

# Nutrition and HIV Infection: Review of Weight Loss and Wasting in the Era of Highly Active Antiretroviral Therapy from the Nutrition for Healthy Living Cohort

A. Mangili,<sup>1,2</sup> D. H. Murman,<sup>2</sup> A. M. Zampini,<sup>3</sup> and C. A. Wanke<sup>1,2</sup>

<sup>1</sup>Tufts–New England Medical Center, Department of Medicine, Division of Geographic Medicine and Infectious Diseases, <sup>2</sup>Tufts University School of Medicine, Department of Public Health and Family Medicine, Nutrition Infection Unit, and <sup>3</sup>Tufts University Friedman School of Nutrition Science and Policy, Boston, Massachusetts

**Despite major advances in the treatment and survival of patients infected with human immunodeficiency virus (HIV), weight loss and wasting remain common problems. In the HIV-infected population, weight loss is associated with lower CD4<sup>+</sup> cell counts and is an independent predictor of mortality. The etiology of weight loss and wasting is complex and multifactorial. We discuss, on the basis of a large longitudinal cohort that examined nutritional status in HIV infection, data on weight loss and wasting from the present clinical era. The definition, prevalence, and significance of HIV-associated weight loss and wasting are summarized. The etiology of weight loss is discussed for 2 main categories: inadequate nutrient intake and altered metabolism. Finally, studies of interventions to treat HIV-associated weight loss and wasting are discussed. This information is intended to raise awareness among health care providers of HIV-infected patients that weight loss and wasting remain important acquired immunodeficiency syndrome–defining conditions, despite the advent of HAART.**

During the HAART era, HIV infection has become a chronic, manageable disease. Nutrition-related complications remain a challenging issue for HIV-infected patients and for those involved in their care. Involuntary weight loss is associated with disease progression and death, even where access to HAART is not limited [1, 2]. HIV-associated weight loss and wasting were among the most frequently occurring AIDS-defining conditions (ADCs) during the pre-HAART era, but the expectation was that viral control with therapy and prophylaxis for opportunistic infections would eliminate nutritional concerns in HIV-infected individuals [3]. The role that nutritional compromise plays, at present, in the morbidity and mortality of HIV-infected patients is a matter of controversy.

The present article focuses on data published from the Nutrition for Healthy Living (NFHL) cohort, describing weight loss and wasting in HIV disease during the HAART era. NFHL

was a longitudinal study of 881 HIV-infected adults in the greater Boston area from 1995 until 2005. The mean age of NFHL participants was 40 years; 29% were female, and 44% were of nonwhite race. The mean CD4<sup>+</sup> cell count and viral load were 377 cells/mm<sup>3</sup> and 67,000 copies/mL, respectively; 50% of participants were receiving HAART, 38% were receiving a protease inhibitor (PI), and 12% were receiving a nonnucleoside reverse-transcriptase inhibitor regimen; and 53% were current smokers.

## DEFINITION OF HIV-ASSOCIATED WEIGHT LOSS AND WASTING

In 1987, the Centers for Disease Control and Prevention (CDC) included HIV-associated wasting as an ADC; it is defined as an involuntary weight loss of >10% of baseline body weight plus either diarrhea, fever, or weakness for  $\geq 30$  days in the absence of a concurrent illness [4]. Because HIV-associated wasting and weight loss can occur without diarrhea, fever, or weakness—it may be argued that unintentional weight loss in the absence of fever or diarrhea is more troubling—other definitions of wasting in HIV have been crafted. The CDC definition of HIV-associated wasting further assumed that baseline weight, which may have been reported and not measured, rep-

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Reprints or correspondence: Dr. Alexandra Mangili, Tufts University School of Medicine, Nutrition Infection Unit, Jaharis 275, 150 Harrison Ave., Boston, MA 02111 (amangili@tufts-NEMC.org).

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resented the patient's usual or ideal weight. This premise is challenged when considering that HIV-infected patients are seen at varying stages of HIV infection and that "baseline" values may be less meaningful. Additionally, the CDC definition does not take into account the rate of weight loss, which may provide valuable information for the assessment of the need for intervention.

Because of these concerns, 3 definitions for wasting or weight loss of concern were used in the NFHL study: (1) unintentional loss of >10% body weight since study entry, (2) a body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) decreasing to <20, or (3) unintentional loss of >5% body weight in 6 months (between 2 study visits) that persisted for at least 1 year [1]. These definitions attempted to include significant weight loss (>10%), weight loss that was progressive and advanced (BMI, <20), and a rapid rate of weight loss (>5% in 6 months). These definitions may better capture medically important weight loss and provide clinical reference points. Other investigators have attempted to provide cutoff points for lean body mass (LBM) that correlate to wasting parameters, but there are fewer data to support this definition, so it was not used in the NFHL study. It is important to clarify terms that have been used in the literature of HIV-associated wasting and weight loss. "Cachexia" describes a preferential loss of LBM, which implies metabolic derangement rather than a nutrient deficiency [5]. "Wasting" is a less precise term that suggests weight loss due to inadequate nutrient intake [6, 7]. The term has also been used for severe weight loss, but the exact point at which progressive weight loss becomes wasting is problematic. Because of the increasing mean BMI in the HIV-infected population, the NFHL study used a BMI of <20, even though this BMI is on the low side of normal (table 1). Whatever the initial BMI may be, unintentional weight loss may be of concern if it is rapid or substantial, even if the BMI remains within the normal range. The cutoff point for wasting is arbitrary, so we focus on weight loss of concern in the present study.

### PREVALENCE OF HIV-ASSOCIATED WEIGHT LOSS AND WASTING

At the beginning of the AIDS epidemic, severe malnutrition and weight loss were common. Wasting was once described as 1 of the 3 most common ADCs [8]. Even during the HAART era, many NFHL study participants met the criteria for serious weight loss and wasting, despite receiving HAART: 13.9% of 633 participants in the NFHL study met the definition of wasting at the time of study entry [1]. Of the 466 participants with sufficient follow-up data to determine whether wasting had occurred, 18% had a loss of body weight of >10% since the baseline visit, 21% had a loss of body weight of >5% that was sustained for 6 months, and 8% had a BMI of <20. The in-

**Table 1. Definitions of body mass index (BMI) categories used in the assessment of the nutritional status of HIV-infected patients.**

Category	BMI
Malnutrition	≤18.5
Normal weight	18.5–24.9
Overweight	25–29.9
Obesity	≥30

**NOTE.** Body mass index was calculated as weight in kilograms divided by the square of height in meters.

cidence of participants who met at least 1 of the 3 criteria since their enrollment in the NFHL study was 33.5%, and the total prevalence in the cohort was 38%. Both weight loss and wasting were found to occur in those treated successfully with HAART, those for whom HAART failed, and those who were HAART naive. This prevalence of weight loss and wasting has not changed over time; it is as frequent at the present time as it was in 1997 [9].

Using this more-inclusive definition of weight loss of concern (or wasting) resulted in a higher prevalence than that in studies that used the strict CDC definition, which indicates that HIV-associated wasting might have previously been underestimated and underappreciated [10]. The present NFHL data also suggest that the use of HAART has not eliminated weight loss as an issue of concern in HIV-infected individuals.

### SIGNIFICANCE OF HIV-ASSOCIATED WEIGHT LOSS AND WASTING

Although wasting generally refers to a loss of body mass, it has been controversial with regard to HIV infection whether weight loss is primarily a loss of LBM or fat. Similar to previous studies, data from the NFHL study indicated that weight loss consisted principally of fat loss in participants with adequate fat stores when CD4<sup>+</sup> cell counts were <600 cells/mm<sup>3</sup> [11]. Weight loss was found to start early, when CD4<sup>+</sup> cell counts are still >200 cells/mm<sup>3</sup>, a level not usually associated with opportunistic infections. Lower CD4<sup>+</sup> cell counts were associated with lower weight. When NFHL patients were grouped into CD4<sup>+</sup> cell count strata, each 100-cell/mm<sup>3</sup> decrease in CD4<sup>+</sup> cell count was associated with a 1.9-kg lower weight. The difference in weight over CD4<sup>+</sup> cell strata was two-thirds fat body mass and one-third LBM. These results suggest that weight loss in HIV-infected adults is not necessarily a loss of LBM but is a complex interplay of lean body and fat mass, depending on the baseline body weight and composition and the etiology of weight loss.

The use of HAART has led to significant reductions in the morbidity and mortality of HIV infection. Whether HAART could completely alleviate weight loss in effectively treated individuals was examined in the NFHL study. HAART was independently associated with improved survival rates but was

neither a confounder nor an effect modifier in the association between weight loss and death [2]. When all wasting definitions were included, there was a significant increase in the risk of death with each 1% increase in weight loss from baseline weight. Weight loss since the preceding visit had the strongest association with risk of death, compared with loss of fat mass, fat-free mass, or body cell mass as measured using bioelectric impedance analysis. For every 1% increase in weight loss since the preceding visit, there was an 11% increase in the risk of death. Tracking a  $\geq 5\%$  weight loss over a 6-month period or a loss of only  $\geq 3\%$  from baseline weight was a significantly predictor of mortality. When weight loss was  $\geq 10\%$  from baseline weight, the relative risk of mortality was increased nearly 6-fold. BMI was inversely associated with risk of death; individuals with a baseline BMI of  $\geq 25$  had a much lower risk of dying than did those with baseline BMI of  $< 25$ . Weight loss was a stronger predictor of death than loss of LBM.

In an analysis of 619 NFHL participants, health-related quality of life (QOL) questionnaires were administered. In men, but not women, a higher LBM was significantly associated with better physical functioning [12]. Lower LBM was found to be strongly associated with decreased health-related QOL in men but not in women. In men, every 10-kg increase in LBM was associated with 3.7-point increase in physical functioning (on a 100-point scale), a 4.8-point increase in general health perceptions, and 0.9 fewer days spent in bed per month. There was no association between LBM and fatigue. Although there has been the presumption that, if weight loss is associated with morbidity and mortality in HIV infection, then improvements in weight would lead to improved QOL, there have been few data that support this. The NFHL data presented here are therefore important in substantiating this relationship.

Distinguishing HIV-associated wasting from other metabolic complications of HIV infection and its therapies has been challenging. The potential overlap of wasting and fat atrophy remains an open concern and likely will continue to complicate diagnosis of these conditions until better diagnostic criteria are available.

## ETIOLOGY

The etiology of HIV-associated wasting is multifactorial, and causes may include socioeconomic status, access to care, cultural practices, psychological factors, and medical complications of and therapies for HIV infection. For the purpose of the present article, we will categorize these into 2 main categories: decreased nutrient intake and altered nutrient metabolism (table 2).

### Abnormalities in Intake

**Dietary intake.** The diet of patients with HIV infection has evolved with changes in their health status. Dietary studies in

**Table 2. Etiology of weight loss in patients with HIV infection.**

Category, symptom
Inadequate nutrient intake
Oral and upper gastrointestinal
Anorexia
Psychosocial-economic
Malabsorption
Altered metabolism
Uncontrolled HIV infection
Metabolic demands of HAART
Opportunistic infections or malignancies (AIDS-defining conditions)
Hormonal deficiencies (testosterone or thyroid)
Cytokine dysregulation

HIV infection have provided conflicting results regarding the relationship between disease state and nutritional intake. To clarify some of those issues, 3-day food records of 516 participants from the NFHL cohort were analyzed stratified by CD4<sup>+</sup> cell-count categories ( $< 200$ , 200–499, and  $> 500$  cells/mm<sup>3</sup>) [13]. BMI and weight were significantly lower in the low CD4<sup>+</sup> cell count stratum than in the high CD4<sup>+</sup> cell count stratum. In the high CD4<sup>+</sup> cell count stratum, BMI and weight did not differ from those of the general population [14]. Men in the lowest CD4<sup>+</sup> cell count stratum required the highest caloric intake (in kilocalories per kilogram of body weight) to maintain a lower BMI. However, the energy intake per day (in kilocalories per day) did not significantly differ from National Health and Nutrition Examination Survey III data for the same age and sex groups in any CD4<sup>+</sup> cell count stratum. Women in the NFHL cohort seemed to be particularly vulnerable to inadequate dietary intake, which may be explained by their lower socioeconomic status and the large proportion who were former or current intravenous drug users. White men had a significantly higher energy intake than did nonwhite men; white and nonwhite women had comparable energy intakes. The study determined that the intake of micronutrients was also higher at decreased CD4<sup>+</sup> cell counts. Many participants, particularly women, consumed amounts of micronutrients that were less than the dietary reference intakes, despite adequate median intake of micronutrients. More than 25% of woman had inadequate dietary intake of vitamins A, C, E, and B6.

**Relationship between gastrointestinal symptoms and acute weight loss.** According to data derived from phone contacts in between formal study visits, 24% of NFHL participants described at least 1 episode of acute weight loss ( $\geq 5\%$  of weight) [15]. Episodes of acute weight loss were associated with oral symptoms and difficulty swallowing but not with anorexia. Among participants without diarrhea, the use of HAART protected against weight loss. Among those with diarrhea, HAART was not associated with weight loss, which suggests that HAART

itself may be associated with diarrhea. Even in the absence of opportunistic infections, many patients with HIV infection may have HIV- or therapy-related reasons to have gastrointestinal symptoms, which may predispose them to weight loss.

**Malabsorption and gastrointestinal dysfunction.** The severe opportunistic diarrheal illnesses that contributed to HIV-associated wasting in the early days of the epidemic have rarely been seen since the beginning of the HAART era. However, gastrointestinal dysfunction may still play a role in weight loss during HIV infection. A striking 88% of the NFHL cohort had at least 1 abnormality in gastrointestinal function [16]; 47.7% of participants had abnormal D-xylose absorption, which may serve as a surrogate marker of intestinal absorption, and 38.9% reported at least 1 episode of diarrhea within the preceding month. Significantly more men than women had diarrhea. Fat malabsorption was observed in 12.8% of subjects. However, there was no association of diarrhea with any measure of absorption, which suggests that the diarrhea is not primarily caused by malabsorption. These analyses suggest the continued frequency of gastrointestinal dysfunction.

**Correlates of reduced intake.** Groups at risk for adverse clinical outcomes are likely to have reduced dietary intakes. In a cross-sectional analysis of 633 NFHL participants, it was found that, as illness progressed, men “engaged in compensatory eating behaviors,” whereas women did not [17]. When rates were adjusted for dieting, 38.4% of women reported inadequate caloric intake. The absence of a caregiver and the use of injection drugs correlated with a lower protein intake in men. This analysis further showed that the inability to meet recommended dietary allowances was largely the result of socioeconomic rather than clinical factors. Approximately 11.3% of participants had inadequate protein intake. A striking 36.1% of participants were classified as “food insecure” (defined as being unsure where meals in the subsequent 3 days will be obtained). Nearly 8% of the cohort classified themselves as hungry—that is, having insufficient access to intake to satisfy hunger. Analysis therefore concluded that, in HIV disease, “dietary intake reflects the confluence of attitudinal, economic, and lifestyle factors” [p. 860, 17].

## Altered Metabolism

**Relationship between HIV load and body weight.** The precise relationship between the level of or changes in viral load and nutritional status in HIV infection has been unclear. In 38 NFHL participants who were receiving their first PI therapy, those who achieved a decrease in viral load had a significantly greater weight gain per month than did those whose viral load did not decrease [18]. The association between changes in viral load and HIV-associated weight loss was examined in 318 NFHL participants with 1886 study visits [19]. It was found that, for participants who were not receiving HAART, each log<sub>10</sub>

increase in HIV RNA load resulted in a 0.92-kg decrease in body weight. Change in weight was independent of the viral load. The relationship between viral load and weight did not hold in participants receiving a stable HAART regimen; a 0.35-kg decrease in body weight was seen with every 100-cell/mm<sup>3</sup> decrease in CD4<sup>+</sup> cell count. For those individuals who stopped or started receiving HAART, changes in viral load were inversely associated with changes in weight. Changes in both viral load and severity of disease (as measured by CD4<sup>+</sup> cell counts) contribute to changes in weight.

**Increased resting energy expenditure.** In a study to determine the effect of viral load and HAART use on resting energy expenditure, 372 NFHL participants were found to have a 90-kJ/day increase in resting energy expenditure per 1-log<sub>10</sub> copy/mL increase in HIV RNA load and a 339-kJ/day higher resting energy expenditure if they were receiving HAART, compared with those who were not receiving HAART [20, 21]. These results suggest that HIV load and HAART have independent effects on resting energy expenditure and that HAART itself may increase resting energy expenditure. This finding was later confirmed in patients who developed lipodystrophy [22]. Higher metabolic rates may partially account for the continued weight loss and wasting observed in HIV infection during the HAART era and may be associated with the metabolic and body-shape abnormalities seen during the present era [23].

**Role of ADCs.** It was long assumed that weight loss in HIV-infected patients was directly associated with episodes of opportunistic infections or malignancies [24]. A longitudinal analysis of 669 NFHL participants suggested that the increased energy requirements of ADCs contribute in a small way to weight loss [25]. Having had a diagnosis of 1 historical ADC in the past did not predict wasting-related outcomes, but having had >1 historical ADC predicted a 30% increase in developing a BMI of <20. The risk of a 10% weight loss increased 20% with each additional historical ADC. If an ADC occurred in the 6 months preceding a study visit, the risk of weight loss increased to 2.5–8.0 fold. No difference was detected in individuals who met the definition of wasting among those whose conditions progressed to AIDS on the basis of the ADC definition, compared with those whose conditions progressed on the basis of the definition of a CD4<sup>+</sup> cell count of >200 cells/mm<sup>3</sup>. During the HAART era, ADCs were increasingly rare among NFHL participants and were associated with a relatively small risk of developing weight loss or wasting; thus, we are not able to explain the majority of the weight loss seen at present in HIV-infected individuals.

**Inflammatory cytokines and wasting.** Disturbances in the production of inflammatory cytokines have been postulated to influence HIV-associated weight loss. A study of 172 men in the NFHL cohort assessed how catabolic cytokines and testosterone affect LBM [21, 26]. This analysis found that TNF- $\alpha$

**Table 3. Findings of intervention studies of HIV-associated weight loss and wasting during the HAART era.**

Intervention	No. of subjects	Duration of study	Change in body weight	Change in LBM	Change in FFM	Change in muscle strength	Reference
Liquid nutrition supplement plus dietary advice vs. placebo	18 subjects	12 weeks	No significant difference	Significant increase, compared with control ( $P < .05$ )	ND	ND	[27]
Testosterone (100 mg/week) with or without PRE vs. placebo	61 male subjects	16 weeks	Significant increase in both groups, compared with placebo	Significant increase with testosterone with or without PRE	No significant difference, compared with placebo	Significantly greater, compared with placebo, but no difference among measurement groups	[28]
Testosterone (200 mg/week) vs. placebo with or without PRE	54 male subjects	12 weeks	Significant increase ( $P = .005$ )	Significant increase with testosterone ( $P \leq .001$ )	ND	Significantly greater with testosterone but not PRE	[29]
Testosterone (300 µg/day) vs. placebo	52 female subjects	24 weeks	No significant change	NA	No significant difference	No significant difference	[30]
Nandrolone (150 mg biweekly) vs. rhGH (6 mg sc/day) vs. placebo	86 male subjects	12 weeks	NA	Significant increase with nandrolone ( $P < .05$ ), compared with placebo but not with rhGH	Significant increase with nandrolone, compared with placebo but not with rhGH	No significant difference	[31]
Megestrol acetate (800 mg/day) with or without oxandrolone (20 mg/day) and dietary advice vs. placebo	40 subjects	7 months <sup>a</sup>	Significant increase with combination (megestrol acetate plus oxandrolone; $P < .01$ )	Significant increase with combination (megestrol acetate plus oxandrolone; $P < .01$ )	ND	ND	[33]
Oxandrolone (20 mg/day) or PRT vs. nutrition counseling	50 subjects	12 weeks	NA	No significant difference between groups	No significant difference between groups	No significant differences between groups	[34]

**NOTE.** FFM, fat-free mass; ND, not done; PRE, progressive resistance exercise; PRT, progressive resistance training; rhGH, recombinant human growth hormone; sc, subcutaneously.

<sup>a</sup> Megestrol acetate or oxandrolone for 2 months and megestrol acetate plus oxandrolone for 5 months.

and IL-1 $\beta$  from stimulated PBMCs independently predicted loss of LBM and changes in resting energy expenditure but that the level of free testosterone did not. In the present study, catabolic cytokines—not decreased dietary intake or hypogonadism—resulted in a loss of LBM. In a smaller group of 24 NFHL participants, cytokines produced by stimulated PBMCs were more associated with nutritional and metabolic abnormalities than were plasma cytokines [26]. IL-1 $\beta$ , IL-6, and TNF- $\alpha$  levels in PBMCs were best able to discriminate between participants with and without HIV-associated wasting according to the CDC definition. IL-6 and TNF- $\alpha$  from plasma were increased in participants with wasting, but these could not reliably distinguish between participants with and without wasting.

## INTERVENTIONS TO TREAT WEIGHT LOSS AND WASTING

In the early days of the HIV epidemic, multiple studies addressed interventions in weight loss. There have been few studies done in the present era (table 3) [27–32]. We briefly summarize intervention studies conducted by NFHL investigators. In a randomized clinical trial of 40 participants who entered the study with a BMI of 21, the effects of megestrol acetate on body weight and composition were compared with those of oxandrolone [33]. A mean weight gain of 2.8 kg over the course of 2 months was found in the group that received megestrol acetate, compared with a 2.5-kg mean weight gain in the group that received oxandrolone. LBM increased 39% with megestrol acetate and 56% with oxandrolone. Both were effective in increasing weight in participants with HIV-associated weight loss and resulted in a significant increase in LBM. An improvement in BMI was associated with a higher QOL. Fifty NFHL participants with HIV-associated wasting were studied in a trial that compared oxandrolone and strength training with nutritional intervention alone [34]. It was found that both treatment arms resulted in an improvement in body composition but that results did not significantly differ from those in participants treated with nutrition alone. Strength training was associated with the highest improvement in QOL and had the lowest intervention cost. Thus, it is possible for an HIV-infected patient's weight and BMI to return to a normal range and, thus, to improve the QOL. These interventions should be individualized and focused on the likely etiologies of weight loss in that patient.

## CONCLUSIONS

NFHL data have suggested that HIV-associated weight loss is common in persons with HIV infection, regardless of whether HAART is used, and that it appears to have a multifactorial etiology. Weight loss was found to start early in disease, before any significant compromise in immune status. Increased caloric

demands and intake of people with HIV infection may be attributed to their HIV disease and its complications, but they may also be associated with HAART. Inadequate dietary intake may be associated with socioeconomic or medical factors. Gastrointestinal dysfunction remains common in persons with HIV infection. The occurrence of ADCs increases the risk of wasting; however, it appears that ADCs are not the major cause of wasting in people with HIV infection. A higher LBM in men with HIV infection is associated with a higher QOL. It is likely that nutritional issues will remain clinically important in HIV infection, especially as the impact of HIV is being assessed globally. Lessons learned from NFHL and other studies of weight loss and wasting in HIV should be applied in the international setting for the development of appropriate targeted nutritional interventions as HAART is being implemented worldwide. There are multiple effective treatments of HIV-associated weight loss and wasting, and interventions should be individualized for each patient.

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