

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

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Access to antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection has expanded rapidly throughout sub-Saharan Africa, but malnutrition and food insecurity have emerged as major barriers to the success of ART programs. Protein-calorie malnutrition (a common form of malnutrition 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 after the start of ART as an independent predictor of early mortality, but the causes of a low body mass index are multifactorial (eg, normal anthropometric variation, chronic inadequate food intake, and/or wasting associated with HIV infection and other infectious diseases). Although there is much information on 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, we report on clinical trials in resource-adequate and resource-constrained settings, and we highlight priority areas for future research.

Since 2003, access to antiretroviral therapy (ART) for human immunodeficiency virus (HIV) infection has expanded rapidly throughout sub-Saharan Africa, and >2.1 million of the estimated 7 million people in need of treatment now receive treatment [1]. Favorable clinical outcomes have been reported from a variety of settings [2–7], but the follow-up periods in most analyses were short; therefore, further data are needed on the clinical outcomes of patients with longer follow-up periods. The geographic overlap of high HIV prevalence, malnutrition, and chronic food insecurity in

much of sub-Saharan Africa has highlighted the need for more comprehensive approaches to health care. There is increasing evidence that a low body mass index (BMI) is a powerful and independent predictor of early mortality after the start of ART [2, 8, 9]. The role of malnutrition in HIV disease progression and poor clinical outcomes is significant and likely underreported [10].

In contrast to the substantial research on micronutrient supplements [11–16], few studies have examined the impact of macronutrient 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 who were given macronutrient supplements as an intervention [17]. Direct clinical impact has not been demonstrated, but food insecurity is a barrier to adherence to ART and may increase

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transmission of HIV [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, theoretically, macronutrient supplementation is considered to be effective, 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 with 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 factors, but an analysis of multiple demographic and nutrition surveys estimated that 10%–20% of African women 20–49 years of age are malnourished (mean BMI, <18.5 kg/m²; similar data for African men not available) [29]. Protein-calorie malnutrition, 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, protein-calorie malnutrition is associated with suppression of the antigen-specific arms of the immune system and several generalized host defense mechanisms [30]. Protein-calorie malnutrition is associated with reactivation of viral infections, reversal of the ratio of T cell helpers to T cell suppressors [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, protein-calorie malnutrition may also induce a generalized proinflammatory response, especially in the mucosal barriers, leading to increased susceptibility to environmental pathogens [37, 38]. Persons with protein-calorie malnutrition 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 (eg, fatigue, fever, and dyspnea), contribute to progressive disability and interfere with an individual's ability to ingest or obtain food [43]. After initiating ART, the adverse effects associated with the use of certain antiretroviral drugs (eg, nausea and insomnia) may be exacerbated if these drugs are taken without food [21, 44], and poor nutrition may potentiate drug toxicity [45–47].

Although work capacity, muscle strength, and physical activity may be reduced in individuals with advanced HIV disease, the total daily energy expenditure may increase because of an increase in the resting metabolic rate. Most studies found an increase in the resting metabolic rate of 10%–30% among HIV-infected persons; the rate was generally higher among patients with secondary infections and correlated with an increasing plasma viral load, although some studies reported no change in the rate among these types of patients [41, 48–54]. An increased resting metabolic rate is caused in part by the metabolic expense of maintaining a proinflammatory state and an elevated rate of protein turnover [55, 56]. In addition, the elevated proinflammatory cytokine levels in patients with untreated HIV infection prevent them from gaining weight, despite sufficient intake of protein [42].

Other conditions further contribute to the malnutrition of individuals with 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 may predispose toward 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 review on macronutrients and HIV/AIDS recommended that daily energy intake should be increased by 10% for patients with asymptomatic HIV infection and by 20%–50% for patients recovering from opportunistic infections [60]. The review found no evidence to support increasing the proportion of protein in the diet beyond the recommended 12%–15%.

LOW BMI AND EARLY MORTALITY AFTER START OF ART

A $\geq 10\%$ decrease in usual body weight, with concomitant chronic diarrhea or chronic weakness and fever, was an early AIDS-defining condition [61]. Weight loss has also been recognized as a significant prognostic factor since the beginning

of the epidemic [62–65]. 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 the 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 [66–69]. The World Health Organization uses BMI to grade nutritional status in the following manner: mild malnutrition (BMI, 17.00–18.49 kg/m²), moderate malnutrition (BMI, 16.00–16.99 kg/m²), and severe malnutrition (BMI, <16.00 kg/m²) [29].

A low BMI at the start of ART 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/m² had a higher mortality rate in the first 90 days of therapy (adjusted hazard ratio [HR], 2.4; 95% confidence interval [CI], 1.8–3.2), compared with patients starting ART with a BMI of >16.0 kg/m² [2]. In a cohort of >1500 persons in rural Malawi, those initiating ART with a BMI of <15.9 kg/m² had a 6-fold increased risk of death at 3 months, compared with those with a BMI of >18.5 kg/m² (adjusted HR, 6.0; 95% CI, 4.6–12.7), and those with a BMI of 16.0–16.9 kg/m² 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 of <16.0 kg/m² at the start of ART had a mortality rate double that of patients with a BMI of >18.5 kg/m² (adjusted HR, 2.1; 95% CI, 1.1–4.2) [9].

The causes of early mortality among patients with a low BMI at the start of 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 play an important role. HIV-associated wasting, compared with starvation, preferentially depletes muscle over adipose tissue and reduces the muscle phosphate stores necessary to replenish serum phosphate. For patients with wasting and anorexia, a low serum phosphate level may be adequate for the relatively low turnover rate of metabolic intermediates (eg, adenosine triphosphate and 2,3-diphosphoglycerate), but with increased food intake after initiation of ART, a precipitous decrease can occur [20, 21, 70–73]. This phenomenon—termed refeeding syndrome—may be exaggerated in areas where staple foods contain a high ratio of carbohydrates to protein and fat [74–76]. As a result of serum phosphate depletion, the homeostasis of potassium, magnesium, and sodium is disrupted, which may cause cardiac arrhythmia, seizure, coma, pulmonary

edema, paralysis, and respiratory arrest [77–79]. Further study to define pathophysiologic processes contributing to early mortality among these patients is needed.

MACRONUTRIENT SUPPLEMENTATION IN RESOURCE-ADEQUATE SETTINGS

There are few studies of macronutrient supplementation that analyzed HIV disease progression among adults, and most of those that did had relatively short follow-up periods (eg, 3–6 months). Table 1 summarizes the 9 randomized controlled trials of macronutrient supplementation conducted in resource-adequate settings [80–88]. Three of the 9 randomized controlled trials addressed the use of amino acid mixtures versus isocaloric or isonitrogenous nutritional placebos for 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 of the 9 randomized controlled trials 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 for patients given macronutrient supplements, compared with patients given placebos or no supplements, but no uniform improvements in body weight, fat mass, or fat-free mass were found. Only 1 of the 9 randomized controlled trials reported a significant improvement in CD4⁺ lymphocyte count with supplementation [88]. 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-constrained environments, which are characterized by food scarcity or limited sources of protein. In addition, the minimum mean BMI across the studies was ≥ 19.6 kg/m², whereas data from sub-Saharan Africa suggests that severe malnutrition (ie, a BMI of <16.0 kg/m²) 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 protein-calorie malnutrition 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 and the Food and Agricultural Organization of the United Nations have tailored interventions to address malnutrition and HIV in many of the most heavily

Table 1. Summary of 9 Randomized Controlled Trials of Macronutrient Supplementation for Adults with Human Immunodeficiency Virus (HIV) in the Developed World

Study	Location	Study population	Mean \pm SD baseline BMI, kg/m ²	Intervention	Duration of treatment	Major findings ^a
Rabeneck et al [80]	Harris County, TX	118 HIV-infected men >18 years of age with CD4 ⁺ lymphocyte count <500 cells/mm ³ , with <90% predicted weight-to-height ratio or >10% weight loss in prior 6 months, life expectancy >12 weeks, and, if on ART, no change in regimen during prior 8 weeks	Experimental group: 21 \pm 3.0; control group: 21 \pm 3.0	Experimental group: medium chain triglyceride formula (amount and composition not specified) and nutrition counseling (with goal of energy intake increase of 960 kcal/day); control group: nutrition counseling alone (with goal of energy intake increase of 960 kcal/day)	6 weeks	56% of experimental group and 50% of control group achieved \geq 80% of the energy intake target; no significant differences in weight gain, FFM, hematologic parameters, CD4 ⁺ lymphocyte count, or albumin between groups
Schwenk et al [81]	Cologne, Germany	55 HIV-infected patients with >5% weight loss since HIV infection or >3% during the prior month	Experimental group: 19.9 \pm 2.1; control group: 19.6 \pm 2.3	Experimental group: 600 kcal/day mixture of oral supplements (liquid, semiliquid dessert, or maltodextrin-based fruit drink) and nutrition counseling; control group: nutrition counseling alone (with goal of energy intake increase of 600 kcal/day)	8 weeks	No significant difference in percentage change in BCM (a primary outcome criterion: 1.2% \pm 5.0% vs. 2.2% \pm 7.5%; $P = .73$), weight (2.6% \pm 5.2% vs. 2.7% \pm 7.4%) or FFM (1.6% \pm 4.5% vs. 3.8% \pm 6.2%) between the experimental and control groups, respectively.
Shabert et al [82]	Broward County, FL	26 HIV-infected patients with >5% weight loss since HIV infection or <90% standard creatinine-to-height index (reflecting loss of lean tissue)	Experimental group: 22 \pm 1.5; control group: 23 \pm 1.3	Experimental group: 40 g/d of L-glutamine and antioxidants; control group: isonitrogenous nutritional placebo	12 weeks	Significant increase in body weight (2.2 vs. 0.3 kg; $P = .04$) and BCM (1.8 vs. 0.4 kg; $P = .007$) in experimental group, compared with control group; CD4 ⁺ lymphocyte counts remained stable throughout the study (140 \pm 115 and 206 \pm 164 cells/mm ³ for experimental and control groups, respectively)
Berneis et al [83]	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 <900 cells/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)	12 weeks	No significant change in weight in either group. Significant percentage increase in lean body mass (from 84% \pm 2% to 86% \pm 2%; $P < .05$) and decrease in fat mass (from 17% \pm 2% to 14% \pm 2%; $P < .05$) in the experimental group; no changes in the control group. Significant decrease in leucine oxidation (surrogate for whole body protein catabolism) in the experimental group (from 0.33 \pm 0.02 to 0.26 \pm 0.02 mmol/kg/min; $P < .05$); no change in the control group. No significant change in nonoxidative 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 [84]	Nassau County, NY	68 HIV-infected patients with >5% weight loss during prior 3 months	Not reported	Experimental group: 200 kcal/day of amino acid mixture containing 14 g arginine, 14 g glutamine, and 3 g β -hydroxy- β -methylbutyrate; control group: 200 kcal/day of maltodextrin	8 weeks	Significant gain in body weight (3.0 vs. 0.4 kg; $P = .009$) and lean body mass (2.55 \pm 0.75 vs. -0.70 \pm 0.69 kg; $P = .003$) in the experimental group, compared with control group. No significant improvement in CD4 ⁺ lymphocyte count or HIV viral load in either group.

Keithley et al [85]	Multiple US medical centers	90 HIV-infected patients 18–65 years of age with CD4 ⁺ lymphocyte counts of 275–550 cells/mm ³ and >1 month of ART	Ensure Plus (Abbott) group: 24 ± 4.0; Advera (Ross Laboratories) group: 25 ± 5.0; control group: 26 ± 6.0	Ensure plus group: Ensure Plus oral formula, 1–2 cans/day (each can: 355 kcal; 53% carbohydrate, 15% protein, and 32% fat) and nutrition counseling. Advera group: Advera oral formula, 1–2 cans/day (each can: 303 kcal; 65% carbohydrate, 19% protein, and 16% fat) and nutrition counseling. Control group: nutrition counseling alone (no intake target specified).	12 months	No significant differences among the 3 groups in body weight, BCM, fat mass, daily caloric intake, or serum albumin level 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 [86]	Not reported	70 HIV-infected patients 20–60 years of age with >5% weight loss during prior 6 months	Not reported	Experimental group: Ensure oral formula, 3329 kJ/day (64% carbohydrate, 32% protein, and 14% fat) and nutrition counseling; control group: nutrition counseling alone (no intake target specified)	12 weeks	Significant increase in total weight (2.75%, <i>P</i> < .05) and fat mass (10.8%; <i>P</i> < .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 [87]	Geneva, Switzerland	46 HIV-infected patients >18 years of age with 5%–15% weight loss since HIV infection, CD4 ⁺ lymphocyte count >150 cells/mm ³ , 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 OKG; control group: isonitrogenous placebo (milk proteins)	12 weeks	Significant increase in BMI (<i>P</i> = .02 vs. baseline) and triceps skinfold thickness (<i>P</i> < .01 vs. baseline) in both groups; no significant difference between groups. Muscle area, FFM, and body fat mass did not significantly change during the course of study in either group. CD4 ⁺ lymphocyte count and HIV viral load unchanged in both groups. Higher incidence of gastrointestinal disturbance with OKG.
Sattler et al [88]	Multiple US medical centers	59 HIV-infected outpatients with <3% weight loss since HIV infection but no change in weight >3% during 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).	12 weeks	No significant increase in weight (0.8 ± 2.4 and 0.7 ± 2.4 kg) or 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 (<i>P</i> = .03). CD4 ⁺ lymphocyte count increased in experimental group (31 ± 84 cells/mm ³) and decreased in control group (–5 ± 124 cells/mm ³ ; <i>P</i> = .03).

NOTE. A *P* value of <.05 was considered to be statistically significant. ART, antiretroviral therapy; BCM, body cell mass; BMI, body mass index; FFM, fat-free mass; OKG, ornithine α -ketoglutarate; SD, standard deviation.
^a Some of the values are expressed as mean values (\pm SD).

Table 2. Comparison of the 3 Major Types of Macronutrient Supplements Proposed for Use in Sub-Saharan Africa

Parameter	Ready-to-use therapeutic food [89]		Fortified blended foods [91]			Common sub-Saharan African staple foods		
	Green banana (ma- tooke, cooked) [76]	Green banana (ma- tooke, cooked) [76]	Corn-soya blend [90]	Corn soya	Wheat soya	Cornmeal (yellow) [75]	Rice (white) [75]	Green banana (ma- tooke, cooked) [76]
Grams	100	100	100	100	100	100	100	100
Calories	557	376	376	380	370	366	365	351
Grams of protein (% kcal)	14 (10)	17 (18)	18 (19)	18 (19)	20 (21)	8.5 (9)	7.1 (8)	5.0 (6)
Grams of fat (% total calories)	35 (59)	7.0 (17)	6.0 (14)	6.0 (14)	6.0 (15)	1.7 (4)	0.7 (2)	0.6 (2)
Carbohydrate, % kcal	31	65	67	67	64	87	90	92
Packaging	Jar or sachet	Sack	Sack or sachet	Sack or sachet	Sack or sachet	Sack	Sack	Plant
Indication	Moderate to severe malnutrition	Mild to moderate malnutrition	Mild to moderate malnutrition	Mild to moderate malnutrition	Mild to moderate malnutrition	Staple food	Staple food	Staple food
Preparation	None	Hydration and heating	Hydration and heating	Hydration and heating	Hydration and heating	Hydration and heating	Hydration and heating	Hydration and heating
Ingredients	Vegetable fat, peanut paste, skimmed milk powder, whey powder, maltodextrin, sugar, and mineral and vita- min complex ^a	Corn and soy blend flour, soy- bean oil, mineral and vita- min complex	Cereals, ^b chickpeas or soy- beans, oil seeds or vegeta- ble oil, sugar, and mineral and vitamin complex	Cereals, ^b chickpeas or soy- beans, oil seeds or vegeta- ble oil, sugar, and mineral and vitamin complex	Cereals, ^b chickpeas or soy- beans, oil seeds or vegeta- ble oil, sugar, and mineral and vitamin complex	Hydration and heating	Hydration and heating	Hydration and heating

^a PlumPyNut.

^b Maize, sorghum, millet, and wheat.

Table 3. Trials of Macronutrient Supplementation for Adults with Human Immunodeficiency Virus (HIV) in Resource-Constrained Settings

Study	Location	Study population	Mean baseline BMI, kg/m ²	Intervention	Duration of treatment	Major findings ^a
Cantrell et al [24]	Zambia	636 food-insecure HIV-infected patients starting ART and meeting local criteria for home-based food support	Experimental group: 19.6 (males) and 21.0 (females); control group: 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	6–12 months ^b	70% of patients in the experimental group achieved a medication possession ratio of 95% (indicative of 95% monthly ART adherence) or greater, compared with 48% of patients in control group (RR, 1.5; 95% CI, 1.2–1.8). No significant differences between experimental and control groups in weight gain at 6 months (5.4 vs. 5.1 kg; $P = .68$) or 12 months (6.3 vs. 5.4 kg; $P = .34$), or CD4 ⁺ lymphocyte response at 6 months (154 vs. 171 cells/mm ³ ; $P = .50$) or 12 months (182 vs. 180 cells/mm ³ ; $P = .96$).
Ndekha et al [103]	Malawi	491 HIV-infected adults with a BMI of <18.5 kg/m ² at the start of ART	16.5 for both experimental and control groups	Experimental group: 245 patients received 260 g/day (1360 kcal/day) of peanut-based RUFs, and 246 patients received 374 g/day (1360 kcal/day) of CSB; control group received nothing.	3.5 months	After 3.5 months, patients receiving RUFs, as compared with patients receiving 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 kg/m ²]) and fat-free mass (2.9 ± 3.2 vs. 2.2 ± 3.0 kg [difference, 0.7 kg; 95% CI, 0.2–1.2 kg]). No significant difference in mortality, immune reconstitution, HIV suppression, adherence to ART, or quality of life was observed between the groups.

NOTE. A P value of <.05 was considered to be statistically significant. ART, antiretroviral therapy; BMI, body mass index; CI, confidence interval; CSB, corn-soya blend; RR, relative risk; RUFs, ready-to-use fortified spread.

^a Some of the values are expressed as mean values (± standard deviation).

^b Depending on interim assessment; total of 12 months of follow-up.

Table 4. Proposed Outcome Measures for Future Trials of Macronutrient Supplementation for Patients with Human Immunodeficiency Virus (HIV) Infection

Parameter	Measure
Mortality	All cause; related to HIV
Anthropometric	Weight, BMI, mid-upper arm circumference, waist and 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 and tongue changes (eg, ulcerations, thrush); abnormal fat distribution (lipodystrophy)
Symptoms	Constitutional, gastrointestinal, respiratory, cardiovascular, neurologic, psychiatric (ie, depression)
Functional status	Quality of life; economic productivity
Immunologic	CD4 ⁺ lymphocyte count; total lymphocyte count, T cell helper to T cell 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 (ie, "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 or recall, household food security
Serum markers	Nutrition status: hemoglobin, albumin, ^a prealbumin, ^a ferritin, ^a 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, ^a α-1 acid glycoprotein ^a

NOTE. ART, antiretroviral therapy; BMI, body mass index; CNS, central nervous system.

^a Acute phase reactant that may be altered as a result of a proinflammatory state.

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. However, a distinction should be made 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, and therapeutic feeding, which aims for the nutritional rehabilitation of severely malnourished adults with specialized foods that are often high in energy and nutrients. Whether an intervention represents supplementary or therapeutic feeding may depend on the target population or the intent of the program, 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, 3 candidate supplements are commonly referenced: high-energy ready-to-use therapeutic foods (RUTFs) [89], corn-soya blends [90], and fortified blended foods [91]. RUTF is a type of highly nutrient-dense spread, 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. RUTFs, like other highly nutrient-dense spreads, can be stored for long periods, do not require refrig-

eration, 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 [92–94] and has been recommended by the World Health Organization for the management of severely malnourished children [95]. Corn-soya blends, also referred to as high-energy protein supplements, are blended flours that have been used effectively in the past in both emergency and protracted food relief operations [96]. Corn-soya blends provide a higher calorie and protein content than do many of the local carbohydrate-rich staple foods that they are programmed to replace, but concerns have been raised regarding their suitability for the treatment of severe malnutrition because of their low essential fatty acid and overall lipid content [97]. Fortified blended foods are blended flours designed to provide more comprehensive nutrition supplementation and contain mixtures of cereals (typically corn or wheat), pulses, fats, vitamins and minerals. The World Food Programme distributed ~300,000 metric tons of fortified blended foods in 2006 [98]. 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 do blended flours, which makes transporting a monthly ration easier [89, 91]. The standard packaging of blended flours in bulk adds uncertainty to the size of the daily ration consumed by the patient. Because patients with advanced HIV infection often rely on others for food preparation, there is greater likelihood that the ration will be shared [99]. 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 (ie, powder mixed into fat) limits exposure to air and prevents vitamin oxidation. The low water content (2%, compared with 8%–12% for flours) prevents soluble minerals from interacting with vitamins, and decreases the likelihood of bacterial and/or insect contamination [100]. Strains of *Escherichia coli* introduced into supplementary spreads do not grow, whereas they grow exponentially in a liquid form [97]. RUTF, however, is not without its drawbacks. It is ~3 times more expensive to produce and requires more sophisticated processing facilities [101]. 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 (~5.1 kg). Half of the patients were unable to consume the entire daily ration because of the poor taste, dietary boredom, or HIV-related complications such as thrush [102].

Our review of the medical literature identified 2 randomized trials of nutritional supplementation for HIV-infected adults in sub-Saharan Africa (table 3) [24, 103]. A study by Cantrell et al [24] compared ART adherence among persons receiving rations from the World Food Programme with persons enrolled in clinics not yet receiving food aid. Criteria for assistance were based on household food insecurity, not anthropometrics, and the mean BMI was 21.0 for women and 19.6 for men in the intervention group and 20.8 for women and 19.7 for men in the control group. Patients in the intervention group were more likely to achieve 95% monthly ART adherence than were patients in the control group (relative risk, 1.5; 95% CI, 1.2–1.8), 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 (eg, 1–2 kg).

A recent trial in urban Malawi randomized 491 adults who started ART with a BMI of <18.5 kg/m² to receive 1360 kcal/day of corn-soya blend or ready-to-use fortified spread, similar to RUTF, for 3.5 months [103]. There was not a study arm without nutritional supplementation. After 3.5 months, patients receiving ready-to-use fortified spread had a significantly greater increase in BMI (\pm standard deviation) (2.2 ± 1.9 kg/m²) than did those receiving RUTF (1.7 ± 1.6 kg/m²), but 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, the duration of supplementation, program exit criteria, logistics, and the uncertainties of human behavior. A caloric target could be the minimum daily intake of 2100 kcal for adults, recommended by the

World Food Programme, increased by an additional 30% (the upper limit of the estimated increase in the resting metabolic rate for patients with advanced HIV infection) to 2730 kcal/day [49, 104]. The proportion of calories supplied could be stratified by anthropometric criteria (eg, the grade of malnutrition). The selected product should match the available distribution network and processing capacity; should account for potential intrafamilial sharing, climate effects, and environmental conditions (eg, 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 underrecognized prognostic indicators, as suggested in table 4.

CONCLUSIONS

Further study of the treatment of malnutrition at the start of ART is critical to the formulation of 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 the start of ART among HIV-infected adults with evidence of moderate to severe malnutrition. In addition, further studies are needed on the pathophysiologic processes responsible for the observed increase in mortality and on improving metrics to identify persons most in need of support. 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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