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JPEN J Parenter Enteral Nutr 1999 23: S195
DOI: 10.1177/014860719902300605

0148-6071/99/2306-S195$03.00/0
JOURNAL OF PARENTERAL AND ENTERAL NUTRITION

Printed in U.S.A.

Can Androgen Therapy Replete Lean Body Mass and Improve Muscle Function in Wasting Associated With Human Immunodeficiency Virus Infection?

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ABSTRACT. A significant number of men who are infected with the human immunodeficiency virus (HIV) have low testosterone levels. Androgen deficiency in HIV-infected patients is associated with decreased muscle mass and function, and adverse disease outcome. Administration of replacement doses of testosterone to healthy hypogonadal men augments lean body mass, muscle size, and maximal voluntary strength. Recent studies have shown that physiologic testosterone replacement in HIV-infected men with weight loss who have low testosterone levels can also increase muscle mass and effort-dependent strength. However, further studies are needed to determine whether androgen therapy can improve physical function and health-related outcomes in HIV-infected men. (*Journal of Parenteral and Enteral Nutrition* **23:**S195–S201, 1999)

In many chronic illnesses such as that associated with the human immunodeficiency virus (HIV), end-stage renal disease, chronic obstructive lung disease, and some types of cancer, we can now achieve disease stability but not a cure. In these chronic disorders, muscle wasting occurs frequently and is associated with debility, impaired quality of life, and poor disease outcome.[1–11] For instance, a substantial proportion of HIV-infected men with acquired immunodeficiency syndrome (AIDS) require assistance with activities of daily life after hospitalization for secondary illnesses. Therefore, strategies that can reverse muscle wasting and augment muscle function may improve quality of life and reduce utilization of health care resources.

Of the various anabolic interventions being considered for promoting restitution of body cell mass in HIV-infected men, testosterone is particularly attractive because it is safe and relatively inexpensive.[12–16] There is agreement that testosterone can increase fat-free mass and muscle strength under specific experimental paradigms.[17–33] However, we do not know whether replacement doses of testosterone can produce clinically meaningful changes in body composition and muscle function in chronic illnesses associated with muscle wasting. Additionally, HIV, like many other chronic diseases, produces a heterogeneous, complex and multisystem syndrome; therefore, anabolic therapy should be viewed as only one component of a multipronged therapeutic strategy.

The rationale for the use of androgenic steroids in chronic illnesses is based on the following hypotheses:

1. There is a high frequency of low testosterone levels in HIV-infected men;
2. Low testosterone levels in HIV-infected men are associated with poor disease outcomes and impaired muscle function;
3. Testosterone replacement of healthy, hypogonadal men produces increases in fat-free mass and muscle strength; and
4. Androgen replacement in HIV-infected men with low testosterone levels will produce improvements in muscle mass and function similar to those observed in healthy, hypogonadal men.

We will evaluate the data pertaining to each of these hypotheses.

HIGH FREQUENCY OF LOW TESTOSTERONE LEVELS IN HIV-INFECTED MEN

Because we do not have good biologic markers of testosterone action, hypogonadism has been defined purely in terms of low testosterone levels. We measured serum total and free testosterone levels in 150 consecutive, HIV-infected men attending our HIV clinic.[34] Approximately, a third of these men had serum total and free testosterone levels in the hypogonadal range.[34] Other investigators have reported similar prevalence of hypogonadism in HIV-infected men.[34–41] Nineteen percent of HIV-infected men with low testosterone levels have elevated LH and follicle-stimulating hormone (FSH) levels and thus have hypergonadotropic hypogonadism. These patients presumably have primary testicular dysfunction. The remaining 81% have either normal or low LH and FSH levels; these men with hypogonadotropic hypogonadism either have a central defect at the hypothalamic or pituitary site or a dual defect involving both the testis and the hypothalamic–pituitary centers. The pathophysiology of hypogonadism in HIV infection is complex and involves defects at multiple levels of the hypothalamic–pituitary–testicular axis.

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Presented at the 23rd Clinical Congress of the American Society for Parenteral and Enteral Nutrition, January 31–February 3, 1999, San Diego, CA.

In a recent study, a majority of men with chronic obstructive lung disease had low total and free testosterone levels.[45] Similarly, there is a high frequency of hypogonadism in patients with cancer, end-stage renal disease on hemodialysis, and liver disease.[46]

The pathophysiology of hypogonadism in chronic illness is multifactorial. Malnutrition, mediators and products of the systemic inflammatory response, drugs such as ketoconazole, and metabolic abnormalities produced by the systemic illness all contribute to a decline in testosterone production.

LOW TESTOSTERONE LEVELS CORRELATE WITH POOR DISEASE OUTCOME

Low testosterone levels correlate with adverse disease outcome in HIV-infected men. Serum testosterone levels are lower in HIV-infected men who have lost weight than in those who have not.[43] Longitudinal follow-up of HIV-infected homosexual men reveals a progressive decrease in serum testosterone levels;[6] this decrease is much greater in HIV-infected men who progress to AIDS than in those who do not.[6] We do not know whether decrease in testosterone levels is a consequence of weight loss or is a contributory factor that precedes muscle wasting. In a longitudinal study, Dobs et al[8] measured serum testosterone levels in a cohort of HIV-infected men and reported that serum testosterone levels decline early in the course of events that culminate in wasting. Testosterone levels correlate with muscle mass and exercise capacity in HIV-infected men,[9] leading to speculation that hypogonadism may contribute to muscle wasting and debility. Although patients with HIV infection may lose both fat and lean tissue, the loss of lean body mass is an important aspect of the weight loss associated with wasting. The magnitude of depletion of nonfat tissues rather than weight loss is related to the death from wasting in AIDS.[2–5,7,10] There is a high prevalence of sexual dysfunction in HIV-infected men.[42,47] With the increasing life expectancy of HIV-infected men, frailty and sexual dysfunction have emerged as important quality-of-life issues.

ANABOLIC EFFECTS OF ANDROGENS IN HEALTHY, HYPOGONADAL AND EUGONADAL MEN

Testosterone replacement increases nitrogen retention in castrated males of several animal species,[23] eunuchoidal men, boys before puberty, and in women.[22] Several recent studies[24–27] have re-examined the effects of testosterone on body composition and muscle mass in hypogonadal men in more detail. We administered 100 mg testosterone enanthate weekly for 10 weeks to 7 hypogonadal men after a 10- to 12-week washout.[24] Testosterone replacement was associated with a 4.5 ± 0.6 kg ($p = .005$) increase in body weight and 5.0 ± 0.8 kg ($p = .004$) increase in fat-free mass, estimated from underwater weight; body fat did not change. Similar increases in fat-free mass were observed using the deuterium water dilution method. Arm and leg muscle cross-sectional areas, assessed by magnetic resonance imaging, increased significantly. Substantial increases in muscle strength were also noted after treatment.

Brodsky et al[25] reported a 15% increase in fat-free mass and an 11% decrease in fat mass in hypogonadal men. The muscle mass increased by 20% and accounted for 65% of the increase in fat-free mass. The muscle accretion during testosterone treatment was associated with a 56% increase in fractional muscle protein synthesis.

A sublingual, cyclodextrin-complexed, testosterone formulation produced a modest increase in fat-free mass (+0.9 kg) and muscle strength (+8.7 kg) in hypogonadal men;[26] however, the testosterone dose used in this study was smaller than the doses used in previous studies.

Percent body fat is significantly greater in hypogonadal than eugonadal men.[27] Testosterone replacement in androgen-deficient men is associated with a significant decrease in body fat.[27]

The effects of testosterone replacement on fat mass in androgen-deficient men are more variable; two studies[25,27] observed a significant decrease in fat mass and two studies[24,26] did not. The reasons for this discrepancy are not apparent; differences in the pretreatment body composition of the treated men and the methods for body composition analysis may in part account for the differences in results.

Effect of Supraphysiologic Doses of Testosterone on Body Composition

Intense controversy persisted until recently with respect to the effects of supraphysiologic doses of androgenic corticosteroids on body composition and muscle strength.[17–20] Many of the previous studies were not blinded, nor placebo-controlled. The doses of androgens used in most studies were relatively low, and it is surprising that any effects were seen at all. In some studies, the energy and protein intake was not controlled. The exercise stimulus was not standardized so that the effects of androgen could not be evaluated independent of the effects of strength training.[18,19] Another confounding factor in some studies was the inclusion of competitive athletes whose desire to win might preclude compliance with standardized regimens of diet, exercise, and drug administration.[17] We conducted a placebo-controlled, double-blind, randomized, clinical trial to assess separately the effects of supraphysiologic doses of testosterone and resistance exercise on fat-free mass, muscle size, and strength.[21] Healthy men, 19 to 40 years of age and within 15% of their ideal weight, were randomly assigned to one of four groups: placebo but no exercise; testosterone but no exercise; placebo plus exercise; and testosterone plus exercise. The men received 600 mg testosterone enanthate or placebo weekly for 10 weeks. To assure compliance, the nursing staff in the Clinical Study Center administered all the injections. Serum total and free testosterone levels, measured 7 days after each injection, increased fivefold; these were nadir levels, and serum testosterone levels at other times must have been higher. Serum LH levels were markedly suppressed in the two testosterone-treated but not place-

bo-treated men, providing additional evidence of compliance. Men in the exercise groups underwent weight lifting exercises three times weekly under supervision; the training stimulus was standardized on the basis of the subjects' initial muscle strength. Fat-free mass by underwater weighing, muscle size by magnetic resonance imaging, and muscle strength of the arms and legs in bench press and squat exercises were measured before and after 10 weeks of treatment.

The men given testosterone alone had greater gains in muscle size in the arm (change in triceps area, 13.2% ± 3.3% *vs* −2.1% ± 2.9%, mean ± SE; $p < .05$) and leg (change in quadriceps area, 6.5% ± 1.3% *vs* −1.0% ± 1.1%, $p < .05$) than those given placebo injections. Testosterone treatment also was associated with greater gains in strength in the bench press (+10% ± 4% *vs* −1% ± 2%, $p < .05$) and squat exercise capacity (+19% ± 6% *vs* 3% ± 1%, $p < .05$) than placebo injections. Testosterone and exercise, given together, produced greater increase in fat-free mass (+9.5% ± 1.0%) and muscle size (+14.7% ± 3.1% in triceps area and +14.1% ± 1.3% in quadriceps area) than either placebo or exercise alone and greater gains in muscle strength (+24% ± 3% in bench press strength and +39% ± 4% in squat exercise capacity) than either nonexercising group. We did not observe any significant changes in red cell counts or liver enzymes in any treatment group. Serum levels of prostate-specific antigen did not change during treatment, and no abnormalities were detected in the prostate on digital rectal examination during the 10-week treatment period. Two men in the testosterone group and one man receiving placebo injections developed acne. These results demonstrate that supraphysiologic doses of testosterone, especially when combined with strength training, increase fat-free mass, muscle size, and strength in normal men.

Griggs et al[30] administered testosterone enanthate at a dose of 3 mg/kg/wk to healthy men, 19 to 40 years of age. This was an open-label study that was not placebo-controlled. Muscle mass, estimated from creatinine excretion, increased by a mean of 20% and ^{40}K mass increased 12% after 12 weeks of testosterone treatment. In a separate study,[31,32] a similar dose of testosterone enanthate given for 12 months to men with muscular dystrophy was associated with a 4.9-kg increase in lean body mass (approximately 10%) at 3 months; these gains were maintained for 12 months.

Young et al[33] examined fat-free mass by dual-energy x-ray absorptiometry (DEXA) scan in 13 nonathletic men treated with 200 mg testosterone enanthate weekly for 6 months during the course of a male contraceptive study. This was an open-label study that included untreated men as controls. Testosterone treatment increased serum testosterone levels by 90% and was associated with 9.6% increase in fat-free mass and 16.2% decrease in fat mass. Changes in muscle strength varied across different muscle groups; most consistent changes were reported in hip abduction, which increased 19.2%.

Collectively, these data[21,29–33] demonstrate that when dietary intake and exercise stimulus are controlled, supraphysiologic doses of testosterone produce further increases in fat-free mass and strength in eugonadal men. It is likely that strength training may augment androgen effects on the muscle.

EFFECTS OF ANDROGEN REPLACEMENT ON BODY COMPOSITION AND MUSCLE FUNCTION IN HIV INFECTION

Several different anabolic interventions have been examined in the treatment of HIV-related wasting, including appetite stimulants such as dronabinol[48] and megesterol acetate,[49] anabolic hormones such as human growth hormone (hGH),[50,51] insulin-like growth factor I (IGF-I),[51] androgens,[52–62] and modulators of immune response such as thalidomide. Dronabinol increases appetite but has not been shown to increase lean body mass.[48] Similarly, megesterol acetate treatment produces a modest weight gain but no significant change in lean body mass.[49] This progestational agent decreases serum testosterone levels and may produce symptoms of androgen deficiency.

In the two recently published clinical trials, treatment of HIV-infected men with hGH was associated with a 1.5-kg increase in lean body mass.[50,51] Although greater gains in weight were recorded after 6 weeks of hGH treatment, these gains were not sustained with continued treatment for 12 weeks. The reasons for the failure to sustain weight gains during hGH treatment are not clear; it is conceivable that weight gain early in the course of treatment is due to water retention. GH administration is associated with a high frequency of side effects including edema, arthralgias, myalgias, and jaw pain.[50,51] Not surprisingly, the treatment discontinuation rates were high (21% to 40%) in the two hGH studies.[50,51] The annual cost of treating HIV-infected men with hGH is substantially greater than that of testosterone replacement therapy using any of the available androgen formulations (source: Price-Probe, 1997 First Data Bank/Hearst Corporation).

Several studies on the effects of androgen supplementation in HIV-infected men have been reported.[51–62] However, many of these studies were not controlled clinical trials. Most of the studies were of short duration, ranging from 12 to 24 weeks. The energy intake and exercise stimulus were not controlled in most of the studies. Several androgenic corticosteroids, including nandrolone decanoate, oxandrolone, oxymetholone, stanozolol, testosterone cypionate, and testosterone enanthate, have been studied in a limited fashion.

Rabkin et al[57] administered 400 mg of testosterone cypionate biweekly in an open-label study to 75 men with HIV infection and serum testosterone levels <400 ng/dL. Improvements in self-reported mood, sexual behavior, energy, and appetite for food were reported. The average weight gain was 1.5 kg. The study was neither placebo-controlled nor blinded. Furthermore, supraphysiological doses of testosterone were used. In a subsequent report, the same group[58] examined the effects of testosterone on body composition. Bioimpedance analysis was conducted on 29 HIV-infected men receiving 400 mg biweekly of testosterone cypionate. The increase in weight consisted of a 1.2-kg increase in fat-free mass ($p < .005$) and a 0.2-kg decrease in body fat (not significant).

In a study by Bucher et al,[52] treatment with intramuscular injections of 100 mg/week nandrolone decanoate was associated with 1.5-kg weight gain in contrast to a mean 0.15-kg weight loss in the placebo group.

Gold et al[53] conducted an open-label study using 100 mg IM injections of nandrolone decanoate every 2 weeks with no placebo controls. The study was conducted in 24 HIV-infected men who had lost 5% to 15% of their usual body weight. Nandrolone treatment produced a significant increase in weight (mean, 0.14 kg/wk; $p < .05$) and lean body mass (mean, 3 kg; $p < .005$). Quality-of-life parameters and functional capacity also improved significantly during the trial.

Berger et al[54] examined the anabolic effects of oxandrolone in a double-blind, placebo controlled, multicenter study. Sixty-three HIV-positive men with >10% weight loss were randomized to receive either a placebo, 5 mg/d oxandrolone, or 15 mg/d of oxandrolone for 16 weeks. The 15 mg/d oxandrolone group demonstrated statistically significant improvement in weight (1.5 lb), with subjects reporting improvements in appetite, physical activity, and strength. Subjects in the 5 mg/d group maintained their body weight, whereas those receiving placebo continued to lose weight. The study failed to demonstrate changes in muscle strength. Furthermore, body composition data were not reported in this study.

The effects of the testosterone derivative oxymetholone were examined by Hengge et al.[55] Thirty HIV-positive men were randomly assigned to receive either oxymetholone monotherapy or oxymetholone in combination with ketotifen, which has been shown to block tumor necrosis factor alpha. The average weight gain over a 30-week period was 8.2 kg in the oxymetholone group ($p < .001$) and 6.1 kg ($p < .005$) in the combination group, whereas untreated controls lost an average of 1.8 kg. Karnofsky scores also improved in both treatment groups. However, this study was neither placebo-controlled nor blinded and body composition was not evaluated.

In a case study of three AIDS patients with HIV-1 wasting myopathy, Berger et al[54] reported favorable response to Stanozolol, as evidenced by improvements in body weight, strength, muscle bulk, and overall sense of well-being.

Coodley et al[59] examined the effects of 200 mg testosterone cypionate given every 2 weeks for 3 months to 40 HIV-seropositive patients with weight loss of >5% of usual body weight and CD4 cell counts of $<2 \times 10^5$/L in a double-blind, placebo controlled study. Among the 35 patients who completed the first 3 months of the study, there was no significant difference between the effects of testosterone and placebo treatment on weight gain. However, testosterone supplementation improved overall sense of well-being ($p = .03$) and increased muscle strength ($p = .08$). The investigators speculated that the level of testosterone supplementation may have been inadequate to obtain an optimal response. The body composition was not assessed.

Grinspoon et al[61] conducted a placebo-controlled, randomized trial of testosterone supplementation in HIV-infected men with weight loss. Testosterone treatment was associated with significant increments in fat-free mass, measured by DEXA, bioelectrical impedance, and ^{40}K counting. However, there was no significant change in muscle strength in either treatment group.

In a placebo-controlled, double-blind, clinical trial, we examined the effects of physiologic testosterone replacement by means of the nongenital patch.[60] Forty-one HIV-positive men with serum testosterone levels <400 ng/dL were randomly assigned to receive either two placebo patches nightly or two testosterone patches, designed to release 5 mg testosterone over a 24-hour period. Results indicate that physiologic testosterone replacement of HIV-infected men with low testosterone levels was associated with a 1.34-kg increase in lean body mass ($p = .02$) and a significantly greater reduction in fat mass than that achieved with placebo treatment alone.

There were no significant changes in liver enzymes, plasma HIV RNA copy number, and CD4 and CD8+ T-cell counts. There were no significant differences in the change in muscle strength between the two treatment groups over the 12-week treatment duration.

Thus, none of the previous studies of androgen replacement has demonstrated improvements in muscle strength, in part because of the failure to control the exercise stimulus, nutritional intake, and the confounding influence of the learning effect (ie, the ability to lift a greater amount of weight as a result of familiarization with the task and the exercise equipment). Also, the effects of resistance training alone or in combination with testosterone in HIV-infected men are unknown. Therefore, we conducted a randomized, placebo-controlled trial to determine the effects of physiologic testosterone replacement, with or without a program of resistance exercise, on muscle strength in HIV-infected men with weight loss and low testosterone levels. Body weight increased significantly in men receiving testosterone but not in those receiving placebo. Men treated with testosterone alone or exercise alone experienced significant increases in muscle maximal voluntary strength in each of the five exercises tested: leg press, bench press, leg curls, latissimus pulls, and overhead press. There was a greater increase in thigh volume in men receiving testosterone without exercise than in those receiving placebo without exercise. These data demonstrate that testosterone and resistance exercise are both safe and effective in promoting gains in body weight, muscle mass, muscle strength, and lean body mass in HIV-infected men with weight loss and low testosterone levels.

These data on the effects of androgen supplementation in HIV-infected men are encouraging. However, most of these studies were of short duration, and it remains to be seen whether these effects can make a difference in the clinical outcomes of patients with HIV infection. We do not know whether physiologic androgen replacement can produce meaningful changes in the muscle performance, physical function, quality of life, and utilization of health care resources in HIV-infected men. Emerging data indicate that testosterone

does not affect HIV replication, but its effects on virus shedding in the genital tract are not known.

TESTOSTERONE EFFECTS ON FAT METABOLISM

Percent body fat is increased in hypogonadal men.[27] Some studies have reported a decrease in fat mass with testosterone replacement[27,29] therapy, whereas others find no change. Epidemiologic studies[63,64] have demonstrated that serum testosterone levels are lower in middle-aged men with visceral obesity and correlate with plasma HDL levels. Testosterone replacement of middle-aged men with visceral obesity improves insulin sensitivity and decreases blood glucose and blood pressure.[65] Testosterone is an important determinant of regional fat distribution and metabolism in men.[66]

DOES A DEFECT IN 5-ALPHA REDUCTION CONTRIBUTE TO WASTING IN HIV-INFECTED MEN?

Although the enzyme 5-α-reductase is expressed at low concentrations within the muscle,[67] we do not know whether conversion of testosterone to dihydrotestosterone is required for mediating the androgen effects on the muscle. The men with benign prostatic hypertrophy who are treated with the 5-α-reductase inhibitor do not experience muscle loss. Similarly, individuals with congenital 5-α-reductase deficiency have normal muscle development at puberty. These data suggest that 5-alpha reduction of testosterone is not obligatory for mediating its effects on the muscle.

Sattler et al[68] have reported that serum dihydrotestosterone (DHT) levels are lower and levels of conversion of testosterone to DHT higher in HIV-infected men than in healthy men. These investigators have proposed that a defect in testosterone to DHT conversion may contribute to wasting in a subset of HIV-infected men. If this hypothesis were true, then it would be rational to treat such patients with DHT rather than testosterone. A DHT gel is currently under clinical investigation. However, it is worth emphasizing that unlike testosterone, DHT can not be aromatized to estradiol. Therefore, there is concern that suppression of endogenous testosterone and estradiol production by exogenous dihydrotestosterone may produce osteoporosis.

MECHANISMS OF TESTOSTERONE'S ANABOLIC EFFECTS ON MUSCLE

Several studies are in agreement that testosterone produces muscle hypertrophy by increasing fractional muscle protein synthesis.[25,32] However, the molecular basis of this anabolic effect is not known. Urban et al[32] have proposed that testosterone stimulates the expression of insulin-like growth factor (IGF-I) and downregulates insulin-like growth factor binding protein 4 (IGFBP-4) in the muscle. Reciprocal changes in IGF-I and its binding protein thus provide a potential mechanism for amplifying the anabolic signal. It is not clear whether the anabolic effects of supraphysiologic doses of testosterone are mediated through an androgen-receptor–mediated mechanism. *In vitro* binding studies[69–71] suggest that the maximum effects of testosterone should be manifest at about 300 ng/dL. ie. serum testosterone levels that are at the lower end of the normal male range. Therefore. it is possible that the supraphysiologic doses of androgen produce muscle hypertrophy through androgen-receptor–independent mechanisms, such as through an antiglucocorticoid effect.[72–74] We cannot exclude the possibility that some androgen effects may be mediated through nonclassical binding sites. Testosterone effects on the muscle are modulated by a number of other factors such as the genetic background, GH secretory status,[74] nutrition, exercise, cytokines, thyroid hormones, and glucocorticoids. Testosterone also may affect muscle function by its effects on neuromuscular transmission.[75,76]

ANDROGEN ADMINISTRATION IN WOMEN

The ovaries and the adrenal glands collectively produce approximately 300 μg testosterone daily in healthy, menstruating women. Serum testosterone levels are lower in older women than younger women.[77] Women who have undergone hysterectomy and bilateral oophorectomy and have been treated with combined estrogen and testosterone therapy report higher rates of sexual desire, arousal, and number of fantasies than those who are given either estradiol alone or left untreated.[78,79] Sherwin has proposed that testosterone may be important for the maintenance of sexual function in postmenopausal women. Postmenopausal women treated with estrogen plus methyl testosterone have lower rates of bone resorption over a 3-month treatment period than those treated with estrogen alone.[80] Most of the published androgen studies in postmenopausal women have used relatively large doses of testosterone.[78–81] It is not surprising that supraphysiologic doses of testosterone increase muscle size and strength in premenopausal and postmenopausal women. We do not know, however, whether addition of physiologic replacement doses of testosterone to a regimen of estrogen replacement can augment fat-free mass, muscle strength, sexual function, and bone density in postmenopausal women. The critical question is whether these beneficial anabolic effects can be achieved by testosterone doses that do not result in virilization.

Using an improved, sensitive equilibrium dialysis method, we defined the range for total and free testosterone levels during the normal menstrual cycle and measured serum free testosterone levels in HIV-infected women.[82] Serum total and free testosterone levels were lower in HIV-infected women than healthy women. Testosterone levels correlated inversely with plasma HIV RNA copy number. Serum FSH, but not LH, levels were significantly higher in HIV-infected women than controls. Serum total and free testosterone levels are lower in HIV-infected women and correlate inversely with plasma HIV RNA levels. Grinspoon et al[83] also have reported that free testosterone levels are significantly lower in HIV-infected women with early and late wasting. Free testosterone levels correlated with muscle mass, leading these investigators to conclude that low testosterone levels contribute to wasting. However, free testosterone levels reported in

that paper were measured by a tracer analog method. The biologic nature of the fraction being measured by the tracer analog method used in the previous publication remains unclear. The hypothesis that androgen deficiency contributes to wasting in HIV-infected women remains to be tested. Initial clinical trials of the effects of testosterone replacement in HIV-infected women with weight loss have not demonstrated significant increases in lean body mass.[62] It remains to be seen whether clinically significant changes in muscle mass and function can be achieved in HIV-infected women at testosterone doses that do not produce virilization.

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