

Acquired Immunodeficiency Syndrome Wasting, Functional Performance, and Quality of Life

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Abstract

Unintentional loss of weight and lean body mass (wasting) is a major cause of morbidity and mortality in patients with acquired immunodeficiency syndrome (AIDS). Patients with AIDS wasting (AW) often experience reductions in lean body mass, muscle strength, and the ability to perform functions of daily living. Dependence on assistance with activities of daily living may be associated with a lower quality of life (QOL) and higher risk of mortality. These factors suggest that slowing or reversing the loss of lean body mass in AW can improve well-being.

Nutritional support or appetite stimulants in the absence of exercise therapy or growth hormone supplementation can increase fat without improving body composition, whereas appropriate exercise programs, androgen therapy, and recombinant human growth hormone (rhGH) therapy may increase lean body mass in patients with AW. Resistance exercise programs can increase muscle strength and lean body mass. In addition, both resistance and endurance (aerobic) exercise augment endogenous growth hormone levels, decrease depression, enhance self-esteem, and may improve immune response. Randomized, double-blind trials

have shown that rhGH therapy increases total body weight, lean body mass, exercise capacity, and QOL. In summary, interventions that improve exercise capacity and functional performance may enhance QOL in patients with AW and may reduce mortality in this group.

(*Am J Manag Care* 2000;6:1003-1016)

During the early 1980s, suspicion that a patient may have acquired immunodeficiency syndrome (AIDS) usually was triggered by a diagnosis of Kaposi's sarcoma or *Pneumocystis carinii* pneumonia.¹ As experience with AIDS grew, clinicians began to recognize the profound and distinctive effect of this disease on the nutritional status of those who suffered from it. In 1987, the Centers for Disease Control and Prevention revised its definition of AIDS to include AIDS wasting (AW). Today, wasting (involuntary weight loss and/or lean tissue depletion) is considered one of the hallmarks of AIDS.²

Wasting in patients with AIDS is a condition with its own medical and social sequelae. This article considers the impact of AW on the quality of life (QOL) and prognosis of patients with AIDS and discusses the effectiveness of certain therapeutic interventions (ie, nutritional evaluation and counseling, exercise therapy, and growth hormone or anabolic steroid therapy) in slowing or reversing AW. It also explores the potential benefits of these therapies for improving lean body mass, exercise capacity, and functional performance in patients with AW.

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... FACTORS INVOLVED IN AIDS WASTING ...

AIDS wasting is characterized by reduced muscle mass, which conventionally is measured as either reduced body cell mass³ or reduced lean body mass (ie, body cell mass plus extracellular fluids and solids other than fat).⁴ Death in AIDS patients correlates more closely with loss of body cell mass than with loss of total body weight.⁵

Metabolic Alterations

During starvation, fat tissue is depleted and muscle protein is spared. In AW, however, the converse appears to be true, with muscle protein lost preferentially. Protein synthesis is reduced in human immunodeficiency virus (HIV)-infected patients compared with healthy subjects, even in the absence of wasting.⁶ In HIV infection, protein synthesis may fail to keep up with breakdown, leading to negative protein balance in muscle and AW.

Some researchers have found that resting energy expenditure is elevated in patients with AIDS,^{7,8} and it may increase as the disease progresses. Accelerated protein breakdown leading to protein-energy malnutrition has been observed in AIDS patients with opportunistic infections.⁹ This increased rate of protein turnover occurs independently of caloric intake, perhaps partly as a result of an increase in the level of tumor necrosis factor (TNF); in conjunction with interleukin 1 (IL-1), TNF induces muscle catabolism and negative nitrogen balance.⁹

Dietary Issues

Anorexia is a frequent cause of insufficient caloric intake in patients with AIDS.¹⁰ Anorexia in AIDS patients can occur as a result of local pathology in the oral cavity or esophagus, dysfunction of the central nervous system (affecting hunger or eating mechanics), or secondary manifestations due to systemic infections, malabsorption, or medications.¹¹ Dementia from HIV encephalopathy or central nervous system effects, weakness, and depression may decrease oral intake and impair a patient's ability or desire to prepare meals.^{12,13} AIDS patients may also have deficiencies of specific nutrients. For example, Baum et al¹⁴ found that HIV-infected men required multiples of recommended daily allowances (RDAs) to achieve normal plasma values for zinc and vitamins A, B₆, B₁₂, and E.

Patients with AIDS who became infected through use of injection drugs have been shown to be at increased risk for AW.^{3,15} Among people with AIDS

in the United States, an estimated 22% of men and 42% of women were initially exposed through injection drug use, while sexual contact has been estimated to be the primary means of exposure in 61% and 40% of men and women, respectively.¹⁶ Use of other drugs, such as cocaine or amphetamines, may further decrease appetite in patients with AIDS.

Gastrointestinal Malfunction

In a recent study,¹⁷ the incidence of diarrhea in HIV-infected patients was found to be 14.2 per 100 person-years. To compare, the prevalence rate per 100 for chronic diarrhea in the general population has been reported to be 7.3.¹⁸ Diarrhea can worsen QOL directly, as well as indirectly as a result of weight loss resulting from malabsorption.¹⁰ Nutrients often are poorly absorbed in patients with AIDS, regardless of the presence of diarrhea, perhaps because of enteropathy induced by HIV infection of the CD4 T-lymphocytes in the intestines. The destruction of intestinal mucosal cells by HIV infection may partly explain this enteropathy.¹⁹⁻²¹ Poor dietary intake may then exacerbate the nutritional deficits caused by these pathologic changes. Furthermore, altered lymphocyte populations in the gastrointestinal mucosa may increase a patient's susceptibility to gastrointestinal infections.^{20,21}

... ASSESSING THE EFFECT OF AIDS WASTING
ON PATIENT STATUS ...

The progression of HIV disease affects many aspects of a patient's life, including physical functioning, psychological well-being, diet, exercise, career, and social life, as well as overall health status. Several tests are available to measure functioning and QOL. These tests are described in this section; they span a range from highly objective but potentially less relevant measures to more relevant but also more subjective.

Exercise Capacity

Exercise capacity is a laboratory-based measure of physical capability that assesses aerobic capacity (eg, maximum oxygen consumption [Vo_{2max}], submaximal tests, or 6-minute walk tests), strength (eg, maximal lifting capacity or isokinetic dynamometry), power, or endurance. A variety of objective physical-function measures may be applicable to clinical assessment of exercise capacity (Table 1), although their true relevance to the health status of patients with AW may not be certain because of individual patient differ-

ences in approaches and attitudes to exercise and varying disease states. Depending on the measure, the score may reflect a patient's ability to perform high-intensity, short-duration exercise, which relies heavily on anaerobic pathways, or prolonged physical activity, which requires energy from aerobic metabolism and can therefore be measured as Vo_{2max} at a plateau level of exertion.²²

Functional Performance Tests

Functional performance tests are laboratory- or field-based observations of functional capacity on a standardized series of tests. Examples include the ability to rise from a chair without using one's arms; timed rising from a chair 5 or 10 times; and 2-, 6-, and 12-minute walk tests. Because the tests are standardized, measurement results are highly objective, and patients can therefore be compared directly with one another or with population norms. The clinical relevance of such measurements may be lessened, however, by the fact that these numbers describing physical functioning may not necessarily translate into a complete picture of patient health. Also, exercise capacity strongly influences functional performance, which can be limited by disease-related factors.

Functional performance scores may be based on assessment of activities of daily living (ADLs) and independent ADLs (IADLs), as well as the aforementioned standardized physical tests. ADLs include basic self-care activities such as dressing, bathing, using the toilet, eating, and communicating with others. IADLs are considered more complex tasks than ADLs and include doing housework, preparing meals, taking medications, shopping, using the telephone, managing money, and traveling.^{23,24} Assessment tools such as computer-assisted programs and rating scales can be employed to produce functional performance scores based on evaluations of ADLs and IADLs. A self-report profile submitted by the patient is an assessment method distinct from functional performance tests. Such self-reports, alone or in combination with physical performance tests, can be administered to assess ADLs in a patient.²⁵ Standardized tests of coordination, such as dexterity tests, also have been used to judge functional performance.²⁶ Scores from these tests can help to predict whether a patient will require institutionalization or will be able to live independently.²⁴

Quality-of-Life Measures

QOL outcomes measure patients' satisfaction with their lives. Because these outcomes are by def-

inition subjective, they are influenced by many factors. Measures of QOL may be highly relevant to assessing the health status of the patient with AW because they reveal how patients perceive their own disease states. A patient's level of physical functioning is an important determinant of QOL, as are psychological and emotional factors, such as self-image, self-esteem, isolation, embarrassment, and fear. According to Chesney and Folkman,²⁷ QOL has 6 measurable dimensions: (1) role functioning (eg, work), (2) social functioning, (3) physical functioning, (4) mental health, (5) general health perceptions, and (6) pain.

A variety of general instruments can be administered to measure functional status and QOL, such as the Health Assessment Questionnaire

Table 1. Measurable Correlates of Physical Function

Measurable Parameter	Definition/Explanation
Maximal aerobic capacity (Vo_{2max})	Maximum oxygen consumption at a plateau level during sustained exercise; measured by maximal treadmill or cycle ergometer exercise test
Muscle strength	Maximum resistance that can be overcome in a single trial by muscle contractile force; correlates with muscle size
Muscle power	The speed at which a muscle can lift a given weight over a given distance
Endurance	The length of time a physical activity can be sustained; depends on amount of glycogen stored in muscle
Exercise capacity	Maximum capability to perform a variety of laboratory-defined exercises
Functional performance	Standardized measure of ability to perform a series of basic, everyday tasks
Exercise tolerance	Maximum time that a given exercise can be continued
Functional status	Self-reported assessment of ability to perform activities of daily living

(HAQ), Medical Outcomes Study Short Form 36 (SF-36), Arthritis Impact Measurement Scales,^{28,29} and HIV-specific instruments, such as the AIDS-HAQ, HIV adaptation of the Medical Outcomes Study questionnaire (MOS-HIV), Functional Assessment of HIV Infection QOL instrument, and HIV Overview of Problems Evaluation System.³⁰⁻³³ The HAQ is the most widely used assessment tool, addressing ADLs and IADLs of 8 domains (dressing, arising, eating, walking, hygiene, reach, grip, and activities) in 24 questions and yielding scores between 0 (complete ability) and 3 (complete inability).²⁸ The SF-36 also covers 8 domains, measuring physical, emotional, and social limitations due to disease,²⁸ with higher scores indicative of better QOL. Specific for HIV-infected patients, the AIDS-HAQ encompasses disability, pain, energy, general health perception, cognitive functioning, social functioning, mental health, and health distress.³⁰ Perhaps the most widely used HIV-specific QOL instrument is the MOS-HIV, which consists of 30 items with 11 subscales surveying physical, role, and social functioning; overall health; pain; energy and fatigue; mental health; health distress; cognitive functioning; health transition; and overall QOL. Each subscale is scored in the range of 0 to 100, where 100 represents the highest possible QOL score.³¹

Impact of AIDS Wasting

In HIV-infected individuals, physical fitness measures may begin to decrease *before* physical examination reveals obvious AW.³⁴ Both peak workload and VO_{2max} continue to decrease as HIV infection progresses.³⁵

Other factors can also reduce exercise capacity in patients with HIV infection. In a study³⁴ of asymptomatic HIV-infected patients, the heart rate-to-oxygen consumption curve was reported to have an abnormally high slope, suggesting that a low rate of oxygen delivery to exercising muscles may limit exercise capacity. On the basis of an analysis of gas exchange patterns during exercise, Pothoff and colleagues³⁵ suggested that exercise limitations in patients with HIV infection may be attributable to anemia and neuromuscular disorders in some patients and to pulmonary limitations in others. In addition, central nervous system damage resulting from HIV invasion of nervous tissue can lead to other debilitating conditions, such as dementia, spinal cord dysfunction, and stroke. The combination of wasting and central nervous system damage can decrease muscle tone, strength, balance, and coordination. Furthermore, HIV infection may lead to damage of the peripheral nervous system, causing additional complications, such as gastric disturbances and disorders of the lower extremities.^{36,37}

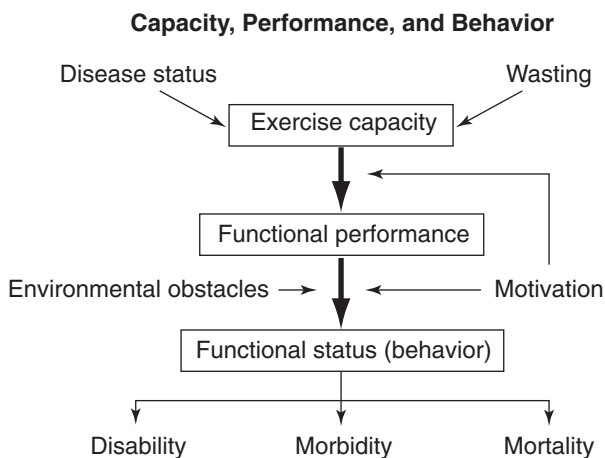
Activities of Daily Living

Psychosocial and cognitive difficulties due to disease, coupled with muscle weakness, may render patients with AIDS both mentally and physically unable to perform basic ADLs, such as bathing, grooming, dressing, eating, communicating, and preserving continence. As the disease progresses, such factors as fatigue, shortness of breath, visual impairments, cancers, opportunistic infections, and cardiovascular problems increasingly limit the ability of patients to perform these activities.³⁸ As patients become less physically fit and ambulatory, opportunities for social interaction and independent living continue to decrease. Consequences can include isolation, depression, loss of professional and social life, and other lifestyle changes that may contribute to disease progression (Figure 1).²⁷

Quality of Life

Patients with HIV infection tend to have significantly lower QOL scores than do patients with other chronic medical conditions, such as diabetes, heart failure, or emphysema ($P < .001$).³⁹ In addition, patients with more advanced HIV disease (defined

Figure 1. The Course of AIDS Wasting Is Affected by Exercise Capacity, Functional Performance, and Behavior



as 4 or more symptoms) have significantly lower overall QOL scores than do patients with fewer symptoms ($P < .05$).^{27,39} Furthermore, relative to their counterparts, significantly lower QOL has been observed in HIV-infected patients with self-perceived reduced access to care ($P < .05$),⁴⁰ more days of hospitalization ($P < .01$),⁴¹ and older age ($P = .01$).^{29,42} In contrast, employment ($P < .001$), higher income ($P = .03$), satisfaction with social support ($P = .05$), and adherence to antiretroviral therapeutic regimens ($P = .006$) are predictors of higher QOL in patients with HIV.²⁹ Such factors affecting QOL in HIV-infected patients can also relate to QOL in patients with AW because of the chronic and progressive nature of symptomatic HIV disease leading to wasting.

In terms of significant psychological factors, emotion-focused coping ($P = .04$), avoidance coping ($P < .001$), and the feeling of hopelessness ($P < .001$) each is associated with poorer QOL, whereas problem-focused coping ($P = .03$) is related to improved QOL.²⁹ Emotion-focused coping is defined as cognitive responses intended to manage the emotional consequences of stressors to maintain emotional equilibrium; avoidance coping is defined as actions evading the confrontation of a problem, denying that the problem exists, or indirectly reducing emotional tension through behaviors such as eating or smoking.²⁹ Psychological factors such as these can exert an impact on the health status of the patient with AW. A recent focus group identified negative feelings about physical appearance, loss of appetite, embarrassment, and social isolation as some QOL issues specifically related to AW.⁴³

QOL and Prognosis

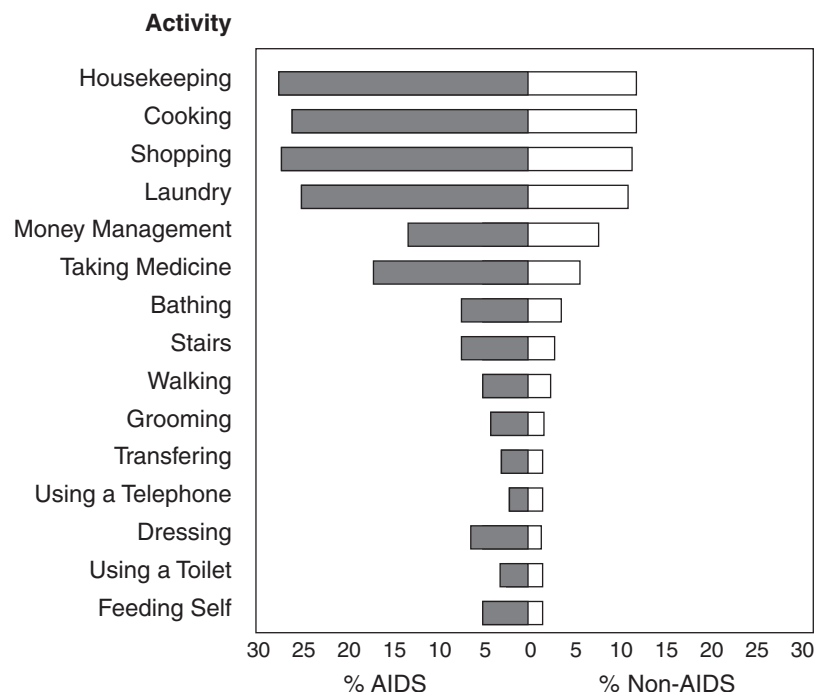
Patients with AIDS who require assistance in performing ADLs have a lower QOL and a higher risk of death than do those who do not require such assistance, and patients who reported an inability to perform 1 or more ADL tended to have a

greater need for assistance with activities necessary for independent living, such as shopping and cooking, than for assistance with personal care functions (Figure 2).⁴⁴ This study also found a higher risk of mortality in patients with advanced HIV disease who had dependencies compared with those without dependencies. In another study,⁴⁵ functional performance based on ADL assessment effectively predicted mortality. The authors reported a clinically significant increase in mortality risk with each increase in prognostic staging based on ADL ($P < .01$); the power of ADL scores to predict mortality was better than that of CD4-cell counts.⁴⁵

... INTERVENTIONS TO IMPROVE EXERCISE CAPACITY AND FUNCTIONAL PERFORMANCE ...

Intervening to increase lean body mass may improve QOL of patients with AW,^{43,44} the assump-

Figure 2. Dependencies, by Activity, for 728 AIDS-Diagnosed Patients (Black Bars) and HIV-Positive (White Bars) Patients



From reference 44 (Stanton DL, Wu AW, Moore RD, et al. Functional status of persons with HIV infection in an ambulatory setting. *J Acquir Immun Defic Syndr* 1994;7:1050-1056), with permission.

tion being that reversal of wasting and increases in muscle mass will help to restore the ability to perform physically demanding activities, such as those requiring muscle torque, power, and force during extension and flexion,⁴⁶ and thus improve QOL. Increased exercise capacity and better functional performance appear to be appropriate measures of improvement in patients with AW. In addition, increasing lean body mass can provide a larger protein store for the body during acute illness and may therefore increase a patient's ability to withstand physiologic stress.

The strong correlation between depleted lean body mass and poor outcome suggests that efforts to manage AW should focus on restoring or maintaining lean body mass, rather than on restoring total body weight. Nevertheless, restoring lean body mass is difficult in AIDS patients, who may have altered metabolism that results in subnormal rates of protein synthesis and elevated resting energy

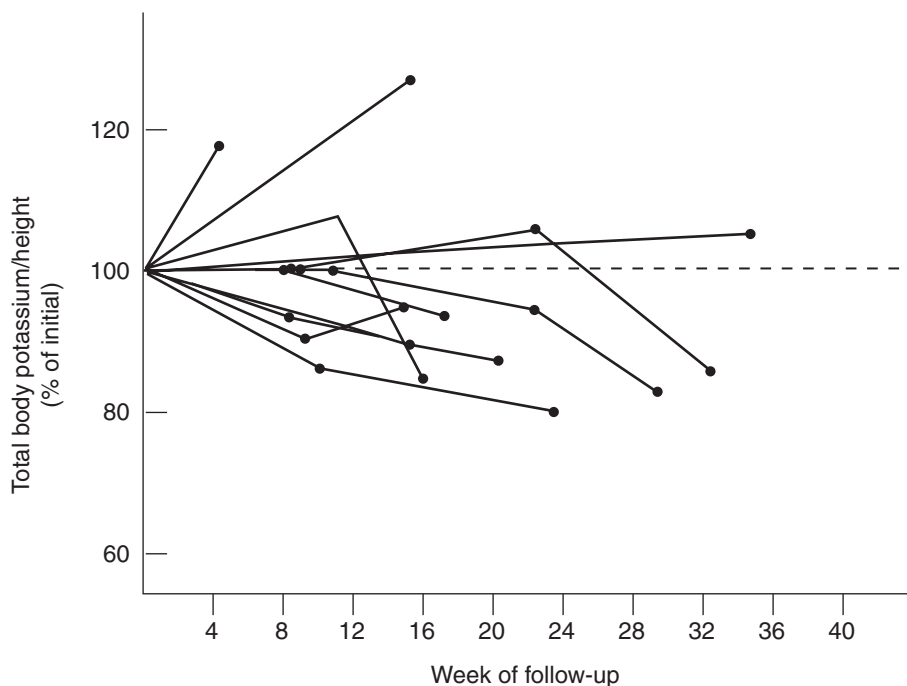
expenditure.⁹ Nutritional therapy, exercise programs, and anabolic/anticatabolic hormone therapy are 3 approaches that can reverse the effects of AW, at least temporarily.

Nutritional Therapy

To assess nutritional status, the clinician should conduct a careful interview and nutritional workup and should provide nutrition education and screening. Generally, each patient's nutritional status, weight and weight history, and results of bioelectrical impedance analysis are recorded. Bioelectrical impedance analysis is a reliable method for measuring body composition.⁴ A consultation with a nutritionist is then arranged, and a diet plan designed on an individual basis.

Nutritional therapy should be started early, as nutritional intervention probably will be of little value after a patient has a weight of 66% of ideal body weight and/or a body cell mass of 54%.⁴⁷

Figure 3. Body Cell Mass Over Time, as Measured by Total Body Potassium/Height. Eight Patients with CDC-Defined AIDS Had Decreasing Body Cell Mass and 3 with CDC-Defined AIDS-Related Complex Had Increasing Body Cell Mass According to This Measure



From reference 50 (Kotler DP, Wang J, Pierson RN Jr. Body composition studies in patients with the acquired immunodeficiency syndrome. *Am J Clin Nutr* 1985;42:1255-1265), with permission. © *The American Journal of Clinical Nutrition*. American Society for Clinical Nutrition.

Providing nutrients in the diet or through parenteral nutrition generally reverses the metabolic abnormalities caused by starvation. In AW, however, dietary intervention will not be effective until the underlying cause of cachexia is corrected. In patients with AW, therapy to increase caloric intake to adequate levels and therapy to increase lean body mass must be administered in conjunction with each other, with the proviso that interventions designed to increase total body weight do not necessarily increase lean body mass. For example, an appetite stimulant, such as megestrol acetate (Megace®, Bristol-Myers Squibb Oncology/Immunology, Princeton, NJ) or dronabinol (Marinol®, Roxane Laboratories, Inc, Columbus, OH, and Unimed Pharmaceuticals, Inc, Buffalo Grove, IL), a synthetic form of tetrahydrocannabinol, the active ingredient in marijuana, may increase body fat without increasing lean body mass.^{48,49}

Kotler et al⁵⁰ documented attempts to replete lean body mass with various nutritional therapies in 11 clinically stable HIV-infected patients (Figure 3). Eight patients had symptomatic disease, and 4 of the 8 had secondary infections, which can contribute to AW. Total body potassium (a measure of body cell mass) decreased over time in the 8 AIDS patients but not in the 3 asymptomatic patients. The authors concluded that even during periods of clinical stability, body cell mass could not be restored in symptomatic AIDS patients, regardless of food intake. It is not clear whether dietary repletion will be more successful in conjunction with highly active anti-retroviral therapy.

In most cases of AW, maintaining a balanced diet and consuming nutrients at RDA levels do not compensate for caloric and protein losses. A normal, healthy person requires a daily caloric intake of roughly 30 kcal/kg and protein intake of approximately 0.8 g/kg/d. In contrast, to compensate for losses in caloric and protein intake, a patient with AIDS typically requires 5 additional kcal/kg/d and a protein intake of about 1 more g/kg/d. Protein-calorie malnutrition and deficiencies of specific micronutrients have profound effects on the immune system.⁵⁰ For example, in HIV-positive individuals, inadequate vitamin B₆ levels have been linked to impaired peripheral blood lymphocyte response to mitogens and to reduced natural killer (NK) cell cytotoxicity.

The use of antioxidants in patients with AW is an area of increasing interest. In a 10-week study,⁵¹ 18 g/d fish oil added to the diets of 20 patients with AW was associated with positive results. Patients

with high triglyceride levels seemed to benefit from this dietary supplementation, as evidenced by reduced serum triglycerides in hypertriglyceridemic patients. Patients who did not develop new AIDS-related complications exhibited gains in weight (2.1 ± 1.3 kg) and decreases in de novo hepatic lipogenesis. In another study involving 26 patients with AW, Shabert et al⁵² found that a combination of the amino acid glutamine and antioxidants given for 12 weeks increased body weight, body cell mass, and intracellular water compared with placebo. There is a belief among some AIDS patients that merely taking massive doses of certain nutrients, such as vitamin C, may be effective in improving health, resistance to infections, or inhibition of HIV replication.¹ Vitamin C added to HIV-infected cell cultures in vitro suppresses replication of HIV, but the efficacy of using large doses of vitamin C to treat wasting is still being debated. Given the dearth of information from controlled studies, no specific recommendations for antioxidant use can be made at this time.

Exercise Programs

Exercise increases and maintains lean body mass while providing other benefits. According to several studies, appropriate physical and occupational therapy can improve exercise capacity and functional performance in patients with AIDS (Table 2). High-intensity resistance exercise training has proved particularly effective for increasing muscle strength, muscle size, and lean body mass in infirm patients.⁶⁴ Aerobic exercise training during a 10-week period improved aerobic fitness (exercise capacity) in HIV-positive men and may have the added benefit of reducing stress.⁶⁵

Exercise has been shown to activate the immune system, producing an immediate, although transient, increase in white blood cell counts. Regular exercise training may attenuate the decrease in the number of NK cells that occurs with HIV infection.⁶⁵ Carefully directed physical exercise programs may improve immunologic parameters in patients with HIV infection.

In contrast to anaerobic and endurance exercise, which increase aerobic capacity but not strength, resistance training is required to increase muscle mass. In a randomized, controlled trial of 37 patients with HIV, supervised physical training over 12 weeks resulted in significant improvements in upper and lower body strength ($P < .001$).⁶⁶ Also, progressive resistance exercise has been shown to significantly improve lower and upper extremity muscle strength

(extension and flexion torque, force, power, and work) in 24 AIDS patients over 6 weeks ($P < .01$).⁴⁶ In a study of 25 HIV-positive patients, resistance training over 8 weeks resulted in a significant increase in lean body mass (1.75 kg, $P < .001$).⁵⁵ Patients with AIDS wasting tended to gain more lean body mass (2.8 kg) than those without wasting (1.4 kg), though this difference did not reach significance ($P = .08$). In a 12-week open trial of 54 HIV-infected patients receiving testosterone therapy, nearly half of whom had AW, resistance training significantly improved body cell mass ($P < .01$) and lean body mass ($P < .001$); no such improvements were observed in nonexercising patients.⁵⁶

Exercise is particularly helpful for increasing the ratio of lean body mass to fat mass, and AIDS patients undergoing resistance training have demonstrated increased arm and thigh girth as well as increased body weight. In the absence of exercise, multinutrient supplements do not counteract muscle weakness or physical frailty.⁶⁴ These data suggest that exercise is a useful therapeutic approach to rebuilding muscle mass in patients able to undergo high-intensity training.

Although inspiring debilitated patients to add daily exercise to their lives can be a challenge, educating them about the beneficial and potentially life-saving connection between exercise and restoration of lean muscle mass is a logical starting

point. Exercise programs should be developed with an eye toward restoring and maintaining function.³⁸ Setting a short-term goal that motivates the patient, such as walking without assistance, dressing, or restoring a vocational goal, might be helpful. Although independence in self-care activities is important, exercise activities might be carried out in a group setting to help counteract the isolation of the disease.²⁶

Recovering strength and function is the major goal of exercise in patients with AW. Therefore, strength training forms the basis of an exercise prescription for this group. Strength training should focus on the large muscle groups of the legs and back, using functional motions such as squats, step-ups, and chair raises. It must also be intensive (ie, 2 to 3 sets of 6 to 8 repetitions should completely fatigue the muscle being trained). Finally, it should be progressive, so that the resistance is increased as the patient becomes stronger.

After strength has increased (usually in 2 to 4 months), an additional aerobic exercise component should be introduced, such as walking, bicycling, or running, that is appropriate for the patient's age and fitness level. This program can be performed for about 1 hour, 2 to 3 times weekly.

As the disease progresses, the introduction of psychosocial strategies to help the patient adapt to the sometimes marked physical and cognitive changes caused by HIV infection becomes increasingly important.³⁸ These strategies include stress management, counseling focused on self-empowerment and motivation, and development of a positive sense of wellness. With such motivational encouragement and psychosocial support for the patient with AW, adherence to exercise and nutritional regimens can be facilitated. Involvement of the patient in the planning and evaluation of treatment along with appropriate feedback with regard to performance can help the patient link the slow daily progress to short- and long-term goals.²⁶

Growth Hormone Therapy

Because altered metabolism and/or reduced caloric intake decrease lean body mass, an ana-

Table 2. Interventions Reported to Preferentially and Significantly Increase Lean Body Mass

Intervention	Study	Randomized, Placebo-Controlled
Resistance exercise training	Spence et al, 1990 ⁴⁶	Yes
	Horber et al, 1996 ⁵⁴	No
	Roubenoff et al, 1999 ⁵⁵	No
	Wagner et al, 1998 ⁵⁶	No
Exogenous growth hormone	Schambelan et al, 1996 ⁵⁷	Yes
	Krentz et al, 1993 ⁵⁸	No
	Waters et al, 1996 ⁵⁹	Yes
	Mulligan et al, 1993 ⁶⁰	No
	Jørgensen et al, 1996 ⁶¹	Yes
Certain androgens	Gold et al, 1996 ⁵³	No
	Berger et al, 1996 ⁴⁸	No
	Berger et al, 1993 ⁶²	No
	Strawford et al, 1999 ⁶³	Yes

bolic/anticatabolic hormone that reverses changes in metabolism may slow the loss of lean body mass in patients with AW. Growth hormone (GH), a peptide hormone secreted by the anterior pituitary gland, alters metabolism in this fashion, promoting increases in lean body mass and nitrogen muscle retention while reducing fat mass.⁶⁷

In young men, exercise is known to stimulate the release of GH, which mediates its effect via insulin-like growth factor (IGF-1).⁶⁸ Studies⁶⁹ in sprint-trained athletes, who must generate energy quickly from anaerobic metabolism, show that serum GH concentrations reached levels 10 times higher than basal levels 1 hour after anaerobic exercise. In healthy elderly people, however, endurance training did not reverse the age-related decrease in IGF-1 levels, although it significantly increased maximal aerobic capacity ($P < .001$) and decreased fat mass ($P < .001$) relative to lean body mass.⁷⁰

GH therapy may have beneficial effects on the immune system in patients with AW, who often suffer massive losses of immune cells and require immune reconstitution.⁷¹ In vitro and in vivo mouse studies show that thymic growth and cellularity,^{72,73} myelopoiesis, and T-cell production are stimulated by GH and IGF-1.^{74,75} Although the clinical benefit of GH on immune function in patients with HIV has not been demonstrated fully, GH therapy does not appear to adversely affect the immune system.⁵⁷

Treatment with recombinant human GH (rhGH) in GH-deficient adults has been shown to have beneficial effects on nitrogen balance, total body weight, lean body mass, and physical fitness.⁶¹ Therapy with GH also appears to improve exercise capacity.^{57,61} In one study, treatment with GH in GH-deficient adults significantly increased Vo_{2max} from 23.2 to 30.0 mL/min/kg ($P < .01$).⁷⁶

In a 12-week comparative study of pharmacologic and physiologic doses of GH in 10 patients with AIDS,⁵⁸ pharmacologic doses of GH (5.0 mg subcutaneous [SC], every other day) significantly increased weight ($P < .05$), lean body mass ($P < .05$), and total body water ($P < .05$) and decreased fat mass ($P < .05$) concurrently compared with the lower physiologic dosage (2.5 mg SC, every other day). Muscle power and endurance also improved, with maximal improvement occurring within the first 6 weeks of therapy. Six weeks after the study and treatment ended, all 4 patients who completed the study again lost weight. No changes were noted in mean CD4-cell counts, a finding echoed in a

12-week study by Lee et al⁷⁷ of combined IGF-1 and low-dose GH therapy for AW.

Similarly, even using what may have been a suboptimal dosage of 1.4 mg/d of GH, Waters et al⁵⁹ found that lean body mass significantly increased while fat mass decreased during the 6-week period in which patients with AIDS or AW received GH ($P = .002$, lean body mass increase; $P < .001$, fat mass decrease), IGF-1 ($P = .005$; $P < .001$), or both agents ($P = .002$; $P < .001$). The group receiving both GH and IGF-1 experienced the greatest increase in lean body mass. These data indicated that rhGH produced small but significant increases in knee ($P = .04$) and upper body power ($P = .02$) at 6 weeks and in upper body strength ($P = .008$) at 12 weeks. In another study,⁷⁸ rhGH-treated patients reported improvement in appearance, less concern about weight (a perceived treatment benefit), and an improved QOL compared with placebo-treated patients.

In a large-scale, 12-week, controlled clinical trial of patients with AIDS, Schambelan et al⁵⁷ confirmed that HIV-infected patients who received rhGH (Serostim[®], Serono Laboratories, Inc, Norwell, MA) 0.1 mg/kg of body weight per day (mean dosage, 6 mg/d) experienced significant increases in weight ($P = .01$) and lean body mass ($P < .001$) relative to patients receiving placebo (Figure 4). These improvements in weight and body composition support rhGH as an anabolic agent that promotes nitrogen retention and increases protein synthesis without fat deposition.

Schambelan's group also found that the increase in lean body mass induced by rhGH therapy correlated with improvement in functional performance as measured by work output during treadmill exercise. Patients with AIDS who were treated with rhGH for 12 weeks demonstrated a 13.2% increase in work output, compared with 2.5% in patients given placebo ($P = .04$). Although some of the increase may have been due to the increased work required to propel the now-somewhat-heavier patients, most of the increase in work output was attributed to increased work speed or intensity (grade).

Because most of the patients in the study by Schambelan et al were in advanced stages of HIV infection (average CD4-cell count, <100 cells/mm³), they generally were seriously ill, and their health perception scores were lower than those reported in other HIV-infected populations.^{57,79} The patients underwent exercise testing according to a protocol

for patients with limited exercise capacity.⁸⁰ Despite relatively low exercise capacity at baseline, patients given rhGH therapy experienced improved work output relative to placebo-treated patients. However, the poor status of the study patients makes it difficult to compare their functional improvements with similar improvements in healthier patients (who are likely to be capable of undertaking rigorous exercise), and it is unclear whether an exercise program would have been feasible in this group.

Short-term (6-week or 12-week) rhGH therapy has been shown to improve body composition.^{57,59,77} Long-term gains after cessation of treatment are possible,⁸¹ although the effects are unlikely to be permanent. The dosage of GH may have an effect on outcome. In the study by Lee et al⁷⁷ using low-dose GH and IGF-1, 0.34 mg of subcutaneous rhGH given twice daily did not change the nutritional status or clinical course of patients nor did it alter immune response.

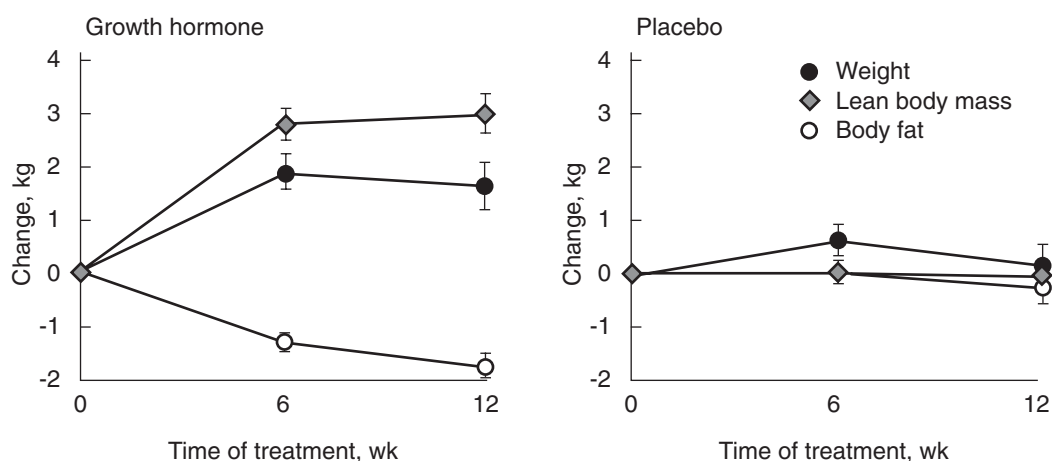
The most commonly reported adverse effects of rhGH therapy include swelling or puffiness, arthralgia or myalgia, and diarrhea. These events are relatively mild or moderate in severity and resolve with continued treatment or reductions in dose.

Reported adverse events that are typical of advanced HIV infection and not associated with rhGH treatment include nausea, fatigue, fever, headache, abdominal pain, lymphadenopathy, and abnormal sensations or diminished sensitivity to stimulation.⁵⁷

GH therapy may not be appropriate for all HIV-infected patients. Such factors as cost, contraindications (ie, GH sensitivity), ability to withstand adverse events, and disease stage must be considered.

In managing patients with AW, it is important to remember that a combination of exercise, nutrition, and hormonal therapy may produce the best results. For example, aging and concomitant declining GH secretion have been associated with decreases in lean body mass and relative increases in fat mass. These changes in body composition can be prevented by regular physical training.⁵⁴ Rall et al found GH levels to be inversely correlated with whole-body protein breakdown, and plasma glucagon levels to be inversely correlated with protein synthesis in adults with rheumatoid arthritis. The increase in protein catabolism in these patients could be prevented by strength training.⁸² As clinical and research experi-

Figure 4. Effect of rhGH Versus Placebo on Weight, Lean Body Mass, and Body Fat in 140 Patients with HIV-Associated Wasting ($P = .011$ for Body Weight; $P < .001$ for Lean Body Mass and Body Fat)



By Week 6, marked differences were noted in weight and lean body mass.

From reference 57 (Schambelan M, Mulligan K, Grunfield C, et al. Recombinant human growth hormone in patients with HIV-associated wasting: A randomized, placebo-controlled trial. *Ann Intern Med* 1996;124:873-882), with permission. © *Annals of Internal Medicine*.

ence with rhGH in patients with AW grows, the benefit of this therapy in conjunction with exercise should become clearer.

Anabolic Steroids

Anabolic-androgenic steroid hormones, which sometimes are used illicitly for weight training and muscle gain,^{83,84} are used clinically to counteract the protein deficiency that occurs with disease-related malnutrition.^{85,86} High doses of testosterone increase muscle mass and strength in young, healthy adult men, especially when combined with strength training.⁸⁷ These agents therefore seem a natural choice as an adjuvant to treatment of AW.

The oral anabolic steroid oxandrolone was found to have a positive effect on overall strength, muscle bulk, weight, and well-being of AIDS patients, but it did not improve muscle strength.⁴⁸ In a recent large-scale study of this agent, the recommended 20-mg daily dose did not produce substantial weight gain or improvements in body cell mass or QOL (C. Grunfeld, oral presentation, 12th World AIDS Conference, Geneva, Switzerland, July 1, 1998). Conversely, in open-label trials without placebo controls, the anabolic steroids stanozolol (Winstrol®, Sanofi Pharmaceuticals, Inc, New York, NY) and nandrolone decanoate (Deca-Durabolin®, Organon Inc, West Orange, NJ) reportedly improved weight, body composition, and strength in AW patients.^{53,62} Indeed, a recent 8-week study conducted in 24 eugonadal, HIV-infected men found that patients treated with progressive resistance exercise, intramuscular testosterone, and oxandrolone (20 mg) significantly increased lean body mass ($P = .005$), weight ($P = .03$), and strength ($P < .05$) relative to patients undergoing exercise, testosterone therapy, and placebo.⁶³ However, in a review of this study, Dobs⁸⁸ suggests that more data on a greater number of patients are required before recommendations can be made about the role of anabolic steroids in AW.

The known adverse effects of these agents include liver damage, mood changes, suppression of testicular function, and prostatic hypertrophy. In addition, the applicability of androgen therapy to women with AW is unclear because of the masculinizing effects of the agents.

... CONCLUSION ...

The effective management of AW is crucial to the well-being of the patient with AIDS. Treatment with rhGH shows great promise, but issues of cost and

coverage for this treatment under managed care programs pose logistic hurdles. In 1995, a standard 12-week course of therapy was estimated to cost \$12,600,⁸⁹ or roughly \$1000 per week.⁹⁰ Reductions in dosage, however, may decrease these costs. Also, a recent decision by the United States Health Care Financing Administration now requires state Medicaid programs to include rhGH therapy for AW on their formularies.⁹¹ Such approved reimbursement through Medicaid may thus make rhGH therapy more accessible.

Loss of weight, strength, and physical abilities are sources of psychologic distress for AIDS patients. Much of the decrease in function and QOL in AW can be related to loss of lean body mass, particularly muscle mass. Several treatments have been shown to reverse AW, including use of rhGH, resistance exercise, and perhaps androgen therapy. Nutritional support plays a major role in maintenance of lean body mass, and its addition to exercise programs as well as growth hormone therapies for AW management may be warranted.

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