Micronutrients in HIV-positive persons receiving highly active antiretroviral therapy[1–3]

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ABSTRACT

In HIV-infected persons, low serum concentrations of vitamins and minerals, termed micronutrients, are associated with an increased risk of HIV disease progression and mortality. Micronutrient supplements can delay HIV disease progression and reduce mortality in HIV-positive persons not receiving highly active antiretroviral therapy (HAART). With the transition to more universal access to HAART, a better understanding of micronutrient deficiencies and the role of micronutrient supplements in HIV-positive persons receiving HAART has become a priority. The provision of simple, inexpensive micronutrient supplements as an adjunct to HAART may have several cellular and clinical benefits, such as a reduction in mitochondrial toxicity and oxidative stress and an improvement in immune reconstitution. We reviewed observational and trial evidence on micronutrients in HIV-positive persons receiving HAART to summarize the current literature and suggest future research priorities. A small number of observational studies have suggested that some, but not all, micronutrients may become replete after HAART initiation, and few intervention studies have found that certain micronutrients may be a beneficial adjunct to HAART. However, most of these studies had some major limitations, including a small sample size, a short duration of follow-up, a lack of adjustment for inflammatory markers, and an inadequate assessment of HIV-related outcomes. Therefore, few data are available to determine whether HAART ameliorates micronutrient deficiencies or to recommend or refute the benefit of providing micronutrient supplements to HIV-positive persons receiving HAART. Because micronutrient supplementation may cause harm, randomized placebo-controlled trials are needed. Future research should determine whether HAART initiation restores micronutrient concentrations, independent of inflammatory markers, and whether micronutrient supplements affect HIV-related outcomes in HIV-positive persons receiving HAART. *Am J Clin Nutr* 2007;85:333–45.

KEY WORDS Vitamins, minerals, micronutrients, selenium, HIV AIDS, highly active antiretroviral therapy, HAART

INTRODUCTION

At the end of 2005, ≈40 million persons were living with HIV AIDS, and nearly 5 million persons had become newly infected with HIV during the same year (1). Although access to HIV medications has been nearly universal to people in developed countries, only 1 in 7 Asians and 1 in 10 Africans who need HIV therapy were receiving HIV medications. Access has been gradually increasing in low- and middle-income countries, and leaders of the 2005 G8 Summit pledged to provide global access to HIV medications by 2010. The transition to greater access to HIV medications will shift the research priorities related to vitamins and minerals, termed micronutrients, in HIV-infected persons.

Micronutrient deficiencies, which are commonly observed with advanced HIV disease, have been associated with higher risks of HIV disease progression and mortality (2, 3). Body weight loss and wasting are also features of HIV disease progression (4) and are strong independent predictors of HIV-related morbidity and mortality (5–9). Micronutrient deficiencies, body weight loss, and wasting in advanced HIV disease are caused by a similar combination of decreased food intake, gastrointestinal malabsorption, increased metabolic demand, and body redistribution (10, 11).

In 1996, highly active antiretroviral therapy (HAART) became the new standard for HIV treatment. HAART regimens comprise 3 HIV medications among the following 4 categories: nucleoside-analog reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs), and entry inhibitors (12). Initiation of HAART is generally recommended for patients with HIV-related opportunistic infections or a CD4 count $<$ 200 cells/μL. HAART restores immunologic function (13), but does not eliminate weight loss and wasting (14, 15), which continue to be strong independent predictors of mortality (16). Because low micronutrient concentrations are caused by similar mechanisms and several micronutrient concentrations are lower among patients with HIV

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wasting syndrome (17), micronutrient deficiencies may also persist in the era of HAART.

Research on micronutrient deficiencies and the role of micronutrient supplements in HIV-infected persons receiving HAART has become a priority (18). Recent review articles have described macronutrients in HIV-infected adults (10) and children (11), micronutrient deficiencies (19, 20) and intervention trials (21) in HIV-positive persons not receiving HAART, and nutritional needs and management in HIV-positive persons receiving HAART (22, 23). Although some researchers have recently called for micronutrient supplements as an adjunct therapy to HAART (19, 24), no review articles, to our knowledge, have summarized studies describing micronutrient concentrations and micronutrient intervention trials in HIV-positive persons receiving HAART. We reviewed published studies of micronutrients and HAART to summarize the literature and suggest future research priorities.

MICRONUTRIENTS IN THE PRE-HAART ERA

Micronutrients are essential for maintaining proper immunologic function (25, 26). Vitamin A deficiency reduces a lymphocyte response (27), vitamin C deficiency depresses a cell-mediated immune response (28), and vitamin E deficiency impairs T cell–mediated function and lymphocyte proliferation (29). Among the B vitamins, riboflavin deficiency impairs the generation of a humoral antibody response, vitamin B-6 deficiency reduces lymphocyte maturation and diminishes antibody production, and vitamin B-12 deficiency impairs neutrophil function (30). Among certain minerals, folic acid deficiency depresses the cell-mediated immunity response (31), zinc deficiency decreases lymphocyte concentrations (32), copper deficiency reduces the cytokine response (33), and selenium is needed for proper functioning of neutrophils and T lymphocytes (34).

Compared with HIV-negative person, HIV-infected persons have lower serum concentrations of several micronutrients and more commonly have micronutrient deficiencies (35–42). Among HIV-positive persons not receiving HAART, observational studies have shown low or deficient serum concentrations of several micronutrients, including thiamine, selenium, zinc, and vitamins A, B-3, B-6, B-12, C, D, and E to be individually associated with either low CD4 cell counts, advanced HIV-related diseases, faster disease progression, or HIV-related mortality (43–57). In addition, micronutrient interventions have been shown to have cellular and clinical benefits in HIV-positive persons not receiving HAART. In HIV-infected T lymphocytes, vitamin C reduces reverse transcriptase activity (58) and vitamin E reduces nuclear transcription factor κB (NF-κB) concentrations and the production of oxidant compounds (59, 60). In randomized placebo-controlled trials, a daily supplement of vitamins C and E for 3 mo reduced oxidative stress (61), a daily multivitamin supplement for 48 wk reduced mortality in subjects with baseline CD4 counts $<$100 cells/μL (62), and a single large dose of vitamin A to neonates improved survival at 6 wk in those who were HIV-positive by polymerase chain reaction (63). In a randomized placebo-controlled trial in HIV-infected pregnant women, a daily multivitamin resulted in significant reductions in clinical HIV disease progression, improvements in CD4 and CD8 counts and HIV viral loads, and a reduction in HIV-related mortality (64, 65).

NUTRITIONAL AND METABOLIC DISTURBANCES OF HIV

Basic nutritional and metabolic disturbances that lead to weight loss and wasting in HIV-infected persons may represent an adaptive response to an inflammatory state (66–68). Proinflammatory cytokine concentrations are significantly higher in HIV-positive persons than in HIV-negative persons (69). Elevated concentrations of interleukin 6 and tumor necrosis factor (TNF) have been associated with higher HIV viral loads (70), and TNF-α and interferon γ can inhibit myosin expression in muscle cells and induce anorexia (71, 72). Elevated cytokines may also contribute to the chronic oxidative stress observed in HIV-positive persons (73), which could lead to HIV disease progression through impairment of immune function (74), enhancement of HIV replication (73), or both.

Nutritional and metabolic disturbances can also lead to altered acute phase response proteins in response to acute or chronic inflammation, which have been observed in persons with advanced HIV disease (75, 76). Changes in acute phase response proteins, mainly decreased albumin and elevated C-reactive protein concentrations, have been shown to be associated with low serum concentrations of several micronutrients in HIV-negative persons (77–87) and with low serum concentrations of vitamin A and selenium in HIV-positive persons not receiving HAART (88, 89). Furthermore, both serum albumin and C-reactive protein are independent predictors of mortality in HIV-positive persons not receiving HAART (8, 90, 91). Although albumin may be a better measure of nutritional status than inflammation (92), these studies suggest that micronutrient deficiencies that persist after HAART initiation could be due to an inflammatory response.

OBSERVATIONAL STUDIES OF MICRONUTRIENTS IN HIV-POSITIVE PERSONS RECEIVING HAART

We identified 5 cross-sectional studies that measured vitamin concentrations in HIV-positive persons receiving HAART (**Table 1**). In a small study of HIV-positive adults (n = 11), 6 participants receiving HAART had significantly lower vitamin A and higher retinol-binding protein concentrations, but no significant differences in HIV plasma viral load or CD4 cell counts were found between them and those not taking any HIV medications (93). In a cohort of 30 HIV-positive persons, most of whom were injecting drugs and 23 of whom were receiving HAART, concentrations of vitamins A and E were not significantly different between those receiving and those not receiving HAART (94). Of 175 HIV-positive males, most of whom were drug-injecting African Americans, 30 receiving HAART had significantly higher adjusted concentrations of α-carotene, β-carotene, and α-tocopherol, but not of vitamin A and γ-tocopherol, than did 80 HIV-positive persons not receiving any HIV medications (95). Although the authors did not adjust the analyses by plasma viral load or CD4 cell count, they reported no significant differences in vitamin concentrations between 3 CD4 cell count categories. Therefore, confounding by CD4 cell count would have been unlikely. Another study found significantly higher folate and vitamin B-12 concentrations in 126 HIV-positive adults receiving HAART than in 109 HIV-positive historical control subjects (96). Given the nature of the study design and lack of adjustment for different historical factors, these results should be interpreted with caution. In a study

TABLE 1
Observational studies of vitamins in HIV-infected persons receiving highly active antiretroviral therapy (HAART)

Reference	Study design, location, and population	Vitamin concentrations[1]	Results and conclusions
Cross-sectional studies			
Toma et al, 2001 (93)	Cross-sectional study in Canada. 11 HIV-positive adults (6 receiving HAART for ≥3 y, 5 not receiving any HIV medications).	Vitamin A: HAART (51 ± 5 μg/dL); no HIV medications (66 ± 11 μg/dL)	Mean plasma concentrations of vitamin A and retinol-binding protein were significantly lower ($P = 0.03$) and higher ($P = 0.04$), respectively, in those receiving HAART.
Rousseau et al, 2000 (94)	Cross-sectional study in France. 30 HIV-positive adults, mostly injection-drug users (23 receiving HAART for ≤3 y, 7 not receiving HAART).	Vitamin A: total (0.66 ± 1.2 μmol/L); 24 of 30 (80%) deficient (<1.5 μmol/L); concentrations not presented for HAART and non-HAART groups Vitamin E: total (9.24 ± 3.4 mg/L); 10 of 29 (34%) deficient (<6 mg/L); concentrations not presented for HAART and non-HAART groups	Mean plasma concentrations of vitamins A and E were not significantly different between those with a CD4 count < and >250 cells/μL, between those with viral load > and <5000 copies/mL, and between those receiving and not receiving HAART.
Tang et al, 2000 (95)	Cross-sectional study in the United States. 175 HIV-positive injection-drug users (30 receiving HAART, 65 receiving dual- or monotherapy, 80 not receiving any HIV medications).	α-Tocopherol[2]: HAART (1076 ± 468 μg/dL); no HIV medications (778 ± 209 μg/dL) α-Carotene[3]: HAART (1.06 ± 0.01 μg/dL); no HIV medications (0.74 ± 0.02 μg/dL) β-Carotene[2]: HAART (8.8 ± 3.1 μg/dL); no HIV medications (5.2 ± 0.9 μg/dL) Vitamin A[2]: HAART (42.0 ± 11.4 μg/dL); no HIV medications (38.4 ± 6.2 μg/dL) γ-Tocopherol[2]: HAART (238 ± 107 μg/dL); no HIV medications (202 ± 59 μg/dL)	Adjusted mean serum concentrations of α-tocopherol ($P = 0.0008$), α-carotene ($P = 0.05$), and β-carotene ($P = 0.02$), but not of vitamin A and γ-tocopherol, were significantly higher in those receiving HAART than in those not taking any HIV medications; no significant differences in adjusted mean serum vitamin concentrations between CD4 cell count categories (<200, 200–499, and ≥500 cells/μL).
Remacha et al, 2003 (96)	Cross-sectional study in Spain. 126 HIV-positive adults receiving HAART compared with 109 HIV-positive historical control subjects from 1989 to 1992 receiving HAART.	Folate: HAART (1473 ± 1087 mmol/L), 1 of 126 (0.8%) deficient (≤450 mmol/L); historical control subjects (1057 ± 665 mmol/L), 19 of 109 (17.4%) deficient Vitamin B-12: HAART (402 ± 218 pmol/L), 2 of 126 (1.2%) deficient (≤150 pmol/L); historical control subjects (330 ± 219 pmol/L), 20 of 109 (18%) deficient	Mean concentrations of red blood cell folate and serum vitamin B-12 were significantly higher in HIV-positive adults receiving HAART than in historical HIV-positive control subjects receiving HAART. Significantly fewer HIV-positive adults receiving HAART than historical control subjects had folate or vitamin B-12 deficiencies.
Woods et al, 2003 (97)	Cross-sectional study from 1995 to 2000 in the United States. 412 HIV-positive adults (615 patient-time intervals in adults receiving HAART, 454 patient-time intervals in adults not receiving HAART).	Vitamin B-12[4]: HAART [491 (382–667) pg/mL], 17% deficient (<350 pg/mL); no HAART [462 (369–617) pg/mL], 22% deficient	Median serum concentration of vitamin B-12 was significantly higher at the beginning of each patient-time interval in HIV-positive adults receiving HAART; multivariate analyses were not performed to account for higher intakes of vitamin B-12 ($P = 0.0002$) in participants receiving HAART.
Longitudinal studies			
Look et al, 2001 (98)	Longitudinal study from 1997 to 1998 in Germany. 17 HIV-positive adults studied at baseline and 100 d after HAART initiation.	Vitamin B-6: baseline [11.9 (10.7–13.2) μmol/L]; follow-up [15.7 (8.8– 22.7) μmol/L] Folate: baseline [3.8 (1.0–6.5) ng/mL]; follow-up [5.2 (1.8–8.5) ng/mL] Methylmalonic acid (surrogate of vitamin B-12)[3]: baseline [138 (100–176) μmol/L]; follow-up [186 (81–291) μmol/L]	Median follow-up serum concentrations of vitamin B-6, folate, and methylmalonic acid were not significantly higher than median baseline concentrations; however, baseline concentrations of vitamin B-6, folate, and methylmalonic acid were not significantly different from those of a cohort of HIV-negative healthy control subjects.

[1] Vitamin concentrations presented as $\bar{x}$ ± SD or as medians (interquartile ranges).
[2] Mean vitamin concentrations adjusted for dietary intake, supplement use, injection drug use, sex, cigarette smoking, and alcohol consumption.
[3] Mean vitamin concentrations adjusted for supplement use, injection drug use, sex, cigarette smoking, and alcohol consumption.
[4] Median vitamin concentrations represent average vitamin B-12 concentrations at the baseline of each patient-time interval.

of 412 HIV-positive adults, participants receiving HAART had significantly higher vitamin B-12 concentrations than did those not receiving HAART (97). However, participants receiving HAART also had significantly higher intakes of vitamin B-12 ($P = 0.0002$), for which multivariate adjustments were not performed.

TABLE 2
Observational studies of minerals in HIV-infected persons receiving highly active antiretroviral therapy (HAART)

Reference	Study design, location, and population	Mineral concentrations	Results and conclusions
Cross-sectional studies			
Batterham et al, 2001 (99)	Cross-sectional study in Australia. 48 HIV-positive adults (35 receiving HAART, 13 not receiving any HIV medications).	Selenium: HAART with detectable (>400 copies/mL) viral load (2.16 ± 0.54 μmol/L); HAART with undetectable viral load (2.22 ± 0.93 μmol/L); no HIV medications (2.40 ± 0.83 μmol/L)	Mean serum concentrations of glutathione peroxidase (P = 0.001), lipid peroxidase (P = 0.03), and uric acid (P = 0.009), but not of selenium, were significantly different between HIV-positive persons receiving HAART and those not taking any HIV medications.
Wellinghausen et al, 2000 (100)	Cross-sectional study in Germany. 79 HIV-positive adults (52 receiving HAART; 4 receiving dual- or monotherapy, 23 not receiving any HIV medications).	Zinc: HAART (12.5 ± 2.8 μmol/L), 25% deficient (<10.5 μmol/L); no HIV medications (12.7 ± 2.7 μmol/L), 22% deficient	Zinc concentrations were not significantly different between those receiving and those not receiving HAART.
Longitudinal studies			
Rousseau et al, 2000 (94)	Longitudinal study from 1995 to 1998 in France. 44 HIV-positive adults, mostly injection-drug users. At baseline, none were receiving HAART, but 80% were receiving dual-combination therapy. Of 30 participants with follow-up data, 23 were receiving HAART and 7 were not receiving any HIV medications.	Selenium: baseline (51.5 ± 15.6 μg/L), 77% deficient (<60 μg/L); follow-up (93.9 ± 21.6 μg/L), 10% deficient Iron: baseline (15.5 ± 5.6 μmol/L), 19% deficient (<11 μmol/L); follow-up (19.0 ± 16 μmol/L), 13% deficient Zinc: baseline (79.0 ± 22.8 μmol/L), 23% deficient (<75 μmol/L); follow-up (71.2 ± 16 μmol/L), 27% deficient Copper: baseline (149 ± 16 μg/100 mL), 98% overloaded (>140 μg/100 mL); follow-up (144 ± 95 μg/100 mL), 43% overloaded	Mean serum concentrations of selenium, iron, zinc, and copper did not significantly increase from baseline; however, significantly fewer participants had selenium deficiency and copper overload at follow-up; at follow-up, mean concentrations of selenium, iron, zinc, and copper were not significantly different between those receiving and those not receiving HAART.

We identified 2 cross-sectional studies that measured mineral concentrations in HIV-positive persons receiving HAART (**Table 2**). In one study, 35 HIV-positive adults receiving HAART had significantly higher concentrations of several antioxidant compounds (glutathione peroxidase, lipid peroxidase, and uric acid), but not of serum selenium, than did 13 HIV-positive persons not receiving HAART (99). These findings suggest that antioxidant capacity could be high in adults receiving HAART, irrespective of selenium concentrations. A study of HIV-positive adults found no significant difference in zinc concentrations between the 52 persons taking HAART and the 23 persons not receiving any HIV medications (100).

We identified 2 longitudinal observational studies that assessed micronutrient concentrations in HIV-positive persons before and after HAART initiation. A small study (n = 17) found slight, but not significant, increases in vitamin B-6, folate, and methylmalonic acid (a surrogate of vitamin B-12) concentrations 100 d (range: 50–188 d) after HAART initiation (Table 1) (98). However, participants in this study were initiated on HAART according to a less stringent threshold (CD4 count <500 cells/μL or HIV viral load >10 000 copies/mL) than is currently practiced, and baseline concentrations of vitamin B-6, folate, and methylmalonic acid were not significantly different than those of a cohort of HIV-negative healthy control subjects. Therefore, the adults initiating HAART in this study may have had higher micronutrient concentrations than did most adults at the time of HAART initiation. Another study measured concentrations of selenium, zinc, and copper in 44 HIV-positive adults in 1995, when 80% were receiving dual-combination therapy, and again in 1998, after 23 of 30 participants with follow-up data had been initiated on HAART (Table 2) (94). The percentage of persons with selenium deficiency (<60 μg/L) decreased significantly from 77% to 10%, and the percentage of persons with copper overload (>140 μg/dL) decreased significantly from 98% to 43% after HAART initiation. Although selenium, zinc, and copper concentrations were neither significantly improved after HAART initiation nor higher in those receiving HAART at follow-up, the study suggests that HAART may reduce selenium deficiency and copper excess.

INTERVENTION STUDIES OF MICRONUTRIENTS IN HIV-POSITIVE PERSONS RECEIVING HAART

We identified 2 nonrandomized intervention studies that assessed the effect of micronutrient supplementation in HIV-positive persons

receiving HAART (**Table 3**). In a small open-label trial, HIV-positive adults ($n = 10$) experiencing either lipoatrophy or sustained hyperlactemia were given vitamins C and E and *N*-acetyl cysteine for 24 wk (101). At baseline, the group had a mean CD4 count of 627 cells/μL, and 9 participants had undetectable viral load concentrations (<400 copies/mL). The investigators noted significant increases in fasting glucose and insulin resistance, a significant decrease in waist-to-hip ratio, a trend for a decrease in LDL, and no significant changes in serum lactate, body fat, lean body mass, CD4 cell count, or plasma viral load. These investigators suggested that these changes may be the result of the natural history of insulin resistance in lipoatrophy. Another nonrandomized intervention study assessed the effects of either a low-dose or high-dose antioxidant regimen (mainly vitamins A, C, and E and selenium) for 12 wk on antioxidant defenses, oxidative stress, and plasma viral load (99). Of the 48 HIV-positive adults who completed the study, of whom 32 were receiving HAART, antioxidant supplements significantly increased antioxidant defenses but had no significant effect on oxidative stress or plasma viral load. No significant differences were observed between those supplemented with low-dose and those supplemented with high-dose antioxidants, and the authors reported no differences between those receiving and not receiving HAART.

We identified 4 randomized trials of micronutrient supplements conducted in HIV-positive persons receiving HAART (Table 3). A small crossover trial ($n = 15$) examined the effect of a 14-d calcium regimen in HIV-infected adults experiencing chronic nelfinavir-associated diarrhea (102). Periods of calcium supplementation had no significant clinical improvements in the diarrhea score. In a placebo-controlled trial, 29 HIV-positive patients with a CD4 count <500 cells/μL received either 6 mo of vitamin E supplements or placebo while simultaneously initiating HAART (103, 104). The authors reported no significant differences in the CD4 count, ratio of CD4 to CD8, and plasma viral load between the 2 groups, but a greater increase in lymphocyte viability was observed in the vitamin E–supplemented group (104). Another placebo-controlled trial assessed the effect of a daily supplement of vitamins A, C, and E for 6 mo on antioxidant defenses, oxidative stress, and CD4 cell count in 30 HIV-infected adults (105). At baseline, concentrations of vitamins A, C, and E were significantly lower among the trial cohort compared with a small group of HIV-negative healthy volunteers. At follow-up, concentrations of vitamins A, C, and E had been restored in the supplemented group, but not in the placebo group. Furthermore, the supplemented group had significantly greater antioxidant defenses and less oxidative stress than did the placebo group. The supplemented group also had a higher mean CD4 count (460 compared with 360 cells/μL), but this difference was not statistically significant. A placebo-controlled trial examined the effect of 2 y of selenium supplementation on CD4 cell counts and hospital admissions in 186 HIV-positive injection-drug users, 85 of whom were receiving HAART (106). The 2 groups were similar at baseline, with the exception that fewer subjects receiving selenium were not taking any HIV medications. At follow-up, the supplemented group had higher serum selenium concentrations and less risk of a decrease in CD4 count of >50 cells/μL. In addition, the supplemented group had fewer hospitalizations for opportunistic infection and other HIV-related conditions than did the placebo group. However, hospitalizations were fewer among the participants receiving HAART than in those not taking any HIV medications, which were not evenly distributed at baseline. In multivariate analyses, adjusted for HAART treatment, other HIV medications, age, baseline CD4 count, baseline viral load, and selenium supplementation were significantly associated with fewer hospitalizations. Finally, a recent randomized controlled trial conducted in 40 HIV-infected adults found that comprehensive micronutrient supplementation for 12 wk significantly increased the CD4 T cell count and had no significant effect on plasma viral load compared with the placebo group (107). Although the intervention group had a lower CD4 T cell count than did the placebo group (357 compared with 467 cells/μL) at baseline, the mean change in CD4 T cell count was also significantly greater in the intervention group than in the placebo group. In addition, the investigators found that micronutrient supplementation had no significant effects on fasting glucose, insulin, lipids, venous lactates, serum creatinine, alanine aminotransferase, total bilirubin, or alkaline phosphatase.

A summary of our review of micronutrient intervention studies in HIV-infected persons receiving HAART suggests that micronutrient supplementation has shown mixed beneficial effects on immunologic status, plasma viral load, and clinical outcomes. Both intervention studies with antioxidants found increased oxidative defenses, but only one of those studies found decreased oxidative stress, and neither study found a reduced plasma viral load. Two intervention studies that examined micronutrient interventions for HAART-related side effects were small and found no significant improvements. One small recent intervention study found significant improvements in CD4 count but not in plasma viral load. However, intervention studies have been few in number and have individually had major limitations, most commonly a small sample size and a short intervention period. The largest and longest randomized trial conducted found that daily selenium supplementation for 2 y decreased hospital admissions in HIV-positive users of injection drugs, but <50% were receiving HAART.

ANEMIA, IRON, AND ERYTHROPOIETIN IN HIV-POSITIVE PERSONS RECEIVING HAART

Anemia is more common and more severe with advanced HIV disease progression (108), and studies disagree on whether this is principally due to iron-deficiency anemia or to anemia of chronic disease (109–112). Several longitudinal studies have reported either a significant increase in hemoglobin concentration or a significant decrease in clinical anemia 1 y after HIV-positive persons began HAART (113–116). In a multivariate analysis in which BMI, opportunistic infections, and sex were adjusted for, mean hemoglobin concentrations increased significantly by 0.223 g/L per month in HIV-positive persons receiving HAART (114). In another multivariate analysis, adjusted for CD4 cell count, plasma viral load, and anemia treatments, HAART was strongly associated with not becoming anemic during the follow-up period (116).

One longitudinal study assessed serum iron concentrations in 30 HIV-infected persons, of whom 23 had been receiving HAART for ≤3 y (Table 2) (94). Although mean iron concentrations had increased from 15.5 μmol/L at baseline to 19.0 μmol/L at follow-up, this change was not significant. At follow-up, iron concentrations were not significantly different between those receiving and those not receiving HAART. Although the results are based on only one small study, they provide little insight on whether improvements in anemia after HAART initiation are primarily related to iron repletion.

TABLE 3
Intervention studies of micronutrients in HIV-infected persons receiving highly active antiretroviral therapy (HAART)

Reference	Study design, population, and inclusion and exclusion criteria	Intervention	Primary outcomes	Major findings	Conclusions
Nonrandomized trials					
McComsey et al, 2003 (101)	Nonrandomized, open-label pilot study without placebo control in the United States. 10 HIV-positive adults receiving HAART for ≥12 mo. 9 had lipoatrophy and 1 had sustained hyperlactemia at enrollment.	Daily vitamin C (1000 mg) and vitamin E (800 IU) and twice-daily *N*-acetyl cysteine (600 mg) for 24 wk.	Fasting glucose, insulin resistance, peripheral fat, lipoatrophy, CD4 cell count, plasma viral load	Intervention significantly increased fasting glucose and insulin resistance and decreased waist-to-hip ratio compared with placebo; intervention had no significant effect on peripheral fat, lipoatrophy, CD4 cell count, or plasma viral load.	24 wk of a supplement worsened fasting glucose and insulin resistance and did not significantly improve peripheral fat, lipoatrophy, immunologic status, or plasma viral load.
Batterham et al, 2001 (99)	Nonrandomized trial without placebo control in Australia. 66 HIV-positive adults enrolled and 48 completed study (32 receiving HAART, 3 receiving dual therapy, 13 not receiving any HIV medications). Exclusion criteria included taking supplements within 4 wk of enrollment, not clinically stable or with active infection, and change of HIV medication regimen within 6 wk of enrollment.	Daily supplementation with either a low-dose[1] or a high-dose[2] antioxidant regimen for 12 wk.	Antioxidant defense (glutathione, glutathione peroxidase), oxidative stress (allantoin, uric acid), plasma viral load	Intervention significantly increased concentrations of glutathione and glutathione peroxidase from baseline, but had no significant effect on allantoin, uric acid, or plasma viral load; no significant differences between those receiving low-dose and those receiving high-dose regimens.	12 wk of an antioxidant supplement increased oxidative defenses, but did not affect oxidative stress or plasma viral load.
Randomized trials					
Jensen-Fangel et al, 2003 (102)	Randomized crossover trial without placebo control in Denmark. 15 HIV-positive adults receiving HAART; all with chronic nelfinavir-associated diarrhea.	Twice-daily calcium carbonate (1350 mg) f or 14 d. A subset of 6 patients additionally treated with twice-daily calcium gluconate (2950 mg) and an extra 300 mg calcium carbonate.	Clinical improvement of diarrhea	Intervention had no significant effect on clinical measurements of diarrhea.	14 d of a calcium carbonate supplement did not clinically improve nelfinavir-associated diarrhea.
Spada et al, 2002 (103); De Souza et al, 2005 (104)	Randomized, placebo-controlled trial in Brazil. 29 HIV-positive adults with CD4 count <500 cells/μL. 26 initiated HAART and 3 initiated dual-combination therapy at study enrollment.	Daily vitamin E (800 mg α-tocopherol) for 6 mo.	Lymphocyte viability, CD4 cell count, CD4:CD8 cells, plasma viral load	Intervention had no significant effect on CD4 cell count, CD4:CD8 cells, or plasma viral load as compared with placebo; intervention significantly increased lymphocyte viability compared with placebo.	6 mo of vitamin E supplementation improved lymphocyte viability, but did not affect immune cell count or plasma viral load.

(*Continued*)

TABLE 3 *(Continued)*

Reference	Study design, population, and inclusion and exclusion criteria	Intervention	Primary outcomes	Major findings	Conclusions
Jaruga et al, 2002 (105)	Randomized, placebo-controlled trial in Poland. 30 HIV-positive adults receiving HAART.	Daily vitamin A (5000 IU), vitamin C (50 mg), and vitamin E (100 IU) for 6 mo.	Antioxidant defense (catalase, superoxide dismutase) oxidative stress; (thiobarbituric acid–reactive substances); CD4 cell count	Intervention significantly increased concentrations of catalase and superoxide dismutase and significantly lowered thiobarbituric acid–reactive substances; the CD4 cell count increased in the intervention group from baseline, whereas the mean CD4 count of the placebo group decreased, but the difference was not statistically significant.	6 mo of an antioxidant multivitamin supplement significantly increased antioxidant defenses, significantly reduced oxidative stress, and possibly improved immunologic status.
Burbano et al, 2002 (106)	Randomized placebo-controlled trial in the United States. 186 HIV-positive injection-drug users (85 receiving HAART, 39 receiving dual- or monodrug therapy, 52 not receiving any HIV medications).	Daily selenium (200 μg) for 2 y.	CD4 cell count, hospital admissions	Significantly fewer participants in the intervention group than in the placebo group had a decrease in CD4 cell count of >50 cells/μL during the study; intervention significantly reduced hospital admissions because of opportunistic infections and other HIV-related conditions; in multivariate analyses,[3] the placebo group had a 2.4 greater risk of hospitalization ($P = 0.01$).	2 y of a selenium supplement decreased large reductions in CD4 cell count and reduced the risk of hospitalization.
Kaiser et al, 2006 (107)	Randomized placebo-controlled trial in the United States. 40 HIV-positive adults receiving HAART.	Micronutrient supplementation twice daily for 12 wk.[4]	Fasting glucose, insulin, lipids, CD4 cell count, plasma viral load	Intervention significantly increased absolute CD4 cell count ($P = 0.03$) and mean change in CD4 cell count from baseline ($P = 0.01$) and had no significant effects on fasting glucose, insulin, lipids, or plasma viral load.	12 wk of micronutrient supplementation increased CD4 cell count.

[1] Included 5450 IU β-carotene, 250 mg vitamin C, 100 IU vitamin E, 100 μg Se, 50 mg coenzyme Q10, 10 mg thiamine, 25 mg vitamin B-6, 55 mg pantothenic acid, 250 μg folate, 50 μg vitamin B-12, and 5 mg Zn.

[2] Included 21800 IU β-carotene, 1000 mg vitamin C, 400 IU vitamin E, 200 μg Se, 200 mg coenzyme Q10, 40 mg thiamine, 100 mg vitamin B-6, 220 mg pantothenic acid, 1000 μg folate, 200 μg vitamin B-12, and 20 mg Zn.

[3] Multivariate analysis adjusted for HAART (yes or no), use of other HIV medications (yes or no), age >50 y, CD4 cell count at baseline, and plasma viral load >10 000 copies/mL at baseline.

[4] Micronutrient supplement included 1200 mg *N*-acetyl cysteine, 1000 mg acetyl L-carnitine, 400 mg α-lipoic acid, 20 000 IU β-carotene, 8000 IU vitamin A, 1800 mg vitamin C, 60 mg thiamine, 60 mg riboflavin, 60 mg pantothenic acid, 60 mg niacinamide, 60 mg inositol, 260 mg vitamin B-6, 2.5 mg vitamin B-12, 400 IU vitamin D, 800 IU vitamin E, 800 μg folic acid, 800 mg Ca, 400 mg Mg, 200 μg Se, 150 μg I, 30 mg Zn, 2 mg Cu, 2 mg B, 99 mg K, 18 mg Fe, 10 mg Mn, 50 μg biotin, 100 μg Cr, 300 μg Mo, 60 mg choline, 300 mg bioflavonoid complex, 100 mg L-glutamine, and 150 mg betaine HCL.

Although HIV-associated anemia is caused by several factors, several intervention trials have found beneficial effects of epoetin-alfa on anemia. Two open-label trials, one in 221 HIV-infected anemic (hemoglobin $\leq$ 11 g/dL) patients taking zidovudine and another in 523 HIV-infected anemic patients not taking zidovudine, both found that epoetin-alfa significantly improved hemoglobin concentrations and reduced the frequency and number of blood transfusions (117, 118). An overview of 4 randomized placebo-controlled trials, which included 225 HIV-infected anemic participants taking zidovudine, also found that epoetin-alfa reduced the number of required blood transfusions (119). Subsequently, an open-label trial showed that once-weekly epoetin-alfa significantly improved hemoglobin concentrations and quality-of-life measurements in anemic (hemoglobin $\leq$ 11 g/dL) HIV-positive participants receiving HAART, independent of HIV disease status (120). Finally, an HIV Working Group recently endorsed initiating weekly epoetin-alfa therapy if correctable causes of anemia have been ruled out and the hemoglobin concentration is $<$13 g/dL in men and $<$12 g/dL in women (121).

CELLULAR AND METABOLIC DISTURBANCES WITH HAART

Although HAART has been shown to be associated with a decreased prevalence of opportunistic gastrointestinal diseases (122) and incidence of malnutrition (123), gastrointestinal infections and severe gastroenteritis, which alter micronutrient absorption, may persist after HAART initiation (11, 124). Several HIV medications, particularly NRTIs, can inhibit the replication of mitochondrial DNA and cause vomiting and diarrhea that can reduce the absorption or increase the losses of several micronutrients (125, 126). Mitochondrial toxicity may also increase the production of reactive oxygen species, resulting in oxidative damage, which can lead to lactic acidosis (127). Mitochondrial dysfunction may be responsible for HAART-associated lipodystrophy (128). Patients initiating HAART often experience a gain in central adiposity and lean mass over the first 24 wk and may develop glucose intolerance, insulin resistance, hyperlipidemia, and peripheral lipoatrophy after 6 mo (129–131).

HIV can also induce chronic oxidative stress, which has been associated with apoptosis of T lymphocytes and increased rates of HIV replication through the activation of NF-κB (73, 132, 133). Studies that have assessed antioxidant capacity and oxidative stress in HIV-positive persons receiving HAART have found conflicting results. A small longitudinal study found that antioxidant capacity increased significantly 2 mo after 20 HIV-positive children were switched from a dual-NRTI regimen to HAART (134). A cross-sectional study found no significant difference in oxidative stress measures between 13 HIV-positive adults receiving HAART and 35 HIV-positive adults not receiving HAART (135). This study also found that greater dietary intakes of selenium, but not of vitamin C, β-carotene, α-tocopherol, or zinc, were inversely related to plasma malondialdehyde, which is an indicator of oxidative stress (135).

HIV medications may also have a direct effect on the synthesis and metabolism of certain micronutrients. Three PIs—ritonavir, indinavir, and saquinavir—have been shown in cell and tissue cultures to significantly increase retinal dehydrogenase activity, an enzyme responsible for the production of *all-trans* retinoic acid, a precursor of vitamin A (93). Furthermore, indinavir also induced retinal dehydrogenase gene expression (93).

THE ROLE OF MICRONUTRIENT SUPPLEMENTS WITH HAART

The restoration of depleted micronutrients through supplementation may have several cellular and clinical benefits in HIV-positive persons receiving HAART. Because zidovudine is associated with lower serum vitamin B-12 concentrations (136), vitamin B-12 could be a useful adjunct to reduce zidovudine-associated hematologic toxicity and anemia, which affect $\approx$5–10% of patients receiving zidovudine (127). In a randomized placebo-controlled trial of 75 HIV-positive persons taking zidovudine, participants receiving daily folinic acid (15 mg) and monthly vitamin B-12 (1 mg) had no significant reductions in hematologic toxicity or myelotoxicity after 12 mo (137). However, HIV-infected patients with lower baseline concentrations of vitamin B-12 had increased incidences of anemia, leucopenia, and neutropenia during the study period (137). Another small trial, also in HIV-positive persons not receiving HAART, found no effect of vitamin B-12 injections on zidovudine-related hematologic toxicity (138).

Micronutrient supplements can also reduce cellular and metabolic complications of HAART. First, a study of 120 HIV-positive adults receiving HAART found that a greater total intake of vitamin E was associated with fewer outcomes of HAART-associated metabolic complications, including body fat redistribution, dyslipidemia, and insulin resistance, which the investigators hypothesized may have been due to changes in the ratio of plasma reduced to oxidized glutathione and oxygen free radicals (139). Second, thiamine (140) and riboflavin (141), which are important for normal mitochondrial function, have both been shown to reduce NRTI-associated lactic acidosis. A case report of 2 persons with lactic acidosis who received high doses of thiamine (100 mg/d) and riboflavin (50 mg/d) were able to resume NRTI-containing HAART regimens without recurrence of hyperlactemia (142). In another case report, high doses of riboflavin (50 mg/d) given to an HIV-positive woman experiencing lactic acidosis and riboflavin deficiency while taking 4 NRTIs resulted in recovered concentrations of blood urea nitrogen, lactic acid, and arterial pH concentrations (143). In addition, regular vitamin E supplementation has also been associated with significantly lower serum lactate concentrations in 30 HIV-positive persons receiving HAART (144). Third, selenium supplements have been shown to stimulate glutathione peroxidase activity, a measure of antioxidant defenses, to reduce NF-κB activation in HIV-1 infected cells (145–147), and possibly to up-regulate the activity of natural killer and cytotoxic T cells (148). Other antioxidants may also be beneficial in reducing oxidative stress, which normally signals NF-κB to activate viral transcription (133). Therefore, several micronutrients may play a role in reducing mitochondrial dysfunction, oxidative stress, and metabolic complications, which are commonly experienced by HIV-positive persons receiving HAART.

POTENTIAL NEGATIVE EFFECTS OF MICRONUTRIENT SUPPLEMENTS

Micronutrient supplements may not always be beneficial in HIV-infected persons. In asymptomatic HIV-positive men,

greater zinc intakes from foods and supplements has been shown to be associated with faster HIV disease progression and mortality in a clear dose-response relation (45, 49). Randomized trials have shown that maternal vitamin A supplements significantly increase the risk of mother-to-child transmission of HIV (149) and can increase mortality in some children born to HIV-positive mothers (63). Other randomized trials have shown that supplementation with vitamin A (150) and with a multivitamin containing selenium (151) can cause increased viral shedding in the female genital tract. Given these previous trials, one should not presume that taking micronutrients are always beneficial, and proposed micronutrient interventions should be scrutinized by well-designed, randomized, placebo-controlled trials.

Micronutrient supplements can also have adverse effects on cellular mechanisms in HIV-positive persons. Iron can enhance the production of reactive iron species and cause more oxidative stress, which could activate NF-κB and increase viral transcription (152). Two patients were reported to have an increase in plasma viral load after the initiation of iron supplementation for iron-deficiency anemia (153). Therefore, increasing iron concentrations could propagate HIV replication despite HAART.

Micronutrient interventions have also been shown to alter the bioavailability, metabolism, and pharmacokinetics of certain HIV medications. A daily vitamin C supplement (1000 g) for 7 d reduced the peak blood concentrations of indinavir by 20% ($P = 0.04$) and the area under the curve by 14% ($P = 0.05$) in 7 HIV-negative healthy volunteers (154). Calcium supplements have been shown to increase serum concentrations of nelfinavir and its metabolite (M8) in 15 HIV-positive persons receiving HAART (102). In a small randomized trial of HIV-positive persons experiencing chronic diarrhea or wasting, 7 d of glutamine or alanyl-glutamine improved clinical outcomes, but increased HIV drug concentrations by 45% compared with the control group ($P = 0.02$) (155). Furthermore, St John's wort and garlic supplements, both popular herbal treatments, have also been shown to significantly reduce plasma concentrations of indinavir and saquinavir, respectively (156, 157). These studies raise concerns about the possibility of micronutrient and herbal supplementation leading to increased toxicity or viral resistance in instances where drug metabolism or clearance is enhanced.

DISCUSSION

A summary of our review of observational studies of micronutrients in HIV-positive persons receiving HAART suggests that some, but not all, micronutrients may increase after HAART initiation. Among cross-sectional studies, concentrations of α-carotene, β-carotene, α-tocopherol, vitamin B-12, and folate, but not of vitamin A, selenium, or zinc, were significantly higher in HIV-positive persons receiving HAART than in HIV-positive persons not receiving HAART. Of the 2 identified longitudinal studies, both of which were small, 100 d of HAART did not significantly increase concentrations of vitamin B-6, vitamin B-12, or folate in 17 HIV-positive adults, and up to 3 y of HAART did not significantly increase concentrations of selenium, iron, zinc, or copper in 23 HIV-positive users of injection drugs. Another longitudinal study, which was not included in the review because it was conducted between 1990 and 2001 and did not define treatment regimens, found adjusted concentrations of serum vitamin B-12, but not of serum folate, increased significantly 6 mo after HIV medications were initiated in 38 HIV-positive adults (158). However, none of these observational studies adjusted micronutrient concentrations by inflammatory markers, which could alter serum concentrations of several micronutrients.

Although we attempted to identify all published studies relevant to micronutrients and HAART, we may not have captured all relevant articles in this review. In addition, the results presented from these published articles may be subject to a publication bias, which typically favors studies reporting significant findings. However, of the data presented in Tables 1 and 2, the results were not significant for 15 of 21 (71%) micronutrients. In addition, the observational and interventional studies presented in this review are subject to their own biases and limitations, and most were limited by small sample sizes.

Despite these limitations, this review helps highlight some research gaps and generates suggestions for future research related to micronutrient supplementation in HIV-positive persons receiving HAART. First, because studies have persistently described high concentrations of inflammatory markers after HAART initiation (159, 160), a longitudinal description of changes in micronutrient concentrations after HAART initiation, with adjustments for acute inflammatory markers, especially C-reactive protein, would be valuable. Second, because no trials have assessed the effect of micronutrient supplements on clinical disease progression or mortality in HIV-positive persons receiving HAART, large randomized placebo-controlled trials should be conducted in HIV-positive persons receiving HAART to determine the effect on clinical, rather than laboratory, HIV-related outcomes and side effects of particular HIV medications.

CONCLUSIONS

In conclusion, although micronutrient supplements have been shown to be beneficial in HIV-infected persons not receiving HAART, few data are available to support or refute the benefits of providing micronutrient supplements to HIV-positive persons receiving HAART. Future research efforts should focus on determining whether certain micronutrients remain depleted after HAART initiation and whether micronutrient supplements would be beneficial in HIV-positive persons receiving HAART. Micronutrients can be an easy and inexpensive adjunctive therapy to decrease the side effects of HIV medications and to improve clinical outcomes in HIV-infected persons in both developed and developing countries.

PKD and WWF designed the project. PKD primarily wrote the manuscript. RK, FM, and WWF provided valuable insight for revising the manuscript. All authors read and approved the final manuscript. None of the authors declared a conflict of interest.

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