Original article

Use of diet, nutritional supplements and exercise in HIV-infected patients receiving combination antiretroviral therapies: a systematic review

Pere Leyes[1], Esteban Martínez[2] and Maria de Talló Forga[1]*

[1]Nutritition and Dietetics Unit, Endocrinology Service, Hospital Clínic de Barcelona, 08036 Barcelona, Spain
[2]Infectious Diseases Unit, Hospital Clínic de Barcelona, University of Barcelona, 08036 Barcelona, Spain

*Corresponding author: E-mail: pleyes@clinic.ub.es

Background: The use of combination antiretroviral therapy (cART) has improved the prognosis of HIV infection, but it has also been linked to a spectrum of body composition changes and metabolic alterations known as the lipodystrophy syndrome. Nutritional status could influence body composition changes.
Methods: We performed a systematic search of published peer-reviewed data on the effects of diet, nutrition support and exercise on body composition and metabolic complications in patients receiving cART.
Results: Few controlled studies, most of them with small sample size, were found. Oral nutritional support increases protein and energy intake, and results in body weight and fat mass gains. Resistance exercise, with or without an aerobic component, increases lean mass and can improve insulin resistance. Low-fat diets or exercise can result in loss of fat mass, and they should be used with caution in subjects with lipoatrophy.
Conclusions: Nutritional support and exercise result in small but significant body composition changes and can be used as complementary interventions. There is a need for further research on nutritional interventions in HIV-infected patients receiving cART.

Introduction

In the era before effective antiretroviral therapy (ART), the progression of HIV infection induced profound changes in body composition similar to those described in consumptive diseases. In the natural history of the disease, progressive weight and muscle loss were observed, and they were more intense during opportunistic infections. Severe weight loss was found to be related to decreased survival [1,2]. Interestingly, the timing of death in patients with end-stage acquired immunodeficiency syndrome was related to the extent of lean body mass (LBM) depletion, suggesting that there is a critical LBM for patient survival [3]. Unfortunately, nutritional interventions were not capable of correcting body composition alterations, as long as underlying metabolism disorders persisted throughout the course of untreated HIV infection.

This scenario changed dramatically after combination antiretroviral therapy (cART) became available. Viral replication was effectively suppressed, immunological status enhanced, and prognosis for most infected individuals improved [4–7]. What had been an ultimately lethal disease, became a chronic condition. In addition, the use of cART was also associated with improvements in nutritional status and weight gain without any specific nutritional intervention [8]. However, survival on cART led to the recognition of a spectrum of body composition changes, known as the lipodystrophy or fat redistribution syndrome [9]. This syndrome included subcutaneous fat atrophy, more evident in extremities, buttocks and facial area, and abdominal visceral fat accumulation [10] or local fat depots in the torso or dorsocervical area [11]. Body fat abnormalities were commonly associated with metabolic disturbances in lipid and carbohydrate metabolism, resembling the metabolic syndrome observed in obese individuals; this situation was different from that previously described in the untreated HIV infection. These alterations have also been recently linked to an increased cardiovascular risk [12]. Despite all these considerations, weight loss and some other aspects of the wasting definition may still be present despite cART use [13]. Even when adjusting for

potential confounders such as cART use or $CD4^+$ T-cell count, weight loss remains as a strong independent predictor of mortality in HIV-infected individuals [14].

No specific guidelines for treating cART-related metabolic disorders have been created, so the same criteria used for the general population have been adopted [15,16]. More troublesome is the management of body alterations, as no effective therapies are available yet and body habitus changes can be very stigmatizing for many patients. Since the widespread use of cART, knowledge on adverse ART effects has evolved, particularly concerning the risk and the intensity of metabolic and body alterations for different families and specific antiretroviral agents. Different studies have shown, in general terms, that switching from classical or boosted protease inhibitors (PI) results in an improved metabolic profile [17], and switching from thymidine analogue nucleoside reverse transcriptase inhibitors (NRTI) can ameliorate both metabolic abnormalities and lipoatrophy [18]. However, the expected improvement is slow and limited. New antiretroviral agents have been developed to have a minimal effect on metabolism and body shape [19–21].

Nutritional status could influence outcome and body composition changes, which may overlap with lipodystrophy in HIV-infected patients. In addition, it might also influence quality of life (QoL) and functional status in these patients. Although diet and exercise have been used in HIV-infected patients, their role in preventing or treating cART-associated metabolic and body alterations is yet to be established. For this purpose, we aimed to analyse peer-reviewed published data regarding dietary modification, use of supplements (nutritional formula or nutraceuticals) or scheduled exercise training, and their effect on body composition or metabolic complications in HIV-infected patients receiving cART.

Methods

We performed a Medline search of the literature from 1996 onwards, using the key words 'HIV' and 'body composition, fat-free mass, body cell mass, skeletal muscle, body fat mass, dyslipidaemia, metabolic syndrome, nutritional assessment, body mass index, BMI, body weight, weight loss, wasting syndrome, muscle wasting, cachexia, obesity, truncal obesity, truncal fat, vitamin status, trace elements, antioxidant, vitamin B_{12}, retinol, carotene, selenium, zinc, vitamin E, homocysteine, ascorbic acid, folate, folic acid, diet, dietary intake, enteral nutrition, parenteral nutrition, nutritional support, supplement, protein intake, omega-3 fatty acids, *n*-3 PUFA, carnitine, uridine, arginine, glutamine, exercise and resistance training'. The search was limited to available clinical trials, as well as meta-analyses. The Cochrane library was also scanned for relevant information. This search was supplemented with reference material from key papers. English and Spanish language selected papers were reviewed. Last update was on March 2007.

Each paper identified was reviewed concerning cART use. For the purpose of this study, we defined cART as any combination of three or more antiretroviral drugs or a combination of at least two antiretroviral drugs including a PI. Four criteria for study entry were defined: prospective clinical trials; cART use in the studied subjects at study entry; in case of studies containing cART- and non-cART-treated individuals (mixed ART studies), those performing a subgroup analysis for cART or at least controlling for cART were also accepted; and use of any intervention refering to the effect of diet, nutritional supplements or exercise training on corporal composition or metabolic profile.

For each study included, five aspects were reviewed: entry criteria (wasting, lipodystrophy or asymptomatic); study design; number of patients; type and length of intervention; and effects on metabolism and body composition.

Primary end-points analysed were changes in weight, fat mass and LBM, and changes in serum cholesterol and triglyceride levels. Secondary end-points were QoL scales, any result contributing to an indirect measurement of body muscle and fat or its distribution, and any variable reflecting insulin resistance. Proportions were rounded to the nearest whole number.

Results

Sixty-three studies were found assessing the effect of diet (*n*=7), nutrition supplements (*n*=34), exercise (*n*=20) and combined nutrition and exercise treatment (*n*=2) on body composition or metabolic profile. Thirty-eight studies were excluded due to non-cART cohort (*n*=19), mixed ART (*n*=13), change of ART during study period (*n*=2) and lack of information on ART (*n*=2). Duplicated cohorts published as substudies were found in two cases. Study design, sample size and main results of selected studies are summarized in Tables 1–5.

Effect of diet

The use of low-fat diets in patients with metabolic complications and hypocaloric diets in obese patients have been investigated (Table 1).

Table 1. Effect of diet

	Barrios *et al.* [22]	Moyle *et al.* [23]*	Terry *et al.* [24]†	Engelson *et al.* [25]
Study design	Open-label	Randomized	Randomized	Open-label
Number of patients (intervention/total)	230/230	16/31	30/30	18/18
Duration	6 Months	24 Weeks	12 Weeks	12 Weeks
Selection criteria	MS: lipodystrophy	MS: lipodystrophy	MS: lipodystrophy	Obesity
Dietary intervention	Low-fat diet	Low-fat diet	Low-fat diet	Hypocaloric diet (1,200 kcal/day)
Co-interventions	No	No	Exercise	Exercise
Results				
Weight	If compliant, -2 kg	–	-2 kg	-6.7 kg
Fat mass	–	–	–	-6.5 kg
Body cell mass	–	–	–	- 0.9 kg
Others	–	–	↓BMI, ↓WHR	↓BMI, ↓waist circumference
Methods of measuring body composition	–	–	Anthropometry	MRI scan, DXA, ^{40}K
Total cholesterol	If compliant, -10%	=	=	–
Triglycerides	If compliant, -23%	=	=	–
Fasting glucose	–	–	–	=
Insulin sensitivity	–	–	–	=

*Effects of diet-alone control group. †Effects on both exercise and stretching control group compared with baseline. '=', no differences versus baseline; BMI, body mass index; DXA, dual-energy X-ray absorptiometry; ^{40}K, total body potassium; MRI, magnetic resonance imaging; MS, metabolic syndrome; WHR, waist-to-hip ratio. –, not measured.

Table 2. Effect of nutraceuticals

	Manfredi *et al.* [34]	Wohl *et al.* [31]	De Truchis *et al.* [32]	Carter *et al.* [33]	Loignon *et al.* [35]	McComsey *et al.* [37]	Kaiser *et al.* [36]
Study design	Open-label observational	Randomized	Randomized double-blind	Randomized-double-blind	Open-label	Open-label pilot	Randomized double-blind
Number of patients (intervention/total)	54/156	26/52	60/122	5/11	16/16	10/10	18/40
Duration	18 Months	16 Weeks	8 Weeks	8 Weeks	8.9 ±5 Months	24 Weeks	12 Weeks
Entry criteria	Hyper-triglyceridaemia	Hyper-triglyceridaemia	Hyper-triglyceridaemia	Hyper-triglyceridaemia	Hyper-triglyceridaemia	Lipoatrophy/ ↑lactataemia	Polyneuropathy
Intervention	Omega-3 FA	Omega-3 FA	Omega-3 FA	Omega-3 FA	Carnitine	Micronutrient supplement	Micronutrient supplement
Fish oil dose	2 g/day	–	6 g/day	9 g/day	–	–	–
EPA/DHA, mg/d	–	1,750/1,150	1,080/720	1,620/1,080	–	–	–
Results							
Triglycerides	-16%	-25% (4 Weeks)	-25.5%	-56.9%	23% (4 Weeks)	=	=
Total cholesterol	–	–	-0.4%	=	–	=	=
LDL cholesterol	–	↑	–	–	–	–	–
Fasting glucose	–	–	=	–	–	↑	=
Fasting insulin	–	–	–	–	–	–	=
HOMA-IR	–	–	–	–	–	↑	–
Limb circumference	–	–	–	–	–	=	–
Skinfolds	–	–	–	–	–	=	–

In randomized studies, numbers reflect the effect of intervention versus baseline when intergroup differences were significant. Arrows reflect differences with the control group in randomized studies, and changes compared with baseline in open-label studies; '=', no differences. EPA/DHA, eicosapentaenoic acid/docosahexaenoic acid (the active components of fish oil); FA, fatty acid; HOMA-IR, homeostasis model assessment of insulin resistance; LDL, low-density lipoprotein. –, not measured.

Patients with metabolic complications

The usefulness of a low-fat diet to reduce plasma lipids has not been proved in randomized trials. In an open-label study with 230 HIV-infected patients with hypertriglyceridaemia, a significant reduction of 10% and 23% for cholesterol and triglyceride levels, respectively, was observed in those patients compliant with diet [22]. In a randomized trial (n= 31) to test the efficacy of pravastatin, no changes in total cholesterol or triglyceride levels were observed in the diet-control group [23]. In another trial (n=30) in which a low-fat diet was used in all patients randomized to exercise or stretching and relaxation, no changes were observed in plasma triglycerides, total cholesterol or high-density lipoprotein (HDL) cholesterol in either group [24]. By contrast, low-fat diets have been associated with weight loss, irrespective of exercise use or not [22,24].

Patients with obesity

The use of a hypocaloric diet and combined aerobic and resistance training in 18 obese HIV-infected women resulted in weight loss (-6.7 kg; 7.3%) and a reduction in waist circumference after 12 weeks. Little lean tissue was lost (6%) in comparison with the loss of fat (94%). No changes in the proportion of visceral adipose tissue (VAT) to subcutaneous adipose tissue (SAT) were observed either; however, no changes in insulin sensitivity or plasma lipids were observed despite weight loss [25].

Effect of nutritional supplements

The effect of nutritional supplements has been investigated in several studies (Tables 2–3). Three studies of patients on cART showed that the use of oral formula supplementation resulted in increased energy and protein intake [26–28].

Patients with weight loss

In a randomized trial including 70 patients, the use of a normocaloric standard formula providing 750 kcal and 28 g protein per day resulted in a significant increase in weight (+1.8 kg; 3%) and fat mass (+1.3 kg; 11%) with no change in fat-free mass. No changes were observed in the control group [26].

By contrast, in a randomized, double-blind, placebo-controlled trial including 68 subjects, supplementation with three amino acids (β-hydroxy-β-methylbutyrate, L-glutamine and L-arginine; HMB/Gln/Arg) resulted in significant weight gain (+3 kg; 4%), which was predominantly LBM (+2.5 kg; 4%), compared with placebo [29].

Table 3. Effect of oral nutrition supplements

	De Luis *et al.* [26]	Clark *et al.* [29]	Sutinen *et al.* [30]	De Luis *et al.* [28]*
Study design	Randomized	Randomized double blind	Randomized double-blind	Randomized
No of patients (intervention/total)	35/70	34/68	10/20	36/74
Duration	3 Months	8 Weeks	3 Months	3 Months
Selection criteria	Wasting–weight loss	Wasting–weight loss	Lipoatrophy	Weight-stable
Nutritional intervention	Standard formula+ counselling	Amino acid mixture (HMB/Gln/Arg)	Uridine	Peptide-based omega-3 fatty acid enriched formula
Control group	Counselling	Maltodextrin-based placebo	Isocaloric placebo	Standard formula
Results				
Caloric intake	↑	–	–	↑
Protein intake	↑	–	–	↑
Weight	+1.8 kg	+3 kg	+2.3 kg	+1.9 kg
Fat mass	+1.3 kg	=	+2.8 kg	+0.7 kg
Limb fat	–	–	↑	–
Truncal fat	–	–	↑	–
Intra-abdominal fat	–	–	↑	–
Tricipital skinfold	+13%	–	–	+8–13%
LBM	=	+2.5 kg	=	=
CSMA	–	=	–	–
Methods of measuring body composition	BIA, anthropometry	Air displacement pletismography, CT scan	DXA, MRI	BIA, anthropometry

*No different to controls; effects compared with baseline. Except for studies marked with an asterisk, numbers reflect the effect of intervention versus baseline when intergroup differences were significant, and arrows reflect differences with control group; '=', no differences. BIA, bio-impedance analysis; CSMA, cross-sectional muscular area; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; HMB/Gln/Arg, hydroxy-methylbutyrate/glutamine/arginine; LBM, lean body mass; MRI, magnetic resonance imaging. –, not measured.

In a randomized three-arm study comparing the effect of a high protein formula supplementation alone or in combination with oxandrolone or resistance training, an increase in LBM was observed in the nutrition alone group compared with baseline, without differences between groups. Lacking a control group without any intervention makes the interpretation of these results difficult [27].

Patients with lipoatrophy

In a randomized placebo-controlled trial including 20 patients with lipoatrophy, uridine supplementation for 3 months resulted in significantly greater increases in limb, intra-abdominal and total fat, compared with placebo. No significant changes were observed in LBM, glucose metabolism and plasma lipids, except for an increase in HDL cholesterol in the placebo group. Viral control and $CD4^+$ T-cell count remained stable in both groups [30].

Weight-stable patients

In a randomized study including 74 weight-stable individuals receiving cART, the use of a normocaloric standard formula was compared with a peptide-based formula enriched with omega-3 fatty acids. After 3 months, both groups increased caloric and protein intake similarly, although formulas had different caloric density and protein content. Weight was increased in both groups (+1.9 kg and +2 kg, respectively; 3% both), mostly due to fat mass (+1.5 kg and +0.7 kg, respectively; 13% and 7%), but no differences between groups were observed. Fat-free mass remained unchanged [28].

Patients with metabolic complications

In three randomized trials, the use of fish oil supplementation in patients with hypertriglyceridaemia resulted in a reduction in triglyceride levels [31–33], which was mantained in only one study under an open-label phase [32]. In the larger randomized

Table 4. Studies with exercise alone

	Terry *et al.* [24]*	Roubenoff *et al.* [39]	Jones *et al.* [45]	Dolan *et al.* [38]	Engelson *et al.* [25]	Yarasheski *et al.* [40]	Roubenoff *et al.* [41]	Shevitz *et al.* [27]
Study design	Randomized	Open-label	Open-label	Randomized	Open-label	Open-label	Open-label	Randomized
No. of patients (intervention/total)	15/30	10/10	6/6	20/40	18/18	18/18	25/25	16/47
Duration	12 Weeks	16 Weeks	10 Weeks	16 Weeks	12 Weeks	16 Weeks	8 Weeks	12 Weeks
Selection criteria	Lipodystrophy Non-specified criteria	Lipodystrophy Self-reported ↑ abdominal girth	Lipodystrophy Self-reported lipoatrophy	Lipodystrophy Self-reported fat redistribution, increased WRH	Obesity	Weight-stable	Weight-stable including six wasted subjects	Wasting
Exercise	Aerobic	Comb. aerobic + res. training	Comb. aerobic + res. training	Comb. aerobic + res. training	Comb. aerobic + res. training	Resistance training	Resistance training	Resistance training
Co-interventions	Low-lipid diet	–	–	–	Hypocaloric diet	–	–	Nutrition support
Controls	Stretching and relaxation	–	–	Normal activity	–	–	–	Nutrition alone
Results								
Weight	-2 kg	=	+3.8 kg	–	-6.7 kg	+1.4 kg	-	-
FM	–	-1.5 kg	↓%	=	-6.5 kg	=	-0.9 kg	-
LBM	–	=	–	–	-	+1.4 kg	+1.7 kg	=
BCM	–	–	–	–	-0.9 kg	-	-	-
CSMA	–	–	–	↑	-	↑	-	=
Methods to measure body composition	–	–	–	DXA, CT scan	MRI scan, DXA, ^{40}K	DXA, MRI	DXA	DXA, CT scan
Other anthropometrics	↓BMI ↓WHR	–	↑Limb cf ↓WHR	↓Waist cf =BMI	↓Waist cf ↓BMI	–	–	–
Muscle strength	–	↑	–	↑	↑	↑	↑	↑
Total cholesterol	=	–	-18 %	=	=	=	–	–
Triglycerides	=	–	-25 %	=	=	-27 %	–	–
Others	–	–	–	= 2h OGTT	= Insulin sensitivity	–	–	Improved QoL

*No different to controls; effects compared with baseline. Except for studies marked with an asterisk, numbers reflect the effect of intervention versus baseline when intergroup differences were significant and arrows reflect differences with the control group in randomized studies. In open-label studies, arrows reflect changes compared with baseline; '=', no differences. BCM, body cell mass; BMI, body mass index; cf, circumference; Comb. aerobic + res. training, combined aerobic and resistance training; CSMA, cross-sectional muscular area; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; ^{40}K, total body potassium; LBM, lean body mass; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; QoL, quality of life; WHR, waist-to-hip ratio. –, not measured.

Table 5. Studies with exercise plus pharmacological therapy

	Strawford *et al.* [43]	Sattler *et al.* [46,47]	Driscoll *et al.* [42,44]
Study design	Randomized double-blind	Randomized	Randomized
No. of patients (intervention/total)	11/22	15/30	11/25
Duration	8 Weeks	12 Weeks	3 Months
Selection criteria	Wasting–weight loss	Weight-stable	Abdominal adiposity and hyperinsulinaemia
Exercise	Resistance training	Resistance training	Aerobic and resistance
Co-interventions	Oxandrolone	Nandrolone	Metformin
Controls	Exercise alone	Nandrolone alone	Metformin alone
Results			
Weight	+4.2	–	–
Fat mass	-1.6 kg	↓	–
Lean body mass	+3.8	↑	–
CSMA	–	=	↑
Methods of measuring body composition	DXA	DXA, MRI, BIA	DXA, CT scan
Others	–	–	↓ WHR ↓ Abdominal SAT
Muscle strength	–	↑	↑
Total cholesterol	–	–	=
Triglycerides	–	–	=
Fasting glucose	–	↓	–
Fasting insulin	–	↓	↓
Insulin AUC	–	–	↓
HOMA-insulin resistance	–	↓	–

Numbers reflecting the effect of exercise alone except [43] in which baseline testosterone replacement was given. Otherwise, arrows reflect differences with control group. '=', no differences; AUC, area under curve; BCM, body cell mass; BIA; bio-impedance analysis; CSMA, cross-sectional muscular area; CT, computed tomography; DXA, dual-energy X-ray absorptiometry; HOMA, homeostasis model assessment; LBM, lean body mass; MRI, magnetic resonance imaging; SAT, subcutaneous adipose tissue; WHR, waist-to-hip ratio. –, not measured.

placebo-controlled trial (n=122), the magnitude of the reduction was 25% at week 8 [32]. Adverse effects reported in the fish oil group were nausea and vomiting in one subject, and bad taste in another [31].

The only long-term data on fish oil supplementation comes from an observational open-label study in 156 patients with moderate hypertriglyceridaemia comparing the effect of omega-3 fatty acids versus fibrate use versus diet plus exercise. In this study, the continued use of omega-3 fatty acids led to a significant decrease of serum triglyceride levels (-16% at 6 months) compared with baseline, which was maintained at 18 months (-12%). Triglycerides were also significantly lower compared with the diet–exercise control group from month 6 until month 18 [34].

In an open-label pilot trial including 16 subjects, the administration of oral carnitine for 8.9 ±5 months showed a significant sustained reduction in plasma triglyceride levels during the study (-39% at first month and -23% when cART was first changed), but no information was provided about the patients and the time at which cART was changed [35]. No randomized trials were found assessing carnitine use.

Micronutrient supplementation in patients receiving cART has not shown any favourable effects on corporal composition or metabolic complications [36,37]. Only a randomized double-blind placebo-controlled trial was found reporting metabolic effects of micronutrients in 40 patients with distal symmetric polyneuropathy. Supplementation with micronutrients in high doses resulted in a significant increase in $CD4^+$ T-cell count. No differences were observed in fasting glucose, insulin or lipids when compared with placebo [36]. The results of increased fasting glucose and insulin resistance, found in an open-label pilot study using high-dose antioxidants (vitamins E and C and *N*-acetyl-cysteine) in 10 HIV-infected patients with lipoatrophy or sustained hyperlactataemia, have not been reproduced in other studies [37].

Effect of exercise

Exercise use has resulted in increased muscle strength [25,27,38–41] and improvements in QoL [25,27] in all studies addressing these issues. Moreover, exercise does not seem to have a detrimental effect on the management of HIV infection, as no changes in $CD4^+$ T-cell count and

viral load in relation to aerobic or resistance exercise were observed [24,25,38,42,43]. Regarding body composition changes and metabolic effects of exercise, different results were found depending on populations studied and type of intervention (Tables 4–5).

Patients with central lipoaccumulation

In a randomized trial in 40 HIV-infected women, 16 weeks of supervised home-based aerobic and resistance training resulted in improvements in fitness and strength measures and increased total muscle area in the exercise group compared with controls. No changes in BMI, total fat, SAT, VAT, plasma lipids and glucose tolerance were observed [38]. In another randomized trial with 30 patients, aerobic exercise in combination with a low-fat diet resulted in similar reductions in weight, estimated body fat and waist-to-hip ratio compared with controls on a stretching and relaxation program in addition to diet [24].

In an open-label pilot study, 16 weeks of resistance training with an aerobic component in 10 patients with self-reported abdominal adiposity resulted in a significant decline in body fat (-1.5 kg, 2%), mostly in trunk fat (-1.1 kg), whereas no changes were seen in weight or LBM [39].

The combination of exercise and metformin seems to produce more profound changes in adipose tissue than metformin alone, as shown in a randomized trial including 25 hyperinsulinaemic subjects with fat redistribution syndrome. The addition of exercise to metformin therapy resulted in significant decreases in waist-to-hip ratio and abdominal subcutaneous adipose tissue compared with metformin alone. A trend towards a greater reduction in subcutaneous leg fat was also observed in the combined therapy group. In addition, thigh muscle cross-sectional area and strength increased in this group compared with those receiving metformin alone [42]. The combined therapy group showed an increased thigh muscle attenuation, reflecting a decreased muscle adiposity, in comparison with metformin alone. These changes were associated with a reduction in plasma fasting insulin [44].

Patients with lipoatrophy

Only a small pilot study of exercise in six patients with self-reported lipoatrophy was found. After 10 weeks, body weight (+3.8 kg; 5%), muscle strength and muscle circumferences increased compared with baseline, whereas a reduction in percentage body fat and waist-to-hip ratio was observed [45].

Weight-stable patients

In two open-label studies, resistance exercise in weight-stable population has produced significant increases in LBM, but different changes in fat mass.

In a study with 18 subjects, 16 weeks of training resulted in increased body weight (+1.4 kg; 2%), LBM (+1.4 kg; 2%), thigh muscle cross-sectional area and muscular strength with no reduction in whole body fat [40]. In another study with 25 subjects, using a more heterogeneous population including six patients with wasting, 8 weeks of resistance training produced significant increases in strength and LBM (+1.7 kg; 3%) with a concomitant decline in fat (-0.9 kg; 4%), in the entire study group [41].

On the other hand, resistance training seems to have an additive effect on anabolic therapy as shown in a randomized study with 30 patients in which the combination of nandrolone and resistance exercise produced greater gains in LBM and strength than nandrolone alone, but also a loss in fat mass [46].

Patients with weight loss

In a randomized three-arm study with 47 subjects, oxandrolone or resistance training in addition to oral nutrition support were compared with nutrition alone. After 12 weeks, LBM increased in the oral formula and oxandrolone groups, and cross-sectional muscular area increased in the oxandrolone and exercise groups compared with baseline, but no differences between groups were observed. However, when QoL was assessed, patients in the exercise arm showed significant improvements in physical function scale and in muscular strength [27].

Patients with weight loss seem to benefit from the combination of anabolic therapy and exercise as shown in an 8-week randomized, double-blind, placebo-controlled trial in 22 eugonadal men. In this trial, the addition of oxandrolone to resistance training produced greater gains in weight, LBM and strength than exercise alone. A decrease in fat mass was also observed in both groups, compared with baseline [43].

Patients with metabolic complications

Exercise does not seem to produce relevant changes in plasma cholesterol levels as shown in most of the studies [25,38,40]. The 18% reduction in plasma cholesterol levels reported in a small pilot study has not been reproduced in larger studies [45].

As for triglyceride levels, no effect was observed in a randomized study (n=30) in which exercise was used in addition to a low-lipid diet [24]. Likewise, no effect was observed in another randomized study (n=25) combining metformin therapy and exercise [42]. In the only randomized study (n=40) comparing home-based training to non-exercising controls and without co-interventions, no significant effect on triglyceride levels was found, but patients had normal triglyceride levels at baseline [38]. Only in two open-label studies, with 6 and

18 patients, was a reduction found in triglyeride levels (-25% to -27%) after exercise [40,45].

Exercise has shown to improve carbohydrate metabolism and hyperinsulinaemia in some [42,47], but not all, studies [25,38].

In a randomized study including 25 subjects with hyperinsulinaemia, the addition of a combined aerobic and resistance training program to metformin treatment resulted in significant decreases in fasting insulin and insulin area under the curve after 3 months, in comparison with metformin alone [42]. In another randomized trial (n=30) to assess the metabolic effects of nandrolone alone or in combination with resistance training, fasting insulin and insulin resistance decreased significantly in the exercise group [47].

By contrast, in an open-label study of hypocaloric diet and exercise in 18 women with obesity [25], no changes in insulin sensitivity were observed despite an amount of weight loss in the range of previously reported data in the general population [48–50]. In another study with 40 women, a supervised home-based exercise program did not produce changes in glucose tolerance, but no changes in BMI or body fat were observed either [38].

Discussion

Although nutrition and exercise play an important role in health, body composition and metabolic profile in the general population, we have found few adequate studies addressing these issues in HIV-infected patients on cART. In addition, some of the studies had a pilot design with small sample sizes. Results from small studies must be interpreted with caution and need to be confirmed in larger studies.

One of the main problems assessing nutritional status in this population is defining protein-energy malnutrition in a context in which its signs overlap with those from lipodystrophy syndrome. Body composition is influenced by many factors making it difficult to distinguish which role nutrition is actually playing. Until recently, diagnosis of lipodystrophy and severity assessment was quite subjective. Lack of consistency in entry criteria in some of the studies reviewed was a great drawback. Definitions for lipodistrophy ranged from self-reported fat wasting to self-reported abdominal adiposity or increased waist-to-hip ratio.

As LBM is considered a determinant of prognosis for several disease states, one of the main goals of exercise and nutrition for subjects with wasting is to gain LBM. Regarding body fat, loss of fat mass can be a desirable outcome for patients with visceral fat accumulation or obesity, but it can also be a deleterious effect in lipoatrophic patients. Unfortunately, most intervention studies reviewed lacked information on the distribution of the fat gained or lost. Objective methods to assess regional body composition such as dual-energy X-ray absorptiometry, sonography, computed tomography or magnetic resonance imaging should be used in studies assessing nutritional intervention. A complete review on the methodology and limitations of the different methods of body composition is published elsewhere [51].

The efficacy of diet in treating cART-related metabolic complications is limited. For those subjects with dyslipidaemia a high treatment failure rate has been described for diet alone [52,53], according to National Cholesterol Education Program guidelines for dyslipidaemia [54]. Lack of compliance with the diet can explain these poor results, as suggested in one study [22] in which a lipid-lowering effect was observed in post hoc analysis of compliant subjects. The effect was within the range observed in studies in the general population [55,56].

According to available data, a low-lipid diet can not be recommended as a first-step approach in cART-related dyslipidaemia. However, cross-sectional studies have identified high intakes of cholesterol, saturated and *trans* fats as potentially modifiable dietary habits in this population [57,58]. As suggested in one study of Mediterranean diet in the general population, increasing the amount of monounsaturated or omega-3 polyunsaturated fats in the diet results in a better metabolic profile than a low-lipid diet [59]. This issue has not been investigated in the HIV population, but changing the lipid pattern of the diet seems a reasonable approach, especially in patients with wasting or lipoatrophy in which weight loss as described in studies using low-lipid diets [22,24] is to be avoided.

Regarding nutraceutical use (Table 2), omega-3 fatty acids from fish oil have been effective in reducing increased serum triglyceride levels [31–34], in the range of the results obtained in some ART-switching studies [60–63]. No controlled data comparing the effect of omega-3 fatty acids with fibrate use is available. However, fish oil can represent a good choice in patients with combined hyperlipidaemia in order to avoid the association of a fibrate with a statin.

Micronutrient use has not shown any favourable effects on corporal composition or metabolic complications. As suggested in one small study in patients with cART-associated polyneuropathy, micronutrient supplementation can result in small increases in $CD4^+$ T-cell count in the short term, at least in patients with evidence of ART toxicity [36]. However, it is uncertain if these results can be expected in all patients on cART and if they translate into better outcomes, so no general recommendations can be made regarding vitamin use for patients on cART.

In patients with lipoatrophy, uridine supplementation can be useful to increase subcutaneous and total fat, as

shown in one randomized study [30]. More research on uridine treatment is needed, controlling for type of antiretrovirals and ART exposure, before any strong recommendation can be made.

Exercise training has shown important effects on body composition without detrimental effects on viral control, irrespective of ART [24,25,38,42,43,64–67]. However, a high attrition rate has been seen in some studies (up to 37%) [25,39,42,64], so exercise cannot be expected to work in all patients. Besides, no controlled long-term studies testing the effect of exercise are available, so it is not known which intensity of exercise can be maintained on a long-term basis and what effects can be expected.

There is conflicting evidence of the metabolic effects of exercise in the cART population. Few studies, some with small sample size, have shown a reduction in triglyceride levels [40,45] and improved insulin resistance [42,47] with exercise. However, these results have not been reproduced in two randomized studies of exercise and diet despite weight loss [24,25]. It is important to notice that metabolic parameters are analysed as secondary endpoints, so substantial differences in the populations studied were found in data such as baseline triglyceride levels. Aside from differences in study design, it is possible that type of antiviral agents used and ART exposure might account for some of the discordant results.

Resistance exercise alone or in combination with an aerobic component can be used to increase muscle mass and strength [38–41,45]. Similar results were obtained in an updated Cochrane's meta-analysis not controlling for ART [67]. The combination of resistance exercise with anabolic agents results in greater gains in muscle mass, but a expenses of a deleterious effect on HDL cholesterol levels [43,47].

Most studies with resistance or combined training showed decreasing fat mass [39,41–46], but few reported the distribution of the lost fat, mostly trunk fat loss [39,45]. Exercise does not necessarily promote fat loss in all patients taking cART, however, as shown in a study with weight-stable subjects performing resistance training alone, in which no changes in body fat were observed in any fat compartment measured [40]. It is difficult to say whether the aerobic component of the exercise has a special effect in promoting fat loss or if it is only a matter of exercise intensity and duration. The loss of trunk and abdominal fat described with a combined exercise program has been correlated with improved glucose metabolism [44]; therefore, this approach seems appropiated for patients with central adiposity. The combination of metformin plus exercise seems to have additional effects in promoting greater fat loss than metformin alone [42], including the loss of subcutaneous fat [44]. This approach should be avoided in lipoatrophic patients, but can be useful in overweight patients in which loss of subcutaneous fat is not of concern. Nutritional advice to increase energy and protein intake or adding supplements to exercise training seems a reasonable approach for non-overweight or lipoatrophic subjects, but no data in the cART population is available to support this recommendation.

In summary, despite the paucity of controlled studies assessing the effect of dietary modification, nutrition support or exercise in subjects receiving cART, oral nutrition support has shown to be effective in increasing protein and energy intake and in gaining body weight and fat mass in patients with both stable weight and weight loss. The use of specific formula does not add further advantages, but some amino acids, at least in combination, are potentially useful in increasing LBM in patients with weight loss. Resistance exercise, with or without an aerobic component, might be useful in increasing LBM. However, low-fat diets or exercise can result in loss of weight and fat mass, which limits its usefulness as unique therapy; their use in lipoatrophic patients warrants proper monitoring. More studies need to be carried out with more homogeneous groups according to baseline body composition and antiretroviral treatment. Special emphasis must be put on adopting objective definitions for entry criteria in order to obtain more reproducible results.

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