Testosterone therapy in HIV wasting syndrome: systematic review and meta-analysis

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Many HIV patients develop weight loss, which increases morbidity and mortality. We aimed to assess the effects of testosterone therapy on lean body mass, total body weight, over-all exercise functional capacity, and perceived quality of life in patients with HIV wasting syndrome and its adverse effects. We systematically reviewed randomised, placebo-controlled trials that compared the effects of testosterone therapy with placebo in HIV patients with wasting. Eight trials met the inclusion criteria and 417 randomised patients were included. Only six trials used lean-body mass, fat-free mass, or body-cell mass as outcome measures. The meta-analysis of the six trials showed a difference in the lean body mass between the testosterone group and placebo group of 1·22 kg (95% CI 0·23–2·22) for the random effect model and 0·51 kg (0·09–0·93) for fixed effect. However, the difference was much greater in the three trials that used the intramuscular route—3·34 kg in the post-hoc analysis. All eight trials included total body weight as an outcome measure, the meta-analysis of which showed a difference of 1·04 kg (−0·01–2·10) between testosterone group and placebo group by random effect and 0·63 kg (−0·01–1·28) for fixed effect models. Over-all, the incidence of adverse effects is similar in both groups. Testosterone therapy has been shown in this review to increase lean body mass more than placebo. The increase is even greater if the therapy is given intramuscularly. There is also a small positive effect in total body weight. The study is, however, limited by the small numbers and heterogeneity of the population, which potentially introduced bias into the methods and results. Testosterone therapy may be considered in patients with HIV wasting syndrome to reverse muscle loss, but there is a concern about the adverse metabolic effects of long-term testosterone administration and long-term follow-up for these patients is needed.

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Many HIV-infected patients develop weight loss and wasting, the cause of which is multifactorial.[1] Wasting can be caused by HIV directly or through secondary causes such as anorexia, malabsorption and diarrhoea, opportunistic infections, and malignancy: the exact mechanisms are not fully known. HIV wasting is characterised by severe muscle loss and deteriorating muscle strength and exercise function. There is evidence that a change in body composition takes place at an early stage of HIV infection even before there is any sign of weight loss. In fact, because the amount of wasting often correlates more closely with changes in body cell mass and lean-body mass than with reduction of total-body weight, the decrease in body cell mass and lean-body mass is a better indicator of malnutrition and protein loss.[2] HIV-infected men can lose a great amount of lean-body mass out of proportion to body weight.[3,4]

The total-body weight can be divided into different compartments and analysed in different models. The body weight, body cell mass, and lean body mass can be related as follows:[5] body weight=body cell mass+extracellular material+fat; lean body mass=body cell mass+extracellular material; and body weight=lean body mass+fat. Lean body mass is fat-free mass minus bone mineral mass. Although there is still debate about the difference between lean-body mass and fat-free mass, most investigators use lean-body mass and fat-free mass interchangeably.[6]

Various treatments have been tried in HIV wasting. Although antiretroviral medications have been shown to increase body weight in HIV patients, the increase is mainly due to an increase in fat mass rather than lean body mass.[7,8] Megestrol acetate can encourage appetite and weight gain but it may decrease testosterone concentrations and cause accumulation of more fat and less lean-body mass.[9–11] Thalidomide has been shown to be effective in HIV wasting but it is limited by its side-effects.[12–14] Growth hormone may increase lean-body mass but is very costly and the long-term safety and tolerability of therapy are unknown.[15–17]

A high proportion of HIV-infected men (up to 30–50%) may have a low testosterone concentration.[18,19] Loss of body and muscle mass and deterioration in exercise functional capacity are highly correlated with androgen concentrations in HIV patients with hypogonadism and wasting.[20] In hypogonadal men without HIV infection, testosterone replacement had been shown to increase fat-free mass, muscle size, and even mood.[21–23] It has also been shown that in healthy men supraphysiological doses of testosterone—especially when combined with exercise training—increase fat-free mass and muscle size.[24] In HIV-infected men, testosterone therapy has been used in both hypogonadal men[25] and eugonadal men.[26] It has been shown to increase lean-body mass and it is also relatively safe and cheap. In various trials, the therapy is frequently combined with resistance exercise.[26,27]

There is evidence that loss of body weight, especially lean-body mass and body cell mass, is associated with shorter

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Table 1. Characteristics of included studies

Study	Methods	Participants	Interventions	Outcomes	Notes	Allocation concealment
Berger 1996[29]	Double-blind, placebo-controlled, randomised study.	HIV men, unknown testosterone level	Oxandrolone 5 mg or 15 ing or placebo for 16 weeks	No significant change in weight. LBM not assessed	Randomisation not described	B
Bhasin 1998[31]	Double-blind, placebo-controlled, randomised study	HIV men with low testosterone level	2 testosterone patches or 2 placebo patches for 12 weeks	LBM and FFM increased, No change in weight.	Randomisation not described	B
Bhosin 2000[27]	Double-blind, placebo-controlled, randomised study.	HIV men with low testosterone level	IM testosterone or placebo +/- exercise for 16 weeks	LBM and FFM and weight increased	Randomisation by randomisation schedules	A
Coodley 1997[32]	Double-blind, placebo-controlled, randomised study.	HIV men with low testosterone level	IM testosterone or placebo for 3 months	No significant change in weight, LBM not assessed	Randomisation not described	B
Dobs 1999[33]	Double-blind, placebo-controlled, randomised study.	HIV men with low testosterone level	Testosterone patch or placebo patch for 12 weeks	No significant differences in weight or BCM in 2 groups after 12 weeks	Randomisation not mentioned	B
Grinspoon 1998[25]	Double-blind, placebo-controlled, randomised study.	HIV men with low testosterone level	Testosterone or placebo for 6 months	FFM and LBM and weight increased in the treatment group	Randomisation by a permuted block algorithm	A
Grinspoon 2000[26]	Double-blind, placebo-controlled, randomised study.	HIV men, normal testosterone level	IM testosterone or placebo +/- exercise for 12 weeks	LBM and weight increased significantly more in the treatment group	Randomisation by a permuted block algorithm	A
Miller 1998[30]	Double-blind, placebo-controlled, randomised study.	HIV women with low testosterone level	Testosterone or placebo patches for 12 weeks	FFM and weight not significantly different between the 3 groups	Randomisation not described but blinded	A

IM=intramuscular, LBM=lean-body mass, FFM=fat-free-mass, BCM=body-cell mass, A=adequate, B=unclear.

survival in HIV patients.[3,28] In addition, loss of body weight and lean-body mass lead to deterioration in exercise functional capacity.[20]

Objective

Here we present a systematic review and meta-analysis on the randomised controlled trials that compare the effects of testosterone therapy and placebo on HIV-positive men with wasting. The primary aim was to assess whether testosterone therapy compared with placebo improves lean-body mass or fat-free mass or body cell mass. The secondary aims were to assess body weight, over-all exercise functional capacity, perceived quality of life, and adverse effects between the two groups.

Methods

Criteria for considering studies for this review

Types of study

Only randomised placebo-controlled trials were included and were either single-blinded or double-blinded. The method of randomisation and quality of concealment of allocation were analysed. In addition, it was considered whether intention-to-treat analysis was applied in the trials.

Types of participant

HIV-positive men or women above the age of 18 were included. The inclusion criteria for weight was either greater than 5% or greater than 10% weight loss or less than 90% ideal body weight. Either eugonadal or hypogonadal patients were included.

Types of intervention

Any type of testosterone therapy, either synthetic or non-synthetic, was included if compared with placebo. The therapy could be given by any route, including oral, patches, and intramuscular injection routes. The duration of each trial was greater than 12 weeks. Resistance exercise combined with testosterone therapy was included.

Types of outcome measure

The primary outcome measure was lean-body mass, fat-free mass, or body cell mass. The secondary outcome measures were body weight, over-all exercise functional capacity, perceived quality of life, and adverse effects.

Review methods

After initial selection of trials for inclusion in the review (see search strategy panel) we used a derived data extraction form to assess the quality of the trials—including the method of randomisation, quality of concealment, and intention-to-treat analysis—and collected data about the participants and interventions. Meta-analysis was done through Cochrane Collaboration's Review Manager Software 4·1. Only continuous data was available for total body weight, lean-body mass, or fat-free mass and body cell mass. All standard errors from the trials are converted to standard deviations unless the standard deviations were already reported. The over-all effect was estimated by weighted mean difference (WMD) and 95% confidence interval. Chi-squared tests were used to test statistical heterogeneity in all trials. Both fixed-effect and random-

Table 2. Characteristics of excluded studies

Study	Reason for exclusion
Gold 1996[34]	Not a randomised placebo-controlled trial.
Grinspoon 1999[35]	Same study as Grinspoon 1998[25]
Hengge 1996[36]	Not a randomised placebo-controlled trial.
Rabkin 1998[37]	Open trial and then double-blind, placebo-controlled discontinuation trial.
Rabkin 1999[38]	Open trial and then randomised, placebo-controlled discontinuation trial.
Rabkin 2000[39]	Not a randomised, placebo-controlled trial
Sattler 1999[40]	Not a placebo-controlled trial.
Strawford 1999[41]	Although it is a randomised controlled trial, all patients received 8 weeks resistance exercise with physiological intramuscular testosterone replacement
Strawford 1999[42]	21 days of placebo-controlled study followed by 12 weeks of open-label follow up. The analysis was only done on 10 out of 18 patients who finished the open-label study and there was no mention of who were in the placebo group among the 10 patients.
Van Loan 1998[43]	There was only 3 weeks of double-blind, randomised, placebo-controlled intervention and then the next 12 weeks was open-label. The outcome analysis was not done on placebo group and done only on 8 out of 18 who finished the study.
Wagner 1999[44]	The double-blind, placebo-controlled trial was only for 6 weeks followed by 12 weeks of open-label maintenance treatment. The assessment of weight was not done after 6 weeks but done after the whole study. The placebo group then received testosterone and the effect of intervention was difficult to determine.

effect models were used to assess the effects on the basis of the presence or absence of heterogeneity ($p<0·05$). There was clinical and statistical heterogeneity between the eight trials. A random-effect model was used in all analysis, except in the case of subgroup analysis when there was significant clinical and statistical homogeneity ($p>0·05$) between the trials.

Due to the heterogeneity of the reporting of adverse effects, a meta-analysis was not appropriate but a table showing the incidence is provided instead. Berger et al[29] used two different doses of testosterone therapy to compare with placebo and Miller et al[30] also had three arms consisting of two testosterone patches, or one testosterone patch and one placebo patch, versus two placebo patches. For these two studies the two different strengths of testosterone were considered as two separate trials in the meta-analysis.

Results

The search found 513 citations, of which 19 articles thought to be relevant were chosen to be assessed by the two reviewers independently. Eight articles were finally agreed for inclusion (table 1) and 11 articles were excluded (table 2). In total there were only 417 randomised patients in the meta-analysis.

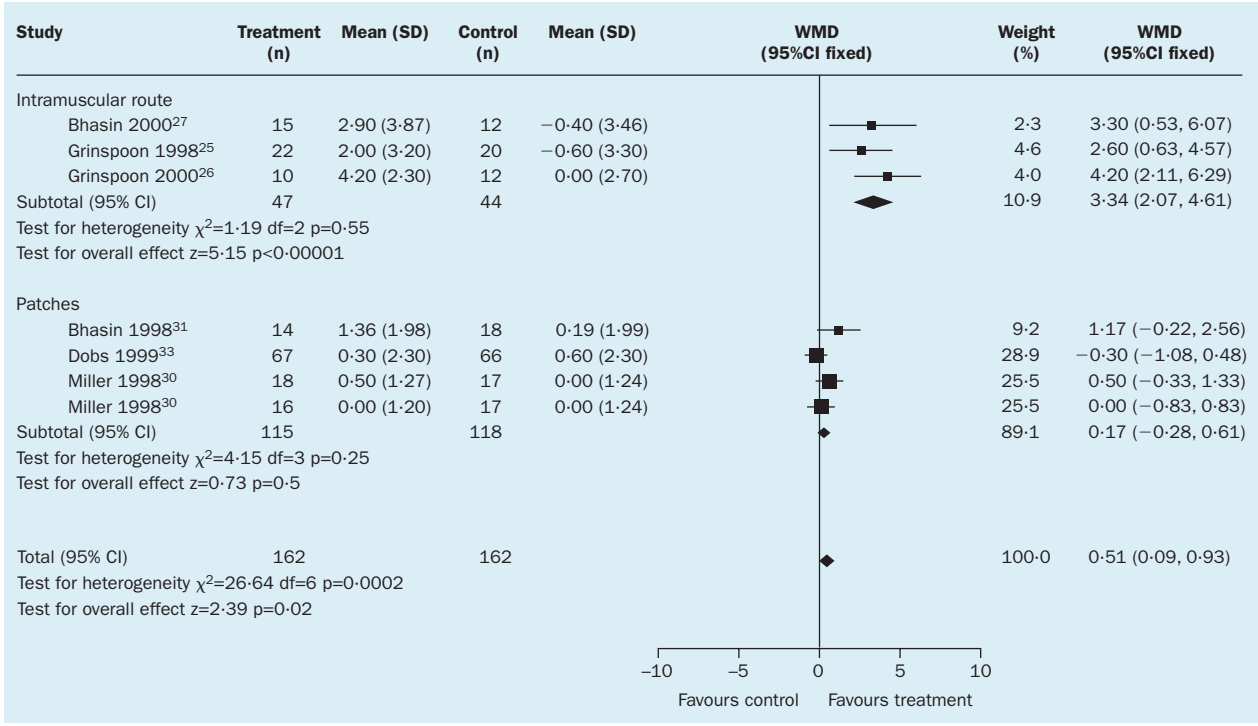

Figure 1. Testosterone versus placebo for lean-body mass, fat-free mass, or body cell mass; intramuscular or patches.

Quality of included studies

All the studies included were double-blind placebo-controlled studies. However, only four of eight studies were thought to have adequate concealment of allocation.[25–27,30] The method of blinding of placebo was only adequately described in four of eight studies.[25,26,30,33] In general, the reporting method of the studies was poor. Intention-to-treat analysis was applied only in three studies.[27]

Change in lean body mass

Berger et al[29] and Coodley et al[32] did not report lean-body mass or fat-free mass. This did not seem to be due to reporting bias but, rather, due to the fact that lean-body mass or fat-free mass were not included in their outcome measures. Therefore, these two studies could not be included in this meta-analysis. Dobs et al[33] used body cell mass rather than lean-body mass or fat-free mass as their outcome measure. But, as mentioned before, lean-body mass is equivalent to body cell mass plus extracellular material. Assuming that there is minimal change in the extracellular material, the change in body cell mass should reflect the change in lean-body mass. Therefore, Dobs et al is included in the meta-analysis although a sensitivity analysis was done to see the effect of excluding this trial. Meta-analysis of the six trials using the random-effect model showed that the difference in the change in lean-body mass favouring testosterone group was 1·22 kg (95% CI 0·23–2·22 kg, p=0·02). The result was 0·51 kg for fixed-effect model (0·09–0·93, p=0·02). Only the fixed-effect model figure is shown in figure 1. The heterogeneity tests revealed χ^2 of p=0·0002, 26·64 (df=6), which confirmed heterogeneity between trials. The heterogeneity shown was due to the differences in the mode of administration of testosterone. Dobs et al, Miller et al, and Bhasin et al used testosterone patches[30–33] while the other three studies, Bhasin et al, Grinspoon et al, and Grinspoon et al used intramuscular injections (figure 1).[25–27] Subgroup analysis of the three trials that used intramuscular testosterone showed no significant heterogeneity between the trials (χ^2=1·19, df=2, p=0·55). All three trials showed positive outcomes and the over-all change in the lean-body mass using fixed-effect model was 3·34 kg (2·07–4·61, p<0·00001) (figure 1). This result was exactly the same if a random-effect model was used. Unfortunately, the subgroup analysis was done post hoc—ie, after the protocol was completed—and may be subject to bias.

In the post-hoc sensitivity analysis, if the women were excluded[30] from the six trials, the over-all increase in lean-body mass, fat-free mass, or body cell mass was 1·99 kg (0·23–3·76, p=0·03) for random effect and 0·79 kg (0·19–1·39) for fixed effect. If Dobs et al[33] (which is the only trial that used body cell mass as an outcome measure) was also excluded, the increase in lean-body mass or fat-free mass was 2·63 kg (1·19–4·06) for random effect and 2·35 kg (1·41–3·29) for fixed effect (figure 2). Therefore, the direction of the over-all effect remains the same although the magnitude of the effect varies depending on which trial was excluded in the sensitivity analysis. This strengthens the confidence that can be placed in the results.

Change in body weight

Meta-analysis of the eight trials using the random-effect model showed that the difference in the mean change in the body weight between the testosterone group and placebo group was 1·04 kg (−0·01–2·10, p=0·05) (figure 3) and 0·63 kg (−0·01–1·28, p=0·05) for fixed-effect model. The

Study	Treatment (n)	Mean (SD)	Control (n)	Mean (SD)	WMD (95%CI fixed)	Weight %	WMD (95%CI fixed)
Men only							
Bhasin 1998[31]	14	1·36 (1·98)	18	0·19 (1·99)		12·9	1·17 (–0·22,2·56)
Bhasin 2000[27]	15	2·90 (3·87)	12	–0·40 (3·46)		3·2	3·30 (0·53,6·07)
Grinspoon 1998[25]	22	2·00 (3·20)	20	–0·60 (3·30)		6·4	2·60 (0·63,4·57)
Grinspoon 2000[26]	10	4·20 (2·30)	12	0·00 (2·70)		5·7	4·20 (2·11,6·29)
Subtotal (95% CI)	61		62			28·3	2·35 (1·41,3·29)
Test for heterogeneity χ^2=6·31 df=3 p=0·097							
Test for overall effect z=4·91 p<0·00001							
Women only							
Miller 1998[30]	18	0·50 (1·27)	17	0·00 (1·24)		35·9	0·50 (–0·33,1·33)
Miller 1998[30]	16	0·00 (1·20)	17	0·00 (1·24)		12·9	0·00 (–0·83,0·83)
Subtotal (95% CI)	34		34			71·7	0·25 (–0·34,0·84)
Test for heterogeneity χ^2=0·69 df=1 p=0·4							
Test for overall effect z=0·83 p=0·4							
Total (95% CI)	95		96			100·0	0·84 (0·34,1·34)
Test for heterogeneity χ^2=20·80 df=5 p=0·0009							
Test for overall effect z=3·32 p=0·0009							

Figure 2. Testosterone versus placebo for lean-body mass or fat-free mass; men only or women only.

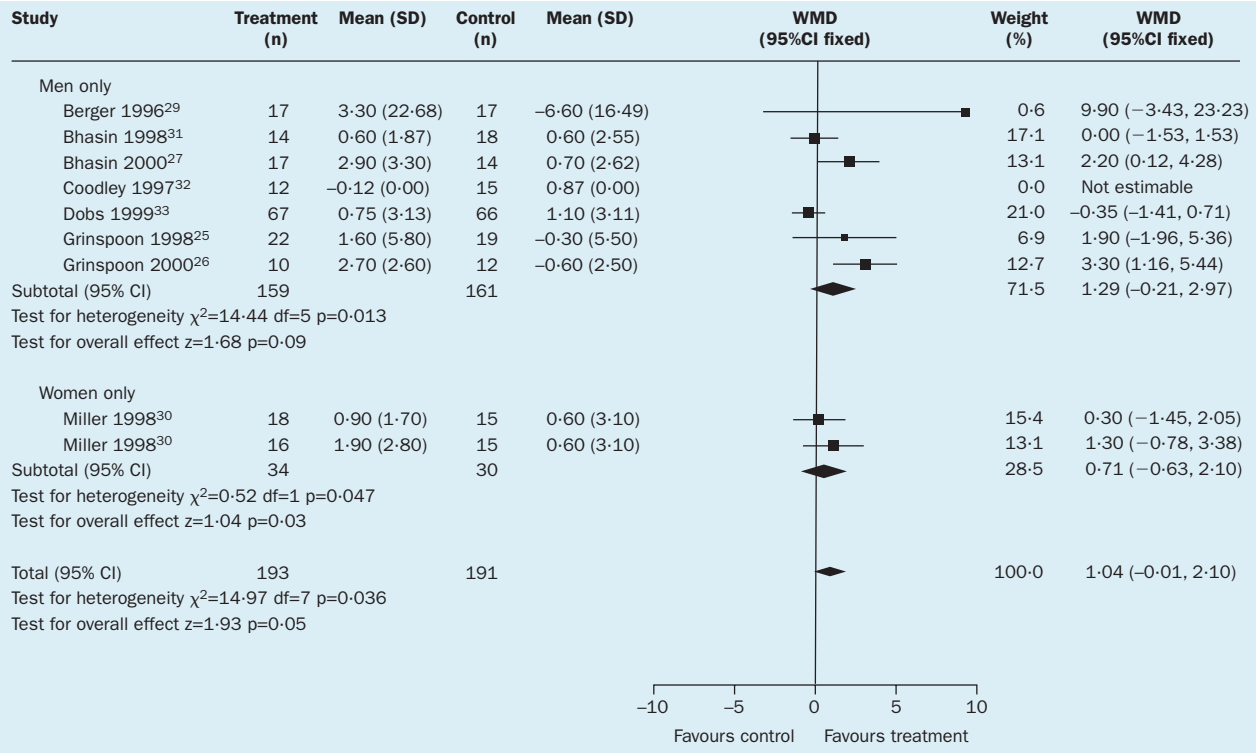

Figure 3. Testosterone versus placebo for total body weight.

heterogeneity tests showed that χ^2 was 17·87 (df=8, p=0·022), which confirmed heterogeneity between the trials. Coodley et al did not give a standard deviation nor a standard error or a confidence interval for us to work out the standard deviation for their results.[32] As a result their contribution to meta-analysis was not estimable. Excluding the women from the trials[30] in the sensitivity analysis marginally increased the total body weight to 1·54 kg (−0·03–3·10, p=0·05).

Resistance exercise as a co-intervention

Only two trials, Bhasin et al and Grinspoon et al, used resistance execise as co-intervention with intramuscular testosterone injection.[26,27] The difference in the lean-body mass between testosterone with exercise group and placebo with exercise group was 1·28 kg (−0·18–2·73) and this was not significant with p=0·077 (figure 4). The difference in the total body weight between the two groups was −0·79 kg (−0·26–0·58, p=0·13).

Over-all exercise functional capacity/muscle strength

The included studies used different methods to assess over-all functional capacity and muscle strength, making meta-analysis of continuous variables impossible. Meta-analysis

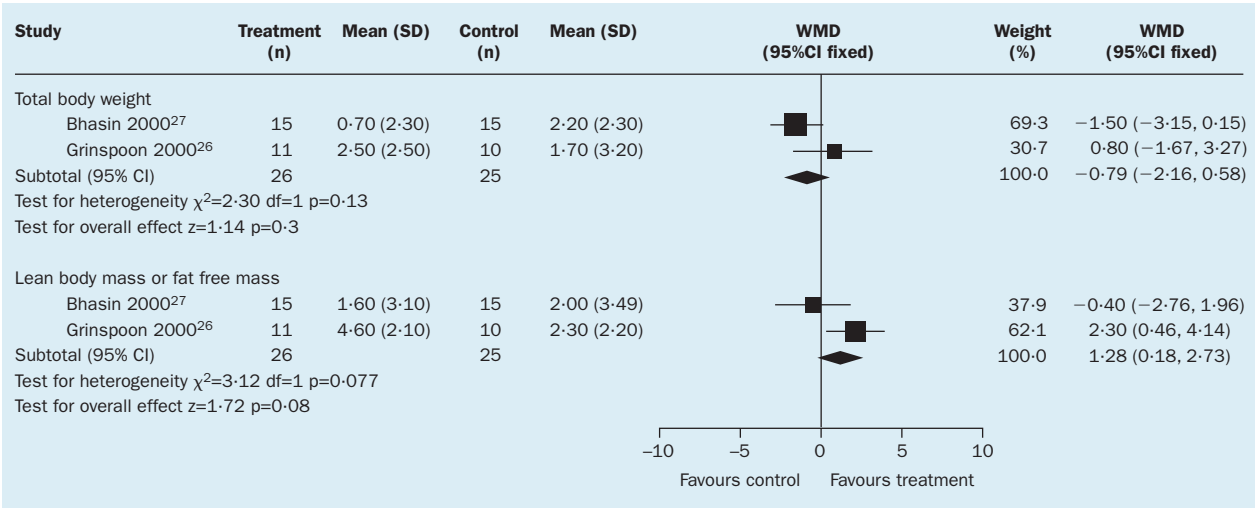

Figure 4. Testosterone with exercise versus placebo with exercise for total body weight and lean-body mass.

Table 3. Adverse effects

Study	Treatment	Control
Berger 1996[29]	36/42	20/21
Bhasin 1998[31]	11/20	9/21
Bhasin 2000[27]	2/32	1/29
Dobs 1999[33]	1/67	1/66
Grinspoon 1998[25]	3/22	4/19
Grinspoon 2000[26]	2/24	1/26
Miller 1998[30]	4/36	3/17

of dichotomous variables was also impossible because there was no number of events—ie, number of people improved in exercise capacity—reported for each group. Of the eight included studies, only three studies reported improved exercise functional capacity or muscle strength in the treatment group compared with placebo group.[26,27,32] Four studies reported no difference in exercise functional capacity or muscle strength between the treatment group and placebo group.[25,29–31] Dobs et al did not include over-all exercise functional capacity as an outcome measure.[33]

Perceived quality of life

Again, meta-analysis could not be done on the included studies because of the different quality-of-life scales used. These included the RAND 36-item health survey questionnaire, perceived well-being assessed using a scale adapted from Oster et al, the HRQL survey, the EUROQOL Feeling Thermometer scale, the sexual functioning questionnaires for males, and quality-of-life indicators. Of the eight included studies, two did not include quality of life as part of the outcome measures.[25,26] Three studies reported improvement in the perceived quality of life in treatment group compared with placebo group.[29,30,32] Three studies reported no significant differences in the perceived quality of life between the treatment group and placebo group.[27,30,33]

Adverse events

Of the eight included studies, Coodley et al did not give the number of adverse events,[32] although the study reported no difference between the two groups in terms of side-effects (which were pain in the injection site, fatigue, and weakness). The other studies did not record or report the adverse events consistently and interpreted adverse events differently. For example, Berger et al[29] noted that all patients for whom data was collected reported at least one adverse event whereas in Dobs et al, the rates of adverse events were less than 2% in both groups.[33] In view of the heterogeneity of the reporting of the adverse effects, meta-analysis is not appropriate, but their incidence is given in table 3. In general, the incidence does not differ much between the two groups. The adverse events include local reaction to patches, acne, gynaecomastia, or breast tenderness.

Discussion

This review supports a small but significant change in lean-body mass and body weight with testosterone therapy. There are limitations, however, to this review. Although the search was meant to be comprehensive, grey literature was not included due to time restraint and limited manpower in searching. The analyses were not based on individual participant data but on the data extracted from published articles, which might have reporting bias. Despite the meta-analysis there were only a small number of randomised patients in total because most included studies only had a few patients, which may exaggerate the treatment effects. There was also significant heterogeneity between the eight included trials in terms of participants, interventions, and outcome measures. For example, in terms of participants, both men and women were included, all of whom had different concentrations of testosterone before the trials. As for interventions, different studies used different types of testosterone therapy with different doses, frequencies, routes, and duration. Different outcome measures were also used in different trials. The small numbers of patients that came from the eight trials with significant heterogeneity potentially introduced bias into the methods and results. A funnel plot was done to exclude publication bias and it showed an asymmetry (only available in Rev Man for reviewers). It was, however, difficult to interpret in this review as small number of trials and significant heterogeneity between trials may both contribute to the asymmetry. However, post-hoc sensitivity analysis was done to test the stability of findings across different participants and routes of intervention, and to test for inconsistencies and prevent misleading conclusions.

In general, testosterone increased lean-body mass or fat-free mass more than placebo group by 1·22 kg (0·23–2·22, p=0·02). There was an obvious difference between the intramuscular route and patches. The subgroup analysis of the three trials using the intramuscular route showed a significant difference in the lean-body mass between the two groups of 3·34 kg (2·07–4·61). There was no evidence from this review to suggest that testosterone patches were more effective than placebo in gaining lean body mass (the difference was 0·20 kg, −0·34–0·73). The subgroup analysis has to be interpreted with caution as it was obtained post-hoc. In addition, the value of randomisation would have been lost since there was no direct randomisation between intramuscular route and patches. Although no definitive conclusion can be drawn from the post-hoc analysis, it does suggest that intramuscular testosterone may be more effective in reversing lean-body mass loss than testosterone patches. All three trials using intramuscular testosterone showed a positive effect on lean-body mass and there was no significant heterogeneity between the trials. The subgoup analysis can serve as a hypothesis for future research.

The difference in the change of mean body weight between treatment group and placebo group was 1·04 kg (−0·01–2·10, p=0·04). Although the total body weight is not the primary outcome measure, testosterone therapy seems to have a small positive effect in total body weight in patients with HIV wasting syndrome. However, the amount of HIV wasting often correlates more closely with changes in lean-body mass than with reduction of total body weight.

Miller et al[30] is the only trial on HIV-positive women to date and the testosterone patches used in that trial did not seem to increase lean-body mass. But intramuscular injection

Search strategy and selection criteria

A search of the following electronic database took place between June and September 2000: Medline, Embase (Ovid search form), Science citation index, Index to scientific and technical proceedings, AIDSLINE, Cochrane database of systematic reviews, Database of abstracts of reviews of effectiveness, and Cochrane clinical trials register. In addition, the references from relevant articles were handsearched. The following keywords were searched: "HIV", "HIV infections", "acquired immunodeficiency syndrome", "HIV wasting syndrome", "wasting syndrome", "weight loss", "cachexia", "clinical trials", "random allocation", "randomised controlled trials", "double-blind method", "placebos", "single-blind method", and "testosterone". The search was not limited to English although only articles in English were identified. There is currently an international multicentre trial on intramuscular testosterone therapy in HIV wasting syndrome . It aims to recruit around 300 patients and will be the biggest randomised placebo trial so far. It is hoped that when this trial is finished and published, the systematic review will be updated to include this study.

may be used in the future for further research in HIV-positive women with wasting syndrome. Intramuscular testosterone may also be relevant to other groups of patients with wasting disease, particularly cancer patients with cachexia and weight loss. It is believed that there are some similarities in the mechanisms of weight loss beween HIV and cancer. So far there have been no randomised controlled trials of intramuscular testosterone for cancer-related weight loss. This may be a topic for future research especially for cachectic cancer patients who are undergoing curative treatments.

Grinspoon et al[35] continued an open-label testosterone administration for an extra 6 months after a double-blind, randomised, placebo-controlled study.[25] Patients initially randomised to placebo gained lean-body mass only after crossover to testosterone administration. By contrast, patients initially randomised to testosterone continued to gain lean-body mass during open-label administration and had gained more lean-body mass at 1 year than did patients receiving testosterone for only the final 6 months of the study.

Testosterone may decrease HDL cholesterol concentrations and there has been a concern about the abnormal lipid profiles in patients recovering from wasting and in patients on protease inhibitors.[26,45] Long-term follow-up on patients receiving testosterone injection is needed. Resistance exercise has been associated with a significant increase in HDL cholesterol and may increase lean-body mass as much as testosterone therapy. Roubenoff et al[46] showed that progressive resistance exercise increased muscle strength and lean body mass (1·75 SD 1·94 kg) in HIV patients. In view of the independent positive effect of resistance exercise on various outcome measures, subgroup analysis on patients who had resistance exercise a co-intervention was done. It showed that testosterone therapy combined with resistance increased lean-body mass more than placebo with exercise (1·28 kg, −0·18–2·79) but not body weight. A larger sample is needed to show a difference because the result was not statistically significant.

Conclusions

Testosterone therapy has been shown in this review to increase lean-body mass more than placebo. The increase is even greater if the therapy is given intramuscularly. There is also a small positive effect on total body weight. The study is, however, limited by the small numbers and heterogeneity of the population, which potentially introduced bias into the methods and results. Testosterone therapy may be considered in patients with HIV wasting syndrome to reverse muscle loss. The results may also be applicable to other diseases with muscle wasting, including malignant disease since there are some similarities between the two conditions, although more research is needed. There is a concern about the adverse metabolic effects of long-term testosterone administration and long-term follow-up for these patients is needed.

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Conflict of interest

None declared

References

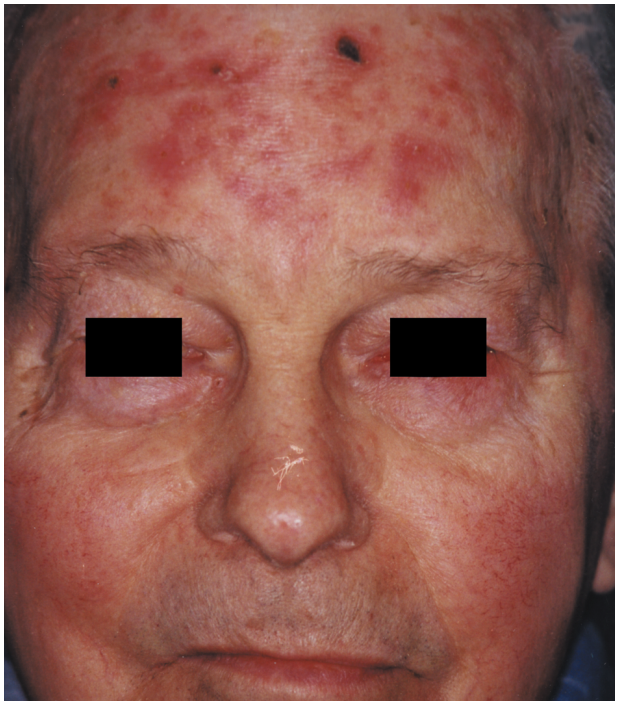
1 Strawford A, Hellerstein M. The aetiology of wasting in HIV and AIDS. *Semin Oncol* 1998; **25:** 76–81.
2 Ott M, Lembcke B, Fischerb H, et al. Early changes of body composition in human immunodefiency virus-infected patients: tetrapolar body impedance analysis indicates significant malnutrition. *Am J Clin Nutr* 1993; **57:** 15-19.
3 Kotler DP, Tierney A, Pierson RN. Magnitude of body cell mass depletion and timing of death from wasting in AIDS. *Am J Clin Nutr* 1989; **50:** 444–47.
4 Kotler DP, Wang J, Pierson RN. Body composition studies in patients with acquired immunodefiency syndrome. *Am J Clin Nutr* 1985; **42:** 1255–65.
5 Nemechek PM, Polsky B, Gottlieb MS. Treatment guidelines for HIV-associated wasting. *Mayo Clin Proc* 2000; **75:** 386–94.
6 Wang ZM, Pierson RN Jr, Heymsfield SB. The five-level model: a new approach to organizing body composition research. *Am J Clin Nutr* 1992; **56:** 19–28.
7 Silva M, Skolnik PR, Gorbach SL, et al. The effect of protease inhibitos on weight and body composition in HIV-infected patients. *AIDS* 1998; **12:** 1645–51.
8 Pernerstorfer-Schoen H, Schndler K, Parschalk B, et al. Beneficial effects of protease inhibitors on body composition and energy expenditure: a comparison between HIV-infected and AIDS patients. *AIDS* 1999; **13:** 2389–96.
9 Engelson ES, Pi-Sunyer FX, Kotler DP. Effects of megestrol acetate therapy on body composition and circulating testosterone concentrations in patients with AIDS. *AIDS* 1995; **9:** 1107–08.
10 Von Roenn JH, Murphy RL, Weber KM, Williams LM, Weitzman SA. Megestrol acetate for treatment of cachexia associated with HIV infection. *Ann Intern Med* 1988; **109:** 840–41.
11 Von Roenn JH, Murphy RL, Wegener N. Megestrol acetate for treatment of anorexia and cachexia associated with HIV infection. *Semin Oncol* 1990; **17:** 13–16.
12 Rebuck JA, Fish DN. Thalidomide pros and cons. *Am J Nurs* 1998; **98:** 63.
13 Reyes-Teran G, Sierra-Madero JG, Martinez del Cerro V, et al. Effects of thalidomide on HIV-associated wasting syndrome: a randomised, double-blind, placebo-controlled clinical trial. *AIDS* 1996; **10:** 1501–07.
14 Kaplan G, Thomas S, Fierer DS, et al. Thalidomide for the treatment of AIDS-associated wasting. *AIDS Res Hum Retroviruses* 2000; **16:** 1345–55.
15 Waters D, Danska J, Hardy K, Koster F, Qualls C, Nickell D. Recombinant human growth hormone, insulin-like growth factor 1, and combination therapy in AIDS-associated wasting. *Ann Intern Med* 1996; **125:** 865–72.
16 Schambelan M, Mulligan K, Grunfeld C, et al. Recombinant human growth hormone in patients with HIV-associated wasting. *Ann Intern Med* 1996; **125:** 873–82.
17 Mulligan K, Tai VW, Schambelan M. Effects of chronic growth hormone treatment on energy intake and resting energy metabolism in patients with HIV-associated wasting—a clinical research centre study. *J Clin Endocrin Metab* 1998; **84:** 1288–93.
18 Croxson TC, Chapman WE, Miller LK, Levitt CD, Semie R, Zumoff B. Changes in the hypothalamic-pituitary-gonadal axis in human immunodefiency virus-infected homosexual men. *J Clin Endocrinol Metab* 1989; **68:** 317–21.
19 Dobs AS, Dempsey MA, Ladenson PW, Polk BF. Endocrine disorders in men infected with human immunodeficiency virus. *Am J Med* 1998; **84:** 611–16.
20 Grinspoon S, Corcoran C, Lee K, et al. Loss of lean body and muscle mass corelates with androgen levels in hypogonal men with acquired immunodefiency wyndrome and wasting. *J Clin Endocrinol Metab* 1996; **81:** 4051–58.
21 Bhasin S, Storer TW, Berman N, et al. Testosterone

replacement increases fat-free mass and muscle size in hypogonal men. *J Clin Endocrinol Metab* 1997; **82:** 407–13.
22 Brodsky IG, Balagopal P, Sreekumaran Nair K. Effects of testosterone replacement on muscle mass and muscle protein synthesis in hypogonadal men—a clinical research centre study. *J Clin Endocrinol Metab* 1996; **81:** 3469–75.
23 Wang C, Alexander G, Berman N, et al. Testosterone replacement therapy improves mood in hypogonadal men—a clinical research centre study. *J Clin Endocrinol Metab* 1996; **81:** 3578–83.
24 Bhasin S, Storer TW, Berman N, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *NEJM* 1996; **335:** 1–7.
25 Grinspoon S, Corcoran C, Askari H, et al. Effects of androgen administration in men with the AIDS wasting syndrome. *Ann Intern Med* 1998; **129:** 18–26.
26 Grinspoon S, Corcoran C, Parlman K, et al. Effects of testosterone and progressive resistance training in eugonadal men with AIDS wasting. *Ann Intern Med* 2000; **133:** 345–55.
27 Bhasin S, Storer TW, Javanbakht M, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. *JAMA* 2000; 283: 763–70.
28 Chlebowski RT, Grosvernor MB, Bernhard NH, Morales Ls, Bulcavage LM. Nutritional status, gastrointestinal dysfunction, and survival in patients with AIDS. *Am J Gastroenterol* 1989; **84:** 1288–93.
29 Berger JR, Pall L, Hall CD, Simpson DM, Berry PS, Dudley R. Oxandrolone in AIDS-wasting myopathy. *AIDS* 1996; **10:** 1657–62.
30 Miller K, Corcoran C, Armstrong C, et al. Trandermal testosterone administration in women with acquired immunodefiency syndrome wasting: a pilot study. *J Clin Endocrinol Metab* 1998; **83:** 2717–25.
31 Bhasin S, Storer TW, Asbel-Sethi N, et al. Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodefiency virus-infected men with low testosterone levels. *J Clin Endocrinol Metab* 1998; **83:** 3155–62.
32 Coodley GO, Coodley Mk. A trial of testosterone therapy for HIV-associated weight loss. *AIDS* 1997; **11:** 1347–52.
33 Dobs AS, Cofrancesco J, Nolten W, et al. The use of a transcrotal testosterone delivery system in the treatment of patients with weight loss related to human immunodefiency virus infection. *Am J Med* 1999; **107:** 126–32.
34 Gold J, High HA, Li Y, et al. Safety and efficacy of nandrolone decanoate for treatment of wasting in patiens with HIV infection. *AIDS* 1996; **10:** 745–52.
35 Grinspoon S, Corcoran C, Anderson E, et al. Sustained anabolic effects of long-term androgen administration in men with AIDS wasting. *Clin Infect Dis* 1999; **28:** 634–36.
36 Hengge UR, Bausmann M, Maleba R, Brockmeyer NH, Goos M. Oxymetholone promotes weight gain in patients with advanced human immunodefiency virus (HIV-1) infection. *Br J Nutr* 1996; **75:** 129–138.
37 Rabkin J, Wagner G, Rabkin R. Testosterone therapy for human immunodefiency virus-positive men with and without hypogonadism. *J Clin Psychopharmacol* 1999; **19:** 19–27.
38 Rabkin JG, Ferrando S, Wagner GJ, Rabkin R. DHEA treatment for HIV positive patients: effects on mood, androgenic and anabolic parameters. *Psychoneuroendocrinology* 1999; **25:** 53–68.
39 Rabkin JG, Wagner G, Rabkin R. A double-blind, placebo-controlled trial of testosterone therapy for HIV-positive men with hypogonadal symptoms. *Arch Gen Psychiatry* 2000; **57:** 141–47.
40 Sattler FR, Jaque SV, Schroeder ET, et al. Effects of pharamacological doses of nandrolone decoate and progressive resistance training in immunodefiency patients infected with human immmunodefiency virus. *J Clin Endocrinol Metab* 1999; **84:** 1268–76.
41 Strawford A, Barbieri T, Van Loan M, et al. Resistance exercise and supraphysiological androgen therapy in eugonadal men with HIV-related weight loss. *JAMA* 1999; **281:** 1282–90.
42 Strawford A, Barbieri T, Neese R, et al. Effects of nandrolone decanoate in borderline hypogonadal men with HIV associated weight loss. *J Acquir Immune Defic Syndr Hum Retrovirol* 1999; **20:** 137–146.
43 Van Loan, Strawford A, Jacob M, Hellerstein M. Monitoring changes in fat-free mass in HIV-positive men with hypotestosteroneaemia and AIDS wasting syndrome treated with gonadal hormone replecement therapy. *AIDS* 1999; **13:** 241–48.
44 Wagner GJ, Rabkin JG, Rabkin R. Effects of testosterone on weight and bodt composition in men with human immunodefiency virus-related weight loss. *Nutr Res* 1999; **19:** 227–33.
45 Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisolm DJ, Cooper DA. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet* 1999; **353:** 2093–99.
46 Roubenoff R, McDermott A, Weiss L, et al. Short term progressive resistance training increases strength and lean body mass in adults infected with human immunodefiency virus. *AIDS* 1999; **13:** 231–39.

Clinical picture

Concomitant bilateral herpes zoster opthalmicus

A 75-year-old man presented with general weakness and nausea for 3 weeks. He had a history of prostate carcinoma, stage III, hormone refractory with metastasis to the bones, for which he underwent radical prostatectomy and was treated with antiandrogens, luteinising-hormone-releasing-hormone agonist, and systemic chemotherapy. Other problems included anaemia of chronic disease, gastro-oesophageal reflux, and osteoarthritis. He received recombinent erythropoetin weekly. Vital signs were stable on presentation and clinical examination was unremarkable. Initial tests revealed white blood cell count $4{\cdot}3\times10^9$/L, haemoglobin 8·5g/dL, platelet count $9{\cdot}5\times10^9$/L, and prostate-specific antigen 1848 units. Within a few days he developed a vesicular rash on the right of his forehead. Within 48 h of the appearance of the first rash he developed similar vesicular eruptions on the contralateral forehead in the distribution of the first branch of the trigeminal nerve (figure). His signs and symptoms were consistent with bilateral herpes zoster opthalmicus and a Tzank smear was positive. The patient responded to systemic acyclovir therapy.



Herpes zoster (shingles) opthalmicus is a sight-threatening condition linked to varicella zoster virus reactivation within the trigeminal ganglion, causing perineuritis, perivascultis, and neuronal death. The frontal branch within the opthalmic division of trigeminal nerve is most commonly involved and 50–72% patients experience direct ocular involvement. Non-contiguous multi-dermatomal herpes zoster is very rare in both immunocompetent and immunosuppressed people. Early diagnosis is critical to prevent progressive corneal involvement and loss of vision. Standard treatment is systemic acyclovir or famciclovir and adjunctive topical steroid drops.

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