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Polsky Bruce, Kotler Donald & Steinhart Corklin

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Treatment Guidelines for HIV-Associated Wasting

Bruce Polsky, MD,¹ Donald Kotler, MD,² and Corklin Steinhart, MD, PhD³

¹Vice Chairman, Department of Medicine, Chief, Division of Infectious Diseases, St. Luke's-Roosevelt Hospital Center, New York, New York, USA; ²Professor of Medicine, Columbia University College of Physicians and Surgeons, St. Luke's-Roosevelt Hospital Center, New York, New York, USA; ³Medical Director, Florida AIDS Education Training Center, University of South Florida, Mercy Hospital, Miami, Florida, USA

INTRODUCTION

During the early years of the AIDS epidemic, HIV-associated wasting was a highly visible sign of the disease's devastating effects. The gaunt appearance of some patients was quite stigmatizing, making it more difficult for them to deal with their disease and its consequences.

Since highly active antiretroviral therapy (HAART) was not available at this time, clinicians and patients were frustrated by the lack of therapeutic options.

Today, HIV disease has come almost full circle, and is now considered by many to be a manageable chronic condition. HAART has provided dramatic reductions in hospitalization and mortality rates. It has also increased the quality of life for many individuals living with this disease. Unfortunately, new advances in therapies have also brought a host of complications, many of which affect body habitus. Fat redistribution syndromes have created a new stigma associated with these emerging side effects of therapy.

Throughout all of these advances in HIV care and treatment, HIV-associated wasting still exists, often masked by many of the morphologic changes brought about by HAART. Today, patients with HIV disease may not be aware they are experiencing wasting, and their clinicians may not recognize the problem. Since HIV-associated wasting has a

significant impact on mortality and quality of life, early diagnosis and treatment are imperative.

The diagnosis of wasting is best achieved by using bioelectrical impedance analysis (BIA) to measure changes in body cell mass (BCM). This necessary evaluation, combined with the proper clinical assessments (history and physical, psychosocial evaluation, laboratory tests, dietary evaluation), allows for the confirmation of a wasting diagnosis. General patient management consists of concurrent interventions to control viral load, correct any immediate causes of wasting, address psychosocial issues, improve nutritional intake, and treat anorexia.

Specific treatments for HIV-associated wasting are always individualized according to the patient's needs. Male patients who are hypogonadal often benefit from testosterone replacement therapy. Recombinant human growth hormone is indicated in patients with normal testosterone levels, female patients, and in male patients for whom testosterone therapy does not give the desired results. Other therapeutic interventions may also be used, such as anabolic steroids, progressive resistance exercise, nutritional supplements, and cytokine modulation. Once therapy is effective, expected clinical outcomes include the replacement of lost body cell mass and weight; improved physical capabilities, quality of life, and physical appearance; decreased frequency of opportunistic infections, hospitalizations, and related complications; and improved survival.

Nearly 20 years into the AIDS epidemic, clinicians and payers continue to struggle with the clinical management of what has become, for

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many, a chronic, manageable disease state. With the continuous refinement of HAART regimens, the frequent utilization of inpatient hospital services has decreased dramatically. Today, the patient with HIV infection may be effectively managed in the outpatient and office settings.

As the paradigm of patient care has shifted, emerging issues have surfaced. One of these is the frequently overlooked complication known as HIV-associated wasting. Although the incidence has decreased since the early years of the epidemic, HIV-associated wasting still occurs. Often, it is masked by complications associated with HAART, specifically the fat redistribution syndromes (lipodystrophy). Since HIV-associated wasting is a serious, debilitating, and sometimes life-threatening condition, clinicians must be vigilant to its presence, identify it early, and treat it appropriately.

The clinical definition of HIV-associated wasting and its appropriate treatment are not well understood, creating confusion for clinicians and payers alike. Various therapies have different efficacies and variable costs. Without fully understanding the condition and its appropriate interventions, both parties may find it difficult to justify the appropriate use of such treatments. Clearly, education on the clinical and reimbursement issues associated with HIV-associated wasting is needed in order for patients to receive and benefit from the most effective therapies.

With this in mind, a Consensus Development Panel met in New York City, NY, July 26, 2000, to discuss the issues associated with HIV-associated wasting from a clinical and reimbursement standpoint. Specifically, the Panel met to achieve the following objectives:

- Review the incidence of HIV-associated wasting in the HAART era;
- Define HIV-associated wasting in patients receiving HAART;
- Identify the most accurate methods for diagnosis;
- Review assessment approaches for initial and ongoing management;
- Analyze currently approved therapies from clinical and cost-effective standpoints; and
- Develop treatment recommendations.

The following guidelines have been specifically designed to benefit reimbursement professionals who are faced with decisions regarding coverage for therapies to treat HIV-associated wasting. The

Panel hopes these guidelines will assist them when making the important decisions that affect patient care.

HISTORY OF HIV-ASSOCIATED WASTING

Early Case Definition

HIV-associated wasting is a primary manifestation of HIV infection. Wasting consists of involuntary loss of usual body weight, reflecting the significant depletion of body cell mass.^{1,2} Wasting was declared an AIDS-defining illness by the Centers for Disease Control and Prevention (CDC) in 1987. The CDC defines wasting as the involuntary loss of at least 10% of ideal body weight with associated symptoms of chronic fever, weakness, or diarrhea in the absence of other related illnesses that could contribute to the weight loss.³

Impact on Morbidity and Mortality

Wasting is associated with significant morbidity and mortality. Death occurs when a person reaches 66% of ideal body weight or 54% of lean body mass (LBM).⁴ Patients with HIV-associated wasting have a decreased rate of survival independent of other risk factors.⁵⁻⁷ Such patients are also at increased risk for hospitalization and decreased quality of life.^{8,9} As little as 5% weight loss is associated with mortality and the development of opportunistic infections, even after controlling for CD4 cell counts and other prognostic parameters.¹⁰

HIV-ASSOCIATED WASTING IN THE HAART ERA

An Overlooked and Underdiagnosed Condition

With an expanding list of approved and experimental treatments, new complications have emerged from the use of HAART.¹¹ These include abnormal fat accumulation (lipohypertrophy), lipoatrophy, dyslipidemia, insulin resistance, diabetes, life-threatening lactic acidosis, and osteopenia. The shift in attention to these complications has overshadowed the fact that HIV-associated wasting occurs in patients today despite the use of HAART. In addition, the development of fat redistribution clearly makes wasting more difficult to diagnose. Patients with wasting do not always

display the characteristics that were so typical of the wasting syndrome observed during the pre-HAART era.

Today's patient with HIV-associated wasting may be maintaining adequate virologic control and immunologic indices. When patients do gain weight on HAART, it is primarily fat with no change in lean body mass.¹² They may, for example, still have abnormal fat accumulation, such as dorsocervical fat deposits and/or visceral adiposity.¹³⁻¹⁶ The diagnosis should also include other factors such as gender and psychosocial issues. These include depression, anxiety, substance use, income, access to food, and the home environment.

Incidence of HIV-Associated Wasting in the HAART Era

The most recent evidence of wasting in patients receiving HAART comes from baseline and prospective data analysis of a large cohort of HIV-infected individuals (N=633) who are participating in the Nutrition for Health Living (NFHL) longitudinal study.¹⁷ Begun in 1995, the NFHL has conducted nutritional and health assessments at baseline and then every six months on men and women who are enrolled. Monthly telephone calls collected information on health status, current weight, and changes in medications. Three definitions of HIV-associated wasting were applied to the cohort. At the time of their enrollment in the cohort, 88 individuals (13.9%) reported wasting at baseline. This group was not analyzed further. Of the remaining 466 men and women, 156 (33.6%) met at least one or more of the three criteria for wasting.

Relationship Between HAART and HIV-Associated Wasting

The study also examined the use of HAART and the development of wasting in the 633 individuals enrolled in the entire cohort. Of these, 422 (67%) subjects had used HAART, consisting of a protease inhibitor (PI) and two nucleosides (NRTIs), at some point in time. Of the remaining 211 subjects who had never used HAART, 16 (7.5%) reported wasting at the time of their study enrollment, 37 (17.0%) had insufficient follow-up data to determine wasting, and 41 (25.9%) met at least one of the wasting definitions during the course of the study.

Within the group of 422 subjects who had used HAART at some point in time, 72 (17.2%) reported wasting at the time of their study enrollment, 22 (5.2%) had insufficient follow-up data to determine wasting, and 95 (28.9%) met at least one of the wasting definitions during the course of the study. Of the 64 individuals who were not receiving HAART at the time of study entry and who met at least one wasting definition during the course of the study, 31 (48.4%) did so after starting HAART therapy. Therefore, HIV-associated wasting can occur in patients who are treatment-naïve, actively being treated with HAART, or who are already HAART-experienced.

Distinguishing Between HIV-Associated Wasting and Lipotrophy

When examining weight loss in patients with HIV infection, it is often difficult to determine if they are losing lean body mass or fat mass. A separate analysis of 497 cohort patients from the NFHL longitudinal study found 289 individuals (58%) had lost >1.5 kg between any two study visits six months apart. In this group, the mean weight loss was 4.0 kg. Using bioelectric impedance analysis (BIA), 1.3 kg of this weight loss was lean body mass, while the remaining 2.7 kg was fat mass.

The type of tissue lost during HIV-related wasting depends on the patient's existing percentage of body fat. In general, patients who have body fat >15% will preferentially lose more fat than lean body mass. Those patients with an initial body fat percentage of <15% will have lean body mass as the predominant tissue loss.¹⁸ Although distinguishing between actual HIV-associated wasting and lipotrophy can be difficult, some general guidelines serve as reference points to distinguish between the two.

The Impact of Wasting in the HAART Era

As noted above, associated wasting occurs even in patients on HAART.^{17,19-21} Loss of body cell mass still takes place in patients who receive protease inhibitors. Although many clinicians believe patients gain weight after receiving HAART, no placebo-controlled trials demonstrate such weight gain.²² In addition, there is no correlation between increased body weight changes and improved viral load.^{23,24}

The diagnosis of wasting has become more confusing in the wake of other morphologic complications associated with HAART. For example, patients can have both wasting and fat redistribution, in the form of lipoatrophy or lipohypertrophy, at the same time. Many clinicians do not include wasting in their routine diagnostic evaluation of patients, do not obtain and record weight histories, and do not monitor body composition. Consequently, often wasting is simply overlooked.

When wasting is severe, it can be quite stigmatizing to the patient. However, one should not view HIV-associated wasting as solely a cosmetic issue. Since it involves the loss of lean body mass, body cell mass, and skeletal muscle, it can have deleterious and sometimes life-threatening physiologic effects. These include the following:

- increased weakness;
- decreased physical functioning;
- decreased quality of life;
- impaired immune functioning;
- increase in disease complications; and
- decreased survival.

HIV-associated wasting is an important disease marker, with the magnitude of weight loss related directly to the risk of death for the patient.⁵ The loss of lean body mass and body weight are associated with poorer survival rates in end-stage AIDS.^{4,5} Moderate-to-severe weight loss, before the onset of other symptoms, predicts decreased survival after the onset of symptomatic AIDS.⁷ Given the significance and impact of HIV-associated wasting in the post-HAART era, clinicians need to assess patients effectively for signs of wasting and treat the condition with proven therapies and interventions.

MEASURING BODY COMPOSITION

The Importance of Body Cell Mass

In order to accurately diagnose HIV-associated wasting, clinicians need to evaluate more than the total body weight of the patient. Total body weight may not change for years after a diagnosis of HIV infection. At the same time, however, body composition changes may be occurring even while the patient is asymptomatic. As lean body mass decreases, it is usually replaced by water and fat. After body cell mass reaches a value of 54% of normal, death ensues.⁴ It is particularly important to remember that patients may show signs of wast-

ing even when their body weight remains unchanged. As such, assessment of body cell mass is key to prevention, early intervention, and the monitoring of responses to treatment for HIV-associated wasting.

Bioelectrical Impedance Analysis

Bioelectrical impedance analysis (BIA) is the preferred method for assessing body cell mass depletion, even in the presence of normal weight.²⁵ BIA can be easily performed with portable equipment in the office setting, involves no radiation, is inexpensive, painless, and has a high degree of accuracy. A low-level current of 800 microamps is introduced into the patient, and voltage changes are recorded via electrodes attached to their hands and feet. Lean tissue contains most of the body's conducting electrolytes, and therefore, conducts electric current more readily than fat tissue, which has a lower water content. The numerical results of BIA are combined with the patient's other statistics (height, weight, sex, and age) to calculate body cell mass, fat-free mass, and other body composition measurements.

Body cell mass consists of metabolically active tissue, which includes muscle tissue, organ tissue, and intracellular water.²⁶ Body cell mass is a component of lean body mass, which also includes extracellular water and bone tissue. Therefore, it is important to remember that lean body mass contains more than just muscle.

BIA is the most accessible, reliable, efficient and accurate test for measuring body cell mass. Not all BIA machines use the same software. Differences among machines and methodologies can result in calculations that can vary by as much as 10%. BIA results may also be affected by the patient's level of hydration. As such, BIA is much less reliable for measuring fat mass. BIA is most effective as an ongoing assessment tool to longitudinally measure changes in body composition.²⁷

DEFINITION OF HIV-ASSOCIATED WASTING

Clearly, the early CDC definition of wasting was useful for epidemiological purposes. Its clinical utility, however, is questionable. Not all patients with wasting have associated symptoms, such as diarrhea or fever. Since the CDC definition was developed in 1987, there has been much debate

regarding an expanded definition for HIV-associated wasting that will be useful in the clinical setting. Such a definition needs to take into account cultural and sex differences. For example, early studies of men focused on the loss of lean body mass and muscle wasting. We know today that women lose more fat than lean body mass. Substantial depletion of lean body mass does occur, however, in women with advanced HIV disease who have a body weight <90% of ideal weight.²⁸

Developing a clinical definition of HIV-associated wasting became an important charge of the Consensus Development Panel. After taking into account body composition changes in the era of HAART, cultural and sexual differences, and the changing nature of wasting, the Panel developed and proposed a definition of HIV-associated wasting which can be applied and used in the current clinical setting.

ASSESSMENT PROTOCOL FOR PATIENTS WITH HIV-ASSOCIATED WASTING

Initial Evaluation and Diagnosis

1. History and physical examination

During the initial evaluation of a patient for HIV-associated wasting, the clinician should perform a thorough and complete history and physical examination. The physical examination must be performed with the patient completely undressed. This way, the clinician can ascertain signs of wasting (abdominal, gluteal, and limb atrophy) that may be hidden by clothing. The physical examination should also rule out any concomitant infections or other medical problems.

During the intake history, the clinician should ask a variety of questions designed to determine an initial impression of the patient's nutritional status, caloric intake, appetite, and gastrointestinal and physiological functioning. Suggested questions may include the following:

- Have you noticed any weight loss?
- Has your appetite changed?
- Have you developed diarrhea?
- Are you feeling weaker and more fatigued than normal?
- Are you having trouble getting around performing daily activities?

Using the patient's answers to these questions, the clinician will be able to formulate a working diagnosis of HIV-associated wasting and its potential causes.

2. Body composition measurements

The following measurements should be taken and calculated related to body composition:

- Age
- Height
- Weight
- Ideal body weight
- Body cell mass (by BIA)
- Body mass index (BMI)

3. Laboratory tests

The laboratory evaluation of the patient should include the following tests:

- Plasma HIV RNA
- CD4 cell count
- Serum testosterone (free and total)
- Serum albumin (as clinically warranted)
- Thyroid function tests (as clinically warranted)

4. Psychosocial evaluation

During the initial evaluation of the patient, the clinician also needs to rule out any psychiatric disorders that might interfere with the patient's ability to eat. For example, anxiety and depression are known causes of anorexia. They are often present in patients with HIV infection. Feelings of anxiety or depression can escalate in the presence of opportunistic infections such as oral thrush, or in the presence of symptoms such as diarrhea.²⁹ Functional status should also be assessed.³⁰

5. Dietary Assessment

Optimally, all patients suspected of having HIV-associated wasting should be referred to a competent registered dietician or nutritionist who is experienced with these patients. Such a referral will refocus a patient's attention on eating properly and selecting the appropriate foods.³¹ The dietician should perform the following assessments on the patient:

- Evaluate intestinal function;
- Review food intake and caloric values; and
- Estimate physical activity level.

The clinician should maintain the relationship with the registered dietitian during subsequent patient visits and throughout the course of treatment.

Follow-Up Visit

Once all laboratory test results are completed and the evaluation by a registered dietitian has been conducted, the patient should return to the clinician for a follow-up visit. During this visit, the clinician should conduct the following activities with the patient:

- Review all laboratory test results;
- Discuss all current medications, including antiretroviral therapy;
- Readjust antiretroviral therapy, as required, based on laboratory evaluation;
- Provide follow-up for any identified medical or psychiatric problems;
- Review the registered dietitian's evaluation of the patient;
- Discuss therapeutic options for HIV-related wasting; and
- Initiate therapy if indicated.

Ongoing Subsequent Visits

Once treatment for HIV-associated wasting has been initiated, the patient should be scheduled for return visits with the clinician every three months or as directed by current symptoms. This is similar to the standard follow-up evaluation recommended for patients on HAART. At these subsequent visits, the clinician once again needs to perform many of the activities first conducted during the initial visit. These include the following:

- Perform an interval history and physical examination with the patient undressed;
- Measure serial body weights and body composition parameters (body cell mass) using bioelectrical impedance analysis (BIA);
- Monitor antiretroviral therapy and adjust as necessary;
- Assess any ongoing medical or psychiatric problems in consultation with outside specialists;
- Maintain patient's relationship with registered dietitian as needed; and

- Measure total and free testosterone on an annual basis or more often as clinically necessary.

It is important to note that the optimal treatment strategies for HIV wasting have not been established. Treatment should be individualized. Patients should be given all their options and allowed to make an informed choice. Selecting the best treatment option must also take into consideration the patient's previous compliance history, as well as the payer source. Clinicians are encouraged to work with the patient's insurance carrier in order to provide reimbursement professionals with ongoing education about this condition and the clinical rationale for recommended treatment options.

GENERAL PATIENT MANAGEMENT PROTOCOL

Address Issues Concurrently

Treatment of all patients with HIV-associated wasting should begin with the clinician implementing five general patient management interventions. In some cases, once these situations are corrected, body cell mass may be restored. Many of these interventions are designed to address the underlying conditions that may contribute to a patient's wasting. All five of these interventions must be addressed concurrently and not in a step-wise fashion.

1. Control viral load and maximize immune competence

As a general standard-of-care, the clinician needs to make certain the patient is maintaining good virologic control on their existing antiretroviral regimen. Optimally, this means the patient should have plasma HIV RNA <50 copies/mL. In addition, the clinician needs to identify any HIV-associated morphologic or metabolic abnormalities. This means distinguishing fat redistribution syndrome from true HIV-related wasting. Adjustments to antiretroviral regimens may be required in order to maintain virologic control and adequate adherence, as well as to minimize the incidence of complications. It is important to remember, however, that an effective HAART regimen may not adequately correct the continued loss of body cell mass in patients with HIV-related wasting.

2. Correct any immediate causes of HIV-related wasting

The clinician also needs to make certain that the patient receives appropriate treatment and interventions for any immediate causes of wasting. Such causes include various opportunistic infections, HIV-related malignancies, diarrhea, and gastrointestinal infections.

3. Address any psychosocial issues or lifestyle-associated situations

A patient with HIV-associated wasting needs to be treated for any underlying psychiatric disorders, such as anxiety or depression. In addition, the clinician needs to address possible lifestyle-associated situations that may interfere with adequate nutritional intake or treatment regimens. For example, the patient may need financial assistance in the form of food stamps or other interventions in order to purchase healthy food. Other patients with transportation difficulties may need assistance in the form of Meals-on-Wheels programs or weekly grocery store deliveries.

4. Improve nutritional intake

HIV-associated wasting may be due, in part, to a patient's poor nutritional intake. Taking appropriate action to improve a patient's intake of food and calories is a critical first step to ensure the success of subsequent therapeutic interventions. This is where the expert consultation of a registered dietitian is invaluable. Improving nutritional intake may take one of several forms, including the following:

- Ensuring that caloric intake is adequate to meet the high metabolic demands of HIV infection;
- Prescribing high-protein, low-fat diets;
- Maximizing the intake of high-calorie, nutrient-dense foods;
- Increasing vitamin supplementation (e.g., A, E, B6, B12, zinc); and
- Providing nutritional supplementation (e.g., oral food supplements, glutamine, enteral nutrition, total parenteral nutrition)

5. Treat anorexia

Various appetite stimulants may be used to increase appetite in patients who have inadequate caloric intake.^{22,32–36} Such agents typically increase a patient's weight in the form of increased fat, with limited gains in lean body mass. The clinician should not rely on appetite stimulants as the only intervention in patients with HIV-related wasting.

TREATMENT OF HYPOGONADAL PATIENTS

Testosterone Replacement Therapy

After the earlier interventions have been implemented in a patient with HIV-associated wasting, specific therapies can be started. If the patient is male and hypogonadal, the Panel recommends replacement therapy with testosterone, which has been shown to increase lean body mass and muscle strength in patients with HIV infection who are hypogonadal.^{37–40}

When used in conjunction with progressive resistance exercise, testosterone produces positive changes in arm and leg muscle mass.⁴¹ Therapy does not affect a patient's viral load or CD4 cell counts. Although there are very few controlled trials, testosterone replacement therapy is generally considered safe. Its main adverse effect is the reduction of HDL cholesterol. Other potential side effects in men include acne, hair loss, dyslipidemia, sleep apnea, and prostate changes. A digital rectal exam (DRE) and prostate-specific antigen (PSA) test should be performed prior to initiating therapy. Once treatment has been started, PSA testing is performed every 3 to 6 months. Testosterone may be administered either by the intramuscular or transdermal route. Similar doses are used as for HIV-negative men. Currently, the optimal replacement doses or modes of administration are not known for men with HIV infection and wasting who are hypogonadal.

After testosterone replacement therapy is initiated, the clinician should reassess the patient for increases in body cell mass after four weeks of therapy. Laboratory samples for serum total and free testosterone levels can also be taken at this time.

TREATMENT WITH RECOMBINANT HUMAN GROWTH HORMONE

Efficacy in Patients with HIV-Related Wasting

Recombinant human growth hormone (Serostim®) is an effective treatment for patients with HIV-associated wasting. Randomized, placebo-controlled clinical trials of recombinant human growth hormone demonstrate increases in lean body mass and protein synthesis, and decreases in urinary nitrogen excretion).^{42,43} In addition, patients receiving growth hormone also experience increased work performance, decreased body fat, increased body weight, and an improvement in their overall quality of life. Gains in lean body mass from treatment with growth hormone are also associated with improved survival in patients with HIV-associated wasting, independent of CD4 cell count and viral load.⁴⁴

In a 12-week trial of recombinant growth hormone, enrollment consisted of 178 patients with HIV infection and weight loss.⁴² Participants had either documented unintentional weight loss of at least 10% or a weight of less than 90% of the lower limit of ideal body weight. They received either recombinant human growth hormone or placebo. Dosing was 0.1 mg/kg of body weight per day, with an average dose of 6 mg/day.

At week 12, there were significant and sustained increases in weight and lean body mass among patients receiving growth hormone. There were no reported net changes in weight for patients in the placebo group. At week 12, the average increase in lean body mass was nearly twice that of the increase in body weight. Growth hormone also produced significant decreases in body fat, which remained unchanged in the placebo group. When study participants were evaluated on their work output while walking on treadmills with increasing workloads, patients receiving growth hormone displayed greater increases in treadmill work output.

The usual dosage of recombinant human growth hormone in these patients is 6 mg/day. Patients have reported mild-to-moderate side effects, including skin turgor, edema, arthralgias, myalgias, and increases in blood glucose concentrations and glycosylated hemoglobin values. Such side effects tend to resolve when the dose is reduced or the drug is temporarily discontinued.

Initial Treatment with Recombinant Human Growth Hormone

The Consensus Development Panel also reviewed best practice recommendations in order to guide clinicians on the use of growth hormone to treat HIV-associated wasting. If the patient meets the definition of wasting, an initial 12-week course of therapy is indicated. The clinician should document the response to therapy by obtaining serial body weights and body cell mass assessments. Treatment may continue on a monthly basis if there has been a positive response to therapy (2% increase in body weight and/or body cell mass) and wasting is still evident.

Indications for Stopping Therapy and Retreatment

Once body cell mass stores are normalized, the clinician can stop growth hormone therapy and observe the patient for an 8-week period. During this time, the clinician needs to monitor body weight, body cell mass, and the clinical symptoms of wasting. If, after eight weeks, clinical signs of wasting reappear, retreatment with growth hormone may be started.

TREATMENT WITH ANABOLIC STEROIDS

Nandrolone Decanoate (Deca Durabolin®)

Nandrolone decanoate is an injectable anabolic steroid. It has been studied in a 16-week, open-label study given at a dose of 100 mg IM every 2 weeks. Subjects who had lost 5% to 15% of their body weight demonstrated a mean weight gain of 2.24 kg and an increase in lean body mass of 3.0 kg.⁴⁵ Quality of life also improved. Two other studies, one of which was placebo-controlled, also demonstrated increases in average weight gain and lean body mass.^{46,47}

Oxandrolone (Oxandrin®)

Oxandrolone is an oral anabolic steroid. It has been studied alone and in combination with progressive resistance exercise (PRE) in men with HIV-related wasting.^{48,49} When used alone, oxandrolone produces increases in average weight gain and lean body mass. In the study involving

the use of PRE, subjects receiving oxandrolone alone had an average weight gain of 2.7 kg. Those who combined oxandrolone with PRE had an average weight gain of 3.9 kg.

Use of Anabolic Steroids in Women

Although androgen deficiency does occur in women with HIV infection, its contribution to wasting in these individuals is not known.^{28,50} Low doses of testosterone have been safely used in androgen-deficient women with HIV infection and wasting.⁵¹ Of the anabolic steroids currently in use, oxandrolone is probably the safest to use in women. When used in women, anabolic steroids produce weight gain, primarily in the form of fat.⁵²

Unanswered Questions Regarding the Use of Anabolic Steroids

The use of the above anabolic agents may be sufficient to reverse the effects of HIV-associated wasting. Although these agents may increase lean body mass, their long-term safety and efficacy remain unknown. Clinicians should monitor long-term side effects and drug-drug interactions when using these agents. In patients with liver disease, they should be avoided altogether or used very cautiously as they can cause liver dysfunction.

However, there remains a great deal of uncertainty regarding their clinical use in this population of patients. Several important issues remain which will require additional investigation. Among these are the following:

- There is a lack of long-term efficacy and safety in placebo-controlled trials.
- Anabolic steroids have the potential for liver toxicity and for the enhancement of neoplastic growth of the prostate.
- Studies of anabolic steroids in women are lacking.
- Dosing and maintenance regimens remain unknown.
- There is a lack of data as to which agents are the most effective.

Finally, it should be noted that anabolic steroids have not received FDA-approval for the treatment of AIDS-related cachexia. Megestrol acetate (Megace®) and recombinant human growth hormone (Serostim®), however, have received FDA approval for this indication.

ADJUNCTIVE TREATMENTS AND INTERVENTIONS

Progressive Resistance Exercise (PRE)

A number of studies have examined the benefits of progressive resistance exercise (PRE) in patients with HIV infection.^{53–56} In these studies, patients participated in six- or eight-week programs consisting of progressive resistance training three-times-a-week. Participants experienced increased muscle function and strength in their arms and legs, as well as increased weight and lean body mass. These studies suggest that supervised progressive resistance exercise and fitness training have a positive influence by increasing lean body mass and muscle strength.

Nutritional Supplements

Regardless of the treatment selected for HIV-associated wasting, all patients should maintain appropriate caloric intake. High-calorie, nutrient-dense foods in the form of supplements may assist with this purpose. Enteral feedings should be reserved for patients with mechanical obstructions who have intact gut function. Such feedings have been shown to increase total body potassium, an index of body cell mass.⁵⁷ Total parenteral nutrition (TPN) is rarely used today in patients with HIV infection. Patients with evidence of malabsorption in the form of intractable vomiting or diarrhea, however, may be candidates for TPN. Those patients with malabsorption alone may respond more favorably to TPN than those patients who have active secondary illness.^{58,59}

Cytokine Modulation

Cytokine modulators, specifically thalidomide and pentoxifylline, have been studied for the treatment of HIV-associated wasting. The role of inflammatory cytokines in wasting is not completely known. It has been hypothesized that the increased production of cytokines, such as tumor necrosis factor (TNF), may result in increased energy expenditure and wasting.⁶⁰ Three studies of thalidomide in patients with and without wasting have shown increases in body cell mass and extracellular fluid, and decreases in urinary nitrogen excretion.^{61,62} Half the weight gain was fat-free mass as measured

by BIA. The most recent study of thalidomide in patients with wasting demonstrated significant weight gain with doses of 100 mg or 200 mg/day after 8 weeks.⁶³ Neither thalidomide nor pentoxifylline has been approved for the treatment of HIV-associated wasting.

EXPECTED CLINICAL OUTCOMES AND CONCLUSIONS

Clinical Outcomes

Patients who meet the definition of HIV-associated wasting can expect a number of beneficial clinical outcomes from therapy. These include the following:

- Replacement of lost body cell mass and weight;
- Improved physical capabilities and quality of life;
- Improved physical appearance;
- Decreased frequency of opportunistic infections, hospitalizations, and related complications; and
- Improved survival.

Conclusions

HIV-associated wasting remains an important complication in patients receiving highly active antiretroviral therapy. The use of HAART, however, does not eliminate HIV-wasting. Clinicians must pay careful attention to changes in body weight, body cell mass, and body habitus in order to accurately diagnose and manage this condition. This includes examining the patient undressed and utilizing body composition analysis on a regular basis.

Early and aggressive intervention is required in patients who display depletion of body cell mass. Clinicians need to utilize the expert consultation of a dietitian or nutritionist who is experienced with this patient population. Ongoing evaluation is critical once therapy is initiated.

Management strategies for all patients with HIV-associated wasting must be implemented concurrently. These strategies consist of controlling viral load, maximizing immune competence, correcting any immediate causes of wasting, addressing any psychosocial issues, improving nutritional intake, and treating anorexia. If wasting still persists after

these interventions have been implemented, specific therapies may then be undertaken. These include testosterone replacement therapy in patients who are hypogonadal and the use of anabolic agents, including recombinant human growth hormone in non-hypogonadal men and women. Treatment with growth hormone results in increases in lean body mass and improved survival in patients with HIV-associated wasting. Other strategies, such as progressive resistance exercise, should be tried on an individual basis. At the moment, optimal evidenced-based algorithms for treating HIV-associated wasting have not been established.

Future directions for research need to center on the following questions:

- What is the best monotherapy or combination anabolic agent therapy (i.e., “wasting cocktail”?)
- What is the role of maintenance therapy and retreatment?
- What are the stages of wasting?
- Can therapy be tailored to a specific stage?
- What is the cost-effectiveness of various therapies and interventions?
- What are the long-term safety issues of these therapies?

Clearly, additional studies will be required to answer these important questions. In the meantime, clinicians and payers need to work together in order to maximize the availability and reimbursement of treatment options for patients with HIV-associated wasting. It is the hope of the Consensus Development Panel that this document will provide the necessary information so that payers can make informed decisions regarding treatments for HIV-associated wasting and work effectively with clinicians treating these patients.

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