Prospective Study of Topical Testosterone Gel (AndroGel) Versus Intramuscular Testosterone in Testosterone-Deficient HIV-Infected Men

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Purpose: Testosterone replacement therapy via deep intramuscular injections causes extraphysiologic variations in serum testosterone concentrations. A topical transdermal testosterone gel formulation (AndroGel®) provides sustained physiologic concentrations of serum testosterone. The objective of this open-label switch study was to compare pharmacokinetics, safety, tolerability, and efficacy of delivery of daily testosterone gel versus intramuscular testosterone injection every 1 or 2 weeks in hypogonadal human immunodeficiency virus (HIV)-infected men. **Method:** Patients received intramuscular testosterone (100–200 mg/wk) for 8 weeks, then switched to daily topical testosterone gel (5–10 g gel/day) for 8 weeks. Study endpoints included free serum testosterone concentrations and quality-of-life scores. **Results:** Thirty patients (average age, 45 years) were recruited; 24 completed the study. Mean peak free testosterone concentrations with intramuscular testosterone and testosterone gel were 42 pg/mL and 23 pg/mL, respectively, and mean peak-trough fluctuations in free testosterone were 26.7 ± 12.8 pg/mL and 2.7 ± 10.7 pg/mL, respectively ($p < .001$). Quality-of-life scores indicated more improved physical and emotional well-being with gel versus intramuscular testosterone. No significant changes in laboratory parameters or lean body mass were noted. **Conclusion:** Daily testosterone gel produced stable testosterone concentrations and improved quality of life compared with intermittent intramuscular testosterone injections. **Key words:** *HIV, hypogonadism, testosterone deficiency, testosterone replacement therapy, transdermal, quality of life*

The prevalence of testosterone deficiency increases with normal aging[1–4] and in patients with chronic diseases such as human immunodeficiency virus (HIV) infection.[5–8] Symptoms associated with low testosterone in non–HIV-infected men include reductions in muscle mass, bone density, lean body mass, exercise capacity, sex drive, energy level, and sense of well-being.[3,9] Testosterone replacement therapy has been reported to improve some symptoms of hypogonadism in men.[9–15]

Testosterone replacement therapy may be achieved by several means, including intramuscular (IM) injection and transdermal gel formulations. The advantages and disadvantages of IM and transdermal testosterone delivery systems have been reviewed by Cofrancesco et al.[16] Traditional treatment of patients with hypogonadism involves deep IM injection of long-acting testosterone esters every 1 or 2 weeks.[9,17,18] IM delivery of testosterone supplementation can result in wide nonphysiologic variations in serum testosterone levels. Supraphysiologic concentrations of testosterone occur shortly after IM injection and decline gradually over the following weeks, often reaching subphysiologic concentrations before the next dose.[16,19,20] These wide nonphysiologic fluctuations in testosterone concentration correlate with adverse changes in mood, muscle function, visceral fat, sexual function, liver transaminase levels, prostate size, hemoglobin level, energy level, and well-being.[16,18] In addition, IM injections can be painful, may result in sterile abscesses if not injected deeply into muscle tissue, and may require the patient to

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make frequent office visits. Transdermal gel testosterone formulations achieve sustained testosterone levels that closely resemble normal physiologic ranges over the dosing period.[21] Transdermal gel formulations may be irritating to the skin, may have a noticeable scent, and must be applied to specific areas of the body according to manufacturer instructions to avoid transfer to other persons through skin-to-skin contact after application.[22,23]

The objective of this study was to compare pharmacokinetics, safety, tolerability, and efficacy of delivery of daily testosterone gel versus IM testosterone injection every 1 or 2 weeks in testosterone-deficient HIV-positive men.

METHOD

For this 16-week, open-label switch study, 30 hypogonadal HIV-positive men (aged ≥18 years) were recruited from a large Los Angeles HIV treatment center from October 2001 to November 2002. This study was conducted with the approval of the institutional review board at the study site and in accordance with the Declaration of Helsinki; all subjects enrolled in the study provided written informed consent.

Prior to enrollment, subjects were on stable regimens of 100 to 200 mg of IM testosterone administered every 1 or 2 weeks, effectively raising testosterone levels into the eugonadal range. Patients were excluded from the study for concurrent use of anabolic agents (e.g., nandrolone decanoate, oxandrolone, oxymetholone), a history of prostate cancer or symptomatic prostatic hyperplasia, hypersensitive skin, use of agents that would compromise compliance with or adherence to the protocol, or clinical laboratory values outside the normal range.

Study drugs consisted of injectable testosterone cypionate (Depo®-Testosterone)[22] and testosterone gel 1% (AndroGel®).[23] For the first 8 weeks (weeks 1 through 8), all patients were treated with 100 or 200 mg IM testosterone every 1 to 2 weeks. For the next 8 weeks (weeks 9 through 16), all patients were switched to testosterone (T) gel 5 g daily, applied to the skin. Doses of testosterone (whether IM or topical gel) were titrated, primarily to achieve serum concentrations in the therapeutic (eugonadal) range and secondarily to achieve improvement in the clinical signs and symptoms of hypogonadism. At 4 to 5 weeks of treatment with testosterone gel, dose adjustment up to 10 g daily was permitted, depending on clinical response (**Figure 1**). Total treatment time was 16 weeks, which was considered long enough for serum testosterone levels to achieve steady state and affect the quality-of-life

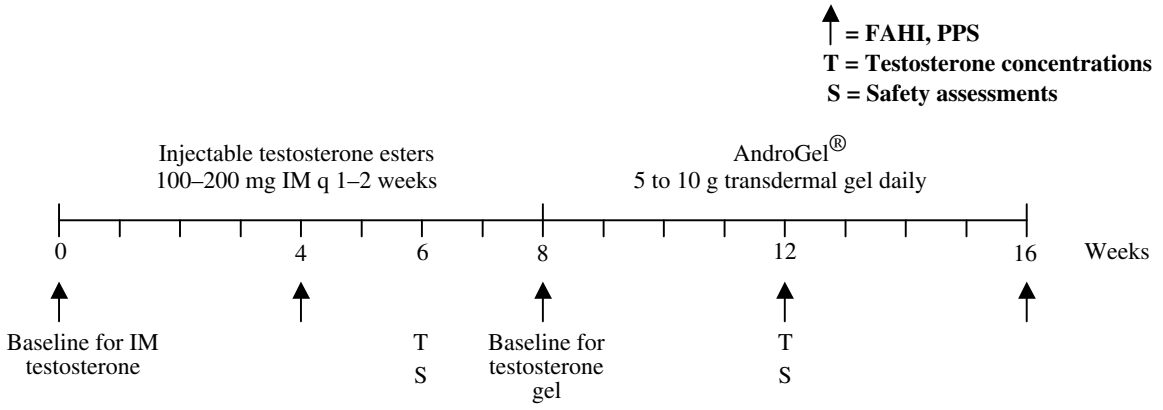

Figure 1. Study schema. All patients received IM testosterone for the first 8 weeks, then were switched to testosterone gel for the next 8 weeks (weeks 9–16). Trough testosterone concentrations were measured on 3 separate days during week 6 and again during week 12, with blood drawn at the same time each day (AM). Peak testosterone concentrations were determined in week 6 at AM+72 hours and in week 12 at AM+12 hours. Quality-of-life and patient perception questionnaires were administered during weeks 0, 4, 8, 12, and 16. Safety assessments were performed at the same time that testosterone concentrations were measured. FAHI = Fundamental Assessment of Human Immunodeficiency Virus Infection; IM = intramuscular; PPS = patient perception survey.

parameters to be assessed, yet short enough to be a logistically feasible study.

During the IM testosterone treatment period (weeks 1 through 8), testosterone concentrations were measured during study weeks 4, 6, and 8. Measurements were taken once just before drug administration (trough) and again at 72 hours after the injection (the approximate time after IM injection of testosterone cypionate when serum testosterone levels peak[24]). During the testosterone gel treatment period (weeks 9 through 16), evaluations were done at the same time on three different mornings of weeks 10, 12, 14, and 16. Measurements were done once just before drug application (trough) and again 12 hours after drug application (the approximate time after application of testosterone gel when serum testosterone levels peak[25]) on each of the 3 days. Because endogenous testosterone concentrations have a circadian rhythm, testosterone concentrations were always evaluated in samples drawn at the same time of day. Free testosterone concentrations were determined with direct solid-phase ^{125}I radioimmunoassay (Coat-A-Count Free Testosterone Assay; Diagnostic Products Corporation, Los Angeles, California, USA). Assays were performed by an independent laboratory (Consolidated Laboratory Services, Van Nuys, California, USA). Published reference ranges for this free testosterone assay are 8.8 to 27 pg/mL for men 20 to 39 years old, 7.2 to 23 pg/mL for men 40 to 59 years old, and 5.6 to 19 pg/mL for men 60 to 80 years old.[26]

Study Endpoints

The primary study endpoints included free serum testosterone concentrations and quality-of-life scores.

Quality-of-Life Assessments

Quality-of-life (QOL) and Patient Perception Survey (PPS) questionnaires were completed during weeks 0, 4, 8, 12, and 16. QOL evaluations included scores on the Functional Assessment of Human Immunodeficiency Virus Infection (FAHI) survey and the site-developed PPS questionnaire. The FAHI survey has been validated for assessment of QOL parameters in patients with HIV infection.[27,28] FAHI questionnaire results were interpreted in accordance with proprietary FAHI scoring guidelines and were then converted to a positive scale; for all subscales, an increasing score correlates with improvement in QOL. The PPS questionnaire was developed by the investigators specifically for use in patients undergoing treatment for HIV infection. This questionnaire, which has not yet been robustly validated, assesses patient perceptions of therapy convenience, benefit, and comfort and physician involvement. Higher scores on the PPS indicate perceived improvement in QOL and satisfaction with therapy.

Safety Assessments

With each testosterone assessment, the safety of each therapy also was assessed through administration of liver function tests and determination of fasting lipid levels, CD4, blood counts, T-cell subsets, and quantitative HIV viral load by polymerase chain reaction. Adverse events (AEs), including skin reactions and gynecomastia, and concomitant medications were recorded. Physical examinations and bioelectric impedance assay (BIA), a noninvasive estimate of fat-free mass and body fat, were performed.

Statistical Analyses

The Mann-Whitney *U* nonparametric test was used to compare study variables during treatment with IM and gel testosterone. Median peak and trough free testosterone concentrations for the IM and gel formulations were compared. For PPS and FAHI scores, values at weeks 4, 8, 12, and 16 were compared with the corresponding baseline values so that changes within treatment periods could be evaluated. A prestudy baseline for injectable testosterone treatment was defined as the value obtained before study treatment began (week 0), and baseline for testosterone gel treatment was the last value obtained during treatment with injectable testosterone (week 8). Values at weeks 4 and 8 (IM formulation) were averaged and compared with the corresponding mean of scores for weeks 12 and 16 (gel formulation) through the use of paired two-tailed *t* tests. Microsoft Excel and the Statistical Package for the Social Sciences (SPSS) for Windows, version 15.0 (SPSS Inc., Chicago, Illinois, USA), were used for analyses. AEs were summarized descriptively.

RESULTS

Patient demographics and disposition are shown in **Table 1**. Thirty patients gave consent to participate, and 24 completed the 16-week study. Of the six who did not complete the study, four patients were lost to follow-up, one withdrew because of a schedule conflict, and one withdrew because of non–study-related hospitalization. Statistical analyses were performed on an "as-treated" basis. Patients had an average age of 45 years, were predominantly White (83%), and had been on highly active antiretroviral therapy (HAART) for an average of 4.8 years. Eleven patients were on protease inhibitors (PIs), 10 on non-nucleoside reverse transcriptase inhibitors (NNRTIs), and 2 on nucleoside reverse transcriptase inhibitors (NRTIs); 1 patient was not on HAART.

Peak and trough free testosterone concentrations for each study drug at endpoint are shown in **Figure 2**. Peak free testosterone concentrations were significantly greater when patients were given IM testosterone than when given testosterone gel ($p < .001$). In addition, the peak-trough fluctuation in free testosterone (mean ± *SD*) was significantly greater after IM testosterone (26.7 ± 12.8 pg/mL) than after testosterone gel (2.7 ± 10.2 pg/mL; $p < .001$). The percentage of patients who achieved therapeutic serum concentrations was 50% during IM and 83% during testosterone gel therapy.

Table 1. Patient demographics ($N = 24$)

Parameter	Value
Age, years (mean ± *SD*)	45 ± 9
Range	31–66
Ethnicity, *n* (%)	
White	20 (83)
Hispanic	4 (17)
Weight, kg (mean ± *SD*)	77 ± 9
Height, cm (mean ± *SD*)	175 ± 7
BMI, kg/m^2 (mean ± *SD*)	25 ± 3
Time on HAART, years (mean ± *SD*)	4.8 ± 2.8
No. on NNRTI HAART (%)	10 (42)
No. on PI HAART (%)	11 (46)
No. on NRTI-only HAART (%)	2 (8)
No. off HAART (%)	1 (4)
Concomitant medications of interest	
Finasteride, *n* (%)	2 (8)
Antihypertensives, *n* (%)	7 (29)
Depressed, *n* (%)	5 (21)

Note: SD = standard deviation; BMI = body mass index; HAART = highly active antiretroviral therapy; NNRTI = non-nucleoside reverse transcriptase inhibitor; PI = protease inhibitor; NRTI = nucleoside reverse transcriptase inhibitor.

The effects of IM testosterone and testosterone gel therapy on FAHI and PPS scores are presented in **Table 2** and **Figure 3**, respectively. Although overall FAHI scores during transdermal treatment

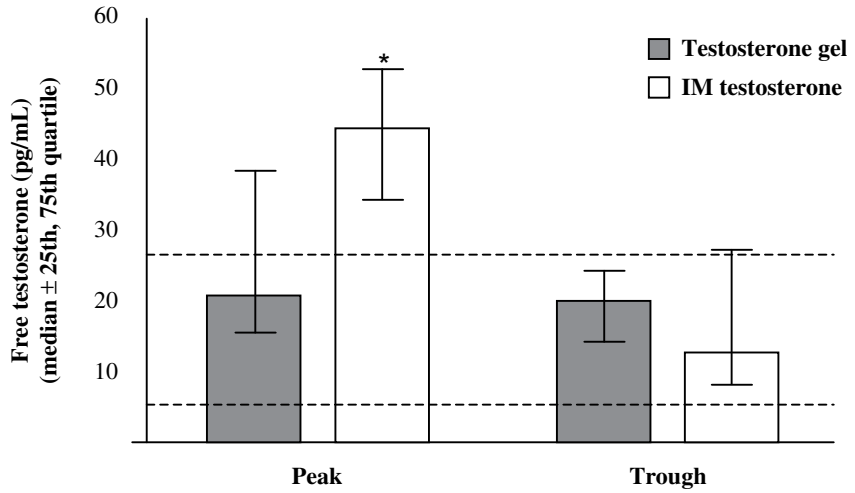

Figure 2. Testosterone concentrations at endpoint after testosterone gel and IM testosterone administration (final $n = 24$). Dotted lines define the normal free testosterone concentrations for men between 20 and 80 years old (5.6–27 pg/mL) as measured with the Diagnostic Products Corporation radioimmunoassay kit. *$p < .001$ vs. gel formulation (peak values). IM = intramuscular.

Table 2. FAHI subscale and total scores, mean change from baseline[a,b]

FAHI subscale	Evaluation	IM testosterone (n = 24)	AndroGel® (n = 24)
Physical well-being	Baseline	2.83	2.87
	Last on treatment[c]	2.87	3.01
	Change from baseline	.04	.14
		(p = .139)	(p = .005)
Emotional well-being	Baseline	2.62	2.67
	Last on treatment	2.67	2.80
	Change from baseline	.05	.13
		(p = .266)	(p = .034)
Functional well-being	Baseline	2.62	2.59
	Last on treatment	2.59	2.69
	Change from baseline	–.03	.10
		(p = .021)	(p = .019)
Social well-being	Baseline	2.52	2.65
	Last on treatment	2.65	2.67
	Change from baseline	.13	.02
		(p = .888)	(p = .147)
Cognitive functioning	Baseline	2.35	2.40
	Last on treatment	2.40	2.51
	Change from baseline	.05	.11
		(p = .462)	(p = .636)
Total	Baseline	12.94	13.18
	Last on treatment	13.18	13.68
	Change from baseline	.24	.50
		(p = .732)	(p < .001)

Note: FAHI = Fundamental Assessment of Human Immunodeficiency Virus Infection; IM = intramuscular.

[a]FAHI scores have been converted to a positive scale; increasing score represents improvement in well-being. Values at baseline and week 8 were averaged and compared (with the use of paired two-tailed t tests) for each formulation.

[b]Baseline for the injectable testosterone treatment (weeks 1–8) was the pretreatment value (week 0), and baseline for the testosterone gel treatment (weeks 9–16) was the last value obtained during treatment with injectable testosterone (week 8).

[c]Last on-treatment value for injectable testosterone was from the week 8 study visit; last on-treatment value for testosterone gel was from the week 16 study visit (week 8 of gel).

increased significantly (p < .001) compared with the last value obtained during IM treatment, scores for IM testosterone did not increase (p = .732) compared with prestudy baseline values. The overall trend was for greater improvement with testosterone gel therapy versus IM therapy, and significant improvements were reported in terms of physical (p = .005), emotional (p = .034), and functional (p = .019) well-being. Differences in scores from the PPS questionnaire at the beginning and end of each treatment for each study drug are shown in **Figure 3**. When average PPS scores before week 12 were compared with scores for weeks 12 and beyond, significant improvements were noted in convenience (p < .001), benefit (p = .002), and comfort (p < .001) scores for the testosterone gel formu-

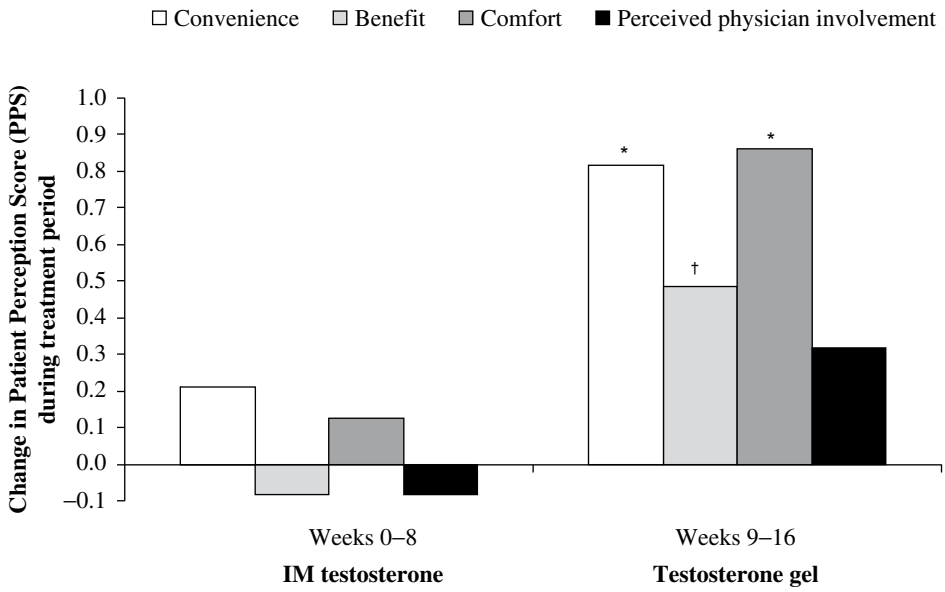

Figure 3. Change in patient perception survey scores during IM testosterone and testosterone gel administration from baseline (week 0 for IM, week 8 for gel) through end of treatment (week 8 for IM, week 16 for gel). *$p < .001$ vs. weeks 0–8. †$p = .002$ vs. weeks 0–8. IM = intramuscular; PPS = Patient Perception Survey.

lation. A nonsignificant improvement in physician involvement score was observed for testosterone gel treatment ($p = .14$).

No clinically meaningful changes in liver function enzymes, hemoglobin, hematocrit, fasting cholesterol and triglycerides, BIA measures, CD4 counts, or viral loads were noted over the duration of the study (**Table 3**). Also, no skin reactions, gynecomastia, or any other AEs were seen with either mode of testosterone therapy during the 16 weeks of the study. No patients withdrew because of medication-related AEs.

Table 3. Safety measures

	Baseline	8 weeks (IM T)	16 weeks (T gel)
Mean ALT (*SD*), U/L	59.96 (42.17)	55.08 (27.65)	55.83 (27.74)
Mean AST (*SD*), U/L	49.75 (34.55)	42.92 (19.28)	42.78 (16.88)
Mean hemoglobin (*SD*), g/dL	15.92 (1.11)	15.86 (1.22)	15.86 (1.21)
Mean hematocrit (*SD*), %	46.61 (3.12)	46.53 (3.96)	46.04 (3.64)
Mean cholesterol (*SD*), mg/dL	205.57 (50.12)	190.35 (43.63)	196.04 (51.18)
Mean triglycerides (*SD*), mg/dL	355.21 (237.19)	378.15 (281.00)	362.88 (266.12)
Mean BCM, pounds	73.42	73.37	73.10
Mean CD4 cells/μL	520.00	596.33	538.21
Number of patients with viral load <400, *n* (%)[a,b]	16 (66.67)	17 (70.83)	16 (66.67)
Mean viral load for patients with ≥400 (*n*)[b]	19243.25 (8)	32028.14 (7)	13957.12 (8)

Note: IM = intramuscular; T = testosterone; ALT = alanine aminotransferase; *SD* = standard deviation; AST = aspartate aminotransferase; BCM = body cell mass.

[a]For these patients, viral load was recorded as "<400 copies/mL."

[b]Viral load is reported as viral equivalents per mL plasma.

DISCUSSION

Our data are consistent with those of other studies that showed benefits of testosterone replacement therapy in hypogonadal HIV-positive men.[11–13,17,29] Transdermal testosterone formulations have proved to be clearly different from IM testosterone formulations in sustaining testosterone concentrations at physiologic levels without wide peak and trough ranges.[15,17,21,25] Our data have confirmed larger peak testosterone concentrations during treatment with IM testosterone than during treatment with testosterone gel. Testosterone gel delivered sustained testosterone concentrations that did not fluctuate widely.

QOL assessments are important in HIV patients because of the chronic nature of the disease, in which "quality of survival" has relevance as an outcome measure,[30] and because some therapies used in the treatment of this disease have severe AEs that affect QOL and threaten compliance. The FAHI questionnaire, a validated instrument with proven sensitivity to change, was used in our study to assess QOL as an efficacy parameter.[27,28] The FAHI questionnaire was developed as a tool that could be used to evaluate health-related QOL issues and general concerns in patients with chronic illness, as well as to assess problems specific to HIV. Our study showed improvement in FAHI scores, with significant improvements noted on the physical, emotional, and functional well-being subscales in patients during treatment with the testosterone gel formulation. In addition, overall improvement in PPS questionnaire scores was reported during treatment with testosterone gel therapy. Both testosterone products were well tolerated, and no study drug-related AEs or discontinuations due to AEs occurred.

HAART has been shown to increase concentrations of testosterone in HIV-infected patients.[31] In a study of 15 patients, Collazos et al. reported a mean increase in serum testosterone from 23.2 to 37.6 nmol/L after treatment with HAART ($p = .02$). The mechanism of this effect is not clear; however, PIs have been shown to inhibit CYP3A4-mediated metabolism of testosterone.[32] Eleven of the patients in our study were receiving treatment with PIs, which may have increased their testosterone levels; however, all patients in this trial had hypogonadal testosterone concentrations before being treated with testosterone, even though 23/24 were already receiving HAART. In addition, the use of PIs did not change during the study period.

Several limitations of this study should be mentioned. This was an open-label study, which introduces the possibility of bias, especially in the assessment of QOL, a subjective evaluation. To eliminate this potential source of bias, a randomized, double-blind, double-dummy study design would be required. This was a switch study with no washout period between treatments and no concurrent comparator groups. All subjects were receiving IM testosterone before the study began; at study start, the dose of IM testosterone was standardized to 100 or 200 mg. IM testosterone was always given first in the treatment sequence, preceding the switch to testosterone gel; the opposite treatment sequence (testosterone gel followed by IM testosterone) was not tested. With no washout between treatments, residual testosterone from IM treatment may have affected serum testosterone concentrations in the initial phase of gel treatment. Therefore, it is not possible to conclude that all variability in peak and trough testosterone concentrations is attributed solely to the formulation of testosterone administered. Although prestudy baseline testosterone levels were recorded, unfortunately the specific data are not available for comparison at the present time. Blood was drawn at times when testosterone concentrations were thought to approach peak and trough levels; however, the actual peak and trough values may have been slightly different. Finally, treatment compliance was not assessed. It has been noted in clinical practice that HIV-positive men have high levels of adherence to testosterone therapy, perhaps because of perceived benefits of treatment. However, patient adherence to medication is often a problem, even in HIV, where nonadherence to antiviral treatment may have serious consequences.[33] It is likely that some of the patients in this study did not adhere to testosterone therapy as prescribed. The higher percentage of patients who achieved eugonadal testosterone levels on transdermal gel may indicate better adherence with the gel than with IM injection. However, we did not measure adherence and cannot draw this conclusion.

Despite these limitations, QOL endpoints were assessed by means of a validated HIV-specific instrument (FAHI), and results are consistent with

those reported in other studies of testosterone therapy in hypogonadal men. This study reflects real-world experience of hypogonadal HIV-positive men and provides evidence for benefits of testosterone gel therapy in this patient population.

Cost differences may be a consideration for the clinician who must decide whether testosterone gel or IM testosterone therapy is the best treatment option. Testosterone gel can be self-administered, whereas patients prescribed IM testosterone who cannot or will not administer self-injections must return to a clinic for treatment. If cost of medication only is considered, testosterone gel is more expensive than IM testosterone. However, if the costs of clinic visits, examination room occupancy, and medical personnel time are considered, the total cost of IM therapy increases sharply. A study by Clay[34] has shown considerable cost savings when patients are switched from IM testosterone to testosterone gel therapy; however, the Clay study did not closely investigate QOL. The data reported here support maintenance of improvement in QOL following such a switch.

Better patient acceptance of testosterone gel versus IM testosterone therapy may be related to sustained testosterone concentrations with the gel formulation that avoid extreme peak and trough testosterone concentrations and associated mood swings. Better acceptance of testosterone therapy results in improved functioning, which may enhance patient compliance with overall therapy.

CONCLUSION

Both IM testosterone and testosterone gel resulted in eugonadal testosterone concentrations and were well tolerated in HIV-positive hypogonadal men in this study. Daily testosterone gel produced stable testosterone concentrations and improved QOL compared with intermittent IM testosterone injections.

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