

HIV-associated lipodystrophy syndrome: A review of clinical aspects

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Approximately two years after the introduction of highly active anti-retroviral therapy for the treatment of HIV infection, body shape changes and metabolic abnormalities were increasingly observed. Initially, these were ascribed to protease inhibitors, but it is now clear that nucleoside reverse transcriptase inhibitors also contribute to lipodystrophy syndrome. The syndrome groups together clinical conditions describing changes in body fat distribution that include lipoatrophy, lipoaccumulation or both. However, there does not appear to be a direct link between lipoatrophy and lipoaccumulation that would support a single mechanism for the redistribution of body fat. Currently, there is no clear definition of lipodystrophy, which explains the difficulty in determining its prevalence and etiology. There are no current guidelines for the treatment of fat distribution abnormalities that occur in the absence of other metabolic complications. The present article reviews the current state of knowledge of the definition, symptoms, risk factors, pathogenesis, diagnosis and treatment of the morphological changes associated with lipodystrophy syndrome.

Key Words: Adverse events; Antiretroviral drugs; Fat accumulation; HIV infection; Lipoatrophy; Lipodystrophy; Metabolic complications

The morphological signs of lipodystrophy were first described approximately two years after the introduction of protease inhibitors (PIs) (1). HIV-infected patients being treated with these drugs presented with progressive and selective thinning of the subcutaneous fat tissue in the cheeks, arms and legs. These symptoms were often, but not always, associated with intra-abdominal and dorsocervical fat accumulation, subcutaneous lipomata, dyslipidemia, insulin resistance, hyperglycemia and/or frank diabetes.

Syndrôme de lipodystrophie associé au VIH : examen des aspects cliniques

Environ deux ans après l'arrivée du traitement antirétroviral hautement actif pour le traitement de l'infection à VIH, on a commencé à observer de plus en plus souvent des changements dans la forme du corps et des anomalies métaboliques. Au début, on a attribué ces changements aux inhibiteurs de protéase, mais maintenant il ne fait aucun doute que les inhibiteurs nucléosidiques de la transcriptase inverse jouent un rôle dans le syndrome de lipodystrophie. Le syndrome groupe des états cliniques qui décrivent des changements dans la répartition du tissu adipeux, notamment la lipoatrophie, la lipoaccumulation ou les deux. Toutefois, il ne semble pas y avoir de lien direct entre la lipoatrophie et la lipoaccumulation qui appuierait l'existence d'un seul mécanisme de redistribution du tissu adipeux. Il n'existe pas actuellement de définition précise de la lipodystrophie, ce qui explique la difficulté d'en déterminer la prévalence et l'étiologie. Il n'existe pas non plus de ligne directrice quant au traitement des anomalies de la répartition du tissu adipeux, qui se produisent en l'absence d'autres complications métaboliques. Le présent article fait le point sur l'état actuel des connaissances en ce qui concerne la définition, les symptômes, les facteurs de risque, la pathogénèse, le diagnostic et le traitement des changements morphologiques associés au syndrome de lipodystrophie.

Lipodystrophy syndrome was initially attributed to the cumulative toxicity of treatment with PIs. However, the introduction of PIs coincided with the inclusion of a second nucleoside reverse transcriptase inhibitor (NRTI), particularly stavudine (d4T), into treatment regimens. It now appears that certain fatty tissue abnormalities may be independently associated with this older class of antiretroviral agents (2).

The present article reviews the current knowledge of the definition, signs and symptoms, risk factors, pathogenesis,

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TABLE 1
Diagnostic model for lipodystrophy

	Parameter	Higher score
Demographic	Sex	If female
	Age	If >40 years of age
	Duration of HIV infection	If >4 years
	HIV disease stage	C>B>A
Clinical	Waist to hip ratio	If elevated
Biological	Anion gap	If increased
	High-density lipoprotein cholesterol	If low
Radiological	Leg fat percentage (by DEXA)	If <21.4%
	Trunk to limb fat ratio (by DEXA)	If elevated
	Intra-abdominal to extra-abdominal fat ratio (by computed tomography)	If >0.45

Data from reference 4. DEXA Dual energy X-ray absorptiometry

diagnosis and treatment of the morphological manifestations of lipodystrophy syndrome. This was achieved by reviewing the literature indexed on MEDLINE and the abstracts of studies presented at international conferences on HIV infection (up to June 2004).

DEFINITION AND DESCRIPTION

Lipodystrophy syndrome groups together three clinical conditions characterized by abnormal body fat distribution: lipoatrophy, lipoaccumulation and a mixed syndrome. To date, there is no universally accepted definition of lipodystrophy, which explains the difficulty in determining its prevalence, etiology and the treatment of fat distribution abnormalities that occur in the absence of other metabolic complications (3).

Most studies of lipodystrophy syndrome are based on the presence of symptoms subjectively reported by patients, the presence of clinical signs observed on examination by a physician or a combination of the two. These observations may or may not be confirmed by anthropometric measurements or radiological examination. There is no consensus as to whether certain nonmorphological criteria, such as abnormal lipid, glucose or lactic acid metabolism, osteoporosis or hypogonadism, should be included in the definition of lipodystrophy syndrome.

Using data from a case-control study in consecutive HIV-infected patients without active AIDS presenting with and without clinical evidence of lipodystrophy, Carr et al (4) formulated a diagnostic model for lipodystrophy syndrome (Table 1). In this model, each parameter (including demographic, clinical, biological and radiological) is weighted by a system of points, and the total score is used to determine whether the patient has lipodystrophy. This model has a sensitivity of 79% and a specificity of 80%. Models that exclude radiological measurements have been developed but show lower sensitivity and specificity (4).

In a different approach, the Fat Redistribution and Metabolism (FRAM) study team (5-9) used radiological and anthropometric measurements to differentiate 1200 HIV-seropositive (HIV+) individuals from 300 HIV-seronegative (HIV-) controls. Compared with controls, HIV+ individuals in this study (even those who showed no clinical signs of lipoatrophy) exhibited a greater loss of subcutaneous adipose tissue (SAT) from the limbs and trunk (8). Thus, the loss of SAT appears to be characteristic of lipodystrophy syndrome.

On the other hand, lipoaccumulation was not found to be a specific characteristic of HIV-associated lipodystrophy (7). In fact, there was less visceral adipose tissue (VAT) in HIV+ individuals than in HIV- controls. It would appear, therefore, that there is no direct link between lipoatrophy and lipoaccumulation that would support a single mechanism for the redistribution of body fat in lipodystrophy.

CLINICAL SIGNS

Lipodystrophy can develop in men, women or children (10-12). Lipoatrophy is most apparent in the face but is also visible in the arms, legs, buttocks and trunk. Lipoaccumulation is characterized by a marked increase in VAT that enlarges abdominal girth. It can also result in increased dorsocervical fat tissue (buffalo hump) and/or unilateral or bilateral gynecomastia. The latter may occur in men (13,14) as well as women, and does not appear to be connected to an endocrine disorder. Gynecomastia may resolve spontaneously within one year in men (15). Occasionally, single or multiple lipomata appear. Enlargement of the supraclavicular fat pads and anterior neck fat accumulation (16) have also been observed. The frequency of lipoatrophy observed in major clinical studies (17-24) varies from 13% to 67% (Table 2). Other data revealed a prevalence of lipoatrophy of 16% to 29% after three years of antiretroviral therapy (25,26). The frequency of lipoaccumulation varies from 6% to 93% in the cohorts cited in Table 2 (17,19-24). Mixed syndrome appeared more frequently than other presentations of lipodystrophy in some cohorts. The prevalence of mixed syndrome has been found to range from 20% to 29% (17,19,21-24), and the prevalence observed at three years has varied from 8% to 12.5% (26,27).

The physical signs of lipodystrophy usually appear progressively, increasing in severity for a period of 18 to 24 months and then apparently stabilizing for at least two years (23,28). The syndrome has been observed in patients being treated during primary HIV infection (29,30), as well as in noninfected individuals who have received multiple episodic postexposure prophylactic antiretroviral treatments (31). In some patients, lipoatrophy precedes lipoaccumulation (17,27). Finally, the adipose tissue abnormalities of lipodystrophy are often associated with metabolic changes, including hyperlipidemia (hypercholesterolemia and/or hypertriglyceridemia), hyperlactatemia, hyperglycemia or diabetes and hyperinsulinism, as well as osteopenia and osteoporosis (32-34).

Lipodystrophy has an important impact on the quality of life of persons living with HIV (35,36), causing both physical and psychological problems. For example, in a sample of 250 HIV+ patients drawn from a closed, prospective cohort study starting antiretroviral therapy in 1996 (35), an impact of body changes on social contacts, daily performance, sexuality and self-esteem was reported by 62.7%, 68%, 68% and 82.7%, respectively. Physically, symptoms of distention and gastroesophageal reflux may arise because of increased abdominal girth. Difficulty in exercising and sleep problems have been observed in clinical practice, while gynecomastia, if significant, can cause localized pain as well as pain in the dorsolumbar region. Psychologically, the morphological changes caused by lipodystrophy can produce anxiety, depression (37) and loss of self-esteem. Emaciation of the face especially stigmatizes HIV+ patients, causing some to stop all antiretroviral medication (38,39). Indeed, a reduction in compliance in certain patient groups (40) and the refusal of treatment have been linked to the lipodystrophy.

TABLE 2
The prevalence of lipodystrophy in different clinical studies

Study	Number of patients	Type	Definition	Prevalence
HOPS (17)	1057 (85% male)	Cross-sectional	Moderate or severe lipoatrophy and/or lipoaccumulation	Lipodystrophy (total) 49%; lipoatrophy 13.3%; lipoaccumulation 13.2%; mixed syndrome 22.7%
HOPS (18) (substudy)	337	Longitudinal (to 20 months)	Lipoatrophy	Lipoatrophy 13.1%
APS (19)	1348 (97% male)	Cross-sectional	Lipoatrophy and lipoaccumulation	Lipodystrophy (total) 53%; lipoatrophy 16%; lipoaccumulation 7%; mixed syndrome 29%
SALSA (20)	526 (84% male)	Cross-sectional	Lipoatrophy and lipoaccumulation (questionnaire)	Lipoatrophy – men 67%, women 59%; lipoaccumulation – men 76%, women 93%
APROCO (21)	614 (80% male)	Cross-sectional (12 to 20 months after starting protease inhibitor)	Lipoatrophy and lipoaccumulation	Lipoatrophy 21%; lipoaccumulation 17%; mixed syndrome 24%
LIPOCO (22)	154 (100% male)	Cross-sectional	Lipoatrophy and/or lipoaccumulation	Lipodystrophy (total) 53.2%; lipoatrophy 22.1%; lipoaccumulation 5.9%; mixed syndrome 25.3%
MACS (23)	868 (100% male)	Cross-sectional	Moderate-to-severe lipoatrophy and lipoaccumulation	Mixed syndrome 20%

APROCO Antiproteases Cohorte; APS Australian Lipodystrophy Prevalence Survey; HOPS HIV Outpatient Study; LIPOCO Lipodystrophie Cohorte; MACS Multicenter AIDS Cohort Study; SALSA Self-Ascertained Lipodystrophy Syndrome Assessment

RISK FACTORS

Host factors

Older age (older than 40 years of age) (25,41-43), female sex (44,45), elevated serum triglyceride level (26), low nadir CD4 cell count (46) and an advanced stage of HIV infection (47) have all been identified as risk factors for lipodystrophy. A longer duration of HIV infection in tandem with a fall in CD4 cell count and a high viral load (greater than 10,000 copies/mL [44] or greater than 100,000 copies/mL [48]) is strongly associated with the development of lipodystrophy syndrome. This could contribute to the development of lipodystrophy in antiretroviral-naïve patients as described in a previous study (19). Lipodystrophy is more severe in treatment-experienced HIV+ patients (19) and in patients with a CD4 cell count of less than 350 cells/mm³ at the time of antiretroviral therapy initiation (18). Other factors, including the presence of established AIDS, coinfection with hepatitis C and better compliance with treatment, may be associated with the development of lipodystrophy (17,40). Interestingly, Caucasians exhibit more lipoatrophy, while non-Caucasians develop more lipoaccumulation (18).

Treatment factors

The development of lipodystrophy syndrome is clearly influenced by the type of antiretroviral therapy and the duration of treatment. NRTIs are strongly associated with the loss of subcutaneous fat and hyperlactatemia, while PIs are more closely associated with lipoaccumulation and effects on lipid metabolism and insulin resistance. The effects of NRTIs appear to be

augmented or accelerated when combined with PIs (49,50), and the manifestations of lipodystrophy are different than in patients receiving NRTIs alone (49,51). NRTIs in combination with PIs result in a greater increase in VAT, hyperinsulinemia, insulin resistance and dyslipidemia. It could be that mixed syndrome is the result of treatment with both classes of antiretroviral agents.

A particular association between lipoatrophy and d4T has been observed in prospective studies (50,52-55) that compared a therapeutic regimen based on d4T with a regimen based on zidovudine in antiretroviral-naïve patients. This association has also been observed in some cohort studies (22,56-58). However, in other cohort studies (48,59,60), host factors and the severity of HIV infection influenced the development of lipodystrophy more than did the type of NRTI. The duration of antiretroviral therapy, especially if longer than two years, was found to be an important factor for the development of lipodystrophy in several studies (1,27,61).

PATHOGENESIS

Lipodystrophy syndrome in HIV+ patients is clearly linked to antiretroviral therapy – PIs and NRTIs have both interactive and independent effects on its development. However, the syndrome has been described in treatment-naïve patients (19), suggesting that other mechanisms, such as those involving proinflammatory cytokines or the direct role of the virus on adipocytes, could also be involved in the pathogenesis of lipodystrophy.

The role of NRTIs

Manifestations of lipodystrophy, such as the loss of fatty tissue, hyperlactatemia and lactic acidosis, may be a consequence of mitochondrial damage (62-64). Results from several studies (65,66) suggest that the toxic effects of NRTIs on mitochondria are responsible for the adverse effects of lipodystrophy. NRTIs have an affinity for human mitochondrial DNA polymerase gamma and can cause a decrease in the content and quality of mitochondrial DNA, resulting in a reduction in the production of encoded proteins and changes in their mitochondrial functions. Severe mitochondrial dysfunction could ultimately lead to apoptosis and the loss of fat cells (67).

The role of PIs

PIs are more strongly associated with the metabolic abnormalities of lipodystrophy syndrome than are NRTIs. Several studies have suggested that the common mechanisms resulting in adipocyte dysfunction underlie the PI-induced development of hypercholesterolemia, hypertriglyceridemia and/or insulin resistance. The differentiation of preadipocytes to adipocytes requires the sequential activation of a number of transcription factors, which in turn regulate the expression of specific adipocyte markers. Animal studies have demonstrated that lipodystrophy can result from the inactivation of adipogenic transcription factors such as sterol-regulatory-element-binding-protein 1 (SREBP-1). PIs inhibit the nuclear translocation of SREBP-1, thus causing it to accumulate beneath the nuclear membrane and rendering it nonfunctional (68). In turn, this causes a decrease in messenger RNA for, among other things, the insulin-responsive glucose transporter GLUT-4, preventing the uptake of glucose into adipose cells (69). Furthermore, SREBP-1c messenger RNA concentrations in SAT from PI-treated HIV+ patients have been found to correlate negatively with glycemia and insulin resistance (68).

The role of cytokines

The gain and loss of fatty tissue may be the result of a change in equilibrium between the genesis and death of cells, with the accumulation of fat cells being more a reflection of lipoprotein lipase activity than a reduction in lipolysis. Lipogenesis and lipolysis can be influenced by proinflammatory cytokines, such as tumour necrosis factor-alpha (TNF- α) (70), that inhibit the former and stimulate the latter process. Albu et al (71) reported that SAT from HIV+ patients with lipodystrophy secretes significantly more TNF- α than SAT from HIV+ patients with no fat redistribution. Adipocytes themselves secrete cytokines such as adiponectin and leptin that increase sensitivity to insulin, while the secretion of TNF- α and interleukin-6 have the opposite effect.

INVESTIGATION

Lipodystrophy is currently defined based on clinical grounds that include a combination of signs and symptoms; however, symptoms may be interpreted subjectively by the patient or physician (72) and, therefore, objective parameters are needed to better identify morphological changes. Such parameters must be specific, sensitive, and take into account the regional distribution of fat tissue between the limbs and abdomen, as well as the distribution between the subcutaneous and visceral compartments. Anthropometric, biological and radiological parameters have all been evaluated with regard to their application in diagnosing lipodystrophy.

Anthropometric parameters

Weight, size and body mass index are important parameters when evaluating lipodystrophy in HIV+ individuals; however, these criteria alone are not sufficient to distinguish lipoatrophy from wasting or lipoaccumulation from obesity. Furthermore, some cases of lipodystrophy, most notably patients with mixed syndrome, are not accompanied by significant changes in weight or body mass index.

Arm, neck, thigh, waist and hip circumference measurements have been used as markers of lipodystrophy. Although there is no threshold value that reliably reflects the presence or absence of fat redistribution (73,74), some authors have employed waist to hip ratios greater than 0.95 in men and 0.85 (75) or 0.90 (76,77) in women as indicators of lipodystrophy. A weak correlation has been shown to exist between anthropometric measurements and the results of dual energy x-ray absorptiometry (DEXA) and computed tomography (CT) scans for evaluating body fat mass (78).

Skin fold measurements with callipers obtained from the chest, biceps, triceps or from the scapular, suprailiac or gluteal regions (79) can also be used to estimate body composition in patients with lipodystrophy. However, even though evaluators may be trained in a standard technique to ensure accuracy and decrease interobserver variability, results to date have been inconsistent.

Biological parameters

Although there is an increased incidence of metabolic abnormalities associated with lipodystrophy, the syndrome can exist in their absence. Lipoaccumulation is often associated with increases in serum cholesterol, triglycerides and insulin (80). Indeed, an increase in triglycerides has been shown to be a predictor of lipodystrophy in a number of studies (81-83). On the other hand, increased lactic acid levels may be associated with a higher risk of lipoatrophy (84). No association between lipodystrophy and other biological parameters has been established.

Bioelectrical impedance analysis

Whole-body bioelectrical impedance analysis has been studied as a quantitative diagnostic tool for lipodystrophy. The different resistance levels of various tissues enable body composition to be analyzed in terms of fat and lean mass (73), and allow changes to be followed over time. However, because bioelectrical impedance analysis does not provide information about the regional distribution of fat, it is not considered to be a valid method for evaluating lipodystrophy, although it may prove useful for assessing the role of wasting in cases of lipoatrophy with weight loss.

Radiological parameters

Ultrasonography, DEXA, CT and magnetic resonance imaging have all been used for the objective measurement of the fat composition of particular body regions or given compartments in patients with lipodystrophy syndrome. However, most of these methods are not used in everyday practice because of the costs and the lack of standardization for assessing lipodystrophy.

The measurement of SAT at malar sites by ultrasonography is used in research to assess the response to corrective treatment and has been shown to be 88% sensitive and 84% specific in identifying lipodystrophy diagnosed according to clinical

criteria. Measurements at other sites, however, are less accurate predictors of lipodystrophy (85).

DEXA scans enable the distribution of fat mass in the trunk and limbs to be evaluated and the ratio of appendicular fat to trunk fat or to total fat to be calculated. These ratios are lower in cases of lipodystrophy (86,87). With DEXA, however, it is difficult to determine the distribution of fat between compartments in the same region.

CT and magnetic resonance imaging are the reference methods used in research because they give a three-dimensional representation of the distribution and volume of fat mass. These methods have been validated in volunteers (88) and compared in patients undergoing CT scanning for various reasons (89). They enable the distribution of fat tissue between specific compartments to be evaluated. From these readings, the VAT to SAT and VAT to total adipose tissue ratios can be determined. A VAT to total adipose tissue ratio higher than 0.4 is considered abnormal (80,90). For now, though, due to insufficient validation and poor access, CT and other imaging modalities are not routinely employed outside of research.

MANAGEMENT

There is still no curative treatment for the morphological changes induced by lipodystrophy. Several avenues, including exercise, nutrition, minimizing drug exposure (with strategies such as delaying the start of antiretroviral therapy, treatment interruptions and changing medication) and specific drug or cosmetic treatments, have been explored with varying degrees of success.

Exercise and nutrition

Regular exercise comprising a combination of cardiovascular training and strengthening exercises can reduce intra-abdominal lipooaccumulation by 1.1 kg after 16 weeks (91), while concurrently improving muscle strength, lean mass and blood lipids (92,93). Exercise can, however, aggravate lipoatrophy (94). Nutrition has not been prospectively evaluated for its impact on morphological changes but, generally speaking, nutritional counselling and follow-up to address lipodystrophy-associated metabolic problems could reduce lipoaccumulation. A retrospective analysis of the dietary intake of HIV+ men (95) indicated that an overall high-quality diet, rich in fibre and adequate in energy and protein, may be beneficial in preventing the development of fat deposition.

Minimizing drug exposure

Delaying the start of antiretroviral therapy in asymptomatic patients with CD4 cell counts above 350 cells/mm³ is a strategy aimed at shortening the time of exposure to treatment to decrease the risk of metabolic complications. However, the long-term benefits of such an approach have yet to be seen, especially considering that a lower nadir of CD4 cells has been found to be associated with higher incidence of lipodystrophy (18,46).

In clinical trials, treatment interruptions have been found to ameliorate dyslipidemia and insulin resistance, but the regression of morphological changes to the face or limbs does not usually occur over the short term (90). Treatment interruptions are not commonly recommended but could be considered in patients who have no symptoms and in whom the number of CD4 cells was greater than 350/mm³ before the start of treatment (96).

Strategies involving switching antiretroviral treatments were studied early on for their impact on the changes associated with lipodystrophy. In accordance with the presumed pathology, the effects of changing from a PI to a non-NRTI or abacavir (an NRTI) were evaluated. Switching from a thymidine analogue NRTI such as d4T or zidovudine to the guanosine analogue abacavir and the effects of NRTI-sparing regimens have also been studied. The principal switch studies (97-122) are summarized in Table 3.

The results of some studies suggest that switching treatment from a PI to a non-NRTI or abacavir may improve the morphological abnormalities of lipodystrophy syndrome, although this has not been demonstrated objectively using radiological methods. However, changing an NRTI (particularly d4T) for abacavir resulted in modest improvements in the signs of lipodystrophy measured by CT and DEXA after 24 to 104 weeks, and a minority of patients reported visible improvements (114-116).

Specific drug treatment

Different pharmacological approaches to the treatment of lipodystrophy that are based on the presumed physiopathology of the syndrome have been examined. They include modulators of anabolism, such as growth hormone (123-127) and anabolic steroids (128,129), modulators of insulin resistance, such as thiazolidinediones (130-134) and metformin (135-137), and mitochondrial antioxidants, such as L-carnitine (138). However, data on the efficacy of these agents are equivocal and preclude the possibility of issuing recommendations for their use at this time. Initially, recombinant human growth hormone seemed promising, but it is expensive and has side effects with respect to glucose metabolism (126). Trials using reduced doses of recombinant human growth hormone are currently in progress (127).

Cosmetic corrective treatment

Liposuction has been used to treat dorsocervical lipoaccumulation (buffalo hump), and published cases have shown satisfactory outcomes (139-141). However, there are anecdotal reports of recurrences of buffalo hump following liposuction (142).

A promising cosmetic treatment of facial atrophy involves injecting polyactic acid into the dermis of both cheeks. Patients have reported more satisfaction with their appearance, as well as improvement in their quality of life, following such treatment (143).

Autologous fat transfer for treating facial atrophy has been examined in three studies that showed satisfactory results in the majority of patients (144-146). However, this procedure may not be feasible in cases of more severe lipoatrophy because there may not be a donor site with sufficient fatty tissue.

Finally, cheek prostheses may be implanted to correct facial lipoatrophy but the esthetic results of this procedure are often disappointing.

CONCLUSIONS

Several elements contribute to lipodystrophy syndrome, supporting a multifactorial etiology. Different classes of antiretroviral drugs are implicated both independently and synergistically in this process. Mitochondrial toxicity caused by NRTIs, metabolic changes induced by PIs, and immune system dysfunction resulting from a sustained elevation of proinflammatory cytokines are all involved in the pathogenesis of

TABLE 3
Summary table of the principal studies implemented to evaluate the effects of switching antiretroviral treatments on lipodystrophy

	Type of switch	Controlled study	Subjects (n)	Duration (weeks)	Radiological evaluation	Main conclusions
Switch from a protease inhibitor to EFV						
Martinez et al (97)	PI→EFV	No	20	24	Ultrasound	No differences
Bonnet et al (98)	PI→EFV	No	43	48	Yes	No differences
Viciano et al (99)	PI→EFV	No	39	24	No	Subjective improvements
Estrada et al (100)	PI→EFV	No	41	52	Yes	Decrease in SAT
Moyle et al (101)	PI→EFV	No	13	12	Yes	Decrease in abdominal circumference
Lafon et al (102)	PI→EFV	No	20	24	Yes	Subjective improvements. No differences on CT scans
Gharakhanian et al (103)	PI→EFV	No	33	40	No	No differences
Knechten et al (104)	PI→EFV	No	64	36	No	Increase (9/27 subjects) or decrease (5/27 subjects) in lipodystrophy
Switch from a protease inhibitor to NVP						
Barreiro et al (105)	PI→NVP	Yes	138	24	No	Subjective improvements in 50% of subjects
Martinez et al (106)	PI→NVP	No	23	24	No	Subjective improvements in 91% of subjects
Tebas et al (107)	PI→NVP	No	40	24	Yes	No differences
Ruiz et al (108)	PI→NVP	Yes	106	48	Yes	No differences
Switch from a protease inhibitor to ABC						
Rozenbaum et al (109)	PI→ABC	Yes	34	48	No	Subjective improvements
Lafeuillade et al (110)	HAART→ ABC/lamivudine/ZDV	Yes	209	48	No	Prevalence of lipodystrophy at 48 weeks: 28% for ABC versus 42% for PI
Switch from a protease inhibitor to EFV, NVP or ABC						
Negredo et al (111)	PI→PI or EFV or NVP	Yes	56	48	Yes	No differences
Fisac et al (112)	PI→ABC or NVP or EFV	Yes	92	48	Yes	Subjective improvements. No differences on CT scans
Casado et al (113)	PI→EFV or NVP	No	100	48	No	No differences
Switch from a nucleoside reverse transcriptase inhibitor to ABC or ZDV						
Carr et al (114) and Martin et al (115)	d4T or ZDV→ABC	Yes	111	104	Yes	Significant improvements in SAT in patients with moderate-to-severe lipodystrophy
McComsey et al (116)	d4T→ABC or ZDV	No	118	48	Yes	4% increase in SAT; 2% decrease in VAT
Saint-Marc et al (117)	d4T stopped	No	36	36	Yes	Increases in SAT of thigh and abdomen
Garcia-Benayas et al (118)	d4T→ABC	Case control study	34	48	No	Nonsignificant increase in skin fold measurements
Multiple strategies						
Carr et al (119)	PI→NVP ABC ADF HU	Yes	81	24	Yes	Decreases in SAT and VAT more marked after switching
Bickel et al (120)	PI→ABC + EFV	No	26	24	Yes	Subjective improvements were reported
John et al (121)	d4T-PI → ABC/lamivudine/ZDV	Yes	37	48	Yes	Increase in peripheral SAT
Moyle et al (122)	d4T→ABC (group 1); PI or NNRTI→ABC (group 2); d4T + PI or NNRTI→ ABC + ZDV (group 3)	Yes	27	48	Yes	Significant increase in total, arm and leg fat mass in group 1; modest decrease in other groups. No change in visceral adiposity in any group

ABC Abacavir; ADF Adefovir; CT Computed tomography; d4T Stavudine; EFV Efavirenz; HAART Highly active antiretroviral therapy; HU Hydroxyurea; NNRTI Non-nucleoside reverse transcriptase inhibitor; NVP Nevirapine; PI Protease inhibitor; SAT Subcutaneous adipose tissue; VAT Visceral adipose tissue; ZDV Zidovudine

lipodystrophy but are modulated by other factors such as genetics, age, comorbidities, length of infection, established AIDS and the duration of antiretroviral therapy.

There are no evidence-based strategies for the prevention or treatment of lipodystrophy syndrome. Although treatment switches have been effective in combating nonmorphological, metabolic complications such as diabetes and hyperlipidemia, the data on morphological complications are less conclusive. Substituting NRTIs with abacavir is the only approach that has produced measurable, although modest, improvements in lipodystrophy.

Certain innovations in antiretroviral treatment show promise. Tenofovir, a new nucleotide inhibitor with weaker anti-polymerase gamma activity, produces less extensive mitochondrial toxicity than do older NRTIs (147,148), while atazanavir, a new PI, appears to have a better lipid profile than other agents of this class (149). However, the long-term effects of fusion inhibitors (the newest class of antiretroviral drug inhibitors) on lipodystrophy are presently unknown. Other studies currently in progress are examining the effect of treatment regimens that exclude NRTIs as first-line drugs on lipodystrophy or determining if earlier treatment could prevent lipodystrophy in some high-risk patients. Specific treatment for established lipodystrophy may involve anti-TNF agents and leptin analogues (150), both of which are being considered for future studies.

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