of NRTI and of PI could explain the additive, even synergistic, effects observed *in vivo* when both classes are combined.

Non-nucleoside reverse transcriptase inhibitors (NNRTI) have traditionally been considered benign towards adipose tissue. The recent results of a study involving efavirenz (EFV) in the development of lipoatrophy[17] have no solid basis in experimental studies. Only one study shows the anti-adipogenic effects of very high (greater than therapeutic) doses of EFV using a molecular mechanism similar to that reported for PI; that is, an effect by which there is an alteration in the nuclear localization of sterol regulatory binding proteins[18]. There is no evidence of anti-adipogenic effects of nevirapine on brown adipocytes[19].

It is unknown whether fusion inhibitors have an effect on adipocyte metabolism, and studies on the new antiretroviral families have not yet been carried out. Nevertheless, integrase inhibitors are not expected to have serious effects on the biological features of adipocytes due to the lack of similarity of the cellular enzymes they act upon. The effect of CCR5 chemokine receptor agonists has not yet been investigated.

Knowledge of the pathogenesis of lipohypertrophy is limited. The exact mechanisms that lead to visceral adiposity are mainly unknown, although antiretroviral drugs have been shown to have characteristic effects on visceral and subcutaneous adipose tissue deposits[20]. Furthermore, in lipohypertrophy of dorsocervical tissue and in other areas of the body, adipocytes have been observed to present a brown fat phenotype[21]. The analysis of gene expression in tissue samples obtained from buffalo humps has revealed the absence of traits of inflammation, whereas the low mitochondrial DNA content and the presence of adipogenesis alteration markers were similar to those observed in subcutaneous fat[21]. Furthermore, markers associated with a high state of proliferation have been detected in the adipose tissue of buffalo humps.

Risk factors

Various studies have identified factors associated with the development of body fat distribution disorders. These factors are associated both with HIV-1 infection itself and with the patient or antiretroviral therapy (Table 2).

As for those factors related to HIV-1 infection, only a few studies have found an association between viral load and a greater probability of developing lipodystrophy[22,23]. To a great extent, it is unknown whether HIV-1 infection affects development of this disorder, since the duration of HIV-infection is generally parallel to the duration of antiretroviral therapy, and the effects of the two variables cannot be separated. In the case-control study used for the case definition of lipodystrophy, patients with this complication presented a significantly greater duration of HIV-1 infection[5].

As for patient-related factors, some authors have found that age and CD4 count are significantly associated with the development of body fat distribution disorders. Older age is associated with the development of lipoatrophy and lipohypertrophy, the lowest nadir of CD4 is associated with lipoatrophy, whereas the increase in CD4 count with therapy has been associated with a greater risk of lipohypertrophy[7]. There is no firm evidence that baseline nutritional status has a significant effect on the onset of these changes, although some studies have shown that patients with a greater BMI than normal (> 25 kg/m^2) present a lower risk of lipoatrophy and a greater risk of developing lipohypertrophy[23]. Finally, although the existence of genetic factors is biologically plausible, we do not yet know to what extent or how these factors can affect the onset of the disorder[10,11].

As for antiretroviral therapy, longer duration and prolonged exposure to thymidine analogs, especially stavudine (d4T), are associated with a greater risk of developing lipoatrophy and lipohypertrophy[2,24-28]. The role of other antiretroviral drugs is controversial, partly due to difficulties in establishing causal relationships in combination regimens. In the nucleoside/nucleotide analog family, tenofovir (TDF) and abacavir (ABC) have shown a beneficial effect on the recovery of subcutaneous fat; therefore, they can be considered as having low-risk for lipodystrophy. The importance of didanosine (ddI) and lamivudine (3TC) or emtricitabine (FTC) in pathogenesis is unknown, although it is generally considered low. With regard to PI, prolonged therapy with indinavir or nelfinavir has been related to a greater probability of suffering from lipoatrophy and lipohypertrophy, whereas preliminary

Table 2. Risk factors for the development of body fat distribution disorders in HIV-1-infected patients receiving antiretroviral therapy

Risk factors for the development of body fat distribution disorders	
Patient-related factors	Age Sex Body mass index Ethnic group Genetic factors
Factors related to HIV-1 infection	Duration of infection AIDS diagnosis $CD4^+$ lymphocyte count Viral load
Factors related to antiretroviral therapy	Duration of therapy Treatment with thymidine analogs Treatment with protease inhibitors Treatment with non-nucleoside analogs (?)
Other factors	Treatment with other drugs

data with PI boosted with low-dose ritonavir (saquinavir, atazanavir, lopinavir, tipranavir, darunavir) seem to show that they represent a lower risk of developing lipodystrophy. As mentioned above, most studies with EFV and nevirapine show that NNRTI have a neutral effect. It has even been observed that prolonged use (> 1 year) of these drugs is associated with a lower probability of developing lipodystrophy[29]. In one study, the use of thymidine analogs with EFV was associated with a greater incidence of lipoatrophy (defined as a limb fat loss of at least 20%) than the same combination with lopinavir/ritonavir (LPV/r)[17]. However, this initial finding has been called into question due to the arbitrariness of the definition of lipoatrophy used, the lack of correlation between the definition and the clinical diagnosis of lipoatrophy, and the role of several independent risk factors in fat loss detected by DXA[30]. In addition, one study of the specific effect on adipose tissue of different antiretroviral drugs has confirmed that the depletion of mitochondrial DNA and the pathological findings of lipoatrophy are specifically associated with thymidine analogs. No association was found with the non-analogs (EFV) or protease inhibitors (LPV) evaluated[31].

Diagnosis

The diagnosis of lipodystrophy is limited by the absence of an agreed definition and a reference for normality. The ideal method for evaluating body composition should be accurate, user-friendly, cheap, fast, reproducible, and harmless. Currently available methods (Table 3) fulfill only a few of these requirements and, therefore, the choice of one or the other will depend first on accessibility and availability, and later on the information we want to obtain, the type of study, and the number of patients.

Methods for the evaluation of body composition

Anthropometry is widely used in clinical practice and epidemiological studies. Skin fold thickness is measured using standardized techniques. The tricipital fold alone shows the best correlation with total fat in the general population. Fat mass can be calculated using different equations constructed from the sum of several folds that are representative of fat thickness in different body segments. The most widely used and validated is the Durnin-Womersley equation, which includes the bicipital, tricipital, subscapular, and suprailiac folds[34,35]. Anthropometry is simple, noninvasive, and affordable, but its greatest limitation lies in the wide differences in the fat distribution pattern.

Some attempts have been made to validate ultrasound for the assessment of subcutaneous adipose tissue (SAT) in several localizations (abdomen, face, arms), but the results have been disparate. Although attractive because of its speed, innocuousness, low price, and convenience for the patient, this technique requires the presence of an experienced examiner[37]. Although it has not been widely evaluated, some recent studies have shown acceptable inter- and intra-observer variability and a good correlation with CT when used for the evaluation of intraabdominal fat and leg fat thickness, but not for the evaluation of subcutaneous abdominal, arm and facial fat[38]. Computed tomography and, to a lesser extent, magnetic resonance imaging (MRI), have been used since the 1980s to measure abdominal fat by a slice at L4, with a considerable predictive value in total adipose tissue[39].

Bioelectric impedance analysis (BIA) brings together many of the characteristics of the ideal method (ease of use, innocuousness, and reproducibility), although it lacks

Table 3. Useful diagnostic methods for measurement of body composition and body fat disorders

Diagnostic methods
Anthropometric measurements
Echography
Bioelectric impedance analysis
Computed tomography
Magnetic resonance
Double-energy x-ray absorptiometry
Laser scan

the accuracy of the reference methods. In addition, BIA calculates total fat with no specific information on the different fat compartments. Furthermore, the redistribution of fat itself affects the calculation of the total fat component. Therefore, measurement of total fat by BIA is even less accurate in the presence of lipodystrophy[40].

One of the most novel diagnostic techniques is DXA, which allows us to evaluate body composition by separating the lean mass and fatty mass components of soft tissue. It is very accurate in stable subjects (± 99%). Its main limitations, aside from the high installation cost and the need for specialized personnel, are the progressive increase in errors with corpulence and the difficulty to detect sudden changes in body composition (e.g. alterations to hydration). Despite the fact that it is currently considered the gold standard for evaluation of total fat, its limitations must be taken into account and further studies are necessary[33,40]. Unfortunately, there is no simple correlation between the objective measurement of body fat using techniques such as DXA and the subjective diagnosis of lipoatrophy. This lack of agreement was made obvious in a recent study in which lipoatrophy was defined arbitrarily as a loss of at least 20% in limb fat and in which this objective diagnosis showed very little correlation with clinical lipoatrophy as perceived by the patient[30]. In fact, further studies have shown that fat loss greater than 35% may be necessary to become clinically evident[32].

None of the methods mentioned above for calculating total fat can distinguish changes in each of the compartments and, therefore, any evaluation of fat redistribution requires the use of several complementary methods[33].

Evaluation of central fat accumulation or lipohypertrophy

Subjective evaluation by the patient and the physician using a systematic questionnaire continues to be the most useful method in clinical practice[7,33,34]. As for anthropometry, the waist-hip index is the most widely accepted indicator of anomalous fat distribution. Abdominal obesity is defined as an index greater than 0.9 in men and 0.8 in women. However, several aspects limit its accuracy: the different measuring points used, the absence of a waist measurement in obese subjects, and the size of abdominal organs and muscles. Measurement of isolated folds or circumferences may be useful when used over time[35,36].

Echography is a simple technique that has shown a good correlation with other techniques, such as CT, for the measurement of intraabdominal fat[37,38]. Nevertheless, the results depend on the expertise of the operator and can be affected by the presence of intraluminal gas or in obese patients[37]. Computed tomography is one of the best methods for measuring the components of abdominal fat. Only one slice is used (at L4, approximately at the level of the navel). Several studies have shown that this is the only slice with a high correlation with multiple slices and lower radiation and examination time. Its main limitations are cost, radiation, the need for specialized personnel, and limited availability[33,40]. Although MRI does not use ionizing radiation, it is more expensive, examination time is longer, and it delimits visceral fat less accurately[40]. Although DXA is increasingly used for the segmental study of fat, (i.e. to evaluate the relationship between trunk fat and limb fat), there are few validation studies. In addition, some limitations should be taken into account: it is difficult to delimit soft tissue over bone, with the result that its composition is extrapolated from neighboring tissue, and it does not allow measurement of the different abdominal fat components[33,40].

Evaluation of lipoatrophy

Although the loss of facial fat is the most stigmatizing external sign that most worries patients with lipodystrophy, there is still no standardized accurate diagnosis. As is the case with central accumulation, subjective evaluation by the patient and physician using a systematic questionnaire continues to be the most useful method in clinical practice for evaluating facial lipoatrophy[7,33,34,41]. The variable results obtained with anthropometry and echography reflect the lack of data in the general population and the absence of a gold standard. Some researchers have observed a good correlation between subcutaneous fat measurement using echography and other methods of diagnosing lipoatrophy[38,40], although these results have not been uniform for other investigators[41]. In several studies, single-slice CT and MRI have proven to be reproducible and able to differentiate between patients with and without lipoatrophy. They also have a high correlation with the loss of subcutaneous fat evaluated by other standard methods[40,42]. Finally, novel techniques such as laser scan or 3-dimensional photography are cheap and easy to perform

and are reasonably able to distinguish affected patients[43]. However, experience is limited and large-scale validation studies are necessary.

In conclusion, accurate diagnosis of lipodystrophy, especially in mild-moderate cases, is difficult, almost always subjective, not standardized, and cannot be carried out by a single method. For lipoatrophy, baseline evaluation is important, as is early, even subclinical diagnosis. In general terms, subjective evaluation by the physician and patient together with simple techniques such as anthropometry can provide highly valuable information, especially when used over time. The use of more complex methods is limited to clinical trials or studies for pathogenic and reversibility analyses for which highly accurate techniques are necessary.

Prevention

Prevention of lipoatrophy

This strategy is very important for patients about to initiate antiretroviral therapy as there is no known therapy to completely reverse this condition once it becomes established. In recent years, the number of new cases of lipoatrophy has fallen due to the choice of drugs, and, more specifically, certain NRTI such as TDF and ABC, which are less harmful for SAT. This choice is based on wide evidence that regimens containing zidovudine (ZDV) or d4T induce lipoatrophy with a greater frequency than those containing TDF or ABC.

Randomized clinical trials of initial regimens have clearly shown the advantages of avoiding thymidine analogs. Studies comparing TDF with d4T or AZT as initial therapy have consistently shown a gain in limb fat content measured by DXA and scarce development of lipoatrophy in patients taking TDF, in contrast with the limb fat loss observed in those taking AZT or d4T[44,45]. These results are supported by the metabolic subanalysis of a large clinical trial with three treatment arms (EFV + two NRTI, LPV/r + two NRTI, and EFV + LPV/r), in which lipoatrophy was defined as a reduction of 20% or more in the adipose tissue of the limbs measured by DXA[17]. Randomization was stratified on the basis of the choice of NRTI, so a suitable balance between the arms was reached. The frequency of lipoatrophy at week 96 was considerably greater in patients receiving d4T (42%) or ZDV (27%) than in those taking TDF (9%). The frequency of lipoatrophy in the latter was very similar to that of patients on the NRTI-sparing EFV + LPV/r regimen (8%), yet another argument in favor of the innocuousness of TDF with regard to peripheral fat[17]. Similar data have been obtained in two clinical trials comparing ABC with d4T. These studies, which used objective baseline values for measuring body fat, showed that the patients treated with ABC gained limb fat, whereas, once again, those treated with d4T lost fat[46,47].

Protease inhibitors can also affect SAT, although there is some variability between them. Clinical trials have provided different results. In study ACTG384, patients treated with nelfinavir showed significant peripheral fat loss by DXA (–13.1%) compared with those who took EFV (+1.8%)[48]. Nevertheless, in a subanalysis of study BMS034, in which sequential examinations with CT and DXA were made, there were no significant changes in subcutaneous body fat with atazanavir or EFV after one year of treatment[49].

The NNRTI are not generally considered to be associated with peripheral lipoatrophy. This assessment is based on clinician's perception after long-term and widespread use of NNRTI, as well as on results of several controlled clinical trials and cohort studies. Recent data from the aforementioned study ACTG5142 are therefore very surprising. The prevalence of subclinical fat loss in that study was greater in patients from the EFV + two NRTI group than in those from the LPV/r + two NRTI group. The DXA findings did, however, not correlate with clinically observed lipoatrophy[30]. Other recent data from a study evaluating an induction strategy with LPV/r + ZDV/3TC followed by a maintenance regimen with LPV/r in monotherapy compared with a standard regimen of EFV + ZDV/3TC are less meaningful to answer this question as patients in the maintenance phase on LPV/r monotherapy had no long-term exposure to ZDV, which as discussed above is associated with lipoatrophy. The patients treated with the ZDV-containing EFV regimen presented a significantly lower limb fat content in the 96-week DXA than those of the LPV/r group as a whole (triple therapy plus monotherapy)[50]. In contrast, another recent long-term study (extension of study CRPCRA016 up to five years) saw no significant differences in body fat changes measured by both anthropometry and bioelectrical impedance between the three antiretroviral strategies compared (PI + two NRTI, NNRTI + two NRTI, and PI + NNRTI)[51].

In summary, an association between lipoatrophy and thymidine analogs seems established, while non-thymidine NRTI , PI, and NNRTI seem less so.

Prevention of lipohypertrophy

Contrary to the situation with lipoatrophy, and consistent with the fact that it has not been possible to establish an association between the development of trunk lipohypertrophy and certain drugs or drug classes, no therapeutic strategy to prevent this condition is known. Furthermore, although it is reasonable to think that suitable diet and physical exercise can help to prevent lipohypertrophy, this

has not yet been demonstrated in patients who already have established disease and in whom abdominal fat content and hypertriglyceridemia fall slightly[52].

Treatment

Medical treatment

Since the first descriptions of lipodystrophy, several strategies based on the state of the art have been tried, with varying success rates. The first therapeutic strategy proposed, based on the belief that PI were the only agents responsible for the disease, was substitution of the PI with an NNRTI[53-55]. Unfortunately, simply switching a PI for an analog did not lead to significant improvement in morphological changes.

It was subsequently shown that NRTI were involved in the pathogenesis of lipodystrophy through mitochondrial dysfunction. *In vitro* results showing a different affinity of analogs for gamma polymerase led to clinical trials. The resultant strategy was substitution of thymidine analogs (AZT or d4T), which were associated with greater mitochondrial toxicity, by other less toxic drugs. One of the first and most representative studies, MITOX, showed a significant recovery of subcutaneous limb fat after replacing the thymidine analog with ABC[56]. Equally favorable results were published after thymidine analogs were replaced by TDF[57,58].

The same pathogenic mechanism was used as an argument in favor of withdrawing nucleosides and using nucleoside-sparing regimens by combining a PI/r with a NNRTI[17,59,60] or PI/r in monotherapy (mainly LPV/r)[61]. Current data suggest a favorable effect, although there are few studies and the regimens used are frequently associated with dyslipidemia and problems of immediate or digestive tolerance. There are no data to allow us to make a recommendation on avoiding NNRTI or whether they should be replaced. Finally, and contrary to expectations, results from studies examining complete interruption of therapy have been controversial, and interruptions are not currently recommended under any circumstances[62-64].

Parallel to this, insulin resistance and the subsequent accumulation of central fat attributed to therapy with some PI mean that co-adjuvant treatments have been proposed to reverse lipohypertrophy. Insulin-sensitizing agents (thiazolidinediones) can correct PI-associated insulin resistance and reverse visceral obesity as does metformin. Hormone treatments, such as testosterone or growth hormone, have been analyzed in several clinical trials with the same objective. However, the limited results obtained in most studies[65], together with the not insignificant toxicity they are often associated with[66], do not speak in favor of generalized use of these treatments to reverse lipodystrophy.

Lastly, promising preliminary results have been obtained with investigational drugs such as uridine[67], leptin[68], or growth hormone analog[69]. In addition to changes in therapy, there is no doubt that changes to lifestyle and diet can be included among the recommendations for the patient with lipodystrophy. A healthy diet with calorie restrictions plus exercise can help to reduce some grades of lipohypertrophy[52,70].

Surgical treatment

Despite the above observations, in recent years we have had to turn to plastic surgery as an alternative to palliate lipodystrophy in those cases where changes in body fat are well established and have significantly reduced the patient's quality of life. Therefore, different techniques have been proposed, depending mainly on whether there is a loss or accumulation of body fat.

Ultrasonic liposuction is used to treat buffalo hump, gynecomasty, increased abdominal contour, or lipomas located in other areas. This technique provides more satisfactory results than those of conventional liposuction, with fewer local postoperative complications. Nevertheless, relapse has been reported in up to 15% of cases[71]. Surgical resection and breast reduction could be indicated when fat deposits are localized.

Fat loss in the buttocks can be repaired using silicone gluteal prostheses, with satisfactory results, although implantation requires admission to hospital, has a painful postoperative period, and is not free from complications. This technique is not recommended for most patients with gluteal lipoatrophy, only in those who complain of difficulty sitting down or who present trophic cutaneous disorders. Lastly, facial atrophy, undoubtedly the most stigmatizing sign, has been treated with several filling products such as autologous fat or synthetic substances. Infiltration of autologous fat can provide lasting results (at least more than one year)[72]. Its advantages over synthetic materials are the low risk of infection or rejection and the lower cost. Its disadvantage is that a large proportion of patients with lipoatrophy do not have sufficient fat to donate. It is not advisable to use fat from the buffalo hump, since it can lead to lipohypertrophy in the area where it is implanted[73]. In addition to autologous fat, several synthetic products are available as fillers. The main difference between them is their durability, and, consequently, the greater or lesser need for subsequent adjustments. The use of permanent synthetic fillers should be recommended with caution: their results can be unsatisfactory due to the natural modification of the facial contour with time, and any complication that arises may be very difficult to treat. The most

widely used reabsorbable implants are polylactic acid and hyaluronic acid, whereas the most widely used permanent implants are polyacrylamides and polyalkylimides[73-76].

To conclude, there is clear evidence that lipoatrophy can be improved by replacing thymidine analogs in certain cases, although this improvement is slow and limited. Similarly, lifestyle changes must be recommended to all patients as they are easy, universally accessible, and beneficial for the patient's general health. Reparative surgery may prove useful in moderate or severe cases where the patient requests it. However, neither the interruption of antiretroviral therapy nor the use of metformin, glitazones, or growth hormone to treat lipodystrophy can be recommended due to their limited efficacy or associated complications. Furthermore, there is little information on the role of nucleoside-sparing regimens or the use of uridine, leptin, or growth hormone analogs in the treatment of lipodystrophy.

Members of the "HIV Body Fat Distribution Workgroup"

Aguirrebengoa K, Hospital de Cruces, Barakaldo (Bizkaia); Asensi V, Hospital Universitario Central de Asturias, Oviedo; Blanco F, Hospital Carlos III, Madrid; Del Pozo M, Hospital Clínico Universitario, Valladolid; Galindo P, Hospital Clínico Universitario, Valencia; Knobel H, Hospital del Mar, Barcelona; López Aldeguer J, Hospital Universitari La Fe, Valencia; Palacios R, Hospital Universitario Virgen de la Victoria, Málaga; Pedrol E, Hospital General de Granollers, Granollers (Barcelona); Pérez-Elías Mª J, Hospital Ramón y Cajal, Madrid; Podzamczer D, Hospital Universitario de Bellvitge, Barcelona; Ribera E, Hospital Universitari Vall d'Hebrón, Barcelona; Rivero A, Hospital Reina Sofía, Córdoba; Sanz J, Hospital Príncipe de Asturias, Alcalá de Henares (Madrid); Suárez I, Hospital Infanta Elena, Huelva; Viciana P, Hospital Universitario Virgen del Rocío, Seville.

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