Historically, wasting syndrome has been described in association with opportunistic infections and/or AIDS-related malignancies. In 1987, the Centers for Disease Control and Prevention defined wasting syndrome as involuntary weight loss (of >10% from baseline) accompanied by chronic diarrhea, documented fever for more than 30 days, and asthenia. This definition included signs of secondary infection during which wasting frequently occurred. However, the progressive and involuntary loss of both lean body mass and adipose tissue (fat mass) is the condicio sine qua non of wasting syndrome. The onset of wasting syndrome continues to be an AIDS-defining event.
Despite the dramatic impact of highly active antiretroviral therapy (HAART) on the progression of HIV infection and CD4+ T-lymphocyte recovery, wasting syndrome is still described in a significant number of patients under care. The syndrome can now be seen among patients with limited access to HAART and patients with advanced AIDS (in the setting of multidrug-resistant HIV infection), and in patients on stable HAART often without underlying opportunistic infections or malignancies.

**Epidemiology**

Recent studies among outpatients document incidence rates of wasting as high as 10.6 per 100 patient-years. An observational study documented a 33.6% incidence of wasting despite the fact that more than 70% of the patients had CD4+ T-cell counts of ≥200/mm³ (24% of the patients had CD4+ T-cell counts >500/mm³). Moyle et al reported that 66.5% of treatment-evaluable patients who demonstrated wasting had baseline viral loads of less than 400 copies/mL.

Early in the epidemic, investigators demonstrated that the degree of weight loss or wasting is independently associated with mortality. Today, the risk of opportunistic infection is significantly increased among patients demonstrating weight loss, and wasting remains linked to mortality despite patient response to HAART. Loss of lean body mass (LBM) and fat mass, as a consequence of wasting, may lead to social isolation and depression, creating an obstacle to therapeutic adherence.

**Etiology**

The etiology of wasting syndrome in a given patient is multifactorial. Wasting syndrome may be driven by decreased nutrient intake or assimilation and/or endocrine dysfunction. Abnormalities of nutritional metabolism include increased resting energy expenditure, diminished mixed muscle protein synthesis as a percentage of whole body protein synthesis, inappropriate de novo lipogenesis, and the futile cycling of lipids resulting in partial loss of the energetic value of nutrient intake.

Reduced food intake due to anorexia is a prominent predictor and mediator of wasting syndrome, often despite the constitutional compensation of lethargy (which attempts to bring total energy expenditure into balance with energy intake). Contrary to uncomplicated starvation, decreased nutrient intake in the setting of HIV infection is not accompanied by compensatory decreases in basal metabolic rate or adaptive metabolic responses that facilitate nitrogen sparing. Refeeding alone will not reverse wasting syndrome (although it does reverse the effects of uncomplicated starvation). In addition, the timing and ratio of LBM-to-fat mass lost is dependent on baseline body composition and/or gender. Patients with higher baseline fat mass (eg, women with a biologically determined higher baseline as compared with men) will demonstrate earlier and greater loss of fat mass.

Hypogonadism may be noted in men demonstrating wasting, however, transient down regulation of testosterone synthesis may occur during clinically active secondary infection. Both primary hypogonadism (testicular failure) and secondary hypogonadism (hypothalamic and/or pituitary failure) are seen in HIV-infected men. Patients with HIV infection may also demonstrate findings consistent with acquired growth hormone resistance at the level of the liver. This finding forms the rationale for the treatment of wasting syndrome with supraphysiologic doses of recombinant human growth hormone (rHGH).

**Clinical Manifestation and Evaluation**

Clinical investigation of involuntary weight loss should include questions regarding the degree and rapidity of weight change, meal frequency and completion, food security (including the ability to prepare food), signs and symptoms of active opportunistic infections and/or malignancies, and depression. Diarrheal disease may be viewed as nutritional deprivation with elevated fluid and electrolyte losses. Patients with diarrheal disease should receive careful evaluation of hydration and serum electrolytes. Diagnosis of wasting may utilize elements of subjective global assessment; mid-upper arm circumference and skin-fold; and guidelines proposed in 2001, delineating parameters of time, body cell mass (BCM) loss, and loss of total body mass (body mass index: BMI) (Table 1).

Physical examination is essential to distinguish patients with wasting syndrome from those with peripheral lipatrophy due to acquired lipodystrophy syndrome. Head and neck may demonstrate temporal wasting, periocular fat wasting, and loss of Bichat’s fat pad. Oral examination should evaluate for missing dentition, oral mucosal ulcers (ie, apthous or viral ulcers), malignancy (ie, Kaposi’s sarcoma), and fungal infections (ie, oral candidiasis), among others. On inspection of the torso, findings consistent with wasting include subclavicular muscle loss (with increased clavicle prominence), angular shoulders due to deltoid muscle loss (with increased acromion process prominence), and visible articulations of the ribs at the junction with the sternum (subcutaneous fat loss). Waist and hip circumferences, and the waist-to-hip ratio, are often helpful in distinguishing wasting syndrome from acquired lipodystrophy syndrome. The patient with wasting is unlikely to experience isolated fat loss in the face, extremities, and buttocks without significant abdominal fat loss (diminished waist circumference). In acquired lipodystrophy syndrome, abdominal (omental and mesenteric) fat mass is preserved or increased in the presence of global or peripheral subcutaneous fat loss. Alternatively, patients with acquired lipodystrophy syndrome may demonstrate...
striking facial lipoatrophy without clinically apparent subcutaneous fat loss in the extremities.

Mid-upper arm circumference is less subject to variability due to edema and hydration than weight or BMI. Loss of LBM and adipose tissue in the in the mid-upper arm may be quantified clinically by circumference and skin fold measurement. The National Health and Nutrition Examination Survey (NHANES) percentiles serve as reference ranges for evaluation. Muscle mass may be clinically evaluated visually by having the patient press the tips of his or her forefinger and thumb together and observing the mass of the interosseus dorsalis muscle or by placing the patient’s leg at a right angle and observing muscle mass at the insertion of the quadriceps femoris and the vastus medialis.

Bioelectrical impedance analysis (BIA) indirectly measures tissue compartments, LBM, BCM, fat mass, and extracellular (interstitial) mass (ECM). BCM by weight is primarily muscle mass. Phase angle is a geometric expression of the resistance and capacitance components of this assay. Ott et al demonstrated that phase angles of less than 5.6 and 4.8 degrees were associated with diminished survival and non-survival, respectively. In addition, an ECM-to-BCM ratio of 1.3 or greater was associated with nonsurvival. Serial BIA studies will describe weight loss or gain over time by soft tissue compartment as well as quantifying response to clinical intervention (for wasting). BIA should be performed at entry to care (baseline) and routinely thereafter.

Clinical Management

Nutrition support of the wasted patient focuses on the following components: inducement of hunger or appetite, avoidance of food odors during periods of nausea, supplementation of dietary intake, alteration of foods (texture, consistency, acidity) to facilitate intake in the presence of oropharyngeal or esophageal lesions, electrolyte management, and parenteral nutrition or enteral tube feeding (Table 2). Nutrition support should be focused on clinically significant caloric and protein intake (particularly during episodes of secondary infection). Attention should also be given to adequate provision of micronutrients, and facilitating antimicrobial absorption. Pharmacologic agents are available to induce hunger, and to promote the preferential accrual of LBM (Table 3). AIDS service organizations (ASOs) and dedicated government programs can provide food security (ie, home meal delivery, congregate meal sites, and food pantries) and arrange for psychiatric counseling and admission to peer support groups. However, patients frequently require an AIDS diagnosis to qualify for these services.

**APPETITE STIMULANTS**

Megestrol acetate oral suspension (Megace, Megace ES; Bristol-Myers Squibb) is a progestational steroid that has been shown to induce hunger and promote weight gain in patients with AIDS wasting.

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**Table 1. Diagnosis of AIDS Wasting Syndrome**

<table>
<thead>
<tr>
<th>Criteria Groups:</th>
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<tbody>
<tr>
<td>• Unintentional weight loss</td>
</tr>
<tr>
<td>&gt;10% over 12 months with physical findings on exam consistent with wasting (see text)*</td>
</tr>
<tr>
<td>&gt;7.5% over 6 months with physical findings consistent with wasting</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mid-upper arm circumference:</th>
</tr>
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<tbody>
<tr>
<td>• &lt;10th percentile with physical findings on exam consistent with wasting</td>
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</table>

<table>
<thead>
<tr>
<th>BCM loss documented by BIA:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• ≥5% over 6 months and physical findings consistent with wasting</td>
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</table>

<table>
<thead>
<tr>
<th>BCM percentage:</th>
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</thead>
<tbody>
<tr>
<td>Male: BCM &lt;35% documented by BIA with BMI &lt;27 kg/m² and physical findings consistent with wasting</td>
</tr>
<tr>
<td>Female: BCM &lt;23% documented by BIA with BMI &lt;27 kg/m² and physical findings consistent with wasting</td>
</tr>
</tbody>
</table>

* Note that individuals transitioning from highly structured environments providing regularly scheduled prepared meals and exercise programs to independent living may experience weight loss unrelated to disease processes (eg, the recently incarcerated).

<table>
<thead>
<tr>
<th>BCM, body cell mass; BIA, bioelectrical impedance analysis;</th>
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<tbody>
<tr>
<td>BMI, body mass index</td>
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</table>

Adapted from references 18-20.

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**Table 2. Components of Nutrition Support for Patients With AIDS Wasting Syndrome**

<table>
<thead>
<tr>
<th>Physiologic:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Fluid and electrolyte management</td>
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<tr>
<td>• Intravenous alimentation</td>
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<tr>
<td>• Alimentation via feeding tube</td>
</tr>
<tr>
<td>• Appetite/hunger stimulant</td>
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<tr>
<td>• Testosterone replacement</td>
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<tr>
<td>• Supraphysiologic recombinant human growth hormone or anabolic-androgenic steroids (outpatient)</td>
</tr>
<tr>
<td>• Avoidance of food odors during periods of nausea</td>
</tr>
<tr>
<td>• Supplementation to optimize dietary intake</td>
</tr>
<tr>
<td>• Alteration of food texture, consistency, acidity, or temperature to facilitate intake</td>
</tr>
<tr>
<td>• Alteration of dietary macronutrient content to facilitate drug absorption</td>
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</table>

<table>
<thead>
<tr>
<th>Psychologic:</th>
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<tbody>
<tr>
<td>• Evaluate for depression (social work, psychiatry, or chaplain consult)</td>
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<tr>
<td>• Peer support group referral</td>
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</table>

<table>
<thead>
<tr>
<th>Social:</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Evaluation of outpatient ability to shop for and prepare food (home attendant)</td>
</tr>
<tr>
<td>• Provision of outpatient food security (home meal delivery, food pantry, or congregate meal sites)</td>
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</tbody>
</table>
syndrome (Table 3).\textsuperscript{22} Investigators have demonstrated that gains of both LBM and fat mass occur in HIV-infected patients receiving megestrol acetate.\textsuperscript{23} It may down-regulate testosterone synthesis and men may experience erectile dysfunction and/or acceleration of wasting with prolonged use. Mulligan et al recently documented the preservation of sexual function among men receiving megestrol acetate by coadministration of testosterone enanthate every other week during the 12-week observation period.\textsuperscript{24} Other side effects described include thomboembolic events, hyperglycemia, and adrenal insufficiency upon discontinuation due to some glucocorticoid activity.\textsuperscript{25}

Patients demonstrating adrenal insufficiency due to long-term receipt of megestrol acetate may require treatment with glucocorticoids during periods of active secondary infection or other physiological stress. Patients and clinicians have found the tablet formulation to not be as effective as a hunger stimulant and burdensome to take in the amount clinically required. In addition, the tablet formulation is not FDA-approved for this indication.

Dronabinol, or 9-9-tetrahydrocannabinol (Marinol, Unimed), is the active component of marijuana and is approved for the treatment of anorexia in patients with AIDS (Table 3). Although not as potent as megestrol acetate, it does have mild antiemetic activity and a more benign side-effect profile.\textsuperscript{26,27} It has not been shown to consistently increase appetite and promote weight gain.\textsuperscript{22,23} Possible side effects may include psychotrophic activity, drowsiness, and hypogonadism. Because of its long half-life, it may be dosed once daily (instead of twice daily)—at bedtime for those patients experiencing drowsiness as a side effect.

**Testosterone Replacement Therapy**

Hypogonadal HIV-infected patients receiving long-term testosterone replacement therapy demonstrate accrual of LBM.\textsuperscript{28} Levels of sex hormone-binding globulin may be elevated in HIV infection, resulting in a normal-range total testosterone but decreased active or free testosterone. Therefore, laboratory evaluation should be of free testosterone levels. Several preparations are available for physiologic testosterone replacement: transdermal patch, topical gels, and formulations for intramuscular injection (Table 3). Patients have to be counseled that topical testosterone gel may be transferred by contact, an important issue for those patients who have female partners (especially when pregnant) and/or who come into close contact with children. Testosterone injections (eg, testosterone enanthate, an unmodified 17β-ester depot formulation) are available for intramuscular delivery and require less frequent administration than the formulations for transdermal delivery (Table 3). This method results in perceptible peak and trough levels during the dosing interval instead of the steady-state physiologic levels obtained with daily use of the gel or patch.

**Testosterone Derivatives or “Anabolic Steroids”**

The pharmacologic dosing of testosterone to achieve anabolic effect on muscle tissue has been investigated in eugonadal men and women with involuntary weight loss and/or wasting syndrome. Nandrolone decanoate (19-normethyl-testosterone 17β-ester) is a depot formulation available for long-acting intramuscular delivery (Table 3). Investigators have documented the association of its off-label use for AIDS wasting syndrome with increases in weight and LBM and improvements in quality of life.\textsuperscript{29} Use of anabolic-androgenic steroids in women has been shown to result in LBM accrual without loss of fat mass, but this remains an area for active investigation because of limited safety data.\textsuperscript{30}

Oxandrolone is a 17α-methylated testosterone derivative for oral administration (Table 2). HIV-infected men who had experienced a mean weight loss of 9% and then received oxandrolone demonstrated significantly greater increases in LBM and strength than did patients in the control group (although both groups participated in a supervised resistance exercise program).\textsuperscript{31} Decreases in high-density lipoprotein (HDL) cholesterol were documented in the oxandrolone arm.\textsuperscript{31} 17α-Methylated testosterone analogs are subject to first-pass hepatic metabolism, and long-term use has been associated with hepatotoxicity.\textsuperscript{32,33} Identification of a single androgen receptor gene (and protein) suggests that at equivalent dosages, all testosterone formulations have essentially the same physiologic effects.\textsuperscript{34} Therefore, testosterone therapy that is not administered orally may be preferred to minimize the potential for hepatotoxicity.

**Recombinant Human Growth Hormone**

Patients with wasting syndrome receiving supra-physiologic doses of rhGH by subcutaneous injection daily for 12 weeks demonstrated increases in LBM, improved functional indices, and a sustained positive nitrogen balance (Table 3).\textsuperscript{35} Side effects may include edema, arthralgias, and myalgias that can be addressed by lowering dietary sodium intake, dose reduction, and/or use of nonsteroidal anti-inflammatory agents. Other significant side effects include hyperglycemia and carpal tunnel syndrome. An oral glucose tolerance test can be considered prior to the initiation of rhGH therapy in candidates with a family history of or other risk factors for diabetes mellitus. It is important to note that patients lose body fat on therapy (an undesired effect in patients with significant lipodystrophy).

Use of a growth hormone releasing-factor (GHRF) analogue (TH9507) is under investigation to address abdominal lipo-accumulation among patients with HIV infection.\textsuperscript{36} Because its activity is subject to insulin-like growth factor-1 feedback inhibition, the supraphysiological levels of growth hormone necessary for a clinically significant preferential accrual of LBM are not
### Table 3. Pharmacologic Agents Used in Nutrition Support for AIDS Wasting

<table>
<thead>
<tr>
<th>Appetite stimulants (orexigenic agents)</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Megestrol acetate (Megace, Bristol-Myers Squibb) (Megace ES, Par)</td>
<td>Oral; 800 mg daily as 20-mL oral suspension Oral; 625 mg daily as 5-mL oral suspension</td>
<td>Yes</td>
<td>12 wk</td>
<td>Increase hunger</td>
<td>Increase food intake</td>
</tr>
<tr>
<td>Dronabinol (Marinol, Unimed)</td>
<td>Oral; 2.5 mg twice daily before lunch and dinner</td>
<td>Yes</td>
<td>6 wk</td>
<td>Increase appetite and decrease nausea</td>
<td>Increase food intake</td>
</tr>
</tbody>
</table>

### Physiologic testosterone replacement

| Testosterone gel (Testim, Auxilium; AndroGel, Unimed) | Topical; 5-g packet/tube daily | No | Ongoing physiologic replacement | Restore physiologic level; protein synthesis, nitrogen retention | Increase or maintain lean body mass | Application site reaction, acne, peripheral edema |
| Testosterone patch (Androderm, Watson) | Topical; 5-mg patch daily | No | Ongoing physiologic replacement | Restore physiologic level; protein synthesis, nitrogen retention | Increase or maintain lean body mass | Application site reaction, acne, peripheral edema |
| Testosterone enanthate | Intramuscular injection; 200 mg every other week | No | Ongoing replacement therapy | Maintain free testosterone at or above physiologic level during dosing interval | Increase or maintain lean body mass | Gynecomastia, acne, edema, excessive frequency and duration of penile erections |

### Supraphysiologic hormone administration

| Growth hormone (Serostim, Serono) | Subcutaneous injection; 6 mg daily | Yes | 12 wk | Preferential accrual lean body mass, nitrogen retention | Increase lean body mass and decrease volume of adipose tissue (visceral and subcutaneous) | Dose-related edema, insulin resistance, fat atrophy, arthralgias, myalgias |
| Nandrolone decanoate | Intramuscular injection; 150-200 mg every other week | No | 12 wk | Protein synthesis, nitrogen retention | Increase lean body mass | Testicular shrinkage, decreased HDL cholesterol, acne, peripheral edema, possible virilization in women |
| Oxandrolone§ (Oxandrin, Savient) | Oral; 20 mg daily | No | 8 wk | Protein synthesis, nitrogen retention | Increase lean body mass§ | Decreased HDL cholesterol, hepatotoxicity, peliosis hepatitis, reduced SHBG, possible virilization in women |

* See package insert for full information.
† For replacement in hypogonadal males.
‡ Male dosage, female use investigational.
§ Requires resistance exercise.

HDL, high-density lipoprotein; SHBG, sex hormone–binding globulin
achieved with GHRF analogue administration. This agent is not indicated for the treatment of wasting.

**ALIMENTATION**

Pharmacologic intervention is of limited benefit in the absence of adequate alimentation. This may occur orally in response to appetite or hunger (volitional) or via tube feeding or I.V. delivery (both nonvolitional). Calculation of maintenance energy requirement for hospitalized patients includes a calculation of the following: basal metabolic rate (Harris-Benedict equation in the absence of indirect calorimetry), dietary thermogenesis, and energy elevation due to disease and activity. Additional energy for anabolism should be provided later in the patient’s medical course. HIV-infected patients (and those with additional active infections) exhibit increased protein requirements. Use of high protein-calorie oral nutritional supplements (or intravenous alimentation) can maintain intake and lead to decreased protein catabolism.

**NONVOLITIONAL ALIMENTATION**

HIV-infected patients who are candidates for enteral tube feeding include those with neurologic disease, oropharyngeal or esophageal lesions, profound anorexia with or without nausea, or mildly impaired gut function, and those who are unable to achieve clinically significant volitional dietary intake. Patients with extensive small-bowel disease, such as jejunoileitis, are candidates for parenteral nutrition. Profoundly immunodeficient patients receiving a 2-month course of home parenteral nutrition demonstrated improved outcome and a low rate of catheter-related septicemia (0.26 per 100 patient-days).

Patients with wasting syndrome with or without diarrhea may have profound electrolyte deficits and are at risk for refeeding syndrome. Refeeding syndrome occurs when an acute volume expansion is precipitated by feeding, and the risk for sudden death due to arrhythmias in the setting of hypophosphatemia, hypokalemia, or hyponaghesemia is increased. The refeeding of hospitalized patients should be initiated at less than the calculated energy requirement, slowly progressing toward goal intake over several days.

Peripheral parenteral nutrition may be particularly useful at initiation of refeeding. Patients with severe wasting or those with a history of chronic alcohol use may require a short course of I.V. thiamine before the initiation of refeeding. Sodium retention is characteristic of the profound undernutrition seen in patients with uncomplicated starvation or with wasting syndrome in the setting of active secondary infections or malignant neoplastic disease. It may promote fluid overload during the early stages of refeeding. The syndrome of inappropriate (secretion of) antidiuretic hormone may occur in patients with central nervous system or lung disease. As a result, fluid balance, urinary output, and urinary electrolytes should be monitored closely.

**Conclusion**

The incidence and prevalence of HIV infection and AIDS continue to increase worldwide. As a result, wasting remains prevalent in both HAART-naive and HAART-treated patients as a consequence of poor nutrition, confections with other agents, presentation in an advanced state of disease, and limited access to care or failure of antiretroviral therapy regimens, among other factors. Wasting in patients receiving long-term suppressive HAART is underestimated and frequently unexpected, and nutrition requirements underrecognized.

At a time of profound advances in HAART allowing immunologic recovery, the achievement of virologic suppression alone is no longer sufficient for the care of these patients. Nutrition, including dietary, pharmacologic, and hormonal assessment, must be included in their comprehensive care. The partnership between infectious disease physicians and clinical nutritionists (registered dietitians), providing specialized metabolic support, is critical for our patients’ longer and healthier lives.

**References**

12. Visnegarwala F, Raghavan SS, Mullin CM, et al. Sex differences in the associations of HIV disease characteristics and body composition in...


33. Wasserman P, Segal-Maurer, Rubin D. Inappropriately low sex-hormone binding globulin with severely depleted total testosterone in two HIV-infected patients on transdermal testosterone replacement therapy, recombinant human growth hormone and oxandrolone. Antivir Ther. 2003;8:1-5.


Patients suffering from AIDS wasting syndrome experience an “involuntary loss” of more than 10% of their body weight in the form of muscle and fat mass; lipodystrophy involves the loss of subcutaneous fat. The condition is linked to AIDS disease progression and death, even among those who have responded successfully to antiretroviral therapy.

**What are the symptoms of AIDS wasting syndrome?**

“Involuntary” loss of more than 10% of body weight—primarily in the form of muscle and fat mass—is the primary symptom of AIDS wasting syndrome. It is a comorbidity for those who are HIV positive or suffering from AIDS. Both AIDS wasting syndrome and lipodystrophy involve significant involuntary loss of body fat. However, fat loss can be an early symptom of AIDS wasting syndrome, particularly in women.

**What is BIA?**

BIA—or, body impedance analysis—is the diagnostic tool used to measure lean body mass or body cell mass. BIA can identify significant loss in body mass; thusly, it is an important tool in the diagnosis of AIDS wasting syndrome.

**How is AIDS wasting syndrome treated?**

Patients with AIDS wasting syndrome are treated through the management of anorexia, the treatment of opportunistic infections, management of any endocrine disorders, and the use of nutritional supplements.

**RESOURCES**

- Gay Men’s Health Crisis
  www.gmhc.org
- HIV Information Resource
  www.centerforAIDS.org
- International AIDS Alliance
  www.aidsalliance.org

From the office of

Directions/comments

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