TREATMENT OF DEPRESSION IN HIV+ MEN: LITERATURE REVIEW AND REPORT OF AN ONGOING STUDY OF TESTOSTERONE REPLACEMENT THERAPY[1]

Judith G. Rabkin, Ph.D., M.P.H.
Columbia University and New York State Psychiatric Institute

Glenn Wagner, Ph.D.
New York State Psychiatric Institute

Richard Rabkin, M.D.
Columbia University and New York State Psychiatric Institute

ABSTRACT

Our research program was designed to assess androgenic, anabolic, and mood effects of testosterone replacement therapy in human immunodeficiency virus positive (HIV+) men with significant immune suppression and hypogonadism. This article focuses on mood effects. Treatment consisted of biweekly intramuscular injections of testosterone cypionate at doses of 200 to 400 mg. Assessments included psychiatric evaluation using the Structured Clinical Interview for DSM-III-R, Hamilton Rating Scale for Depression, and Brief Symptom Inventory. This is an interim report of 73 men who completed at least eight weeks of treatment. Responders continued for four more weeks and then entered a double-blind placebo controlled discontinuation phase.

At study entry, 49% had CD4 counts under 50, and 84% had an acquired immune deficiency syndrome (AIDS)-defining condition. In terms of sexual desire and function, 76% were clear-cut responders at Week 8. Of the 31 study completers who had mood problems at baseline, 26 (84%) were rated as much improved in mood. Mean changes in CD4 cell count and beta 2 microglobulin after treatment were not statistically significant. These findings suggest that testosterone replacement therapy has significant antidepressant effects for men with significant immunodeficiency and clinical manifestations of hypogonadism.

(Ann Behav Med 1996, *18*(1):24–29)

INTRODUCTION

Prevalence of Depressive Disorders in HIV Samples

Both doctors and patients often assume that people with serious and progressive illnesses are likely to be clinically depressed, especially as death approaches. In the context of human immunodeficiency virus (HIV), both cross-sectional and longitudinal studies of men and women have accumulated evidence that contradicts the notion that clinical depression is an inevitable or even likely concomitant of potentially fatal illness.

Cross-Sectional Studies of Depression in Community Samples: Several community-based studies of the natural history of HIV illness and associated psychological adjustment were initiated in the mid-1980s. Findings from formal clinical diagnostic evaluations of HIV-positive (HIV+) asymptomatic or mildly symptomatic subjects indicate a modest increase in rates of Axis I current depressive disorder compared to general population rates, and the rates are in the range reported for patients with other chronic illnesses (1). Most studies report a one-month prevalence rate between 4% and 8% using *DSM-III-R* criteria (2–4), with only minimal differences compared to HIV seronegative matched comparison groups.

Cross-sectional studies of patients at different stages of illness have yielded mixed findings regarding the rates of psychopathology in patients with constitutional symptoms or acquired immune deficiency syndrome (AIDS)-defining conditions compared to asymptomatic HIV+ men and women (5–7). In our study of AIDS long-term survivors (8), we did not find increased rates of Axis I depressive disorders compared to rates for asymptomatic HIV+ gay men or to total population rates (9).

The sparse data available for injection drug users (IDU) suggests a similar picture. Lipsitz and colleagues (10) conducted structured psychiatric evaluations with predominantly (70%) African–American injection drug using men (N = 147) and women (N = 76). Rates of current depressive disorder were higher in all groups (overall average of 23%) than in non-drug-using samples, but did not differ between serostatus groups. The authors concluded that HIV status seems less relevant than IDU status in understanding psychopathology in this population.

Longitudinal Studies of Depression and HIV Illness Stage: Investigators conducting the community studies (described above) published their initial reports of depressive prevalence as determined at the baseline visits when subjects were mostly healthy. Semi-annual reassessments have been conducted in the ensuing years, and longitudinal data are beginning to emerge regarding changes in rates of either syndromal disorders or psychiatric symptomatology with progressive HIV illness.

Joseph and colleagues (11) used the Center for Epidemiological Studies Depression (CES-D) and the Symptom Checklist-90 (SCL-90) self-rating scales to assess depressive symptoms at six semi-annual visits of the Chicago Multicenter AIDS Cohort Study (MACS) between 1984 and 1988, and found stable scores over time with no increase in psychopathology despite HIV

[1] Preparation of this manuscript was supported in part by NIMH Grant #MH5 2037 (Dr. J. Rabkin). Upjohn Inc. provided matched placebo and active medication.

Reprint Address: J. G. Rabkin, Ph.D., New York State Psychiatric Institute, Unit 35, 722 West 168 Street, New York, NY 10032.

illness progression. Perry and colleagues (12) conducted a six-month and one-year follow-up of 328 gay and heterosexual men and women, both HIV-negative (HIV−) and HIV+, who sought HIV antibody testing. They found a decline in depressive symptom severity over time on both clinician and self-rated scales, but no difference between HIV+ and HIV− subjects on any occasion.

Two studies (13,14), together with an editorial (15), were published in the *Journal of the American Medical Association* in late 1993. Both studies had followed community cohorts of gay men semiannually since 1985, and both used the same self-report screening scale for mood problems (CES-D). As noted editorially by Perry and Fishman (15), both studies found that "the sicker one felt physically, the more likely one was to feel hopeless and despondent. And of particular note, both studies also found no significant relationship between CES-D scores and the time to either AIDS or death." The studies differed regarding the effect of depressive symptoms on the rate of CD4 decline. Both studies support the conclusion that "depressive symptoms do not in themselves increase the progression of HIV disease."

Risk Factors for Depression in HIV Illness

A history of depressive disorder prior to HIV illness has been reported in treatment studies of depression in HIV+ patients. Among 97 clinically depressed HIV+ men and women who participated in an antidepressant trial, 78% had a prior history of depression (16). Other factors associated with risk of depression in HIV+ people (as well as HIV− people) include a family history of depression, alcohol, intravenous drug or other significant substance abuse, and loss or absence of social ties. However, the causal direction of these associations remains unclear. For example, people who are chronically depressed may never form close ties to others and may seek out (illicit) drugs to alleviate their distress.

High lifetime rates of clinical depressive disorders have been reported in both the Columbia (2) and Cornell (12) cohorts. Their low rates of current depression are particularly surprising in this context, although such histories may indicate a vulnerability to recurrent depression with more serious illness.

It has been suggested that HIV itself causes mood changes and that AIDS-related dementia may manifest itself as depression. These hypotheses have not been supported in the research literature, however. Apathy rather than depression is the predominant effect in AIDS-related dementia (17). Stern and colleagues (18) did not find depressed mood associated with early cognitive changes in HIV+ men.

Antiretroviral medications such as zidovudine (AZT) have been proposed in case reports as risk factors for depression, as well as mania, but again this is not substantiated by consistent evidence. Admittedly, it is difficult to distinguish between the symbolic effects on mood of the first HIV medication (historically, AZT) one receives, initiating the person into "patienthood," from the direct effects of the drug itself. The negative psychological impact on "novice" patients of starting AZT back in the late 1980s is contrasted today by a widespread sense of triumph among more experienced patients who succeed in gaining access to newly available drugs such as protease inhibitors or 3TC, alone or in combination with other antiretrovirals.

In late-stage HIV illness, when patients typically are taking multiple potent drugs with major side effects such as gancyclovir or foscarnet, clarithromycin, rifampin, sulfamethoxazole/trimethoprim, as well as an antiretroviral such as AZT or ddI, the methodological difficulties of isolating the effects of any one medication from each other, their possible interactions, or the symptoms of the infections themselves become nearly insurmountable. Overall, however, with the exception of alpha interferon which is a cancer chemotherapy, general experience has not revealed any major, common, or persistent effects of HIV therapies on mood.

TREATMENT OF DEPRESSION IN HIV ILLNESS

Standard Treatments

Several open and double blind treatment studies have been conducted with HIV+ depressed patients. Most have used antidepressant treatment, although there are some data regarding effects of time-limited structured psychotherapies.

Antidepressant Treatments: Although published research on antidepressant treatments for HIV+ patients is limited, results to date endorse the efficacy and safety of tricyclic antidepressants as well as serotonin reuptake inhibitors (SRI) (fluoxetine, sertraline) and psychostimulants.

Imipramine, a tricyclic antidepressant, has been studied both at Columbia and Cornell in six-week placebo controlled trials (16,19). Among 80 completers in the Columbia study, 39% had a Centers for Disease Control and Prevention (CDC) (1987) diagnosis of AIDS. Imipramine response was 74% and placebo response rate was 26%. There were no differences in response rate between patients with more or less advanced HIV illness, nor was there a difference in side effects or tolerated dose. In the Cornell study, 40 patients were treated with 67% responding to imipramine and 47% to placebo (an unusually high placebo response rate). These results suggest that patients with HIV disease respond to imipramine at the same rate as medically healthy patients. No changes were found in enumerative measures of immune status after treatment.

Open studies of serotonin reuptake inhibitors (fluoxetine, sertraline) have been conducted by our group (20,21) and others (22). In general, response rates among HIV+ patients approximate those in the literature for medically healthy patients. SRIs have several advantages over tricyclics: milder and more transient side effects, less risk of toxicity in overdose, and none of the anticholinergic effects (e.g. drowsiness, sedation, tremor, muscle pain) that are common with tricyclic antidepressants and that may be particularly difficult for HIV+ patients.

Psychotherapy: Structured psychotherapy also has been demonstrably helpful with HIV+ patients. Markowitz et al. (23) have shown that interpersonal therapy is more effective than clinical management in treating depressed HIV+ patients. Kelly and colleagues (24) compared group cognitive–behavioral therapy and supportive–expressive psychotherapy and found no advantage for the former, contrary to expectations.

Factors that may influence the choice of treatment modality for depression include personal preference, as well as stage of HIV illness and the associated considerations of stamina, mobility, and insurance coverage. Psychotherapy may be more feasible for depressed asymptomatic or mildly symptomatic HIV patients who can attend weekly sessions without difficulty. Patients with later-stage illness may lack the stamina and energy to make extra medical visits or may already be taking a low dose of antidepressant medication for neurological indications, so that the most efficient strategy in treating their depression is to raise the dose to a therapeutic antidepressant level as side effects permit. Primary care physicians often can successfully

prescribe and manage SRIs for depressed patients with late-stage HIV illness, once the depression is brought to their attention.

In general then, standard antidepressant treatment is as effective in depressed HIV+ patients as in other depressed patients. Response rate to an initial antidepressant medication that is prescribed correctly in terms of dose and duration (eight to ten weeks) is in the range of 65–75%. If the first medication is not effective, another is likely to be. Overall, treatment of depression is one of psychiatry's success stories.

Mood Effects of Testosterone

For symptomatic HIV+ patients facing a foreshortened life expectancy and symptoms associated not only with depression but also HIV illness and side effects of multiple concomitant medications, standard antidepressant medication has some limitations. Even if mood improves, lethargy and nutritional problems (such as wasting, loss of muscle mass) may persist. Libido may remain low or be further compromised by side effects of antidepressant medications themselves. Sexual dysfunction as a side effect of serotonin reuptake inhibitors and tricyclic antidepressants is estimated to occur in up to 20% of treated patients (25).

Testosterone is an unusual choice for the treatment of depression. Indeed, our initial experience with testosterone for symptomatic HIV patients was as an adjunct to antidepressants for those whose mood had improved but who had residual problems of low libido and low energy. We then designed research to evaluate the androgenic (virilizing) and anabolic (nutritional) effects of steroids on HIV+ men with significant immunosuppression, clinical symptoms of hypogonadism, and low serum levels of testosterone. Direct effect of testosterone replacement therapy on depressed mood in the context of HIV illness was unanticipated. In fact, at the outset, we conducted diagnostic evaluations in order to exclude from the protocol men with current Axis I depressive disorders, to whom we offered standard antidepressant treatment instead. However, we found that most of those seeking testosterone replacement therapy refused to take pills for a mental disorder and thus got no treatment at all. We amended our protocol, with Institutional Review Board (IRB) approval, to include such patients with the intention of adding antidepressant medication to their treatment program if they remained depressed. To our surprise, we found that this was seldom indicated, since most of the men with depressive disorder at study baseline showed significant improvement in mood, as well as androgenic and anabolic effects after treatment with testosterone.

The modest case report literature on antidepressant effects of testosterone in medically healthy depressed men, mostly conducted in the 1930s and 1940s, is inconclusive (26). A more recent trial comparing a pharmacologic dose of mesterolone with amitriptyline found equal antidepressant efficacy in 34 depressed male outpatients (27).

In testosterone treatment studies with small samples of hypogonadal men whose mood was not assessed before treatment, mood effects tended to be positive (27–29) or absent (30–32). In contrast, major adverse mood effects have been observed in athletes taking high doses of anabolic steroids. These athletes have normal testosterone levels at the outset, which may be raised to serum levels that can be ten times the upper reference range limit of 990 ng/dl. Pope and colleagues (33,34) and others (35) have recorded increased irritability, aggression, and manic-like symptoms associated with steroid use in two studies of athletes. Rage episodes experienced by well-known athletes, termed "roid rage" (36), are given generous coverage in the popular press. However, this has not been reported when testosterone is prescribed for medical indications.

Our major research question addresses the efficacy of testosterone replacement therapy for depression in a sample of HIV+ men who presented with both loss of sexual desire and/or sexual dysfunction and depressed mood. A second question concerns the interaction between sexual problems and mood: since diminished sexual interest and sexual dysfunction may be secondary to depression as well as low serum testosterone, we were interested in whether the two outcomes would occur separately. Inclusion of men with diminished sexual interest and/or sexual dysfunction, only some of whom were depressed, made it possible to address this question.

METHOD

Study Inclusion Criteria

These included CD4 cell count less than 400 cells/mm^3, serum testosterone levels under 400 ng/dl, and significant diminution of sexual desire and/or problems in erectile function. Low mood, low energy, low appetite, and weight loss were common associated problems but were not required for study entry. Exclusion criteria included current or recent substance abuse/dependence, psychotic symptoms, significant suicidal risk, or unstable medical condition. Those who met criteria for major depression were offered antidepressant medication and advised to try that treatment before starting the testosterone study. Men over age 55 were required to have negative prostate specific antigen test findings. Patients had to have their HIV physician agree to their study participation.

Procedure

After establishing eligibility, men were treated openly for eight weeks with biweekly intramuscular injections of testosterone cypionate and had serum testosterone levels assayed in the interim weeks. Responders were maintained for at least four more weeks and were then randomized to testosterone or placebo for six weeks or until relapse.

Measures

These included psychiatric diagnoses with the Structured Clinical Interview for DSM-IIIR (SCID) (37), as well as clinician (Hamilton Depression Rating Scale) (38) and self-ratings of mood (Brief Symptom Inventory) (39), sexual interest and sexual function (Visual Analog Scales; Reynolds Sexual Functioning Inventory–Revised) (40), and quality-of-life (Endicott Quality-of-Life, Enjoyment, and Satisfaction Questionnaire) (41). Laboratory tests at baseline, performed by Metpath Laboratories (Teeterboro, NJ), included CBD, chemscreen, T-cell subsets, and serum testosterone. Baseline blood samples were drawn between 10 A.M. and noon.

Medication

Intramuscular injections of testosterone cypionate were used. Starting dose was 200 mg, increasing at Week 2 to 400 mg biweekly in the absence of adverse reactions or testosterone serum levels exceeding twice the upper limit of the laboratory reference range. In the Phase 2 double-blind period, three injections of either active or placebo medication (provided in

coded vials by Upjohn) were administered at the same dose as that given at Week 12.

Data Analyses

Independent t-tests (two-tailed) and analyses of variance models were used to assess differences between groups for continuous variables, while chi-square analyses were used to assess group differences for categorical variables. Paired t-tests (two-tailed) were used to assess change over time. Tukey HSD tests were used for multiple comparisons to control for Type 1 errors. For analyses of change from baseline to Week 12, Week 8 data were carried forward to Week 12 for those who ended treatment at Week 8.

RESULTS

Sample Description

Demographics: To date, we have analyzed data for the first 80 men to enter the study with the intention of completing the two-phase treatment protocol. For the entire sample, mean age was 41 years (range: 28–62), 20% were Hispanic or African–American, 90% had attended at least some college, 40% were in a relationship, 38% were employed, and 51% were on Disability. Most men were identified as gay or bisexual. Two men had a history of intravenous drug abuse.

Baseline Medical Status: As a group, the men had relatively advanced HIV illness, with 84% meeting 1993 CDC criteria for an AIDS diagnosis. The mean length of time between testing HIV+ and study entry was five years (range: three months to eleven years). Mean CD4 cell count was 104 cells/mm^3 (SD = 110, range: 3–408). Fifty percent had baseline CD4 cell counts under 50 cells/mm^3. A CD4 cell count below 200 cells/mm^3 is sufficient to meet criteria for an AIDS diagnosis as defined by the CDC in 1993. The mean beta$_2$ microglobulin was 3.5 mg/L (SD = 1.3, range: 1.7–7.1). The laboratory reference range for beta$_2$ microglobulin is 0.7 to 3.4 mg/L. The mean number of HIV medications was five, with 58% taking an antiretroviral at study baseline.

Presenting Problems

Sexual Problems: Four men reported no loss of sexual interest but only sexual dysfunction problems, and twelve men reported loss of sexual interest and no sexual dysfunction problems. The other 64 men complained of both. Only eight of the men complained exclusively of sexual problems; the others had at least one ancillary problem (i.e. low mood, energy, or appetite).

Mood Disorders: Twenty-one men (26%) had current syndromal major depression. An additional 14 men had depressive symptoms (HAM-D score of eight or more, including low mood and/or loss of interest in usual activities) equivalent to "Minor Depression" in the DSM-IV. Together, a total of 35 (44%) men had depressed mood.

Clinical Outcomes

Dropouts: Of the 80 men who entered the study, 73 completed at least eight weeks of treatment. There were seven dropouts (9%): two men discontinued treatment because of purported side effects (discussed later), two were unable to adhere to a regular appointment schedule, and three had prolonged hospitalizations for AIDS-related conditions.

TABLE 1

Change in Clinician-Rated and Self-Report Scales of Depression, Psychologial Distress, and Quality-of-Life among Completers with Mood Problems at Baseline (N = 31)

Scale	Baseline	Week 12	t	p
HAM-D: Total	15.6 ± 4.5	4.1 ± 3.3	11.3	.000
HAM-D: Vegetative	6.1 ± 2.4	0.8 ± 0.9	9.5	.000
HAM-D: Cognitive	7.6 ± 2.9	1.2 ± 1.9	9.3	.000
BSI: Total	2.2 ± 0.5	1.8 ± 0.5	5.3	.000
BSI: Depression	2.8 ± 0.6	2.0 ± 0.7	5.8	.000
BSI: Anxiety	2.0 ± 0.6	1.7 ± 0.6	2.3	.031
Quality-of-Life	2.9 ± 0.6	3.4 ± 0.6	4.1	.001

Changes in Sexual Interest and Functioning: Of the 73 completers of the open treatment phase, 67 (92%) were rated as clear-cut responders by themselves and the study doctor [Clinical Global Impressions Scale (CGI) score of 1 (very much improved) or 2 (much improved)]. Concurrent use of medications associated with lowered testosterone levels (ketoconazole, megestrol, cimetidine) was *not* associated with treatment outcome. The mean testosterone level at baseline was 302 ng/dl, increasing to 1162 ng/dl after four biweekly injections. Degree of testosterone deficiency at baseline was not associated with response (t = 1.9, df = 71, p = NS). Self-ratings of sexual interest, erectile functioning and satisfaction with one's sex life revealed significant improvement in all areas (paired t-tests: $p < .000$ in all comparisons).

Fifty-seven men entered into the double-blind discontinuation phase and were randomized either to placebo or to continue on testosterone. Fifty-three men completed the phase, with four dropping out due to AIDS-related complications (three died and one was hospitalized). Twenty-five of 27 patients randomized to placebo injections completed the double-blind phase, of whom 5 maintained their response with regard to sexual interest and/or functioning and 20 (80%) relapsed. Twenty-eight of 30 patients randomized to continue on active testosterone completed the double-blind phase, of whom 21 maintained their response and 7 (25%) relapsed. (This difference is statistically significant: Chi square = 16.0, 1 df, $p < .000$).

Changes in Mood: Both clinician-rated and self-report measures of psychological distress and depressive symptoms revealed significant improvement from baseline to Week 12 for the sample of completers as a whole. Of the 35 men who had mood problems at baseline, 31 completed at least eight weeks of treatment, of whom 26 (84%) were rated as much improved by the study psychiatrist. For the subset of 31 patients, scores on the HAM-D declined significantly from 15.6 (SD = 4.5) at baseline to 4.1 (SD = 3.3) at Week 12 (t = 11.3, df = 27, $p <$ .000). When analyzing the vegetative and cognitive–affective items of the HAM-D separately, both sets of items showed significant, clinical improvement from baseline to Week 12 (see Table 1). Self-report measures confirmed the doctor's improvement ratings. Mood-related data collected during the double-blind discontinuation phase was insufficient in number to allow for statistical analyses.

Of the 31 men who had mood problems at baseline and completed at least eight weeks of the study, 30 (97%) were rated as responders with regard to improved sexual interest and/or sexual functioning. The one patient whose sexual problems did not improve also reported no improvement in his mood. All

TABLE 2
Change in HAM-D Scores after Six Weeks of Treatment: Comparing Testosterone Replacement Therapy and Standard Antidepressants

Treatment	*N*	Baseline	Week 6	t	*p*
Imipramine	38	17.3 ± 4.0	5.7 ± 4.6	12.6	.000
Fluoxetine	30	19.2 ± 4.8	7.0 ± 4.4	11.0	.000
Sertraline	20	18.0 ± 5.2	5.2 ± 4.5	8.3	.000
Testosterone*	31	15.6 ± 4.5	3.7 ± 4.7	8.7	.000

* Testosterone data are after eight weeks of treatment.

26 men who were rated as responders with regard to improved mood also responded with regard to sexual problems; of the five men whose mood did not improve, four were rated as responders with regard to sexual problems.

Side Effects

Two men discontinued the first phase of the study due to side effects: irritability and hair loss. Other treatment-emergent side effects (absent at baseline but present at some point during the study) that were reported but did not lead to study discontinuation included truncal acne, fatigue, tension, uncharacteristic assertiveness, feeling "high," decreased ejaculate, testicular atrophy, breast tenderness, and in one instance, undesired weight gain. Irritability was the most commonly cited treatment-emergent side effect with 22 men reporting its presence. The side effects that were reported for at least two consecutive assessments (two weeks apart) were irritability, fatigue, acne, tension, and uncharacteristic assertiveness, but only irritability was reported on three or more consecutive study occasions. In most cases, treatment-emergent side effects diminished without a change in dosage.

Immune Status Changes

For the 63 men for whom T cell subsets were repeated at study endpoint, mean baseline CD4 cell count was 109 cells/mm3 (SD = 110). At study endpoint, after an average of 15 weeks, mean CD4 cell count was 113 cells/mm3 (SD = 140) (paired t = 0.6, df = 62, p = NS), indicating no significant change from baseline. For the 37 men who had $beta_2$ microglobulin assays repeated at study endpoint (these tests began midway through the study, hence the smaller N), mean $beta_2$ microglobulin remained unchanged from baseline (3.6 mg/L, SD = 1.3) to end of study (3.6 mg/L, SD = 1.2), an average of 14 weeks later (paired t = 0.7, df = 36, p = NS).

Comparison of Testosterone Replacement Therapy with Standard Antidepressants in the Treatment of Depressed Mood

To compare the antidepressant efficacy of testosterone with that of standard antidepressants such as fluoxetine, sertraline, and imipramine, we compiled data from our clinical trials of each of these treatments and compared Hamilton Depression Rating Scale change scores. As shown in Table 2, HAM-D scores declined significantly from baseline to Week 6 (Week 6 was a common assessment period across all protocols) within each of the four clinical trials, with no single treatment being superior to any other treatment (F(3,120) = 0.2, p = NS).

DISCUSSION

In this study of 80 men with late-stage HIV illness and subjective complaints of diminished sexual interest/sexual function with or without depressed mood, testosterone replacement therapy was effective and well tolerated. We found improvements in sexual interest and erectile functioning, even in the presence of significant HIV illness and for men taking medications associated with lowered testosterone levels. More surprisingly, we found a clear-cut mood effect, equivalent to that reported in the literature on standard antidepressant trials for treatment of clinical depression.

The question has been asked whether restoration of sexual function among HIV+ men is in the best interest of the public health in terms of risk for HIV transmission. We assessed frequency and types of sexual behavior at study baseline and after twelve weeks of treatment. We found that safer sex practices actually increased over time for the practical reason that it became easier to put on a condom when sexual function was restored. Most of the men who resumed having sex with partners were in stable relationships; otherwise, masturbation rather than sex with a partner showed the most significant increase with treatment.

Progressive HIV illness entails many kinds of losses. Restoration of sexual desire and function made a great difference in overall attitude and outlook, even if sexual activity with a partner did not increase. Further, we found that severity of chronic HIV conditions did not necessarily preclude a robust response to testosterone replacement therapy using somewhat higher doses than those used by endocrinologists for hypogonadism, and achieving serum levels somewhat above the reference range.

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