Resistance Exercise and Supraphysiologic Androgen Therapy in Eugonadal Men With HIV-Related Weight Loss

A Randomized Controlled Trial

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Context Repletion of lean body mass (LBM) that patients lose in human immunodeficiency virus (HIV) infection has proved difficult. In healthy, HIV-seronegative men, synergy between progressive resistance exercise (PRE) and very high-dose testosterone therapy has been reported for gains in LBM and muscle strength.

Objective To determine whether a moderately supraphysiologic androgen regimen, including an anabolic steroid, would improve LBM and strength gains of PRE in HIV-infected men with prior weight loss and whether protease inhibitor antiretroviral therapy prevents lean tissue anabolism.

Design Double-blind, randomized, placebo-controlled trial; post hoc analysis for effect of HIV-protease inhibitor therapy conducted from January to October 1997.

Setting Referral center in San Francisco, Calif.

Patients Volunteer sample of 24 eugonadal men with HIV-associated weight loss (mean, 9% body weight loss), recruited from an AIDS clinic and by referral and by advertisement.

Intervention For 8 weeks, all subjects received supervised PRE with physiologic intramuscular testosterone replacement (100 mg/wk) to suppress endogenous testosterone production. Randomization was between an anabolic steroid, oxandrolone, 20 mg/d, and placebo.

Main Outcome Measures Lean body mass, nitrogen balance (10-day metabolic ward measurements), body weight, muscle strength, and androgen status.

Results Twenty-two subjects completed the study (11 per group). Both groups showed significant nitrogen retention and increases in LBM, weight, and strength. The mean (SD) gains were significantly greater in the oxandrolone group than in the placebo group (5.6 [2.1] vs 3.8 [1.8] g of nitrogen per day [$P = .05$]; 6.9 [1.7] vs 3.8 [2.9] kg of LBM [$P = .005$]; greater strength gains for various upper and lower body muscle groups by maximum weight lifted [$P = .02$-$.05$] and dynamometry [$P = .01$-$.05$]). The mean (SD) high-density lipoprotein cholesterol level declined 0.25 (0.14) mmol/L (9.8 [5.4] mg/dL) significantly in the oxandrolone group ($P < .001$ compared with placebo). Results were similar whether or not patients were taking protease inhibitors. One subject in the oxandrolone group discontinued the study because of elevated liver function test results.

Conclusions A moderately supraphysiologic androgen regimen that included an anabolic steroid, oxandrolone, substantially increased the lean tissue accrual and strength gains from PRE, compared with physiologic testosterone replacement alone, in eugonadal men with HIV-associated weight loss. Protease inhibitors did not prevent lean tissue anabolism.

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THE PRIMARY AIM OF THERAPY IN wasting syndromes is to restore lean tissue.[1,2] The use of alimentation or appetite stimulants in wasting due to human immunodeficiency virus (HIV) has, however, resulted in fat deposition with little lean tissue gains.[3-6] Administration of HIV-protease inhibitors to patients with acquired immunodeficiency syndrome (AIDS) also results in weight gain, but most of the weight gained is body fat.[7-10] Alterations in the metabolic or endocrine milieu,[11,12] inadequate exercise, or other factors may be responsible for disproportionate fat vs lean body mass (LBM) gains in HIV infection. Recombinant growth hormone (rGH)[13,14] and androgen replacement therapy in men with low or borderline low serum testosterone concentrations[15,16] are effective in restoring LBM in men with HIV infection.

See also pp 1275 and 1326.

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The high cost of rGH has limited its use in clinical practice; however, many men with HIV-related weight loss are eugonadal. The use of androgens has not proved effective in the latter group. The optimal strategy for increasing LBM in eugonadal men with HIV-associated weight loss remains uncertain.[17]

Bhasin et al[18] performed an important study documenting the interaction between progressive resistance exercise (PRE) and very high intramuscular dosages of testosterone (600 mg/wk, or 6 times the usual replacement dosage) in healthy, eugonadal men. The combined intervention resulted in significantly greater increases in LBM, muscle size, and strength than either intervention alone. However, the long-term safety and behavioral consequences of testosterone at dosages as high as 600 mg/wk are unknown.

Based on these results in healthy men,[18] we performed a randomized, placebo-controlled trial among men with HIV infection. The prospectively defined hypotheses were, first, that a supraphysiologic androgen regimen would increase the LBM and strength gains from PRE in eugonadal men with HIV-associated weight loss and, second, that this interaction would not require extremely high doses of androgens. A subgroup analysis was also included addressing whether protease inhibitor antiretroviral therapy prevents lean tissue anabolic response in HIV-infected men.

METHODS

Experimental Design

The design was a prospective, randomized, placebo-controlled trial to compare supervised PRE plus physiologic testosterone replacement (placebo) with the same regimen combined with supplementation with an anabolic steroid, oxandrolone, at a dose that is approved and is well tolerated over the long-term.[19-21] All subjects received intramuscular injections of testosterone enanthate (100 mg/wk). Those in the placebo group took placebo tablets and those in the oxandrolone group took oxandrolone tablets 20 mg/d (both tablets were provided by Bio-Technology General Corporation, Iselin, NJ) (FIGURE 1). Oxandrolone and placebo tablets were identical in appearance, taste, and texture. The supervised PRE program was held 3 times a week. Individual treatment group assignments were based on a random number–generated sequence generated by an independent study monitor (Bio-Technology General Corporation), which was double-blinded to all study personnel, including exercise trainers. The assignment was executed independently by study personnel (A.S.) in San Francisco, Calif. The subjects were stratified post hoc for use of protease inhibitors. The code was held by the independent study monitor who remained anonymous to all study personnel. The envelope containing the randomization code was delivered to the principal investigator and the code was broken in San Francisco with the study personnel present. All data analyses and statistical comparisons were completed before the code was broken.

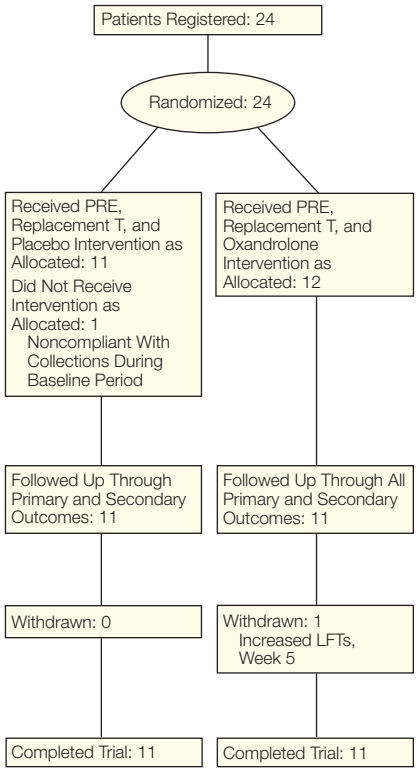
The therapeutic trial lasted 8 weeks (Figure 1). Two 10-day inpatient admissions to a metabolic research unit (MRU) were carried out to assess nitrogen balance and measures of metabolism. The first MRU admission began 10 days prior to treatment (days –10 to 0), and the second between days 21 and 30 of treatment.

Subjects. Twenty-four men who acquired HIV or AIDS through homosexual transmission were recruited from the AIDS-wasting clinic at San Francisco General Hospital, through referrals, and through advertisements at a San Francisco food bank. The protocol was approved by the committees on human research of the University of California, San Francisco, University of California, Berkeley, and the US Department of Agriculture. Informed consent was obtained for all procedures.

Inclusion Criteria. Patients were included if they (1) were HIV-seropositive; (2) had experienced at least a 5% weight loss during the preceding 2 years; (3) were clinically stable with no active opportunistic infections and weight stable during the preceding 3 months; (4) were eugonadal (serum total testosterone concentration of 7.8-31.2 nmol/L [225-900 ng/dL]); (5) had maintained a stable antiretroviral regimen for at least 3 months; (6) were not currently or previously participating in PRE or aerobic exercise; and (7) could comply with protocol and give informed consent.

Exclusion Criteria Patients were excluded if they had (1) used testosterone or other androgens in the 3 months preceding the study; (2) used medications or dietary supplements known to alter nutritional status including marinol, megestrol acetate, rGH, thalidomide, pentoxifylline, glucocorticoids, or dehydroepiandrosterone in the 3 preceding months; (3) used investigational agents; (4) had severe diarrhea

Figure 1. Progress of Patients Through Randomized Controlled Trial



T indicates testosterone enanthate, 100 mg intramuscularly per week; PRE, progressive resistance exercise; and LFT, liver function test results.

Table 1. Baseline Characteristics of Subjects Who Completed the Metabolic Research Unit Phase of the Study*

	Placebo (n = 11)	Oxandrolone (n = 11)
Age, y	40 (8)	42 (7)
Serum total testosterone levels, nmol/L [ng/dL]	22.7 (11.2) [655 (322)]	20.9 (6.7) [603 (192)]
CD4 cells, $\times 10^9$/L	0.337 (0.236)	0.234 (0.097)
Plasma viral load, $\log_{10}$ copies/mL	4.9 (5.3)	3.9 (4.3)
Weight, kg	73.3 (14.7)	68.8 (9.6)
Percentage of usual body weight	91 (4)	92 (2)
Body mass index, kg/m^2	23.1 (3.5)	22.3 (2.5)

*Data are presented as mean (SD). No group measures were significantly different by unpaired *t* test at baseline. All patients participated in progressive resistance exercise.

(≥3 loose bowel movements per day), chewing or swallowing difficulties, oropharyngeal pain, or inadequate access to food; and (5) had comorbid medical conditions or abnormalities in screening laboratory test results (blood cell count, chemistry profile).

Thirteen of 24 subjects were taking HIV-protease inhibitor antiretroviral agents in combination with nucleoside and/or nonnucleoside reverse transcriptase inhibitors. Other patient characteristics are shown in TABLE 1. There were no significant differences between assignment groups for any potential prognostic variables (eg, age, weight, prior weight loss, CD4 cell counts, viral load, serum testosterone levels).

Metabolic Ward Protocol

Subjects were confined to the MRU of the Western Human Nutrition Research Center in San Francisco for both 10-day inpatient periods. Energy requirements were estimated using the Harris-Benedict equation with a physical activity level of 1.6.[22] Food was provided to match these requirements. Meals were under strict supervision and subjects were required to eat all food provided. Food not eaten was presented at the next meal. During the baseline MRU study, exercise level was sustained through 2 chaperoned walks of 1 km daily. No other exercise was permitted. Weight remained stable to within 2% of starting weight, or dietary alterations were made. For the follow-up MRU admission, the energy requirements were calculated based on readmission weight; food was adjusted during the first 4 days in response to reports of hunger (increments of 418 kJ/d).

During the free-living periods, subjects returned to the study site weekly to receive medication and testosterone injections.

Exercise Protocol. The major muscle groups were worked according to a defined protocol individually tailored to each subject's exercise capacity, based on the 1-repetition maximum (1-RM) measured at baseline.[23] Each subject was assigned to a personal trainer who was present at every exercise session. Three exercise trainers participated in the study. The protocol involved three, 1-hour training sessions of resistance exercise per week on nonconsecutive days, alternating between upper and lower body workouts, consisting of 6 upper body exercises and 3 lower-body exercises performed on standard weight-stack isotonic exercise equipment. Three sets of each exercise were performed during a session; each set consisted of 10 repetitions of the exercise at approximately 80% of the subject's 1-RM. Reassessment of 1-RM was performed at week 4, and the weights were adjusted accordingly. All subjects were able to progress appropriately during the study. No subjects complained about the exercise intensity or dropped out because the exercise was too difficult.

Nitrogen Balance. Twenty-four-hour urine and stool collections were carried out each day in the MRU. Nitrogen balance assessment began on the fourth day of each 10-day inpatient phase to allow initial equilibration.

Total urinary nitrogen was analyzed by combustion[24] (LECO nitrogen determinator, FP-428 Corporation, St Joseph, Mich). Daily urinary creatinine levels were analyzed by spectrophotometric assay (Roche Diagnostic Systems, Somerville, NJ).[25] Stool aliquots were homogenized, lyophilized, crushed, dried, and analyzed for nitrogen content using the LECO analyzer. The SD of repeated measurements of 24-hour nitrogen output in this MRU is less than 0.5 g/d (M.V.L., J.K. unpublished data, April 1997).

Diet composition for both MRU admissions was the same. The mean (SD) protein intake was 1.47 (0.0) g/kg per day (16.1% [0.4%] of dietary energy); 53.4% (0.8%) of dietary intake was from carbohydrate, and 30.7% (0.3%) from fat. The nitrogen content of the diet was verified by combustion. This protein intake is within the range of recommended dietary intake for wasted patients and is the same as we have used previously.[15]

Stable Isotope/Mass Spectrometric Studies of de Novo Lipogenesis. De novo lipogenesis was measured by mass isotopomer distribution analysis.[26-28] A constant intravenous infusion of sodium [1-^{13}C]acetate (99% atom enriched, Isotec Inc, Miamisburg, Ohio) at 5.2 mmol/h was performed from 2 AM to 6 PM. Subjects fasted from 8 PM until 9 AM, then ate ad libitum.

Very low-density lipoprotein was isolated from plasma by ultracentrifugation and transesterified for analysis by gas chromatography-mass spectrometry.[26] The isotopic enrichment of the intrahepatic acetyl-coenzyme A precursor pool and the contribution from de novo lipogenesis to very low-density lipoprotein palmitate were calculated by mass isotopomer distribution analysis.[26,27]

Weight, Height, and Body Composition. Each morning before breakfast subjects were weighed. Body composition was measured by dual-energy x-

ray absorptiometry (DEXA; Model DPX, Lunar, Madison, Wis). The reproducibility of DEXA for repeated measurements of body composition in the same individual is better than 0.5% (M.V.L., unpublished data, May 1997).

Resting Energy Expenditure (REE). Resting energy expenditure was measured by indirect calorimetry using a Deltatrac metabolic monitor (SensorMedics, Yorba Linda, Calif) in the canopy mode for 30 minutes shortly after awakening.

Muscle Strength Testing. *One-Repetition Maximum Testing.* One-repetition maximum testing was carried out with the same exercise equipment used for training. Subjects were given instruction and an opportunity to practice during a trial session.

Isokinetic Dynamometer Testing. Strength and endurance were tested by an isokinetic dynamometer (Cybex 6000, Ronkonkoma, NY). Cybex testing was chosen to minimize the effects of neuromuscular learning on measurement outcome since the subjects' training regimen did not involve the Cybex. Right quadriceps and shoulder muscle strength were assessed by measurement of peak torque (maximal force) during 3 complete repetitions of flexion and extension at a constant angular velocity of 60° per second.

Serum Gonadal Hormones and Urine Androgen Screening. Serum gonadal hormone levels were measured by radioimmunoassay (Diagnostic Products Corporation, Los Angeles, Calif). In addition, liquid chromatography–mass spectrometry–mass spectrometry and gas chromatography–mass spectrometry were used to screen urine samples at baseline and week 8 for metabolites of oxandrolone and other widely available testosterone analogs (nandrolone, danazol, stanozolol, methyltestosterone, and fluoxymesterone) as a check of compliance.[29,30] The urine testosterone to epitestosterone ratio was also measured as an index of exogenous testosterone administration.[29,30]

Quality of Life Measurements. A portion of the Medical Outcomes Study–HIV Specific Questionnaire[31] was administered before and after intervention.

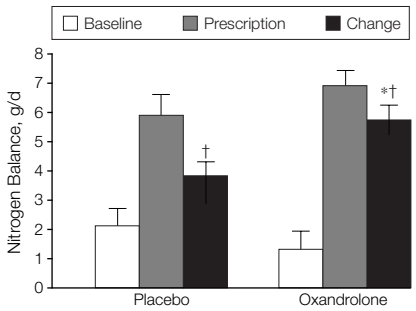
Blood Chemistries. Routine blood chemistries, CD4 lymphocyte count, and measurement of serum HIV viral load were carried out by SmithKline-Beecham Laboratories (San Francisco, Calif).

Open-Label Phase. A 12-week open-label phase was offered to subjects who completed the placebo-controlled study, during which time testosterone, oxandrolone, and supervised PRE continued to be provided. DEXA scans were performed at the conclusion of the 12 weeks. Reassessment of 1-RM was performed every 4 weeks and the weights were adjusted accordingly.

Statistical Analysis

Results are expressed as mean (SD) unless otherwise indicated. Statistical significance was determined using Statview computer software (Abacus Concepts, Berkeley, Calif). A significance level of .05 was used. Unpaired 2-tailed *t* tests were used to assess differences between groups at baseline. Repeated measures analysis of variance was used to compare treatment effects over time, with a group factor (treatment) and a trial factor (time). When a significant treatment by time interaction was observed, follow-up comparison was performed using the Tukey Studentized range test at a procedurewise rate of 0.05. Correlations were performed using the Pearson product moment. Analyses were performed on study completers, not on an intention-to-treat basis. The primary outcome measures were nitrogen retention, body composition changes, and muscle strength. Secondary outcome measures were gonadal hormone concentrations, REE, and de novo lipogenesis. The sample size of 12 was calculated to detect a standardized effect size of 0.9 (for effect within each group) and 1.2 (for comparison of effect between groups) for change in LBM, using (1) an estimated SD of between 1.0 and 2.0 kg LBM for the response to effective anabolic therapies in HIV-associated wasting,[14,15] and (2) the uncertain biologic significance of LBM changes less than about 1.0 to 1.5 kg in magnitude. Accordingly, n = 12 per group was selected to detect differences in LBM of 2 kg between groups at $P = .05$, with 80% power.

Figure 2. Nitrogen Retention Following Treatment



Data are presented as mean (SD) grams of nitrogen retained per day. The asterisk indicates significantly different change between groups by repeated measures analysis of variance ($P<.05$); the dagger, significantly different change from baseline by the Tukey follow-up procedure ($P<.05$). The coefficient of variation in the creatinine levels, which were measured every 24 hours, for the study group was 17.8% (5.3%), which is within the published acceptable range[25] and which indicates satisfactory completeness of daily urine collection.

RESULTS

Subject Completion

Of the 24 subjects enrolled, 23 completed both inpatient studies, with 22 completing the 8-week study (Figure 1). One subject from the placebo group was disqualified from the study for noncompliance with sample collections during the first inpatient phase. Another subject in the oxandrolone group discontinued at week 5 because of elevated liver function test results. Seventeen of the 22 subjects entered the open-label phase of the study; all 17 completed the 12-week follow-up.

Nitrogen Balance

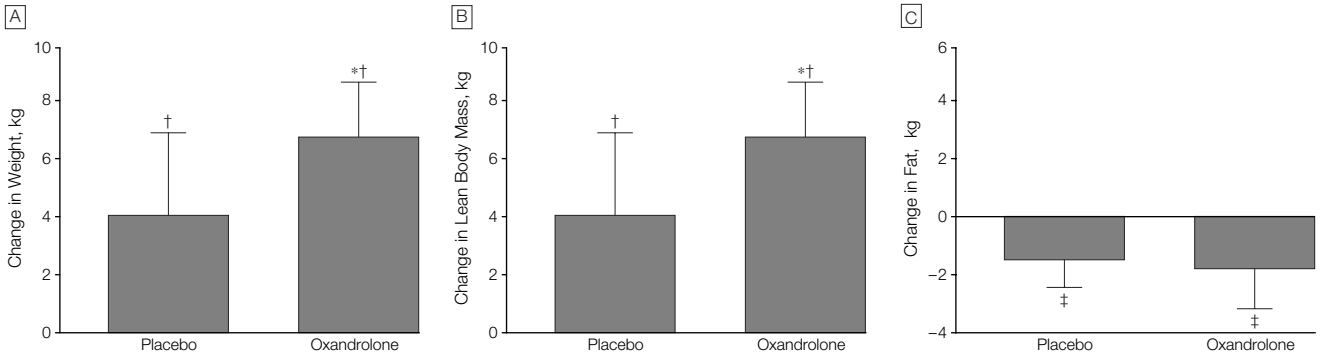
There was a significantly greater cumulative nitrogen retention observed in the oxandrolone group compared with the placebo group (5.6 [2.1] g/d vs 3.8 [1.8] g/d). The change from baseline was significant for both groups (FIGURE 2). All 22 subjects showed an increase in nitrogen retention. There were no differences between the 2

groups for baseline nitrogen balance. Five of the 22 subjects had slightly negative nitrogen balance at baseline, 2 in the placebo group and 3 in the oxandrolone group. Assuming that each gram of retained nitrogen represents 32 g of LBM,[31] the predicted LBM gains are 0.9 (0.4) kg/wk in the placebo group and 1.3 (0.5) kg/wk in the oxandrolone group. Use of protease inhibitors had no effect on nitrogen retention.

Weight and Body Composition

There was significant weight gain in both groups ($P<.05$ for time effect vs baseline); the mean (SD) gains were significantly greater in the oxandrolone group than in the placebo group(6.7 [2.0] kg vs 4.2 [2.8] kg; $P=.03$)(FIGURE 3, A). Increases in LBM were significant in both groups relative to baseline ($P<<.05$ for time effect), with a significantly greater increase in the oxandrolone group than in the placebo group (6.9 [1.7] kg vs 3.8 [2.9] kg; $P<=.005$) (Figure 3, B). Regional distribution of accrued LBM by DEXA was not significantly different between the groups. The percentages of total LBM gain by region for those in the oxandrolone group were arms, 20.4% (1.9%); legs, 34.4% (2.3%); and trunk, 45.2% (3.3%). For those in the placebo group, it was arms, 21.2% (8.7%); legs, 21.3% (7.0%); and trunk 57.5% (7.0%).

Figure 3. Change in Body Weight and Body Composition by Dual-Energy X-ray Absorptiometry at Week 8



Data are presented as mean (SD). The asterisk indicates significantly different change between the groups by repeated measures analysis of variance ($P<.05$); dagger, significantly different change from baseline by the Tukey test follow-up procedure ($P<.05$); and double dagger, significant change from baseline in both groups ($P<.05$), which is not significantly different between the groups by repeated measures analysis of variance.

Table 2. Exercise Capacity*

	Placebo			Oxandrolone		
	Baseline	8 Week	Change	Baseline	8 Week	Change
			1 Repetition, Maximum lbs			
Chest press	138 (38)	159 (36)	21 (31)‡	143.0 (40)	190.0 (54)	47 (25)†‡
Shoulder press	76.5 (39)	90.5 (36)	14.0 (16)§	61 (15)	84 (16)	23 (12)§
Biceps pull	41.7 (16)	48.1 (18)	6.4 (6)‡	36.0 (10)	50.0 (15)	14 (9)†‡
Triceps push	57.0 (13)	66.3 (15)	9.3 (7)‡	59.1 (10)	77 (13)	17 (11)†‡
Leg press	186 (75)	232 (80)	46 (18)‡	177 (25)	241 (38)	64 (35)†‡
Leg extension	129 (69)	168.8 (76)	39.8 (27)§	126 (30)	173 (46)	47 (31)§
			Cybex Shoulder Strength, ft-16			
Shoulder strength						
Flexion, PT 60°/s	37.2 (8.3)	37.7 (9.0)	0.5 (4.4)	34.3 (5.2)	39.1 (8.1)	4.8 (4.8)†‡
Extension, PT 60°/s	50.5 (9.6)	54.7 (12.4)	4.2 (5.4)	49.4 (8.6)	60.6 (12.9)	11.2 (6.2)†‡
Flexion, TW	84.0 (17.9)	81.5 (17.6)	−2.5 (12.1)	76.6 (13.6)	83.0 (21.9)	6.4 (14.8)‡
Extension, TW	126.0 (26.6)	125.5 (25.3)	−0.5 (13.2)	120.0 (23.3)	132.7 (27.5)	12.7 (18.6)‡
Knee strength						
Flexion, PT 60°/s	72.1 (20.2)	75.4 (17.7)	3.3 (10.7)§	67.8 (10.0)	77.3 (14.6)	9.5 (9.9)§
Extension, PT 60°/s	104.4 (34.5)	111.5 (28.4)	7.1 (16.2)§	106.7 (18.0)	120.5 (26.5)	13.8 (17.4)
Flexion, TW	83.5 (22.4)	84.2 (20.3)	0.7 (10.9)	83.3 (8.9)	85.7 (17.3)	2.4 (19.6)
Extension, TW	107.7 (32.5)	111.8 (26.7)	4.1 (20.5)	115.8 (13.7)	122.8 (28.7)	7.0 (23.8)

*Data are presented as mean (SD). All patients received testosterone and participated progressive resistance exercise. PT indicated peak torque; TW, total work.
†Significantly different change between groups by repeated measures analysis of variance ($P<.05$).
‡Significantly different change from baseline by Tukey test follow-up ($P<0.5$).
§Significant change from baseline in both groups by repeated measures analysis of variance.

The rate of LBM gain for those in the oxandrolone group was 0.9 (0.2) kg/wk, and for those in the placebo group, it was 0.5 (0.4) kg/wk. There were no differences in weight, LBM, or fat changes between subjects taking and those not taking protease inhibitors. The correlation between the change in nitrogen balance and the change in LBM was significant ($P<.05$, $r^2 = 0.46$).

A statistically significant decrease in fat occurred in both groups at week 8 ($P = .005$), which was not different between groups (oxandrolone, 1.7 [2.8] kg; placebo, 1.6 [1.9] kg). A significant increase in bone mineral content was also observed in both groups ($P<.001$ for time effect), which was not different between groups (oxandrolone, 105 [101] g; placebo, 80 [83] g).

Resting Energy Expenditure. Baseline REE was not significantly different between groups. For the placebo group it was 7414 (874) kJ/d (1772 [209] kcal/d), and for the oxandrolone group it was 6916 (1004) kJ/d (1653 [240] kcal/d), which was 106% (14%) of the values predicted. After the treatment phase, there was a significant increase in REE in the oxandrolone group compared with the placebo group (1213 [1004] kJ/d [290 {240} kcal/d] vs 377 [753] kJ/d [90 {180} kcal/d]; $P = .03$). When expressed per kilogram of LBM, the difference in REE between groups was no longer significant.

One-Repetition Maximum Testing. Improvements in strength from baseline were observed for all upper and lower body muscle groups in the oxandrolone and the placebo groups ($P<.05$) (TABLE 2). The increase in the oxandrolone group was significantly greater than in the placebo group for chest press ($P = .04$), biceps pull ($P = .04$), triceps push ($P = .05$), and leg press ($P = .02$). There were no differences between subjects taking and those not taking protease inhibitors.

Cybex Testing

Significant improvements from baseline were also seen in force of flexion, extension, and total work measured by dynamometer testing of both the shoulder and knee muscles in both groups (Table 2). The changes in shoulder strength were significantly greater in the oxandrolone group than in the placebo group for measures of both flexion ($P = .04$) and extension ($P = .01$). The changes in lower body (knee) strength were not significantly different between groups. There were no differences between subjects taking and not taking protease inhibitors.

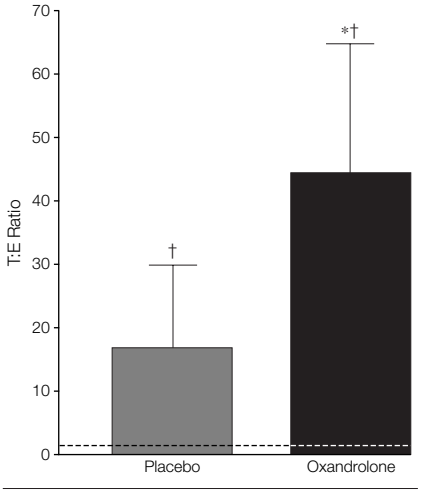
Table 3. Change in Serum Hormone Status After Treatment*

Measurement	Placebo	Oxandrolone
Total testosterone levels, nmol/L [ng/dL]		
After treatment	19.0 (3.2) [548 (92)]	16.9 (4.2) [486 (122)]
Change from baseline values	–3.7 (3.3) [–108 (95)]	4.1 (5.1) [–117 (148)]
Luteinizing hormone, IU/L		
After treatment	0.5 (0.2)†	0.1 (0.1)†
Change from baseline values	–1.8 (0.5)	–3.0 (0.5)
Follicle-stimulating hormone, IU/L		
After treatment	1.2 (0.4)†	0.1 (0.1)†
Change from baseline values	–3.7 (1.1)	–4.7 (1.1)

*The posttreatment value was measured at the 7-day nadir after the weekly 100-mg intramuscular testosterone injection. Data are presented as mean (SEM). All patients received testosterone and participated in progressive resistance exercise.
†Significant change from baseline for the 2 groups ($P<.05$), which was not significantly different between the groups by repeated measures analysis of variance. Normal ranges for serum total testosterone levels are 7.8 to 31.2 nmol/L [225-900 ng/dL]; luteinizing hormone, 0.4 to 5.7 IU/L; and follicle-stimulating hormone, 1.1 to 13.5 IU/L.

Serum Gonadal Hormone Concentrations and Urine Screening for Androgens. The endogenous gonadal axis was suppressed in both groups compared with baseline, with significant decreases in luteinizing hormone ($P<.001$) and follicle-stimulating hormone levels ($P<.001$), but there were no differences between groups (TABLE 3). Serum total testosterone levels were within the normal range and were not significantly different between groups or from baseline. All subjects' urine tested negative for all anabolic steroids other than oxandrolone at baseline and during the treatment period. Oxandrolone was undetectable in all subjects at baseline and in the placebo group during treatment but was present in all subjects in the oxandrolone group during treatment. The testosterone to epitestosterone ratio was similar to published normal values (median, 1.1)[30] in both groups at baseline (oxandrolone, 1.4 [1.4]; placebo, 1.1 [1.1]), and increased significantly from baseline in both groups ($P<.05$ for time effect). The significantly greater increase in testosterone to epitestosterone ratio in the oxandrolone group compared with the placebo group (44.0 [25.0] vs 16.7 [12.8], after treatment; $P = .002$) (FIGURE 4) suggests that residual endogenous androgen synthesis in the presence of testosterone replacement alone was more completely suppressed by the addition of oxandrolone.

Figure 4. Change in Testosterone-Epitestosterone (T:E) Ratio Following Treatment at Week 4



The asterisk indicates significantly different change between groups by repeated measures analysis of variance ($P = .002$); dagger, significantly different change from baseline by the Tukey test follow-up procedure ($P<.05$); and dotted line, T:E ratio.

Stable Isotope/Mass Spectrometric Measurement of de Novo Lipogenesis. Baseline de novo lipogenesis was elevated in both groups, compared with

Table 4. Change in Blood Parameters*

Measurements	Placebo	Oxandrolone
CD4 cell count, $\times 10^9$/L		
After treatment	0.310 (0.260)	0.234 (0.108)
Change from baseline values	−0.028 (0.087)	0.0 (0.057)
High-density lipoprotein cholesterol, mmol/L [mg/dL]		
After treatment	0.89 (0.46) [34.2 (17.8)]	0.44 (1.1) [16.9 (4.1)]†
Change from baseline values	−0.02 (0.11) [−0.7 (4.4)]	−0.25 (0.14) [−9.8 (5.4)]‡
Total cholesterol, mmol/L [mg/dL]		
After treatment	4.5 (1.1) [173 (42)]	4.5 (1.6) [175 (60)]
Change from baseline values	−0.06 (0.50) [−2.4 (19.4)]	1.1 (0.80) [−4.3 (30.9)]

*Data are presented as mean (SD). All patients received testosterone and participated in progressive resistance exercise.
†Significantly different change from baseline between groups ($P<.05$).
‡Significantly different from baseline ($P<.05$).

age and weight-matched HIV-seronegative controls (after eating, 7.9% [0.8%] in combined groups at baseline vs 3.0% [0.3%] in healthy controls; $P<.05$) and increased significantly from baseline in both the oxandrolone and placebo groups, after treatment (13.9% [2.1%] vs 15.2% [1.8%]) ($P<.001$ for time effect); there were no significant differences between groups.

Quality of Life Measurements

No change was observed for overall health or energy/fatigue domains,[31] although there were significant increases in the physical function domain ($P = .001$ for time effect).

Blood Chemistries. There were no significant changes in CD4 cell counts during the study (TABLE 4). Viral load decreased nonsignificantly in both groups (oxandrolone, 3.9 [4.3] to 3.7 [4.0] $\log_{10}$ copies/mL; placebo, 4.9 [5.3] to 4.8 [5.1] $\log_{10}$ copies/mL). There was a statistically significant decrease in high-density lipoprotein cholesterol (HDL-C) and increase in the total cholesterol–HDL-C ratio in the oxandrolone group, but there was no change in either parameter in the placebo group ($P<.001$ between groups).

Adverse Effects. Two subjects in the oxandrolone group had elevations in liver function test results, which led to 1 subject's discontinuing medication before the end of the 8-week study. Both of these patients were also receiving protease inhibitors. Mood swings were reported in 8 subjects, 5 in the oxandrolone group and 3 in the placebo group. In the oxandrolone group, 4 subjects experienced anxiety and 1 reported nausea. Finally, 4 subjects, 2 in each group, reported an increase in libido during the study.

Open-Label Phase. The group as a whole continued to gain LBM over 12 weeks (1.0 [0.6] kg), with loss of fat (−0.9 [0.6] kg) ($P<.05$ for both vs preopen label). When stratified by preceding study arm, subjects who were oxandrolone-naive had significantly greater gains in LBM (1.8 [0.5] kg) than subjects who previously had taken oxandrolone (0.4 [0.6] kg; $P<.05$).

COMMENT

Perhaps the most important finding of this study is that extremely high dosages of androgens were not required for a significant beneficial interaction with PRE in men with HIV-related weight loss. In their study, Bhasin et al[18] gave intramuscular testosterone at 600 mg/wk. We gave a physiologic replacement dosage of intramuscular testosterone (100 mg/wk) plus an oral anabolic steroid, oxandrolone, at a dosage of 20 mg/d, previously shown to be well tolerated for long-term use in humans.[19-21] There is no simple way to compare relative potencies of different testosterone analogs[17,32]; our intent was not to establish the androgen dose-response curve for synergy with PRE but to test the efficacy of a dose and form that has been given safely over the long-term to patients, eg, with alcoholic hepatitis.[19-21] In contrast, the safety and behavioral consequences of extremely high doses of testosterone[18] have not been established.

Several independent measures confirmed that LBM gains represent functional lean tissue. Strength was markedly improved; nitrogen retention was substantial and correlated with accrual of LBM; and REE increased. These complementary findings strengthen the external validity of the conclusion that lean tissue anabolism was significantly improved. Because the precision of measures such as DEXA and nitrogen balance is extremely good, the central issue of interpretation in studies attempting to alter body composition relates more to external validity (ie, biological meaning of measured changes) than to internal validity (ie, precision and accuracy of the measurements).

Comparison of these results with nutritional and anabolic therapies reported previously in AIDS patients is instructive (TABLE 5). The LBM gains and nitrogen retention in members of the oxandrolone group in the current study are considerably greater than with previously reported therapies in HIV infection or cancer cachexia.[33] The remarkable increases observed in LBM and strength in the oxandrolone group obviate the need to consider massive doses of androgens or anabolic steroids for the treatment of weight loss in HIV-infected men, in our view.

Moreover, the use of protease inhibitor therapy did not affect the gains in lean tissue or muscle strength, based on our post hoc analysis. This is an important point because weight gain after initiation of protease inhibitor treatment represents predominantly body fat.[7-10] Although our post hoc analysis must be interpreted with caution, the use of protease inhibitors did not prevent substantial gains in LBM. Finally, it is interesting to compare these results in men with HIV infection and prior weight loss with results previously reported by Bhasin et al[18] using high-dose testosterone with PRE and

placebo with PRE in healthy men. We observed a 7-kg LBM increase in the oxandrolone group and 4 kg in the placebo group compared with the report of Bhasin et al[18] of 6 kg and 2 kg of fat-free mass, respectively, in HIV-seronegative men. Strength improvements were also comparable. (Lean body mass and fat-free mass differ operationally by the mode of measurement [DEXA and underwater weighing, respectively], but gains in either parameter represent metabolically active, nonfat tissue in this setting.)

Certain design features of this study should be noted. We confirmed compliance and excluded exogenous anabolic steroid use by monitoring urine and blood.[29,30] The exercise regimens were supervised and strictly controlled. The intervention was blinded to all study participants, including the exercise trainers. Finally, both the placebo and the oxandrolone groups received a physiologic replacement dose of testosterone. This last feature was included for several reasons: (1) to make hormonal status more comparable between groups, by suppressing endogenous testosterone production[17,34]; (2) to ensure that borderline hypogonadism[11,15] was not present in either group; and (3) to avoid the possibility of inducing hypothalamic hypogonadism secondary to the exercise program, as has been reported in other clinical settings.[35,36]

The exercise regimen was well tolerated. Although overtraining can suppress immune function,[37] we found no evidence of worsening immunologic or virologic status (Table 4). We did observe significantly elevated de novo lipogenesis after PRE in both groups. We speculate that this reflects the systemic effects of cytokine release induced by muscle damage,[38,39] but we have no direct evidence to support this hypothesis. The lipid profile deteriorated in the oxandrolone group (Table 4), including substantially reduced HDL-C concentrations. Other 17a-methylated androgens also reduce HDL-C concentrations.[40] This effect on plasma lipid levels could be important in HIV-infected patients, in view of lipid abnormalities associated with HIV infection[12,41] that can be exacerbated by HIV-protease inhibitors.[7] One subject in the oxandrolone group was forced to discontinue the study because of elevation of liver enzyme levels. Other adverse effects were modest.

Table 5. Comparison of Therapeutic Regimens for HIV–Related Weight Loss*

Source, y	Nutritional or Anabolic Therapy	Nitrogen Retention, g/d	Rate of Change in Body Composition, kg/wk	
			LBM†	Weight
Von Roenn et al,[5] 1994; and Oster et al,[6] 1994	Megestrol acetate	. . .	0.00-0.15	0.45
Kotler et al,[3] 1990	Parenteral nutrition	. . .	0	0.30
Mulligan et al,[13] 1993; and Schambelan et al,[14] 1996	rGH	4.0	0.25	0.13
Strawford et al,[15] 1998	Nandrolone decanoate (hypogonadal)‡	3.7	0.25	0.41
Current study	PRE	3.8	0.48	0.53
Current study	PRE and oxandrolone	5.6	0.86	0.84

*HIV indicates human immunodeficiency virus; ellipses, information not available; rGH, recombinant human growth hormone; and PRE, progressive resistance exercise.
†Lean body mass (LBM) was determined by dual-energy x-ray absorptiometry.
‡Hypogonadal indicates treatment of men with borderline levels of testosterone (lowest quartile of testosterone serum levels).

The subjects in this study had experienced on average 8% to 9% weight loss and were currently weight stable. Weight loss of more than 5% is associated with reduced survival and higher rates of opportunistic infections.[42] Moreover, the goal for patients like these is often to increase strength and exercise capacity. Therefore, we believe that it is reasonable to consider HIV-seropositive patients with this degree of weight loss for a regimen similar to that used in our study, even if their weight is currently stable.

This study was not designed to differentiate between the possible anabolic roles played by the components provided to both study groups (eg, the exercise regimen, replacement dosage of testosterone, diet, or personal attention received through participation). The study was designed to address whether the addition of 20 mg/d of oxandrolone improves the anabolic and functional response to a regimen of PRE and physiologic testosterone replacement. These results answer this question definitively but do not reveal which factors were responsible for gains in the placebo group. Grinspoon et al[16] showed that administration of testosterone at replacement dosages in frankly hypogonadal men with HIV-related weight loss increases LBM; Strawford et al[15] demonstrated that nandrolone administration in borderline hypogonadal men also increases LBM. Neither of these studies were performed in eugonadal men, however, and neither involved exercise training. It will be important in future studies to assess the independent role of specific components.

In conclusion, the combination of PRE with a moderately supraphysiologic androgen regimen that included an anabolic steroid, oxandrolone, resulted in significantly greater increases in lean tissue and muscle strength than PRE with physiologic testosterone replacement alone in eugonadal, HIV-infected men with prior weight loss. The use of protease inhibitor therapy did not affect the lean tissue response.

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