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Macronutrient Supplementation for Malnourished HIV-infected Adults: A Review of the Evidence in Resource-Adequate and Resource-Constrained Settings

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Abstract

Access to antiretroviral therapy (ART) for HIV infection has expanded rapidly throughout sub-Saharan Africa, but malnutrition and food insecurity have emerged as major barriers to program success. Protein-calorie malnutrition (a common form in the region) hastens HIV disease progression, and food insecurity is a barrier to medication adherence. Analyses of patient outcomes have identified a low body mass index (BMI) at ART initiation as an independent predictor of early mortality, but the causes of low BMI are multi-factorial may represent normal anthropometric variation, chronic inadequate food intake, or wasting associated with HIV and other infections. While there is much experience population-level humanitarian food assistance, few data exist to measure the effectiveness of macronutrient supplementation or to identify individuals most likely to benefit. In this report, we review the current evidence supporting macronutrient supplementation for HIV-infected adults; clinical trials in resource-adequate and resource-constrained settings; and highlight priority areas for future research.

Keywords

AIDS; HIV; nutrition; supplementation; sub-Saharan Africa

Introduction

Since 2003, access to antiretroviral therapy (ART) for HIV infection has expanded rapidly throughout sub-Saharan Africa, and more than 2.1 million of the estimated 7 million people in need of treatment now have access[1]. Favorable clinical outcomes have been reported from a variety of settings [2–7], but the follow-up period in most analyses is short and further long-term data are needed. The geographic overlap of high HIV prevalence, malnutrition, and chronic food insecurity in much of sub-Saharan Africa has highlighted need for more comprehensive approaches to health care. There is increasing evidence that a

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low body mass index (BMI) is a powerful and independent predictor of early mortality following ART initiation [2, 8, 9]. The role of malnutrition in HIV disease progression and poor clinical outcomes is significant and likely under-reported [10].

In contrast to the substantial research on *micro*nutrient supplements [11–16], few studies have examined the impact of *macro*nutrient supplementation on limiting HIV disease progression or improving survival in adults in resource-constrained settings. A 2007 review, for example, found inconsistent and minimal improvements in weight or CD4+ lymphocyte response among HIV-infected individuals provided such an intervention [17]. Direct clinical impact has not been demonstrated, but food insecurity is a barrier to ART adherence and may increase HIV transmission [18–23]. Early evidence suggests that food supplementation programs can help to improve patient retention and ART adherence [24, 25], but the implication of these findings for survival, virologic response, and ART regimen durability is unknown. Nutritional supplementation has been successfully integrated into large ART programs in sub-Saharan Africa, and some funding agencies permit supplementation as a component of care [24, 26–28].

Integrating nutritional supplementation into large ART programs is expensive, but if the health care of clients is substantially improved, then the commitment of resources may be justified. Although there is strong theoretical grounding for its effectiveness, the benefits of macronutrient supplementation should be demonstrated at a population level to support implementation. To this end, we provide a review of the current evidence around this issue, with a focus on resource-constrained settings. We assess the effects of malnutrition on HIV disease progression, discuss potential etiologies for increased mortality among malnourished persons on ART, and evaluate macronutrient supplements readily available in the developing world. We highlight trials of food supplementation conducted in both the developed and developing world and conclude with recommendations for supplement selection and outcome measures for future clinical trials.

Protein-calorie malnutrition and HIV-associated weight loss

The prevalence of adult malnutrition in sub-Saharan Africa is difficult to estimate and varies with natural and man-made disasters, but an analysis of multiple demographic and nutrition surveys estimated that 10–20% of African women age 20–49 are malnourished (BMI <18.5 kg/m^2; similar data for men not available) [29]. Protein-calorie malnutrition (PCM), the result of the insufficient intake of both protein and energy, is a common form of malnutrition in areas characterized by food scarcity. Similar to AIDS, PCM is associated with suppression of the antigen-specific arms of the immune system and several generalized host defense mechanisms [30]. PCM is associated with reactivation of viral infections, reversal of the T-helper/suppressor ratio [31, 32], decreased T-cell primary antibody response and memory response [33], and atrophy of the lymph tissues [34, 35]. Peripheral lymphocyte and eosinophil counts may be reduced and natural killer cells show reduced activity [36]. As with HIV infection, PCM may also induce a generalized pro-inflammatory response, especially in the mucosal barriers, leading to increased susceptibility to environmental pathogens [37, 38]. Persons with PCM are more susceptible to opportunistic infections and suffer greater morbidity [39, 40].

The primary cause of weight loss in HIV-infected patients is thought to be anorexia caused by elevated interleukin-1, interleukin-6, and tumor necrosis factor α [41, 42]. Oral and gastrointestinal infections, and constitutional manifestations of advanced HIV disease (e.g. fatigue, fever, dyspnea), contribute to progressive disability and interfere with an individual's ability to ingest or obtain food [43]. After initiating ART, side effects to certain

antiretroviral drugs (e.g. nausea, insomnia) may be exacerbated if taken without food [21, 44]. and poor nutrition may potentiate drug toxicity [45–47].

While work capacity, muscle strength, and physical activity may be reduced in advanced HIV disease, the total daily energy expenditure may rise due to an increase in the resting metabolic rate (RMR). Most studies found an increase in RMR in HIV-infected persons of 10–30%, which was generally higher in the presence of secondary infections and correlated with increasing plasma viral load, though some reported no change [41, 48–54]. The increased RMR is caused in part by the metabolic expense of maintaining a pro-inflammatory state and an elevated rate of protein turnover [55, 56]. Additionally, elevated pro-inflammatory cytokines in untreated HIV infection prevent weight gain despite sufficient intake of protein [42].

Other conditions further contribute to malnutrition in advanced HIV disease. Infection by intestinal parasites and mycobacterium, decreased small bowel transit time, decreased carbohydrate absorption, bowel wall edema due to serum hypoalbuminemia, and abnormally high fecal fat excretion can lead to severe malabsorption [57]. The loss of gut-associated lymphoid tissue during the initial phase of HIV infection can cause lasting impairment in the integrity of the gastrointestinal epithelial mucosal barrier [58], and predispose towards bacterial translocation across the gut wall [59].

The optimum daily energy and protein intake to prevent HIV-associated weight loss is uncertain. A 2005 World Health Organization (WHO) review on macronutrients and HIV/AIDS recommended that daily energy intake should be increased by 10% in asymptomatic HIV infection or 20–50% during the convalescent period following opportunistic infections [60]. The report found no evidence to support increasing the proportion of protein in the diet beyond the recommended 12–15%.

Low body mass index and early mortality after ART initiation

A 10% or greater decrease from usual body weight, with concomitant chronic diarrhea or chronic weakness and fever, was an early AIDS-defining condition [62]. Weight loss has also been recognized as a significant prognostic factor since the beginning of the epidemic [63–66]. In resource-constrained settings, patients may present for evaluation after significant unmeasured weight loss and, the use of BMI in many ART program outcome analyses may ignore important factors in prognosis and potential response to treatment. A low BMI might be indicative of normal anthropometric variation, chronic inadequate food intake, or wasting associated with HIV and other infections. BMI is an imperfect marker of nutritional status, but studies in developed countries have shown that a low BMI is an independent predictor of mortality and morbidity in HIV-infected patients, even after the introduction of combination ART [67–70]. WHO uses BMI to grade nutritional status in the following manner: mild malnutrition (BMI = 17.00–18.49 kg/m^2), moderate malnutrition (BMI = 16.00–16.99 kg/m^2), and severe malnutrition (BMI <16.00 kg/m^2)[29].

Low BMI at ART initation is an independent predictor of early mortality in several analyses from sub-Saharan Africa. In Zambia, we found that patients starting ART with a BMI of <16.0 kg/m^2 had higher mortality in the first 90 days on therapy (adjusted hazard ratio [HR]: 2.4, 95%CI: 1.8–3.2) when compared to those above this BMI threshold [2]. In a cohort of over 1500 persons in rural Malawi, those initiating ART with a BMI ≤15.9 kg/m^2 had a 6-fold increased risk of death at three months compared to those with a BMI ≥18.5 kg/m^2 (adjusted HR: 6.0, 95%CI: 4.6–12.7), and those with a BMI between 16.0 and 16.9 kg/m^2 had more than a 2-fold increased risk (adjusted HR: 2.4, 95%CI: 1.7–6.3) [8]. Similar data were reported from Tanzania, where patients with a BMI <16.0 kg/m^2 at ART initiation had

a mortality rate double that of patients with a BMI ≥18.5 (adjusted HR: 2.1, 95%CI: 1.1–4.2) [9].

The causes of early mortality in patients with low BMI initiating ART are poorly understood. A higher burden of opportunistic infections may cause more rapid weight loss and increase the incidence of immune reconstitution inflammatory syndrome. Metabolic derangements related to rapid depletion of muscle mass may also be important. HIV-associated wasting, in comparison to starvation, preferentially depletes muscle over adipose tissue and reduces the muscle phosphate stores necessary to replenish serum phosphate. In patients with wasting and anorexia, a low serum phosphate may be adequate for the relatively low turn-over rate of metabolic intermediates (e.g. ATP and 2,3-DPG), but with increased food intake following ART initiation a precipitous decline can occur [20, 21, 72–75]. This phenomenon – termed "refeeding syndrome" – may be exaggerated in areas when staple foods contain a high carbohydrate to protein and fat ratio [76–78]. As a result of serum phosphate depletion, potassium, magnesium, and sodium homeostasis is disrupted, which may cause cardiac arrhythmias, seizures, coma, pulmonary edema, paralysis and respiratory arrest [79–81]. Further study to define pathophysiologic processes contributing to early mortality in these patients is needed.

Macronutrient supplementation in resource-adequate settings

There are few studies of macronutrient supplementation on HIV disease progression or survival in adults, and most had relatively short follow-up periods (e.g. 3–6 months). Table 1 summarizes the nine randomized controlled trials (RCTs) of macronutrient supplementation conducted in resource-adequate settings [82–90]. Three trials address the use of amino acid mixtures versus isocaloric or isonitrogenous nutritional placebos in HIV-infected persons. The amino acid mixtures were effective in increasing patient weight; however, there was no evidence of improved immunologic recovery or survival. Six RCTs compared the addition of a balanced oral supplement to a normal diet, with the goal of increasing total energy intake by 560–960 kcal/day. These studies did not include HIV-negative controls or account for baseline dietary adequacy, and all-cause or HIV-related mortality were not included as primary outcome measures.

These trials demonstrated an improvement in energy and protein intake when compared to placebo or no supplementation, but no uniform improvements in body weight, fat mass, or fat-free mass. Only one study reports a significant improvement in CD4+ lymphocyte count with supplementation [90]. All of the studies were conducted in resource-adequate settings where malnutrition is commonly the result of HIV-associated wasting or poor choice of foods. This is in stark contrast to resource-contained environments characterized by food scarcity or limited sources of protein. In addition, mean BMI across the studies were 19.6 kg/m^2 or higher, whereas data from sub-Saharan Africa suggests that severe malnutrition (i.e. BMI <16.0 kg/m^2) is associated with the greatest risk of early mortality on ART. In these studies, supplementation may have failed to show a benefit because the deleterious conditions associated with a low BMI were not present or were less pronounced; for example, immunosuppression related to PCM was less advanced, there was a lower burden of opportunistic infections, or metabolic abnormalities related to HIV-associated wasting were less severe.

Macronutrient supplementation in resource-constrained settings

The World Food Programme (WFP) and the Food and Agricultural Organization (FAO) of the United Nations have tailored interventions to address malnutrition and HIV in many of the most heavily affected countries in sub-Saharan Africa. Most of these programs deliver staple foods to areas of scarcity or agricultural training and assistance to promote local

production, in a community-level effort to prevent the development or arrest the progression of malnutrition. This “food first” approach is predicated on the observation that the prevalence and severity of a range of diseases are increased in poorly nourished populations. A distinction is necessary, however, between supplementary feeding, which is the provision of food rations (either local staples or specialized foods) to vulnerable or malnourished persons to supplement the local diet and provide balanced and/or adequate daily energy intake, versus therapeutic feeding, which aims for the nutritional rehabilitation of severely malnourished adults with specialized foods that are often energy and nutrient dense. Whether an intervention represents supplementary and therapeutic feeding may depend on the target population or the program intent, but some products may be more suitable to the latter.

The optimal composition of macronutrient supplementation for malnourished adults is still a matter of debate. As a replacement or an addition to local staple foods, three candidate supplements are commonly referenced: high-energy Ready-to-Use Therapeutic Foods (RUTF) [91], corn-soya blends [92], and fortified blended foods (FBF) [93]. RUTF is a type of highly nutrient-dense spread (HNDS), a food product high in energy and micronutrients in which all powdered ingredients are suspended in fat and do not require any preparation or the addition of water before ingestion. RUTF, like other HNDS, can be stored for long periods, do not require refrigeration, and can be individually packaged and used effectively in areas where hygiene conditions are not optimal. RUTF has been used successfully for community therapeutic care and nutritional rehabilitation in the pediatric population [94–96] and recommended by WHO for the management of severely malnourished children [97]. Corn-soya blends, also referred to as High-Energy Protein Supplements, are blended flours which have been used effectively in the past in both emergency and protracted food relief operations [98]. Corn-soya blends provide a higher calorie and protein content than many local carbohydrate-rich staple foods they are programmed to replace, but concerns have been raised regarding their suitability for the treatment of severe malnutrition given the low essential fatty acid and overall lipid content [99]. FBF are also blended flours designed to provide more comprehensive nutrition supplementation, and contain mixtures of cereals (typically corn or wheat), pulses, fats, vitamins and minerals. The WFP distributed almost 300,000 metric tons of FBF in 2006 [100]. Table 2 compares the nutritional content of these supplements and local staples.

RUTF has the advantage of higher calorie-to-weight and calorie-to-volume ratios than blended flours, which makes transporting a monthly ration easier [91, 93]. The standard packaging of blended flours in bulk adds uncertainty to the size of the daily ration consumed by the patient. Since patients with advanced HIV often rely on others for food preparation, there is greater likelihood that the ration will be shared [101]. The higher viscosity of RUTF allows for higher levels of vitamin and mineral supplementation without sedimentation during storage, and the physical structure of a spread (i.e. powder mixed into fat) limits exposure to air and prevents vitamin oxidation. The low water content (2% compared to 8–12% for flours) prevents soluble minerals from interacting with vitamins, and decreases bacterial and insect contamination [102]. *E. coli* introduced into supplementary spreads do not grow, while they grow exponentially in a liquid form [99]. RUTF, however, is not without its drawbacks. It is approximately three times more expensive to produce and requires more sophisticated processing facilities [103]. A recent qualitative study by Medicins Sans Frontiers found that some patients were unable to carry home more than a 2-week ration of RUTF (approximately 5.1 kg). Half of the patients were unable to consume the entire daily ration due to poor taste, dietary boredom, or HIV-related complications such as thrush [104].

Our review of the medical literature identified two randomized trials of nutritional supplementation for HIV-infected adults in sub-Saharan Africa (Table 3) [24, 105]. A study by Cantrell et al compared ART adherence among persons receiving WFP rations and persons enrolled in clinics not yet receiving food aid. Criteria for assistance were based on household food insecurity, not anthropometrics, and the mean patient BMI in the intervention and control group was 21.0 and 20.8 (women) and 19.6 and 19.7 (men), respectively. Patients in the intervention group were more likely to achieve 95% monthly ARV adherence than patients in the control group (RR 1.5; 95% CI 1.2 to 1.8), but there was no significant difference in weight gain, CD4+ cell response, or mortality. However, the study lacked sufficient power to detect small but potentially relevant weight change differences between groups (e.g. 1–2 kg).

A recent trial in urban Malawi randomized 491 adults initiating ART with a BMI <18.5 kg/m^2 to receive 1,360 kcal/day of CSB or Ready-to-Use Fortified Spread (RUFS), similar to RUTF, for 3.5 months. There was not a study arm without nutritional supplementation. After 3.5 months, patients receiving RUFS has a significantly greater increase in BMI (2.2 ±1.9 vs. 1.7 ± 1.6 kg/m^2) than those receiving RUFS, buts there were no significant differences in survival, HIV viral load, CD4 count change, or quality of life.

Future directions

The design of future macronutrient supplementation trials must consider a range of variables, including the proportion of daily calories to supply, the choice of supplement, duration of supplementation, program exit criteria, logistics, and the uncertainties of human behavior. A caloric target could be the WFP recommended minimum daily intake of 2100 kcal for adults, increased by an additional 30% (the upper limit of the estimated increase in RMR in advanced HIV infection) to 2,730 kcal/day [49, 106]. The proportion of calories supplied could be stratified by anthropometric criteria (e.g the grade of malnutrition). The selected product should match the available distribution network and processing capacity; account for potential intrafamilal sharing, climate effects and environmental conditions (e.g. lack of clean water); and should be culturally appropriate. Future trials of macronutrient supplementation should assess a broad range of short and long-term outcome measures to uncover potentially under-recognized prognostic indicators, as suggested in Table 4.

Conclusions

Further study of the treatment of malnutrition at ART initiation is critical to global policy and the treatment of HIV-infected persons in many areas of the developing world. Decisions of this magnitude must be informed by solid evidence, not speculation, but these critically important data do not yet exist. There is a need for a well designed and adequately powered trial of supplementation at ART initiation among HIV-infected adults with evidence of moderate to severe malnutrition. In addition, further studies of the pathophysiologic processes responsible for the observed rise in mortality and improved metrics to identify persons most in need of support are needed. The intersection of malnutrition and HIV infection affects millions of HIV-infected adults in sub-Saharan Africa and represents a critical uncertainty and a major challenge to the success of ART programs.

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Table 1

Randomized Controlled Trials of Macronutrient Supplementation in HIV-Infected Adults in the Developed World

Study	Location and population	Baseline BMI (kg/m^2)	Intervention	Major findings
Rabeneck *et al.* 1998 [82]	Harris County, Texas, USA 118 HIV-infected men, age >18 years, CD4+ lymphocyte count <500/mm^3, with <90% predicted weight-for-height ratio or >10% weight loss in prior 6 months, life expectancy >12 weeks, and, if on ART, no change in regimen over prior 8 weeks.	Experimental group: 21 ± 3.0 Control group: 21 ± 3.0	Experimental group: medium chain triglyceride formula (amount and composition not specified) and nutrition counseling (goal energy intake increase of 960 kcal/day). Control group: nutrition counseling alone (goal energy intake increase of 960 kcal/day). Treatment duration: 6 weeks	56% of experimental group and 50% of control group achieved 80% or more of the energy intake target. No significant differences in weight gain, FFM, hematologic parameters, CD4+ lymphocyte count, or albumin between groups.
Schwenk *et al.* 1999 [83]	Cologne, Germany 55 HIV-infected patients with >5% weight loss since HIV infection or >3% in the prior month.	Experimental group: 19.9 ± 2.1 Control group: 19.6 ± 2.3	Experimental group: 600 kcal/day mixture of oral supplements (liquid, semi liquid dessert, or maltodextrin-based fruit drink) and nutrition counseling. Control group: nutrition counseling alone (goal energy intake increase of 600 kcal/day). Treatment duration: 8 weeks	No significant difference in change in BCM (primary outcome critierion; 1.2 ± 5.0 2.2 ± 7.5%, p=0.73), weight (2.6 ± 5.2 vs. 2.7 ± 7.4%) or FFM (1.6 ± 4.5 vs. 3.8 ± 6.2%) between the experimental and control groups, respectively.
Shabert *et al.* 1999 [84]	Broward County, Florida, USA 26 HIV-infected patients with >5% weight loss since HIV infection or <90% standard creatinine/height index (reflecting loss of lean tissue).	Experimental group: 22 ±1.5 Control group: 23 ±1.3	Experimental group: 40 g/d of L-glutamine and antioxidants. Control group: isonitrogenous nutritional placebo. Treatment duration:12 weeks	Significant increase in body weight (2.2 vs. 0.3 kg, p=0.04) and BCM (1.8 vs. 0.4 kg, p=0.007) in experimental versus control group. CD4+ lymphocyte counts remained stable throughout the study (mean ± SD: 140 ± 115 and 206 ± 164 cells/mm^3) in the experimental and control groups, respectively.
Berneis *et al.* 2000 [85]	Basel, Switzerland 18 HIV-infected patients with >5% weight loss in prior 6 months, a BMI <21 kg/m^2 or a CD4+ lymphocyte count <500/mm^3.	Not reported	Experimental group: 2510 kJ/day of supplement (26 g whey protein, 88 g carbohydrates, 17 g fat as corn oil, trace elements and vitamins) and nutrition counseling. Control group: nutrition counseling alone (no intake target specified). Treatment duration: 12 weeks	No significant change in weight in either group. Significant increase in lean body mass percentage in the experimental group (84% ± 2 to 86% ± 2, p<0.05) and decrease in fat mass (17% ± 2 to 14% ± 2, p<0.05). No changes in the control group. Significant decrease in leucine oxidation (surrogate for whole body protein catabolism) in the experimental group (0.33 ± 0.02 to 0.26 ± 0.02 mmol/kg/min, p<0.05), no change in the control group. No significant change in non-oxidative leucine disappearance (suggesting no increase in whole body protein synthesis) in either group. No significant change in CD4+ lymphocyte count in either group.
Clark *et al.* 2000 [86]	Nassau County, USA	Not reported	Experimental group: 200 kcal/day of amino acid mixture containing 14g	Significant gain in body weight (3.0 vs. 0.4 kg, p=0.009) and lean body mass (2.55 ± 0.75 vs.

Study	Location and population	Baseline BMI (kg/m^2)	Intervention	Major findings
	68 HIV-infected patients with >5% weight loss over prior 3 months.		arginine, 14g glutamine and 3g β-hydroxy-β-methylbutyrate. Control group: 200 kcal/day of maltodextrin. Treatment duration: 8 weeks	−0.70 ± 0.69 kg, p=0.003) in the experimental group compared to control group. No significant improvement in CD4+ lymphocyte count or HIV viral load in either group.
Keithley *et al.* 2002 [87]	Multicenter, USA 90 HIV-infected patients, age 18–65 years, CD4+ lymphocyte count between 275 and 550/mm^3, and >1 month of ART.	Ensure Plus group: 24 ± 4.0 Advera group: 25 ± 5.0 Control group: 26 ± 6.0	Experimental group: Ensure Plus oral formula, 1–2 cans/day (each can: 355 kcal; 53% carbohydrate, 15% protein, 32% fat) and nutrition counseling. Experimental group: Advera oral formula, 1–2 cans/day (each can: 303 kcal; 65% carbohydrate, 19% protein, 16% fat) and nutrition counseling. Control group: nutrition counseling alone (no intake target specified). Treatment duration: 12 months	No significant differences among the 3 groups in body weight, BCM, fat mass, daily caloric intake, and serum albumin at any of the study visits. CD4+ lymphocyte count and percentage did not differ significantly at any time point among the 3 groups.
De Luis *et al.* 2003 [88]	Location not reported 70 HIV-infected patients age 20–60 years with >5% weight loss in prior 6 months.	Not reported	Experimental group: Ensure oral formula, 3329kJ/day (54% carbohydrate, 32% protein, 14% fat) and nutrition counseling. Control group: nutrition counseling alone (no intake target specified). Treatment duration: 12 weeks	Significant increase in total weight (2.75%, p<0.05) and fat mass (10.8%, p<0.05) in the experimental group, no change in the control group. FFM unchanged in both groups. CD4+ lymphocyte count and HIV viral load unchanged in both groups.
Karsegard *et al.* 2004 [89]	Geneva, Switzerland 46 HIV-infected patients, age >18 years with 5 to 15% weight loss since HIV infection, CD4+ lymphocyte count >150/mm3, body fat mass >5% of body weight, and regular food intake.	Experimental group: 20 ± 2.4 Control group: 21 ± 3.0	Experimental group:10 g/d ornithine alpha-ketoglutarate (OKG). Control group: isonitrogenous placebo (milk proteins). Treatment duration: 12 weeks	Significant increase in BMI (p=0.02 versus baseline) and triceps skinfold thickness (p<0.01 versus baseline) in both groups, no significant difference between groups. Muscle area, FFM, and body fat mass did not significantly change during the study course in either group. CD4+ lymphocyte count and HIV viral load unchanged in both groups. Higher incidence of gastrointestinal disturbance with OKG.
Sattler *et al.* 2008 [90]	Multicenter, USA 59 HIV-infected outpatients with >3% weight loss since HIV infection, but no change in weight >3% over prior 2 months. ART not required.	Experimental group: 20.7 ± 2.3 Control group: 21.1 ± 2.8	Experimental group: 560 kcal/day of a high-protein supplement (40 g whey protein, 20.5 g carbohydrate, and 4.0 g fat per 280-kcal serving). Control group: 560 kcal/day of control supplement without the added protein (0.6 g casein, 60.8 g carbohydrate [high-maltose rice syrup solids], and 4.0 g fat per 280-kcal serving). Treatment duration: 12 weeks	No significant increase in weight (0.8 ± 2.4 and 0.7 ± 2.4 kg) and lean body mass (0.3 ± 1.4 and 0.3 ± 1.5 kg) in the experimental and control groups, respectively. Fasting triacylglycerol decreased in experimental group(16 ± 62 mg/dL) and increased in control group (39 ± 98 mg/dL) at week 12 (p=0.03). CD4+ lymphocyte count increased in experimental group (31 ± 84 cells/mm^3) and decreased in control group (−5 ± 124 cells/mm^3, p=0.03).

ART = antiretroviral therapy; BCM = body cell mass; BMI = body mass index; FFM = fat-free mass. Significance = p<0.05.

Table 2

Comparison of the three major types of macronutrient supplements proposed for use in sub-Saharan Africa

	Ready-to-Use Therapeutic Food [91]	Corn-Soya Blend [92]	Fortified Blended Foods [93]		Common sub-Saharan African Staple Foods		
			Corn-soya	Wheat-soya	Cornmeal (yellow) [77]	Rice (white) [77]	Green Banana (*matooke*, cooked) [78]
Grams:	100	100	100	100	100	100	100
Calories:	557	376	380	370	366	365	351
Protein grams (% kcal):	14 (10%)	17 (18%)	18 (19%)	20 (21%)	8.5 (9%)	7.1 (8%)	5.0 (6%)
Fat grams (% kcal):	35 (59%)	7.0 (17%)	6.0 (14%)	6.0 (15%)	1.7 (4%)	0.7 (2%)	0.6 (2%)
Carbohydrate % kcal:	31%	65%	67%	64%	87%	90%	92%
Packaging:	Jar or sachet	Sack	Sack or sachet		Sack	Sack	Plant
Indication:	Moderate to severe malnutrition	Mild to moderate malnutrition	Mild to moderate malnutrition		Staple food		
Preparation:	None	Hydration and heating	Hydration and heating		Hydration and heating		
Ingredients:	Plumpy'Nut: vegetable fat, peanut paste, skimmed milk powder, whey powder, malto-dextrin, sugar, mineral and vitamin complex.	Corn and soy blend flour, soybean oil, mineral and vitamin complex.	Cereals (maize, sorghum, millet, wheat), chickpeas or soybeans, oilseeds or vegetable oil, sugar, mineral and vitamin complex.				

Table 3

Trials of Macronutrient Supplementation in HIV-Infected Adults in Resource-Constrained Settings

Study	Location and population	Baseline BMI (kg/m^2)	Intervention	Major findings
Cantrell *et al*. 2008 [24]	Zambia 636 food insecure HIV-infected patients initiating ART and meeting local criteria for home-based food support	Experimental group: mean BMI 19.6 (males) and 21.0 (females) Control group: mean BMI 19.7 (males) and 20.8 (females)	Experimental group: 442 patients in 4 clinics received an individual ration of micronutrient-fortified CSB and vegetable oil (970 kcal/day) or, if the patient was a primary income earner, a family ration of CSB, oil, maize meal and beans (1571 kcal/day). Control group: 194 patients enrolled in 4 control clinics received no intervention. Duration: 6–12 months intervention (depending upon interim assessment), total of 12 months follow-up.	70% of patients in the experimental group achieved a medication possession ratio of 95% (indicative of 95% monthly ART adherence) or greater versus 48% in control group (RR 1.5; 95% CI 1.2 to 1.8). No significant differences between experimental and control groups in weight gain at 6 months (5.4 vs. 5.1 kg, p=0.68) or 12 months (6.3 vs. 5.4 kg, p=0.34), or CD4+ lymphocyte response at 6 months (154 vs. 171 cells/mm^3, p=0.50) or 12 months (182 vs. 180 cells/mm^3, p=0.96).
Ndekha *et al*. 2009 [105]	Malawi 491 HIV-infected adults with BMI <18.5 kg/m^2 initiating ART.	Mean BMI 16.5 in both groups	Experimental group: 245 patients, 260 g/day (1,360 kcal/day) of peanut-based ready-to-use fortified spread (RUFS). Experimental group: 246 patients, 374 g/day (1,360 kcal/day) of corn-soya blend (CSB). Control group: none. Duration: 3.5 months	After 3.5 months, patients receiving RUFS, as compared to CSB, had a greater increase in BMI (2.2 ±1.9 vs. 1.7 ± 1.6 kg/m^2 [difference 0.5 kg/m^2 95% CI 0.2, 0.8]) and fat-free mass (2.9 ± 3.2 vs. 2.2 ±3.0 kg [difference 0.7 kg 95% CI 0.2, 1.2]). No significant difference in mortality, immune reconstitution, HIV suppression, adherence to ART, or quality of life was observed between the groups.

ART = antiretroviral therapy; BMI = body mass index. Significance = p<0.05.

Table 4

Proposed outcome measures for future trials of macronutrient supplementation in HIV-infected patients

Parameter	Measure
Mortality	All cause HIV-related
Anthropometric	Weight, body mass index, mid-upper arm circumference, waist & hip circumferences, triceps skinfold thickness
Body composition	Bioelectrical impedance measurement of body cell mass, fat-free mass, fat mass, total body water
Physical findings	Peripheral and pulmonary edema CNS abnormalities Mouth & tongue changes (e.g ulcerations, thrush) Abnormal fat distribution (lipodystrophy)
Symptoms	Constitutional, gastrointestinal, respiratory, cardiovascular, neurologic, psychiatric (i.e. depression)
Functional status	Quality of life Economic productivity
Immunologic	CD4+ lymphocyte count Total lymphocyte count, T-cell helper/suppressor ratio, T-cell response Peripheral eosinophil count Time to ART initiation
Metabolic	Resting metabolic rate
Response to ART	Time to viral suppression Durability of viral suppression “suppressed survival” Incidence of new opportunistic infections
ART tolerance and adherence	Incidence of drug toxicities and side effects Adherence (pill counts and days late to pharmacy) Serum drug levels Incidence of regimen change due to drug intolerance
Dietary	Dietary intake/recall, household food security
Serum markers:	Nutrition status: hemoglobin, albumin,* pre-albumin,* ferritin,* vitamin B_{12}, folic acid, 25-hydroxyvitamin D, vitamin A (retinol) Metabolic processes: phosphate, potassium, magnesium, sodium, serum lipids, hepatic function, fasting insulin Systemic inflammation: C-reactive protein, α-1 acid glycoprotein

*Acute phase reactants that may be altered as a result of a pro-inflammatory state.