# Nutrition and disease progression pre–highly active antiretroviral therapy (HAART) and post-HAART: can good nutrition delay time to HAART and affect response to HAART?[1–4]

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**ABSTRACT**

Several studies have investigated a variety of nutritional supplementation interventions in adults with HIV. In this narrative review, we summarize the evidence from 31 clinical trials that explore clinical benefits of macronutrient and micronutrient supplementation in this population while attempting to answer the question of whether good nutrition can delay the time to highly active antiretroviral therapy (HAART) initiation and response. We focused on trials published in English between 1990 and 2010 that reported on CD4 count, viral load, and disease progression or survival. Among 9 macronutrient and 22 micronutrient trials, we found that evidence for improved CD4 count and HIV viral load with nutritional supplementation was limited; only 11.1% and 36.8% of macronutrient and micronutrient supplementation trials, respectively, reported improved CD4 count; and 33.3% and 12.5% of macronutrient and micronutrient trials, respectively, reported decreased viral load. Given their utility as surrogate markers of HIV disease progression, this suggests limited evidence for nutritional interventions having an impact on delaying HAART initiation or on improving HAART response. However, there are challenges in evaluating the effects of nutritional supplementation on clinical disease in that comparisons are difficult due to heterogeneity in study design, patient population, nutrient doses and combinations, baseline levels of deficiency, and study endpoints, including lack of clarity in defining and reporting HAART status. Future studies need to adopt a more rigorous standard design with adequate power and follow-up and require a consensus on composition and dose of nutrient interventions to be tested to more specifically answer the question on the impact of nutritional interventions on HIV disease progression and HAART response. *Am J Clin Nutr* 2011;94(suppl):1703S–15S.

## INTRODUCTION

There has been considerable interest in studying the effects of nutritional supplementation in patients with HIV; in particular, with the advent of HAART[5], some studies have recently sought to clarify the role of supplementation in patients receiving HAART. There have been prior summaries examining the effects of macronutrient and micronutrient nutritional supplementation separately (1–6). We conducted a literature review of clinical trials on macronutrient and micronutrient nutritional supplementation in adults infected with HIV; in this article, we summarize the results in an attempt to answer how nutritional supplementation affects disease progression. We also assess the evidence for the effects of nutritional supplementation on time to HAART initiation and response and outline the potential for future research. Similar to the approach taken by Forrester and Sztam (7), our review focused on clinical trials that reported on at least one of our primary outcomes of interest—CD4 count, HIV viral load, and disease progression or survival—and that excluded observational studies because such studies do not allow an assessment of causality or the consequences of nutrient supplementation on HIV disease progression. Our primary search strategy was based on identifying trials included in previous reviews and included more recent articles based on a PubMed search (www.ncbi.nlm.nih.gov/pubmed) that included the search terms "micronutrient," "macronutrient," and "HIV." We included articles published in English between 1993 and 2010 and that focused on HIV-infected adults. We, however, did not conduct a formal systematic review, and therefore the results and conclusions provided in this article reflect a narrative review.

## ASSESSMENT OF NUTRITION AND DISEASE PROGRESSION

One of the challenges in the assessment of nutrition and disease progression is that several definitions of malnutrition exist and several methods and approaches exist to assess nutritional status as well as disease progression. These include psychosocial factors (eg, food insecurity, depression, and alcohol and smoking behaviors), dietary intake [eg, food frequency and 24-h recall intake (although these are difficult to standardize across

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[5] Abbreviations used: ART, antiretroviral therapy; HAART, highly active antiretroviral therapy; MUAC, mid–upper arm circumference; PCM, protein calorie malnutrition; RUF, ready-to-use food.

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settings)]; clinical features (which are often nonspecific and usually occur only in advanced deficiency), and anthropometric measurements (8). More involved assessments include laboratory biomarkers (eg, ferritin, retinol), but such markers are often affected by inflammation and may not be reflective of total body deficiency, although they are nevertheless useful for identification of subclinical or multiple concurrent deficiencies. Biophysical or radiologic assessments such as dual-energy X-ray absorptiometry scans or functional assessments such as measurements of immune competence or muscle function also exist. However, there is no universally accepted approach. The most commonly used methods typically include anthropometric measurements such as BMI, weight, mid-arm circumference, body fat, and laboratory markers of micronutrient concentrations.

Disease progression measurements range from HIV-specific clinical endpoints such as time-to-incident opportunistic infections, AIDS-free survival, HIV-specific surrogate markers (ie, viral load suppression or CD4 cell count increase), as well as use of more general clinical endpoints such as weight or BMI change, working capacity as assessed by functional status scales, quality of life scales, or morbidity assessed by incident hospitalization. There has been a call to try and suggest some standard measures for nutritional intervention trials in HIV-infected persons, but these have yet to be uniformly adopted (5).

## IS MACRONUTRIENT SUPPLEMENTATION ASSOCIATED WITH HIV DISEASE PROGRESSION?

Macronutrients include protein, fats, and carbohydrates. Although globally there is increasing attention to the obesity epidemic, the majority of nutrition and HIV studies to date have addressed wasting (eg, rapid weight loss usually defined as >10% within the past 30 d) and undernutrition, such as PCM. When macronutrient malnutrition exists, particularly PCM, adverse effects on immune function have been noted. For example, PCM has been associated with immune dysfunction such as suppression of antigen-specific immune responses, decreased T cell responses, and increase in proinflammatory responses (9). These effects on host immune response are thought to be a key mechanism by which macronutrient malnutrition is associated with disease progression. Furthermore, undernutrition appears to affect the invading microorganism, making some infections more virulent (10). There is a substantial difference in dietary energy consumption that exists across nations (11), and hence macronutrient studies have to be interpreted in local and regional dietary contexts. Furthermore, the optimal composition of macronutrient supplementation or mechanism of delivery is debated. Nevertheless, several clinical trials have been conducted that have attempted to assess the effects of macronutrient supplementation in adults with HIV.

We found at least 9 such trials (12–20) (**Table 1**). These trials were conducted between 1998 and 2010, and only 3 (12–14) were conducted in World Bank–defined low-income countries (India, Malawi, and Zambia, respectively), with no studies from low-income settings before 2008. Most trials had small sample sizes with only 4 that enrolled >100 patients (12–14, 20). Two trials were nonrandomized, and both of these were from low-income settings (12, 14). Several trials restricted enrollment on the basis of BMI, weight loss, viral load, or CD4 count. The proportion of patients receiving HAART was unknown in 4 studies and varied from ~18% to 100% in the other studies. Two trials (13, 14) assessed the combination of starting HAART with a macronutrient supplementation, whereas the rest initiated HAART during follow-up.

### CD4 cell count and HIV viral load

All 9 studies assessed the impact of macronutrient supplementation on CD4 count and only one (11.1%) of these studies reported finding a significant effect. Sattler et al (15) reported a higher CD4 count in HIV-positive patients who were supplemented with a high-calorie protein supplement compared than in those receiving an isocaloric control without added protein ($P$ = 0.03). This trial had a small sample size and restricted enrollment to patients with HIV RNA of <5000 copies/mL in a high-income setting, resulting in poor generalizability to other settings and populations. Only 3 studies (13, 16, 18) assessed the relation between viral load and macronutrient supplementation, with one (33.3%) reporting significant results. Clark et al (18) reported significantly lower viral loads in HIV-positive patients who received a nutrient mixture containing a combination of L-glutamine, L-arginine, and a metabolite of leucine compared with those who received a placebo. Patients receiving the intervention registered a reduction in viral loads, whereas those receiving the placebo had an increase in viral loads ($P$ = 0.007); the point estimates for the 2 groups were even wider apart when patients with a viral load of <400 copies/mL were excluded ($P$ = 0.007). Again, the study had limitations in generalizability and ability to detect significant differences due to its small sample size, high-income setting, and enrollment that was restricted to patients with ≥5% weight loss in the past 3 mo. Thus, there appears to be little clear evidence from existing clinical trials for improved virologic or immunologic outcomes with macronutrient supplementation, but most of these trials had design limitations (small sample size, insufficient follow-up, lack of robust HIV disease progression endpoints) and used diverse macronutrient supplementation interventions for varying durations.

### Survival

Only one study from Malawi reported on survival differences between patients receiving and those not receiving macronutrient supplementation (a peanut-based RUF) but found no difference in survival between the 2 groups (13).

### Other clinical outcomes related to disease progression

Although trials on macronutrient supplementation reported on a variety of other outcomes (Table 1), the most consistently reported outcomes were anthropometric measures including body weight, BMI, and MUAC. Some studies also reported on body composition indexes such as body mass, total cell mass, and fat mass or on biochemical markers such as serum albumin. Nine (100%) trials reported on weight changes (12–15, 17–20), and one (11.1%) reported significant effects in macronutrient-supplemented groups (18). Clark et al (18) reported that at 8 wk, patients who received a macronutrient supplement containing amino acids reported a mean (±SD) weight gain of 3.0 ± 0.5 kg compared with a weight gain of 0.37 ± 0.84 kg in those who received placebo ($P$ = 0.009). However, this trial had a small sample size ($n$ = 68) and was conducted in patients reporting

**TABLE 1**
Summary of trials on the role of macronutrients and HIV progression in adults[1]

| First author (reference), country (year) | Study population (no. or % receiving HAART)[2] | Nutritional intervention | Control group | Effect on | | | Other outcomes |
|---|---|---|---|---|---|---|---|
| | | | | CD4 count | Viral load | Survival | |
| Low-income settings | | | | | | | |
| Swaminathan (12), India (2010) | 636 HIV+ patients (~40%) | 100 mg/d of a mixture of whole-wheat and soybean flour fortified with vitamins A, B-1 (thiamine), B-2 (riboflavin), B-12 and C; niacin; and folate plus standard care[3] for 6 mo (nonrandomized) | Standard care alone[3] | No significant effect | Not reported | Not reported | No significant changes in weight, BMI, body fat, body cell mass, mid-arm circumference, or concentrations of hemoglobin, albumin, or lipids between the 2 groups. |
| Ndekha (13), Malawi (2009) | 491 HIV+ patients with BMI (in kg/m$^2$) <18.5 (491) | 245 g peanut-based RUFs/d for 3.5 mo | 374 g corn-soy blend/d | No significant effect | No significant effect | No significant effect | Intervention group had significant gains in BMI and MUAC. No significant effect on quality of life, weight gain, or fat-free body mass. |
| Cantrell (14), Zambia (2008) | 636 HIV+ patients (636) | Home-based adherence follow-up with food supplementation (nonrandomized) | No intervention | No significant effect | Not reported | Not reported | Significantly improved adherence with food supplementation. No significant effect on weight gain. |
| High-income settings | | | | | | | |
| Sattler (15), United States (2008) | 59 HIV+ patients with HIV RNA <5000 copies/mL (56) | High-calorie protein supplement twice daily for 12 wk | Isocaloric control supplement without added protein | Significantly increased | Not reported | Not reported | Significantly increased fasting triacylglycerol in intervention group. No significant difference in total energy intake, weight change, lean body mass, waist-to-hip ratio, waist-to-thigh ratio, or thigh-to-waist-to-hip ratio. |

*(Continued)*

**TABLE 1** (*Continued*)

| First author (reference), country (year) | Study population (no. or % receiving HAART)[2] | Nutritional intervention | Control group | Effect on | | | Other outcomes |
|---|---|---|---|---|---|---|---|
| | | | | CD4 count | Viral load | Survival | |
| Karsegard (16), Switzerland (2004) | 46 HIV+ patients (8) | 10 g monohydrated OKG/d for 12 wk | Isonitrogenous placebo containing milk proteins + nutritional counseling | No significant effect | No significant effect | Not reported | Significantly greater frequency of gastrointestinal symptoms in intervention group. No significant difference in muscle area, fat-free mass, or bodyfat mass. |
| Keithley (17), United States (2002) | 90 HIV+ patients with CD4 counts between 275 and 550 cells/mm$^3$ (unknown) | Group 1: immune-enhancing oral formula group (Advera) for 12 mo + basic nutritional counseling<br>Group 2: standard oral formula (Ensure plus) + basic nutritional counseling | Basic nutritional counseling alone | No significant effect | Not reported | Not reported | No significant differences in body weight, body cell mass, fat mass, daily caloric intake, or serum albumin. |
| Berneis (19), Switzerland (2000) | 18 HIV+ patients with ≥5% weight loss in past 6 mo or BMI <21 or CD4 count <500 cells/mm$^3$ (unknown) | Oral nutritional supplements + dietary counseling | No nutritional therapy | No significant effect | Not reported | Not reported | Significantly reduced leucine oxidation rate in intervention group. No significant differences in total body weight, lean mass, or fat mass between the 2 groups. |
| Clark (18), United States (2000) | 68 HIV+ patients with >5% weight loss in past 3 mo (68) | Nutrient mixture (HMB/Arg/Gln) for 8 wk | Placebo (maltodextrin) | No significant effect | Significantly decreased | Not reported | Significant increase in body weight, lean body mass, CD3 cells, and CD8 cells, but no difference in fat mass. |

*(Continued)*

**TABLE 1** (*Continued*)

| First author (reference), country (year) | Study population (no. or % receiving HAART)[2] | Nutritional intervention | Control group | Effect on | | | Other outcomes |
|---|---|---|---|---|---|---|---|
| | | | | CD4 count | Viral load | Survival | |
| Rabeneck (20), United States (1998) | 118 HIV+ men who were <90% of usual weight for height or had lost >10% body weight (unknown) | Enteral supplementation with a specialized medium-chain triglyceride formula + nutritional counseling for 6 wk | Nutritional counseling alone | No significant effect | Not reported | Not reported | No significant differences in weight, skinfold thickness, quality of life, fat-free mass, or grip strength. Intervention group had some significantly better cognitive outcomes (short-term recall and long-term storage) but no difference in sum of recall or long-term retrieval. |

[1] Results compared the intervention groups with control group; changes within groups over time are not reported. HAART, highly active antiretroviral therapy; HMB, β-hydroxy β-methylbutyrate; MUAC, mid–upper arm circumference; OKG, L-ornithine α-ketoglutarate; RUFs, ready-to-use foods.

[2] Single-drug and 2-drug combinations were included in the definition of HAART; status was reported as unknown if sufficient details of regimens were not provided to confirm definition of HAART.

[3] Standard care included cotrimoxazole, multivitamins, nutritional counseling, and psychosocial support.

recent weight loss in a high-income setting. The evidence for improved BMI and MUAC with macronutrient supplementation was also limited, because only one trial (13) found significantly improved outcomes in Malawian patients who were supplemented with peanut-based RUF compared with those receiving a corn-soy blend. This trial had a relatively larger sample size ($n$ = 491) but restricted entry to patients with a BMI (in kg/m$^2$) <18.

## IS MICRONUTRIENT SUPPLEMENTATION ASSOCIATED WITH HIV DISEASE PROGRESSION?

Micronutrient deficiencies, which include deficiencies in vitamins and trace minerals, are estimated to be highly prevalent, with 2 billion individuals showing reduced physical and mental performance and 500 million with overt clinical symptoms (21). The majority of these individuals reside in low-income, resource-constrained regions of the world, and many individuals are simultaneously deficient in multiple micronutrients. Furthermore, micronutrient deficiencies can be associated with a wide range of impaired immune responses and clinical sequelae such as increased susceptibility to infection and increased morbidity and mortality (9, 22). In HIV, several micronutrient deficiencies are thought to result from or at least be associated with conditions common in HIV such as malabsorption and diarrhea as well as inadequate intake, and this may contribute to HIV disease progression (23). In the pre-HAART era, PCM and micronutrient deficiencies were common, ranging from a prevalence of 10% to 77% depending on the population studied (24–26).

The review by Forrester and Sztam (7) summarizes trials of multiple micronutrients published since 2003, the time when the WHO made its last recommendation regarding nutrition and HIV. In our review, we assessed both single and multiple micronutrient studies to more broadly assess the impact of nutrient supplementation on HIV disease progression pre- and post-HAART initiation. We found ≥22 trials that assessed the effects of micronutrient supplementation in adults with HIV (**Table 2**). Most of the trials were conducted in North America ($n$ = 10) (27–36) or sub-Saharan Africa ($n$ = 7) (37–43). Of the remaining trials, 2 were from Brazil (44, 45) and 1 each from Thailand (46), Poland (47), and Australia (48). The sample sizes ranged from 18 (45) to 1078 (37). Most early studies were from North America and had relatively small sample sizes. With the exception of one study from Thailand ($n$ = 481) (46), all of the larger studies were from one group of researchers in Tanzania (37, 40, 42, 43). Although most studies restricted inclusion to only HIV-positive patients, 2 trials also enrolled HIV-negative patients (38, 43). Three studies enrolled only HIV-positive pregnant women (37, 40, 42), and 2 enrolled only nonpregnant women (33, 41). Some trials had more specific study populations, including zinc-deficient patients (29), patients coinfected with tuberculosis (43), or patients with persistent diarrhea (39). All studies were randomized controlled trials except for one nonrandomized dose comparison study (48). Two randomized trials adopted a crossover design (32, 38), and one was a factorial study (37). As Forrester and Sztam also noted, there was substantial heterogeneity in the combinations of nutritional interventions provided and their doses, making it difficult to compare outcomes across studies (**Table 3**). The control arm for most studies was placebo alone ($n$ = 14). The proportion of patients receiving HAART was

**TABLE 2**
Summary of trials on the role of micronutrients and HIV progression in adults[1]

| First author (reference), country (year) | Study population (no. receiving HAART)[2] | Nutritional intervention | Control group | Effect on | | | |
|---|---|---|---|---|---|---|---|
| | | | | CD4 count | Viral load | Progression and/or survival | Other outcomes |
| Low-income settings | | | | | | | |
| Kelly (38), Zambia (2008) | 276 HIV+ and 224 HIV− patients (26) | Combination of 15 micronutrients for 1.9 y then crossover until 3.4 y (crossover trial) | Placebo | No significant effect | Not reported | Decreased Mortality | Significantly reduced severity of diarrhea but no significant difference in incidence of diarrhea, respiratory illness, or nutritional indexes |
| Kupka (40), Tanzania (2008) | 913 pregnant HIV+ women (31) | Selenium + prenatal iron, folic acid, and vitamins from enrollment to 6 mo postpartum | Placebo + prenatal iron, folic acid and vitamins | No significant effect | No significant effect | No significant effect | Significantly reduced risk of child mortality after 6 wk but no significant effect on LBW, fetal death, or other infant outcomes |
| Villamor (43), Tanzania (2008) | 471 HIV+ and 416 HIV− patients with tuberculosis (0) | Combination of 10 micronutrients for median follow-up of 30 mo in HIV+ patients and 52 mo in HIV− patients | Placebo | No significant effect | No significant effect | No significant effect on mortality overall but marginally decreased mortality in HIV-negative | Significantly reduced incidence of peripheral neuropathy regardless of HIV status |
| Villamor (42), Tanzania (2006) | 400 pregnant HIV+ women (0) | Zinc + vitamins B-1 (thiamine), B-2 (riboflavin), B-3, B-6, B-12, C, and E; antenatal iron and folate from first antenatal visit to 6 wk postpartum | Vitamins B-1, B-2, B-3, B-6, B-12, C, and E; antenatal iron and folate | Not Reported | No significant effect | Not Reported | Significantly increased risk of wasting (MUAC <22 cm) but no significant effect on MTCT or other anthropometric indexes |
| de Souza Jr (44), Brazil (2005) | 29 HIV+ patients (26) | α-Tocopherol for 180 d | Placebo | No significant effect | No significant effect | Not reported | Significantly improved lymphocyte viability |
| Fawzi (37), Tanzania (2004) | 1078 pregnant HIV+ women (0) | Factorial design: *1*) vitamin A alone; *2*) vitamins B-1, B-2, B-3, B-6, B-12, C, and E; *3*) both *1*) and *2*); all received antenatal iron and folate | Placebo + antenatal iron and folate | Increased in non–vitamin A group | Decreased in non–vitamin A group | Decreased progression/ improved survival (composite) in non–vitamin A group | Significantly reduced incidence of oral ulcers, cheilitis, difficulty swallowing, dysentery, and fatigue. No significant effect on diarrhea. |
| McClelland (41), Kenya (2004) | 400 HIV+ women (0) | Combination of 9 micronutrients for 6 wk | Placebo | No significant effect | No significant effect | Not reported | Significantly higher vaginal HIV shedding |

*(Continued)*

**TABLE 2** (*Continued*)

| First author (reference), country (year) | Study population (no. receiving HAART)[2] | Nutritional intervention | Control group | Effect on | | | Other outcomes |
|---|---|---|---|---|---|---|---|
| | | | | CD4 count | Viral load | Progression and/or survival | |
| Jiamton (46), Thailand (2003) | 481 HIV+ patients (10) | Combination of 21 micronutrients for 48 wk | Placebo | No significant effect | No significant effect | Improved survival in patients with CD4 counts <200 | No significant difference in hospitalization |
| Spada (45), Brazil (2002) | 18 HIV+ patients (18) | α-Tocopherol for 60 d + HAART | Placebo + HAART | No significant effect | No significant effect | Not reported | None |
| Kelly (39), Zambia (1999) | 135 HIV+ patients with persistent diarrhea (Unknown) | Combination of 5 micronutrients + 800 mg twice-daily albendazole for 14 d | Placebo + 800 mg twice-daily albendazole | No significant effect | Not reported | No significant effect | No significant difference in diarrhea outcomes |
| High-income settings | | | | | | | |
| Baum (29), United States (2010) | 231 Zinc deficient HIV+ patients (144) | Elemental zinc for 18 mo | Placebo | Prevented immunologic failure | No significant effect | No significant effect | Significantly reduced diarrhea but no significant differences in upper or lower respiratory disease |
| Hurwitz (34), United States (2007) | 310 HIV+ patients (240) | High-selenium yeast for 9 mo | Placebo | Increased (used modeling) | Decreased (used modeling) | Not reported | None |
| Austin (28), Canada (2006) | 331 HIV+ patients (259) | Natural mixed carotenoids + 28 micronutrients for median follow-up of 13 mo | 28 micronutrients only | No significant effect | No significant effect | No significant effect | None |
| Kaiser (35), United States (2006) | 40 HIV+ patients (40) | Combination of 33 micronutrients for 12 wk | Placebo | Increased | No significant effect | Not reported | No significant effect on peripheral neuropathy or metabolic indexes |
| Burbano (30), United States (2002) | 186 HIV+ patients (85) | Selenium for 2 y | Placebo | Increased | Not reported | Not reported | Significantly decreased hospitalization rates, frequency, and costs but no significant effect on duration |
| Jaruga (47), Poland (2002) | 30 HIV+ patients (30) | Vitamins A, E, and C for 6 mo | Placebo | No significant effect | Not reported | Not reported | Significantly reduced oxidant stress |
| Batterham (48), Australia (2001) | 66 HIV+ patients (50) | Combination of 11 micronutrients, milk thistle, and grapeseed for 12 wk at a higher dose than control group (nonrandomized) | Combination of 11 micronutrients, milk thistle, and grapeseed at a lower dose than study group | Not reported | No significant effect | Not reported | No significant effect on oxidant stress markers |

(*Continued*)

**TABLE 2** (*Continued*)

| First author (reference), country (year) | Study population (no. receiving HAART)[2] | Nutritional intervention | Control group | Effect on | | | Other outcomes |
|---|---|---|---|---|---|---|---|
| | | | | CD4 count | Viral load | Progression and/or survival | |
| Humphrey (33), United States (1999) | 40 HIV+ women (0) | Single dose of vitamin A | Placebo | Increased | No significant effect | Not reported | No significant difference in lymphocyte proliferation response to PHA or candida |
| Allard (27), Canada (1998) | 49 HIV+ patients (unknown) | α-Tocopherol and vitamin C for 3 mo | Placebo | Not reported | No significant effect | No significant effect on new OIs | Significantly reduced oxidant stress (lipid peroxidation) |
| Semba (36), United States (1998) | 120 HIV+ patients (0) | Single dose of vitamin A for a follow-up of 4 wk | Placebo | No significant effect | No significant effect | Not reported | None |
| Coodley (31), United States (1996) | 72 HIV+ patients (unknown) | β-Carotene + multivitamin supplement for 3 mo | Placebo + multivitamin supplement | No significant effect | Not reported | Not reported | No significant difference in NK cells or p24 antigen |
| Coodley (32), United States (1993) | 21 HIV+ patients (0) | β-Carotene for 4 wk (crossover trial) | Placebo | No significant effect | Not reported | Not reported | Significant increase in white blood cell count |

[1] Results compared the intervention group with control groups; changes within group over time are not reported. HAART, highly active anti-retroviral therapy; LBW, low birth weight; MTCT, mother-to-child transmission; MUAC, mid–upper arm circumference; NK, natural killer; PHA, phytohemagglutinin,

[2] Single-drug and 2-drug combinations not included in our definition of HAART; status reported as unknown if sufficient details of regimens were not provided to confirm definition of HAART.

**TABLE 3**
Composition and dosage of micronutrients used in reviewed trials

| First author (reference) | Vitamin A | β-Carotene | Vitamin B-1 (thiamine) | Vitamin B-2 (riboflavin) | Vitamin B-6 | Niacin | Vitamin B-12 | Folic acid | Pantothenic acid | Vitamin C | Vitamin D | Vitamin E | Vitamin K | Iron | Zinc | Selenium | Calcium | Magnesium | Iodine | Copper | Manganese | Chromium |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *IU/D* | *mg/d* | *mg/d* | *mg/d* | *mg/d* | *mg/d* | *μg/d* | *μg/d* | *mg/d* | *mg/d* | *IU/D* | *mg/d* | *μg/d* | *mg/d* | *mg/d* | *μg/d* | *mg/d* | *mg/d* | *μg/d* | *mg/d* | *mg/d* | *μg/d* |
| Baum (29) | | | | | | | | | | | | | | | 12 (males); 15 (females) | | | | | | | |
| Kelly (38) | | 4.8 | 1.4 | 1.4 | 1.9 | 18 | 2.6 | 400 | | 70 | 5[1] | 10 | | 30 | 15 | 65 | | | 150 | 2 | | |
| Kupka (40) | | | | | | | | | | | | | | | | 200 | | | | | | |
| Villamor (43) | 5000 | | 20 | 20 | 25 | 100 | 50 | 800 | | 500 | | 200 | | | | 100 | | | | | | |
| Hurwitz (34) | | | | | | | | | | | | | | | | 200 | | | | | | |
| Austin (28) | | 120,000[2] | | | | | | | | | | | | | | | | | | | | |
| Kaiser[3] (35) | 8000 | 200,000[2] | 60 | 60 | 260 | 60 | 2500 | 800 | 60 | 1800 | 400 | 800[2] | | 18 | 30 | 200 | 800 | 400 | 150 | 2 | 10 | 100 |
| Villamor (42) | | | | | | | | | | | | | | | 25 | | | | | | | |
| de Souza Jr (44) | | | | | | | | | | | | 800 | | | | | | | | | | |
| Fawzi[4] (37) | 5000 | 30 | 20 | 20 | 25 | 100 | 50 | 800 | | 500 | | 30 | | | | | | | | | | |
| McClelland (41) | | | 20 | 20 | 25 | 100 | 50 | 800 | | 500 | | 30 | | | | 200 | | | | | | |
| Jiamton[5] (46) | 3000[1] | 6 | 24 | 15 | 40 | | 30 | 100 | 40 | 400 | 20 | 80 | 180 | 10 | 30 | 400 | | 200 | 300 | 3 | 8 | 150 |
| Burbano (30) | | | | | | | | | | | | | | | | 200 | | | | | | |
| Jaruga[5] (47) | 5000 | | | | | | | | | 50 | | 100[2] | | | | | | | | | | |
| Spada (45) | | | | | | | | | | | | 800 | | | | | | | | | | |
| Batterham[6] (48) | 21,800 | | 40 | | 100 | | 200 | 1000 | 220 | 1000 | | 400[2] | | | 20 | 200 | | | | | | |
| Humphrey (33) | 300,000[7] | | | | | | | | | | | | | | | | | | | | | |
| Kelly (39) | 10,500 | | | | | | | | | 300 | | 300 | | | 200 | 150 | | | | | | |
| Allard (27) | | | | | | | | | | 1000 | | 800[2] | | | | | | | | | | |
| Semba (36) | 200,000[7] | | | | | | | | | | | | | | | | | | | | | |
| Coodley (31) | | 180 | | | | | | | | | | | | | | | | | | | | |
| Coodley (32) | | 180 | | | | | | | | | | | | | | | | | | | | |

[1] In μg/d.
[2] In IU/d,
[3] Study arm also received a daily dose of 50 μg biotin, 2 mg boron, 60 mg choline, 100 mg L-glutamine, 300 μg molybdenum, 150 mg betaine, 60 mg inositol, 99 mg potassium, 400 mg α-lipoic acid, 1000 mg acetyl L-carnitine, 1200 mg *N*-acetyl cysteine, and 300 mg bioflavinoid complex.
[4] This study had a factorial design (*see* Table 1).
[5] Study arm also received a daily dose of 66 mg of cysteine.
[6] Study arm also received a daily dose of 4800 mg grapeseed, 2800 mg milk thistle, and 200 mg coenzyme Q10; control group received same micronutrients as study group but at a lower dose.
[7] One-time dose only.

unknown in 2 studies and varied from 0% to 100% in the other studies.

### CD4 cell count and HIV viral load

There is evidence for multiple micronutrient supplementation resulting in increased CD4 cell count despite broad differences in study design and analysis [*see* also Forrester and Sztam (7) for commentary of multiple micronutrient studies published since 2003]. Nineteen studies (86.4%) reported on the effect of micronutrient supplementation on CD4 cell count (28–41, 43–47), and 7 (36.8%) reported finding significantly improved outcomes in the supplemented group (28–30, 33–35, 37). A small US trial (35) ($n = 40$) reported a significant increase in absolute CD4 cell count in patients supplemented with a combination of micronutrients compared with those on placebo (24% compared with 0% at 12 wk, $P = 0.01$; mean CD4 change: +65 cells compared with −6 cells; $P = 0.029$). A factorial trial in pregnant women (37) reported mean CD4 counts higher by 48 cells/mm$^3$ in women who received multivitamins than in those receiving placebo during the entire study duration of 4 y ($P = 0.01$). However, the effect was maximal at 2 y, when women receiving multivitamins had an increase of 50 cells/mm$^3$ ($P < 0.001$).

Relatively few studies have attempted to tease apart the difference by supplementing individual micronutrients. Three studies (30, 34, 40) specifically assessed the effect of selenium supplementation on CD4 counts, but the evidence was less clear on account of the differences in reporting outcomes between these studies. Two of these US studies (30, 34) found some significant effect, whereas Kupka et al (40) found no significant changes in CD4 cell count in HIV-positive pregnant Tanzanian women supplemented with selenium and standard antenatal supplements compared with those receiving only standard antenatal supplements alone. The first study (30) reported stable CD4 cell counts in both those receiving selenium and placebo; however, it found that a significantly higher proportion of patients in the placebo arm had a decline in CD4 to <50 cells/mm$^3$ ($P = 0.01$). The other study (34) reported a significantly increased CD4 in patients supplemented with high-selenium yeast with the use of modeling but suggested that, based on the modeling, this was an indirect effect mediated via change in the viral load. The only study that specifically assessed the effect of zinc supplementation on CD4 count (29) found a significant 4-fold reduction in the likelihood of immunologic failure (defined as CD4 <200 cells/mm$^3$) in patients supplemented with zinc for 18 mo compared with placebo by using multiple event modeling analyses (adjusted RR: 0.24; $P = 0.002$).

Some of the earlier studies assessed the effects of supplementation with vitamin A or $\beta$-carotene alone on CD4 cell count (31–33, 36). Of these, only one (33) identified a significant finding: a higher median CD4 percentage in the second week in patients administered a single dose of vitamin A compared with placebo (29% compared with 23.5%, $P < 0.05$). However, all of these early studies had short durations of follow-up and small sample sizes. The 2 trials that studied the effect of $\alpha$-tocopherol supplementation alone did not find any significant effect on the CD4 count (44, 45), nor did a trial that used a combination of vitamins A, C, and E (47). One newer trial (28) that assessed effects of supplementation with $\beta$-carotene on CD4 cell count found a significant increase from baseline in the supplemented group at 12, 15, and 18 mo ($P = 0.04$, $P = 0.007$, and $P = 0.008$, respectively), but despite this trend there appeared to be no significant difference in CD4 between the groups receiving and those not receiving $\beta$-carotene.

In contrast to the CD4 data, there is a paucity of evidence showing that micronutrient supplementation is associated with reduced viral load. Sixteen trials (72.7%) (27–29, 33–37, 40–46, 48) included in our review assessed the effect of micronutrient supplementation on viral load. The evidence for any association was small because only 2 trials (12.5%) (34, 37) reported significant associations. Fawzi et al (37) reported that HIV-positive pregnant women supplemented with higher than Recommended Dietary Allowance amounts of multivitamins showed a significant reduction in viral load by 0.18 log ($P = 0.02$), but those receiving vitamin A, alone or in combination with other multivitamins, did not show any significant reduction in viral load. Although these results appear fairly robust, their generalizability to a wider population of HIV-positive patients is limited because the trial enrolled only HIV-infected pregnant women in Tanzania. The other study to find a significant association (34) used statistical modeling to show an association between increased serum selenium concentrations and decreased plasma viral load ($P < 0.02$) in US patients; however, not all trial participants showed increased selenium concentrations in response to supplementation with high-selenium yeast, and the trial may not have adequately controlled for HAART use.

### Survival

Nine studies (27–29, 37–40, 43, 46) assessed disease progression and/or survival outcomes in supplemented patients, and 3 (37, 38, 46) reported finding some significant associations. Kelly et al (38) reported reduced mortality in HIV-positive Zambian patients receiving micronutrients compared with those receiving placebo ($P = 0.029$). Interestingly, this effect was not seen in the entire cohort that included HIV-negative patients, and there appeared to be no significant changes in CD4 cell count or anthropometric measurements in patients with HIV, suggesting that the survival benefit was not be mediated through changes in HIV progression or nutritional levels. Jiamton et al (46) reported a survival benefit in HIV-positive Thai patients supplemented with micronutrients among those with CD4 counts of <100 cells/mm$^3$ (HR: 0.27; $P = 0.03$) and a trend for improved survival among those with CD4 counts of <200 cells/mm$^3$ (HR: 0.37; $P = 0.052$).

A trial in Tanzanian pregnant women (37) reported reduced risk of AIDS-related death in those who received multivitamin supplementation higher than Recommended Dietary Allowance amounts, but the difference was not significant (RR: 0.73; $P = 0.09$). However, a significantly lower progression to WHO stage 4 (RR: 0.50; $P = 0.02$) and progression to WHO stage 3 or higher (RR: 0.72; $P = 0.003$) was observed; these benefits were sustained through 4 y after the intervention. Interestingly, vitamin A supplementation alone was not associated with significant improvements in the same outcomes, other than a small advantage in reducing progression to WHO stage 3 or higher (RR: 0.81; $P = 0.05$). On the basis of this study and others, as Forrester and Sztam (7) highlight in their review, there is a need to further examine the risks and benefits of vitamin A supplementation in HIV-infected postpartum women.

**Other clinical outcomes related to disease progression**

Eighteen of 22 studies presented findings on a range of other clinical outcomes.

*Diarrhea*

Four studies assessed the effect of micronutrient supplementation on diarrhea (29, 37–39); 2 of these (29, 38) reported at least some improvement in outcomes with supplementation. Baum et al (29) reported that supplementing US patients with zinc significantly reduced the odds of diarrhea by 60% (OR: 0.4; $P = 0.019$) compared with placebo. The reduction was evident after 12 mo of zinc supplementation and was maintained through 18 mo after study entry. Higher rates of diarrhea were also correlated with lower plasma zinc concentrations after adjustment for ART, CD4 counts, viral load, and concentrations of C-reactive protein ($P = 0.006$). A crossover trial from Zambia (38), which included both HIV-positive and HIV-negative patients, found that supplementation with a combination of 15 micronutrients resulted in reduced severity of diarrhea (OR: 0.5; $P = 0.017$), defined by the number of times patients sought medical consultation for an episode of diarrhea. However, there was no difference in diarrhea incidence ($P = 0.29$) or in duration of diarrheal episodes ($P = 0.38$) between the treatment and control groups, regardless of HIV status. Another Zambian trial (39) found no difference in diarrhea outcomes, defined as proportion of weeks with diarrhea, after supplementing HIV-positive patients with 5 micronutrients, compared with those on placebo ($P = 0.40$ and $P = 0.97$ at 4 wk and 12 wk, respectively). However, this trial restricted enrollment only to patients with persistent diarrhea (>1 mo), provided daily albendazole to both arms, and had a short duration of intervention (2 wk) and follow-up (12 wk). Last, Fawzi et al (37) found no significant difference in the relative risk of diarrhea in pregnant Tanzanian women supplemented with vitamin A or multivitamins or both compared with placebo.

*Respiratory illness*

Three studies (29, 37, 38) reported on respiratory disease outcomes, and only one reported a benefit to supplementation. Fawzi et al (37) reported that pregnant women supplemented with multivitamins were significantly less likely to develop acute upper respiratory tract illness (RR: 0.79; $P = 0.02$); however, women receiving vitamin A alone and those receiving a combination of multivitamins (RR: 0.87; $P = 0.11$) and vitamin A (RR, 0.96; $P = 0.62$) appeared to be less protected. A Zambian crossover trial (38) found that supplementation with a combination of micronutrients did not produce significant differences in incidence ($P = 0.36$) or duration ($P = 0.36$) of respiratory infection or incidence of tuberculosis ($P = 0.54$). Similarly, a US trial (29) failed to find any difference in upper or lower respiratory disease between zinc and placebo recipients.

*Peripheral neuropathy*

Two studies reported on micronutrient supplementation and rates of peripheral neuropathy (35, 43). Villamor et al (43) conducted a trial in tuberculosis patients (both HIV-positive and HIV-negative and receiving antituberculosis therapy), in which they supplemented patients in the intervention arm with a combination of 10 micronutrients. There was a significant reduction in peripheral neuropathy incidence in the intervention compared with the placebo arm, regardless of HIV status ($P < 0.001$). The second study (35) supplemented HIV-positive patients receiving stavudine or didanosine or both based on HAART regimens with a combination of 33 micronutrients for 12 wk and evaluated distal symmetric polyneuropathy score. At 12 wk, a nonsignificant improvement in neuropathy scores was observed in the supplemented compared with the placebo group (42% compared with 33%, $P > 0.05$); the authors suggested that the duration of follow-up may have been too short to detect a difference.

*Hospitalization*

Two studies (30, 46) assessed the effect of micronutrient supplementation on hospitalization rates. A US study (30) found significant differences in hospitalization outcomes in the selenium-supplemented group compared with placebo. Patients receiving selenium had lower total admission rates (RR: 0.38; $P = 0.02$) and costs of hospitalization ($P = 0.001$), and selenium therapy was found to be an independent factor associated with lower risk of hospitalization ($P = 0.001$). However, a Thai study (46) that supplemented patients with a combination of 21 micronutrients for 48 wk did not find any significant difference in hospitalization (HR: 0.76; $P = 0.4$), even in those with CD4 counts of <200 cells/mm$^3$.

## DOES NUTRITION PLAY A ROLE IN TUBERCULOSIS OR EARLY MORTALITY AFTER HAART INITIATION?

A key consideration for future studies is the need to study the interaction between tuberculosis, HIV, and malnutrition. Tuberculosis is a key cause of morbidity and mortality in HIV-infected individuals who have not yet initiated HAART as well as those who have recently initiated HAART (49). Malnutrition has been associated with increased risk of tuberculosis in a variety of studies involving HIV-negative persons (50), and a study of micronutrient supplementation in HIV/tuberculosis coinfected adults was associated with a reduction in tuberculosis recurrence in HIV-infected adults (43).

Despite the advent of HAART, early mortality and increased mortality rates have been observed among HIV-infected adults residing in low-income regions of the world compared with those in high-income regions of the world (51). In a systematic review of 50 studies, low BMI, low CD4 counts, and anemia have been shown to be independent risk factors for early mortality post-HAART initiation (A Gupta, G Nadkarni, A Chandrasekhar, et al, unpublished observations). These factors can all be affected by malnutrition, yet there are no robust trials assessing whether nutritional interventions combined with HAART can truly reduce the burden of early mortality in low-income settings. Furthermore, it is unknown whether malnutrition affects HAART response. Therefore, well-designed studies focused on assessing the relation between nutritional status and HIV disease progression, including the assessment of specific nutritional interventions to reduce tuberculosis risk as well as early mortality in the era of HAART, would be of great value.

## SUMMARY AND FUTURE DIRECTIONS

Although several trials have been conducted, the current evidence on the benefits of macronutrient and micronutrient supplementation is mixed and presents significant limitations that

need to be overcome by future trials. Trials that assessed the effect of macronutrient and micronutrient supplementation in HIV-positive patients were often small, resulting in low power to detect any difference between intervention and placebo. Given that some of the strongest evidence of benefit came from studies with larger sample sizes, future studies need to adequately powered to detect meaningful differences in outcomes. Future trials must also provide for longer follow-up periods to detect differences in clinically meaningful endpoints of disease progression and survival. Furthermore, there are certain populations with significant HIV burden that remain unexplored. In particular, the paucity of evidence from Asia, where in some regions malnutrition is a major health problem, presents a research gap that should be addressed by future studies. Future trials must also explore the opportunities to conduct multiregional trials to provide more generalizable results to help develop a sound global policy for macronutrient and micronutrient supplementation. Several global programs, particularly those within the US President's Emergency Program for AIDS Relief (PEPFAR), have worked alongside food assistance programs to provide food supplement packages to HIV-infected persons who enroll into antiretroviral treatment centers in low-income, resource-constrained settings. However, the impact of these food assistance programs has remained largely unevaluated. Operations research studies will likely yield data more readily with regard to optimal nutritional interventions than would waiting for the design and completion of large community-based or facility-based clinical trials. For example, one such study conducted by Rawat et al (52) assessed the impact of food assistance on weight gain and disease progression in 14,481 Ugandan adults accessing AIDS care and treatment in Uganda by using program data. They compared 12-mo outcomes among food assistance recipients with a control group and used a statistical method known as propensity score matching to make the groups comparable.

Future studies also need to focus on assessing the appropriate dosage of nutrients and determining effects of individual nutrients included in combinations that have shown benefit in previous trials. These trials also need to better assess the impact of HAART on supplementation by comparing effects between those receiving HAART and those not receiving HAART. Future studies also need to account for baseline levels of nutrient deficiency and to assess standard clinical and immunologic endpoints, including patient survival, incidence of opportunistic infections, CD4 cell count, and viral load.

To date, many of the nutritional intervention studies have focused on HIV wasting and undernourished adults. With increasing HAART exposure, longer life expectancy, and a worsening epidemic of obesity globally, non-AIDS-defining illnesses such as cardiovascular disease (myocardial infarction, stroke) and diabetes are becoming more relevant concerns (53). None of the trials we reviewed addressed the role of nutritional interventions on obesity, metabolic disorders, or cardiovascular-related disease progression; therefore, these relations need to be further elucidated. There is also a need to examine the specific role of vitamin D supplementation because many observational studies have found a high prevalence of vitamin D deficiency in HIV-infected adults (54), and in turn vitamin D deficiency has been associated with poor health outcomes (eg, osteoporosis, cancer, cardiovascular disease, and all-cause mortality) (55). In conclusion, evidence from existing studies presents significant challenges in comparison due to the heterogeneous nature of study designs and interventions; however, there appears to be some evidence for improvement in clinical outcomes in HIV-positive patients supplemented with macronutrients and micronutrients. Future studies need to adopt rigorous study design standards with robust study endpoints, adequate power, and adequate follow-up.

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