ORIGINAL ARTICLE

A Double-blind, Placebo-Controlled Trial of Testosterone Therapy for HIV-Positive Men With Hypogonadal Symptoms

Judith G. Rabkin, PhD, MPH; Glenn J. Wagner, PhD; Richard Rabkin, MD

Background: The goal was to evaluate the efficacy of testosterone in alleviation of hypogonadal symptoms (diminished libido, depressed mood, low energy, and depleted muscle mass) in men with symptomatic human immunodeficiency virus illness.

Methods: Seventy-four patients were enrolled in a double-blind, placebo-controlled 6-week trial with biweekly testosterone injections, followed by 12 weeks of open-label maintenance treatment. Major outcome measures were Clinical Global Impressions Scale ratings for libido, mood, energy, and erectile function; Hamilton Depression Rating Scale scores, and Chalder Fatigue Scale scores. Body composition changes were assessed with bioelectric impedance analysis.

Results: Seventy men completed the 6-week trial. Response rates, defined as much or very much improved libido, were 74% (28/38) for patients randomized to testosterone, and 19% (6/32) for placebo-treated patients ($P<.001$). Of the 62 completers with fatigue at baseline, 59% (20/34) receiving testosterone and 25% (7/28) receiving placebo reported improved energy ($P<.01$). Among the 26 completers with an Axis I depressive disorder at baseline, 58% of the testosterone-treated patients reported improved mood compared with 14% of placebo-treated patients (Fisher exact test = .08). With testosterone treatment, average increase in muscle mass over 12 weeks was 1.6 kg for the whole group, and 2.2 kg for the 14 men with wasting at baseline. Improvement on all parameters was maintained during subsequent open-label treatment for up to 18 weeks.

Conclusion: Testosterone is well tolerated and effective in the short-term treatment of symptoms of clinical hypogonadism in men with symptomatic human immunodeficiency virus illness, restoring libido and energy, alleviating depressed mood, and increasing muscle mass.

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From the New York State Psychiatric Institute (Drs J. Rabkin and R. Rabkin), Department of Psychiatry, College of Physicians and Surgeons, Columbia University, New York, NY (Drs J. Rabkin and R. Rabkin); and RAND Corporation, Santa Monica, Calif (Dr Wagner).

In earlier studies of marketed antidepressants for treatment of syndromal depression in men with symptomatic human immunodeficiency virus (HIV) illness,[1,2] we found that even when depressed mood was alleviated, residual problems often included diminished libido, low energy, and loss of weight and muscle mass. These symptoms resemble the clinical presentation of otherwise medically healthy men with testosterone deficiency,[3] for whom the benefits of testosterone replacement therapy are well established.[4] By the early 1990s it was also becoming recognized that endocrine abnormalities are common in HIV illness, of which the most common is testosterone deficiency.[5-7] These observations together led us to work with testosterone as a therapeutic agent for men with symptomatic HIV illness.

Defining hypogonadism in the context of HIV illness is complicated by patients' relative youth and the fact that the reference ranges of commercial laboratories are not age adjusted, although testosterone levels peak in adolescence and decline substantially with age.[8] For younger patients, "normal" levels may be at the upper end or even above the standard reference range. Thus, a young man's

See also pages 133, 149, and 155

"normal" testosterone level might be 27.8 nmol/L, and decline by 50% after HIV infection yet still fall within the "normal" range. In addition, the laboratory reference limits themselves have been changed 3 times since we began testosterone studies in 1993, reflecting the dearth of empirical evidence for their definition.

Another significant issue is the wide variability in serum testosterone levels of the same patient across occasions, even when time of day is kept constant, as well as nondiurnal variability from hour to hour

SUBJECTS AND METHODS

SUBJECTS

Participants were recruited by means of notices in HIV community publications, physician referral, and word of mouth. They were told that the study was designed to determine whether testosterone is an effective treatment for low libido, depressed mood, and low energy and/or loss of muscle mass. The men were required to be 18 years or older; be HIV seropositive with CD4 cell counts less than 0.4×10^9/L (400 cells/mm^3); have clinically deficient (below the laboratory reference range) or low-normal serum testosterone levels (<17.4 nmol/L, except for men with a diagnosis of acquired immunodeficiency syndrome who had wasting or severe fatigue at baseline, for whom the upper limit was 22.6 nmol/L); have sexual dysfunction defined as substantial loss of sexual desire and/or erectile dysfunction; and have at least one associated hypogonadal mood symptom. All participants were required to be receiving medical care for HIV illness.

Exclusion criteria consisted of current or recent (past 6 months) substance use disorder, psychotic symptoms, significant suicidal risk, significant cognitive impairment likely to interfere with study procedures or informed consent, unstable medical condition including new onset or a new episode of an opportunistic infection in the past month, symptomatic benign prostate hyperplasia, current or anticipated use of a new antiretroviral medication within 4 weeks, or use of anabolic steroids in the past month. Those who had current major depression were encouraged to enter a treatment study with antidepressants that we were simultaneously conducting, although enrollment in this study was permitted if they so chose. Men who engaged in unprotected anal or vaginal intercourse with partners of seronegative or unknown HIV status in the past 3 months were excluded because of ethical concerns about providing a potentially libido-enhancing treatment with negative public health consequences. Men older than 55 years were required to have a negative prostate specific antigen test (<4.0 µg/L). In addition, we required the agreement of the patients' primary care physician to their study participation and a signed statement from the physician declaring that there were no known medical contraindications to their participation in this institutional review board–approved study, as well as the written informed consent of the patient. The study was conducted between May 1995 and December 1997.

PROCEDURES

Prospective patients were screened by telephone (J.G.R. and G.J.W.) when the presence of sexual dysfunction was established as a required criterion for study participation. Potentially eligible men were evaluated at an initial visit including psychiatric assessment as well as social, sexual, medical, and family histories and self-report forms. Blood was drawn for laboratory tests. In addition, a neuropsychological screen including Digit Symbol and Trail-Making Test A and B was administered only at baseline to rule out patients with significant cognitive impairment (defined as scores below the 25th percentile) who would be unlikely to be able to comply with protocol requirements. Those who continued to be eligible returned within 1 week for their baseline study visit with the study psychiatrist including written informed consent, a confirmatory psychiatric evaluation, and initiation of treatment. Randomization was performed by using a computer-generated list of numbers (1 = placebo, 2 = active treatment) in blocks of 4. The next available number was assigned to the entering patient without substitution for dropouts. Intramuscular injections of testosterone cypionate were used. The initial dose was 200 mg, which was increased thereafter to 400 mg biweekly and maintained at that dose in the absence of adverse reactions or serum testosterone levels more than twice the value of the upper limit of the laboratory reference range. This is the same dosing schedule used in our earlier trial where it was found to be effective and safe. Matching coded vials containing testosterone or placebo,

on the same day.[9(Table 1)] While some investigators recommend measuring free rather than total testosterone, experts assert that "there are no well-designed clinical trials that have indicated that one method of testosterone measurement is better than any other"[10(p3437)] in identifying treatment-responsive men.[11,12]

Previously we reported results of an open-label 12-week trial of testosterone therapy, followed by a 6-week double-blind discontinuation phase,[13] for the treatment of hypogonadal symptoms in men with symptomatic HIV illness. The primary outcome measure was increased libido. Eighty-four men entered the study and 77 men completed the double-blind phase; of those randomized to testosterone maintenance, 78% (29/37) retained their response compared with 13% (5/40) randomized to placebo. Treatment was well tolerated and effective in ameliorating presenting symptoms, and equally so for men whose serum testosterone levels were below or within the reference range.

We now describe a 6-week double-blind trial followed by 12 weeks of open-label maintenance treatment with biweekly injections of testosterone cypionate. In view of the aforementioned considerations, we included men whose serum testosterone levels were in the lower end of the reference range as well as those with levels below this range. The study goals were to evaluate the efficacy of treatment for alleviation of androgenic (sexual), mood, and anabolic (fatigue, loss of muscle mass) symptoms in men with HIV illness. A secondary goal was to confirm earlier findings regarding the lack of relationship between initial testosterone level and treatment outcome.

RESULTS

SAMPLE COMPOSITION AND PATIENT FLOW

A total of 104 men were screened; 74 eligible men entered the study, of whom 70 completed the 6-week double-blind trial (**Figure**). Of the 30 who were ineligible, 23 had serum testosterone levels above the cutoff, 3 were currently using drugs, 1 had a concurrent unrelated medi-

provided by Pharmacia & Upjohn (Kalamazoo, Mich), were used during the double-blind phase.

At week 6, physician and patient together assessed treatment efficacy after all rating scales were completed separately. Testosterone responders and placebo nonresponders who so chose were treated with testosterone for the next 12 weeks. Testosterone nonresponders were withdrawn from the protocol and offered open treatment as clinically indicated, and placebo responders were followed up to monitor maintenance of response.

MEASURES

Unless otherwise specified, higher scores signify more of the construct being measured. Clinical Global Impressions Scale (CGI) ratings and side effects measures were assessed biweekly (every 2 weeks) during the double-blind trial, and other measures were assessed at baseline and week 6. All were repeated at 12 and 18 weeks after baseline for those who continued in open-label treatment. The CGI[14] was expanded to include ratings for sexual interest (the major dependent variable) as well as erectile function, energy, and mood (this modification proved useful in earlier work[13]). On this 7-point scale, ratings of "much improved" or "very much improved" were used as the criterion of clinical response at week 6.

Biweekly self-report ratings on a 10-point scale of libido and erectile problems with anchors at "1" and "10" were augmented with items from the Reynolds Sexual Function Scale.[15] The sexual dysfunction inclusion criteria were based on subjective report. The Chalder Fatigue Scale[16] was used to assess energy level. Side effects were assessed using a modified version of SAFTEE (Structured Assessment of Treatment Emergent Events).[17]

Mood was assessed at study baseline with the Structured Clinical Interview for *DSM-IV* (SCID),[18] including the depression and substance abuse modules and psychotic screen (the latter two to address exclusion criteria). The clinician-rated structured version of the 21-item Hamilton Depression Rating Scale (HAM-D)[19] and the self-report Beck Depression Inventory[20] were used to assess depressive severity. "Depressed mood" was defined as scores greater than 8 on the HAM-D, including mood or interest. Additional self-report scales included the Brief Symptom Inventory,[21] using subscale scores for depression and anxiety and an overall score of general distress (Global Severity Index). The short form (16 items) of the self-report Endicott Quality of Life Enjoyment and Satisfaction Questionnaire[22] was used to assess quality of life.

Medical histories and current medications were elicited at baseline. Inquiries covered HIV and non-HIV conditions, as well as developmental and medical factors related to sexual development. Laboratory assays were performed by a local commercial laboratory (Metpath, now Quest) and included complete blood cell count, T-cell subsets, chemistry screen, cholesterol, and total serum testosterone. Serum testosterone levels were assessed at baseline and weeks 5, 11, and 17.

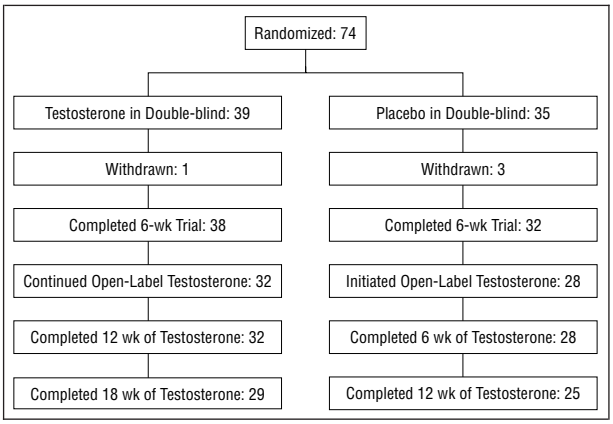
Body composition was measured with bioelectric impedance analysis (RJL Systems, Clinton Township, Mich) at baseline and after 12 weeks of testosterone therapy (baseline and week 12 for those randomized to testosterone; weeks 6 and 18 for those initially randomized to placebo but who started testosterone at week 6). The ratio of body cell mass to height was used to define the presence of wasting (defined as <90% of age-, sex-, and race/ethnicity–adjusted norms developed for an HIV-positive sample).

STATISTICAL ANALYSES

χ^2 Tests were used for analyses of categorical variables, *t* tests were used for analysis of continuous measures, and analysis of covariance was used to assess change over time, with baseline values as the covariate. The assumption of homogeneity of regression was tested before conducting the analyses. This assumption was supported for all variables. Because 95% of the sample completed the trial, we did not perform an intention-to-treat analysis, but rather evaluated outcome for completers only. All tests were 2-tailed, with $\alpha = .05$.

cal disease, and in 3 cases, the primary care provider did not approve study participation. Three men dropped out (2 were hospitalized due to HIV illness and 1 moved to another state); data from the fourth were excluded because of an error in medication administration.

Considering completers only, patients in the 2 treatment groups did not differ on any sociodemographic or medical variable or any measure of distress (**Table 1**). Although only 2 symptoms (low libido and one other) were required for study entry, 53 men (76%) had 3 or more. There was no between-group difference in percentage with current major depression and/or dysthymia ($\chi^2_1 = 0.8, P = .36$), but 7 patients randomized to testosterone and none to placebo had either minor depression or major depression in partial remission. Among those with current depression, 8 were taking antidepressants at study entry, as were 3 others in full remission. Nearly all patients had symptomatic HIV illness although none were currently acutely ill. Twenty-seven men (39%) were taking 2 or more antiretroviral drugs; the others were taking one (n = 11) or none (n = 32). Fourteen patients (20%) had baseline serum testosterone levels below 10.4 nmol/L, technically meeting laboratory criteria for hypogonadism. The other 56 patients had testosterone levels within the reference range (10.4-34.4 nmol/L). Baseline testosterone level was not correlated with CD4 cell count ($r = 0.01$).



Flowchart of randomized patients.

Table 1. Baseline Demographic, Psychiatric, and Medical Characteristics of Study Completers Randomized to Testosterone or Placebo*

Variable	Testosterone Group (n = 38)	Placebo Group (n = 32)	t (or χ^2)	P
Demographic characteristics				
Age, mean (SD), y	38.1 (7.3)	40.1 (9.0)	1.04	.30
Nonwhite, No. (%)	18 (47)	18 (56)	0.55	.46
Post high school education, No. (%)	24 (63)	21 (66)	0.05	.83
Currently employed, No. (%)	13 (34)	9 (28)	0.30	.58
Risk factors, No. (%)				
Sex	31 (82)	23 (72)	$\chi^2 = 0.93$	.34
Drug use/other	7 (18)	9 (28)		
Medical characteristics				
CD4 cell count, mean (SD), $\times 10^9$/L	0.17 (0.13)	0.22 (0.19)	1.04	.30
With AIDS diagnosis, No. (%)	28 (74)	24 (75)	0.02	.90
Taking ≥2 antiviral drugs, No. (%)	14 (37)	13 (41)	$\chi^2 = 0.19$	.74
Taking protease inhibitors, No. (%)	6 (16)	10 (31)	$\chi^2 = 2.35$	.13
Baseline testosterone level, mean (SD), nmol/L	13.1 (4.8)	13.2 (3.7)	0.06	.95
Testosterone level <10.4 nmol/L, No. (%)	7 (18)	7 (22)	$\chi^2 = 0.13$	.72
Associated problems, No. (%)				
Depressed mood	23 (61)	15 (47)	1.3	.25
Low energy	34 (89)	28 (88)	0.07	.80
Loss of muscle mass	13 (34)	5 (16)	3.1	.08
Axis I diagnoses (current), No. (%)				
MDD	10 (26)	5 (16)	0.8	.36
Dysthymia or	2 (5)	2 (6)	0.8	
Minor depression or MDD in partial remission	7 (18)	0		
Any depressive disorder	19 (50)	7 (22)	5.9	.02
Symptom severity, mean (SD) ratings				
HAM-D	12 (6.4)	9.4 (5.8)	1.75	.08
BSI				
Depression	1.42 (0.85)	1.13 (1.00)	1.29	.20
Anxiety	0.90 (0.66)	0.84 (0.87)	0.35	.73
Total	1.05 (0.60)	0.91 (0.76)	0.85	.40
BDI	14.2 (8.0)	13.9 (9.6)	0.11	.91
Visual analog scale (10-point)				
Energy	4.2 (1.9)	4.8 (1.7)	1.45	.15
Libido	2.6 (1.7)	3.2 (2.2)	1.21	.23
Morning erections	2.3 (1.8)	2.5 (2.0)	0.49	.63
Fatigue	24.3 (6.0)	22.5 (4.9)	1.39	.17
Bioelectric impedance analysis	1.02 (0.42)	1.00 (0.10)	0.28	.78

*AIDS indicates acquired immunodeficiency syndrome; MDD, major depressive disorder; HAM-D, Hamilton Depression Rating Scale; BSI, Brief Symptom Inventory; BDI, Beck Depression Inventory; and Fatigue, Chalder Fatigue Scale.

All 70 men reported sexual dysfunction, a mandatory inclusion criterion. Two reported no loss of libido but only erectile dysfunction (and their outcome was thus change in erectile dysfunction); 18 reported no erectile problems but low libido, and the remainder had both diminished sexual desire and erectile dysfunction. Many (n = 29; 41%) had not been sexually active with a partner within the past month. Low energy was a problem for 62 (89%), and 18 (26%) had significant body cell mass depletion (90% or less of normative body cell mass).

WEEK 6 TREATMENT OUTCOME

Of study completers, 38 were randomized to testosterone and 32 to placebo. Based on CGI ratings, response to testosterone was 74% (28/38), and to placebo, 19% (6/32) ($\chi^2_1 = 20.9$, $P<.001$). In the testosterone group, responders and nonresponders did not differ in terms of mean baseline serum testosterone levels (means [SDs] of 12.3 [5.0] nmol/L and 15.3 [3.1] nmol/L; $t_{36} = 1.7$, $P = .09$, respectively) or use of 2 or more antiretroviral drugs (Fisher exact test, $P = .51$). Using the technical definition of hypogonadism (testosterone level below the reference range of 10.4 nmol/L), rate of response did not differ between men who were frankly hypogonadal and those with serum levels in the reference range (Fisher exact test, $P = .61$).

For those randomized to testosterone, mean (SD) change in serum testosterone levels between baseline and week 5 did not differ between responders (34.6 [14.8] nmol/L) and nonresponders (34.5 [14.5] nmol/L) ($t_{31} = .015$, P = NS) (2 responders and 3 nonresponders had week 5 missing data). However, for those randomized to placebo, the mean testosterone increase for placebo responders (11.4 [7.4] nmol/L) significantly exceeded that of placebo nonresponders (2.0 [6.4] nmol/L) ($t = 3.1$, $P = .005$).

Of the 32 testosterone completers who experienced erectile dysfunction at baseline, 20 (63%) were rated as much or very much improved on the CGI, compared with 4 (20%) of the 20 placebo completers who experienced baseline erectile dysfunction (Fisher exact test = .006). On 10-point scales of strength of morning erections, all patients randomized to testosterone showed greater increase than those taking placebo (**Table 2**) as did patients with erectile problems at baseline (**Table 3**).

Of the 26 completers with a current syndromal mood disorder, 11 (58%) of 19 randomized to testosterone and 1 (14%) of 7 randomized to placebo were judged to be mood "responders" based on CGI scores of 1 or 2 (Fisher exact test = .08). Of the 11 patients taking antidepressants, 7 were randomized to testosterone and 4 to placebo. Using the Fisher exact test, response rates to either testosterone or placebo did not differ significantly from those not taking antidepressants ($P = .51$ and $P = .10$, respectively). For all completers, declines in HAM-D, Beck Depression Inventory, and Brief Symptom Inventory scores were significantly greater in the testosterone group than in the placebo group (Table 2), and quality of life (Endicott scale) improved more among those taking testosterone.

Table 2. Analysis of Covariance Comparing Testosterone and Placebo Groups on Week 6 Outcome Measures, Controlling for Baseline Values*

Week 6 Measure	Adjusted Mean (SE) Ratings: Testosterone Group (n = 38)	Adjusted Mean (SE) Ratings: Placebo Group (n = 32)	F	P
HAM-D				
Total	3.3 (0.7)	6.4 (0.8)	7.7	.007
Vegetative	1.7 (0.4)	3.6 (0.4)	11.0	.001
Affective	1.5 (0.4)	2.6 (0.5)	3.1	.08
BSI	0.50 (0.07)	0.72 (0.08)	4.7	.03
BDI	7.2 (1.1)	10.8 (1.1)	5.0	.03
Q-LES-Q	52.4 (1.6)	45.6 (1.7)	8.0	.007
Fatigue	18.8 (0.9)	21.1 (0.9)	3.1	.08
Visual analog scale				
Libido	6.4 (0.4)	4.6 (0.4)	9.1	.004
Irritability	4.2 (0.3)	4.9 (0.4)	1.8	.19
Morning erections	5.4 (0.4)	3.8 (0.4)	7.4	.008

**Abbreviations are explained in the footnote to Table 1. Q-LES-Q indicates Endicott Quality of Life Enjoyment and Satisfaction Questionnaire.*

Table 3 shows mood changes for the subset of 26 patients with depression at baseline. As seen for the entire sample, patients randomized to testosterone showed significantly more improvement than placebo-treated patients on all measures except the HAM-D affective subscale.

Sixty-two of the 70 completers reported fatigue at baseline; 34 were randomized to testosterone and 28 to placebo. After 6 weeks, there was a trend for all those taking testosterone to report greater decline on Chalder Fatigue Scale scores ($P = .08$) compared with all those taking placebo (Table 2), and significantly more so for those with fatigue at baseline ($P = .05$) (Table 3). Among the 62 men reporting fatigue at the outset, CGI ratings show that 59% improved while taking testosterone and 25% improved while taking placebo ($\chi^2_1 = 7.1$, $P<.01$).

EXTENDED TREATMENT OUTCOME

While efficacy achieved after 6 weeks of treatment is encouraging, longer-term outcome is of major interest. **Table 4** shows that, for every measure, statistically significant improvement was observed after 12 weeks of testosterone therapy compared with baseline.

Twenty-nine men received testosterone for 18 weeks (excluding those who started active treatment at week 6 who received only 12 weeks of open-label study treatment). All measures of depressive symptoms, distress, quality-of-life satisfaction and enjoyment, fatigue, libido, and erectile response showed a statistically significant improvement from study baseline (data not shown).

Body composition was assessed monthly. Because a 6-week time frame is too brief to observe significant change in body composition, and because a common unit of time used in treatment studies of wasting is 12 weeks, we used a 12-week time frame. Of the 56 men who completed bioelectric impedance analysis assessments, average weight gain was 2.6 kg ($t_{55} = 2.6$, $P<.01$), of which

Table 3. Analysis of Covariance Comparing Testosterone and Placebo Groups on Week 6 Outcome Measures for Patients Reporting the Problem at Study Baseline*

Week 6 Measure	Adjusted Mean (SE) Ratings: Testosterone Group (n = 38)	Adjusted Mean (SE) Ratings: Placebo Group (n = 32)	F	P
HAM-D				
Total	5.0 (1.4)	12.0 (2.3)	6.7	.02
Vegetative	2.1 (0.6)	6.0 (1.0)	10.7	.003
Affective	2.8 (0.8)	5.3 (1.4)	2.3	.14
BSI	0.74 (0.14)	1.45 (0.24)	6.3	.02
BDI	10.1 (2.1)	19.0 (3.4)	4.3	.052
Fatigue	19.0 (0.9)	21.8 (1.0)	3.9	.054
Visual analog scale				
Libido	6.3 (0.4)	4.7 (0.4)	7.5	.008
Morning erections	5.3 (0.5)	3.7 (0.6)	4.7	.04

**Abbreviations are explained in the footnote to Table 1.*

Table 4. Results After 12 Weeks of Testosterone Treatment for 57 Placebo-Treated Patients (Weeks 6-18)*

Measure	Mean ± SD Ratings: Baseline	Mean ± SD Ratings: Week 12	t	df	P
HAM-D					
Total	9.6 ± 6.4	2.5 ± 3.5	8.1	53	<.001
Vegetative	5.1 ± 3.0	1.1 ± 1.6	9.1	53	<.001
Affective	3.8 ± 3.5	1.1 ± 1.8	5.5	53	<.001
BSI	0.90 ± 0.69	0.57 ± 0.55	4.1	49	.003
BDI	13.9 ± 8.7	9.0 ± 10.1	3.1	45	.004
Q-LES-Q					
Item 16	3.0 ± 0.8	3.6 ± 0.9	3.8	43	.001
Total score	42.8 ± 8.7	50.7 ± 9.3	5.7	45	<.001
Fatigue	22.7 ± 5.5	18.4 ± 6.0	5.2	50	<.001
Visual analog scale					
Libido	3.4 ± 2.1	6.7 ± 2.4	9.6	54	<.001
Irritability	5.1 ± 2.2	4.2 ± 2.4	2.0	54	.047
Morning erections	3.1 ± 2.2	5.9 ± 2.4	7.0	54	<.001
Erectile function, masturbation	4.1 ± 1.6	5.2 ± 1.4	3.8	33	.001

**Abbreviations are explained in the footnote to Table 1. Q-LES-Q indicates Endicott Quality of Life Enjoyment and Satisfaction Questionnaire.*

1.6 kg was body cell mass ($t_{55} = 6.2$, $P<.001$). Exercise was not related to change in weight or body cell mass.

Of the 14 men who had wasting at study entry and who completed at least 12 weeks of active treatment, 11 achieved an increase in body cell mass of at least 5% (considered an effective therapeutic outcome; Donald Kotler, MD, oral communication, March 1999). Mean increase in muscle mass for this subset was 2.2 kg ($t_{13} = 6.2$, $P<.001$).

TREATMENT-EMERGENT SIDE EFFECTS

In these analyses, all 74 patients are included, since attrition may have been related to side effects. During the 6-week double-blind phase, patients randomized to testosterone and placebo reported in equal proportions irritability, tension, and decreased ejaculate (**Table 5**),

Table 5. Treatment-Emergent Side Effects During 6-Week Trial Reported at Weeks 2, 4, and 6

Side Effects	No. (%) of Patients: Testosterone Group (n = 39)	Placebo Group (n = 35)
Irritability	7 (18)	6 (17)
Acne	8 (21)	0
Tension	2 (5)	3 (9)
Bossiness	1 (3)	0
Hair loss	1 (3)	0
Testicular atrophy	2 (5)	0
Decreased ejaculate	1 (3)	1 (3)

while more testosterone-treated patients reported acne. However, the number of testosterone-treated patients reporting 1 or more side effects while taking testosterone was significantly greater than those receiving placebo (16/39 vs 7/35; $\chi^2_1 = 3.8$, $P = .05$). Over the total 18-week period of observation, 69 of the 74 patients received testosterone for varying lengths of time. Of these, 32 (46%) never reported side effects. Among the remainder, the most commonly reported side effects were testicular atrophy in 16 patients (23%), irritability in 15 (22%), acne in 13 (19%), and decreased ejaculate in 7 (10%). Hair loss was reported by 3 men (4%), as was overstimulation.

COMMENT

In this 6-week trial of testosterone therapy for the treatment of symptoms of clinical hypogonadism (diminished libido, depressed mood, low energy, and loss of muscle mass), active treatment was more effective than placebo. Assessments of patients who received testosterone for 12 weeks (n = 60) and 18 weeks (n = 29) showed maintenance of improvement from baseline in all parameters. We conclude that, for men with symptomatic HIV illness, testosterone therapy appears to be effective and well tolerated. No difference in response rate was found between men with serum testosterone levels below vs within the laboratory reference range among the 38 men randomized to testosterone. Similar findings emerged in 2 earlier studies we conducted, including a pilot study of 23 men with serum testosterone levels greater than 17.4 nmol/L (range, 17.4-23.3 nmol/L) at study baseline,[23] and the open-label study cited earlier.[13] Our initial work with testosterone was based on a deficit model with treatment regarded as replacement therapy. These results cumulatively suggest, however, that men with "normal" testosterone levels, at least those with levels in the lower half of the reference range, also show clear treatment benefit. Testosterone deficiency, to the extent it is adequately identified by commercial laboratory tests, is evidently not required for therapeutic efficacy, nor is it necessarily the only cause of these androgenic, anabolic, and mood symptoms in HIV-positive samples. However, their simultaneous presence (76% of the present study sample had 3 or more of these symptoms) suggests the effectiveness of using testosterone to treat them all, rather than separate treatments for each.

Among 26 study completers with Axis I depressive disorders, 58% of those randomized to testosterone vs 14% of placebo-treated patients were judged to have much or very much improved mood. This is within the range of effect observed for marketed antidepressants in clinical trials.[24,25] Preliminary supporting evidence of the effects of anabolic steroid treatment on psychological status is provided by recently reported placebo-controlled studies of testosterone,[26] and dehydroepiandrosterone (DHEA) administered to 15 patients with midlife dysthymia for 3 weeks.[27] In another study of more than 800 men over age 50 years, an inverse correlation was found between bioavailable (but not total or free) testosterone levels and Beck Depression Inventory scores.[28]

Advantages to testosterone include relative infrequent treatment-specific side effects, low cost, and availability in any medical setting. Its classification as a controlled substance should not preclude its use for clinically indicated treatment. At least among HIV-positive patients, testosterone is a more readily accepted treatment than standard antidepressants.

The risks of medically prescribed and supervised testosterone are fairly well characterized in both medically healthy patients[4] and those with HIV infection (see Rabkin et al[29] for a review of the latter literature). The most serious risk concerns exacerbation (but not causation) of prostate cancer.[30] The major mood swings (mania, rage outbursts) associated with the steroid megadoses, as used by some athletes,[31] have not been reported with the moderate doses that are medically prescribed.

Study limitations include the brief duration of the double-blind phase of treatment and the exclusion of women, for whom testosterone is not approved. Our findings with respect to alleviation of depressed mood are limited by sample size: only 26 completers had any Axis I depressive disorder at study baseline.

The present study replicates and extends findings of our earlier open-label trial, and broadens the findings of positive testosterone treatment effect to a sample including fewer men with advanced HIV illness and a larger proportion of nonwhite men (49% vs 29% in the earlier trial). In these respects, the present sample more closely resembles the contemporary population of men with HIV illness.

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Reprints: Judith G. Rabkin, PhD, New York State Psychiatric Institute, Unit 51, 1051 Riverside Dr, New York, NY 10032 (e-mail: jgr1@Columbia.edu).

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