Serostim® Clinical Profile

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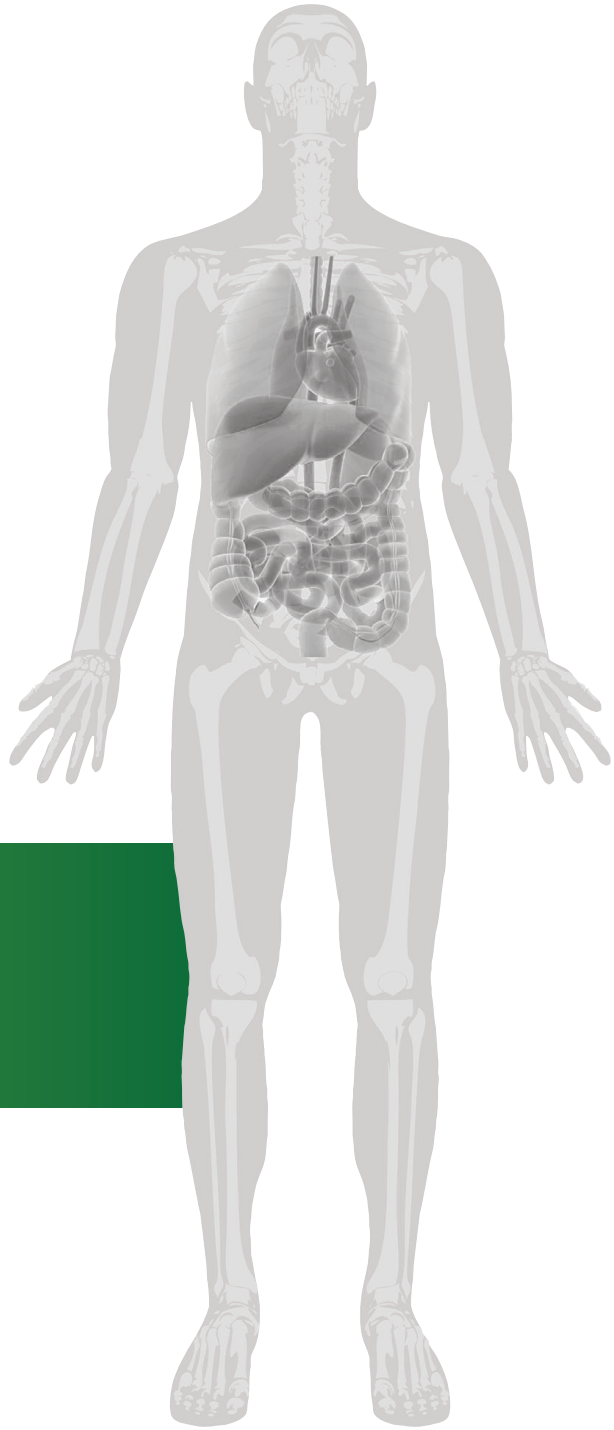
HIV-associated Wasting

Introduction

HIV-associated wasting, or cachexia, is characterized by abnormalities in the way the body uses carbohydrates, fats, and proteins to meet energy and tissue-building needs, which results in decreased physical endurance, involuntary weight loss, and loss of lean body mass (LBM).[1,2]

Energy is drawn from the breakdown of LBM, resulting in depletion of[3,4]:

- Skeletal muscle
- Organ tissue
- Blood and blood constituents
- Intracellular and extracellular water



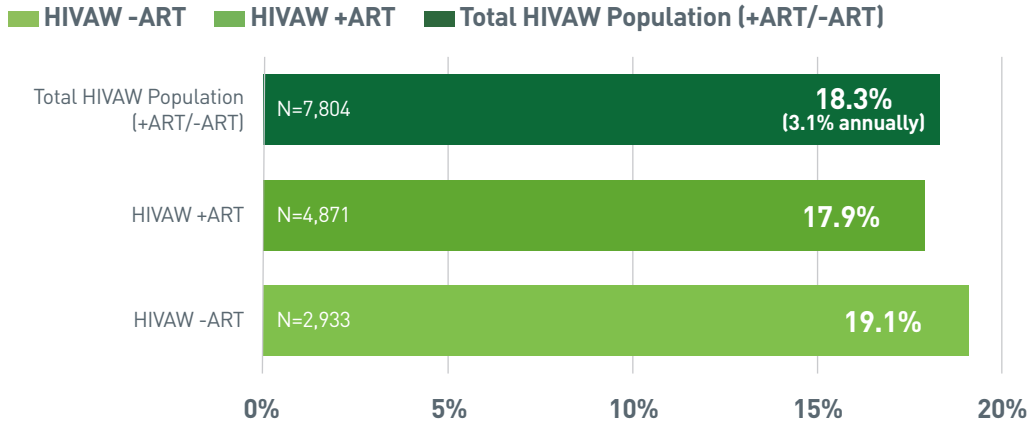
Approximately 50% of LBM is composed of skeletal muscle.[5]

Who May Be at Risk

According to CDC estimates, there were more than one million people living with HIV in the United States in 2019. 36,398 additional people were diagnosed with HIV infection that year.[6] A recently published retrospective medical and pharmacy claims study found that over approximately 6 years, 18.3% of people with HIV receiving medical care met the definition of HIV-associated wasting (approximately 3.1% annually). The HIV-associated wasting cohort had higher proportions of opportunistic infections and HIV/AIDs-related conditions, as well as a significantly higher comorbidity burden as per the Charlson Comorbidity Index, compared with the non-HIV associated wasting cohort.[7]

Numerous factors were found to be correlates of HIV-associated wasting, the strongest associations being Medicaid insurance and hospitalization(s) post-HIV index.[7] The data from this study suggests that HIV-associated wasting remains an underappreciated comorbidity in people living with HIV in the era of modern antiretroviral therapy.

Estimated HIV-associated Wasting Prevalence Over 6 Year Period (2012-2018)[7]



Patients with HIV-associated wasting may include:[8]

- Newly diagnosed patients
- HIV Long-Term Survivors
- HIV-positive patients with normal CD4 counts and controlled viral loads
- Patients on ART who fail to gain weight
- Patients on ART with acute infection
- Patients with advanced HIV disease
- Poor virologic responders
- Patients who have been nonadherent to ART

Pathophysiology

Although it is well known that HIV can disrupt the body's anabolic/catabolic process, the exact cause(s) of HIV-associated wasting remain unknown. Many factors are associated with reduced caloric intake and/or altered metabolism. These may be important individually or collectively in triggering unintentional weight loss, loss of LBM, and reduced physical endurance in HIV-positive individuals. HIV-associated wasting is a clinical diagnosis and necessitates the exclusion of other reasons of weight loss. Underlying conditions and comorbidities should be addressed individually as appropriate.[9, 10]

Immune Dysfunction

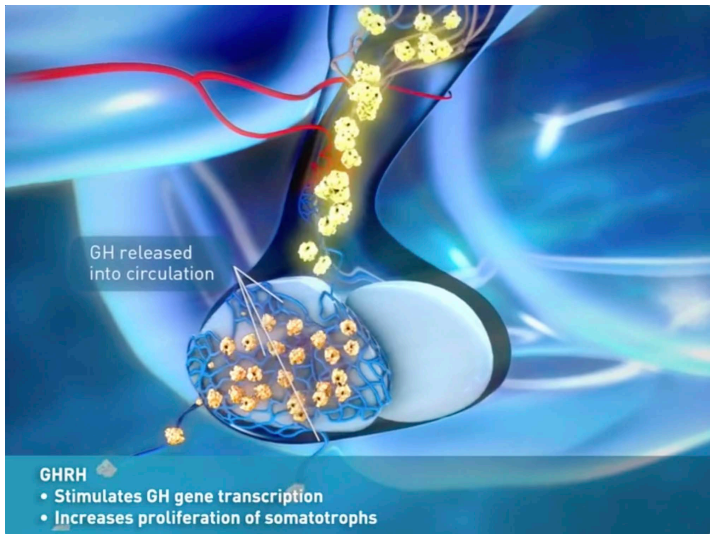
With the availability of cART, people living with HIV are able to achieve undetectable viral loads. Despite viral suppression, patients can still experience unintentional weight loss, loss of LBM, and loss of physical endurance—the hallmarks of HIV-associated wasting.

- **Inflammatory Responses:** The innate immune system releases proinflammatory cytokines upon first exposure to HIV.[11] In the presence of these cytokines, a breakdown of protein known as muscle proteolysis occurs. As this response becomes chronic, the continuing breakdown of muscle can lead to loss of LBM, which may lead to unintentional weight loss.[12] This long-term immune activation and chronic inflammation can happen even in HIV-positive patients on ART with undetectable viral loads.[8]
- **Opportunistic Infection:** A profound loss of adaptive immune system protection can occur with CD4+ and CD8+ T-cell depletion and dysfunction.[13, 14] This loss happens concurrently with an increased resting energy expenditure (REE) and increased protein catabolism, accelerating the loss of LBM.[14, 15] Opportunistic infections related to HIV have been shown to increase the risk of unintentional weight loss and may lead to metabolic changes.[8]

  It is also important to remember that swallowing difficulty can be indicative of some systemic infections.[16] This may lead to prolonged loss of appetite that can result in reduced nutritional intake during active opportunistic infection.[15]

Endocrine Dysfunction

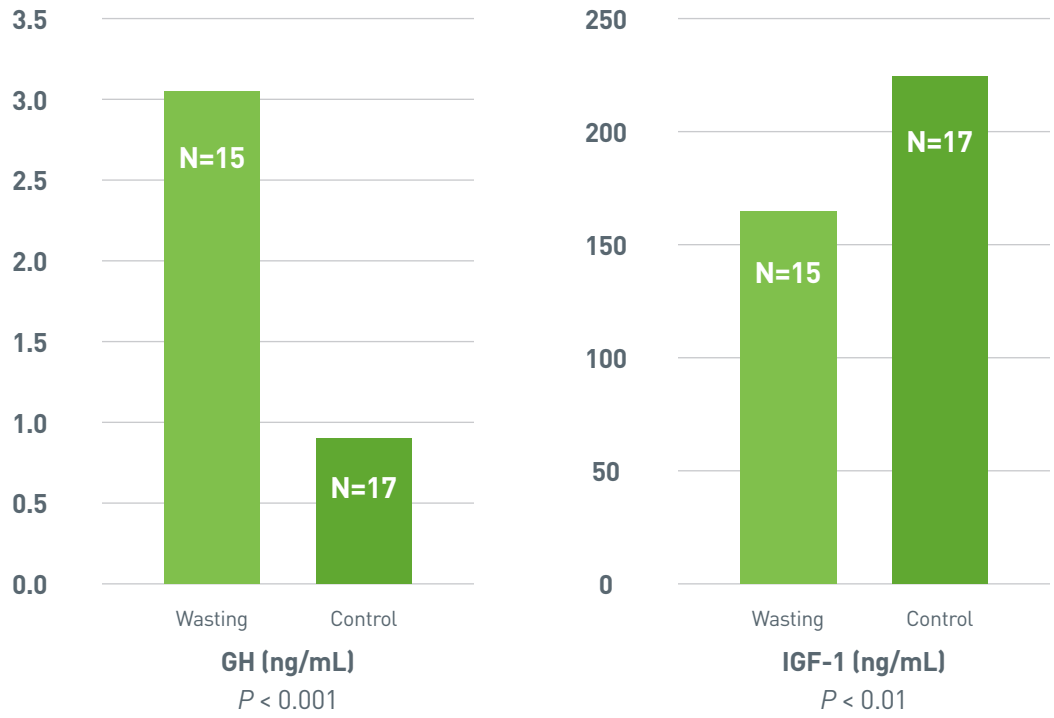
HIV-associated endocrine dysfunction is characterized by disruption of the hormonal regulatory axis and abnormal levels of hormones, such as glucagon, insulin, epinephrine, and glucocorticoids like cortisol, which are involved in regulating the metabolism of proteins, lipids, and carbohydrates.[10] There is a high correlation between loss of LBM and hypogonadism in HIV-positive men who are on ART.[8]



Pathophysiology (cont.)

- **Growth hormone (GH) resistance:** GH is synthesized and secreted in the anterior pituitary gland and stimulates muscle growth and protein synthesis. GH promotes anabolism and accumulation of LBM as well as the metabolism of fat or energy in preference to proteins and glucose. GH receptors are found in most organs and tissues, especially the liver.[5, 9] In HIV-associated wasting patients, a pattern of acquired GH resistance is seen, with increased GH and simultaneously decreased concentrations of insulin-like growth factor-1 (IGF-1).[8]

GH and IGF-1 mean overnight levels in men with AIDS wasting[19]



Insulin-like growth factor (IGF-1) is mainly secreted by the liver as a result of stimulation by GH. Higher levels of GH/IGF-1 are associated with protein synthesis. Reduced serum IGF-1 levels may lead to increased protein degradation and the loss of LBM.[17] The shift in endocrine function toward increased levels of the catabolic hormone cortisol may also contribute to a higher rate of protein degradation and to increased muscle atrophy.[18]

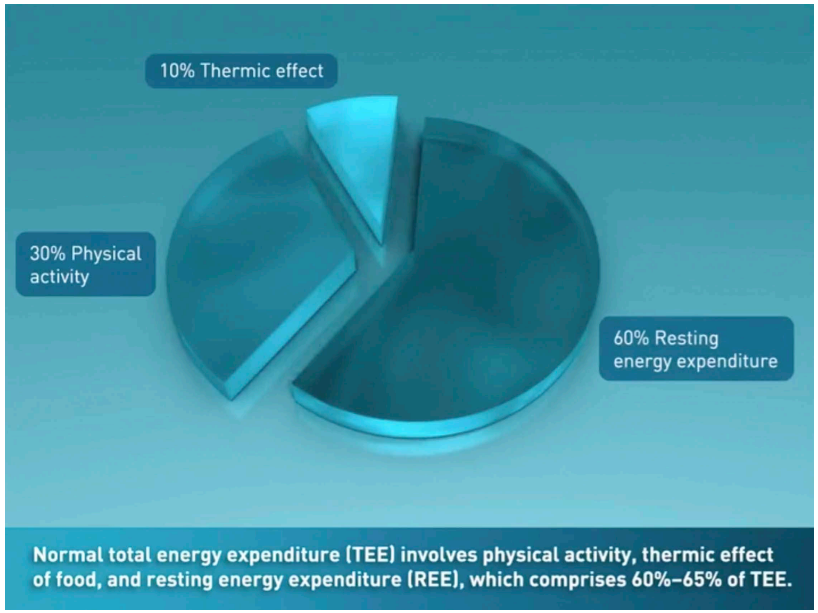
Twenty hypogonadal male subjects with weight loss (>10% of pre-illness weight or absolute weight <90% of ideal body weight) were enrolled in the study.[19]

- **Testosterone:** Hypogonadism has been shown to impact as high as 29% of HIV-positive men on cART.[20] Among HIV infected women, lower testosterone levels have been found, compared with age- and sex-matched groups, which are significantly associated with HIV-associated wasting.[8, 21]

Pathophysiology (cont.)

Metabolic Pathways

Multiple cellular pathways are involved in the normal regulation of metabolic function. However, in HIV-infected patients, dysregulation of one or more of these cellular pathways can lead to weight loss, inappropriate depletion of LBM, and paradoxical preservation of body fat.[22] A number of factors may promote excessive catabolic activity, including proinflammatory cytokines, hormonal imbalances, elevated resting energy expenditure, and increased cortisol levels.[23-26] Changes affecting other cellular pathways, such as the phosphoinositide 3-kinase (PI3K) pathway, may also occur and lead to accelerating protein degradation of LBM, loss of muscle strength, and reduced physical endurance.[27]



Normal total energy expenditure (TEE) involves physical activity, thermic effect of food, and resting energy expenditure (REE), which comprises 60%–65% of TEE.

Gastrointestinal Changes

The largest component of the mucosal immune system is gut-associated lymphoid tissue (GALT), one of the primary target tissues during acute HIV infection. Even in patients with undetectable viral loads, GALT can still serve as a reservoir of the virus, stimulating chronic inflammation and immune activation.[28]

In addition, HIV alters the gut flora and can lead to long-term effects on epithelial barrier and T-cell function in the gut, even after years on antiretroviral treatment. Over time, these changes continue to diminish the integrity of the protective mucosal barrier. These disruptions of the GI tract are associated with inflammation and malabsorption of vital nutrients, which can contribute to HIV-associated wasting.[29]

Other Potential Contributing Factors to Unintentional Weight Loss

Other factors that are associated with reduced caloric intake include:

- **Depression:** In general, depression is one of the strongest predictors of poor adherence and treatment outcomes in the management of HIV, and may cause chronic loss of appetite, which can contribute to malnutrition.[30, 31]
- **Drug use:** Substance use is associated with decreased nutritional intake.[32] In one study, among male non-dieters, injection drug users had marginally less protein intake compared to non-drug users.[33]

Screening Patients for HIV-associated Wasting[8]

Initiating a Conversation

Proactively speak to patients about potential HIV-associated wasting symptoms.
Consider asking your patients:

- Have you had unintentional weight loss?
- Have you recently lost weight without trying?
- Does your unintentional weight loss affect your health?
- Do your clothes fit more loosely due to unintentional weight loss?
- Have friends, family, or coworkers noticed any changes in your weight?
- Do you have a loss of energy, along with unintentional weight loss?
- Do you frequently feel tired?
- Are you exercising less?
- Do you need to rest more often?
- Is it more difficult to complete some of your activities?

Other Screening Methods

In addition to speaking with your patients, other methods that can help you screen for gradual, unintentional weight loss include measuring weight, calculating body mass index (BMI), and reviewing weight history, as well as evaluating physical endurance, LBM and visually examining physical appearance.

You can also manage your patients by asking them to keep a record of their weight, and inquire about involuntary changes in body habitus, physical endurance, as well as whether their clothing fits differently.

Rationale for Use[8]

Serostim® is the only product with anabolic and anticatabolic properties to treat HIV-associated wasting. Concomitant antiretroviral therapy is necessary.

Serostim® is an anabolic and anticatabolic agent that exerts its influence in HIV-associated wasting by interacting with specific receptors on a variety of cell types including myocytes, hepatocytes, adipocytes, lymphocytes, and hematopoietic cells. Some, but not all of its effects, are mediated by insulin-like growth factor-1 (IGF-1).

Clinical trials have demonstrated that Serostim® provided statistically significantly increases in body weight and LBM and improvements in physical endurance in patients with HIV-associated wasting receiving concomitant antiretroviral therapy. Patients also reported improvements in their perceptions of their HIV-associated wasting symptoms after 12 weeks of treatment.

Clinical trials excluded patients with a history of diabetes, impaired fasting glucose, or impaired glucose.

Please note: Serostim® (somatropin) is indicated to treat HIV-associated wasting only, and is not indicated to treat any of the underlying conditions

INDICATIONS AND USAGE

Serostim® (somatropin) for injection is indicated for the treatment of HIV patients with wasting or cachexia to increase lean body mass and body weight, and improve physical endurance.

Concomitant antiretroviral therapy is necessary.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Acute Critical Illness: Serostim® should not be initiated in patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma or acute respiratory failure.

Active Malignancy: Somatropin is contraindicated in the presence of active malignancy.
Any preexisting malignancy should be inactive and its treatment complete prior to instituting therapy with somatropin. Discontinue somatropin if there is evidence of recurrent activity.

Please see Important Safety Information on pages 9-20 and Full Prescribing Information.

Clinical Pharmacology[34]

Mechanism of Action

Serostim® is an anabolic and anticatabolic agent which exerts its influence by interacting with specific receptors on a variety of cell types including myocytes, hepatocytes, adipocytes, lymphocytes, and hematopoietic cells. Some, but not all of its effects, are mediated by insulin-like growth factor-1 (IGF-1).

Pharmacodynamics

Effects on Protein, Lipid, and Carbohydrate Metabolism

A one-week study in 6 patients with HIV-associated wasting has shown that treatment with Serostim® 0.1 mg/kg/day improved nitrogen balance, increased protein-sparing lipid oxidation, and had little effect on overall carbohydrate metabolism.

Decreases in trunk fat and total body fat, and increases in lean body mass were observed during two double-blind, placebo-controlled studies wherein Serostim® vs placebo were administered daily for 12 weeks to patients with HIV lipodystrophy. Serostim® is not approved for the treatment of HIV lipodystrophy.

Effects on Nitrogen and Mineral Retention

In the one-week study in 6 patients with HIV-associated wasting, treatment with Serostim® resulted in the retention of phosphorous, potassium, nitrogen, and sodium. The ratio of retained potassium and nitrogen during Serostim® therapy was consistent with retention of these elements in lean tissue.

IMPORTANT SAFETY INFORMATION (continued)

CONTRAINDICATIONS (continued)

Hypersensitivity: Serostim® is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients. Systemic hypersensitivity reactions have been reported.

Diabetic Retinopathy: Somatropin is contraindicated in patients with active proliferative or severe non-proliferative diabetic retinopathy.

Clinical Pharmacology (cont.)

Physical Performance

Cycle ergometry work output and treadmill performance were examined in separate 12-week, placebo-controlled trials. In both studies, work output improved significantly in the group receiving Serostim® 0.1 mg/kg/day subcutaneously vs placebo. Isometric muscle performance, as measured by grip strength dynamometry, declined, probably as a result of a transient increase in tissue turgor known to occur with Serostim® therapy.

In some experimental systems, somatropin has been shown to potentiate HIV replication in-vitro at concentrations ranging from 50–250 ng/mL. There was no increase in virus production when the antiretroviral agents, zidovudine, didanosine or lamivudine were added to the culture medium. Additional in-vitro studies have shown that somatropin does not interfere with the antiviral activity of zalcitabine or stavudine.

Pharmacokinetics

Absorption: The absolute bioavailability after subcutaneous administration was determined to be 70% to 90%. The mean t½ (half life) after subcutaneous administration is significantly longer than that seen after intravenous administration in normal male volunteers down-regulated with somatostatin (approximately 4.0 hrs vs 0.6 hrs), indicating that the subcutaneous absorption of somatropin is a rate-limiting process.

Distribution: The steady-state volume of distribution (Mean ± SD) following intravenous administration of somatropin in normal male volunteers is 12.0 ± 1.08 L.

Metabolism: Although the liver plays a role in the metabolism of GH, GH is primarily cleaved in the kidney. GH undergoes glomerular filtration and, after cleavage within the renal cells, the peptides and amino acids are returned to the systemic circulation.

Elimination: The t½ (half life) in nine patients with HIV-associated wasting with an average weight of 56.7 ± 6.8 kg, given a fixed dose of 6.0 mg somatropin subcutaneously, was 4.28 ± 2.15 hrs, similar to that observed in normal male volunteers. The renal clearance of r-hGH after subcutaneous administration in nine patients with HIV-associated wasting was 0.0015 ± 0.0037 L/h. No significant accumulation of r-hGH appears to occur after six weeks of daily dosing as indicated.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

Acute Critical Illness: Increased mortality (42% vs 19% in somatropin compared to placebo treated) in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure has been reported after treatment with pharmacologic amounts of somatropin.

Clinical Pharmacology (cont.)

Use in Specific Populations

Pediatric: Available evidence suggests that r-hGH clearances are similar in adults and children, but no pharmacokinetic studies have been conducted in children with HIV.

Gender: Biomedical literature indicates that a gender-related difference in the mean clearance of r-hGH could exist (clearance of r-hGH in males > clearance of r-hGH in females). However, no gender-based analysis is available in normal volunteers or patients infected with HIV.

Race: No studies have been conducted to determine the effect of race on the pharmacokinetics of Serostim®.

Renal Impairment: Subjects with chronic renal failure tend to have decreased somatropin clearance compared to those with normal renal function. However, no studies have been conducted to determine the effect of renal impairment on the pharmacokinetics of Serostim®.

Hepatic Impairment: No studies have been conducted to determine the effect of hepatic impairment on the pharmacokinetics of Serostim®.

Pregnancy/Nursing Mothers: Somatropin should be used during pregnancy only if clearly needed and with caution in nursing mothers because it is not known whether somatropin is excreted in human milk.

Geriatric: Clinical studies with Serostim® did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Elderly patients may be more sensitive to the action of somatropin, and therefore, may be more prone to develop adverse reactions. A lower starting dose and smaller dose increments should be considered for older patients.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Concomitant Antiretroviral Therapy: Somatropin has been shown to potentiate HIV replication in vitro, and there was no increase in virus production when antiretroviral agents were added to the culture medium. No significant somatropin-associated increase in viral burden was observed. All patients received antiretroviral therapy for the duration of treatment during Serostim® clinical trials.

Please see Important Safety Information on pages 9-20 and Full Prescribing Information.

Clinical Studies—Efficacy[34]

The clinical efficacy of Serostim® (somatropin) for injection in HIV-associated wasting, or cachexia, was assessed in 2 placebo-controlled trials. All study subjects received concomitant antiretroviral therapy. There was no increase in the incidence of Kaposi sarcoma (KS) or lymphoma, or in the progression of cutaneous KS in clinical studies of Serostim®. Patients with internal KS lesions were excluded from the studies. Potential effects on other malignancies are unknown.

Clinical Trial 1

A 12-week, randomized, double-blind, placebo-controlled study followed by an open-label extension phase enrolled 178 patients with severe HIV wasting taking nucleoside analogue therapy (pre-HAART era). The primary endpoint was body weight. Body composition was assessed using dual energy X-ray absorptiometry (DXA) and physical function was assessed by treadmill exercise testing. Patients meeting the inclusion/exclusion criteria were treated with either placebo or Serostim® 0.1 mg/kg daily. Ninety-six percent (96%) were male. The average baseline CD4 count/microliter was 85. The results from 140 evaluable patients were analyzed (those completing the 12-week course of treatment and who were at least 80% compliant with study drug). After 12 weeks of therapy, the mean difference in weight increase between the Serostim®-treated group and the placebo-treated group was 1.6 kg (3.5 lb).

Mean difference in LBM change between the Serostim®-treated group and the placebo-treated group was 3.1 kg (6.8 lbs) as measured by DXA. Mean increase in weight and LBM, and mean decrease in body fat, were significantly greater in the Serostim®-treated group than in the placebo group ($p=0.011$, $p<0.001$, $p<0.001$, respectively) after 12 weeks of treatment (Figure 1). There were no significant changes with continued treatment beyond 12 weeks, suggesting that the original gains of weight and LBM were maintained (Figure 1).

Treatment with Serostim® resulted in a significant increase in physical function as assessed by treadmill exercise testing. The median treadmill work output increased by 13% ($p=0.039$) at 12 weeks in the group receiving Serostim® (Figure 2). There was no improvement in the placebo-treated group at 12 weeks. Changes in treadmill performance were significantly related with changes in LBM.

IMPORTANT SAFETY INFORMATION (continued)

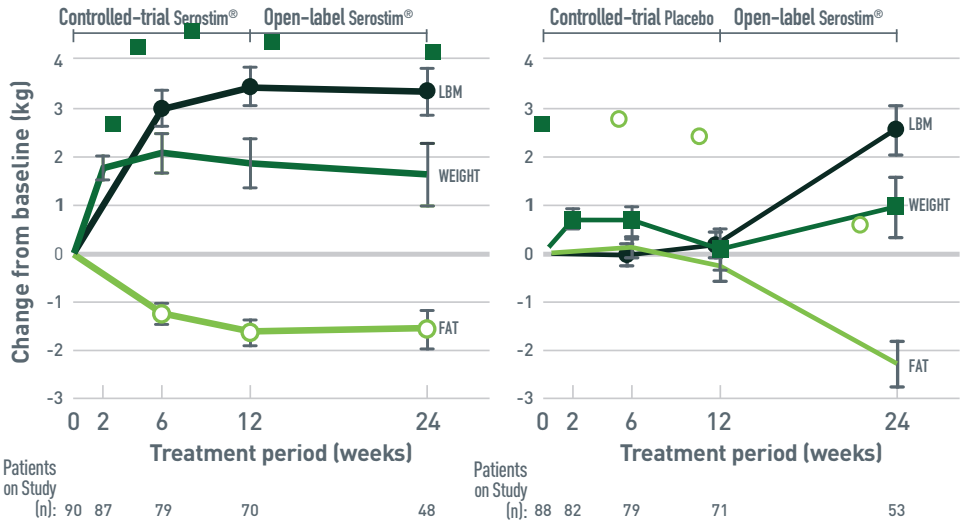
WARNINGS AND PRECAUTIONS (continued)

Neoplasms: Patients with preexisting tumors should be monitored for progression or reoccurrence. Monitor patients on somatropin therapy carefully for preexisting nevi.

Clinical Studies—Efficacy (cont.)

Serostim® (somatropin) for injection treatment significantly increased LBM and weight after 12 weeks, suggesting gains were maintained beyond 12 weeks[34]

Figure 1: Mean changes in body composition



IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Impaired Glucose Tolerance/Diabetes: Patients with other risk factors for glucose intolerance should be monitored closely during Serostim® therapy. Cases of new onset impaired glucose tolerance, new onset type 2 diabetes, and exacerbation of preexisting diabetes have been reported in patients receiving Serostim®. Some patients developed diabetic ketoacidosis and diabetic coma and, in some, improved when Serostim® was discontinued and in others persisted. Some of these patients required initiation or adjustment of antidiabetic treatment.

Please see Important Safety Information on pages 9-20 and Full Prescribing Information.

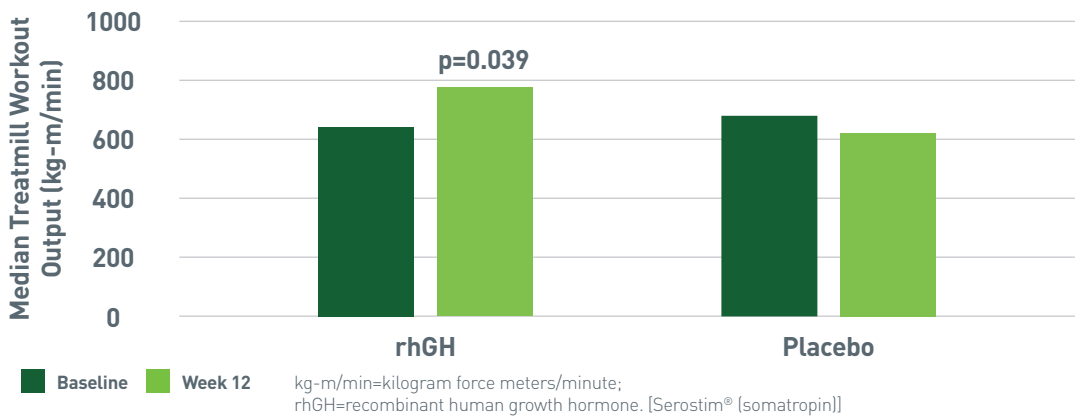
Clinical Studies—Efficacy (cont.)

- Serostim® treatment significantly increased physical function as assessed by treadmill exercise
- Median treadmill work output increased by 13% (p=0.039) at 12 weeks in the Serostim® group
- Changes in treadmill performance were significantly correlated with changes in LBM
- There were no significant changes with continued treatment beyond 12 weeks suggesting the original gains of weight and LBM were maintained

Mean increase in weight and LBM and mean decrease in body fat were also significantly greater in the Serostim®-treated group than in the placebo group (p=0.011, p<0.001, p<0.001, respectively) after 12 weeks of treatment.

Serostim® treatment significantly increased physical function as assessed by treadmill exercise testing after 12 weeks[34]

Figure 2: Serostim® improved physical endurance
Median Treadmill Work Output



kg-m/min=kilogram force meters/minute;
rhGH=recombinant human growth hormone. [Serostim® (somatropin)]

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Intracranial Hypertension: Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported usually within the first 8 weeks of somatropin therapy and rapidly resolved after stopping or reducing the somatropin dose. Funduscopic examination should be performed prior to initiating treatment with somatropin and periodically during treatment. If papilledema is observed, treatment should be stopped and restarted at a lower dose after IH-associated symptoms have resolved.

Please see Important Safety Information on pages 9-20 and Full Prescribing Information.

Clinical Studies—Efficacy (cont.)

Clinical Trial 2

A 12-week, randomized, double-blind, placebo-controlled study enrolled 757 patients with HIV-associated wasting, or cachexia. The primary efficacy endpoint was physical function as measured by cycle ergometry work output. Body composition was assessed using bioelectrical impedance spectroscopy (BIS) and also by DXA at a subset of centers. Patients meeting the inclusion/exclusion criteria were treated with either placebo, approximately 0.1 mg/kg every other day (qod) of Serostim®, or approximately 0.1 mg/kg daily at bedtime of Serostim®. All results were analyzed in intent-to-treat populations (for cycle ergometry work output, n=670). Ninety-one percent (91%) were male and 88% were on HAART. At study entry, mean body weight for wasting patients was 144 pounds. The average baseline CD4 count/μL was 446. A total of 646 patients completed the 12-week study and continued in the Serostim® treatment extension phase of the trial. Clinical Trial 2 results are summarized in Tables 1 and 2.[34]

Serostim® (somatropin) for injection significantly improved physical endurance for patients, as assessed by a stationary bike exercise in a 12-week clinical study[34]

Table 1: Mean (median) of cycle work output (kJ) response after 12 weeks of treatment, ITT population

	Placebo	Alternate-dose Serostim®[a]	Daily-dose Serostim®[b]
Cycle work output (kJ)	n=222	n=230	n=218
Baseline	25.92 (25.05)	27.79 (26.65)	27.57 (26.30)
Change from baseline	-0.05 (-0.25)	2.48 (2.30)	2.52 (2.40)
Percentage change from baseline	0.2%	8.9%	9.1%
Difference from placebo			
Mean (2-sided 95% CI)	-	2.53[c] (0.81, 4.25)	2.57[c] (0.83, 4.31)
Median	-	2.55	2.65

[a] Approximately 0.1 mg/kg every other day. [b] Approximately 0.1 mg/kg daily. [c] p<0.01.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Severe Hypersensitivity: Serious systemic hypersensitivity reactions including anaphylactic reactions and angioedema have been reported with postmarketing use of somatropin products. Patients and caregivers should be informed that such reactions are possible and that prompt medical attention should be sought if an allergic reaction occurs.

Clinical Studies—Efficacy (cont.)

Serostim® treatment significantly increased LBM and weight, and maintained gains with continued treatment[34]

Table 2: Mean (median) change from baseline for lean body mass, fat mass,and body weight[34]

	Placebo		Half-Dose Serostim®[a]		Full-Dose Serostim®[b]	
	n	Mean (Median)	n	Mean (Median)	n	Mean (Median)
Lean body mass (kg) (by BIS)	222	0.97 (0.67)	223	3.89 (3.65)	205	5.84 (5.47)
Fat mass (kg) (by DXA)	94	0.03 (0.01)	100	-1.25 (-1.23)	85	-1.72 (-1.51)
Body weight (kg)	247	0.69 (0.68)	257	2.18 (2.15)	253	2.79 (2.65)

[a] Approximately 0.1 mg/kg every other day. [b] Approximately 0.1 mg/kg daily.

The mean maximum cycle work output until exhaustion increased after 12 weeks by 2.57 kilojoules (kJ) in the Serostim® 0.1 mg/kg daily group ($p<0.01$) and by 2.53 kJ in the Serostim® 0.1 mg/kg every other day group ($p<0.01$) compared with placebo (Table 1). Cycle work output improved approximately 9% in both active treatment arms and decreased <1% in the placebo group. Lean body mass (LBM) and body weight (BW) increased, and fat mass decreased, in a dose-related fashion after treatment with Serostim® and placebo (Table 2). The LBM results obtained by BIS were confirmed with DXA.

Patients' perceptions of the impact of 12 weeks of treatment on their wasting symptoms as assessed by the Bristol-Meyers Anorexia/Cachexia Recovery Instrument improved with both doses of Serostim® in Clinical Trial 2.

Extension Phase: All patients (n=646) completing the 12-week placebo-controlled phase of Clinical Trial 2 continued Serostim® treatment into an extension phase. Five hundred and forty eight of these patients completed an additional 12 weeks of active treatment. In these patients, changes in cycle ergometry work output, LBM, BW, and fat mass either improved further or were maintained with continued Serostim® treatment.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Fluid Retention/Carpal Tunnel Syndrome: Increased tissue turgor (swelling, particularly in the hands and feet) and musculoskeletal discomfort (pain, swelling and/or stiffness) may occur during treatment with Serostim®, but may resolve spontaneously, with analgesic therapy, or after reducing the frequency of dosing. Carpal tunnel syndrome may occur and if the symptoms of carpal tunnel do not resolve by decreasing the weekly number of doses, it is recommended that Serostim® treatment be discontinued.

Please see Important Safety Information on pages 9-20 and Full Prescribing Information.

Clinical Studies—Safety[34]

In the 12-week, placebo-controlled Clinical Trial 2,510 patients were treated with Serostim®. The most common adverse reactions judged to be associated with Serostim® were musculoskeletal discomfort and increased tissue turgor (swelling, particularly of the hands or feet), and were more frequently observed when Serostim® 0.1 mg/kg was administered on a daily basis. These symptoms, summarized in Table 3, often subsided with continued treatment or dose reduction. Approximately 23% of patients receiving Serostim® 0.1 mg/kg daily and 11% of patients receiving 0.1 mg/kg every other day required dose reductions. Discontinuations as a result of adverse reactions occurred in 10.3% of patients receiving Serostim® 0.1 mg/kg daily and 6.6% of patients receiving 0.1 mg/kg every other day. The most common reasons for dose reduction and/or drug discontinuation were arthralgia, myalgia, edema, carpal tunnel syndrome, elevated glucose levels, and elevated triglyceride levels.

Clinical adverse reactions, which occurred during the first 12 weeks of study in at least 5% of the patients in either active treatment group and at an incidence greater than placebo, are listed below, without regard to causality assessment.

Adverse reactions that occurred in 1% to less than 5% of trial participants receiving Serostim® during the first 12 weeks of Clinical Trial 2 thought to be related to Serostim® included dose dependent edema, periorbital edema, carpal tunnel syndrome, hyperglycemia and hypertriglyceridemia.

During the 12-week, placebo-controlled portion of Clinical Trial 2, the incidence of hyperglycemia reported as an adverse reaction was 3.6% for the placebo group, 1.9% for the 0.1 mg/kg every other day group, and 3.2% for the 0.1 mg/kg daily group. One case of diabetes mellitus was noted in the 0.1 mg/kg daily group during the first 12-weeks of therapy. In addition, during the extension phase of Clinical Trial 2, two patients who converted from placebo to full-dose Serostim®, and 1 patient who converted from placebo to half-dose Serostim®, were discontinued because of the development of diabetes mellitus. The types and incidences of adverse reactions reported during the Clinical Trial 2 extension phase were not different from, or greater in frequency than, those observed during the 12-week, placebo-controlled portion of Clinical Trial 2.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS (continued)

Skin Atrophy: Rotate the injection site to avoid tissue atrophy.

Pancreatitis: Cases of pancreatitis have been reported rarely. Consider pancreatitis in patients who develop persistent severe abdominal pain

Clinical Studies—Safety[34] (cont.)

Clinical Adverse Reactions[34]

Table 3: Controlled Clinical Trial 2 adverse reactions occurring in at least 5% of patients in one of the treatment groups and at an incidence greater than placebo

	Placebo	0.1 mg/kg every other day Serostim®	0.1 mg/kg daily Serostim®
	Patients (n=247)	Patients (n=257)	Patients (n=253)
Body System Preferred term	%	%	%
Musculoskeletal System Disorders			
Arthralgia	11.3	24.5	36.4
Myalgia	11.7	17.9	30.4
Arthrosis	3.6	7.8	10.7
Gastrointestinal System Disorders			
Nausea	4.9	5.4	9.1
Body as a Whole—General Disorders			
Edema peripheral	2.8	11.3	26.1
Fatigue	4.5	3.5	5.1
Endocrine Disorders			
Gynecomastia	0.4	3.5	5.5
Central and Peripheral Nervous System Disorders			
Paresthesia	4.5	7.4	7.9
Hypoesthesia	2.4	1.6	5.1
Metabolic and Nutritional Disorders			
Edema generalized	1.2	1.2	5.9

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

In clinical trials in HIV-associated wasting or cachexia the most common adverse reactions (incidence >5%) were arthralgia, myalgia, peripheral edema, arthrosis, nausea, paresthesia, generalized edema, gynecomastia, hypoesthesia and fatigue.

Please see Important Safety Information on pages 9-20 and Full Prescribing Information.

Description[34]

Serostim® is a human growth hormone (hGH) produced by recombinant DNA technology. Serostim® has 191 amino acid residues and a molecular weight of 22,125 daltons. Its amino acid sequence and structure are identical to the dominant form of human pituitary growth hormone. Serostim® is produced by a mammalian cell line (mouse C127) that has been modified by the addition of the hGH gene. Serostim® is secreted directly through the cell membrane into the cell-culture medium for collection and purification.

Serostim® is a sterile lyophilized powder intended for subcutaneous injection after reconstitution to its liquid form.

Vials of Serostim® contain either 4 mg, 5 mg, or 6 mg. Each vial contains somatropin, sucrose, and phosphoric acid.

Each 4 mg multi-vial is supplied in a combination package with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol). The pH is adjusted with sodium hydroxide of phosphoric acid to give a pH of 7.4 to 8.5 after reconstitution.

Each 5 mg single-use vial is supplied in a combination package with Sterile Water for Injection, USP. The pH is adjusted with sodium hydroxide or phosphoric acid to give a pH of 6.5 to 8.5 after reconstitution.

Each 6 mg single-use vial is supplied in a combination package with Sterile Water for Injection, USP. The pH is adjusted with sodium hydroxide of phosphoric acid to give a pH of 7.4 to 8.5 after reconstitution.

IMPORTANT SAFETY INFORMATION (continued)

SPECIAL POPULATIONS:

Somatropin should be used during pregnancy only if clearly neede d and with caution in nursing mothers because it is not known whether somatropin is excreted in human milk. The safety and effectiveness of somatropin in pediatric patients with HIV have not been established. Clinical studies did not include sufficient numbers of subjects > 65 to determine a response different from that of younger patients. Studies have not been conducted in patients with hepatic or renal impairment. Gender-based analysis is not available.

Please see the full Prescribing Information for a complete discussion of Serostim® risks.

Dosage Information[34]

The usual starting dose of Serostim® is 0.1 mg/kg subcutaneously once daily (up to a total dose of 6 mg). Serostim® should be administered subcutaneously once daily at bedtime according to the following body weight-based dosage recommendations:

Weight range	Dosage
> 55 kg (>121 lb)	6 mg* SC daily
45-55 kg (99-121 lb)	5 mg* SC daily
35-45 kg (75-99 lb)	4 mg* SC daily
< 35 kg (<75 lb)	0.1 mg/kg SC daily

*Based on an approximate daily dosage of 0.1 mg/kg.

A starting dose of Serostim® 0.1 mg/kg every other day should be considered in patients at increased risk for adverse effects related to recombinant human growth hormone therapy (i.e., glucose intolerance). In general, dose reductions (i.e., reducing the total daily dose or the number of doses per week) should be considered for side effects potentially related to recombinant human growth hormone therapy.

Injection sites should be rotated to avoid localized skin irritation.

In view of the potential for acceleration of virus replication, it is recommended that HIV patients be maintained on antiretroviral therapy for the duration of Serostim® treatment.

Dosage Information (cont.)

BMI Table

This BMI chart is provided as a reference to determine a patient's weight category and should not be used for dosing.

		Underweight					Normal						Overweight			
		14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Height									**Weight (lb)**							
Feet	**Inches**															
4'10"	58"	67	72	76	81	86	91	96	100	105	110	115	119	124	129	134
4'11"	59"	69	75	79	84	89	94	99	104	109	114	119	124	128	133	138
5'0"	60"	72	77	82	87	92	97	102	107	112	118	123	128	133	138	143
5'1"	61"	74	79	85	90	95	100	106	111	116	122	127	132	137	143	148
5'2"	62"	76	82	87	93	98	104	109	115	120	126	131	136	142	147	153
5'3"	63"	79	85	90	96	102	107	113	118	124	130	135	141	146	152	158
5'4"	64"	81	87	93	99	105	110	116	122	128	134	140	145	151	157	163
5'5"	65"	84	90	96	102	108	114	120	126	132	138	144	150	156	162	168
5'6"	66"	87	93	99	105	112	118	124	130	136	142	148	155	161	167	173
5'7"	67"	89	96	102	108	115	121	127	134	140	146	153	159	166	172	178
5'8"	68"	92	98	105	112	118	125	131	138	144	151	158	164	171	177	184
5'9"	69"	95	101	108	115	122	128	135	142	149	155	162	169	176	182	189
5'10"	70"	97	104	111	118	126	132	139	146	153	160	167	174	181	188	195
5'11"	71"	100	107	114	122	129	136	143	150	157	165	172	179	186	193	200
6'0"	72"	103	110	118	125	132	140	147	154	162	169	177	184	191	199	206
6'1"	73"	106	113	121	129	136	144	151	159	166	174	182	189	197	204	212
6'2"	74"	109	117	124	132	141	148	155	163	171	179	186	194	202	210	218
6'3"	75"	112	120	128	136	144	152	160	168	176	184	192	200	208	216	224
6'4"	76"	115	123	131	139	148	156	164	172	180	189	197	205	213	221	230
6'5"	77"	118	126	135	143	151	160	168	176	185	193	202	210	218	227	235
6'6"	78"	121	130	138	147	155	164	172	181	190	198	207	216	224	233	241

Source: National Institute of Health (NIH)/National Heart, Lung, and Blood Institute (NHLBI).
https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmi_tbl.htm
https://www.nhlbi.nih.gov/health/educational/lose_wt/BMI/bmicalc.htm
Accessed May 10th, 2022

Stability, Storage, and Forms[34]

Storage and Handling

Before reconstitution:

Vials of Serostim® and diluent should be stored at room temperature, (15°–30°C/59°–86°F). Expiration dates are stated on product labels.

Single-use vials: After reconstitution with Sterile Water for Injection, USP, the reconstituted solution should be used immediately and any unused portion should be discarded.

Multi-use vials: After reconstitution with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol), the reconstituted solution should be stored under refrigeration (2°–8°C/36°–46°F) for up to 14 days. Avoid freezing reconstituted vials of Serostim®.

How Supplied

Serostim® is available in the following forms:

- Serostim® single-use vials containing 5 mg with Sterile Water for Injection, USP. Package of 7 vials.
- Serostim® single-use vials containing 6 mg with Sterile Water for Injection, USP. Package of 7 vials.
- Serostim® multiple-use vials containing 4 mg with Bacteriostatic Water for Injection, USP (0.9% Benzyl Alcohol). Package of 7 vials.

Please see Important Safety Information on pages 9-20 and Full Prescribing Information.

Patient Considerations[34]

Patient Counseling Information

Patients being treated with Serostim® should be informed of the potential benefits and risks associated with treatment. Patients should be instructed to contact their physician should they experience any side effects or discomfort during treatment with Serostim®.

It is recommended that Serostim® be administered using sterile, disposable syringes and needles. Patients should be thoroughly instructed in the importance of proper disposal and cautioned against any reuse of needles and syringes. An appropriate container for the disposal of used syringes and needles should be employed.

Patients should be instructed to rotate injection sites to avoid localized tissue atrophy.

Never Share Serostim® Needle Between Patients

Counsel patients that they should never share Serostim® or Serostim® injection devices with another person, even if the needle is changed. Sharing of Serostim® or Serostim® injection devices between patients may pose a risk of transmission of infection.

Patients should be informed about the management of common side effects related to tissue turgor, glucose intolerance, and musculoskeletal discomfort.

References

1. Coats AJ. Origin of symptoms in patients with cachexia with special reference to weakness and shortness of breath. *Int J Cardiol.* 2002;85:133-139.
2. Data on file. Study 9037 (r-hGH) Integrated Clinical and Statistical Final Report. Merck KGaA, Darmstadt, Germany. 2002.
3. Roubenoff R, Grinspoon S, Skolnik PR, et al. Role of cytokines and testosterone in regulating lean body mass and resting energy expenditure in HIV-infected men. *Am J Physiol Endocrinol Metab.* 2002;283(1):E138-E145.
4. Kotler DP, Wang J, Pierson RN. Body composition studies in patients with the acquired immunodeficiency syndrome. *Am J Clin Nutr.* 1985;42(6):1255-1265.
5. Dudgeon WD, Phillips KD, Carson JA, et al. Counteracting muscle wasting in HIV-infected individuals. *HIV Med.* 2006;7:299-310.
6. Centers for Disease Control and Prevention. HIV Surveillance Report, 2019; vol.32. http://www.cdc.gov/hiv/library/reports/hiv-surveillance.html. Published May 2021. Accessed March 24, 2022.
7. Siddiqui, J., Samuel, S. K., Hayward, B., Wirka, K. A., Deering, K. L., Harshaw, Q., Phillips, A., Harbour, M. HIV-associated wasting prevalence in the era of modern antiretroviral therapy. *AIDS (London, England).* 2022;36(1):127–135.
8. Data on File. Serostim Clinical Profile Updated CVA. January 2022. EMD Serono, Inc.
9. Gelato M, McNurlan M, Freedland E. Role of recombinant human growth hormone in HIV-associated wasting and cachexia: pathophysiology and rationale for treatment. *Clin Ther.* 2007;29(11):2269-2288.
10. Grinspoon S, Mulligan K; Department of Health and Human Services Working Group on the Prevention and Treatment of Wasting and Weight Loss. Weight loss and wasting in patients infected with human immunodeficiency virus. *Clin Infect Dis.* 2003;36 (suppl 2):S69-S78.
11. Cray C, Zaias J, Altman NH. Acute phase response in animals: a review. *Comp Med.* 2009;59(6):517-526.
12. Castaneda C. Muscle wasting and protein metabolism. *J Anim Sci.* 2002;80 (suppl 2):E98-E105.
13. Boasso A, Shearer GM, Chougnet C. Immune dysregulation in human immunodeficiency virus infection: know it, fix it, prevent it? *J Intern Med.* 2009;265(1):78-96.
14. Koethe JR, Heimburger DC, PrayGod G, Filteau S. From wasting to obesity: the contribution of nutritional status to immune activation in HIV infection. *J Infect Dis.* 2016;214 (suppl 2):S75-S82.
15. Chang E, Sekhar R, Patel S, Balasubramanyam A. Dysregulated energy expenditure in HIV-infected patients: a mechanistic review. *Clin Infect Dis.* 2007;44(11):1509-1517.
16. Williams B, Waters D, Parker K. Evaluation and treatment of weight loss in adults with HIV disease. *Am Fam Physician.*1999;60(3):843-854.
17. Melmed S. Disorders of the anterior pituitary and hypothalamus. In: Kasper DL, Fauci AS, Hauser SL, Longo DL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine.* 19th ed. New York, NY: McGraw-Hill; 2015.
18. Morgan SA, Hassan-Smith ZK, Doig CL, et al. Glucocorticoids and 11ß-HSD1 are major regulators of intramyocellular protein metabolism. *J Endocrinol.* 2016;229(3):277-286.
19. Grinspoon S, Corcoran C, Lee K, et al. Loss of lean body and muscle mass correlates with androgen levels in hypogonadal men with acquired immunodeficiency syndrome and wasting. *J Clin Endocrinol Metab.* 1996;81(11):4051-4058.
20. Gomes AR, Souteiro P, Silva CG, et al. Prevalence of testosterone deficiency in HIV-infected men under antiretroviral therapy. *BMC Infect Dis.* 2016;16:628.
21. Grinspoon S, Corcoran C, Miller K, et al. Body composition and endocrine function in women with acquired immunodeficiency syndrome wasting. *J Clin Endocrinol Metab.*1997;82:1332-1337.
22. Perry CM, Wagstaff AJ. Recombinant mammalian cell-derived somatropin: a review of its pharmacological properties and therapeutic potential in the management of wasting associated with HIV infection. *BioDrugs*. 1997;8(5):394-414.
23. Spate U, Schulze PC. Proinflammatory cytokines and skeletal muscle. *Curr Opin Clin Nutr Metab Care.* 2004;7:265–269.
24. Roubenoff R, Grinspoon S, Skolnik PR, et al. Role of cytokines and testosterone in regulating lean body mass and resting energy expenditure in HIV-infected men. *Am J Physiol Endocrinol Metab.* 2002;283:e138–e145.
25. Kosmiski L. Energy expenditure in HIV infection. *Am J Clin Nutr.* 2011;94(suppl):1677s-82s
26. Alberti KG, Johnston DG. Cortisol and Catabolism: A new perspective. *Clin Sci Mol Med.* 1977;52(4):333-336.
27. Cohen S, Nathan JA, Goldberg AL. Muscle wasting in disease: molecular mechanisms and promising therapies. *Nat Rev Drug Discov.* 2015;14(1):58-74.
28. Mehandru S, Poles MA, Tenner-Racz K, et al. Primary HIV-1 infection is associated with preferential depletion of CD4+ T lymphocytes from effector sites in the gastrointestinal tract. *J Exp Med.* 2004;200(6):761-770.
29. Zilberman-Schapira G, Zmora N, Itav S, Bashiardes S, Elinav H, Elinav E. The gut microbiome in human immunodeficiency virus infection. *BMC Med.* 2016;14(1):83.
30. Simoni JM, Safren SA, Manhart LE, et al. Challenges in addressing depression in HIV research: assessment, cultural context, and methods. *AIDS Behav.* 2011;15(2):376–388.
31. R**ab**kin JG. HIV and depression: 2008 review and update. *Curr HIV/AIDS Rep.* 2008;5(4):163-171**.**
32. Hendricks K, Gorbach S. Nutrition issues in chronic drug users living with HIV infection. *Addict Sci Clin Pract.* 2009;5(1):16-23.
33. Kim JH, Spiegelman D, Rimm E, Gorbach SL. The correlates of dietary intake among HIV-positive adults. *Am J Clin Nutr.* 2001;74:852-861.
34. Serostim® (somatropin) for injection Prescribing Information. EMD Serono, Inc.

Serostim® 4 mg 5 mg 6 mg (somatropin) for injection