A comparison of the clinical and cost-effectiveness of 3 intervention strategies for AIDS wasting


Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study compared three intervention strategies for acquired immunodeficiency syndrome (AIDS) wasting. The strategies were:

- an intensive nutrition intervention with placebo tablets (i.e. nutrition alone, NA group), which consisted of dietary recommendations based on body weight and included higher than maintenance recommendations to achieve weight gain;
- an intensive nutrition intervention with 20 mg/day oxandrolone (OX) (OX group); and
- an intensive nutrition intervention with progressive resistance training (PRT group), in which strength training was performed on a thrice-weekly basis according to a one-on-one, periodised programme with a research technician, using well-described procedures.

Patients who were not allocated to the PRT arm spent an additional 30 to 60 minutes weekly with the study personnel to provide comparable levels of attention.

Type of intervention
Primary prevention.

Economic study type
Cost-utility analysis.

Study population
The study population comprised human immunodeficiency virus (HIV)-seropositive patients who met at least one of the definitions of wasting: a documented unintentional weight loss of 10% from pre-morbid weight, a documented unintentional weight loss of 5% in the last 6 months, or a body mass index (BMI) of less than 20 kg/m2. The exclusion criteria were:

- excessive vomiting or diarrhoea;
- fever;
- AIDS-defining complication within 4 weeks before enrolment;
- corticosteroid, oestrogen, progesterone, androgen, anticoagulant, or growth hormone use within the last 3 months;
- a history of life-threatening reaction to androgens;
- pregnancy;
cardiovascular disease, uncontrolled hypertension, hepatic or renal failure, bleeding disorder, diabetes, breast or prostate cancer, or hypercalcaemia;
milk allergy;
current use of injected drugs;
participation in supervised exercise in the last 4 weeks;
physical incapability to exercise;
total serum testosterone level of less than 300 ng/mL in men (unless receiving testosterone replacement); and
a change in anti-HIV medication within 30 days.

Setting
The study setting was primary care. The economic study was carried out in the USA.

Dates to which data relate
The effectiveness and resource use data were collected between March 1998 and January 2001. The price year was 2000.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness study.

Study sample
No study sample size was determined in the planning phase of the study. In addition, no retrospective power calculations were reported. Fifty patients with AIDS wasting were enrolled during the study period, of which 18 were enrolled in the NA group, 16 in the OX group and 16 in the PRT group. The number of females was 3 (17%) in the NA group, 5 (31%) in the OX group and 7 (44%) in the PRT group. The median age of the patients was 43.6 years (interquartile range, IQR: 37.3 - 48.6) in the NA group, 40.8 years (IQR: 36.2 - 45.2) in the OX group and 43.2 years (IQR: 38.4 - 45.9) in the PRT group.

Study design
The study was a randomised controlled trial (RCT) that was carried out in a single centre (Tufts University/New England Medical Centre, Boston). The patients were followed up for a total of 12 weeks. Three patients did not complete the study (2 men and 1 woman), of whom 2 were in the NA group and 1 was in the PRT group. No blinding of the outcome assessment was reported.

Analysis of effectiveness
The analysis of the clinical study was conducted on the basis of treatment completers only (n=47). The outcome measures used were:

mid-thigh cross-sectional muscle area (CSMA), which was measured from images taken with computed tomography;
physical functioning (PF) assessed by a verbally administered health-related quality of life (HRQL) questionnaire, with
the 9-item PF score analysed from the relevant items in the questionnaire;
muscle strength, as assessed by leg press, chest press, leg extension and seated row;
strength of the knee extensors, as measured by isokinetic dynamometer (CYBEX II; Medway);
abdominal muscle endurance, as assessed by counting the number of curl-ups completed in one minute;
physical performance, as assessed with a timed 10-repetition chair stand test;
aerobic endurance, as estimated by the 6-minute walk test;
whole-body composition; and
adverse events.

The patient groups were shown to be comparable in terms of baseline highly active antiretroviral therapy use, laboratory values and clinical characteristics, although there was a slight imbalance of gender amongst arms which was not statistically significant. In addition, although BMI was comparable among study arms, initial fat-free mass and muscle area were greatest in the NA arm, which included the greatest proportion of men. Statistically significant differences in the pre- and post-treatment changes within groups were evaluated by linear models with robust variance. Changes in the major outcomes (CSMA and PF) were tested with and without the inclusion of outliers, which were defined as observations having values outside the IQR.

**Effectiveness results**

Self-reported PF improved significantly over time only in the PRT group (10.4 +/- 3.8* points; p=0.02), an increase relative to the patients’ baseline PF of 16% (+/- 6.3). (* Table 2 reported +/- 14.7 points.)

There were no overall statistically significant differences in the crude PF responses between the OX and NA groups, (p=0.24), or between PRT and NA, (p=0.58).

The term for interaction between PF and the PRT intervention was statistically significant (OX versus NA, p=0.55; PRT versus NA, p=0.003). The inclusion of interaction terms in the models revealed a net treatment effect of significantly greater improvement with PRT than with NA, (p<0.001), and greater improvement with NA than with OX, (p=0.005).

The total energy intake improved significantly over time for the NA group (542 +/- 974 kcal/day; p<0.05) and the PRT group (724 +/- 844 kcal/day; p<0.01).

Protein intake increased significantly in all three groups. Intake was 38.6 (+/- 33.5) g/day in the NA group, (p<0.01), 32.3 (+/- 36) g/day in the OX group, (p<0.01), and 40.8 (+/- 30.7) g/day in the PRT group, (p<0.01).

Models that included interactions for baseline values demonstrated a significantly greater improvement in energy and protein intake with NA than with OX and with PRT than with OX.

There were no significant changes in BMI within any treatment arm.

Patients in the PRT groups significantly improved in all the four different tests for strength and power. Their improvement was 158 (+/- 132) psi in the leg press, (p<0.01), 22 (+/- 16.3) psi in the chest press, (p<0.01), 11.0 (+/- 11.6) psi in the knee extension, (p<0.01), and 16.6 (+/- 16.5) psi in the seated row, (p<0.01). In the other two groups, the only significant improvement was in the seated row test for OX patients (6.4 +/- 9.2 psi; p<0.05).

There were also significant improvements in all groups in the 6-minute walk, (p<0.05 in the NA and OX groups; p<0.01 in the PRT group) and repeated chair stand test, (p<0.01).

There were no deaths, or serious or unexpected adverse reactions to the study interventions.
Clinical conclusions
The authors concluded that OX and strength training induced similar improvements in body composition, but PRT improved quality of life more than NA or OX, particularly in patients with impaired PF.

Measure of benefits used in the economic analysis
The measure of benefits used was the quality-adjusted life-years (QALYs). Patients were verbally administered the HRQL questionnaire used in the HIV costs and services utilisation study (HCSUS) by trained personnel. HRQL scores were then translated into a single health state classification (QALY) using the methods of Brazier et al. (see 'Other Publications of Related Interest' below for bibliographic details)

Direct costs
The direct costs of the health care provider were included in the analysis. These included the costs of the NA intervention, OX intervention and PRT intervention. The nutrition intervention costs included counselling sessions, food record collections, and 12 weeks of canned supplements. The OX intervention costs included the nutrition intervention costs plus the drug costs. The PRT intervention costs included nutrition costs plus 3 months of gym fees and 36 personal training sessions. Also included in the analysis were the expenses to the individual, such as transportation and time (opportunity) costs.

The authors also developed an estimated community-adapted model (ECM). This was a protocol of these interventions at an intensity level at which community resources or reimbursement would be more feasible, with the interventions being extended from 12 to 24 weeks to achieve theoretically comparable effectiveness to the study protocol. However, OX was only proposed for 12 weeks for reasons of safety.

The sources of the costs were not reported. As all costs were incurred during less than one year, discounting was not relevant and was not performed. The mean costs were reported. The price year was 2000.

Statistical analysis of costs
The costs were treated as point estimates (i.e. the data were deterministic).

Indirect Costs
The indirect costs were not included.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analyses were performed.

Estimated benefits used in the economic analysis
The change in QALYs 12 weeks after the intervention was 0.001 in the NA group, (p=0.82), 0.022 in the OX group, (p=0.61), and 0.045 in the PRT group, (p=0.20).

Cost results
The total study cost per patient was $983.36 in the NA group, $3,772.16 in the OX group and $3,189.38 in the PRT group.
The total ECM costs per patient were $595.75 in the NA group, $3,384.55 in the OX group and $2,987.38 in the PRT group.

**Synthesis of costs and benefits**
The costs and benefits were combined using a cost-utility ratio (i.e. the ECM cost per QALY gained). It was unclear, however, if the authors calculated an incremental cost-utility ratio when comparing OX and PRT with NA.

The ECM cost per QALY gained was:

- for the NA group, $45,243 (range: 45,243 - 64,335);
- for the OX group, $146,709 (range: 63,163 - 146,709); and
- for the PRT group, $30,708 (range: 3,551 - $21,152).

**Authors' conclusions**
Oxandrolone (OX) and progressive resistance training (PRT) induced similar improvements in body composition, but physical strength training improved quality of life more than nutrition or OX, particularly among patients with impaired physical functioning (PF) at a lower cost. Thus, PRT was the most cost-effective intervention and OX was the least cost-effective.

**CRD COMMENTARY - Selection of comparators**
A justification was given for using NA as the comparator. It represented the standard care. You should decide if this comparator represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**
The study was based on an RCT. This was appropriate for the study question, as well-conducted RCTs are considered the 'gold' standard study design when comparing health interventions. Although the study was an RCT, several caveats should be taken into consideration. In particular, the absence of power calculations in determining the sample size and the treatment completers only analysis represented significant drawbacks. Consequently, the study might not have had sufficient power to detect differences in outcomes between the two groups. In addition, the lack of reported blinding of the outcome assessment or the method of randomisation presented potential limitations to the reliability of the findings. All these factors could introduce bias into the results.

The study sample appears to have been representative of the study population. However, the authors provided a very strict and exhaustive list of exclusions for participation in the trial, which might limit the generalisability of the authors’ results. The patient groups were shown to be comparable in terms of their baseline clinical characteristics, and nutrition and PF values. The authors undertook an appropriate statistical analysis to show if differences between and within the groups were statistically significant. In addition, the extent to which baseline values affected the results was appropriately tested using a regression analysis.

**Validity of estimate of measure of benefit**
The estimation of benefits was obtained directly from the effectiveness analysis.

**Validity of estimate of costs**
Although the authors reported that costs to society were included in the analysis, they did not include the indirect costs. The authors reported that they had not included the costs of food provision into the analysis, as this was considered standard care. Nevertheless, they stated that securing adequate food and/or its cost must be a major focus for providers treating AIDS wasting in resource-poor settings. The costs and the quantities were not reported separately, which will
limit the generalisability of the results. However, the authors did report the total costs incurred by the institution, and the total costs including time and costs to the patient. No sensitivity or statistical analyses of the costs were performed. Hence, it is unclear how robust the cost estimates are, or if any differences are statistically significant. Since all the costs were incurred during less than one year discounting was not necessary and was not performed. The price year was reported, which will facilitate inflation exercises in the future.

Other issues
The authors reported that their findings differed from others in that earlier studies demonstrated a greater success in increasing weight with OX or exercise. Several possible explanations for this difference were given. The issue of generalisability to other settings was not addressed. The authors do not appear to have reported their results selectively and their conclusions reflected the scope of the analysis. However, it was unclear how the cost-utility ratios were calculated, and it appears that an incremental analysis has not been performed. If an incremental analysis was performed, with the cost and QALY results provided by the authors and comparing OX and PRT with NA, then the authors would have found that OX was dominated by PRT (PRT being both cheaper and more effective than OX). In addition, the incremental cost of PRT compared with NA would have been approximately $50,000 per QALY gained, the threshold usually used in the USA for cost-effectiveness. The authors reported no further limitations to their study.

Implications of the study
The authors reported that their results should encourage providers, patients and third-party payers as to the benefits of strength training as a medical therapy. The results also confirmed the ability of dietary counselling with supplementation to improve nutrition, increasing caloric and protein intake rather than just displacing other sources of energy, and lean body mass.

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Other publications of related interest

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Subject indexing assigned by NLM