Double-blind, randomized, placebo-controlled phase III trial of oxymetholone for the treatment of HIV wasting

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**Background:** Despite highly active antiretroviral therapy (HAART), chronic involuntary weight loss still remains a serious problem in the care of HIV patients. Various alterations in energy metabolism and endocrine regulation have been found to cause loss of lean body mass (LBM) and body cell mass (BCM). Previous studies in HIV-positive men undergoing androgen replacement therapy or treatment with recombinant growth hormone (rGH) have shown partial restoration of LBM, but these treatments have largely been ineffective in eugonadal individuals.

**Study design:** Double-blind, randomized, placebo-controlled trial of 89 HIV-positive women and men with wasting assigned to the anabolic steroid oxymetholone [50 mg twice (BID) or three times daily (TID)] or placebo for 16 weeks followed by open-label treatment.

**Study endpoints:** Body weight, bioimpedance measurements, quality of life parameters and appetite.

**Results:** Oxymetholone led to a significant weight gain of 3.0 ± 0.5 and 3.5 ± 0.7 kg in the TID and BID groups, respectively (\( P < 0.05 \) for each treatment versus placebo), whereas individuals in the placebo group gained an average of 1.0 ± 0.7 kg. Body cell mass increased in the oxymetholone BID group (3.8 ± 0.4 kg; \( P < 0.0001 \)) and in the oxymetholone TID group (2.1 ± 0.6 kg; \( P < 0.005 \)), corresponding to 12.4 and 7.4% of baseline BCM, respectively. Significant improvements were noted in appetite and food intake, increased well-being and reduced weakness by self-examination. The most important adverse event was liver-associated toxicity. Overall, 35% of patients in the TID, 27% of patients in the BID oxymetholone group and no patients in the placebo group had a greater than five times baseline increase for alanine aminotransferase during the double-blind phase of the study.

**Conclusions:** Oxymetholone can be considered an effective anabolic steroid in eugonadal male and female patients with AIDS-associated wasting. The BID (100 mg/day) regimen appeared to be equally effective as the TID (150 mg/day) regimen in terms of weight gain, LBM and BCM and was associated with less, but still significant liver toxicity.

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**Keywords:** wasting, weight loss, anabolic steroids, oxymetholone, HIV, testosterone, liver, quality of life

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Introduction

Although wasting was one of the early manifestations of symptomatic AIDS, its prevalence has considerably decreased in the era of highly active antiretroviral therapy (HAART). However, chronic involuntary weight loss still remains a serious problem even with HAART [1,2]. Various alterations in the metabolic or endocrine regulation, inadequate exercise or other factors (e.g. resistance to growth hormone) may be responsible for a disproportion of fat versus lean body mass (LBM) in HIV infection [3,4]. As advanced HIV patients frequently present with hypogonadism, a reduction in LBM may be a consequence of abnormally low testosterone levels, especially in patients with CD4 lymphocytes less than $200 \times 10^6/l$ [5,6]. In addition to inadequate intake, malabsorption and diarrhoea many patients experience anorexia and weight loss without easily identifiable and treatable causes [3,7]. Although the administration of protease inhibitors to patients with AIDS results in weight gain, most of the added weight is body fat [4,8,9]. However, in about 24% of patients, aggressive HAART did not control weight loss [10,11]. In addition, lipodystrophy represents another unresolved issue that occurs with HAART.

The use of hyperalimentation or various appetite stimulants in HIV wasting has resulted in fat deposition with little gain in LBM [12–14]. Previous studies in HIV-positive men undergoing androgen replacement therapy and resistance exercise, or treatment with recombinant growth hormone (rGH) have shown a partial restoration of LBM [15–17], especially when they had low serum testosterone.

Anabolic steroids are known to cause protein anabolism leading to an increase in LBM [18,19]. Oxymetholone, 17-\(\alpha\)-methyl-2-hydroxymethylene dihydrotestosterone, has an anabolic potency compared to its androgenic effect of 8.75 : 1 relative to methyltestosterone [20–22]. The selection of a drug with only moderate androgenic properties allowed its use in both male and female patients [20,21,23]. On the basis of our earlier findings with oxymetholone suggesting a significant weight gain in advanced HIV patients, we performed a double-blind, randomized, placebo-controlled trial in 89 women and men with HIV infection [23,24]. The prospectively defined hypotheses were that a supraphysiologic androgen treatment regimen would increase body weight, body cell mass (BCM) and LBM in eugonadal patients of both sexes. This result could be achieved with moderate doses of androgens and acceptable toxicity in HIV patients on concomitant HAART.

Materials and methods

Experimental study design

Our study was a double-blind, randomized, placebo-controlled trial to compare the long-term effects of two different doses of oral oxymetholone with placebo (Fig. 1). The oxymetholone (50 mg) tablets were identical in appearance, taste and texture to placebo.

The double-blind phase lasted 16 weeks (Fig. 1). Individual treatment group assignment was based on a random number of computer-generated sequences, generated by an independent statistician, which was double-blinded to all study personnel. Individuals were randomized to one of four arms: 50 mg oxymetholone three times daily (TID), 50 mg oxymetholone twice daily (BID), and matching placebo BID or TID.

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**Fig. 1. Study design.** BID, twice daily; TID, three times daily.
Nutritional intake was surveyed at 4-weekly intervals by a nutritional diary that listed all nutrients for a period of three consecutive days (Thursday, Friday, Saturday). From this list the caloric intake was calculated.

Subjects
A total of 89 patients [79 men and 10 women: 69 homo-/bisexual; 12 intravenous drug users (IVDU); seven heterosexual contact; one transfusion recipient] were enrolled. All patients were recruited from the STD-Unit, Department of Dermatology, University of Essen, between 1998 and 2000. The protocol was approved by the local institutional review board, ethical committee, and informed consent was obtained for all procedures.

Inclusion criteria
Women/men over 18 years were included, if they:

1. were HIV seropositive;
2. had experienced at least a 5% weight loss during the preceding 6 months or had a sustained weight loss of 10% below ideal body weight according to Broca that occurred up to 12 months prior to screening;
3. were on stable HAART (> 3 months) with at least three approved antiretroviral drugs, including one protease inhibitor;
4. had sufficient liver function [aspartate transaminase (AST) < 75 U/L, alanine aminotransferase (ALT) < 150 U/L and total bilirubin < 2.0 mg/dl];
5. were not currently participating in progressive resistance exercise or aerobic exercise;
6. had a negative pregnancy test, if they were of childbearing age;
7. had an unremarkable prostate on prostate-specific antigen (PSA) (< 4 mg/dl) and clinical examination.

Exclusion criteria
Patients were excluded, if they:

1. had active opportunistic infections in the previous 4 months;
2. had uncontrolled diarrhoea, chronic fever, or active hepatitis;
3. used concurrent medications known to alter the nutritional status including testosterone derivatives, dronabinol, megestrol acetate, rGH, thalidomide, pentoxiphylline, glucocorticoids, spironolacton, or interferon-α;
4. used other investigational agents;
5. had a history of malignancy (excluding Kaposi’s sarcoma);
6. had inadequate access to food, chewing/swallowing difficulties or oropharyngeal pain;
7. had active drug or alcohol abuse;
8. had been receiving any form of gonadal hormone replacement therapy.

Serum gonadal hormones
Serum gonadal hormone [total serum testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH)] levels were measured by radioimmunoassay (Abbott, Wiesbaden, Germany) every 4 weeks. In men, PSA was determined at baseline, week 16 and week 32 (Architect, Abbott, Wiesbaden, Germany).

Nutritional assessment and quality of life measurements
Nutritional assessment was performed at determined intervals (weeks 0, 1, 4, 8, 12, 16) by a certified nutritionist. The body mass index [BMI = weight (W)/height squared (H²)] was calculated by measuring the patient’s height in the standing position. Weight was measured on a standing scale for medical use (Seca 910; Seca, Hamburg, Germany). Usual body weight was used as documented in the patient’s file and was used to calculate body weight loss (BWL) upon comparison with the actual measured weight. BWL was defined as the percentage of usual body weight according to the formula: BWL = 100 – ([current body weight/usual body weight] × 100). Ideal body weight was calculated according to Broca [25].

LBM and its components (intracellular water, extracellular water and BCM) were calculated with tetrapolar bioelectrical impedance analysis using frequencies of 5 kHz and 1 MHz (BIA 2000-M; Data Input, Frankfurt, Germany; Software Diacos Nutri 4). This method has been validated in HIV-infected patients [5,7,26,27], but was recently questioned upon comparison with dual-energy X-ray absorption measurement [28].

Quality of life was assessed by the Medical Outcome Study – HIV Health Survey (MOS–HIV), a widely used questionnaire, which has established reliability and validity [29]. It comprises ten subscales: physical role, social function, cognitive function, mental health, energy, fatigue, health distress, health perceptions, pain and overall quality of life. The questionnaire was administered before and every 4 weeks after intervention. The subscale variables were scored using a rating system from 0 (not at all) to 6 (very much).
Blood analysis
Routine blood chemistries were obtained every 4 weeks. CD4 lymphocyte counts and plasma HIV RNA load was performed by fluorescence-activated cell sorting and bDNA (Bayer Diagnostics, Leverkusen, Germany), respectively. Toxicity was graded according to WHO standards.

Open-label phase
The 16-week open-label phase (week 17–32) with oxymetholone 50 mg BID was offered to all subjects who completed the placebo-controlled study.

Statistical analysis
Results are expressed as means (± standard deviation) unless otherwise indicated. All primary analyses were performed on an ‘intention-to-treat’ basis. The primary outcome measure was change in body weight. Secondary outcome measures were body composition changes, gonadal hormone concentrations, quality of life items including alterations in appetite (Visual Analogue Scale of Appetite; VASA), and changes in liver enzymes. Analyses of mean change from baseline required at least one post-randomization assessment. All computations for statistical analyses were performed using SAS version 6.12 (SAS Inc., Cary, North Carolina, USA). All hypothesis testing used two-sided tests performed at a 0.05 level of statistical significance.

Patient disposition, demographics and baseline disease characteristics were summarized for each treatment group. All available patient data were analyzed with descriptive statistics. Mean changes from baseline to week 16 were computed for each body composition variable, hormones and VASA using analysis of variance with treatment group as the single factor; pair-wise comparisons between treatment groups were made using paired t-tests. Treatment-emergent adverse events (i.e., events with an onset date after day 1 (post-drug) to the end of the study) were summarized for each treatment group, as well as percentages of patients with ALT, AST, or gamma glutamyl transpeptidase (γGT) values greater than five times times the baseline value.

Results

Double-blind phase
Study completion
Eighty-nine patients were randomized into the double-blind phase of the study. Unfortunately, randomization led to an uneven distribution of women across groups and consequently to lower LBM and BCM in the placebo group (Table 1). Seventeen patients (19%) discontinued treatment during the double-blind phase (Fig. 1). Fourteen patients (16%) were lost to follow-up or discontinued for personal or unknown reasons. One patient in the oxymetholone BID group discontinued due to adverse events (nausea and vomiting), and two patients in the oxymetholone TID group discontinued due to elevated liver enzymes.

Patient demographic data was very similar in patients randomized to either oxymetholone group, but the individuals assigned to the placebo group had lower BCM and LBM at baseline (Table 1). Many of the patients had a history of previous hepatitis. Eighteen patients (60%) in the oxymetholone TID and 10 (36%) in the BID group had serological evidence for hepatitis B and/or C compared with 17 patients (65%) in the placebo group, respectively.

The maximal cumulative dose given during treatment was 10.2 g of oxymetholone in the BID group compared with 14.8 g in the oxymetholone TID group.

<table>
<thead>
<tr>
<th>Table 1. Patients’ characteristics at baseline.</th>
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<tr>
<td>Patients completing double-blind phase (n)</td>
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<tr>
<td>Age (years) mean (range)</td>
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<tr>
<td>Sex</td>
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<tr>
<td>Female</td>
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<tr>
<td>Male</td>
</tr>
<tr>
<td>Race</td>
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<tr>
<td>Black/Latino</td>
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<tr>
<td>Caucasian</td>
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<tr>
<td>CD4 cells (× 10⁶/ℓ)</td>
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<tr>
<td>b-DNA (Eq/ml)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Body cell mass (kg)</td>
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<tr>
<td>Lean body mass (kg)</td>
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<tr>
<td>Body mass index (kg/m²)</td>
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</table>

Significant differences (one-way ANOVA) across treatment groups existed at baseline for body cell mass (∗P = 0.0029), lean body mass (∗∗P = 0.0072) and BMI (∗∗∗P = 0.0047). The difference in body weight across treatment groups was not significant at baseline (P = 0.0866). BID, twice daily; TID, three times daily.
Mean change of body weight
The onset of weight gain was observed after an average of 2 weeks after the start of therapy (Fig. 2). Although the initial increase was rapid until week 4, the body weight remained at the same level thereafter (Fig. 2). Peak weight was reached between weeks 8 and 12 in both oxymetholone groups. Thirty-nine of 61 patients (64%) receiving oxymetholone and six of 28 (21%) receiving placebo experienced a weight gain of more than 2 kg while taking part in the study. The average weight gain was 3.0 ± 0.5 and 3.5 ± 0.7 kg in the oxymetholone TID and BID groups (P < 0.05 for each treatment versus placebo), respectively, whereas individuals in the placebo group gained an average of 1.0 ± 0.7 kg (Table 2). This translates to 4.5 and 5.3% of total body weight at baseline in the TID and BID oxymetholone groups, respectively. Interestingly, weight gain continued while patients were receiving oxymetholone despite an intercurrent opportunistic infection in two patients, which is usually associated with acute weight loss. There was no correlation between the extent of weight gain and age, sex, or disease stage. We concluded that the onset of weight gain occurred within 4 weeks after starting oxymetholone and led to weight gains of up to 3.5 kg.

Body composition
With regard to LBM, a 2.9 ± 0.54 kg gain was observed in the oxymetholone BID group (P < 0.0001), whereas patients in the oxymetholone TID group gained 1.8 ± 0.8 kg (Tables 2 and 3). This difference was probably due to the more frequent treatment interruptions in the TID arm (data not shown). The BMI was significantly higher at the end of 16 weeks in comparison with the baseline in both groups assigned to oxymetholone (1.0 ± 0.2 kg/m²) in comparison with placebo (0.4 ± 0.2 kg/m²; P < 0.05) (Table 2). When BCM was compared at baseline and week 16, a significant increase was seen for the oxymetholone BID group (3.8 ± 0.4 kg; P < 0.0001) and the oxymetholone TID group (2.1 ± 0.6 kg; P < 0.005) in comparison with placebo (0.5 ± 0.8 kg), respectively (Table 2). This corresponds to 7.4 and 12.4% of baseline BCM in the TID and the BID oxymetholone groups, respectively. Similar to LBM, the BCM increase was higher in the BID group, most likely since these patients had significantly fewer therapy interruptions than the TID group. The increase in BCM in the BID oxymetholone group was significantly greater than in the placebo group (P < 0.005). In this regard, gains in BCM as the metabolically active tissue are particularly important for maintaining body functions. The extracellular mass (ECM) did not change in any group (data not shown). However, the ECM/BCM ratio decreased significantly over the study period in the oxymetholone TID and BID groups (P < 0.05 and P < 0.0001), respectively (Table 2). The body fat did not change over the course of the study in any of the groups (Table 2).

Side effects
Side effects are shown in Table 3. In the double-blind phase, adverse events involving liver function (e.g., elevated liver enzymes, jaundice and hepatomegaly) were experienced only by patients randomized to

Fig. 2. Weight change (kg) over time. The absolute weight change is indicated for the three different groups. While the onset of weight gain was rapid, the body weight gain maintained a steady level between weeks 8 and 12. Upon switching the placebo patients to oxymetholone 50 mg twice daily (BID), this patient group experienced similar body weight gain as patients who were initially treated with oxymetholone. TID, three times daily.
In the oxymetholone BID group 10% developed jaundice. One patient in the oxymetholone TID group and three unique patients in the oxymetholone BID group. Most of the liver toxicity in four patients mainly due to canaliculous cholestasis and hepatomegaly.

Table 2. Body composition changes over the course of the study. Important parameters of body composition were compared at the beginning and the end (week 16) of the double-blind study.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Week 16</th>
<th>Change</th>
<th>Baseline</th>
<th>Week 16</th>
<th>Change</th>
<th>Baseline</th>
<th>Week 16</th>
<th>Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (kg)</td>
<td>66.4 ± 10.4</td>
<td>66.1 ± 9.0</td>
<td>0.3 ± 1.4</td>
<td>69.4 ± 9.9</td>
<td>69.6 ± 10.2</td>
<td>0.2 ± 0.3</td>
<td>60.9 ± 8.0</td>
<td>61.9 ± 8.4</td>
<td>0.6 ± 0.8</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>21.0 ± 2.5</td>
<td>21.0 ± 2.4</td>
<td>0.0 ± 0.1</td>
<td>22.0 ± 2.4</td>
<td>22.0 ± 2.2</td>
<td>0.0 ± 0.1</td>
<td>19.4 ± 1.7</td>
<td>19.8 ± 2.1</td>
<td>0.4 ± 0.4</td>
</tr>
<tr>
<td>LBM (kg)</td>
<td>28.3 ± 5.4</td>
<td>30.5 ± 4.2</td>
<td>2.2 ± 0.8</td>
<td>34.3 ± 5.1</td>
<td>24.9 ± 4.4</td>
<td>9.4 ± 1.7</td>
<td>24.2 ± 3.5</td>
<td>24.9 ± 4.4</td>
<td>7.3 ± 3.5</td>
</tr>
<tr>
<td>Body fat (kg)</td>
<td>11.8 ± 6.4</td>
<td>9.7 ± 3.6</td>
<td>2.1 ± 2.8</td>
<td>24.9 ± 4.4</td>
<td>2.1 ± 0.6</td>
<td>0.8 ± 0.2</td>
<td>9.5 ± 3.1</td>
<td>9.5 ± 3.1</td>
<td>0.8 ± 0.2</td>
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<tr>
<td>Body water (kg)</td>
<td>39.7 ± 7.0</td>
<td>41.7 ± 4.8</td>
<td>2.0 ± 1.8</td>
<td>44.0 ± 5.5</td>
<td>35.8 ± 5.4</td>
<td>0.8 ± 0.4</td>
<td>35.4 ± 4.5</td>
<td>35.8 ± 5.4</td>
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<tr>
<td>Change</td>
<td>9.6 ± 4.8</td>
<td>22.0 ± 2.4</td>
<td>12.4 ± 3.8</td>
<td>5.4 ± 2.9</td>
<td>0.5 ± 0.8</td>
<td>0.8 ± 0.2</td>
<td>0.5 ± 0.8</td>
<td>0.8 ± 0.2</td>
<td>0.5 ± 0.8</td>
</tr>
<tr>
<td>BMI/BCM</td>
<td>0.92 ± 0.1</td>
<td>0.88 ± 0.09</td>
<td>0.04 ± 0.03</td>
<td>0.92 ± 0.1</td>
<td>0.88 ± 0.09</td>
<td>0.04 ± 0.03</td>
<td>0.92 ± 0.1</td>
<td>0.88 ± 0.09</td>
<td>0.04 ± 0.03</td>
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</tbody>
</table>

Table 3. Most frequently reported adverse events. Listed are liver-associated and non-liver associated adverse events that occurred in the treatment groups during the double-blind and the open-label study. An intercurrent hepatitis A (n = 1; oxymetholone BID group), cholelithiasis (n = 1; placebo) and concurrent alcohol abuse (n = 2; one each in the oxymetholone TID and BID group, respectively) were the probable causes of liver toxicity in four patients. Most of the non-liver-associated side effects were not considered related to the study drug.

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Double-blind phase</th>
<th>Placebo</th>
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<tbody>
<tr>
<td></td>
<td>50 mg TID</td>
<td>50 mg BID</td>
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<tr>
<td></td>
<td>n = 31</td>
<td>n = 30</td>
</tr>
<tr>
<td>Non-liver associated</td>
<td>30</td>
<td>33</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>11</td>
<td>8</td>
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<table>
<thead>
<tr>
<th>Side effects</th>
<th>Open-label phase</th>
<th>Placebo</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>50 mg TID</td>
<td>50 mg BID</td>
</tr>
<tr>
<td></td>
<td>n = 25</td>
<td>n = 25</td>
</tr>
<tr>
<td>Non-liver associated</td>
<td>14</td>
<td>15</td>
</tr>
<tr>
<td>Abnormal liver function</td>
<td>7</td>
<td>8</td>
</tr>
</tbody>
</table>

Liver-related side effects led to the interruption of oxymetholone treatment [i.e. five patients (16%) in the oxymetholone TID group and three unique patients (10%) in the oxymetholone BID group]. One patient in the oxymetholone BID group developed jaundice probably due to canaliculous cholestasis and hepatomegaly.
treatment during the double-blind phase in five patients (16%) in the TID and one patient (3%) in the BID oxymetholone groups, respectively (Table 3). An intercurrent hepatitis A (n = 1), cholelithiasis (n = 1) and concurrent alcohol abuse (n = 2) were the probable causes of liver toxicity in four patients. Special emphasis was placed on concomitant therapy. Aside from HAART, other potential hepatoxic agents such as fluconazole were administered to 23.9% of the study patients.

Non-liver-associated adverse effects included intercurrent infection, pain, flu, diarrhoea, bronchitis and others that occurred with comparable frequency in all three groups (Table 3). In contrast, the incidence of non-liver side effects commonly associated with the use of anabolic steroids was greater in the TID and BID groups than in the placebo group. In the TID group, adverse events (and the percentage of patients reporting them) included gastrointestinal complaints (e.g. nausea, diarrhoea and vomiting, 32%), liver function abnormalities (16%), changes in libido (6%) and muscle cramps, alopecia, insomnia and clitoris enlargement (3% each). The incidence of patients in the BID group reporting these side effects was as follows: gastrointestinal complaints (27%), liver function abnormalities (13%), acne (13%), changes in libido, gynecomastia, hypogonadism and impotence (3% each). Gastrointestinal complaints (18%), acne (7%), changes in libido and muscle cramps (4% each) were noted for patients in the placebo group.

When the percentage of patients with grade 3/4 liver toxicity (AST, ALT or γGT greater than five times baseline) was analyzed, the dose dependence became clearly evident (Fig. 3). As soon as 4 weeks after beginning treatment, 23% of patients receiving 50 mg TID experienced grade 3/4 increases in liver function tests as compared with 8% of patients receiving 50 mg BID and none of the placebo patients, respectively. The difference was statistically significant at weeks 4 and 8 (P < 0.01). However, at week 16 similar percentages of oxymetholone-treated patients developed grade 3/4 liver toxicity, indicating that liver toxicity is dose-related.

In the double-blind phase, the most frequent laboratory abnormality indicative of liver function changes was an increase in ALT values to greater than five times baseline. This was observed in 11 patients (35%) receiving oxymetholone 50 mg TID and eight patients (27%) receiving oxymetholone 50 mg BID. Total bilirubin did not significantly change in any study group. All liver-related grade 4 side effects were reversible upon cessation of the study drug.

**Blood chemistries**

With the exception of significant changes in liver function tests, there were no alterations in renal function tests, alkaline phosphatase, albumin, coagulation parameters (prothrombin time, partial thromboplastin time), triglycerides, cholesterol, complete blood counts or PSA. Aside from an increase in CD4 cell counts (417 to 520 × 10^6 cells/l; P < 0.05) in the oxymetholone BID group, no alterations of CD4 cell counts occurred in the oxymetholone TID and placebo groups. However, the observed increase was most likely due to the intensification of HAART that was deemed necessary by the treating physician. The HIV RNA load did not change in any group during the entire trial.

**Serum gonadal hormone concentrations**

All patients in our trial were eugonadal at the beginning of the trial (Table 4). Total serum testosterone significantly declined in patients receiving oxymetholone BID or TID by 71 and 59%, respectively (each

![Fig. 3. Percentage of patients with elevated aspartate transaminase (AST), alanine aminotransferase (ALT), or gamma glutamyl transpepsidase (γ-GT) > 5 times baseline (WHO Grade 3/4) measured during the course of the study.](image-url)


There was a parallel significant decline of LH and FSH, the regulators of testosterone production and gonadal function.

**Quality of life measurements**

Questionnaires at baseline and week 16 revealed a significant increase in appetite and food intake in 79% ($P < 0.01$), improved well-being in 61% ($P < 0.05$) and a reduction in weakness and fatigue in 58% ($P < 0.05$) of the combined oxymetholone-treated patients, whereas the respective parameters did not significantly change in the placebo group.

**Visual analogue scale for appetite**

As a more accurate measure, appetite was self-rated by the study participants every week on a linear scale from 1–10. Interestingly, appetite increased rapidly in the two groups receiving oxymetholone in contrast to patients on placebo. The VASA scores in patients randomized to oxymetholone increased from 5.2 to 6.3 ($P < 0.01$) and 5.6 to 7.5 ($P < 0.005$) in the BID and TID groups, respectively, as opposed to minimal change (5.9 to 6.0) in the placebo group.

**Open-label phase**

**Study completion**

Seventy-two patients continued into the open-label phase of the study and 13 patients (18%) discontinued participation before its completion. Three patients were lost to follow-up or discontinued for other or unknown reasons, one patient each discontinued due to jaundice and hepatomegaly, depression, eczema, pain and pharyngeal swelling, and five patients discontinued due to increases in liver enzyme levels.

**Mean change of body weight**

Patients initially randomized to receive placebo showed a sudden onset of weight gain during the open-label phase (week 17–36) leading to comparable weight changes (+3.9 kg) such as observed in the oxymetholone groups during the double-blind phase (Fig. 2, Table 2). Patients who initially received oxymetholone (TID or BID) maintained their weight upon BID dosing in the open-label phase.

**Side effects**

In the open-label phase when oxymetholone 50 mg BID was provided to all patients, adverse events involving liver function (includes liver enzyme elevations, jaundice and bilirubinemia) were reported for 14 unique patients (19%) (Table 3). Of these, seven patients, four unique patients and three unique patients had been randomized to the oxymetholone TID group, oxymetholone BID group and placebo group, respectively, during the double-blind phase of the study.

Liver-related side effects led to the interruption of treatment during the open-label phase in 11 patients. Five of these patients were in the TID group, three patients were in the BID group and three patients were in the placebo group during the double-blind phase of the trial.

During the open-label phase, the observed incidence of side effects commonly associated with administration of anabolic steroids was as follows: gastrointestinal complaints (e.g., nausea, diarrhoea and vomiting, 28%), liver function abnormalities (19%), acne (11%), muscle cramps (6%), menstrual abnormalities (4%), oedema, changes in libido, insomnia and alopecia (3% each) and gynecomastia (1%). Although all patients were prescribed 50 mg BID during the open-label phase, the incidence of some of these side effects, such as liver function abnormalities, changes in libido, acne and alopecia, was higher in patients who had been randomized to the TID or BID group during the double-blind phase of the study.

Once again, the single most frequent laboratory abnormality indicative of altered liver function was an
Discussion

Wasting, fatigue and weakness are common multifactorial problems in patients infected with HIV [30]. In general, wasting in AIDS is predominantly characterized by loss of LBM and BCM that can serve as predictors of survival [5,31]. Importantly, BCM represents the metabolically active tissue exclusive of extracellular water and, therefore, represents a particularly useful index of wasting [32]. A recent prospective analysis found wasting to affect 33.5% of 156 patients with 66% of the cohort receiving HAART [2]. Reduced testosterone levels represent one important reason for loss of BCM [3,33]. However, the prevalence of reduced testosterone levels in male HIV patients has recently been re-estimated and found to be in the order of 13% [34], thus being considerably lower that reported at the onset of the epidemic [5]. Androgen deficiency has also been found to occur in HIV-infected women [35].

Anabolic steroids are known to cause protein anabolism in the majority of patients leading to the accrual of LBM and BCM [18,19]. Oxymetholone has been found to promote gain of body mass [21–23]. Its anabolic potency compared with its androgenic effect is 8.75:1 relative to methyltestosterone [20–22]. In that regard, it is important to note that only one female patient developed a self-reported clitoris enlargement, whereas changes in libido were similar across groups. Oxymetholone has been used for aplastic anemia and antithrombin III deficiency [22,36].

Our favourable results compare with studies, in which other therapeutic agents have been used to promote weight gain in AIDS patients. For example, megestrol acetate has been evaluated in the pre-HAART era and was shown to increase weight in 64% of AIDS patients [12,13], with weight gained consisting mainly of fat tissue [14,37]). An 8-week double-blind, placebo-controlled trial of thalidomide, a tumour necrosis factor-α inhibitor, plus HAART showed a weight gain of 2.2 kg (with about half consisting of LBM) in the 100 mg dose group [38]. However, drug intolerance limited its use [38]. Another recent trial examined whether a combination of beta-hydroxy-beta-methylbutyrate, L-glutamine and L-arginine could improve muscle wasting in AIDS patients [39]. At 8 weeks, the subjects randomized to the mixture gained an average of 3.0 kg of body weight with a high proportion of LBM [39]. A smaller study showed similar increases in body weight and BCM [40].

The anabolic steroid testosterone enanthate (300 mg intramuscularly every 3 weeks) has been shown to increase LBM by 2.0 kg during the first 6 months of treatment in a randomized, controlled study in 51 HIV-infected men with hypogonadism [41]. In a cross-sectional study of HIV-infected women, total testosterone concentrations in serum were below the normal range for sex and age in more than half of the women affected by wasting [34]. In a recent pilot study, transdermal administration of two doses of testosterone patches for 12 weeks (estimated delivery rates 150 and 300 µg/day) was found to be a safe and effective means of increasing serum testosterone without causing virilization, hirsutism or changes in serum lipid concentrations [42]. In this study, the lower but not the higher dose of testosterone resulted in normal serum testosterone concentrations and a mean weight gain of 1.9 kg as compared to 0.6 kg in the placebo group [42].

Other androgenic agents have also shown increased weight gain in HIV patients not receiving concurrent HAART. The testosterone derivatives nandrolone decanoate and oxandrolone have also been evaluated for the treatment of wasting in HIV. In a randomized, dose-ranging study of oral oxandrolone (15 mg/day for 16 weeks) in men with AIDS wasting, there was a mean weight gain of 1.8 kg in men after 14 weeks as compared with 0.7 kg in the placebo group [43]; however, body composition measurements were not performed [43]. In a 16-week, open-label study nandrolone decanoate, a synthetic injectable testosterone analogue, was injected intramuscularly at a dose of 100 mg every 2 weeks in HIV-infected men with wasting [44]. The treatment resulted in a mean weight gain of 2.2 kg and an increase in LBM of 3.0 kg [44]. Similar effects were observed in another small study on 10 HIV-positive men over 12 weeks treated with either 60 or 200 mg of nandrolone decanoate [45]. Several different studies have shown that resistance exercise can further increase the benefit from treatment with anabolic steroids [16,17,46,47].

In patients with AIDS-related wasting and loss of significant weight and muscle mass, a pattern of acquired GH resistance is seen with increased GH concentrations and simultaneously decreased concentrations of insulin-like growth factor I [48,49]. In a randomized, placebo-controlled trial of high dose rGH (0.1 mg/kg per day given subcutaneously for 12 weeks, equalling an average dose of 6 mg/day) involving 178 AIDS patients with moderate wasting (mean body weight: 87% of ideal weight) in the pre-HAART setting, the rGH-treated patients gained 1.6 kg of body
in 15 patients [15]. Common side effects were oedema, arthralgias, myalgias, as well as increased concentrations of blood glucose and glycosylated haemoglobin, resulting in dose reductions in 15 patients [15]. In a recent study by Lo et al., a lower dose of 3 mg/day of rGH has been evaluated in patients with HIV lipodystrophy [50]. Reduced total body fat and a trend towards reduction of visceral adipose tissue were observed while LBM increased [50]. Potential side effects of long-term non-physiological rGH-dosing such as worsening of glucose tolerance, insulin resistance or potential stimulation of HIV-associated malignancies remain open questions. While treatment with rGH seems effective, the long-term safety and tolerability remain unknown.

While oxymetholone equalled or surpassed the gains in weight and LBM observed with cytokine inhibitors, nutritional supplements and rGH, its side-effect profile was different. As expected, side effects were predominantly hepatic in nature and were frequently therapy-limiting. The rate and development of hepatic dysfunction were dose-dependent [51]. In addition, the more frequent treatment interruptions that were necessary in the TID group indicated its higher potential for drug-induced hepatitis. It is well known that the susceptibility to adverse hepatic effects of anabolic steroids is modified by various host factors such as previous viral hepatitis or other hepatotoxic medications, which were both present in the majority of our patients [51]. Hepatic adverse events of oxymetholone treatment such as canaliculous cholestasis occurred in one patient. Other side effects known to be caused by oxymetholone like peliosis hepatis [52], hyperglucagonemia [53], oedema and hypertension were not observed in our study. The suppression of pituitary gonadotropins, that regulate the endogenous testosterone, occurs by a negative feed back loop and represents a well-known side effect of anabolic steroids [19,21–23]; it is generally reversible upon cessation of the drug [19]; consequently, therapy with oxymetholone has to be tapered in order to restore endogenous production of testosterone. In addition, this makes therapy more delicate in patients with hypogonadism, where particular attention should be given.

The relation between LBM and measures of health-related quality of life, including physical functioning and better general health perceptions as well as with fewer days in bed in men, but not in women [54]. Our trial confirmed these improved quality of life aspects in both, male and female, patients.

In summary, the severe weight loss in many AIDS patients and its various physical and psychosocial implications may justify the use of anabolic steroids in selected patients. When other first-line therapies such as optimizing nutritional status and gonadal function or the use of exercise have failed, oxymetholone can be considered an effective anabolic steroid in male and female patients with AIDS wasting, promoting significant gains in LBM and BCM. The BID (100 mg/day) dosing appeared to be equally efficacious as the TID (150 mg/day) regimen and caused less, although still significant, liver toxicity. As a guideline for clinical practice we would suggest, an ‘induction’ period of 8 to 10 weeks (with 50 mg BID) and thereafter ‘maintenance’ therapy with 50 mg once daily or every other day. This regimen has shown sufficient weight and LBM gain while reducing hepatic side effects in subsequent patients.

Contributors
U. R. Hengge and R. Dudley were project leaders and designed the protocol. K. Stocks, H. Wiehler, S. Faulkner, S. Esser, D. Hengge and M. Goos contributed to data collection and interpretation. C. Lorenz was the responsible hospital pharmacist. W. Jentzen did the statistical analysis. All investigators were involved in preparation of the report.

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