Authors' objectives
To assess the effect of testosterone compared with placebo on lean-body mass, fat-free mass or body cell mass in human immunodeficiency virus (HIV)-positive people with wasting.

Searching
MEDLINE, EMBASE, the Science Citation Index, the Index to Scientific and Technical Proceedings, AIDSLINE, the Cochrane Database of Systematic Reviews, DARE and the Cochrane Controlled Trials Register were searched between June and September 2000. In addition, the reference lists in identified studies were handsearched. The keywords used were stated and the searches were not restricted by language.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that lasted more than 12 weeks were eligible for inclusion. All of the included RCTs were double-blind.

Specific interventions included in the review
Comparisons of any type of testosterone therapy (synthetic or nonsynthetic) with placebo were eligible for inclusion. Testosterone could be given using any mode of administration, including oral, patches or intramuscular (i.m.) injection. Studies that used resistance exercise in combination with testosterone were included. The included studies used oxandrolone (5 or 15 mg), testosterone patches, and i.m. testosterone with and without exercise. The duration of the intervention ranged from 12 weeks to 6 months.

Participants included in the review
Studies of HIV-positive men or women aged older than 18 years were eligible for inclusion. The participants had to have lost greater than 5% or greater than 10% of their weight, or be less than 90% of their ideal body weight. Eugonadal and hypogonadal men were eligible. The men in the included studies had unknown, low or normal testosterone levels. One of the included studies was of women with low testosterone levels.

Outcomes assessed in the review
The primary outcome assessed in the review was lean-body mass, fat-free mass or body cell mass. The secondary outcomes in the review were body weight, overall exercise functional capacity, perceived quality of life, and adverse effects. The included studies assessed quality of life using different scales, such as the RAND 36-item health survey questionnaire, a scale adapted from Oster, the HRQL survey, the EUROQUOL Feeling Thermometer Scale, the sexual functioning questionnaires for males, and quality of life indicators.

How were decisions on the relevance of primary studies made?
Two authors independently selected studies and agreed on the studies to be included.

Assessment of study quality
Validity was assessed on the basis of methods of randomisation, adequacy of allocation concealment and whether an intention-to-treat analysis was conducted. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.

Data extraction
The data were extracted using a data extraction form. The authors did not state how many reviewers performed the data extraction. The tabulated information included study design, testosterone status of male participants, intervention
details, outcomes and validity criteria. Standard deviations that were not reported in studies were estimated from standard errors. In studies with more than one testosterone treatment arm, each treatment arm was treated as a separate trial.

**Methods of synthesis**

How were the studies combined?
An overall effect for testosterone versus placebo was estimated for lean-body mass and total body weight using the weighted mean difference (WMD) and 95% confidence interval (CI). A random-effects model was used, except in subgroup analyses where there was significant clinical and statistical (P>0.05) homogeneity. Data on functional capacity/muscle strength and quality of life were combined in a narrative synthesis. Adverse effects were summarised by tabulating the incidence in individual studies. The possibility of publication bias was explored using a funnel plot.

How were differences between studies investigated?
Statistical heterogeneity was tested using the chi-squared statistic. The influence of statistical heterogeneity was assessed by comparing the results from fixed-effect and random-effects models. In post-hoc subgroup analyses, trials of men only and of women only were pooled separately. The influence of the mode of administration (i.m. versus patches) on the results was also assessed. A sensitivity analysis was undertaken after excluding one RCT that reported body cell mass rather than lean-body mass or fat-free mass. Studies that used exercise as a cointervention were analysed separately.

**Results of the review**

Eight RCTs (417 patients) were included.

Study quality: the reporting of studies was generally poor. Four of the 8 RCTS were considered to have adequate allocation concealment and 4 RCTs adequately described blinding.

Change in lean-body mass (5 RCTs, 324 patients): testosterone significantly increased lean-body mass in comparison with placebo. The WMD (random-effects model) was 1.22 kg (95% CI: 0.23, 2.22). A post-hoc subgroup analysis was performed since significant heterogeneity was found (P=0.0002); the heterogeneity was due to differences in the mode of administration. The WMD for i.m. testosterone versus placebo (3 RCTs, 91 patients) was 3.34 (95% CI: 2.07, 4.61); no significant heterogeneity was found (P=0.55). The WMD for testosterone patches versus placebo (4 RCTs, 233 patients) was 0.17 (95% CI: -0.28, +0.61); no significant heterogeneity was found (P=0.25). Omitting the trial in women and the trial that reported body cell mass changed the effect size, but not the direction of effect.

Change in total body weight (8 RCTs, 384 people): there was no significant difference in body weight change between testosterone and placebo. The WMD (random-effects model) was 1.04 kg (95% CI -0.01, +2.10); significant heterogeneity was found (P=0.022). The results were similar for men only data.

Testosterone i.m. plus resistance exercise (2 RCTs, 53 people): there was no significant difference in lean-body mass between testosterone plus exercise and placebo plus exercise. The WMD was 1.28 kg (-0.18, +2.73).

Overall exercise functional capacity or muscle strength: studies used different methods to assess functional capacity and muscle strength. Three of the 7 RCTs that assessed this outcome found that testosterone increased functional capacity or muscle strength compared with placebo; the other 4 RCTs found no significant difference.

Quality of life (6 RCTs): 3 RCTs found that testosterone improved quality of life, while 3 RCTs found no significant difference.

Adverse events: one RCT did not report the number of adverse events, while the other RCTs did not report the adverse effects consistently. In the individual studies, the rates of adverse events ranged from 1 to 86% with testosterone and from 4 to 95% with placebo. The overall rates of adverse events appeared similar with testosterone and with placebo. Adverse events included local reaction to patches, acne, gynaecomastia and breast tenderness.

The funnel plot showed asymmetry so publication bias could not be excluded.
Authors' conclusions
Testosterone increases lean-body mass more than placebo, especially if the testosterone is given intramuscularly. The authors also concluded that the evidence was limited by the small number of studies with heterogeneous populations.

CRD commentary
The review question was clear in terms of the study design, intervention and participants. Several relevant sources were searched. Some details of the methods used to select the studies and extract the data were described. Validity was formally assessed using appropriate criteria, and results of this assessment were reported but not used in the analysis. Relevant information on the included studies was tabulated, apart from details of the participants. Data on body mass were combined in meta-analyses and where statistical heterogeneity was found, a post-hoc subgroup analysis was used to investigate potential reasons. As the authors stated, the results from the post-hoc subgroup analysis should be interpreted with caution in view of potential bias. The authors described the studies as being clinically heterogeneous with respect to the participants, but no details were given of these differences. Furthermore, their summary estimates of effect may not be reliable due to flaws in the meta-analysis. The authors were correct to conclude that the evidence was limited by the small number of participants.

Implications of the review for practice and research
Practice: The authors stated that testosterone should be considered in HIV-positive patients with wasting, but that potential long-term adverse effects should be taken into account.

Research: The authors stated that long-term follow-up of patients given testosterone is required to monitor potential adverse metabolic effects.

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.