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# A Randomized, Placebo-Controlled Trial of Nandrolone Decanoate in Human Immunodeficiency Virus-Infected Men with Mild to Moderate Weight Loss with Recombinant Human Growth Hormone as Active Reference Treatment

Thomas W. Storer, Linda J. Woodhouse, Fred Sattler, Atam B. Singh, E. Todd Schroeder, Keith Beck, MaClara Padero, Phong Mac, Kevin E. Yarasheski, Paul Geurts, Arnold Willemsen, Marloes K. Harms, and Shalender Bhasin

*Division of Endocrinology, Metabolism, and Molecular Medicine (T.W.S., L.J.W., A.B.S., M.P., P.M., S.B.), Charles R. Drew University of Medicine and Science, Los Angeles, California 90059; Laboratory for Exercise Science (T.W.S.), El Camino College, Torrance, California 90506; Departments of Medicine and Biokinesiology and Physical Therapy (F.S., E.T.S.), Keck School of Medicine, University of Southern California, Los Angeles, California 90033; Division of Allergy and Immunology (K.B.), Harbor-University of California Los Angeles Medical Center, Torrance, California 90502; Division of Endocrinology, Metabolism, and Lipid Research (K.E.Y.), Washington University School of Medicine, St. Louis, Missouri 63110; and International Medical Services (P.G., M.K.H.) and Clinical Trials Operations-Biometrics (A.W.), Organon, 5340 BH Oss, The Netherlands*

**Objective:** We compared the effectiveness of a biweekly regimen of 150 mg nandrolone with placebo in HIV-infected men with mild to moderate weight loss and contrasted its effects against a Food and Drug Administration-approved regimen of recombinant human (rh)GH.

**Methods:** In this placebo-controlled, randomized, 12-wk trial, placebo and nandrolone (150 mg im biweekly) were administered double blind, and rhGH (6 mg sc daily) was administered in an open-label manner. Participants were HIV-infected men with 5–15% weight loss over 6 months and on stable antiretroviral therapy for more than 12 wk. Lean body mass (LBM), muscle performance, physical function, endurance, hormone levels, insulin sensitivity, sexual function, quality of life, and appetite were assessed at baseline and after 12 wk.

**Results:** Nandrolone administration was associated with a greater increase in LBM (+1.6 ± 0.3 kg) by dual-energy x-ray absorptiometry scan than placebo (+0.4 ± 0.3 kg; $P < 0.05$); however, the change in LBMs with nandrolone was not significantly different from rhGH (+2.5 ± 0.3 kg). Nandrolone administration was also associated with significantly greater gains in fat-free mass (+1.6 ± 0.3 kg), body cell mass (+1.0 ± 0.2 kg), and intracellular water (+0.9 ± 0.2 kg) than placebo; these changes in the nandrolone group were not significantly different from the rhGH group. rhGH administration was associated with greater loss of whole body fat mass and higher frequency of drug-related adverse effects and treatment discontinuations than nandrolone and placebo and a greater increase in extracellular water than nandrolone. Nandrolone treatment was associated with greater improvements in perception of health than rhGH and sexual function than placebo. The cachexia/anorexia scores, health care resource use, and insulin sensitivity did not significantly change.

**Conclusion:** We conclude that nandrolone is superior to placebo and not significantly different from a Food and Drug Administration-approved regimen of rhGH in improving lean body mass in HIV-infected men with mild to moderate weight loss. (***J Clin Endocrinol Metab* 90: 4474–4482, 2005**)

WITH THE ADVENT of highly active antiretroviral therapy, the prevalence of wasting has decreased in the developed countries (1, 2). However, in Africa and Asia where most HIV-infected individuals reside, weight loss is a highly prevalent AIDS-defining illness (3). Even in the United States, weight loss continues to be a significant issue, affecting 31% of HIV-infected individuals during the course of their illness (2, 4). Weight loss during the course of HIV infection is a poor prognostic indicator that is associated with increased risk of hospitalization, opportunistic infection, disability, and death (5–10). Loss of lean body mass (LBM) in HIV-infected individuals is associated with poor health-related quality of life (11). Thus, anabolic interventions that can prevent or reverse weight loss and restore LBM are desirable.

Orexigenic drugs such as tetrahydrocannabinol (12) and megestrol acetate (13) improve appetite and promote weight gain, but they do not restore LBM. Recombinant human (rh)GH has been approved conditionally in the United States for the treatment of HIV-associated weight loss and shown to increase LBM (14–16); however, high frequency of adverse effects and its high cost limit its widespread use. Furthermore, improvements in muscle strength have not been demonstrated with rhGH.

Testosterone supplementation increases LBM, muscle size

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Abbreviations: DEXA, Dual-energy x-ray absorptiometry; FFM, fat-free mass; LBM, lean body mass; PSA, prostate-specific antigen; rh, recombinant human; 1-RM, one-repetition maximum; $\dot{V}O_2$max, a measure of aerobic capacity.

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and strength in HIV-infected men with weight loss (17–19). Nandrolone decanoate (nandrolone), sold under the brand name Deca-Durabolin (Organon, Oss, The Netherlands), is an androgen that is used commonly in the HIV community. Open-label trials suggest that nandrolone increases LBM (20); one randomized trial of nandrolone conducted in Thailand and Brazil (21) demonstrated its superiority over placebo in promoting weight gain. A placebo-controlled trial to test its efficacy in improving LBM in HIV-associated weight loss has not been conducted.

In light of the medical consequences of HIV-associated weight loss, a less expensive, effective, and safer alternative to rhGH could be a useful adjunct in the management of HIV-associated weight loss. We hypothesized that an androgen would be as effective as rhGH in increasing LBM and more effective than rhGH in increasing muscle strength. The primary objective of this study was to compare the effectiveness of 12 wk of nandrolone administration on LBM against a placebo control. Because a direct comparison of rhGH against an androgen has never been conducted, the secondary objectives were to compare the effectiveness of nandrolone treatment on LBM against a rhGH regimen, approved by the Food and Drug Administration (FDA) for HIV-associated weight loss. We also determined the effectiveness of nandrolone and rhGH in improving muscle performance, physical function, endurance, health-related quality of life, sexual function, and appetite.

## Subjects and Methods

### *Human subject review*

Participants signed a consent form approved by the Institutional Review Boards of Charles Drew University, Research and Education Institute, and University of Southern California School of Medicine.

### *Study design*

This was a 12-wk, two-site, randomized trial in which nandrolone and placebo injections were administered double blind, whereas rhGH was administered in an open-label manner. A double-blind design with daily placebo injections was viewed as unacceptable to many patients; also, blinding with rhGH is difficult in practice because of its side effects. The trial was conducted in the General Clinical Research Centers of Research and Education Institute and Keck School of Medicine from December 2000 to October 2002.

### *Participants*

The participants were HIV-infected men older than 18 yr of age with 5–15% weight loss in the preceding 12 months or body mass index between 17 and 19 kg/m$^2$. We excluded subjects who had gained more than 3% body weight over the preceding 2 months. For subjects for whom medical records were available, the weight change was verified from records. The subjects were required to have been on stable antiretroviral therapy with at least two drugs for 12 wk, have CD4+ T lymphocyte count more than 50/cmm, HIV copy number less than 5000/ml, and energy intake more than 80% of recommended daily allowance. We excluded patients with diabetes mellitus, prostate or breast cancer, prostate-specific antigen (PSA) greater than 4 ng/ml, aspartate aminotransferase and alanine aminotransferase more than five times the upper limit of normal, cholesterol or triglyceride more than three times the upper limit of normal, serum creatinine more than 3 mg/dl, and hematocrit less than 0.250 liter/liter or more than 0.500 liter/liter. We excluded men who had in the previous 3 months taken any anabolic agent, including androgens, rhGH, or appetite stimulants. Patients with lipodystrophy were not eligible. Patients who were involved in resistance exercise training or moderate to heavy endurance exercise program were excluded.

### *Randomization and treatment groups*

Eligible subjects were randomly assigned, using computer-generated randomization tables, to one of three groups. Randomization was concealed from the investigating team and the subjects. Group I received arachis oil injections im biweekly, group II 150 mg nandrolone in arachis oil im biweekly, and group III rhGH 6 mg sc daily. The subject allocation was designed to achieve a ratio of 1:2:1 among the three groups. Treatment duration was 12 wk because previous studies of androgens and rhGH have demonstrated significant anabolic effects over this duration.

### *Energy intake and exercise stimulus*

The energy and macronutrient content of the diet were estimated at baseline and 6 and 12 wk from 3-d food records and 24-h food recall. Participants were counseled not to change their nutritional intake during the study; these instructions were repeated every 6 wk. The objective of nutritional counseling was to assure energy intake more than 80% of recommended daily allowance.

Subjects were not allowed to undertake resistance exercise or moderate to heavy endurance training; those involved in mild endurance exercise were allowed to continue.

### *Outcomes*

The primary outcome variable was change from baseline to wk 12 in LBM measured by dual-energy x-ray absorptiometry (DEXA). Secondary outcome variables were other changes in body composition measured by DEXA and bioelectrical impedance, sc fat volume in thigh, sc and visceral fat volume in the abdomen, total body water by deuterium oxide dilution method, and waist to hip ratio. We also measured changes in maximal voluntary strength in the leg press and chest press exercises, leg power, and muscle fatigability. Stair climbing time and power, 400-m walk time, and time to carry a load equal to 15% of body weight were measured. HIV disease status was evaluated by measurements of CD4+ T lymphocyte count and HIV copy number. Insulin sensitivity and glucose disposal indices were assessed by the frequently sampled iv glucose tolerance test, using the Bergman minimal model (22). Total and free testosterone level, LH, FSH, and SHBG levels were measured at baseline and during wk 6 and 12. The Anorexia/Cachexia Recovery Instrument (Bristol-Myers, Princeton, NJ) was used to evaluate appetite, Medical Outcomes Study–Short Form 30 questionnaire to evaluate quality of life, a self-reported diary to assess sexual function, and Depression, Anxiety, Stress Scale-21 questionnaire to evaluate mood.

### *Total body, appendicular and trunk lean, and fat mass by DEXA*

DEXA scan (Hologic QDR 4500A, Waltham, MA), calibrated by using a phantom before each scan, was used to measure lean and fat mass at baseline and during treatment wk 6 and 12. Appendicular lean and fat mass were determined by adding the bilateral arm and leg lean and fat masses (17, 23).

### *Subcutaneous and intraabdominal adipose tissue volumes by magnetic resonance imaging*

Multislice magnetic resonance imaging scans of the thigh and abdomen were obtained using a 1.5 Tesla whole-body Signa Horizon LX scanner, using previously described axial T1-weighted spin-echo sequence (General Electric Medical Systems, Milwaukee, WI) (23). Seventeen transverse slices (10 mm thick, 15 mm apart) were obtained for right thigh, starting with distal border of lateral femoral condyle. Subcutaneous thigh adipose tissue volumes were determined for five sequential slices of the right thigh, including the slice with the largest cross-sectional area plus two slices immediately above and below. Intraabdominal adipose tissue was quantified as the adipose tissue that lay in the intraabdominal cavity, delineated at the inner most aspect of the abdominal and oblique muscle walls surrounding the cavity and anterior aspect of the vertebral body. The images were analyzed by using

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customized software (SliceOmatic version 4.2, TomoVision, Montreal, Canada).

### *Muscle performance, physical function, and endurance*

We measured maximal voluntary strength in the leg press and chest press exercises using the one-repetition maximum (1-RM) method and Keiser equipment with pneumatic resistance (Keiser Sport, Fresno, CA) (24, 25). After a familiarization and warm-up period, the load was increased progressively until the 1-RM was identified as the greatest amount of weight lifted through the complete range of motion. Strength tests were conducted in duplicate on nonconsecutive days with scores required to be within 5%. Failure to meet this criterion required a third test. Only 15% of our subjects required a third test and none required a fourth.

Power in the lower extremity was assessed by using a leg extensor power rig. After an instruction period, subjects performed five to 10 trials of right leg and hip extension, attempting to generate as much force as possible, accelerating the weighted flywheel from rest.

For measurement of muscle fatigability, subjects performed repetitions to failure using 70% of their pretreatment 1-RM for the chest press exercise and 80% of pretreatment 1-RM for the leg press. Total number of repetitions to failure for each exercise was recorded.

We selected three important lower extremity functions for evaluation: stair climbing, walking, and load carrying. Using a modification of the Margaria stair climb test, subjects were asked to ascend a 12-step staircase as fast as possible; the step rise was 17.5 cm. Time of ascent was recorded by photoelectric cells. Three trials were given with the best time taken as the stair-climb score.

Walking speed was determined over a 400-m course. A self-selected walking pace that is as fast as possible was encouraged on a continuous, flat course. We also used a timed load-carrying task that required subjects to traverse a 20-m flat course as fast as possible while carrying a load equal to 15% of their body weight.

### *Cardiopulmonary exercise testing*

To assess aerobic capacity ($\dot{V}O_2max$) and the anaerobic threshold, each participant completed a maximal incremental cardiopulmonary exercise test (26, 27) on a electrically braked cycle ergometer with work rate increments of 10–20 W to provide test durations of 8–12 min. Minute ventilation and gas exchange were measured breath by breath with an automated system (Vmax 229, SensorMedics, Yorba Linda, CA). Maximal oxygen uptake was identified as the highest oxygen uptake observed from 20-sec averages during exhausting work (27). The gas exchange anaerobic threshold was discerned graphically from plots of carbon dioxide output *vs.* oxygen uptake. The oxygen uptake corresponding with the first nonlinear increase in carbon dioxide output was chosen as the anaerobic threshold.

### *Hormone assays*

Hormone levels were measured at baseline, and during wk 6 and 12, 2 wk after previous nandrolone or placebo injection, and 24 h after previous rhGH injection. Serum total testosterone was measured by a previously reported RIA (25, 28) that has been validated against liquid chromatography-mass spectrometry/mass spectrometry. Free testosterone was separated by an equilibrium dialysis procedure and measured by RIA (28). The sensitivity of the total testosterone assay was 0.6 ng/dl; intraassay coefficient of variation was 8.2% and interassay coefficient of variation 13.2%. The cross-reactivity of dihydrotestosterone and nandrolone in the testosterone assay was less than 0.1%. For free testosterone assay, the sensitivity was 0.22 pg/ml, and intra- and interassay coefficients of variation were 4.2 and 12.3%, respectively. LH and SHBG levels were measured by immunoradiometric assays (25).

### *Statistical analyses*

The sample size estimate was based on the results of a randomized trial (21) in which weekly administration of 100 mg testosterone enanthate was associated with 2.3 kg increase in fat-free mass (FFM) with SD of 2 kg after 12 wk. Because an intent-to-treat approach might result in a smaller effect size, we assumed that 150 mg nandrolone biweekly would produce a 2-kg increase in LBM with SD of 2.3 kg. A recent study in Thailand that demonstrated a 2.4-kg average gain in LBM with a similar nandrolone regimen supported these assumptions. A sample size of 40 men in the nandrolone and 20 men in the placebo group had 80% power, at two-sided alpha of 0.05, to detect these differences between nandrolone and placebo groups. All analyses were performed using SAS (version 6.12; SAS Institute, Cary, NC).

Primary analysis was an intent-to-treat analysis that included all subjects who received at least one dose of trial medication and had at least one posttreatment LBM measurement by DEXA. A per-protocol analysis was performed using all subjects from the intent-to-treat group who had no major protocol violations. The efficacy analysis was performed for both the intent-to-treat group and per-protocol group. For the intent-to-treat group, missing values were imputed by carrying the last observation forward.

The primary analysis determined whether nandrolone was superior to placebo in increasing LBM by DEXA, using an intent-to-treat strategy. We used an ANOVA on change in LBM with center and treatment as factors. Secondary analyses included comparison of change in LBM and other outcome variables in the rhGH group against the placebo and nandrolone groups, using a similar approach. $P$ values and confidence intervals for the contrasts between nandrolone and placebo, nandrolone and rhGH, and rhGH and placebo were calculated. All tests were two tailed; $P \leq 0.05$ was considered significant. Because analyses of intent-to-treat and per-protocol groups provided qualitatively similar results, the analyses are presented only for the intent-to-treat group for most variables. No center effect was observed for any variable.

## Results

### *Flow of subjects*

Of 86 subjects who were randomized (43 to nandrolone group, 22 to placebo group, and 21 to rhGH group, Table 1), 85 were treated, 82 completed 6 wk, and 69 completed 12 wk of treatment. Sixteen subjects discontinued prematurely; treatment discontinuation rates were higher in the rhGH group (33%) than in placebo (14%) or nandrolone (14%) groups. Three subjects, receiving rhGH, discontinued because of adverse events, and 13 subjects discontinued due to other reasons. The primary intent-to-treat analysis was performed on 82 subjects.

### *Baseline characteristics of the participants*

The three groups were comparable in their baseline characteristics (Table 2). The intent-to-treat group did not differ significantly from the per-protocol group in its baseline characteristics.

### *Treatment exposure and compliance*

Placebo and nandrolone groups, each received on average 5.7 injections. The average total dose of nandrolone decanoate was 851 mg. The rhGH-treated men received an average of 67 injections and 403 mg rhGH. Compliance was 99.4, 98.8, and 105.1%, for nandrolone, placebo, and rhGH groups, respectively.

**TABLE 1.** Flow of subjects through the study

| No. of subjects | Nandrolone | Placebo | rhGH | Total |
|---|---|---|---|---|
| Randomized | 43 | 22 | 21 | 86 |
| Treated | 43 | 21 | 21 | 85 |
| Assessment at wk 6 | 41 | 21 | 20 | 82 |
| Assessment at wk 12 | 37 | 18 | 14 | 69 |
| Intent-to-treat group | 41 | 21 | 20 | 82 |

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**TABLE 2.** Baseline characteristics of the participants

| Variable | Placebo (n = 21) | Nandrolone (n = 43) | rhGH (n = 21) | All subjects (n = 85) |
|---|---|---|---|---|
| Age (yr) | 41.1 ± 7.4 | 43.9 ± 8.8 | 41.0 ± 6.9 | 42.5 ± 8.1 |
| Height (cm) | 173.7 ± 7.1 | 174.1 ± 8.6 | 176.5 ± 5.8 | 174.6 ± 7.7 |
| Body weight (kg) | 77.2 ± 13.0 | 70.3 ± 10.1 | 74.2 ± 11.5 | 72.9 ± 11.5 |
| Race [n (%)] | | | | |
| Black | 9 (43) | 18 (42) | 8 (38) | 35 (41) |
| Caucasian | 4 (19) | 13 (30) | 5 (24) | 22 (26) |
| Hispanic | 8 (38) | 12 (28) | 8 (38) | 28 (33) |
| Weight loss (%) | 9.4 ± 3.4 | 11.0 ± 4.6 | 9.3 ± 4.8 | 10.2 ± 4.4 |
| CD4+ T lymphocyte (10E6/liter) | 451 ± 267 | 441 ± 281 | 326 ± 216 | 414 ± 265 |
| HIV copy no. (10E3 copies/ml) | 24 ± 75 | 11 ± 25 | 18 ± 36 | 16 ± 43 |
| Total testosterone (nmol/liter) | 16.6 ± 4.9 | 16.9 ± 11.1 | 15.5 ± 3.9 | 16.5 ± 8.5 |

Data are mean ± SD.

*Primary efficacy variable: change in LBM*

By intent-to-treat analysis, there was a significant treatment effect ($P < 0.05$) but no significant center effect ($P = 0.6$) or interaction between treatment and center ($P = 0.8$). The change in LBM from baseline to wk 12, measured by DEXA, was greater in men treated with nandrolone (Fig. 1 and Table 3) than that in men receiving placebo. The change in LBM in the rhGH group was greater than that in placebo. However, there was no significant difference in the change in LBM between men receiving nandrolone or rhGH ($P = 0.3$, Fig. 1).

Analysis of the per-protocol group also revealed a significant treatment effect ($P < 0.01$) and confirmed the superiority of nandrolone (Table 3) and rhGH over placebo. There was no significant difference between change in LBM between the nandrolone and rhGH groups ($P = 0.2$).

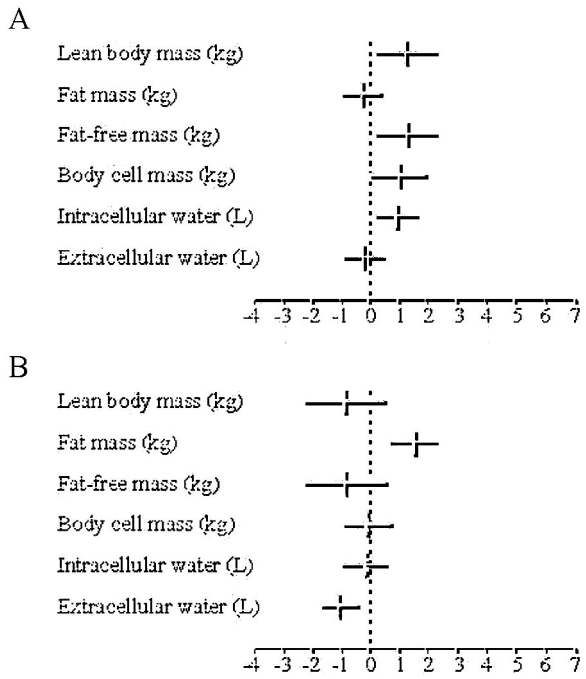


FIG. 1. The 95% confidence intervals of differences between nandrolone and placebo (A) and nandrolone and rhGH (B) in changes in key measures of body composition in the intent-to-treat group, as assessed by DEXA scanning and bioelectrical impedance. LBM, fat mass, and FFM were measured by DEXA scanning. Body cell mass, extracellular water, and intracellular water were calculated from bioelectrical impedance, using a formula validated previously by Kotler *et al.* (7). The *horizontal lines* represent the 95% confidence intervals for contrasts between the nandrolone and placebo groups (A) and between the nandrolone and rhGH groups (B). The *vertical lines* represent the mean contrast between the nandrolone and placebo groups (A) and between the nandrolone and rhGH groups (B). The measurement units are shown in *parentheses*. In comparison with nandrolone treatment, administration of rhGH was associated with greater loss of whole-body fat mass and greater gain in extracellular water.

*Body composition assessment*

Treatment with nandrolone and rhGH each resulted in greater gains in FFM than placebo (Table 3). The changes in FFM in the nandrolone and rhGH groups were, however, not significantly different ($P = 0.3$). Analyses of per protocol group confirmed the superiority of nandrolone over placebo but showed no significant difference from rhGH in altering FFM. The change in FFM during treatment was inversely correlated with the degree of weight loss at study entry but not with baseline serum total or free testosterone level, CD4 T cell count, or HIV copy number.

Total body water measured by deuterium oxide dilution method increased by 1.5 kg in rhGH-treated men and decreased by 1.0 kg in nandrolone-treated men, but these differences were not statistically significant ($P = 0.3$).

**TABLE 3.** Body composition changes by DEXA

| | Placebo | Nandrolone | rhGH |
|---|---|---|---|
| LBM (kg): intent-to-treat group | | | |
| Baseline | 58.6 ± 2.2 | 55.5 ± 1.1 | 56.9 ± 1.2 |
| Wk 12 | 59.0 ± 2.0 | 57.2 ± 1.1 | 59.3 ± 1.5 |
| Change from baseline | 0.4 ± 0.3 | 1.6 ± 0.3[a,b] | 2.5 ± 0.8[a] |
| LBM (kg): per protocol group | | | |
| Baseline | 58.4 ± 2.3 | 55.1 ± 1.3 | 57.6 ± 1.5 |
| Wk 12 | 59.3 ± 2.7 | 56.8 ± 1.4 | 61.0 ± 2.8 |
| Change from baseline | 0.5 ± 0.4 | 2.2 ± 0.4[c,d] | 3.6 ± 1.4[a] |
| FFM (kg) by DEXA: intent-to-treat group | | | |
| Baseline | 61.3 ± 2.2 | 58.1 ± 1.1 | 59.5 ± 1.3 |
| Wk 12 | 61.6 ± 2.0 | 59.7 ± 1.1 | 61.9 ± 1.5 |
| Change from baseline | 0.4 ± 0.3 | 1.6 ± 0.3[a,b] | 2.4 ± 0.5[a] |
| FFM (kg) by DEXA: per protocol group | | | |
| Baseline | 61.0 ± 2.3 | 57.7 ± 1.3 | 60.2 ± 1.6 |
| Wk 12 | 61.9 ± 2.8 | 59.3 ± 1.5 | 63.7 ± 2.8 |
| Change from baseline | 0.4 ± 0.4 | 2.2 ± 0.4[c,d] | 3.6 ± 1.4[c] |

Data are mean ± SEM.
[a] $P$ *vs.* placebo $< 0.05$.
[b] $P$ *vs.* rhGH $= 0.3$.
[c] $P$ *vs.* placebo $< 0.01$.
[d] $P$ *vs.* rhGH $= 0.2$.

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The body composition changes measured by bioelectrical impedance in the intent-to-treat group were similar to those obtained by DEXA (Table 4). The nandrolone group experienced greater gains in LBM, body cell mass, and intracellular water in comparison with placebo (Table 4 and Fig. 1). Changes in LBM ($P = 0.12$), body cell mass ($P = 0.8$), and intracellular water ($P = 0.8$) were not significantly different between the nandrolone and rhGH groups. However, treatment with rhGH was associated with greater increases in extracellular water than placebo ($P = 0.05$) and nandrolone ($P < 0.01$).

*Whole-body and regional fat mass*

Nandrolone (−0.3 kg) and rhGH (−1.9 kg) treatments were each associated with reductions in fat mass; the loss of fat mass was significantly greater in the rhGH group, compared with placebo ($P < 0.01$) and nandrolone ($P < 0.01$) (Table 5).

There was a significantly greater reduction in visceral adipose tissue cross-sectional area in rhGH-treated men (−16.4 $cm^2$) than nandrolone-treated men (+10 $cm^2$, $P < 0.01$) and placebo (−0.1 $cm^2$, $P = 0.17$). The sc adipose tissue in thigh ($P = 0.13$) and waist to hip ratios ($P = 0.4$) did not significantly change.

*Measures of muscle performance, physical function, and endurance (Table 6)*

Maximal voluntary strength in the chest press (change +1.4 kg) and leg press (change +7.8 kg) exercises increased from baseline in men treated with nandrolone ($P < 0.05$ for each); however, these gains in muscle strength were not significantly greater than in placebo ($P = 0.3$ and 0.4, respectively) and rhGH-treated men ($P = 0.3$ and 0.2, respectively; Table 6). Similarly, leg power increased from baseline in nandrolone-treated men (+13.1 W), but these gains were not significantly greater than those in placebo- ($P = 0.13$) or rhGH-treated men ($P = 0.06$).

The 400-m walk time, stair climbing time and power, and time carrying load did not show significant treatment effects. There were no significant changes from baseline in lactate threshold, endurance time, or $\dot{V}O_2$max in any treatment group.

*Health-related outcomes*

Perception of overall health, assessed by the Medical Outcomes Study–Short Form 30 questionnaire, improved to a greater extent in men treated with nandrolone (change score +9.4) than in those receiving rhGH (change −5.3, contrast 15.0, 95% confidence interval 1.3, 28.6; $P < 0.05$). Anorexia/cachexia scores did not change significantly in any group. The percentage of subjects who responded affirmatively to items "easy to achieve an erection" and "satisfied with the sex I have" was higher in the nandrolone (24.4 and 43.9%) and rhGH (35.0 and 45.0%) groups than in the placebo (4.8 and 9.5%) group. Percentage of subjects who reported "lost interest in sex," "difficult to sustain an erection," or "problems achieving an erection" was lower in the nandrolone (22.0, 19.5, and 17.1%) group in comparison with the placebo group (33.3, 28.6, and 33.3%). The number of subjects using sildenafil was similar in the three groups.

**TABLE 4.** Changes in body composition from baseline to wk 12, assessed by bioelectrical impedance: intent-to-treat group

| | Placebo (n = 20) | Nandrolone (n = 37) | rhGH (n = 19) |
|---|---|---|---|
| LBM (kg) | 0.1 ± 0.4 | 1.0 ± 0.2 | 1.9 ± 0.7[a] |
| Body cell mass (kg) | 0.0 ± 0.4 | 1.0 ± 0.2[b] | 1.1 ± 0.4 |
| Fat mass (kg) | 0.3 ± 0.4 | −0.0 ± 0.2[c] | −1.3 ± 0.3[b] |
| Intracellular water (kg) | 0.0 ± 0.4 | 1.0 ± 0.2[b] | 1.0 ± 0.4 |
| Extracellular water (kg) | 0.0 ± 0.2 | −0.0 ± 0.2[d] | 0.9 ± 0.4 |

Data are mean ± SEM.
[a] $P < 0.05$ *vs.* placebo; [b] $P < 0.01$ *vs.* placebo; [c] $P < 0.01$ *vs.* rhGH; [d] $P < 0.05$ *vs.* rhGH.

**TABLE 5.** Changes in whole body fat mass and regional fat distribution: intent-to-treat analysis

| | Placebo | Nandrolone decanoate | rhGH |
|---|---|---|---|
| Whole body fat mass (kg) | 0.0 ± 0.2 | −0.3 ± 0.2[b] | −1.9 ± 0.4[a] |
| Visceral fat volume ($cm^3$) | −0.1 ± 6.7 | 10.0 ± 4.4[b] | −16.4 ± 6.4 |
| Subcutaneous fat volume in abdomen ($cm^3$) | 7.0 ± 5.2 | −0.6 ± 5.1 | −18.1 ± 12.3[c] |
| Subcutaneous fat volume in thigh ($cm^3$) | 46.6 ± 33.1 | −5.4 ± 26.7 | −43.2 ± 26.0[c] |

Whole body fat mass was measured by DEXA scan and visceral, and sc fat volumes were measured by magnetic resonance imaging. Data are mean ± SEM.
[a] $P < 0.01$ *vs.* placebo; [b] $P < 0.01$ *vs.* rhGH; [c] $P < 0.05$ *vs.* placebo.

*Hormone levels*

Nandrolone administration was associated with greater reductions in LH, FSH, and total and free testosterone levels than placebo and rhGH (Table 7). Serum SHBG levels did not change significantly. Serum IGF-I levels increased in rhGH-treated men; the increment in IGF-I levels in the rhGH group was greater than that in the placebo and nandrolone groups ($P < 0.01$ for each comparison; Table 7).

*Safety data*

The percentage of subjects experiencing a drug-related adverse event was higher in the rhGH group (47.6%) than in placebo (4.8%) or nandrolone (4.7%) groups. The most frequent adverse events included peripheral edema (four in the rhGH group), arthralgia (three in the nandrolone group, nine in the rhGH group), and carpal tunnel syndrome (four in the rhGH group). Three subjects, all in the rhGH group, discontinued treatment due to an adverse event. The increment in IGF-I levels in rhGH-treated men who experienced at least one GH-related adverse events (arthralgia, myalgia, leg edema, and carpal tunnel syndrome) was greater than that in men who did not experience these adverse events (147.2 *vs.* 79.7 ng/ml, $P < 0.01$). CD4+ T lymphocyte count, HIV copy number, total cholesterol, plasma high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, and PSA levels did not change significantly (Table 8). Hemoglobin and hematocrit increased in nandrolone-treated men but not in rhGH and placebo groups.

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**TABLE 6.** Changes from baseline in measures of muscle performance, physical function, and endurance: intent-to-treat group

| | Placebo | Nandrolone | rhGH |
|---|---|---|---|
| Measures of muscle performance | | | |
| Leg press strength (kg) | 3.7 ± 4.5 | 7.8 ± 3.0 | −1.8 ± 9.3 |
| Chest press strength (kg) | 0.3 ± 0.9 | 1.4 ± 0.7 | −0.3 ± 1.5 |
| Leg power (W) | −20.7 ± 30.5 | 13.1 ± 4.9 | −29.9 ± 35.5 |
| Fatigability (repetitions) | −0.7 ± 1.4 | 1.2 ± 1.1 | 1.6 ± 2.7 |
| Measures of physical function | | | |
| 400-m walk time (sec) | −1.8 ± 3.6 | −3.4 ± 2.6 | −0.7 ± 4.4 |
| Stair-climbing time (sec) | −0.0 ± 0.0 | −0.0 ± 0.0 | −0.0 ± 0.1 |
| Stair-climbing power (W) | 67.5 ± 34.2 | 27.9 ± 24.9 | 45.9 ± 51.2 |
| Time-carrying load (sec) | −0.2 ± 0.6 | 10.6 ± 11.3 | 0.8 ± 0.8 |
| Measures of endurance | | | |
| Lactate threshold (liters/min) | 0.1 ± 0.1 | 0.0 ± 0.0 | 0.1 ± 0.1 |
| Endurance time (sec) | 23.3 ± 40.4 | 79.3 ± 36.0 | 41.3 ± 73.8 |
| $\dot{V}O_2$ max (liters/min) | 0.1 ± 0.1 | 0.0 ± 0.0 | −0.0 ± 0.1 |

For all parameters, the contrasts nandrolone *vs.* placebo and rhGH and rhGH *vs.* placebo were not significant at the 5% level. Data are mean ± SEM.

*Insulin sensitivity and glucose disposal*

Insulin sensitivity index, measured by the frequently sampled iv glucose tolerance test by using the Bergman minimal model, did not change significantly in any group. Similarly, glucose disposal rates did not show a significant treatment effect ($P = 0.2$).

## Discussion

This randomized, placebo-controlled trial of nandrolone in HIV-infected men with mild to moderate weight loss represents the first, head-to-head comparison of an androgen with rhGH. Administration of nandrolone and rhGH each was associated with significantly greater gains in LBM and FFM than placebo in HIV-infected men with mild to moderate weight loss. The gains in LBM, body cell mass, and intracellular water associated with nandrolone treatment were not significantly different from those associated with rhGH. Whereas nandrolone was associated with modest increments in muscle strength and perception of overall health, rhGH was associated with significant reductions in whole body and visceral adipose tissue mass. rhGH treatment was associated with higher frequency of drug-related adverse events and treatment discontinuations due to adverse events than placebo and nandrolone. Whereas confirming the previously reported effects of rhGH on LBM and body water (15, 16), our study demonstrates that this nandrolone regimen is not significantly different from an FDA-approved rhGH regimen in improving LBM in HIV-infected men with mild to moderate weight loss. The study compared only single-dose regi-

**TABLE 7.** Hormone levels (intent-to-treat group)

| | Placebo | Nandrolone | rhGH |
|---|---|---|---|
| Testosterone (nmol/liter) | | | |
| Baseline | 16.6 ± 1.1 | 16.8 ± 1.9 | 15.7 ± 1.0 |
| Wk 12 | 18.3 ± 1.0 | 6.1 ± 2.2 | 15.1 ± 1.3 |
| Change from baseline | 1.9 ± 1.4 | −10.8 ± 2.9[a,b] | −0.5 ± 1.5 |
| Free testosterone (pmol/liter) | | | |
| Baseline | 145.9 ± 13.3 | 153.3 ± 21.7 | 131.0 ± 11.0 |
| Wk 12 | 158.2 ± 14.4 | 62.1 ± 19.4 | 139.6 ± 14.3 |
| Change from baseline | 14.2 ± 14.3 | −92.1 ± 24.4[a,b] | 1.9 ± 15.0 |
| LH (U/liter) | | | |
| Baseline | 6.2 ± 0.9 | 5.5 ± 0.7 | 5.3 ± 0.6 |
| Wk 12 | 7.4 ± 2.4 | 1.4 ± 0.2 | 4.3 ± 0.7 |
| Change from baseline | −1.0 ± 0.6 | −4.2 ± 0.7[a,c] | −0.9 ± 0.8 |
| FSH (U/liter) | | | |
| Baseline | 5.7 ± 1.3 | 5.3 ± 0.6 | 4.7 ± 0.8 |
| Wk 12 | 4.9 ± 1.0 | 2.0 ± 0.2 | 3.8 ± 0.5 |
| Change from baseline | −0.8 ± 0.5 | −3.5 ± 0.5[a,c] | −1.0 ± 0.6 |
| SHBG (nmol/liter) | | | |
| Baseline | 62.6 ± 10.2 | 64.1 ± 7.2 | 59.7 ± 7.2 |
| Wk 12 | 60.0 ± 8.5 | 54.9 ± 5.4 | 48.7 ± 6.98 |
| Change from baseline | −4.6 ± 3.1 | −7.9 ± 4.5 | −6.5 ± 6.2 |
| IGF-I (μg/liter) | | | |
| Baseline | 183.1 ± 17.6 | 194.2 ± 9.9 | 199.5 ± 15.0 |
| Wk 12 | 187.2 ± 18.9 | 169.0 ± 10.2 | 344.2 ± 56.4[a] |
| Change from baseline | 1.9 ± 10.7 | −18.7 ± 7.6[c] | 126.5 ± 31.8[a] |

Data are mean ± SEM.
[a] *P vs.* placebo < 0.01.
[b] *P vs.* rhGH group < 0.05.
[c] *P vs.* rhGH group < 0.01.

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**TABLE 8.** Changes in safety measures (all-subjects-treated group)

| | Placebo | Nandrolone | rhGH |
|---|---|---|---|
| PSA (μg/liter) | 0.14 ± 0.81 | −0.18 ± 0.56 | −0.39 ± 0.43 |
| Hemoglobin (g/liter) | −8.4 ± 10.5 | 5.2 ± 9.4[a] | −10.4 ± 11.3 |
| Hematocrit (liter/liter) | −0.025 ± 0.033 | 0.013 ± 0.041[a] | −0.032 ± 0.033 |
| Plasma HDL cholesterol (mmol/liter) | −0.2 ± 0.3 | −0.2 ± 0.3 | −0.1 ± 0.3 |
| Creatinine (μmol/liter) | 2.5 ± 13.1 | 11.0 ± 13.6 | 8.2 ± 14.5 |
| CD4+ T lymphocyte counts (*10E6/liter) | 14 ± 24 | 5 ± 18 | 14 ± 16 |
| HIV copy number (*10E3 copies/liter) | 50.7 ± 31.9 | 20.7 ± 16.0 | −8.3 ± 8.0 |

Data are mean ± SEM change from baseline to wk 12 or the last available value. HDL, High-density lipoprotein.
[a] $P < 0.05$ *vs.* placebo and rhGH. For all other parameters, the contrasts nandrolone *vs.* placebo and rhGH and rhGH *vs.* placebo were not significant at the 5% level.

mens of rhGH and nandrolone that had been approved previously by the FDA for HIV-associated wasting or other indications; therefore, these data do not permit a comparison of the relative potency of the two compounds.

The FDA-approved, 6-mg daily dose of rhGH was associated with high frequency of adverse events, including arthralgias, myalgias, leg edema, and carpal tunnel syndrome. Consistent with previous reports (15, 16), one third of rhGH-treated subjects discontinued treatment. Serum IGF-I levels were higher in those rhGH-treated men who experienced at least one GH-related adverse event (arthralgias, myalgias, leg edema, and carpal tunnel syndrome) than in those who did not experience any GH-related adverse event. Lower doses of rhGH might be associated with lower frequency of adverse events than the 6-mg dose; trials to evaluate the efficacy of a lower rhGH dose are in progress. The nandrolone regimen employed a relatively low dose of 150 mg administered every 2 wk. Because the anabolic effects of androgens are related to androgen dose (24, 25), higher doses of nandrolone might induce greater gains in LBM and muscle performance than the dose used in this trial.

Serum LH and FSH levels were suppressed by nandrolone administration; suppression of LH levels was associated with lowering of circulating total and free testosterone concentrations. These data demonstrate that nandrolone is a potent androgen.

More than two thirds of our participants described themselves as either African-American or Hispanic; body mass index of these patients was higher than that reported in some other trials that recruited predominantly Caucasian men. We do not know whether baseline body mass index affects response to anabolic therapy. We selected HIV-infected patients who were medically stable, on stable antiretroviral drug therapy, and ingesting more than 80% of the recommended daily allowance. We do not know whether similar anabolic effects of nandrolone or rhGH can be achieved in HIV-infected patients with more severe disease and reduced energy intake, as is the case with many HIV-infected patients in developing countries.

We do not know how much gain in LBM is needed to improve health-related outcomes. An AIDS Clinical Trials Group expert panel suggested that a 1.5-kg increase in LBM over baseline is clinically meaningful. Therefore, the 1.65-kg gain in nandrolone-treated men and 2.45-kg gain in LBM in rhGH-treated men might be viewed arguably as clinically significant. Nandrolone administration was associated with modest gains in leg press strength and leg power and perceptions of overall health, although these gains were not significantly greater than those observed in the placebo group. This study did not have sufficient power to detect these modest but meaningful differences in the gains in muscle strength and leg power between the nandrolone and placebo groups. Because the measures of physical function used in this study are susceptible to ceiling effects, it is possible that the failure to demonstrate improvements in physical function might have been due to the fact that the baseline function of these medically stable patients exceeded the ceiling required for maximal performance in these tests of physical function.

Several studies of androgen supplementation in HIV-infected men have been reported (17–21, 29–34). Of the five placebo-controlled studies of testosterone replacement in HIV-infected men with weight loss, three (17–19) demonstrated an increase in FFM, and two (31, 32) did not. A systematic review of randomized trials of testosterone therapy in HIV patients with wasting (34) showed a difference in LBM between the testosterone and placebo groups of 1.22 kg for the random effect model. The LBM gains in randomized, testosterone trials ranged from 1.3 to 2.9 kg by DEXA scan. The 1.6-kg gain in LBM in the intent-to-treat group and 2.2 kg gain in per-protocol group associated with nandrolone administration is in line with gains observed in testosterone trials.

rhGH treatment was associated with significant reductions in whole-body and visceral fat mass, whereas nandrolone and placebo treatment had no significant effect. Administration of androgens as well rhGH has been reported to reduce whole body and regional adipose tissue depots (35–39). The lipolytic effects of rhGH have been demonstrated in HIV-infected patients with fat redistribution syndromes (36, 37, 39) and in non-HIV infected, obese individuals (35). Because the effects of testosterone on fat mass are dependent on the dose (23), it is not surprising that the relatively small dose of nandrolone used in this trial had no significant effect on whole-body and visceral fat mass. Previous studies that have reported significant reductions in fat mass, especially visceral fat mass, were of longer duration (23). It is possible that higher doses of nandrolone than those used in this study, administered for a longer treatment duration than that used in this study, might have resulted in a decrease in visceral fat mass; however, this is only a speculation. Whereas rhGH promotes lipolysis (39), there is growing evidence that androgens inhibit the differentiation of pluripotent mesenchymal cells into adipogenic lineage (40).

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Nandrolone and rhGH were both effective in increasing LBM in HIV-infected men with mild to moderate weight loss. rhGH is expensive and its administration is associated with high frequency of adverse events and treatment discontinuations due to adverse events. Therefore, an androgen regimen might be an attractive alternative or an adjunct to rhGH therapy because of its lower cost, lower frequency of adverse events, and greater potential for augmenting muscle strength and power. rhGH was more effective in decreasing whole-body and visceral fat mass than placebo and nandrolone, and its usefulness in the treatment of fat redistribution syndromes is being evaluated.

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Address all correspondence and requests for reprints to: Thomas W. Storer, Ph.D., Professor of Medicine, University of California, Los Angeles School of Medicine, Director, Laboratory of Exercise Sciences, El Camino College, Division of Endocrinology, Metabolism, and Molecular Medicine, Charles R. Drew University of Medicine and Science, Los Angeles, California 90059. E-mail: tstorer@elcamino.edu.

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