

Oxymetholone promotes weight gain in patients with advanced human immunodeficiency virus (HIV-1) infection*

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The effect of the testosterone derivative oxymetholone alone or in combination with the H₁-receptor antagonist ketotifen, which has recently been shown to block tumour necrosis factor α (TNF α), on weight gain and performance status in human immunodeficiency virus (HIV) patients with chronic cachexia was evaluated in a 30-week prospective pilot study. Thirty patients were randomly assigned to either oxymetholone monotherapy (*n* 14) or oxymetholone plus ketotifen (*n* 16). Patients receiving treatment were compared with a group of thirty untreated matched controls, who met the same inclusion criteria. Body weight and the Karnofsky index, which assesses the ability to perform activities of daily life, and several quality-of-life variables were measured to evaluate response to therapy. The average weight gain at peak was 8.2 (SD 6.2) kg (+14.5% of body weight at study entry) in the oxymetholone group ($P < 0.001$), and 6.1 (SD 4.6) kg (+10.9%) in the combination group ($P < 0.005$), compared with an average weight loss of 1.8 (SD 0.7) kg in the untreated controls. The mean time to peak weight was 19.6 weeks in the monotherapy group and 20.8 weeks in the combination group. The Karnofsky index improved equally in both groups from 56% before to 67% after 20 weeks of treatment ($P < 0.05$). The quality of life variables (activities of daily life, and appetite/nutrition) improved in 68% ($P < 0.05$) and 91% ($P < 0.01$) of the treated patients respectively. Oxymetholone was safe and promoted weight gain in cachectic patients with advanced HIV-1 infection. The addition of ketotifen did not further support weight gain. These results suggest the need for a randomized, double-blind, placebo-controlled multicentre trial.

Cachexia: Human immunodeficiency virus: Oxymetholone

Cachexia, fatigue and weakness are common multifactorial problems in patients infected with the human immunodeficiency virus (HIV). Chronic cachexia has been shown to affect cellular immune functions and to increase the risk of infection (Hughes *et al.* 1974; Beisel *et al.* 1981; Chandra, 1983). Since the magnitude of body cell mass depletion correlates with timing of death in patients with the acquired immune deficiency syndrome (AIDS), treatment of progressive weight loss and its causes may potentially enhance survival in AIDS patients (Kotler *et al.* 1989b).

The mechanisms of weight loss in AIDS have not been clearly elucidated. Gastrointestinal pathogens or chronic consumptive infections such as cytomegalovirus or atypical mycobacteriosis can cause significant weight loss; their effective treatment frequently leads to the repletion of total body cell mass (Kotler *et al.* 1989a). Decreased energy intake and malabsorption without detectable pathogens have also been identified (Ullrich *et al.* 1989; Kotler *et al.* 1991). Increased resting energy expenditure and hypertriglycerolaemia are

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common metabolic abnormalities associated with HIV infection leading to energy wasting (Hommes *et al.* 1991; Grunfeld & Feingold, 1992). The impact of several cytokines such as tumour necrosis factor α (TNF α), interferon α (INF α) and interleukin-1 (IL-1) on hyperlipidaemia and weight loss in HIV infection has been discussed controversially (Patton *et al.* 1986; Grunfeld & Feingold, 1992). In HIV patients only IFN α , but not TNF α , levels have consistently been found to be elevated (Lahdvirta *et al.* 1988; Reddy *et al.* 1988; Grunfeld & Feingold, 1991). Overexpression of TNF α in mice leads to wasting, ischaemia and lymphoid abnormalities (Probert *et al.* 1993).

Since hypogonadism frequently occurs in HIV and AIDS patients and since it has been shown to correlate with weight loss (Dobs *et al.* 1988), reduced lean body mass may represent a consequence of abnormally low testosterone levels in these individuals. A recent study by Coodley *et al.* (1994) showed significantly lower total and free testosterone levels in AIDS patients with less than 200 CD4 lymphocytes/ μ l and wasting than in the same group of patients without wasting. Nevertheless, the dominant mechanism of weight loss in HIV infection is likely to be different between patients and disease stages. Many patients experience anorexia and weight loss without easily identifiable or treatable causes.

Several weight-gain and appetite-stimulating agents have been tested in AIDS patients. Megestrol acetate, a synthetic progestational agent has been shown to accrue fat instead of lean tissue (Loprinzi, 1992; Oster *et al.* 1994; von Roenn *et al.* 1994). Human growth hormone was found to increase lean body mass while decreasing body fat stores in a short-term study in six AIDS patients (Mulligan *et al.* 1993).

Anabolic steroids are known to cause protein anabolism in the majority of cases, accruing lean body mass (Williams-Ashman, 1971; Freed *et al.* 1975; Forbes *et al.* 1992). Despite the high frequency of HIV-associated weight loss the usefulness of anabolic steroids for this condition has not been assessed previously. Oxymetholone, 17 α -methyl-2-hydroxymethylene dihydrotestosterone, is associated with gain of lean body mass (Camerino & Sala, 1960; Kochakian, 1976). Its anabolic potency compared with its androgenic effect is 8.75:1 relative to methyltestosterone (Camerino & Sala, 1960; Arnold *et al.* 1963). Its predominant indications are aplastic anaemia (Doney *et al.* 1992) and antithrombin III deficiency (Shibuya *et al.* 1988).

The aim of the present pilot study was to examine the effect of the anabolic steroid oxymetholone on weight gain in otherwise stable HIV patients with chronic unremitting weight loss. To evaluate the potential contribution of TNF α to this condition, a second group was treated with additional ketotifen, an anti-asthmatic drug blocking histamine release, which has recently been shown to block TNF α production in peripheral blood mononuclear cells of HIV patients (Schedel *et al.* 1994).

METHODS

Subjects

The study sample consisted of patients with advanced AIDS-related complex (n 6) or AIDS (n 24) and cachexia (Table 1). Advanced AIDS-related complex was characterized by the history or presence of oral candidiasis, oral hairy leucoplakia, varicella zoster virus infection, and a CD4 lymphocyte count of less than 300/ μ l. AIDS was defined by the occurrence of an opportunistic infection or another AIDS-defining condition according to the Centers for Disease Control (CDC) criteria. Cachexia in the present study was defined as chronic unremitting progressive weight loss of > 10% of body weight in the previous 4 months leading to emaciation. It is distinct from 'wasting syndrome', a condition with chronic fever and diarrhoea without identifiable causes. Exclusion criteria were the presence of active opportunistic infections in the previous 6 months, wasting syndrome, a

Table 1. *Patients' characteristics by treatment group*

Characteristics	Oxymetholone (n 14)	Oxymetholone + ketotifen (n 16)	Controls (n 30)
Median age (years)	35.2	36.8	33.8
Sex			
Male	12	12	26
Female	2	4	4
Risk group			
Homosexual	9	9	20
Heterosexual	0	0	1
Intravenous drug abuse	3	5	6
Blood transfusion	1	2	3
Unknown	1	0	0
HIV state			
AIDS-related complex	4	3	9
AIDS	10	13	21
CD4 lymphocyte count/ μ l (%)			
< 100/ μ l	8 (1.9)	9 (2.3)	16 (2.0)
< 200/ μ l	5 (7.3)	5 (6.1)	11 (8.8)
< 300/ μ l	1 (14.8)	1 (11.2)	2 (10.1)
Serum testosterone (nmol/l)*	12.2 (SD 2.4)	11.5 (SD 1.5)	12.9 (SD 1.8)

HIV, human immunodeficiency virus; AIDS, acquired immune deficiency syndrome.

* Male study participants only (normal range 14–28 nmol/l).

Karnofsky index of less than 50% (Mor *et al.* 1984) and the presence of any obvious gastrointestinal symptom.

A group of thirty HIV-positive controls with similar disease stages, previous medical conditions and CD4 lymphocyte counts, who met the same inclusion and exclusion criteria, but did not desire therapy (henceforth called 'matched controls'), was followed prospectively and compared with the treatment groups.

All patients had maintained stable medication for the last 4 months before enrolment and received inhaled pentamidine isethionate and at least one antiretroviral drug. Maintenance therapy for other AIDS-related opportunistic infections was allowed. Informed consent was obtained from all patients.

Study design and treatment regimen

The study was a non-blind, prospective trial performed in a tertiary-care centre with inpatient and outpatient facilities. Between January and April 1992 thirty patients were randomized at 1:1 to receive oxymetholone or oxymetholone plus ketotifen. Fourteen patients were randomly assigned to oxymetholone (Anapolon[™], Syntex, Palo Alto, CA, USA) given as 50 mg capsules three times daily. Sixteen patients were randomly assigned to take the H₁-receptor antagonist ketotifen (Zaditen[™], Wander Pharma, Nürnberg, Germany) as 50 mg capsules twice daily in conjunction with oxymetholone. Treatment duration was 30 weeks. Treated patients were compared with thirty HIV-positive individuals, who met the same inclusion and exclusion criteria, and maintained their previous medications. They were evaluated and documented accordingly. All participants in the study received protein and vitamin supplements.

Evaluation of patients

The pretreatment evaluation included a medical history, a physical examination, a signs-and-symptoms questionnaire, the Karnofsky index (Mor *et al.* 1984), and routine

laboratory studies. Endogenous testosterone levels were determined at study entry using a radioimmunoassay (Medgenics, Göttingen, Germany).

Outcome measures for comparison in the present study were body weight and quality of life. Body weight was assessed against a reference scale every other week. Objective response to therapy was defined as an increase in weight of at least 2 kg or 4% of body weight at study entry. Stable weight was considered as entry weight ± 2 kg. Treatment failure was defined as a continuous loss of body weight. The BMI, an index of adiposity, was calculated using the formula: weight/height² (kg/m²) (Micozzi *et al.* 1986).

Quality of life was assessed using the Karnofsky index, and activities of daily life, perception of own health, involvement in own occupation, and eating behaviour (appetite and food intake) were measured using a modified patient questionnaire every 4 weeks (Spitzer *et al.* 1981; Block *et al.* 1986). These variables were scored using a rating system from 0 (not at all) to 4 (very much).

Routine laboratory studies included differential blood counts, coagulation variables (prothrombin time, partial thromboplastin time), assessments of renal and liver function, protein electrophoresis and cholinesterase, which were performed every 2 weeks. HIVp24 antigen determinations (Abbott, Wiesbaden, Germany) and the lymphocyte phenotyping were performed at 8-week intervals by the whole-blood lysis method and flow cytometry. TNF α (Medgenics, Göttingen, Germany) was measured by ELISA at study entry and every 2 months thereafter.

Data analysis

Values are shown as means and standard deviations. Values from four patients, who died during the study, were excluded from the analysis. Missing values for one time point for each variable were estimated by regression from the available subsequent data. Continuous variables (body weight, CD4 lymphocyte counts, TNF α) were analysed using ANOVA (three groups, two interventions) with statistical significance set at $P = 0.05$.

A non-parametric ANOVA (Kruskal-Wallis) was used to test for differences between groups in Karnofsky scores and for each variable of the patient questionnaire.

RESULTS

Subjects were reasonably similar at study entry in all three groups (Table 1). Twenty-seven patients completed the study. Two patients died during the first 12 weeks in the oxymetholone group from atypical mycobacteriosis (n 1) and disseminated cytomegalovirus (CMV) infection (n 1); one patient died from aspergillosis at week 10 in the combination group. One patient died in the control group from atypical mycobacteriosis at week 14. These patients were excluded from the analysis.

Three opportunistic infections occurred in each treatment group and four in the controls. Three of the six patients with an intercurrent opportunistic infection (*Pneumocystis carinii* pneumonia (n 2), CMV retinitis (n 1)), who remained on treatment, continued to gain weight. Two of these individuals were in the combination group and one was in the oxymetholone group. The three remaining patients suffered from HIV encephalitis (n 3), CMV retinitis (n 2), and atypical mycobacteriosis (n 1). These patients decided to remain in the study, but their weight decreased.

Mean treatment duration was 31.6 (range 29–36) weeks. The mean cumulative dose of oxymetholone in the monotherapy group was 32 g compared with 34.2 g in the oxymetholone plus ketotifen group. The onset of weight gain was observed after an average of 3.9 (range 1.8–5.8) weeks in both treatment groups. Weight gain of more than 2 kg occurred in twenty-three of the twenty-seven surviving patients ($P < 0.001$) and in one of the twenty-nine control subjects. Three patients on treatment showed stable weight; one patient continued to lose weight despite treatment. In the control group twenty patients

Table 2. Weight at study entry, weight after 12 weeks, and peak weight (kg) for patients with acquired immune deficiency syndrome treated with oxymetholone, oxymetholone + ketotifen, or untreated (controls)

	Oxymetholone (n 12)		Oxymetholone + ketotifen (n 15)		Controls (n 29)	
	Mean	SD	Mean	SD	Mean	SD
Pre-illness weight	68.9	8.8	68.2	6.3	69.7	7.9
Weight at study entry	56.5	8.2	56.0	4.6	57.0	5.1
Weight after 12 weeks	62.2	3.7	60.4	2.7	55.7	5.9
Peak weight†	64.7***	6.2	62.1**	4.6	55.2	4.0
Response to therapy	11 (91.7%)‡		12 (86.7%)§			

Mean values were significantly different from that for the control group: ** $P < 0.005$, *** $P < 0.001$.

† Time to peak weight was 19.6 weeks in the oxymetholone group and 20.8 weeks in the oxymetholone plus ketotifen group; weight at week 20 is shown for the control group.

‡ One patient with an intercurrent opportunistic infection on therapy continued to gain weight.

§ Two patients with an intercurrent opportunistic infection on therapy continued to gain weight.

Table 3. BMI at study entry and at peak weight for patients with acquired immune deficiency syndrome treated with oxymetholone, oxymetholone + ketotifen, or untreated (controls)

Patient group	Sex	BMI at study entry†		BMI at peak weight	
		Mean	SD	Mean	SD
Oxymetholone (n 10)	Male	19.5	0.78	21.2**	1.76
Oxymetholone (n 2)	Female	16.5	1.43	19.8**	1.5
Oxymetholone plus ketotifen (n 12)	Male	18.0	1.38	19.7*	1.84
Oxymetholone plus ketotifen (n 3)	Female	16.9	1.1	19.1*	1.62
Matched controls (n 25)	Male	18.9	1.3	18.3	1.5
Matched controls (n 4)	Female	17.1	1.9	16.7	1.3

Mean values were significantly different from those at study entry: * $P < 0.05$, ** $P < 0.01$ (Student's *t* test).

† Normal values for BMI (from sixty-six healthy controls) are: male, 24.7 (SD 3.1) kg/m² and female, 23.4 (SD 4.1) kg/m² (Allen *et al.* 1990).

showed stable weight, eight lost more than 2 kg and one patient gained more than 2 kg. The body weight after 12 weeks and the peak weight for both treatment groups and the control group are shown in Table 2. Mean weight change after 12 weeks was 5.7 (SD 3.7) kg in the oxymetholone group and 4.4 (SD 2.7) kg in the oxymetholone plus ketotifen group, whereas the control group lost an average 1.3 (SD 0.5) kg. The mean weight change at peak was 8.2 (SD 6.2) kg in the oxymetholone group ($P < 0.001$) and 6.1 (SD 4.2) kg in the oxymetholone plus ketotifen group ($P < 0.005$), the mean times to peak weight were 19.6 and 20.8 weeks respectively. The BMI, a crude estimate of the distribution of adipose and lean tissue (Micozzi *et al.* 1986), increased with both oxymetholone and oxymetholone plus ketotifen treatments (Table 3). There was no significant change of BMI in control patients during the study. The relative changes in body weight over time are shown for the individuals on oxymetholone, on oxymetholone plus ketotifen, and for the control group (Fig. 1). There was no correlation between weight gain and age, sex, stage of the disease or CD4 lymphocyte counts.

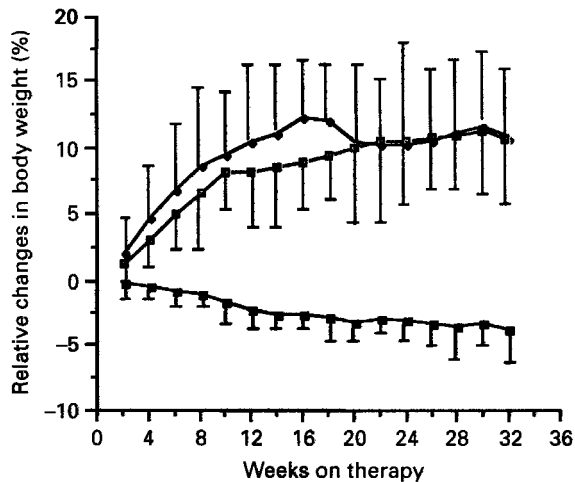


Fig. 1. Relative increase in body weight of patients with acquired immune deficiency syndrome during therapy with oxymetholone (□, *n* 12), or oxymetholone plus ketotifen (◆, *n* 15) compared with untreated controls (■, *n* 29). Values are means with standard deviations indicated by vertical bars. Mean values were significantly different from those for controls at week 6 for the oxymetholone monotherapy group, and at week 8 for the oxymetholone plus ketotifen group.

Table 4. Karnofsky index values (% of normal) for patients with acquired immune deficiency syndrome treated with oxymetholone, oxymetholone + ketotifen, or untreated (controls)

Study group	Study entry		20 weeks	
	Mean	SD	Mean	SD
Oxymetholone (<i>n</i> 12)	56	5	67*	5
Oxymetholone + ketotifen (<i>n</i> 15)	56	4	67*	6
Matched controls (<i>n</i> 29)	59	6	59	8

* Mean values were significantly different from those at study entry, $P < 0.05$.

The reflections of increasing body weight on the physical condition and social interactions were assessed by the Karnofsky index (Table 4). Treatment with either regimen led to significantly increased Karnofsky indices reflecting more independence in performing personal activities. The evaluation of the quality of life questionnaires at the time of peak weight revealed a significant increase in appetite and food intake (91%; $P < 0.01$), a reduction of weakness and fatigue in 68%, and improved well-being in 61% (each $P < 0.05$) of the combined treated patients compared with the untreated control patients. The scores for the patients' own perception of their health and the involvement in their own occupation did not change during therapy.

To evaluate the effect of additional ketotifen therapy, $TNF\alpha$ levels were measured. $TNF\alpha$ levels were not significantly different between the three groups.

Since HIV contains glucocorticoid-responsive elements in the long terminal repeat (promoter enhancer region of HIV), which upon activation by steroids could lead to increased HIV viraemia, we assessed HIV replication and determined T-lymphocyte subsets in our patients. HIV replication could be estimated by measuring the p24 core protein, which correlates with HIV viraemia (Escaich *et al.* 1991). T-cell subsets in the patients' blood analysed by flow cytometry did not change during treatment. Pretreatment CD4 lymphocyte counts and CD4 counts after 20 weeks were $103/\mu\text{l}$ and $95/\mu\text{l}$ in the

oxymetholone group and 98/ μ l and 90/ μ l in the oxymetholone plus ketotifen group respectively. CD4 lymphocyte counts in the control group were 101/ μ l and 107/ μ l respectively. HIVp24 antigen levels were measured every 8 weeks during treatment. In twenty-four (88.9%) patients, HIV replication was not significantly altered and stayed below 25 pg/ml. However, in two patients of the oxymetholone group and one patient of the combination group HIVp24 antigen levels increased to 69, 104 and 74 pg/ml respectively, indicating enhanced replication of HIV. Both patients of the oxymetholone group had concomitant increases in TNF α levels (39 to 233, and 11 to 169 pg/ml). The TNF α level in the patient treated with concomitant ketotifen remained stable at 33 pg/ml. It should be noted that these three patients subsequently developed HIV encephalitis despite treatment with zidovudine (250 mg four times daily).

All patients tolerated the drug(s) well. Potential side-effects of treatment were increased fatigue (n 2) and impotence (n 1). Peripheral oedema, deep venous thrombosis, hypertension, increased libido or signs of virilization were not observed. There were no significant alterations in coagulation profiles (prothrombin time, partial thromboplastin time), complete blood counts or renal and liver function tests that were related to treatment.

DISCUSSION

Since treatment with protein anabolic steroids led to an increase in lean body mass in several studies (Williams-Ashman, 1971; Freed *et al.* 1975; Hervey *et al.* 1981; Welle *et al.* 1992), we investigated the potential of anabolic steroids as candidate agents in the therapy of HIV-related cachexia. HIV patients with a history of an opportunistic infection in the previous 6 months were excluded from the study, since it has been shown that episodes of acute weight loss during infectious complications are frequently followed by partial weight gain in the recovery period (Kotler *et al.* 1989a; Macallan *et al.* 1993).

Treatment with oxymetholone in patients with HIV-related cachexia led to significant weight gain in 91.7% of patients compared with 85% of patients treated with oxymetholone plus ketotifen. The BMI, an estimate of adipose tissue (Micozzi *et al.* 1986), increased during treatment with oxymetholone and oxymetholone plus ketotifen. Moreover, the relative increase in BMI compared with the changes in body weight also suggests an augmentation of lean body mass. The addition of ketotifen, which was found to inhibit the synthesis of TNF α by peripheral mononuclear blood cells *in vitro* (Schedel *et al.* 1994), did not promote weight gain in the present study or alter TNF α serum levels. This suggests that other factors such as cytokines IL-1, IL-6 and IFN α might contribute to weight loss in advanced HIV infection (Patton *et al.* 1986; Grunfeld & Feingold, 1991). Moreover, plasma levels of TNF α may not represent tissue concentrations. It is remarkable that weight gain during treatment with oxymetholone continued in three of six patients despite an intercurrent opportunistic infection, which is usually associated with acute and severe weight loss (Macallan *et al.* 1993). In general, weight loss in AIDS is predominantly characterized by the loss of muscle protein, whereas in starvation lean body mass seems to be largely preserved through adaptive mechanisms (Kotler *et al.* 1989b).

The increases in quality of life and in Karnofsky indices represent significant improvements in the daily life of the patients who needed considerable assistance before the initiation of therapy. Many of them regained strength and the ability to care for the majority of their personal needs.

Our favourable results compare with studies in which other therapeutic agents have been used to promote weight gain in AIDS patients. Megestrol acetate, for example, has been shown to increase weight in 64% of AIDS patients (Oster *et al.* 1994; von Roenn *et al.* 1994), the increment consisting predominantly of fat tissue (Loprinzi *et al.* 1993). Megestrol acetate has also been shown to affect the pituitary-adrenal axis in humans resulting in

suppression of cortisol and corticotropin (Loprinzi, 1992), an undesirable effect in the treatment of HIV patients who already have reduced levels of cortisol in advanced disease stages (Dobs *et al.* 1988). Studies in AIDS patients using recombinant human growth hormone are promising, but need to be extended (Krentz *et al.* 1993; Mulligan *et al.* 1993). The limited reports on insulin-like growth factor-1 in energy-restricted normal volunteers and in catabolic AIDS patients also suggest an anabolic effect (Kupfer *et al.* 1993; Liebermann *et al.* 1993). The results with the cannabis derivative dronabinol (Δ -9-tetrahydrocannabinol) appeared to be unsuccessful (Struwe *et al.* 1993).

In the present study adverse events were infrequent and mild. Increased fatigue is a known side-effect of many H_1 -antagonists, which can be avoided in most cases by dosage reduction. We suspect that the occurrence of impotence is coincidental since it frequently occurs in AIDS patients, although it has been reported with anabolic steroid treatment (Freed *et al.* 1975). Known side-effects of oxymetholone such as peliosis hepatis (Turani *et al.* 1983), hyperglucagonaemia (Williams *et al.* 1986), oedema or hypertension were not observed. Whether oxymetholone treatment promoted HIV encephalitis observed in three patients, or whether ketotifen prevented the increase of $TNF\alpha$ observed in one individual of the combination group cannot be answered because of the small study sample. The onset of HIV encephalitis in three individuals of the treatment group (and two of the control group) was considered to be consistent with its normal incidence (Navia *et al.* 1986). The number of deaths observed in the treatment groups (n 3) and the control group (n 1) are comparable and were most probably caused by the identified underlying infectious complication.

Since death from wasting is ultimately related to the magnitude of tissue depletion (Kotler *et al.* 1989*b*), resulting in deficits of vital functions, restoration of body cell mass may enhance survival, which will be assessed in a larger trial. Moreover, chronic cachexia in immunodeficient patients, which represents the loss of lean body mass and adipose tissue, may preclude recovery from infectious complications that otherwise would not represent a lethal challenge. In our opinion, the severe weight loss in many AIDS patients and its various physical and psychosociological implications justify the use of anabolic steroids in certain patients, in particular, if their endogenous testosterone levels are below normal. Administration of anabolic steroids has been shown to correlate with the increment in lean body mass in a logarithmic dose-response fashion (Forbes, 1985). In this study a threshold of 2.5 g was described before a significant effect on lean body weight was observed. In the present trial the cumulative dose of 2.5 g was reached after 2.5 weeks of therapy, preceding the onset of weight gain by 1.5 weeks.

As a limitation of the present study, body composition measurements were not performed. However, the increase in lean body mass during treatment with anabolic steroids has been demonstrated by myotrophic measurements (Arnold *et al.* 1963), by N retention (Camerino & Sala, 1960; Kochakian, 1976), and by ^{40}K counting in animals and men (Hervey *et al.* 1981; Forbes *et al.* 1992). The mechanism of action has been partly elucidated (Mayer & Rosen, 1975). Our findings suggest that anabolic steroids can exert their biological effects in cachectic HIV patients who exhibit a wide pattern of endocrine abnormalities (Dobs *et al.* 1988; Coodley *et al.* 1994). The selection of a drug with only moderate androgenic properties allowed its use in both male and female patients (Camerino & Sala, 1960; Arnold *et al.* 1963).

The present pilot study showed promising effects of oxymetholone on weight gain in selected, otherwise clinically stable, patients with advanced HIV-1 infection. The improved well-being helped many patients to perform their personal activities in daily life. The results of this pilot study have prompted the initiation of a randomized, double-blind, placebo-controlled multi-centre trial in a larger number of patients.

Note added in proof. A dramatic reduction of circulating testosterone concentrations during therapy with megestrol acetate in AIDS patients has been demonstrated suggesting an explanation for the predominant accumulation of fat instead of lean body mass seen with megestrol acetate treatment (Engelson *et al.* 1995).

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