Drug Safety 2001; 24 (3): 157-166
0114-5916/01/0003-0157/$22.00/0

Lipodystrophy Syndrome in Patients with HIV Infection

Quality of Life Issues

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Abstract

Current antiretroviral therapy has lead to longer survival in patients infected with HIV, but it is also associated with new and important problems. Body fat redistribution and metabolic abnormalities, the so-called lipodystrophy syndrome, are among the most prevalent and worrisome ones. While an increasing number of patients infected with HIV are becoming affected by this syndrome, the pathogenesis of this syndrome and how to prevent and treat the problem all remain largely unknown.

Body fat changes stigmatise the bodies of patients infected with HIV giving them a similar look to that seen in patients some years ago when the wasting syndrome was more prevalent and HIV infection was ultimately fatal. The psychological impact of body fat changes may be severe enough to affect a patients' desire to continue with antiretroviral therapy. Metabolic abnormalities, probably with the exception of symptomatic diabetes mellitus and hypertriglyceridaemia-induced pancreatitis, do not have an immediate impact on the quality of the lives of patients with HIV. However, their potential long term cardiovascular and bone consequences may increase the morbidity and the mortality of patients infected with HIV through noninfectious diseases. The impact of lipodystrophy on patients infected with HIV is not readily captured with the classic instruments used to measure quality of life and hence it is necessary to modify them urgently. Though treating lipodystrophy seems fully justified, there is no proven treatment for this problem, although a number of treatments have been used with varying success. Despite the recognition that lipodystrophy may have important psychological repercussions, the best psychological approach for this problem is not known at present. Although lipodystrophy has its own peculiarities, existing knowledge about how to psychologically help other patients with deforming body changes might be of help for patients infected with HIV, or at least may act as a starting point.

1. An Historical Perspective of Lipodystrophy

The introduction of triple antiretroviral therapy (the so-called 'highly active antiretroviral therapy' or HAART) and the routine monitoring of HIV RNA (the so-called 'viral load') in plasma have resulted in an unprecedented decrease in the morbidity and the mortality associated with AIDS.[1,2] However, the antiretroviral drugs and therapy strategies currently available are unable to eradicate HIV infection[3,4] and consequently HAART must be administered indefinitely. In this setting, the risks of drug toxicity and failure caused by viral resistance represent the new issues of concern for patients receiving HAART.[5,6]

Fig. 1. Increased abdominal girth attributable to intra-abdominal fat accumulation in a man infected with HIV. The accumulation of intra-abdominal fat may cause digestive or respiratory problems because of compression of the nearby anatomical structures.

During the 5th Conference on Retroviruses and Opportunistic Infections held in Chicago in 1998, delegates heard about a number of problems that had not been previously reported. Several groups of physicians from different parts of the world described cases of patients infected with HIV with body fat redistribution and metabolic abnormalities. Reports were heterogeneous, but they shared similarities. Body changes included an increase in truncal (intra-abdominal, dorsocervical, or breast) fat (fig. 1) and a decrease in subcutaneous fat (fig. 2). Metabolic abnormalities consisted of hypertriglyceridaemia with or without hypercholesterolaemia and insulin resistance with or without diabetes mellitus (fig. 3). More recently, bone metabolic abnormalities have been also detected in persons infected with HIV with lipodystrophy.[8,9] Although it remains unclear whether the metabolic and clinical abnormalities are entirely related to each other, these problems are commonly named lipodystrophy.[7] Initially thought to be associated with the use of HIV protease inhibitors (PI), at present we know that lipodystrophy may affect persons infected with HIV who have received only reverse transcriptase inhibitors.[10] The pathogenesis of lipodystrophy is not known, although this problem is considered to be an untoward effect of long term antiretroviral therapy (table I).

What we call lipodystrophy had not been recognised prior to HAART. In the pre-HAART era there existed body and metabolic abnormalities that shared similarities with HAART-associated lipodystrophy. In the past, some patients lost bodyweight at the expense of both fat and lean body mass. In this situation, called wasting syndrome,[19] there was a disproportionately high resting energy expenditure, sometimes intensified by concurrent opportunistic infections. In addition, persistent diarrhoea and subsequent undernourishment were not unusual. Patients experiencing wasting had an increased risk of dying. Consequently, wasting syndrome was considered an AIDS-defining condition.[20] Interestingly, some reports have also noted a lack of bodyweight gain[21,22] and an elevated resting energy expenditure[23] among patients receiv-

ing HAART irrespective of the control of viral replication. Conversely, other investigators have noted an improved nutritional status and an increase in bodyweight in persons infected with HIV with wasting treated with PI-containing HAART.[24,25] Hypertriglyceridaemia was a relatively common abnormal finding in the patients with advanced HIV infection.[26] The pathogenesis of pre-HAART hypertriglyceridaemia was linked to an increase of certain cytokines such as interferon-α and tumour necrosis factor α (TNF-α), both markers of progression of HIV infection. Recently, TNF-α has been also implicated in the pathogenesis of lipodystrophy in patients infected with HIV.[17] Nevertheless, in contrast to lipodystrophy, hypertriglyceridaemia in advanced HIV infection was usually associated with hypocholesterolaemia and increased insulin sensitivity.[27]

Fig. 2. Facial lipoatrophy in a man infected with HIV. There is a noticeable fat loss in the cheeks giving the face a typical sharp-edged contour.

2. Living with HIV in the Present Day

The availability of HAART has changed the horizon of daily life for patients infected with HIV.[28] In contrast with the pre-HAART era, few patients infected with HIV experience an opportunistic infection.[29] Those patients who do are either patients already known to be infected with HIV who develop an opportunistic infection because they have not responded to HAART or patients not known to be infected with HIV in whom the opportunistic infection is the condition that leads to the diagnosis of HIV infection. Most of the former patients are unfortunately dead because major opportunistic infections are still associated with a bad prognosis if immune reconstitution does not occur, whereas the latter ones would be expected to appear one by one and it is hoped that their immune status may improve enough after HAART to keep the risk of opportunistic infections away. Therefore, successfully treated patients infected with HIV at present are not afraid of experiencing major opportunistic infections. They understand that HIV infection can be a chronic but manageable disease.[28]

At present and certainly in developed countries, HIV infection is also more accepted in the society than it used to be. Our knowledge about HIV infection has greatly increased in recent years. The media have readily translated the news on advances of HIV infection to the general population. Knowledge about the routes of transmission of HIV infection has lowered unjustified fears about contagion. The existence of nongovernmental organisations gathering together people infected with HIV has helped patients to cope with HIV better and live normal lives in society. Specific laws in many developed countries have been addressed to defend people infected with HIV against discrimination. These facts do not mean that living with HIV at present is easy, but they represent clear advances in comparison with some years ago. However, all those advances can only be applied to developed countries because the success in communicating with the general population about the risks of HIV infection and the ways it can be managed have not been readily taken up by individuals or governments in many developing countries. It is still a taboo for the majority of patients to report HIV infection and this issue represents a major obstacle to their living a normal life.[30]

Along with the improved prognosis of survival, many successfully treated patients infected with HIV have been able to normalise their lives. They

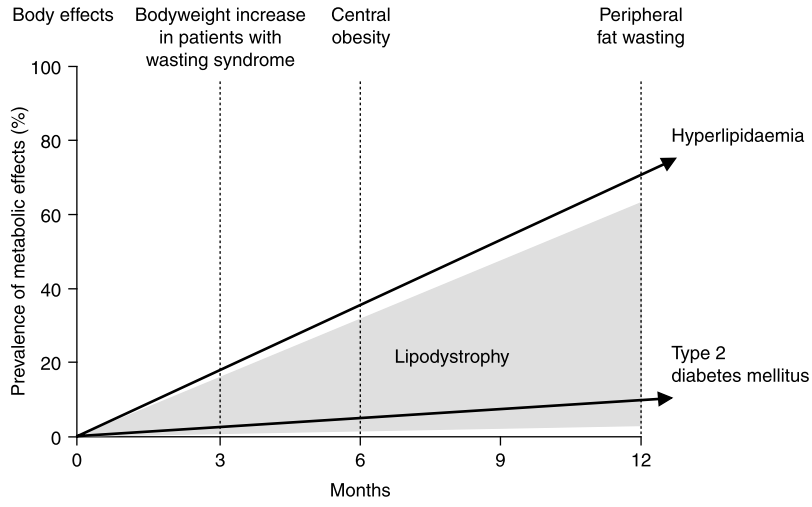

Fig. 3. Temporal trend in the prevalence of metabolic abnormalities and body fat changes in patients infected with HIV treated with highly active antiretroviral therapy including protease inhibitors. The predominant body changes that may occur in patients receiving such therapy are as follows: at 3 months bodyweight increases in patients with wasting syndrome; at 6 months central obesity may appear; and at 12 months subcutaneous fat wasting may appear (after Martinez and Gatell,[7] with permission).

feel physically and psychologically autonomous, they can work, they may look forward to building a family and to face the long term future without fear. Expecting this standard of life, patients may now insist on solutions for minor problems that did not exist in the past or, if they did, they were accepted because the priority was simply to survive. These problems refer mainly to the antiretroviral regimen they have to take: how to fit the drugs into routine daily activities, how to remember to take the drugs properly, and how to avoid immediate untoward effects. New simpler, more convenient antiretroviral drugs and regimens may help to ameliorate these problems while retaining the efficacy with respect to suppression of viral replication.[6] In this context, with the advantages of a more guaranteed survival and the limitations of complex HAART regimens, lipodystrophy unexpectedly appeared.[7]

3. What Does Lipodystrophy Mean for Patients Infected with HIV?

Although the term 'lipodystrophy' is commonly used to describe the combination of fat redistribution and metabolic abnormalities, body fat changes have the main impact on the quality of life of the patients. Lipodystrophy is easy to detect, but it is very difficult to define and to monitor with time.[10] Body changes are usually first perceived by the patient, sometimes through persistent comments from relatives or friends. The subjective magnitude of body changes may not be related to the perceptions of other people or to objective measurements of regional body fat. The most widely accepted definition of lipodystrophy body changes takes into account consistent reports from the patient and the subsequent confirmation by the physician.[31] However, some patients do believe that they have consistent body changes although these may be not apparent to an objective observer, whereas some other patients believe that they have the same physical aspect as usual, though many doctors familiar with this problem would say that they have lipodystrophy.

Not only the spectrum,[7] but also the degree of body fat changes is heterogeneous.[31] Most patients with lipodystrophy usually have mild or moderate body changes. Severe changes have been

Table I. Pathogenetic mechanisms proposed for lipodystrophy in persons infected with HIV receiving antiretroviral therapy

Direct effect of antiretroviral therapy
Nonspecificity of HIV-1 protease inhibitors[11,12]
Mitochondrial toxicity of nucleoside analogues[13,14]
Indirect effect of antiretroviral therapy
Transformation of HIV infection into a chronic disease[15]
Immune reconstitution[16]
Cytokine dysfunction[17]
Endocrine dysfunction[18]

described to affect approximately 20% of patients infected with HIV.[31,32] In contrast to metabolic parameters, there are no reference values for regional fat in the general population. Moreover, the procedures used to measure regional fat are not standardised (table II). Finally, the natural history of lipodystrophy is not known and therefore it is not possible to predict how this problem will evolve in the individual patient. All these limitations interfere with the definition and the follow-up of lipodystrophy.

Several reasons justify the impact of body changes on the quality of life of patients. Body changes are usually noticed suddenly. They may produce an unhealthy or undernourished aspect that resembles wasting, or they may disfigure the body of the patient. Early changes attributable to lipodystrophy may be acceptable if they make patients look better but then, when more advanced, may look grotesque and are not well tolerated. Exceptionally, certain body changes such as an increased breast size for a woman or a decrease in the subcutaneous adipose tissue for a person who had higher than normal subcutaneous thickness may not be considered so negative because those changes are prized in the general population. With the widespread knowledge of the potential risk of lipodystrophy, patients infected with HIV may be afraid in advance of experiencing body fat changes in the future. If body changes have been already noticed, patients may overestimate these changes if they know and feel anxious about lipodystrophy.

Probably, the main negative impact of lipodystrophy is attributable to stigmatisation. Lipodystrophy body changes that can be readily seen by others, particularly facial lipoatrophy, may identify AIDS in a way that is similar to that of wasting the past. Some patients with facial lipoatrophy feel that they have the word 'AIDS' permanently written on their face. This situation may become very unpleasant for the patients. Their relations with others, with their partners, and with themselves may become deeply affected. Lipodystrophy deteriorates the quality of their lives by limiting physical activity, lowering self-esteem, and bringing fear, despondency, loneliness, and isolation. In a culture that prizes appearance, body shape distortions have driven some patients to retreat from social activities. Patients feel less attractive, and therefore have given up dating and, for the most part, hoping for a partner. They may refuse to dress up and go places. They are permanently self-conscious about their bodies. For many patients, the benefit of survival outweighs these limitations. But for some others, they may become depressed, losing their interest in complying with the complex antiretroviral regimens. The final result for the latter patients may be a lack of control of HIV infection.[33]

Although metabolic abnormalities usually do not have a direct impact on the quality of life of the patients, their consequences and their treatment may do. Hyperlipidaemia and insulin resistance are well known risk factors for cardiovascular disease.[34] The long term natural history of lipodystrophy metabolic abnormalities is unknown. Fortunately, epidemiological studies so far have not demonstrated a major impact on the incidence of cardiovascular disease.[35,36] The medical approach for these metabolic abnormalities is not well defined. Guidelines recommending therapy above

Table II. Procedures to measure regional fat that can be useful to monitor lipodystrophy

Anthropometry (waist-to-hip circumference ratio and skin fold thickness)
Dual energy x-ray absorptiometry
Computerised tomography
Magnetic resonance imaging
Sonography

certain threshold of lipid level similarly to the general population have been recently issued.[37] The addition of new lipid-lowering drugs to patients who are already taking complex antiretroviral regimens may also have a negative impact on the quality of their lives.

4. Evaluation of the Impact of Lipodystrophy on the Quality of Life of Persons Infected with HIV

There is increasing interest in measuring the quality of life in patients infected with HIV. Several instruments have been developed which are specific for patients infected with HIV. We will give details of some, but a summary of available tests to measure quality of life in HIV-infected persons can be seen at the following internet site: http//www.qlmed.org.

The Quality of Life Index (QL-Index)[38] was developed for and has been used largely with patients with cancer. It is a 5-item index which measures quality of life in 5 domains: work activities, self-care activities of daily living, general health, social support and outlook on life.

The European Organisation for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-30)[39] is a 30-item self-report questionnaire with 9 subscales (5 functional subscales, 3 symptom subscales, an overall quality of life subscale) and 6 individual items.

The Health Assessment Questionnaire (AIDS-HAQ)[40] is a self-reported instrument with 8 functional subscales (disability, general health perception, social functioning, mental health, cognitive functioning, energy/fatigue, pain, disease worry) with 33 items and a checklist of 68 physical symptoms.

The HIV Overview of Problems-Evaluation System (HOPES)[41] has been adapted from an established cancer-specific quality of life instrument named Cancer Rehabilitation Evaluation System (CARES). It has 165 items, although not all apply to all patients. The instrument uses screening questions that determine whether a person should complete a particular section or skip it and move to the next one. Five higher-order summary scales which include the following domains are defined: physical functioning, psychosocial functioning, medical interaction, marital relationship, sexual functioning and a miscellaneous group of subscales and items not identified with the primary summary scales.

The Medical Outcome study (MOS) HIV Health Survey[42] is a 30-item questionnaire that is derived from lengthier MOS instruments. The authors of this instrument used the majority of items from the MOS-SF20 and then adding items that were deemed relevant to HIV infection. The MOS-HIV can be summarised into the following 11 dimensions: general health, pain, physical function, role function, social functioning, mental health, energy/fatigue, health distress, cognitive functioning, overall quality of life, and health transition.

The HIV/AIDS-targeted quality of life (HAT-QoL) instrument has been developed very recently.[43] The latest version of this instrument[44] has 76 items and 5 dimensions: overall function, disclosure worries, health worries, financial worries and life satisfaction.

The Multidimensional Quality of Life Questionnaire for HIV/AIDS (MQoL-HIV)[45] is a 40-item instrument measuring 10 domains: mental health, physical health, physical functioning, social functioning, social support, cognitive functioning, financial status, partner intimacy, sexual functioning and medical care.

Most of these instruments were adapted from previous scales developed for patients with cancer. New questions about social functioning, for instance, had to be added to better fit with the conflicts experienced by people with HIV infection. Furthermore, these questionnaires were mostly designed in the pre-HAART era when HIV infection was ultimately a fatal disease. Therefore, their ability to capture the domains that are now related to the quality of life of patients infected with HIV may be lower than in the past. For instance, with the exception of the HOPES questionnaire, none of the instruments previously described specifically addresses the issue of body appearance that is crucial

for the evaluation of lipodystrophy. These limitations need to be solved for a proper measurement of the quality of life of patients infected with HIV in the HAART era. In the meanwhile, we think that the best approach to assessing the impact of lipodystrophy on the quality of life should be an individualised detailed interview. Some recent reports have been specifically addressed to study the impact of lipodystrophy on the quality of life of persons infected with HIV.[46-49] Their results confirm the severe impact that lipodystrophy may have on self-esteem, sexuality, daily performance, and social functioning of persons with HIV, putting at risk the decision of maintaining antiretroviral therapy.

While health authorities have remained passive and physicians have not been able to find solutions for this problem, patients and nongovernmental organisations have actively mobilised to diminish the impact of lipodystrophy on the quality of their lives. They have set up hotlines and e-mail lists, conducted surveys and held community forums and teleconferences, seeking to monitor the adverse effects of antiretroviral therapy and share slivers of available information. Advocates met with drug companies and health authorities in the US [the Food and Drug Administration (FDA)] and in Europe [the European Medicines Evaluation Agency (EMEA)] to demand the actions that have been recently set up. Several comprehensive, multicentre studies such as the Lipodystrophy Case Definition Study coordinated by the National Centre for Epidemiology and Clinical Research (Sydney, Australia) and the Study on Metabolic Dysfunction and Body Shape Changes in HIV Infection coordinated by the HIV Trialists Collaborative Group at the Medical Research Council (London, England) under the auspices of the EMEA, and the Fat Redistribution and Metabolic (FRAM) Study coordinated by Carl Grunfeld from the University of California, San Francisco (US) under the auspices of the FDA are currently under way.

5. Treating Lipodystrophy

Though some physicians consider lipodystrophy as merely a cosmetic problem, many others and patients infected with HIV do not see it this way. Therefore, trying to treat lipodystrophy seems fully justified. Physicians have to keep a receptive attitude towards this problem, and they need to dedicate enough time to talk with the patients who complain about it. Patients should be informed that there is limited knowledge on the pathogenesis and the epidemiology of lipodystrophy. In addition, there is no proven treatment for this problem although a number of treatments have been used with varying success (table III).

We do not even know if lipodystrophy may be completely reversed. Central obesity may revert at least partially after switching from a PI to a non-nucleoside reverse transcriptase inhibitor.[55,56] Physical training,[57] or therapy with metformin[51,52] or recombinant growth hormone[58] have been also reported to improve central obesity without discontinuation of PI therapy. Conversely, the reversibility of subcutaneous fat loss in patients infected with HIV-1 with lipodystrophy has been less obvious. Two recent studies that involved a small number of patients, reported that is might be possible to ameliorate subcutaneous fat loss by discontinuing stavudine therapy irrespective of continuing PI therapy.[60,61] However, the recent news from a group of investigators reporting apoptosis in the subcutaneous fat tissue from patients with subcutaneous fat loss were disappointing.[65] Their results suggested that subcutaneous fat loss may not be completely reversible. The role of plastic surgery may be important for localised accessible fat deposits[59] and the short term prognosis for refilling the Bichat fat pads seems promising.[62-64] The surgical approach is merely aesthetic, but if its results prove to be safe and durable, it may be of use for selected patients who are severely affected in the absence of other specific therapies.

Despite the recognition that lipodystrophy may have important psychological repercussions, the best psychological approach for this problem is not known at present. People with surgical or traumatic

Table III. Measures reported to produce at least a partial response in metabolic abnormalities or body fat redistribution in patients infected with HIV with lipodystrophy[a]

Condition	Drug/treatment	References
Metabolic abnormalities		
Hypertriglyceridaemia	Gemfibrozil	50
Hypercholesterolaemia	HMG-CoA reductase inhibitors	50
Diabetes mellitus	Metformin	51,52
	Benfluorex	53
	Troglitazone	54
	Insulin	7
All metabolic abnormalities	Withdrawal of HIV-1 protease inhibitors	55,56
Body fat redistribution		
Central obesity	Physical training	57
	Metformin	51,52
	Recombinant growth hormone	58
	Withdrawal of HIV-1 protease inhibitors	55,56
	Surgery[b]	59
Lipoatrophy	Troglitazone	54
	Withdrawal of stavudine	60,61
	Facial recontouring[c]	62-64

a It should be clearly stated that none of these approaches has been completely validated and therefore they cannot be indiscriminately recommended.

b For localised accessible fat deposits only.

c For facial lipoatrophy only.

mutilations, such as mastectomy or limb amputations, may also experience important psychological repercussions because of unwanted body changes. However, the localised nature of the changes and the possibility of aesthetic and functional recovery with specifically designed prosthetic devices makes these situations different from lipodystrophy. Other people with unwanted body changes such as those ones with morbid obesity or pronounced kyphoscoliosis may also experience important repercussions and psychological approaches to help such people have been designed. Although lipodystrophy has its own peculiarities, existing knowledge about how to psychologically help other patients with deforming body changes might be of help for patients infected with HIV, or at least may act as a starting point.

6. 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. No qualitative changes in antiretroviral drugs and therapeutic strategies to treat HIV infection are expected for the next years. While awaiting to discover its pathogenesis and to design effective preventive and therapeutic approaches, we need to assess the impact that lipodystrophy may have on the every day life of patients infected with HIV who experience it. Avoiding minimising the importance of this problem and investigating ways of developing useful instruments to measure its impact on the quality of life are the best starting points to help those patients affected by this condition.

Acknowledgements

This work was supported in part by grant FIS 98/1227 from the Spanish Ministry of Health.

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