Weight Loss and Wasting in Patients Infected with Human Immunodeficiency Virus

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Weight loss and muscle wasting remain significant clinical problems, even in the era of potent antiretroviral therapy. In patients infected with human immunodeficiency virus (HIV), wasting, particularly loss of metabolically active lean tissue, has been associated with increased mortality, accelerated disease progression, loss of muscle protein mass, and impairment of strength and functional status. Factors that may contribute to wasting include inadequate intake, malabsorptive disorders, metabolic alterations, hypogonadism, and excessive cytokine production. Evidence now demonstrates that nutritional counseling and support, appetite stimulants, progressive resistance training, and anabolic hormones can reverse weight loss and increase lean body mass in HIV-infected patients. Despite a growing body of evidence on the importance of nutritional intervention to prevent wasting in adults, maintain growth velocity in children, and promote restoration of weight and lean body mass in stable, low-weight patients, no therapeutic guidelines currently exist for the management of weight loss and wasting in HIV-infected patients. Principles and guidelines for assessment and management of weight loss and wasting in patients with HIV/AIDS are presented.

Weight loss and muscle wasting were unique identifying characteristics of HIV infection early in the epidemic [1, 2] and remain significant clinical problems for adults and children, even in the modern era of potent antiretroviral therapy. Surveillance data by the Centers for Disease Control and Prevention (CDC) [3] suggest that the incidence of new wasting has declined in proportion to opportunistic infections, but data from other studies indicate that wasting remains a significant complication, even in populations with widespread access to highly active antiretroviral therapy (HAART). For example, in a cohort of HIV-infected subjects followed in Boston, Wanke et al. [4] demonstrated that 18% of patients followed longitudinally lost >10% of body weight over serial visits, whereas 21% lost >5% of body weight, sustained for 1 year, and 8% had a body mass index (BMI) of <20. A majority of the patients with wasting in this study were receiving HAART. In another recent article that compared trends in patients followed at the Johns Hopkins AIDS Service in 1994 with those in 1998, wasting, lymphoma, and cervical cancer were the only complications that did not decline in incidence over that period [5].

In patients with HIV infection, wasting, particularly loss of metabolically active lean tissue, has been associated with increased mortality [6–15], accelerated disease progression [13], loss of muscle protein mass [16], and impairment of strength and functional status [17]. Although the CDC [18] case definition of wasting as an AIDS-defining event requires a net weight loss of at least 10%, a weight loss of as little as 5% has been

Financial support: NIH DK 54167 (S.G.) and DK 54615 (K.M.). S. G. has received unrestricted educational grant support from Serono Inc, Pfizer Inc, Bristol Myers Squibb Inc, and Glaxo Smith Kline Inc. K. M. has received grant support from Serono Inc and has served as a consultant to Serono Inc and Bristol Myers Squibb.

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Clinical Infectious Diseases 2003; 36(Suppl 2):S69–78

1058-4838/2003/3607S2-0004$15.00

associated with increased morbidity and mortality [13]. These observations make it critically important to identify and characterize early risk factors for wasting in HIV-infected patients and to monitor wasting with a standardized set of strategies for diagnosis, surveillance, and appropriate treatment. Unfortunately, the appropriate nutritional evaluation of such patients is often not performed, and it is assumed that treatment with potent antiretroviral therapy will ameliorate nutritional deficiencies. This is not consistently the case [19], and nutritional management during the transition to improved immune function is critical.

Among the factors that have been demonstrated or hypothesized to contribute to wasting are inadequate intake, malabsorptive disorders, metabolic alterations, hypogonadism, and excessive cytokine production. Because wasting is a multifactorial phenomenon, strategies for its prevention, interruption, or reversal are complex. Despite a growing body of evidence on the importance of nutritional intervention to prevent wasting in adults, maintain growth velocity in children, and promote restoration of weight and lean body mass (LBM) in stable, low-weight patients, no therapeutic guidelines exist for the management of weight loss and wasting in HIV-infected patients. The Working Group on the Prevention and Treatment of Wasting and Weight Loss (the "Working Group") strongly recommends the promulgation of guidelines in this area. Furthermore, we recommend a parallel set of guidelines for pediatric patients, for whom optimal nutrition equates with optimal linear growth, optimal development, and improved quality of life. Proposed guidelines on the diagnosis and management of wasting are listed at the end of this report. The rationale for these proposed guidelines is reviewed throughout this report.

DEFINITION OF SIGNIFICANT WEIGHT LOSS AND WASTING

Weight loss in HIV infection features depletion of both lean and fat tissue [20–28]. Initial studies among men suggested a disproportionate loss of LBM. Subsequent studies in men and women suggested a greater degree of fat loss relative to LBM [27, 28]. The loss of fat and lean mass may in part be dictated by the severity of illness and initial body composition before weight loss, with fat loss more prominent among persons with a greater percentage of body fat at baseline [27]. A number of studies suggest that loss of LBM and/or weight may be independent predictors of survival in adult patients with HIV infection. In an early study, Kotler et al. [6] demonstrated that loss of body cell mass as determined by potassium-40 isotope analysis was an important determinant of increased mortality in patients with advanced HIV disease. Other more derivative body composition determinants, such as phase angle and body cell mass by bioelectric impedance analysis, have also been shown to predict mortality [11, 12, 14]. In studies performed before the current treatment era, Suttmann et al. [11] demonstrated a statistically greater survival in AIDS patients with a body cell mass >30% weight or albumin >30 g/L. Using weight and weight loss as predictors of survival, Wheeler et al. [13] showed an increased risk of death with progressive weight loss. The risk of death rose from 1.26 with a weight loss of 0%–5% over 4 months to 2.22 with a weight loss of 5%–10% over 4 months [13]. Similarly, Guenter et al. [8] demonstrated an 8.3-fold increased risk of death with weight <90% ideal body weight (IBW) in HIV-seropositive outpatients [8]. Using an absolute criterion, Palenicek et al. [9] demonstrated a significantly reduced (1.05 vs. 1.48 years, $P = .0001$) survival in men who had lost >4.5 kg 3–9 months before the development of AIDS [9]. More recently, Thiebaut et al. [15] demonstrated adjusted survival hazard ratios of 1.9 (95% CI, 1.4–2.6), 3.3 (95% CI, 2.4–4.4), and 6.7 (95% CI, 5.2–8.6) for weight loss of <5%, 5%–10%, and >10% from baseline, respectively, over a mean follow-up period of 19.9 months. Furthermore, a low BMI (16–18.4) was associated with a 2.2 (95% CI, 1.6–3.0) increased risk of death, whereas a BMI of <16 was associated with a 4.4-fold (95% CI, 3.1–6.3) increased risk of death [15].

A number of additional factors must be considered in the evaluation of wasting in the current era of HAART. First, it is critical to distinguish between voluntary and involuntary weight loss. Classical wasting, involving changes in whole body lean and fat mass, must be distinguished from the changes in fat distribution, often referred to as lipodystrophy. Although HIV-associated lipodystrophy often involves increased fat in the trunk area, considerable loss of fat in the face and extremities is also often seen. To date, the etiology and standardized definitions for such fat loss have not been developed. However, it is critical to distinguish between classical wasting and changes in fat distribution so that appropriate management strategies can be applied.

Classical wasting may be more likely to occur in the context of virologic or immunologic failure, a secondary infection, or clinically significant diarrhea or anorexia. In contrast, in patients with peripheral lipoatrophy (loss of subcutaneous fat in the appendages, buttocks, or face) in the presence of retention or increases of fat in the central region, malnutrition per se is unlikely to be the primary factor. In fact, it has been suggested that some fat-distribution abnormalities are more likely to occur in patients who have experienced the most robust responses to antiretroviral therapy [29, 30]. Moreover, lactic acidosis, a rare but potentially fatal condition, is often accompanied by rapid weight loss, abdominal pain, and fatigue [31] and thus might be misclassified as classic wasting. Until universally recognized diagnostic criteria are developed, clinical judgment will

be required for the proper diagnosis and management of weight loss in the current treatment era.

To date, standardized recommendations on the appropriate weight and body composition criteria to define wasting have not been made. One of the major goals of the Working Group, therefore, has been to define an absolute weight, degree of weight loss, and time frame for weight loss that are significant and predictive of excess morbidity and mortality in HIV-infected patients. On the basis of the published data, we recommend expansion of the current definition of wasting to include patients with rapid but lesser degrees of weight loss than currently included under the existing CDC standards for wasting—for example, weight loss of 5% within 6 months.

CONSIDERATIONS IN CHILDREN

In children, the definition of altered nutritional status is more complicated because of the need to consider the dynamic changes involved in growth. Therefore, the accepted criteria for significant growth failure in pediatric HIV infection are (1) weight growth velocity that is <5% for >2 months, (2) a significant decrease in the growth centile over time (e.g., from the 50th to the 25th percentile), (3) weight percentage standard or weight-for-height percentage standard that is <90%, (4) weight for height that is <5%, (5) a loss of >5% of LBM, or (6) serum albumin <3 g/dL [32]. Recommendations for the assessment of lean and fat mass will also be made in conjunction with the Assessment of Nutritional Status, Body Composition, and HIV-Associated Morphologic Changes Working Group.

PREVENTION OF WEIGHT LOSS

The significant impact of wasting on survival, disease progression, and functional status highlights the need to prevent muscle wasting and weight loss in HIV-infected patients. However, evaluation of weight and nutritional status are most often not part of the initial or subsequent evaluation of the HIV-infected patient. Weight history is often not obtained, and potential risk factors for wasting are too often not evaluated before weight loss. Recommendations on the method and frequency of weight monitoring and the minimum basic investigation of risk factors for weight loss, including reduced caloric intake due to anorexia or multiple factors leading to inaccessibility of food, opportunistic infections, gastrointestinal disease, malignancies, and other endocrine or metabolic conditions, will be made, with the goal of avoiding reliance on pharmacologic interventions to reverse wasting. Education on appropriate nutritional practices, exercise, and the importance of maintaining energy balance should be emphasized. For many patients, especially children, nutritional status is often related directly to the socioeconomic considerations that need to be recognized as an important determinant of overall nutritional status and growth. Recommendations on the appropriate monitoring of weight and growth in children will include consideration of increased energy requirements required for normal growth.

TREATMENT OF ACTIVE WASTING

In contrast to the treatment of other HIV-related complications, a standardized approach to the management of active weight loss has not been established. A comprehensive assessment of comorbidities, including evaluation for gastrointestinal disease, opportunistic infections, malignancy, hypogonadism, adrenal insufficiency, or medication-related side effects, is critical in patients with active weight loss. Studies have shown a significant mismatch between energy intake, which is often reduced, and energy expenditure during opportunistic infection [33, 34]. These findings underscore the need to assess the adequacy of energy and nutrient intake and to treat opportunistic infections or related conditions that may alter energy requirements and exacerbate acute weight loss.

RESTORATION OF HEALTHY WEIGHT IN STABLE PATIENTS WITH A HISTORY OF WEIGHT LOSS

Restoration of a healthy weight in stable subjects with a history of weight loss, and catch-up growth for children, are important goals for a large number of HIV-infected patients. Significant loss of LBM and muscle mass is seen in such patients, emphasizing the need to consider intervention with nutrition, exercise, and/or pharmacologic therapies. An important consideration for such patients is identification of a reasonable target weight. Fat redistribution, dyslipidemia, and hyperinsulinemia can occur among patients with weight loss [35], suggesting the importance of counseling on appropriate carbohydrate, lipid, protein, and cholesterol intake. Early nutritional intervention is important in such patients to maximize gain of LBM and minimize gain of visceral fat.

POTENTIAL THERAPEUTIC INTERVENTIONS

A significant body of evidence now demonstrates that use of nutritional counseling and support [36, 37], appetite stimulants, progressive resistance training (PRT), and anabolic hormones can reverse weight loss and increase LBM in HIV-infected patients. Treatment of associated opportunistic infections and optimization of antiretroviral therapy should be the first goal in patients with wasting, followed by an assessment for adequate caloric intake and food absorption. Although current evidence suggests that total energy expenditure is not increased in patients with HIV infection, recognition of increased resting

energy expenditure among HIV-infected patients may result in a recommendation for increased caloric and nutrient intake, particularly during periods of active weight loss. Use of HAART itself may result in increased weight, but not increased LBM. Care must be taken to modify any recommendation of increased caloric intake after patients have achieved target weight, to prevent the development of obesity, insulin resistance, and dyslipidemia that may be associated with weight gain in the setting of HAART.

NUTRITIONAL SUPPLEMENTATION

Children and adults receiving enteral or parenteral feeding or oral nutritional supplements have commonly been reported to gain weight and in some cases body cell mass [38–46]. Other forms of nutritional supplementation, including total parenteral nutrition (TPN), β-hydoxy β-methylbutyrate (β-HMB), and high-quality oral protein have been assessed [38, 39, 47]. Initial studies that used TPN in patients with severe wasting showed significant improvement in weight (e.g., an 8-kg increase compared with a 3-kg loss in the dietary counseling group over 8 weeks) [39]. In contrast, the effects of TPN on LBM were greatest among those with documented malabsorption, compared with results in patients with active secondary infections [38]. In a 12-week study of patients with AIDS wasting, a supplement containing glutamine was shown to increase LBM 1.7 kg as compared with only 0.4 kg in the placebo-treated group [44]. More recently, HIV-infected patients with unintentional weight loss >3% but weight stability for 3 months were randomized to receive a whey protein supplement (80 g/d) or an isocaloric control supplement (carbohydrate) for 12 weeks [48]. Whey protein did not increase weight or LBM, but carbohydrate supplementation increased triglyceride levels.

Overall, studies suggest that increases in net daily energy and macronutrient intake can be achieved with the oral supplements, and their use may be an effective means of maintaining or increasing intake for some patients. A variety of conventional preparations are available, as well as specialized formulas for patients with specific intolerances. Although some studies have suggested that there is increased benefit from supplements specifically designed for people with HIV infection, such benefits have not been confirmed, and the primary criteria for selection of a specific supplement should be tolerability and cost.

RESISTANCE EXERCISE TRAINING

Resistance exercise can increase lean tissue in HIV-infected patients [49–51]. An early controlled study of PRT for HIV-infected men recovering from *Pneumocystis carinii* pneumonia (PCP) demonstrated significant increases in weight (1.7 vs. −1.9 in exercising vs. nonexercising patients) [52]. By use of a combination of bicycle and resistance exercises, Rigsby et al. [53] demonstrated an increase in strength and aerobic capacity. In an open-label study, Roubenoff et al. [49] demonstrated a 2.1-kg increase in LBM as compared with baseline among HIV-infected patients. In a randomized study of eugonadal men with AIDS wasting (weight <90% of IBW or weight loss >10%), a standardized PRT regimen performed 3 times weekly over 12 weeks resulted in a 2.1-kg increase in LBM and significant increases in high-density lipoprotein (HDL) cholesterol [54]. In another recent study in asymptomatic HIV-infected men, almost all of whom were receiving HAART, a supervised 16-week weight-lifting program was associated with a 1.4-kg increase in LBM) and significant increases in thigh muscle area [50]. Although triglycerides decreased in this latter study, there were no changes in HDL cholesterol. Studies to date on PRT for HIV-related wasting have focused primarily on men. However, in one recent study in women, PRT over 14 weeks was shown to increase fat-free mass by 1.6 kg in association with increased muscle strength [55].

As is the case in noninfected populations, the ability of some subjects to adhere to exercise regimens can be problematic [56, 57] and thus can present a barrier to their long-term efficacy. However, nonpharmacologic measures such as nutritional supplementation and exercise should always be considered and encouraged before pharmacologic interventions are instituted.

APPETITE STIMULATION

Placebo-controlled trials have demonstrated the efficacy of a variety of pharmacologic agents in promoting weight gain or lean tissue accrual. Megestrol acetate, a synthetic progestational agent, is a potent appetite stimulant and effectively increases weight, although the weight gain is predominantly or exclusively fat [58, 59]. In a large study of 271 patients, patients with AIDS wasting receiving 800 mg of megestrol acetate per day consumed ~500 kcal more per day and gained ~4 kg compared with placebo-treated patients, in association with an improved quality of life. In a second study, similar weight gains were seen, but sustained effects on caloric intake were not seen after 8 weeks. Megestrol acetate has potent glucocorticoid-like activity, which may account for its relatively greater effects on fat rather than on lean mass, and use of this agent is associated with adrenal insufficiency and hypogonadism. Replacement of testosterone with a conventional dosage (200 mg every other week) did not augment LBM accrual in men treated with megestrol acetate but did help to maintain sexual function [60]. Published data on the use of megestrol acetate are available only in men, and the effects of megestrol acetate on weight gain and body composition in women remain unknown.

Dronabinol (Δ^9-tetrahydrocannabinol), the primary active compound in marijuana, is approved by the US Food and Drug

Administration for HIV-associated anorexia. In a randomized, double-blind, placebo-controlled multicenter trial in patients with HIV-associated weight loss, treatment with dronabinol (2.5 mg bid) produced significant increases in self-reported appetite and decreases in nausea but did not significantly increase weight over a 6-week blinded treatment period [61]. In a randomized, 4-arm, open-label pharmacokinetic study, use of dronabinol in combination with megestrol acetate was shown to have no increased benefit over megestrol acetate alone [62]. Significant increases in weight (~6 kg) were seen in patients in each of 2 groups randomized to receive 750 mg megestrol acetate daily. However, the addition of dronabinol produced no further weight gain. The predominant side effects associated with dronabinol in these trials were neurologic (euphoria, dizziness, thinking abnormalities, confusion, anxiety, and emotional lability).

Significant weight gain was reported in a study of HIV-infected subjects receiving protease inhibitors who were randomized either to receive dronabinol or to smoke marijuana in a 3-week metabolic ward study of the safety of cannabinoids compared with oral placebo [63]. However, wasting was not an eligibility criterion for enrollment in this study, and few patients would have met any criteria for wasting. Moreover, >80% of the weight gained was fat mass [64]. Overall, the absence of evidence that cannabinoids produce improvements in objective outcomes (weight, LBM, or energy intake) in patients with HIV-associated wasting limits our ability to make a recommendation regarding the use of cannabinoids in this group.

ANABOLIC ANDROGENIC STEROIDS

Use of testosterone has been shown to increase LBM among hypogonadal men with AIDS wasting [65, 66]. Before the current treatment era, hypogonadism was seen in up to 50% of men with AIDS wasting [67]. More recent studies of patients in the era of HAART demonstrate a lower, but nonetheless significant, 20% prevalence of hypogonadism among men with AIDS wasting [68]. In an initial, randomized, placebo-controlled study of 51 hypogonadal men with classically defined AIDS wasting (weight loss >10% and/or weight <90% IBW), physiologic testosterone replacement (testosterone enanthate, 300 mg im every 3 weeks) increased LBM 2.6 kg relative to placebo over 6 months [65]. Of note, the effects of testosterone were sustained over 12 months in an open-label extension study [69]. Furthermore, testosterone administration resulted in improved insulin sensitivity and decreased depression indexes in hypogonadal patients with AIDS wasting [70]. Bhasin et al. [51] demonstrated similar results with intramuscular testosterone (testosterone enanthate, 100 mg/week) over 12 weeks, with a relative increase in LBM of 1.4 kg compared with placebo. In contrast, Dobs et al. [71] did not show an increase in weight or body cell mass among relatively hypogonadal men receiving transdermal testosterone (6 mg/d via transscrotal patch) over 12 weeks. Overall, natural testosterone esters, rather than synthetic anabolic steroids, should be used as androgen replacement in hypogonadal men. Men receiving natural testosterone esters or synthetic testosterone derivatives should undergo a yearly prostate examination and prostate-specific antigen monitoring during long-term therapy. In addition, hematocrit and lipid levels should also be monitored. Use of physiologic testosterone replacement in hypogonadal men is unlikely to result in dyslipidemia, liver dysfunction, or insulin resistance [54, 72, 73].

Studies suggest that use of synthetic anabolic agents, such as oxandrolone, nandrolone, and oxymetholone, can increase weight and LBM in patients with wasting [74–78]. Oxandrolone administration at 15 mg/d has been shown to increase weight by 1.8 kg over 14 weeks in a randomized, placebo-controlled study [74]. Body composition was not measured in this study. More recently, Mulligan et al. [79] demonstrated increases in both weight and LBM of (1.8 and 2.0 kg, respectively, as compared with placebo), in a randomized, placebo-controlled 12-week study of nandrolone (200 mg im every week). However, supraphysiologic use of testosterone or its derivatives in eugonadal men, although effective in increasing LBM, may reduce HDL levels [54, 78, 79]. Furthermore, anabolic steroids may cause liver dysfunction and hypogonadism and should be used with caution in HIV-infected patients.

The combination of testosterone analogs and exercise has also been shown to increase LBM [51, 54, 78, 80]. In a 4-arm randomized study performed in eugonadal men with AIDS wasting, Grinspoon et al. [54] demonstrated a 4.6-kg gain in LBM and significant improvements in muscle strength over 12 weeks in response to combined testosterone administration (testosterone enanthate 200 mg im every week) and PRT. Similarly, Bhasin et al. [51] demonstrated significant improvements in response to combined testosterone enanthate (100 mg im every week) and PRT in hypogonadal men with AIDS wasting. Randomization of HIV-infected men with weight loss treated with PRT and testosterone enanthate (100 mg im every week) to oxandrolone (20 mg/d po) or placebo resulted in a net weight increase of 2.9 kg and significantly increased muscle strength [78]. In a study that used a different approach, a group of asymptomatic HIV-infected men who were randomized to receive PRT in addition to supraphysiologic doses of nandrolone (600 mg im every week) demonstrated a net increase of 2.9 kg in LBM and increased strength [80].

Emerging studies on the use of testosterone and anabolic steroids also suggest a potential role of these hormones in the treatment of AIDS wasting in women. Androgen deficiency is common among women with AIDS wasting, seen in up to 60%

of such patients [28]. Recent studies suggest decreased adrenal androgen production and increased cortisol production in women with AIDS wasting [81]. Preliminary studies indicate that physiologic testosterone replacement (150 μg/d) for 12 weeks increased body weight by 1.9 kg in HIV-infected women [82]. Treatment with nandrolone (100 mg every 2 weeks for 12 weeks) was associated with significant increases in weight and LBM (4.5 and 3.9 kg, respectively, relative to placebo) in a randomized, double-blind, placebo-controlled trial in HIV-infected women with weight loss [83]. Given the potential risk associated with testosterone and androgenic anabolic steroid administration to women, a general recommendation for the use of these agents in HIV-infected women cannot be made until further studies are performed.

GROWTH HORMONE

Pharmacologic use of growth hormone (GH) has been shown to improve nitrogen balance and increase LBM in HIV-infected patients with wasting [84–87] and to promote lean tissue retention in those with secondary infections [88]. In a randomized, double-blind, placebo-controlled trial in 178 patients with HIV-associated wasting, treatment with GH (~6 mg/d) for 3 months produced significant increases in weight (1.6 kg) that were exceeded by increases in LBM (3.0 kg) and accompanied by decreases in fat (−1.7 kg). Treadmill work output at volitional exhaustion increased significantly in patients treated with GH, and changes in work output and time to exhaustion were significantly and positively correlated with changes in LBM [86].

In another placebo-controlled study, a lower dosage of GH (1.4 mg/d; $n = 15$) was evaluated over a 12-week period [87]. LBM increased modestly after 6 weeks of treatment (~1 kg), but this increase was not significant after 12 weeks. Indexes of muscle function and quality of life increased significantly in patients treated with GH. Use of insulinlike growth factor 1 (IGF-1), alone or in combination with GH, failed to produce increases in weight or LBM that were superior to those achieved with GH alone [87, 89, 90]. Overall, there is no therapeutic rationale for combining these 2 injectable drugs. Side effects associated with GH treatment in these studies include arthralgias, myalgia, fluid accumulation (primarily in the extremities), diarrhea, and, less commonly, carpal tunnel compression. GH can also cause or exacerbate glucose intolerance. The optimal therapeutic and maintenance dosing regimens of GH for HIV-associated wasting have not been identified.

In a randomized, placebo-controlled study of GH in HIV-infected subjects with newly diagnosed opportunistic infections, Paton et al. [88] reported that patients treated with GH for 2 weeks had increases in weight and LBM (1.6 and 1.8 kg, respectively, vs. placebo) and decreases in the rates of protein breakdown. These data suggest that there might be a role for short-term treatment with GH or other protein anabolic agents in prevention or attenuation of the rapid weight loss that often accompanies acute infections.

CYTOKINE SUPPRESSION

Although no direct, mechanistic role for cytokines has been demonstrated in HIV-associated wasting, many studies have suggested that proinflammatory cytokines, acting alone or in combination, may contribute to the metabolic abnormalities associated with wasting. Accordingly, several weak cytokine suppressors have been evaluated as potential treatments for wasting. For example, thalidomide suppresses TNF-α production in vitro [91] and has been shown to promote nitrogen retention in a metabolic ward study [92] and weight gain in 3 placebo-controlled studies in patients with HIV infection [93–95]. In the largest such study [95], patients with >10% weight loss who were randomized to thalidomide in a dosage of 100 mg/d for 8 weeks experienced a significant weight gain (1.7 kg vs. placebo), approximately half of which was LBM. In this trial, a higher dosage of thalidomide (200 mg/d) was associated with more side effects but not with a greater weight gain.

In another randomized, double-blind, placebo-controlled multicenter trial, treatment with thalidomide reversed HIV-associated oral aphthous ulcers and secondarily produced increases in weight [96]. Modest but statistically significant increases in virus load have been seen in 2 placebo-controlled studies of thalidomide treatment in patients with HIV infection, and paradoxical increases in TNF-α levels have also been seen [95, 96]. Thalidomide is approved by the US Food and Drug Administration for patients with erythema nodosum leprosum. Because of the well-known potential for teratogenic effects, women of childbearing potential who elect to use thalidomide must be warned to use at least 2 methods of contraception, and all patients must be instructed not to share this drug with anyone else. The most prevalent side effects of thalidomide in patients with HIV-associated wasting have been somnolence, peripheral neuropathy, hypersensitivity, and neutropenia. Until the mechanism by which thalidomide causes weight gain and the clinical significance of the increases in virus load and TNF-α are understood, it is difficult to define a specific role for thalidomide in the treatment of HIV-associated wasting. A variety of other weak cytokine suppressors, including pentoxifylline [97], *N*-3 fatty acids [98], and ketotifen [76, 99] have been studied in subjects with HIV-associated weight loss, but their use for this indication is not supported by current data.

INTERVENTIONS IN CHILDREN

To date, there are no published data from placebo-controlled trials of nutritional or pharmacologic treatment of wasting in children. In an observational study of tube feeding (nasogastric or gastrostomy) in 18 children with growth failure who ranged in age from 3 to 159 months, significant increases in weight and arm fat were observed, but feeding did not accelerate linear growth [46]. Similarly, Miller et al. [45] reported that gastrostomy tube supplementation in 23 HIV-infected children resulted in increased weight and weight-for-height *z* scores but no improvement in height or arm muscle circumference. Among pharmacologic interventions, megestrol acetate, oxandrolone, and GH have been evaluated in open-label observational studies in small groups of HIV-infected children with growth failure. In 19 HIV-infected children with growth failure treated for 7 months, megestrol acetate use was associated with weight gain, without affecting linear growth [100]. In 9 children (ages 4–14) treated with oxandrolone (0.1 mg/kg/d) for 3 months, weight and muscle mass tended to increase, and treatment was considered to be well tolerated [101]. Neither linear growth nor bone age was affected by treatment. In 5 children (ages 8.5–13.9 years), short-term treatment with a pharmacologic dosage of GH (0.067 mg/kg/d for 28 days) was associated with a significant increase in weight but variable changes in LBM [102].

One child in this latter study had IGF-1 levels that were below the normal range, potentially presenting a rationale for GH replacement in this individual. However, IGF-1 levels in the other children in this study were in the normal range. Preliminary results of an earlier study in which children were randomized to GH (40 μg/kg/d) or IGF-1 (90 μg/kg/d) for 6 months suggested that these agents might improve linear growth and LBM [103]. Until results of controlled studies are available, this group cannot recommend use of protein anabolic agents (anabolic steroids or GH) in children with HIV-associated growth failure in the absence of evidence of a specific deficiency.

CONCLUSION

A large body of evidence demonstrates that weight loss and decreased LBM are common in HIV-infected patients, even in the era of HAART. A number of studies suggest that loss of weight and LBM are independent predictors of increased morbidity and mortality in HIV-infected patients. Furthermore, data from randomized, placebo-controlled studies suggest that treatment strategies for weight loss, including PRT, testosterone, megestrol acetate, GH, anabolic steroids, and combination therapies, can increase weight and, in many cases, LBM, although the long-term effects of such interventions on survival and disease progression have not been determined. The Working Group urges the adoption of the following principles for the diagnosis and management of weight loss in HIV-infected patients.

RECOMMENDATIONS

To prevent loss of weight and LBM, all HIV-infected patients should be encouraged to maintain adequate energy intake and engage in moderate exercise.

DIAGNOSIS

- Monitor weight every 6 months in HIV-infected patients and every 3 months in patients with weight loss. Keep a weight chart in the patient's medical record [104].
- Expand CDC definition of wasting to include patients with weight <90% IBW (or BMI <18.5) and weight loss >10% from pre-illness maximum or >5% in the previous 6 months.
- Assess adequacy and quality (protein, micronutrients) of dietary intake and malabsorption in all patients with weight loss.
- Distinguish between classic wasting (generalized weight loss) and lipoatrophy (disproportionate loss of fat in the limbs, face, or buttocks), considering immunologic and virologic status and medications.
- Assess potential underlying mechanisms of wasting, as follows:
    - Inadequate food intake due to anorexia, gastrointestinal disturbances, or oral or esophageal lesions.
    - Active secondary infection.
    - Hypogonadism and other endocrine abnormalities.
    - Malabsorption and diarrhea.
    - Hyperlactatemia or lactic acidosis in patients with rapid weight loss, anorexia, gastrointestinal disturbances, dyspnea, or fatigue.
- Determine impact of psychosocial factors (e.g.. access to food, depression) on food intake.

TREATMENT

- Provide nutrition counseling to increase caloric intake in patients with inadequate intake; maintain or increase intake in patients whose intake supports their current weight but is not sufficient to increase weight. Ensure adequate balance of protein, fat, and carbohydrate and micronutrient intake.
- Optimize antiretroviral therapy.
- Consider PRT in stable, ambulatory patients with wasting.

PRT may be used in conjunction with other therapies.

- Administer testosterone replacement in HIV-infected men with significant weight loss and low testosterone levels.
- Consider stimulating the appetite with megestrol acetate for patients who are unable to voluntarily increase or maintain total energy intake.
- Consider other pharmacologic interventions, such as GH and anabolic steroids, for rapid weight loss associated with acute infection and in severe cases of continued weight loss refractory to nonpharmacologic therapies. Ensure adequate caloric intake during pharmacologic interventions.
- Reassess need for continued anabolic therapies in the context of the patient's overall health every 3–6 months.

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