Nutritional Supplementation in HIV-Infected Individuals in South India: A Prospective Interventional Study

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Background. Malnutrition in human immunodeficiency virus (HIV)–infected individuals is associated with faster disease progression, higher mortality rates, and suboptimal response to antiretroviral therapy (ART).

Methods. We conducted a prospective interventional study to evaluate the effects of an oral macronutrient supplement among HIV-infected adults in South India. Patients attending Tuberculosis Research Centre clinics from June 2005 through December 2007 had baseline nutritional assessment and laboratory investigations performed. Patients at 1 center received nutritional counseling and standard care, whereas patients at 2 centers additionally received a macronutrient providing 400 cal and 15 g of protein daily. Study outcomes were changes in anthropometry, body composition, blood chemistry, and immune status at 6 months.

Results. In total, 636 ART-naive patients were enrolled in the study; 361 completed 6 months of follow-up (282 received supplements and 79 received standard care). Mean age ± standard deviation (SD) was 31 ± 7 years, mean weight ± SD was 50 ± 10 kg, and 42% were male. Significant increases in body weight, body mass index, midarm circumference, fat-free mass, and body cell mass were observed in the supplement group but not in the control group at 6 months; gains were greater in patients with CD4 cell counts <200 cells/μL. No changes were observed in lipid levels, whereas the CD4 cell count decreased in the control group. However, after adjusting for baseline differences, these changes were not statistically significantly different between the groups.

Conclusions. Macronutrient supplementation did not result in significantly increased weight gain compared with standard care (including nutritional counseling) among patients with moderately advanced HIV disease. The effect of supplementation on specific subsets of patients and on preserving immune function needs further research.

During the past decade, which saw wide and easy access to antiretroviral therapy (ART) in the developed world, a significant number of life-years were saved among patients infected with human immunodeficiency virus (HIV) [1]. Recent guidelines recommend initiation of ART before CD4 cell counts decrease below 350 cells/μL [2]. However, in resource-poor countries of Africa and Asia, where most of the world's HIV-infected people live and where food insecurity is widespread [3, 4], diagnosis of HIV infection is often made only at the advanced stage. Furthermore, malnutrition is endemic in these countries and is a common manifestation among HIV-infected individuals. We have previously shown that HIV-infected individuals have higher rates of malnutrition, anemia, and hypoalbuminemia than do socioeconomically matched HIV-uninfected individuals, despite similar caloric intake [5, 6].

Rates of HIV disease progression and mortality are higher in the presence of severe malnutrition [7, 8]. Furthermore, malnourished patients have a higher risk of death and suboptimal response to treatment when ART is initiated [9]. Studies of body composition have identified predominant loss of either lean muscle mass or fat mass during AIDS wasting [10]. Although randomized trials of nutritional supplementation are few, it has been shown that it is acceptable and feasible to improve food intake in malnourished HIV-infected pa-

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tients [11–13]. The National AIDS Control Program in India began its free antiretroviral treatment program in 2004 and targeted patients with advanced (stage 3 or 4) disease or CD4 cell counts <200 cells/μL. Those not eligible for ART receive multivitamins and cotrimoxazole prophylaxis, as well as treatment for associated opportunistic infections. We hypothesized that supplementation with additional calories and protein would improve nutritional status and possibly have an effect on the body composition and immunologic status of these individuals. At the Tuberculosis Research Centre (TRC), Tamil Nadu, South India, we conducted a prospective interventional study to evaluate the effects of an energy-dense macronutrient supplement provided for 6 months on the anthropometric, body composition, and immunologic status of HIV-infected adults at different stages of disease. The study was conducted in collaboration and with financial support from the World Food Program in India.

METHODS

Study population. HIV-infected individuals attending local government hospitals for medical care were referred to TRC clinics at Chennai and Madurai, India, for screening and enrollment into various ongoing research studies. They were approached for participation in this prospective interventional study. To be eligible, they had to be 18 years or older, ART naive, and willing to consume the supplement as instructed and to follow study procedures. Patients were excluded if they had any of the following: active tuberculosis or other serious opportunistic infections, dysphagia, odynophagia, severe diarrhea (>6 watery stools per day for $\geq$7 days), allergy to soybean, or unwillingness to follow study protocols. Informed consent was obtained from all patients, and the study was approved by the Institutional Ethics Committee of the TRC.

Nutritional assessment. At the first visit, a history was taken, a physical examination was performed, and a blood sample was obtained for analysis (blood cell counts, chemical analysis, and CD4 cell count). The study nutritionist obtained a 24-h recall diet history [14]; Digest [15], a software package specially designed to analyze South Indian diets, was used to calculate the intake of calories, protein, and fat.

At the second visit and all subsequent visits, nutritional status was assessed. Height (to the nearest centimeter), weight (to the nearest 0.1 kg), and midarm circumference (to the nearest 0.1 cm) were measured. Anthropometric measurements were performed by 2 trained nutritionists (one nutritionist each in Chennai and Madurai), and interobserver variability between them was limited by standardization of methods before study initiation. Bioelectrical impedance measurements were obtained with a bioimpedance analyzer (Quantum handheld analyzer; RJL Systems) using standard techniques at the Chennai center only [16].

Of the 3 outpatient clinics (2 in Chennai and 1 in Madurai), patients attending one of the clinics in Chennai received standard of care alone and served as the control group, whereas those attending the other clinic in Chennai and the clinic in Madurai received the nutritional supplement along with standard of care. Standard of care consisted of prophylaxis and treatment of common opportunistic infections (including cotrimoxazole for all and isoniazid in some cases), multivitamin tablets (vitamin A, 5000 IU; vitamin D, 200 IU; vitamin E, 7.5 mg; vitamin B, 2.5 mg; vitamin C, 40 mg; nicotinamide, 25 mg; D-pantothenol, 2.5 mg; folic acid, 500 μg; vitamin B_{12}, 2.5 mg; copper sulfate pentahydrate, 0.1 mg; magnesium sulfate monohydrate, 0.01 mg; zinc sulfate, 31.2 mg; and potassium iodide, 15 mg), nutritional counseling, and psychosocial support. Compliance with drug therapy was checked by pill counts during monthly visits.

During the intervention period, patients were assessed clinically every month, whereas 24-h dietary recall, anthropometric parameters, body composition, blood chemical analysis, and CD4 cell counts were measured at the 6-month visit. Because of ethical concerns about withholding nutritional supplements from HIV-infected patients, the selection of groups (control vs supplement) was done at a ratio of 1:3. After 6 months of the study period, all patients (including those in the control group) were offered the supplement.

Nutritional supplement. The high-calorie, high-protein macronutrient supplement Indiamix, which was provided by the World Food Program in India, is a blended, fortified mixture of whole wheat and soya bean flour fortified with vitamins A, B_1, B_2, B_{12}, and C as well as niacin and folic acid but no iron. One hundred grams of the supplement provided 400 cal, 15 g of protein, 6 g of fat, and 1 recommended daily allowance of each vitamin. Study participants were instructed to consume 100 g/d and were given a month's supply of Indiamix, which was available in 3-kg packs. Study nutritionists discussed various recipes and suggested ways of preparing the supplement—the easiest was to cook it as porridge with water. Compliance with the supplement regimen was checked by random home visits by fieldworkers and by questioning patients during their monthly visits. Additional food packets were issued to the participants if required to avoid sharing of the rations with other family members.

Outcomes. The outcomes assessed were changes in anthropometric parameters (weight; body mass index [BMI], calculated as the weight in kilograms divided by the square of height in meters; and midarm circumference), blood chemical analysis (hemoglobin, serum albumin, triglyceride, and cholesterol levels), immune status (CD4 cell count), and body composition (fat, fat-free mass, and body cell mass).

Data analysis. The distribution of all variables was checked, and skewed variables were log transformed. The mean,

Table 1. Comparison of Baseline Characteristics of Patients Who Completed 6 Months of Follow-up (Completers) versus Those Who Did Not (Noncompleters)

Characteristic	Completers		Noncompleters		P
	No. of patients	Value	No. of patients	Value	
Age, years	361	31 ± 7	275	32 ± 7	.03
Weight, kg	361	50.3 ± 10.4	275	50.0 ± 9.5	.71
BMI	361	20.6 ± 3.9	275	19.9 ± 3.4	.02
Midarm circumference, cm	361	23.7 ± 3.5	275	23.5 ± 3.8	.35
Hemoglobin level, g/dL	357	11.9 ± 1.8	260	11.9 ± 2.1	.87
Albumin level, g/dL	312	4.0 ± 0.6	210	3.8 ± 0.6	<.001
Total cholesterol level, mg/dL	308	144 ± 34.7	209	137 ± 29.9	.01
Triglyceride level, mg/dL	305	124 ± 66.7	208	122 ± 61	.77
CD4 cell count, cells/μL					
Mean ± SD	357	391 ± 245	259	298 ± 200	<.001
Median (range)	357	338 (24–1550)	259	279 (6–1247)	...
Caloric intake, kcal/day	361	1846 ± 533	274	1853 ± 609	.87
Protein intake, g/day	361	57 ± 23	274	60 ± 30	.10
Fat intake, g/day	361	35 ± 18	274	36 ± 21	.52
Body fat, kg	149	12.3 ± 8.6	146	10.6 ± 6.9	.07
Fat-free mass, kg	149	40.5 ± 8.3	146	41.2 ± 8.5	.44
Body cell mass, kg	149	18.5 ± 4.3	146	18.8 ± 4.4	.59

NOTE. Data are means ± standard deviations (SDs), unless otherwise indicated. BMI, body mass index.

the median, and the 25th and 75th percentiles were determined for all continuous variables. Because there were a sizeable number of exclusions from the study, we compared the baseline characteristics of those who completed the study with those who did not, using the independent *t* test and the χ^2 test.

Mixed-model analysis incorporating the repeated measurements was used to analyze the absolute changes at 6 months in anthropometric parameters, laboratory measurements, and body composition between the supplement and control groups after controlling for baseline CD4 cell count, age, and sex. Analysis was also performed by stage of immunosuppression, with patients in the following CD4 cell count categories being compared: <200 cells/μL, 200–499 cells/μL, and ⩾500 cells/μL. Data were analyzed using SAS statistical software, version 9.1.0 (SAS Institute).

RESULTS

From June 2005 through December 2007, a total of 636 HIV-infected individuals were screened and enrolled in the study. Two hundred seventy-five did not initiate use of the supplement, became ineligible, or discontinued use of the supplement within the first few weeks because of a variety of reasons (noncompleters). Of these, ~40% initiated ART and another 20% were hospitalized for management of their medical problems and therefore were ineligible for inclusion. A total of 10% of patients died, and 30% discontinued participation in the study for various reasons, such as distaste for food, nausea, early satiety, inability to cook, and/or embarrassment regarding carrying the supplement home. A total of 361 patients completed 6 months of supplementation (completers) and were available for evaluation. The baseline characteristics of the noncompleters and completers are given in Table 1. The noncompleters were older and had lower BMIs, CD4 cell counts, serum albumin levels, and blood cholesterol levels, indicating more advanced disease. However, the 2 groups were similar in terms of marital status, income level, years of education (two-thirds had <8 years of schooling), dietary intake, and body weight and composition. No imputation was done for missing data, and only data from completers were used for analysis.

Of the 361 completers, 282 were in the supplement group and 79 were in the control group. The mean age ± SD was 30.9 ± 7 years, and the mean weight ± SD was 50.3 ± 10.4 kg. A total of 36% of men and 30% of women were severely malnourished, with a BMI <18.5 at baseline. The patients attending the 3 centers were demographically similar in terms of socioeconomic status, literacy levels, and dietary habits. Most patients belonged to the lower socioeconomic strata, with a monthly income of 2000–5000 rupees (<$100). Most patients were asymptomatic at the time of enrollment, although a third had a history of tuberculosis treatment. At baseline, body weight, BMI, serum albumin level, and body composition were comparable between the supplement and control groups (Table 2). However, CD4 cell counts were significantly higher in the control group, but caloric and protein intake were lower.

Table 2. Comparison of Baseline Characteristics of Patients Who Received Supplements (Supplement Group) versus Those Who Did Not (Control Group)

Characteristic	Supplement group		Control group		P
	No. of patients	Value	No. of patients	Value	
Weight, kg	282	49.9 ± 9.8	79	51.6 ± 12.1	.24
BMI	282	20.5 ± 3.7	79	21.1 ± 4.7	.28
Midarm circumference, cm	282	23.7 ± 3.3	79	24.1 ± 4.2	.39
Hemoglobin level, g/dL	282	11.8 ± 1.8	75	12.1 ± 1.9	.18
Albumin level, g/dL	260	4.0 ± 0.6	52	3.9 ± 0.4	.22
Total cholesterol level, mg/dL	256	143.5 ± 35.6	52	148.2 ± 29.4	.37
Triglyceride level, log mg/dL	254	4.7 ± 0.4	51	4.7 ± 0.5	.95
CD4 cell count, log cells/μL	282	5.7 ± 0.7	75	6.0 ± 0.6	<.001
CD4 cell count, absolute cells/μL	282	365 ± 233	75	488 ± 266	.001
Caloric intake, kcal/day	282	1911 ± 543	75	1616 ± 427	<.001
Protein intake, g/day	282	58.2 ± 23.3	75	51.0 ± 20.1	.01
Body fat, kg	113	11.7 ± 8.1	36	14.0 ± 9.9	.16
Fat-free mass, kg	113	40.7 ± 8.5	36	39.9 ± 8.0	.63
Body cell mass, kg	113	18.6 ± 4.3	36	18.3 ± 4.1	.69

NOTE. Data are means ± standard deviations. BMI, body mass index.

At the end of 6 months, the supplement group showed significant increases in weight, BMI, and midarm circumference, whereas in the control group the only significant change was a decrease in log CD4 cell count (Table 3). However, using mixed-model analysis and adjusting for the baseline differences in CD4 cell count, age, and sex between the 2 groups, none of these changes were statistically significant.

Patients who received the supplement were further categorized into 3 categories based on level of immunodeficiency: CD4 cell count <200 cells/μL, CD4 cell count of 200–499 cells/μL, and CD4 count ⩾500 cells/μL. Table 4 shows the changes at 6 months from baseline in these 3 groups of patients. A significant increase was noticed in weight, BMI, and midarm circumference in all 3 immune categories, whereas an increase in fat-free mass and body cell mass was observed in patients in the mild to moderately immunodeficient categories. The

Table 3. Changes in Various Parameters at 6 Months in the Supplement and Control Groups, with Comparison of Differences

Parameter	Absolute change at 6 months from baseline within groups				Difference of differences at 6 months
	Supplement group		Control group		
	Baseline estimate	Change at 6 months (change 1)	Baseline estimate	Change at 6 months (change 2)	
Weight, kg	51.3 (50.1 to 52.5)	0.9 (1.2 to 0.6)[a]	52.3 (50.1 to 54.6)	0.6 (−0.02 to 1.3)	−0.3 (−1.0 to 0.4)
BMI	20.5 (20.1 to 21.0)	0.4 (0.5 to 0.2)[a]	20.9 (19.9 to 21.7)	0.2 (−0.1 to 0.5)	−0.2 (−0.5 to 0.1)
Midarm circumference, cm	24.1 (23.7 to 24.5)	0.6 (0.9 to 0.3)[a]	24.2 (23.4 to 25.0)	0.4 (−0.1 to 0.9)	− 0.2 (−0.7 to 0.4)
Hemoglobin level, g/dL	12.1 (11.9 to 12.2)	−0.02 (−0.2 to 0.2)	12.2 (11.9 to 12.6)	0.1 (−0.3 to 0.5)	0.1 (−0.3 to 0.5)
Albumin level, g/dL	3.9 (3.9 to 4.0)	−0.13 (−0.06 to −0.2)[a]	3.8 (3.7 to 3.9)	−0.15 (−0.3 to 0.01)	−0.01 (−0.2 to 0.2)
Total cholesterol level, mg/dL	144 (139.9 to 147.3)	0.4 (−4.6 to 5.4)	143 (136 to 151)	4.5 (−6.3 to 15.3)	4.1 (−7.8 to 16)
Triglyceride level, log mg/dL	4.7 (4.6 to 4.8)	−0.02 (−0.1 to 0.04)	4.6 (4.5 to 4.8)	−0.1 (−0.3 to 0.02)	−0.1 (−0.3 to 0.05)
CD4 cell count, log cells/μL	5.6 (5.6 to 5.7)	0.01 (−0.07 to 0.06)	5.9 (5.8 to 6.1)	−0.14 (−0.01 to −0.3)[a]	−0.13 (−0.3 to 0.02)
CD4 cell count, absolute cells/μL	358 (331 to 385)	12.5 (36 to −10.6)	443 (392 to 494)	−59.8 (−11.6 to −107.9)	−72.3 (−18.9 to −125.7)
Body fat by BIA, kg	11.9 (10.5 to 13.2)	0.5 (−0.1 to 1.0)	12.4 (9.8 to 14.9)	0.4 (−0.8 to 1.5)	−0.09 (−1.4 to 1.2)
Fat-free mass by BIA, kg	41.7 (40.8 to 42.6)	1.0 (1.4 to 0.7)[a]	41.5 (39.7 to 43.2)	0.5 (−0.3 to 1.2)	−0.6 (−1.4 to 0.3)
Body cell mass by BIA, kg	19.1 (18.6 to 19.6)	0.5 (0.8 to 0.2)[a]	19.1 (18.2 to 20.1)	0.2 (−0.4 to 0.9)	−0.28 (−1.0 to 0.4)

NOTE. Data in parentheses are 95% confidence intervals. Estimates were calculated by repeated-measurements analysis of variance, adjusting for baseline CD4 cell count, age, and sex. The difference of the differences between the 2 groups (change 1 and change 2) was not statistically significant for any of the parameters. BIA, bioimpedance analysis; BMI, body mass index.

[a] Significant change from baseline at 6 months ($P < .001$).

Table 4. Changes in Various Parameters at 6 Months in the Supplement Group, Categorized by Level of Immunodeficiency

	Absolute change at 6 months from baseline, by CD4 cell count					
	<200 cells/μL (*n* = 81)		200–499 cells/μL (*n* = 133)		≥500 cells/μL (*n* = 68)	
Parameter	Baseline estimate	Change at 6 months	Baseline estimate	Change at 6 months	Baseline estimate	Change at 6 months
Weight, kg	48.6 (46.5 to 50.7)	1.2 (1.8 to 0.6)[a]	52.2 (50.5 to 53.8)	0.8 (1.3 to 0.4)[a]	52.1 (49.7 to 54.4)	0.7 (1.4 to 0.07)[a]
BMI	19.4 (18.7 to 20.3)	0.4 (0.7 to 0.1)[a]	20.9 (20.3 to 21.5)	0.3 (0.5 to 0.1)[a]	21.0 (20.1 to 21.9)	0.3 (0.6 to 0.04)[a]
Midarm circumference, cm	23.1 (22.4 to 23.9)	0.8 (1.3 to 0.3)[a]	24.5 (23.9 to 25.1)	0.5 (0.9 to 0.1)[a]	24.4 (23.5 to 25.2)	0.5 (1.1 to 0.02)[a]
Hemoglobin level, g/dL	11.0 (10.7 to 11.3)	−0.3 (−0.7 to 0.03)	12.3 (12.1 to 12.6)	0.08 (−0.2 to 0.3)	12.6 (12.2 to 12.9)	0.1 (−0.2 to 0.5)
Albumin level, g/dL	3.7 (3.6 to 3.8)	−0.06 (−0.2 to 0.07)	4.0 (3.9 to 4.2)	−0.2 (−0.1 to −0.3)[a]	4.1 (3.9 to 4.2)	−0.08 (−0.2 to 0.07)
Cholesterol level, mg/dL	128 (122 to 135)	2.5 (−7.6 to 12.6)	145 (140 to 150)	−2.0 (−9.4 to 5.5)	154 (147 to 161)	2.6 (−7.7 to 12.9)
Triglyceride level, log mg/dL	4.7 (4.6 to 4.8)	0.04 (−0.08 to 0.2)	4.7 (4.6 to 4.7)	−0.02 (−0.1 to 0.1)	4.7 (4.6 to 4.8)	−0.08 (−0.2 to 0.04)
CD4 cell count, log cells/μL	4.8 (4.7 to 4.9)	0.09 (−0.03 to 0.2)	5.8 (5.7 to 5.8)	−0.01 (−0.1 to 0.08)	6.4 (6.3 to 6.5)	−0.1 (−0.2 to 0.02)
CD4 cell count, absolute cells/μL	131 (108 to 154)	36.6 (80 to −6.3)	336 (318 to 354)	23.7 (56.8 to −9.4)	690 (664 to 716)	−34.9 (11.9 to −81.7)
Body fat by BIA, kg	10.8 (8.5 to 13.1)	0.6 (−0.5 to 1.6)	11.5 (9.7 to 13.2)	0.4 (−0.4 to 1.2)	13.2 (10.4 to 15.9)	0.4 (−0.9 to 1.6)
Fat-free mass by BIA, kg	41.5 (39.7 to 43.2)	1.2 (1.8 to 0.6)[a]	41.8 (40.5 to 43.1)	1.2 (1.6 to 0.7)[a]	41.2 (39.2 to 43.3)	0.4 (−0.3 to 1.2)
Body cell mass by BIA, kg	19.1 (18.1 to 20)	0.7 (1.4 to 0.1)[a]	19.2 (18.5 to 19.9)	0.6 (1.0 to 0.1)[a]	18.8 (17.7 to 19.9)	0.03 (−0.7 to 0.8)

NOTE. Data in parentheses are 95% confidence intervals. Estimates were calculated by repeated-measurements analysis of variance, adjusting for baseline CD4 cell count, age, and sex. BIA, bioimpedance analysis; BMI, body mass index.

[a] Significant increase or decrease from baseline at 6 months ($P < .05$).

absolute changes, however, were not significantly different between the 3 categories of patients, except for log CD4 cell count between the <200 cells/μL and ≥500 cells/μL CD4 cell count groups.

DISCUSSION

In this nonrandomized comparison of macronutrient supplementation among HIV-infected patients at various stages of HIV disease in India, we observed an improvement in various nutritional parameters in the supplement group, but this was not statistically significantly different from the members of the control group, who were provided standard of care. There could be several potential reasons for the lack of noticeable effect, some of which are related to study design and others to biological and behavioral factors. Patients who were severely ill, who were about to initiate ART, or who required hospitalization were not included in the study, and this may have been the group most likely to benefit. Randomized clinical trials, while the ideal way to prove the efficacy of an intervention, present ethical problems when dealing with nutritional supplements. Often, all patients are uniformly food insecure, and investigators find it awkward and uncomfortable to allocate extra food to some and not to other patients in their care. We tried to overcome this difficulty by performing a nonrandomized comparison enrolling patients at different sites into the 2 arms and providing access to the supplement to all individuals at the end of the study period. This resulted in enrollment of patients with different baseline characteristics; the problem was addressed by performing mixed-model analysis controlling for baseline differences.

Furthermore, we did not analyze the record of hospitalizations or intercurrent infections or compare deaths between the 2 groups; hence, the effect of supplementation on mortality and morbidity was not determined. Although caloric and protein intakes were statistically different between the supplement and control groups, we believe that this finding was likely due to chance. We also had a sizeable number of patients who were excluded in the first days and weeks of the study from the supplement group (mainly because of initiation of ART or disinterest in the intervention), leading to a further bias in our comparison groups. Finally, both groups were provided excellent medical care, treatment for and prevention of opportunistic infections, multivitamins, and nutritional counseling, which could have led to changes in patient behavior (and diet) that reduced the difference between the 2 groups at 6 months.

A recent review of randomized clinical trials of macronutrient supplements in HIV-infected populations did not observe an effect on body weight, BMI, or clinical outcomes [17]. It is noteworthy, however, that one multicentric study of whey protein supplement in weight-stable patients with a history of weight loss found an increase in CD4 cell counts relative to those in control subjects, even though there was no significant improvement in weight [12]. Only 2 trials have been conducted in resource-poor settings. Cantrell et al [18] found improved adherence to ART among food-insecure patients provided macronutrients, compared with that among patients who were not. A randomized trial in Malawi found that the ready-to-use spread was significantly more effective than corn soy blend in increasing BMI among HIV-infected adults with wasting; no differences in CD4 cell counts, viral loads, or mortality were

observed between the 2 groups. However, there was no group that did not receive supplementation [19]. This suggests that end points for future supplementation trials should be carefully chosen (a slowing of decline in immune function is an observation made by us and Sattler et al [12] and may be worth exploring further).

As HIV infection progresses, it produces a catabolic state and increased susceptibility to other infections; when this is compounded by a lack of food, progressive malnutrition ensues. Weight loss and low BMI, especially when associated with low CD4 cell counts, are strong and independent predictors of survival in HIV infection [20]. Similarly, lower levels of hemoglobin, albumin, and serum cholesterol have been identified as predictors of faster disease progression and decreased survival [21, 22]. The long-term prognosis in patients with severe weight loss is guarded, especially when patients are waiting or not willing to start ART. Studies have also documented the deleterious effect of tuberculosis and other opportunistic infections on nutritional status (infection and malnutrition often form a vicious cycle, along with poverty and food insecurity) [5, 23, 24]. Preventing weight loss, therefore, could potentially have multiple benefits in terms of reducing mortality and morbidity, contributing to increased productivity and economic stability and perhaps improving responses to ART. Although there have been many calls for integration of HIV and nutrition programs, data are lacking on how such programs can be implemented in resource-constrained settings, what the composition of the supplement should be, and which subgroups should be targeted [25].

Our study has made important contributions to the limited knowledge base in this field. We have demonstrated the acceptability and feasibility of providing macronutrient supplements using a clinic-based approach in this largely food-insecure population. Sharing of food supplements among family members was not encouraged, but additional supplies were provided if requested so that the patients in this study could take the recommended 100 g per day. We showed significant improvements in various nutritional parameters and documented a slower decrease in CD4 cell counts among patients who were provided supplements. The absolute gains in weight, BMI, CD4 cell count, fat-free mass, and body cell mass were higher among patients with severe immunodeficiency, indicating that demonstrable improvements are most likely to be seen among the most immunosuppressed, who are also the most malnourished. However, changes in body composition as measured by the bioimpedance analyzer are not reliable, especially in patient populations with shifts in hydration [26]. The question of the most appropriate stage of HIV infection at which supplementation is likely to have a maximum benefit remains to be answered. Furthermore, our study included an HIV-infected comparison group as a control, was conducted in real-life situations, was clinic based, and did not have strict inclusion and exclusion criteria. Patients were free to initiate ART or withdraw from the study at any time, and we had patients at all stages of HIV disease. It also brought out practical problems, such as difficulty in proper storage of flour (due to humidity), early satiety during consumption, difficulty in preparation, and boredom with the same food item. Nevertheless, most patients opted to continue taking the supplements even after the study period ended.

Policy makers in resource-poor regions need information on both the efficacy and feasibility of providing nutritional supplements (of various types) in different settings [18, 27]. The state of Tamil Nadu in India implemented a macronutrient supplementation program for all HIV-infected patients initiating ART at government ART centers. Three of these sites had additional resources from the Children's Investment Fund Foundation in the United States and provided a supplement similar to that used in our study to all patients attending the center regardless of ART status. The ART-naive patients showed a weight gain of 2.7 kg ($P < .01$) for 1 year, after controlling for supplementation adherence, number of nutritional counseling sessions, and sex. Furthermore, a weight gain of 300 g for every 10% increase in adherence to the macronutrient supplement regimen was observed, after adjusting for ART, micronutrient supplement regimen adherence, and counseling [28]. The program was appreciated by patients, provided an incentive for regular attendance, and is being replicated in other states in India.

In summary, an energy-dense oral macronutrient supplement did not have additional benefits on nutritional parameters or immune function among ART-naive HIV-infected individuals in South India, compared with high-quality standard of care. The effect of supplementation on specific subsets of patients and on preserving immune function needs further research.

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Potential conflicts of interest. All authors: no conflicts.

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