

GENERAL NUTRITION, WEIGHT LOSS, AND WASTING SYNDROME

KEY TO ABBREVIATED TERMS WITHIN GUIDELINES

ACTH	adrenocorticotropin hormone	GERD	gastroesophageal reflux disease
ATP	adenosine triphosphate	HAART	highly active antiretroviral therapy
BCM	body cell mass	IL	interleukin
BIA	bioelectric impedance analysis	LBM	lean body mass
BUN	blood urea nitrogen	PRE	progressive resistance exercise
BW	body weight	rhGH	recombinant human growth hormone
CI	caloric intake	REE	resting energy expenditure
CMV	cytomegalovirus	TBW	total body weight
CPK	creatine phosphokinase	TEE	total energy expenditure
DEXA	dual energy x-ray absorptiometry	TNF	tumor necrosis factor
DT	dietary thermogenesis	TPN	total parenteral nutrition
EEA	energy expenditure of activity	UBW	usual body weight
EM	extracellular material	VAT	visceral adipose tissue
Fat	fat compartment	VLDL	very low density lipoprotein

I. INTRODUCTION

RECOMMENDATION:

The clinician should ensure that patients with HIV-associated weight loss are receiving effective ARV therapy (see Chapter 4: *Guidelines for the Use of Antiretroviral Therapy*).

Significant weight loss negatively impacts a patient's quality of life and self-image. Despite advances in the treatment of HIV/AIDS, the majority of HIV-infected patients experience weight loss at some time during the course of the disease.

The Nutrition for Healthy Living study has been longitudinally following HIV-infected participants to examine the causes and consequences of malnutrition.¹ Between 1995 and 2000, there were 552 evaluable patients, and weight loss was the strongest independent predictor of mortality despite the availability of HAART. A 4- to 6-fold increase in mortality was seen in patients with $\geq 10\%$ weight loss from baseline or the previous visit.

For patients experiencing weight loss, the clinician's tasks include documenting the character and circumstances of the weight loss, estimating the major alteration of body composition, attempting to understand the mechanisms contributing to the weight loss, and treating both the underlying metabolic derangement as well as any confounding conditions present. The expectation of treatment for the weight loss should be an improved quality of life and performance status.

Although much remains to be understood about the relationship between losses of body mass and HIV infection, the following principles are essential to the effective management of weight loss and nutrition in HIV-infected patients:

- Rapid loss of weight (more than 5% of usual body weight over a 2- to 3-month period) and lean body mass are highly associated with impending hospitalization and mortality.²
- Therapeutic attention to reversing weight loss without addressing the etiology has never been convincingly proven to improve overall prognosis.³
- Although new HAART regimens have reduced the prevalence of wasting syndrome, they have at the same time been associated with previously unrecognized variations to body composition.⁴
- The mechanisms that cause weight loss are myriad and usually multifactorial.

Key Point:

Weight loss is a symptom that warrants a carefully executed diagnostic evaluation for correctable or treatable confounding conditions.

As further research uncovers the pathophysiologic mechanisms of weight loss in HIV infection, more effective therapies can be anticipated.

II. ASSESSMENT OF BODY COMPOSITION

RECOMMENDATION:

The clinician should measure and record the weight of HIV-infected patients at each visit.

For the purposes of this chapter, the following definitions concerning body composition will be used:

- Body weight (BW) is the total mass constituting all cellular and non-cellular components and can be simply measured by an office scale.
- The body cell mass (BCM) includes all non-adipose cells as well as the aqueous compartments of the fat cells.
- The fat compartment (Fat) represents the non-aqueous component of adipocytes.
- The lean body mass (LBM) represents the BCM and extracellular material (EM) exclusive of fat.

The body composition compartments relate as shown below:

$$\mathbf{BW = BCM + EM + Fat}$$

$$\mathbf{LBM = BCM + EM}$$

Accurate assessment of body composition can be accomplished by one of three methods. Sophisticated isotope dilution studies and dual energy x-ray absorptiometry (DEXA) scans are research techniques that may not be generally available to most physicians in their day-to-day management of patients. Bioelectric impedance analysis (BIA) is practical and relatively inexpensive and should be used, if possible. However, BIA can lead to misinterpretation of body composition when there are significant volume shifts or regions of active inflammation. Measurement of skin folds is an inexpensive method of assessing body fat; however, to obtain reproducible results, an experienced healthcare provider should obtain the measurements.

Key Point:

The clinician should be vigilant for HIV-associated malnutrition, even in patients who appear to be maintaining their usual body weight. Weighing the patient should not be the sole method used to detect nutritional deficiencies.

Loss of BW in HIV-infected adults usually signifies a perturbation of more than a single compartment (see Table 1). Generally, it will be possible to identify the compartment that is most significantly decreased, although a marked decrease in one compartment may be counterbalanced by increases in another, with little net change in the measured BW. For example, a patient with marked reduction in BCM due to severe deconditioning may have no net change in BW because of increases in fat. Therefore, depending solely on the examining room scale to detect nutritional deficiencies can be misleading.

Studies have confirmed that malnutrition with alterations in BCM and fat occurs at all stages of HIV infection.⁵ For individual patients, such body composition changes may not correlate with a decline in CD4 cell counts or a history of opportunistic diseases. However, certain alterations in body composition are directly linked to prognosis and even time to death. Regression analysis studies have linked time of death to a point in time when the BCM and BW reach 54% and 66% of ideal values, respectively.² Significant unintentional loss of body mass is usually considered to be >5% of the usual BW over 1 to 2 months. A $\geq 10\%$ decrease in the usual BW is one criterion for wasting syndrome⁶ (see Section VI: *The Wasting Syndrome*). Although many presume that delay or reversal of lost BW could improve life expectancy, this has never been confirmed by controlled clinical studies. Hence, simply supplementing caloric intake without addressing reversible causes of weight loss is not generally beneficial.

TABLE 1
CLINICAL DETERMINATION OF CHANGES IN BODY COMPOSITION

Change in Body Composition	History	Physical Examinations	Laboratory
↓ Body Cell Mass	Fatigue, weakness, decreased exercise tolerance	Proximal muscle wasting, weakness of deltoids/iliopsoas, peripheral edema	↑ CPK (if myopathy present) ↑ BUN/creatinine ↓ albumin
↓ Extracellular/ ↓ Intravascular H₂O	Orthostatic dizziness, polydipsia, dry skin and xerostomia, alimentary difficulty, polyuria, diarrhea	Orthostatic hypotension, decreased skin turgor, dry mucosa	↑ or ↓ Na ↑ BUN/creatinine ↓ HCO ₃ ↓ K, Mg
↓ Fat	Change in body habitus	Prominent venous pattern/extremities, facial wasting	↑ triglycerides

III. ASSESSING NUTRITIONAL STATUS

RECOMMENDATION:

A careful nutritional assessment should be conducted by a registered dietitian for any patient who has involuntary weight loss of at least 5% of the UBW, demonstrates clinical evidence of LBM loss, or follows a restrictive diet involving major food groups.

Poor nutrition may be one of many co-factors encountered in HIV-infected patients. In the United States, poor socioeconomic status and other factors, such as dietary restrictions mandated by HAART, co-existent gastrointestinal disease, alternative therapy diets, psychiatric disorders, active drug and alcohol use, and/or hospitalization for opportunistic diseases, may result in inadequate caloric consumption or assimilation.⁷

Key Point:

A thorough medical history and a focused physical examination are the most valuable tools in assessing nutritional status.

A careful nutritional assessment is an important part of the management of HIV-infected patients. Food diaries that are maintained by the patient are often incomplete but can be useful to the clinician for estimating the frequency, quality, and size of meals. It is especially useful to enlist the help of a registered dietitian when attempting to assess the adequacy of a patient's nutritional intake. A thorough medical history is the most valuable tool in assessing nutritional status. Emphasis on the review of systems will occasionally uncover symptoms indicative of a co-morbid condition that influences the nutritional state. A focused physical examination is similarly important.

IV. ENERGY EXPENDITURE

Energy expenditure needs to be met by caloric intake to avoid catabolism and weight loss. Total energy expenditure (TEE) equals resting energy expenditure (REE) plus dietary thermogenesis (DT) plus the energy expenditure of activity (EEA). When weight is stable, the TEE needs to equal the caloric intake (CI). Therefore, it follows that weight loss might occur because of decreases in the caloric intake or because of increases in energy expenditure.

$$\text{In Steady State: CI} = \text{TEE} = \text{REE} + \text{DT} + \text{EEA}$$

Decreased caloric intake can occur for a variety of reasons in HIV-infected patients. For the TEE to decrease in this setting, there needs to be a decrease in the EEA. It is postulated that the lethargy and fatigue that often accompany the malnutrition of AIDS are compensatory in nature.⁵

Key Point:

Resting energy expenditure in all stages of HIV/AIDS may be increased by >10% when compared with non-HIV-infected individuals.⁵

The REE in the HIV-infected patient is typically increased by >10%, which is similar in degree to severe thyrotoxicosis. The pathogenic reasons for this observation are discussed in Section V: *Weight Loss*.

Lipid abnormalities, such as hypertriglyceridemia, elevation of the serum very low density lipoprotein (VLDL), and hypocholesterolemia, are frequently observed in patients with symptomatic HIV/AIDS. These lipid aberrations are contributed to by substrate futile cycling. Futile cycling of free fatty acids between the liver and the peripheral fat cells requires adenosine triphosphate (ATP) energy expenditure that is not replenished because the free fatty acids are not oxidized in this process.

V. WEIGHT LOSS

A. Pathophysiology

The pathophysiology of weight loss in HIV/AIDS is not completely understood. However, many features of catabolism in HIV infection are similar to other chronic illnesses. The mechanisms can be divided into three categories:

- Decreased nutrient intake
- Decreased nutrient absorption
- Disturbances of metabolism

1. Decreased Nutrient Intake

RECOMMENDATIONS:

When patients present with dysphagia or odynophagia, the clinician should evaluate for causes of neoplasms, stomatitis, and/or esophagitis, especially when the patient's CD4 count is <200 cells/mm³.

After active opportunistic diseases have been excluded in patients with voluntary restricted caloric intake, clinicians should consult with or refer the patient to a dietitian, psychiatrist/psychologist, or social worker.

There are myriad causes of inadequate oral intake of caloric substrate for patients with HIV/AIDS. Anorexia is prevalent, and in patients receiving HAART, it is most often related to medication toxicity. Less frequently, anorexia may result from opportunistic conditions of the oral cavity, upper gastrointestinal tract, endocrine, or central nervous system, especially in patients with CD4 cell counts <200 cells/mm³. Endogenous cytokines and interferons also may precipitate a significant loss of appetite.⁸ Active substance use and depression are also causes of decreased nutrient intake.

Key Point:

Dietary restrictions for some HAART regimens pose significant barriers to adequate caloric intake and good nutrition. It may be necessary to consider a change in HAART under these circumstances (see Table 2).

Dysphagia and odynophagia are barriers to adequate nutrition. Examples of conditions causing dysphagia include aphthous and chemotherapy-induced stomatitis; herpes simplex and CMV infections; candidal esophagitis; or neoplasms of the oral cavity, posterior pharynx, or esophagus.

In patients with CD4 cell counts >200 cells/mm³, the most common cause of voluntary decrease in oral intake is anorexia as a result of medications that cause nausea, alteration in taste, and/or gastroesophageal reflux disease (GERD). Voluntary restriction of caloric intake may occur because of difficulty with complex medical regimens; economic barriers to good nutrition; avoidance due to holistic or alternative therapy restrictive diets; psychiatric disorders, including depression and bipolar disease; and physician-recommended restrictive diets for medical reasons, such as pancreatitis, renal disease, or HAART.

TABLE 2
MANUFACTURERS' GUIDELINES COMBINING ANTIRETROVIRAL MEDICATION AND FOOD

ARV Drug	To be taken on empty stomach	To be taken with food	Can be taken with or without food	Comments
Abacavir (ABC)			X	No food effect.
Amprenavir (APV)			X	Avoid meals with >50 g fat. Avoid vitamin E supplements. Do not take antacids 1 hour before or after taking APV.
Atazanavir (ATZ)		X		Light meal increases AUC 70%, Cmax 57%.
Delavirdine (DLV)			X	Take with acidic beverage. Do not take antacids or magnesium supplements 1 hour before or after taking DLV.
Didanosine (ddI)	X*			Take 1 hour before or 2 hours after meals. Alcohol may exacerbate toxicity. Avoid acidic beverages. Do not take aluminum- or magnesium-containing antacids.
Efavirenz (EFV)	X			Avoid meals with >40-60 g fat.
Emtricitabine (FTC)			X	No food effect.
Enfuvirtide (T-20)			X	No food effect.
Fosamprenavir (f-APV)			X	No food effect.
Indinavir (IDV)	X			Take 1 hour before or 2 hours after meals. Drink plenty of fluids (8-10 cups/day). Grapefruit juice may affect absorption.
Lamivudine (3TC)			X	Although absorption is decreased with food, systemic availability is not affected.
Lopinavir/ritonavir (LPV/r)		X		To increase absorption by 50-80%, take with meal containing >15 g of fat.
Nelfinavir (NFP)		X		To increase absorption, take with meal containing 500-1000 kcal (20-50% fat).
Nevirapine (NVP)			X	No food effect.
Ritonavir (RTV)		X		Take with food that contains both protein and fat. To increase absorption, take with a meal containing >15 g fat.
Saquinavir (SQV)		X		Take within 2 hours of high-fat meal or snack. Grapefruit juice may increase retention.
Stavudine (d4T)				No food effect.
Tenofovir (TDF)			X*	Fatty meal increases TDF AUC by 40%.
Zalcitabine (ddC)			X	Food decreases ddC AUC by 14%.
Zidovudine (ZDV)			X	Fatty food may decrease bioavailability (clinical significance unknown).

Data are from manufacturers' information and Fields-Gardner C, Salomon S, Davis M. *Living Well With HIV and AIDS: A Guide to Nutrition*. Chicago, IL: The American Dietetic Association, 2003.

* TDF + ddI EC can be taken on an empty stomach or with a light meal; TDF + ddI buffered tablets should be taken on an empty stomach.

2. Decreased Nutrient Absorption

RECOMMENDATIONS:

For all patients with chronic diarrhea, the clinician should examine for and treat gastrointestinal opportunistic infections (*Mycobacterium avium* complex, bacterial pathogens such as *Salmonella*, *Cryptosporidium*, microsporidia, *Isospora*, *Giardia*, *Entamoeba*, *Clostridium difficile*), as well as assess for ARV-induced diarrhea.

The clinician should evaluate patients with chronic diarrhea in the setting of weight loss for malabsorption by 3-day fecal fat measurement, D-xylose absorption studies, and jejunal and/or colon biopsy.

Chronic diarrhea can be defined as at least two watery stools per day lasting for more than 3 weeks. When malnutrition and weight loss are caused by chronic diarrhea, malabsorption of essential nutrients is usually associated. Despite an adequate or even supra-normal nutrient consumption, these patients suffer malnutrition because of intestinal malabsorption caused by chronic intestinal microbial colonization with such pathogens as *M. avium* complex, *Cryptosporidium*, *Isospora*, or microsporidia. An in-depth discussion of gastrointestinal pathogens can be found in Chapter 9: *Gastrointestinal Complications of HIV*. Molecular hybridization studies have confirmed the presence of HIV in the bowel walls of patients with AIDS enteropathy.⁹ Although there is no definitive evidence that HIV enteropathy results in malabsorption, it is a theoretical contributory factor after other etiologies have been excluded.

Common features of the malabsorptive syndromes are steatorrhea, villous atrophy, and diminished absorptive surface area, along with functional defects in pathogen-injured cells and poor differentiation of villous epithelial cells due to rapid cell turnover. Patients with nutrient malabsorption generally report several episodes of diarrhea daily, occasionally with steatorrhea, and they may have an associated vitamin B₁₂ deficiency.

Evaluation of patients with chronic diarrhea may include stool studies for enteric pathogens, ova and parasites, *Clostridium difficile* toxin, acid-fast bacilli stain, and modified acid fast stain for organisms such as cryptosporidium. Antigen testing of stool is available in some laboratories for infections such as cryptosporidiosis and giardiasis. If this evaluation is non-diagnostic, colonoscopy with biopsy may be indicated to look for certain infections such as CMV, or non-infectious processes such as inflammatory bowel disease. Chronic malabsorption from pathogens such as *M. avium* complex requires upper endoscopy with small bowel biopsy for diagnosis.

Several studies indicate that selenium deficiency correlates with HIV progression and mortality. More studies are required to determine whether the selenium deficiency is a cause or an effect of clinical disease progression. Serum carotene levels may be reduced in patients with the wasting syndrome. It is likely that patients who have limited access to micronutrients would benefit from supplementation.

3. Disturbances of Metabolism

RECOMMENDATIONS:

The clinician should perform a comprehensive medical evaluation when rapid unintentional weight loss ($\geq 10\%$ of the UBW) occurs over weeks to months because it is frequently associated with a life-threatening opportunistic infection or neoplasm.

Clinicians should consider measuring total and free testosterone levels in all HIV-infected men with changes in libido, loss of LBM, or fatigue.

Key Point:

Because women lose a disproportionate amount of body fat at all stages of HIV infection, malnutrition should be suspected in women demonstrating fat loss.

Deranged metabolism may induce weight loss either through ineffective or excessive utilization of energy substrate (see Table 3). Abnormal energy expenditure at rest has been described in the setting of HIV infection.¹⁰ Certain opportunistic infections, such as disseminated *M. avium* complex, may induce extraordinary consumption of energy substrate. Although REE may be elevated during the course of HIV infection, in patients with rapid weight loss despite adequate caloric consumption, an evaluation for an opportunistic infection or neoplasm should be performed. The mechanisms by which HIV infection triggers an increase in REE are not fully understood.

TABLE 3
METABOLIC ABNORMALITIES ASSOCIATED WITH WEIGHT LOSS IN HIV/AIDS

- Abnormal energy expenditure/hypermetabolism
- Cytokines—the cachectin theory
- Cytokine induction of other catabolic agents
- Futile cycling
- Inappropriate substrate usage
- Protein wasting
- Endocrine factors
- Fat redistribution/“lipodystrophy”
- HAART-associated hypercholesterolemia, hypertriglyceridemia, and insulin resistance/hyperglycemia
- Myopathy due to HIV and/or nucleoside mitochondrial toxicity

After early reports of elevated levels of tumor necrosis factor (TNF) in HIV/AIDS, this cachexin was implicated as a cause of wasting.¹¹ However, subsequent studies failed to document consistent elevation of TNF levels. Other cytokines, including interleukin-1, IL-2, IL-6, and α -interferon, also have been measured at elevated levels compared with non-HIV-infected persons. Some animal models have implicated cytokines as a cause of weight loss. It is plausible that, for some patients, synergy between one or more cytokines contributes to observed catabolism and weight loss. Cytokines have many physiologic effects including the induction of other catabolic agents, such as cortisol, catecholamines, adrenocorticotropin hormone (ACTH), and glucagon.

Futile cycling refers to the inappropriate mobilization of peripheral free fatty acids, which are then re-esterified into triglycerides rather than being oxidized by the liver. Thus, cytokines redirect energy away from the periphery and toward the liver to fuel an acute phase response. This results in an increased VLDL level with a net consumption of energy in the form of ATP. Animal models have implicated TNF in futile cycling, although its quantitative impact in humans with HIV infection has not been established.^{5,12}

Under circumstances of starvation, the body can regulate the catabolism of muscle and fat separately. In prolonged fasting states, there is generally protein sparing relative to the loss of fat. In contrast, in HIV/AIDS and other conditions (e.g., septicemia), protein wasting seems to occur at an increased rate. It has been postulated that this proteolysis adaptation is cytokine mediated.

Endocrine Factors

Serum testosterone levels have a circadian rhythm and are standardized to morning samplings. Studies of endocrine function in men with AIDS have documented low serum testosterone levels.¹³ Testosterone is an anabolic steroid that, if deficient, could contribute to protein wasting. Elevated prolactin levels also have been documented, especially in patients with CD4 counts ≤ 200 cells/mm³. The observed elevations of prolactin raise the probability of a hypothalamic hypogonadism. Interestingly, certain cytokines, including IL-1, can reduce the responsiveness of the testicular Leydig cells, which sets the stage for primary hypogonadism as well. Body composition studies have defined differences in the patterns of weight loss between men and women.^{14,15} Men generally demonstrate a disproportionate decrease in LBM relative to fat loss. In contrast, women lose a disproportionate amount of body fat relative to LBM at all stages of HIV infection. Testosterone is difficult to accurately measure in women because levels are normally low in women. Free testosterone levels are thought to give a more accurate representation of available testosterone in both HIV-infected men and women. Less is understood about the impact of low testosterone levels in women, although in one study, HIV-infected women either of low weight or losing significant weight had a greater likelihood of hypoandrogenemia compared with non-HIV-infected controls.¹⁶ Further studies to demonstrate whether HIV-infected women with hypoandrogenemia might benefit from testosterone replacement are needed.

Key Point:

When weight loss is associated with profound fatigue, postural hypotension, hyperkalemia and/or hyponatremia, clinicians should consider adrenal insufficiency, especially in cases of disseminated *M. avium* complex and CMV infection.

Cortisol is generally elevated in patients with opportunistic infections, most notably *M. avium* complex. Cytokines may contribute to the induction of cortisol. Adrenal insufficiency also may be seen in patients with HIV/AIDS. Generally, this is in the setting of advanced disease complicated by multiple opportunistic infections. One mechanism for adrenal failure may be the infiltration and ablation of adrenal tissue by CMV or other pathogens.

The euthyroid sick state has been well described in many chronic illnesses. This condition is associated with an increase in reverse T3 and results in a reduction of energy consumption. Patients with AIDS were studied and found to have normal levels of reverse T3. It has been postulated that preservation of normal thyroid function in the setting of AIDS might lead to an inappropriately high basal metabolic rate and contribute to weight loss.⁵

Myopathy

Myopathy has been described as a complication of HIV infection, as well as of NRTIs. The pathogenesis of the myopathic changes has been attributed to mitochondrial toxicity. In its full expression, the myopathy may be severe with marked muscle atrophy and weakness predominantly involving the proximal muscle groups, myalgias, elevated serum creatine phosphokinase (CPK), abnormal electromyograms with irritative features, and abnormal muscle biopsies.

B. Management of Gradual HIV-Associated Weight Loss (see Figure 1)

1. Nutritional Supplementation

RECOMMENDATIONS:

Although nutritional supplementation is indicated for all patients with weight loss, the clinician should not supplement caloric intake without first addressing reversible causes of weight loss.

Clinicians should recommend the use of “once daily” multivitamin supplements containing selenium (20-40 mcg) for all HIV-infected patients experiencing weight loss.

Clinicians should not recommend high-dose vitamin therapy because this might exacerbate pre-existing gastrointestinal dysfunction and/or anorexia.

Clinicians should consider medical conditions, such as pancreatitis, diabetes mellitus, or renal insufficiency, in planning macronutrient balances.

In general, a good target for daily caloric intake should be 1.3 times the caloric demands needed to maintain a basal metabolic rate. A simple estimate of basal metabolic requirements is 25 to 30 Kcal/kg. Hence, for a healthy 70-kg patient, 1750 to 2100 Kcal are required to maintain the basal metabolic rate. For the same patient infected with HIV, 2730 to 3640 Kcal would be needed. To achieve anabolic effects, an additional 5 to 10 Kcal/kg is required.¹⁷ The proportion of macronutrients should approximate 50% to 55% carbohydrates, 15% to 20% protein, and 30% fat. However, medical conditions such as pancreatitis, diabetes mellitus, or renal insufficiency need to be considered in planning the macronutrient balances.

Consultation with a registered dietitian is a valuable resource for the patient and the clinician. The dietitian is often able to determine the causes of eating difficulties through use of food diaries, food models, or direct measurement of ingested food products.

Gastric hyperacidity, early satiety, irritable bowel, and lactose intolerance frequently confound the management of HIV-infected patients. Frequently spaced, small-volume meals may be better tolerated. Liquid nutritional supplements are useful for patients who have limited access to prepared meals or for those who require complex medication regimens requiring fasting at odd times throughout the day. A list of some of the available oral nutritional supplements can be found in Table 4. In general, patients who have severe wasting ($\geq 10\%$ of the UBW) should receive supplements with higher caloric content, such as EnsurePlus or Perative. The latter product is a semi-elemental formulation that is better tolerated when intestinal malabsorption is present. The higher osmolarity products, such as EnsurePlus, Criticare, and Peptomen, may be more likely to induce diarrhea and often require dilution. Juven is a nutritional mixture of β -hydroxy β -methylbutyrate, glutamine, and arginine. Studies of Juven have demonstrated enhancement of LBM in patients with AIDS.¹⁸ Prescribed micronutrients and vitamin supplementation are especially advisable for indigent patients or for those with possible malabsorption. A multivitamin with minerals is generally adequate. The use of high-dose vitamin “therapy” should be discouraged as this might exacerbate pre-existing gastrointestinal dysfunction and/or anorexia. Selenium supplementation in HIV/AIDS has been the subject of a number of studies.^{19,20} Serum selenium deficiency has been correlated with a higher risk of AIDS mortality, and *in vitro* studies suggest that selenium may suppress TNF α -induced HIV replication. The use of daily multivitamin supplements containing selenium (20-40 mcg) is advisable, especially in patients experiencing weight loss. In patients with evidence of severe, long-standing malnutrition, measurement of serum selenium levels may be indicated.

FIGURE 1
MANAGEMENT OF GRADUAL WEIGHT LOSS IN THE HIV-INFECTED PATIENT

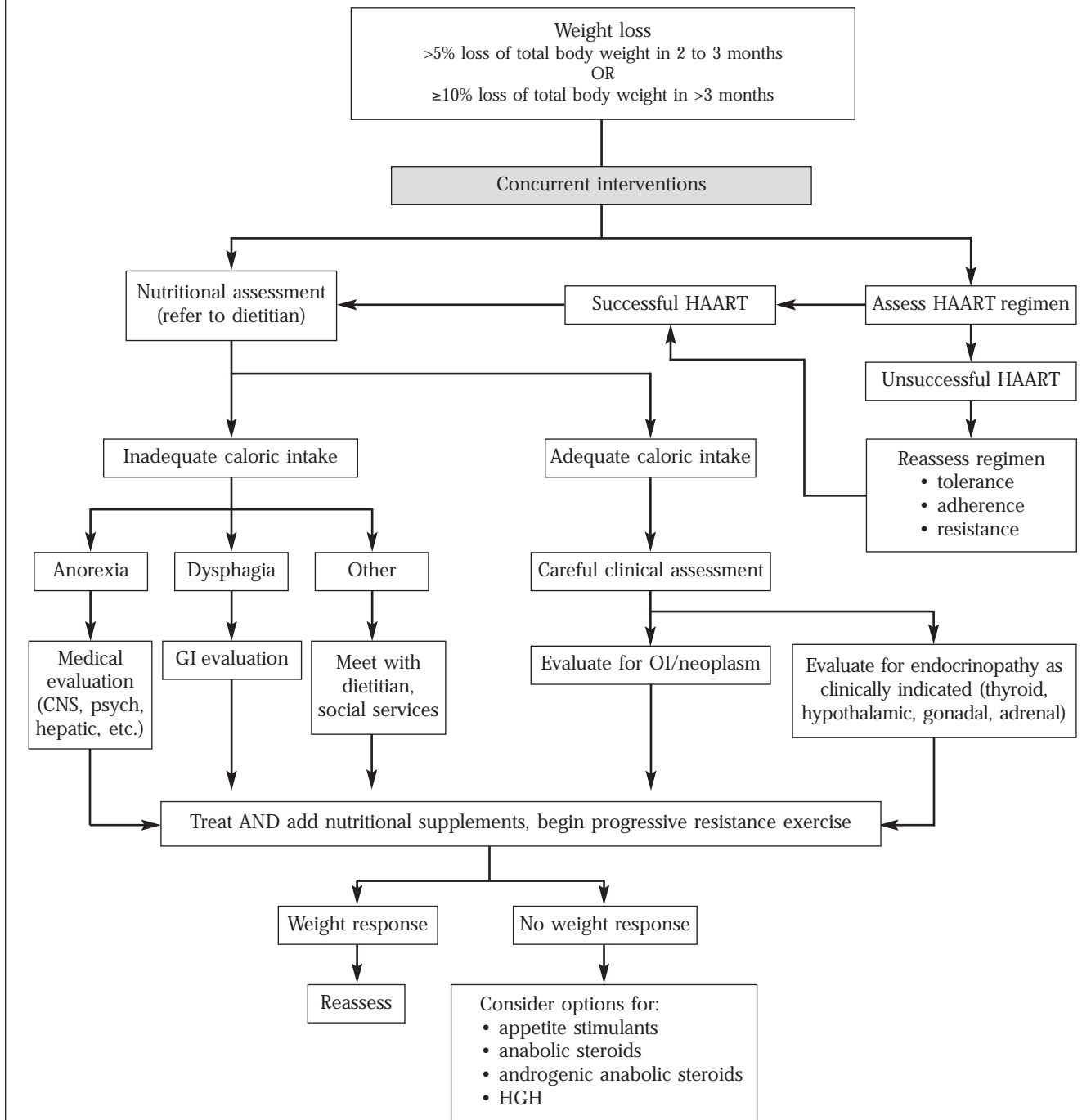


TABLE 4 SELECTED COMMERCIALY AVAILABLE LIQUID NUTRITIONAL SUPPLEMENTS*						
Products	Calories/cc	% Carbo	% Protein	% Fat	Osmols	Features
Osmolite	1.06	57%	14%	29%	300	Low residue, lactose and gluten free
Juven	90 cal/ packet	2-3 g/ packet depending on flavor	0, contains amino acids argi- nine and glutamine	0	450-470, depend- ing on flavor	Contains β -hydroxy, β -methylbutyrate, a metabolite of amino acid leucine to decrease muscle protein breakdown
Glucerna shake	0.93	47%	18%	35%	530	Designed for diabetics or those with impaired glucose tolerance
Nepro	2.0	43%	14%	43%	665	Designed for patients on dialysis
Jevity	1.06	54.3%	16.7%	29%	300	High fiber, lactose and gluten free
EnsurePlus	1.5	53.3%	16.7%	30%	650	Low residue, gluten and lactose free
Criticare	1.06	82%	14%	4%	650	Low residue, low-fat elemental
Peptamen 1.5	1.0	51%	16%	33%	450	Calorically dense peptide based elemental for malabsorption
Perative	1.3	54.5%	20.5%	25%	385	Peptides and free amino acids semi-elemental for malabsorption
Suplena	2.0	51%	6%	43%	600	Designed for patients with ESRD and liver failure. Low in protein, adjusted mineral content.

* The products listed above do not represent a complete listing of the commercially available supplements.

2. Treatment of Anorexia

RECOMMENDATION:

When patients present with anorexia, clinicians should perform a careful review of the medication list to determine whether the anorexia is medication-induced.

Anorexia is an obstacle to adequate nutrition and needs to be addressed when present. Careful and frequent review of medications should be undertaken to determine whether any of them are implicated. Neuropsychiatric testing is often helpful in the evaluation of anorexia when the cause cannot be determined by clinical evaluation.⁸ Appetite stimulants should be considered when the cause of anorexia cannot be determined or reversed (see Appendix A). Periactin may be an effective appetite stimulant for some patients. Megestrol acetate and dronabinol result in modest increases in appetite. Many patients do not tolerate the CNS effects of dronabinol, even at low doses. Dronabinol, despite improving appetite, has not been convincingly shown to increase TBW. Megestrol does result in slow and modest increases in TBW, but this is usually associated with increases in fat and little change in the BCM. Megestrol can lower the serum testosterone levels. This raises the possibility that a eugonadal male patient receiving megestrol may become

hypogonadal. In addition, there is a potential for adrenal insufficiency when long-term use of megestrol is discontinued.⁷ Clinicians should screen for hypogonadism and adrenal insufficiency in patients receiving megestrol for prolonged periods.

3. Treatment of Non-Infectious Diarrhea

RECOMMENDATION:

When recalcitrant diarrhea occurs as a complication of HAART, clinicians should consider a change in therapy if suitable alternatives with a high likelihood of successful viral suppression are available (based on HIV resistance testing).

HIV-infected patients experience diarrhea for a variety of reasons. Several reports have underscored the usefulness of calcium supplements for patients experiencing nelfinavir-induced diarrhea. Other modalities, such as pancreatic enzymes and psyllium fiber supplements have been useful for PI-induced diarrhea. Many patients note an increase in symptoms following meals and will voluntarily avoid adequate alimentation to reduce bowel frequency. When pancreatic insufficiency is present, supplemental pancreatic enzymes may be helpful in reducing diarrhea and post-prandial bloating. As previously noted, avoidance of lactose-containing foods and the use of lactase supplements may be useful. Cautious use of antimotility agents such as loperamide or diphenoxylate hydrochloride is sometimes helpful. For severe cases, octreotide and tincture of opium have also been used.

4. The Role of Exercise

RECOMMENDATION:

Clinicians should advise patients to participate in a fitness program that uses progressive resistance exercise.

The benefits of an adequate fitness program cannot be overemphasized. Progressive resistance exercise (PRE) increases LBM in conjunction with adequate caloric intake.²¹ The effects of resistance exercise are potentiated by anabolic steroids and are diminished in the hypogonadal male (see Section 5: *Anabolic Steroids*).

Aerobic exercise results in little or no increase in BCM as compared to PRE. Aerobic exercise may increase CD4 counts, but such exercise has no definite effect on T-cell function. In addition, aerobic activity without sufficient energy substrate may induce further weight loss. Reported effects of aerobic exercise on CD4 cell function have been variable.²² Aerobic fitness programs do, however, improve performance status and quality-of-life measures.

5. Anabolic Steroids

RECOMMENDATIONS:

Clinicians should exclude specific endocrine abnormalities, such as hypothalamic hypogonadism and hyperthyroidism, before prescribing oxandrolone.

Clinicians should monitor for hypogonadism in eugonadal men who are receiving long-term nandrolone or oxandrolone.

Anabolic steroids are the most effective long-term means of restoring BCM (see Appendix A). Nandrolone has a high anabolic/low androgenic profile. It must be administered parenterally. Oxandrolone is probably the most effective oral agent for restoring BCM. It is moderately expensive, although it is now being reimbursed by most third-party payers. It is likely that nandrolone and oxandrolone are safe for use in women. There is a potential for these agents to “turn off” endogenous testosterone production in eugonadal men; therefore, long-term use requires monitoring for hypogonadism.²³ Both oxandrolone and nandrolone have a relatively low potential to cause hepatic toxicity

when compared with oral androgenic anabolic steroids.²³ These agents are non-narcotic Schedule III drugs under the Anabolic Steroids Control Act of 1990. Although the use of oxandrolone is indicated by the FDA to promote weight gain following surgery or trauma, it is not specifically approved for HIV-associated weight loss. Polycythemia, injection site infection, or local nerve trauma are unusual complications of nandrolone use.

6. Androgenic Anabolic Steroids

RECOMMENDATIONS:

Clinicians should consider short-term (several months) testosterone therapy with supraphysiologic doses, in conjunction with PRE, to achieve BCM increase in selected male patients demonstrating a rapid rate of muscle loss.

Because androgenic anabolic steroids cause virilization, a general recommendation for their use in women cannot be made until further studies have been completed.

Because androgen enhances libido, clinicians should strongly reinforce safer sexual practices for patients receiving androgenic anabolic steroids.

The androgenic anabolic steroids include testosterone. As noted previously, hypogonadism can be associated with HIV infection in men. The attendant decrease in libido, depression, and loss of muscle mass may be reversed to some degree by replacement therapy. Although not FDA-approved, supraphysiologic doses of testosterone in conjunction with PRE result in significant increase in the BCM.²⁴ Unwanted side effects include acne, accelerated hair loss, and behavioral changes. Virilization makes use of such available agents unsuitable for use in women; however, new studies of experimental low-dose testosterone patches in women are underway.

There is a strong association between Kaposi's sarcoma (KS) and the human herpes virus type 8. However, the male preponderance in cases of KS has led to studies linking serum testosterone levels and KS occurrence. There is epidemiologic evidence implicating androgenic steroids as a promoter of KS in the setting of AIDS.²⁵ Although there is no firm evidence that androgenic steroids promote KS, many HIV Specialists suggest caution in prescribing androgenic steroids for patients with pre-existing KS.

Testosterone can also cause prostate cancer and hepatic toxicity, including cholestasis, peliosis hepatitis, and primary hepatic carcinoma. A natural consequence of exogenous testosterone replacement is testicular atrophy, if not already present. Increases in libido mandate the reinforcement of safer sexual practices for all patients receiving this form of therapy. The transdermal testosterone preparations seem to have the safest therapeutic profiles. Local irritation of the adhesive/accelerant is common, and patients complain about the cosmetic and emotional impact of wearing a transdermal patch throughout the day. Androgel, a transdermal testosterone gel preparation, has been approved by the FDA for the treatment of hypogonadism. This topical preparation is applied directly onto the skin without a patch; transfer of drug from patient to others by direct contact with the skin application site is a potential problem. A newer form of testosterone replacement with buccal absorption (applied under the upper lip) has also become available. All of the androgenic anabolic agents are non-narcotic Schedule III drugs under the Anabolic Steroids Control Act of 1990. They are approved for the treatment of male hypogonadism. With the improvement of immune function and overall well-being, hypogonadism may improve, and exogenous testosterone can be discontinued with careful monitoring of testosterone levels. Clinicians should be aware of the potential for steroid abuse.

7. Recombinant Human Growth Hormone

RECOMMENDATIONS:

Clinicians should consider prescribing a 12-week course of recombinant human growth hormone (rhGH) after hypogonadism and active opportunistic diseases have been excluded.

Clinicians should discontinue rhGH treatment if no weight gain is observed after the initial 3 to 4 weeks of therapy.

If weight loss continues despite several weeks of rhGH therapy, the clinician should re-evaluate for co-existent opportunistic infections.

rhGH (Serostim) is the only drug that is FDA-approved for treatment of HIV/AIDS-associated weight loss and seems to be a highly effective agent for improving both TBW and BCM (see Appendix A).²⁶ It should be considered only when hypogonadism has been excluded and after treatment of conditions leading to malabsorption or anorexia are addressed. A wide array of side effects is associated with its use. These include muscle and joint pain, carpal tunnel syndrome, peripheral neuropathy, peripheral edema, hyperglycemia, and pancreatitis. Some of these symptoms and signs may improve with dose reduction. Reduced doses of 3 to 4 mg/day have been better tolerated by some, without necessarily compromising efficacy. rhGH is expensive, thus many third-party payers will not cover its cost. The duration of therapy is unclear, but a number of studies have shown prolonged maintenance of BCM after a 12-week course.²⁷ The patient's response should be monitored closely. If weight loss continues despite several weeks of rhGH therapy, an investigation for co-existent opportunistic infection is warranted.

Growth hormone has also been studied in syndromes of fat accumulation. In one study, there was a significant reduction in visceral adipose tissue (VAT) among 30 patients after 6 months of treatment with recombinant human growth hormone, but VAT re-accumulated 12 weeks after discontinuation.²⁸ A large clinical trial showed a significant decrease in visceral fat content when 4 mg/day rhGH was injected subcutaneously and a trend toward significance when 4 mg every other day was used.²⁹ rhGH is not FDA-approved for the treatment of lipodystrophy.

8. Experimental Cytokine Mediators

Interest in using agents that modify circulating levels of cytokines, especially TNF, was reflected by a number of uncontrolled clinical studies in the early 1990s.³⁰ The use of cytokine modifiers as a treatment for HIV/AIDS-associated wasting is of unproven efficacy. As discussed in Section V-A: *Weight Loss: Pathophysiology*, although TNF levels may be elevated in some patients with wasting, this observation is not uniform, and elevated levels are unlikely to be the primary cause of weight loss in most patients. Furthermore, technical difficulties in performing assays for TNF make it impossible to compare studies using different methodology. The effectiveness of agents such as pentoxifylline and thalidomide are modest at best. Thalidomide has shown some promise in Africa in promoting weight gain in persons with AIDS and mycobacterial disease. In this country, increases in LBM have been demonstrated with thalidomide.³¹ Thalidomide is available on a restricted basis for the treatment of HIV-associated aphthous stomatitis or wasting syndrome. Registration with the manufacturer Celgene (phone: 888-423-5436) is required.

VI. THE WASTING SYNDROME

RECOMMENDATION:

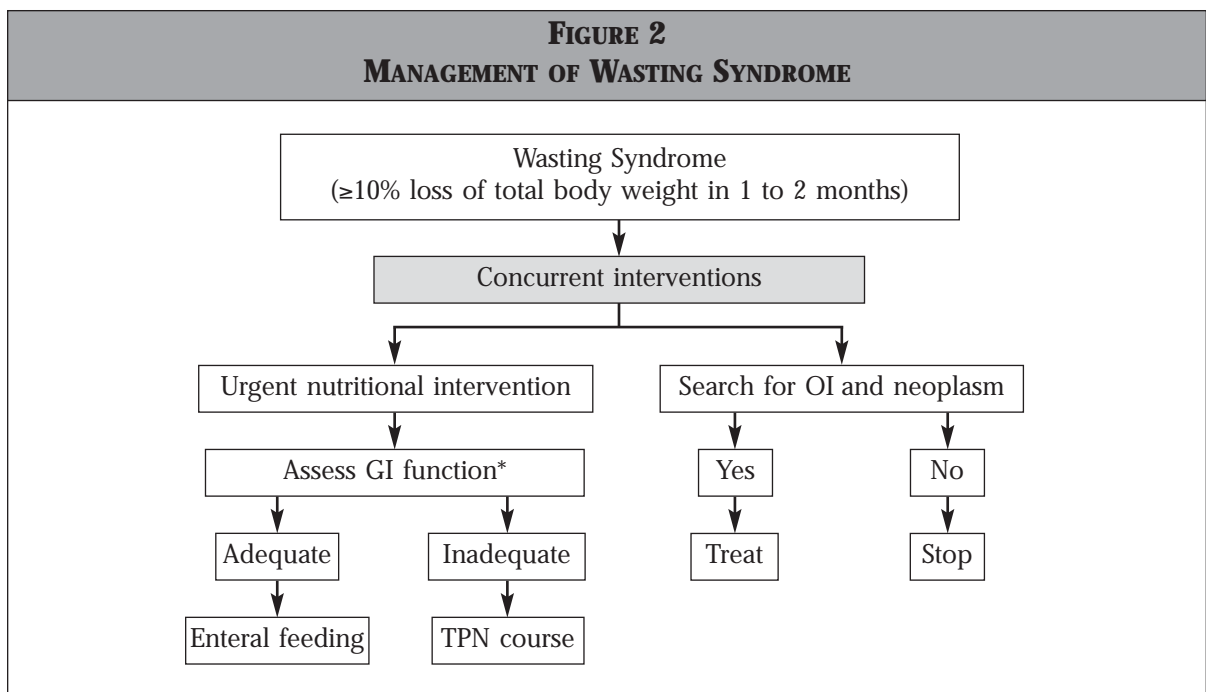
Clinicians should perform a detailed evaluation for opportunistic infections or malignancies in all patients with wasting syndrome.

Wasting syndrome was added to the AIDS surveillance case definition in 1987. Not surprisingly, because of the non-specific nature of wasting syndrome, there was a high concordance with other opportunistic conditions, including cryptosporidiosis, *M. avium* complex, and CMV infection. In the era of HAART, the incidence of reported cases of wasting syndrome has decreased dramatically, nearly paralleling the decreases in incidence of AIDS and AIDS-associated mortality.

A. Diagnosis

Wasting syndrome, as defined by the Centers for Disease Control and Prevention (CDC), is an involuntary loss of $\geq 10\%$ of the baseline (usual) body weight plus either chronic diarrhea, weakness, or documented fever, in the absence of a concurrent illness or condition.^{6,32}

Wasting syndrome is predictive of the onset of opportunistic infections and neoplasms. An aggressive diagnostic program is indicated with the appearance of the wasting syndrome (see Figure 2).



* See Section V: *Weight Loss*

B. Nutritional Intervention in the Wasting Syndrome

RECOMMENDATIONS:

The clinician should perform an immediate evaluation to determine the cause of the wasting syndrome.

For patients with conditions that prevent enteral feeding, total parenteral nutrition (TPN) may be indicated for short-term management.

The clinician should monitor supplementation with micronutrients by frequently assessing serum electrolytes and blood glucose in the first several weeks of re-feeding.

The goals of therapy are three-fold:

- 1) To undertake nutritional triage and to supplement nutrition in patients for whom urgent nutritional support might be life-saving.
- 2) To treat and control all complicating conditions that are contributory to malnutrition.
- 3) To attempt to intervene with therapies matched to the metabolic derangement(s) most likely to be operative.

Emergency treatment of patients who have lost excessive body weight ($\geq 10\%$), especially over a brief period of time, can prove to be life-saving (see Figure 2). Such persons usually have a poor performance status with Karnofsky scores of ≤ 60 , suffer inanition, and may require acute hospitalization.⁷ An immediate evaluation needs to be performed to determine the cause of the wasting syndrome. Enteral alimentation should be considered when gastrointestinal function is adequate. In some patients with partial malabsorption, an elemental or semi-elemental caloric supplement is well tolerated. However, for patients with conditions that prevent enteral feeding, TPN is indicated for short-term management. Close attention should be given to supplementation with micronutrients, and frequent assessments of the electrolytes and blood glucose are necessary in the first several weeks of re-feeding. As discussed earlier, the long-term prognosis of AIDS is not affected by hyperalimentation. The goals should be to acutely stop the catabolic reduction of BCM while secondary opportunistic conditions are identified and treated. Except in rare instances of intractable and massive diarrhea with malabsorption, TPN nutrition is generally not needed for more than 1 or 2 months.

VII. FAT REDISTRIBUTION (LIPODYSTROPHY) SYNDROMES

Although HAART has resulted in a dramatic decrease in AIDS-associated morbidity, it is estimated that as many as 60% to 80% of patients receiving HAART for more than 1 year will demonstrate changes in body composition and/or blood lipids.³³ Two new syndromes of abnormal body morphology or lipodystrophy have been described that seem to be associated with the newer treatment modalities³⁴: 1) fat accumulation/redistribution syndrome, and 2) lipoatrophy syndrome. A more thorough discussion of these syndromes is covered in Chapter 4B: *Long-Term Complications of Antiretroviral Therapy*.

PIs were the first to be implicated in the fat redistribution syndrome, and the NRTIs have been proposed as triggers for the lipoatrophy syndrome. Of note, patients may also present with a mixed picture of morphological changes. Definitive etiologies of these abnormal body morphology syndromes remain unknown.

The fat redistribution syndrome is important in the discussion of body composition and weight loss. The total body weight of patients exhibiting the fat redistribution syndrome usually varies little from their usual body weight. In addition to the somatic changes, a number of metabolic disturbances have been described. Insulin resistance with hyperglycemia, hyperlipidemia (with elevated triglycerides, elevated LDL cholesterol, and decreased HDL cholesterol), and decreased hemostasis in patients with hemophilia have been reported.²⁶ These metabolic abnormalities may also occur independently of the fat redistribution syndromes. Initially termed lipodystrophy, this syndrome is best described as fat accumulation or redistribution syndrome. The most prominent signs are somatic and dysmorphic changes, including facial and limb fat wasting, central and/or localized adiposity, and visceral fat accumulation. Localized fat accumulation may take the form of an enlarged dorsocervical fat pad, multiple lipomata, or breast enlargement in both women and men. The proportionate involvement of the involved sites varies dramatically among patients. The mechanism of these abnormalities remains unclear. Although these complications have historically been attributed to PIs, they can also be seen in patients receiving non-PI-based HAART.

There is concern for increased cardiovascular risk among patients with these dyslipidemias, with some studies suggesting increased risk, and others finding no increased risk.³⁵ Regardless, it is important to address any lipid abnormalities found, based on the current National

Cholesterol Education Program (NCEP) guidelines and the Adult AIDS Clinical Trials Group (AACTG) Cardiovascular Focus Group recommendations.

The lipoatrophy syndrome, the other pattern of abnormal body morphology, is marked by predominant loss of subcutaneous fat resulting in severe peripheral fat wasting without localized fat accumulation. HAART is expected to generally improve overall nutritional status with increases in total body weight and intracellular (relative to extracellular) water.⁴ Thus, loss of body weight should not be interpreted as an acceptable side effect of HAART. The major aberrations in body composition changes are in the fat compartment with significant decrease in fat content. Severe instances of lipoatrophy can result in a 5- to 10-kg decrease in body weight.

Key Point:

Clinicians should consider the possibility of concurrent lactic acidosis and/or hepatic dysfunction in patients with lipoatrophy.

These morphologic changes are sometimes associated with lactic acidosis, abnormal liver chemistries, fatigue, hypoalbuminemia, and elevated triglycerides and total cholesterol. The current theory regarding lactic acidosis is that it may be caused by nucleoside analogue-associated mitochondrial toxicity. Although rare, lactic acidosis may be intractable and fatal; pregnant women are particularly vulnerable. When lactic acidosis syndrome occurs, it is usually in association with constitutional symptoms of fatigue, abdominal pain, anorexia, nausea and vomiting, myalgias, shortness of breath with tachypnea, and abnormal liver chemistries.³⁴ In this setting, it is important to measure serum CO₂ and lactic acid levels. ARV therapy should be interrupted for symptomatic lactic acidosis. Routine monitoring of lactic acid is not recommended. However, in patients with prior lactic acidosis in whom nucleoside analogue therapy is being resumed, monitoring lactic acid levels for the first 3 to 6 months after reinstatement should be considered.

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APPENDIX A

THERAPY FOR GRADUAL HIV-ASSOCIATED WEIGHT LOSS

TABLE A-1 THERAPY FOR GRADUAL HIV-ASSOCIATED WEIGHT LOSS			
	Anticipated Effects	Daily Dose Range	Comments
Appetite Stimulants			
Megestrol Acetate (Megace)	↑ appetite, ↑ BM, ↔ BCM, ↑ Fat	400-800 mg/day with meals	May ↓ testosterone levels; may cause impotence; risk of thromboembolism, adrenal insufficiency
Dronabinol (Marinol)	↑ appetite, ↑ BM, ↔ BCM, ↑ Fat	2.5-10 mg bid with meals	Patients may not tolerate CNS effects
Cyproheptadine (Periactin)	↑ appetite, ↑ BM, ↔ BCM	4-8 mg bid with meals	Can cause drowsiness, dry mouth
Anabolic Steroids			
Testosterone (Gel form, topical patch, buccal mucoadhesive, IM injection)	↑ performance status, ↑ appetite, ↑ BCM, ↑ BM, ↑ mood/libido	1 gel-pak daily, or 1 patch/24 hr, or 1 buccal application q 12 hr, or 200-400 mg IM q 2-4 wk	Preferred when serum free testosterone levels are ↓; testicular atrophy; PSA should be followed Androgenic >> Anabolic
Oxandrolone (Oxandrin)	↑ BM, ↑ BCM, ↑ appetite	5-20 mg/day	Best with resistance exercise; be vigilant for peliosis hepatitis Androgenic << Anabolic
Oxymetholone (Anadrol-50)	↑ BM, ↑ BCM	1-2 mg/kg/day	Best with resistance exercise; be vigilant for peliosis hepatitis Androgenic << Anabolic
Nandrolone (Deca-durabolin)	↑ BM, ↑ BCM	100-200 mg q2 weeks	Best with resistance exercise; be vigilant for peliosis hepatitis Androgenic << Anabolic
Growth Hormone			
Recombinant Somato-Tropin (Serostim)	↑ appetite, ↑ BM, ↑ BCM	3-6 mg sq qHS	Expensive Usual 12-week course; can be repeated.
Cytokine Inhibitors*			
Thalidomide	↔ appetite, ↑ BM	100-300 mg/d	Available to registered prescribers for oral aphthae and wasting. Lowers serum TNF. Efficacy for wasting not established.
Pentoxifylline (Trental)	↔ appetite, ↔ BCM	400 mg tid	Lowered serum TNF in several studies. No clinical benefit.

* Because a central role of TNF in wasting has not been established, this treatment approach should be considered speculative and of unproven effectiveness.