Safety and Efficacy of Two Preparations of Megestrol Acetate in HIV-Infected Individuals with Weight Loss in Africa, India, and the United States

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ABSTRACT

Objective: To compare the safety and efficacy of a concentrated megestrol acetate oral suspension and traditional megestrol acetate in a randomized, controlled trial in HIV-infected patients with weight loss.

Materials and Methods: The efficacy and safety of a new formulation of megestrol acetate concentrated suspension (575 mg/5 mL; MA-CS) was compared with traditional megestrol acetate oral suspension (800 mg/20 mL; MA-OS) in 63 HIV-infected adults with weight loss in South Africa, India, and the United States. Safety monitoring included measures of serum cortisol and adrenocorticotropic hormone stimulation testing, liver function, lipid panel, fasting glucose, and hemoglobin A1c prior to and after the 12-week trial. To assess the efficacy of the medication, patients' dietary intake, and body weight and composition were monitored during the trial. Quality of life, including appetite, was also assessed by visual analogue scales.

Results: Body weight in the concentrated suspension group increased significantly more (5.4 kg) than in the in the traditional group (3.5 kg, $P = 0.024$). Body mass index (BMI) was >21 kg/m^2 in both groups after intervention. Weight increased earlier in the concentrated suspension group. Bioelectrical impedance analysis showed that 37%-40% of the weight increase was lean and 60%-63% was fat. Baseline and stimulated serum cortisol were normal; levels in both groups were low at 12 weeks (122 µg/dL and 302 µg/dL in the concentrated group and 120 µg/dL and 334 µg/dL in the traditional group). Cortisol levels 30 days after the trial were normal in both groups. Quality of life, including appetite, was assessed by the Bristol-

Table 1. Demographics and Baseline Characteristics

	Overall	MA-CS	MA-OS
N	63	32	31
Age	36.8 ± 7.2	37.3 ± 7.3	36.3 ± 7.2
Gender (male)	36 (57%)	21 (66%)	15 (48%)
Ethnicity			
Caucasian	6 (10%	3 (9%)	3 (10%)
Black	29 (46%)	15 (47%)	15 (48%)
Asian	27 (43%)	14 (44%)	13 (42%
Other	1 (2%)	1 (3%)	0
Weight (kg)	55.0 ± 12.0	55.6 ± 13.4	54.4 ± 10.5
BMI (kg/m^2)	19.9 ± 3.6	19.8 ± 4.1	20.1 ± 3.11
(range)	(12-31.0)	(12.0-31.0)	(14.3-27.1)
Body fat (range)	10.0 (0.6-35.5)	9.8 (0.7-35.5)	10.2 (0.6-24.0)
Body lean (range)	45.1 (27.1-66.7)	46.1 (27.1-66.7)	44.1 (30.0-64.8)
Fat (%)(range)	17.5 (1.2-41.5)	16.4 (1.6-41.5)	18.6 (1.2-37.3)
CD4 mean (range)	226 (3-607)	247 (6-533)	203 (3-607)
HAART	100%	100%	100%
NNRTI based	92.1%	93.7%	90.3%
PI based	7.9%	6.3%	9.7%
CDC category			
A	28 (44%)	13 (41%)	15 (48%)
B	10 (16%)	5 (16%)	5 (16%)
C	16 (25%)	8 (25%)	8 (26%)
Total calories	1836 ± 857	1810 ± 823	1866 ± 896
Calories/kg	34.7 ± 14.7	34.2 ± 13.6	35.3 ± 15.9
Albumin (g/L)	38.8 ± 6.45	38.3 ± 7.02	39.4 ± 5.81
Hemoglobin (g/L)	132.7 ± 19.1	133.9 ± 20.6	131.5 ± 17.4

MA-CS = megestrol acetate concentrated solution; MA-OS = megestrol acetate oral suspension; BMI = body mass index; HAART = highly active retroviral therapy; NNRTI = non-nucleotide reverse transcriptase inhibitor; PI = protease inhibitor; CDC = Centers for Disease Control

Myers Anorexia/Cachexia Recovery Instrument.

Conclusions: Both formulations of megestrol acetate improved BMI; weight gain was significantly more rapid and substantial with the concentrated suspension. Both treatment groups had compromised adrenal function, which normalized within 30 days of completing the trial.

INTRODUCTION

Weight loss remains a frequent and troubling complication in patients infected with HIV, even in the era of highly active antiretroviral therapy (HAART).[1,2] In a study following a cohort with HIV, the 6-month risk of 5% or more unintended weight loss was 52% higher in the later HAART years (1998-2003) compared with pre-HAART or early HAART years.[1] As additional attention is paid to individuals infected with HIV who live in parts of the world with limited resources, the issue of weight loss will gain additional momentum as weight loss has been a

Table 2. Change from Baseline

	MA-CS	MA-OS	*P*[*]
Week 1			
Change in weight (kg)	0.6 ± 1.71	-0.2 ± 1.46	0.024
Change in total calories	382 ± 1100	-3.56 ± 873	0.22
Week 6			
Change in weight (kg)	3.4 ± 3.24	1.6 ± 2.67	0.01
Week 12			
Change in weight (kg)	5.4 ± 5.32	3.5 ± 4.03	0.024
Change in total calories	216 ± 830	151 ± 1044	0.81
Change in Kcal/kg	1.66 ± 14.24	-0.18 ± 18.97	0.70
BMI (kg/m^2)	21.7 ± 3.55	21.5 ± 3.65	
Change in BMI (kg/m^2)	1.9 ± 1.93	1.3 ± 1.51	0.061
Change in triceps (mm)	1.0 ± 2.58	1.5 ± 5.35	0.59
Change in MAC (cm)	1.4 ± 3.25	1.1 ± 1.52	0.71
Change in waist (cm)	7.1 ± 4.93	5.3 ± 4.69	0.15
Change in hip (cm)	2.5 ± 3.67	1.8 ± 3.58	0.48

[*]t-test was used for all variables except change in weight, for which the Wilcoxon-Rank Sum test was used
MA-CS = megestrol acetate concentrated solution; MA-OS = megestrol acetate oral suspension; BMI = body mass index; MAC = mid arm circumference

hallmark in HIV-infected populations. HIV infection was originally known as "slim disease" in Africa, as wasting was such a frequent outcome.[3-6]

Even in the HAART era, weight loss remains a predictor of mortality in HIV infection.[7,8] Weight loss or loss of lean body mass also contributes to morbidity and a lower quality of life.[9,10] While there may be multiple etiologies for weight loss in the HIV-infected population, including disease activity or presence of opportunistic infections, a substantial proportion of patients who lose weight will do so because they are not consuming sufficient calories.[11,12] In parts of the world with limited resources, this may be related to insufficient access to food, but it may also be due to loss of appetite. The use of an appetite stimulant such as megestrol acetate has been shown to dramatically increase caloric intake in patients infected with HIV and can contribute to an increase in weight.[13-20] Traditionally, the weight gain in HIV-infected patients who use megestrol acetate has been approximately 50% lean body mass and 50% fat mass.[13,14,16,17] There has been concern that the use of megestrol acetate contributes to glucose intolerance and adrenal suppression.[21-24]

A concentrated megestrol acetate oral suspension (Megace ES 625 mg/5 mL; Par Pharmaceutical, Spring Valley, NY) has been approved by the US Food and Drug Administration as an appetite stimulant in patients with acquired immunodeficiency syndrome (AIDS), and is bioequivalent to traditional megestrol acetate (Megace 800 mg/20 mL) (MA-OS; Bristol-Myers Squibb, Princeton, NJ) in fed conditions. The concentrated suspension was developed using nanocrystalline dispersion (NanoCrystal; Elan Drug Delivery, Inc., King of Prussia, PA) technology. In unfed conditions, the absorption of the concentrated suspension is substantially less affected by food than is traditional

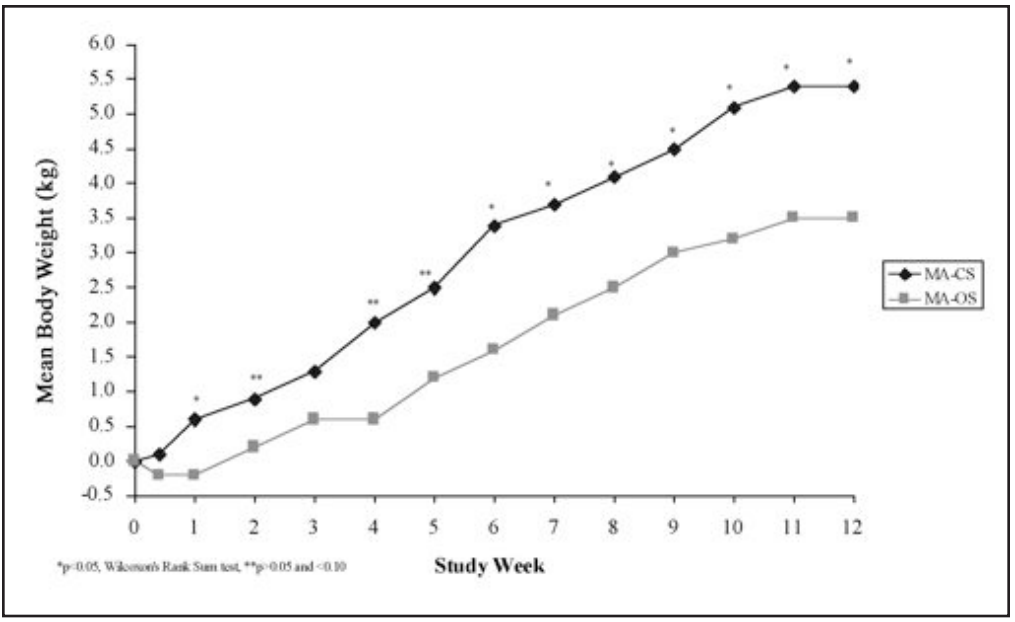

Figure 1. Mean body weight change from baseline.
*P<0.05, Wilcoxon's Rank Sum Test; **P>0.05 and <0.10
MA-CS = megestrol acetate concentrated solution; MA-OS = megestrol acetate oral suspension

megestrol acetate oral suspension. This new formulation of megestrol acetate concentration suspension (MA-CS) therefore has the potential to increase appetite and weight more rapidly, which may permit a lower total treatment dose or duration and improved efficacy.

We performed an open, randomized, controlled trial of the new formulation of megestrol acetate concentrated suspension (575 mg/5 mL) and traditional megestrol acetate oral suspension (800 mg/20 mL; MA-OS) in HIV-infected patients with weight loss in South Africa, India, and the United States to evaluate the efficacy and safety of this preparation in these populations. In South Africa and India HIV infection exists in endemic proportions and malnutrition continues to be a substantial problem in the general as well as the HIV-infected population. Safety monitoring included measures of serum cortisol and adrenocorticotropic hormone (ACTH) stimulation testing, liver function, lipid panel, fasting glucose and hemoglobin A1c (HbA1c), prior to and after the 12-week trial. Assessment of efficacy included monitoring of patients' dietary intake and body weight and composition during the trial.

SUBJECTS AND METHODS

Subjects

HIV-infected men and women between the ages of 18 and 70 years who reported loss of more than 10% of their body weight or had a body weight of less than 90% of the ideal body weight from the Metropolitan Height and Weight Table (1999 version) were recruited from HIV clinics in South Africa, India, and the United States. Individuals with intentional weight loss or other clear etiology for weight loss were excluded from the study. Pregnant women were also excluded from the study. To be included, individuals needed to provide informed consent, abstain from recreational drug and alcohol use for the duration of the

Table 3. Change in Body Composition by Bioelectrical Impedance Analysis

	MA-CS	MA-OS	*P*
Lean (kg)			
Baseline	46.1 ± 10.1	44.1 ± 9.7	0.443
6 week	1.8 ± 3.2	1.1 ± 2.1	0.319
12 week	2.3 ± 3.7	1.3 ± 2.8	0.241
Fat (kg)			
Baseline	9.8 ± 7.84	10.2 ± 5.65	0.827
6 week	2.0 ± 2.92	0.7 ± 2.34	0.062
12 week	3.4 ± 4.00	2.2 ± 3.42	0.230
Fat (%)			
Baseline	16.4 ± 10.67	18.6 ± 9.46	NA
6 week	18.9 ± 9.38	19.1 ± 11.04	NA
12 week	20.5 ± 9.04	21.0 ± 11.42	NA

MA-CS = megestrol acetate concentrated solution; MA-OS = megestrol acetate oral suspension

study, be available for study visits, and avoid any medications that would be expected to influence weight or appetite (including steroids, except inhaled steroids for asthma).

Individuals were screened for diabetes and adrenal insufficiency, with basal cortisol levels and an ACTH stimulation test at the time of study entry and were excluded if either was identified. Individuals with a history of thromboembolic events or a psychiatric condition precluding cooperation with the study requirements were also excluded from the study. All participants were required to be on a stable antiretroviral regimen prior to initiation of the study.

The protocol was reviewed and approved by ethical review committees at all sites. Informed consent was obtained before patients were screened for eligibility.

Methods

Weight was obtained in street clothing without shoes, and anthropometry (midarm, waist, and hip circumference and triceps skin fold measurement) was performed by trained study personnel. Body composition was assessed by bioelectrical impedance analysis (BIA) performed on the Quantum II analyzer (RJL Systems; Clinton, MI) with included software (Cyprus 2.7; RJL Systems).

Laboratory samples obtained and sent to a central laboratory for processing for the following tests: CBC, WBC, platelets, HbA1c, sodium, potassium, chloride, bicarbonate, BUN, albumin, glucose, creatinine, alkaline phosphatase, total bilirubin, AST/ALT, LDH, lipid panel, and urine analysis. ACTH stimulation tests were performed using an intravenous injection of 0.25 mg of synthetic ACTH with samples collected 30 and 60 minutes after stimulation. All subjects were screened for depression with the Hamilton Rating Scale for depression (HAMD-17). Quality of life, including appetite, was assessed by visual analogue scales included in the Bristol-Myers Anorexia/Cachexia Recovery Instrument (BACRI).[25] Dietary intake was recorded by 24-hour recall, and analyzed using the Nutritional Data System, version 5.0_35 (2004) (Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN). Subjects were randomized to

Table 4. Metabolic Effects

	MA-CS baseline	MA-CS 12 week	MA-OS baseline	MA-OS 12 week
WBC	5.8 ± 1.9	7.0 ± 2.3	4.9 ± 1.4	6.2 ± 2.2
TLC	1.7 ± 0.7	0.3 ± 0.6	1.7 ± 0.7	0.2 ± 0.6
Hg mg/L	13.4 ± 2.0	13.8 ±1.9	13.1 ± 1.7	13.1 ± 2.0
Albumin mg/dL	3.8 ± 0.7	4.1 ± 0.4	3.9 ± 0.6	3.9 ± 0.6
AST	34.3 ± 25.7	42.3 ± 35.9	36.6 ± 21.8	40.5 ± 29.0
ALT	38.0 ± 42.3	48.2 ± 42.0	29.7 ± 30.1	44.0 ± 43.2
Total C (mmol/L)	4.7 ± 1.3	4.9 ± 1.4	4.4 ± 1.3	4.4 ± 1.4
HDL C (mmol/L)	1.3 ± 0.3	1.3 ± 0.5	1.2 ± 0.6	1.3 ± 0.7
LDL C (mmol/L)	2.6 ± 0.8	2.5 ± 1.1	2.4 ± 0.9	2.3 ± 1.1
Triglyceride (mmol/L)	1.7 ± 1.3	2.0 ± 1.7	1.7 ± 1.2	1.6 ± 0.8
Glucose (mmol/L)	4.5 ± 0.58	4.8 ± 0.86	4.8 ± 0.5	5.2 ± 1.2
Hemoglobin A1c	5.0 ± 0.6	5.1 ± 0.7	5.0 ± 0.9	5.4 ± 0.9
Basal cortisol	446 ± 166	122 ± 196	419 ± 125	120 ± 137
Stimulated cortisol	809 ± 149	302 ± 290	808 ± 195	334 ± 255
Basal cortisol 30 day f/u	257 ± 167	—	366 ± 255	—
Basal cortisol 60 day f/u	283 ± 90	—	439 ± 211	—

MA-CS = megestrol acetate concentrated solution; MA-OS = megestrol acetate oral suspension; HDL C high-density lipoprotein cholesterol; LDL C = low-density lipoprotein cholesterol; f/u = follow-up

receive either MA-CS 575 mg or MA-OS 800 mg given once daily for both.

Subjects were stratified by country and randomized from a central site in a 1:1 ratio, using a block size of 2. Study visits were conducted weekly to monitor safety and adherence to study drug. Assessments of weight, anthropometry, and the BACRI were repeated weekly, with additional weight and BACRI assessments at day 3. BIA was repeated at week 6 and week 12 and 24-hour dietary recall was repeated for weeks 1-4, 8, and 12. Thirty days after completion of the study drug, subjects were seen for assessments of safety. Subjects returned for additional laboratory tests as needed.

Statistical Analysis

Efficacy analyses were performed on the intention-to-treat basis on all randomized subjects who were dispensed medication and had at least one postrandomization visit. Safety summaries were performed on all subjects who received at least one dose of study medication. All analyses were performed using SAS statistical software, version 8.2 (SAS Institute Inc, Cary, NC).

The focus of all efficacy analyses was to characterize the change from baseline over the course of the 12-week treatment period. All efficacy endpoints were summarized descriptively. Parametric (ANOVA) and non-parametric (Wilcoxon Rank Sum) inferential analyses were performed comparing the change from baseline between treatments. Safety information was analyzed descriptively.

RESULTS

A total of 121 subjects were screened

Table 5. Change in Dietary Intake from Baseline

Men	MA-CS	MA-OS	*P*
Week 1			
kcal	195 ± 870	-307 ± 831	0.17
Kcal/kg	2.8 ± 17.9	-6.4 ± 14.6	0.20
Week 12			
kcal	141 ± 906	-150 ± 1054	0.44
Kcal/kg	-1.1 ± 15.5	-5.1 ± 18.8	0.55
Protein (kg)	13.5 ± 36.9	-16.8 ± 38.2	0.046
Fat (kg)	-4.9 ± 44.5	13.39 ± 46.1	0.30
Carbohydrate	33.5 ± 136	-46.4 ± 159	0.17
Women			
Week 1			
Kcal	714 ± 1420	300 ± 850	0.46
Kcal/kg	17.0 ± 32.6	6.3 ± 17.2	0.40
Week 12			
Kcal	343 ± 710	451 ± 990	0.78
Kcal/kg	6.4 ± 10.9	4.7 ± 18.7	0.81
Protein (kg)	6.7 ± 45.7	13.4 ± 50.5	0.75
Fat (kg)	4.5 ± 32.3	22.4 ± 48.2	0.34
Carbohydrate	72 ± 135	48 ± 144	0.70

and 63 subjects were randomized in the study from 6 sites in South Africa, 4 sites in India, and 1 site in the United States. The majority of patients screened but not randomized were excluded on the basis of either abnormal HbA1c or, more commonly, due to abnormal baseline cortisol levels. Patients were recruited from HIV and general practice clinics as well as hospital-based clinics. Demographic data on the randomized patients is shown in Table 1. One subject was enrolled in the United States, 35 were enrolled in South Africa, and 27 were enrolled in India.

All participants were on stable HAART at the time of study entry. The majority of participants were taking a non-nucleotide reverse transcriptase inhibitor-based regimen, using either nevirapine or efavirenz; the small remainder were on boosted protease inhibitor-based regimens. Although all participants were on HAART, the range of CD4 counts (3-607 cells/mm^3) among individuals enrolled in the study was wide. At baseline the cohort had a mean BMI of 19.9 kg/m^2, which is less than the desired "normal" BMI of >22 kg/m^2, but not within the range considered severely malnourished (<18.5 kg/m^2).

Table 2 shows the changes in weight and dietary intake at week 1, week 6, and week 12 (the end of treatment). Figure 1 depicts body weight change from baseline over 12 weeks. A positive weight trend was observed by day 3 and continued for the remainder of the study for the MA-CS group. The patients in the MA-OS group continued to lose weight at the start of treatment and began to gain weight by week 2. At weeks 1, 6, and 12, weight gain was significantly greater in the MA-CS arm than the MA-OS arm. Caloric intake

Table 6. Change in Bristol-Myers Anorexia/Cachexia Recovery Instrument (BACRI)-7: Quality of Life*

	MA-CS	MA-OS	*P*
Day 3	40.8 ± 7.36	39.2 ± 5.70	0.33
Week 1	46.1 ± 5.62	44.5 ± 6.23	0.30
Week 6	54.2 ± 8.45	52.5 ± 10.70	0.50
Week 12	56.2 ± 9.52	53.2 ± 12.82	0.30

*Score on 7 items assessing patients' perception of weight, appearance, appetite, enjoyment of eating, well-being, and overall quality of life. Each item score ranged from 0-10, with a score of 0 corresponding to the lowest (worst) possible rating, and 10 to the highest (best) possible rating for each item.
MA-CS = megestrol acetate concentrated solution; MA-OS = megestrol acetate oral suspension

increased in both arms of the study, but varied widely; differences between the two groups were not significant. At 12 weeks, both groups had increased BMI and both groups had increased triceps skin folds, waist, hip, and mid-arm circumference. Table 3 shows the change in body composition during the course of the study, as determined by BIA. Patients in the MA-CS arm increased a total of 5.4 kg in weight; 2.3 kg (40%) was lean and 3.4 kg (60%) was fat. Patients in the MA-OS arm gained a total of 3.5 kg over the course of the study; 1.3 kg (37%) was lean and 2.2 kg (63%) was fat.

Laboratory parameters for the two arms of the study over the course of the 12 weeks are shown in Table 4. Results on tests of WBC, hemoglobin, albumin, glucose, and HbA1c were not different at the end of the study compared with baseline. Basal morning cortisol was within normal range (>138 µg/dL) for both arms of the study at baseline (446 µg/dL and 419 µg/dL, respectively, for the MA-CS and the MA-OS arm), as would be expected from the entry screening, and decreased at 12 weeks in both arms (122 µg/dL and 120 µg/dL, respectively). The ACTH-stimulated cortisol levels obtained at the baseline visit were also within the normal range (>500-550 µg/dL) for both arms of the study (809 µg/dL for both), as expected, and decreased at 12 weeks in both arms (MA-CS, 302 µg/dL; MA-OS, 334 µg/dL). Basal cortisol levels had returned to the normal range at 30 days after completion of the study for both arms (257 µg/dL and 366 µg/dL, respectively) and remained in the normal range at 60 days after the completion of the study (283 µg/dL and 439 µg/dL).

Change in dietary intake for the study participants over the 12 weeks is shown in Table 5. Men and women are reported separately as men and women may be expected to consume different amounts of calories. There was no significant difference in the amount of calories consumed by men or women in either arm of the study, and the variation in intake was wide throughout the course of the study. There were also no significant differences in the types of calories (protein, carbohydrate, fat) consumed.

The results of the BACRI quality of life assessment (BACRI-7) showed improvement in quality of life parameters in both arms of the study at 6 weeks and 12 weeks, with no difference between arms (Table 6). Increases in appetite by visual analogue scale were also reported in both arms of the study. In addition, the patients' perception of benefit of treatment (BACRI-1) improved during treatment with both MA-CS and MA-OS (Table 7).

Table 7. Change in Bristol-Myers Anorexia/Cachexia Recovery Instrument (BACRI)-1: Treatment Benefit

	MA-CS	MA-OS	*P*
Day 3	6.1 ± 1.48	5.6 ± 1.19	0.20
Week 1	6.9 ± 1.10	6.7 ± 1.22	0.52
Week 6	8.0 ± 1.33	7.7 ± 1.66	0.43
Week 12	8.2 ± 1.34	7.6 ± 2.63	0.21

MA-CS = megestrol acetate concentrated solution; MA-OS = megestrol acetate oral suspension

Adverse events were similar for the two treatment groups and were frequent in the study. Thirty-one of 32 individuals in the MA-CS arm reported an adverse event, and 30 of 31 individuals in the MA-OS arm reported an adverse event. Forty-five percent of the individuals reported at least one serious adverse event, 2 subjects in the MA-CS arm withdrew because of an adverse event, and 3 subjects in the MA-OS arm withdrew because of an adverse event. Three subjects in the MA-OS arm died; however, the events were not considered related to study drug (1 occurred during the study, 2 occurred 53 days and 66 days, respectively, after study completion). There were no deaths in the MA-CS arm.

DISCUSSION

We were able to successfully conduct a randomized, controlled trial of two formulations of megestrol acetate in HIV-infected patients, living predominantly in the resource-constrained countries of South Africa and India, who had suffered a 10% weight loss or had a body weight 10% less than ideal. This trial is the first that we are aware of to examine the safety and efficacy of megestrol acetate in detail, including measures of basal and stimulated serum cortisol. The trial was successful in that an increase in weight (fat and lean) was noted in both groups, with significantly more weight gained in the arm that received the MA-CS formulation than in the arm that received the MA-OS formulation. A positive weight trend emerged by day 3 for the MA-CS group. BMI in both groups returned to near normal at the end of the study (21.7 kg/m^2 and 21.5 kg/m^2, respectively). Weight gain in both groups was approximately 40% lean and 60% fat, with a final total body fat percentage of 23% in the MA-CS group (from a baseline of 18.5%) and 21% in the MA-OS group (from a baseline of 18.5%), according to BIA. This new formulation has the potential to increase appetite and weight more rapidly, which may ultimately permit a lower total treatment dose or duration.

The results of this trial are similar to what has been seen in other trials of megestrol acetate in HIV-infected patients in the HAART era, but are unique in the fact that the trial was conducted in parts of the world that are resource limited.[13-16,20] There is good evidence to suggest that weight loss promotes increased morbidity and mortality in patients infected with HIV, and compromises quality of life. There are also data that strongly suggest that the use of HAART alone in HIV-infected populations will not totally eliminate malnutrition in this population.[25] We have been able to demonstrate that use of an appetite stimulant could safely encourage dietary intake and result in gain of both lean and fat weight, suggesting that interventions such as this will be useful in populations with HIV infection and malnutrition, particularly in parts of the

world with limited resources.

Our trial was the first conducted in HIV-infected patients to document the degree and reversibility of the adrenal suppression seen in patients treated with a 12-week course of megestrol acetate. While adrenal suppression occurred, it was mild and generally reversed within 30 days of cessation of the agent. These data suggest that the use of megestrol acetate will be safe in the HIV-infected populations with weight loss. The results of the ACTH stimulation test are quite reassuring, although the results may be affected by medical conditions or concurrently used medications, which may not have been captured in this study. The results may also have been affected by the need for the subject to rest quietly for 30 minutes before the test was performed.

Both formulations of megestrol acetate were demonstrated to be safe and successful in the treatment of HIV-associated weight loss; the use of the MA-CS formulation led to a significantly greater weight gain throughout the course of the trial. Both preparations improved quality of life as well as weight. The evidence appears to suggest that the use of the MA-CS formulation may be preferable to MA-OS. The absorption of the MA-CS formulation in the unfed state is a potential benefit for patients who are seriously anorectic. Further trials to determine if a shorter course of therapy would be as successful would be beneficial.

The results of this trial are limited by the lack of complete data on CD4 levels and viral load data, which would help to determine the impact of ongoing viral replication on the ability of megestrol acetate to improve weight and body composition. It is known that ongoing viral replication as reflected by increasing viral load can predictably lead to weight loss and a decrease in viral load can lead to an increase in weight.[26] It is also not clear how much the degree of change in weight in this trial was limited by lack of access to food for participants, especially female patients.

As HAART is implemented in parts of the world that have limited resources and where HIV is epidemic, there is a need to manage the ongoing nutritional complications of HIV infection. This trial demonstrates that use of appetite stimulants that result in weight gain is one strategy that is of benefit to HIV-infected patients treated with HAART who suffer from ongoing weight loss. While the use of HAART has limited the frequency of severe malnutrition in HIV-infected individuals in parts of the world where resources are sufficient, weight loss remains a frequent complication in HIV-infected individuals in this setting. The availability of a safe and effective short-term oral intervention to increase BMI, and both lean and fat mass in these individuals, is of value.

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