The Effect of Multiple Micronutrient Supplementation on Mortality and Morbidity of HIV-Infected Adults: A Meta-Analysis of Randomized Controlled Trials

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(Received October 12, 2011)

Summary Numerous preclinical studies have suggested that micronutrient status is associated with the progression of human immunodeficiency virus (HIV) disease, but results from observational studies are still controversial. The objective was to systematically review the efficacy of multiple micronutrient supplementation on mortality and morbidity in HIV-infected adults. A comprehensive search of the PubMed/MEDLINE, EMBASE and Cochrane Library was performed. Six randomized controlled trials assessing the effect of multiple micronutrient supplementation on HIV-infected adults were included. Relative risk was used as an effect measure to compare the intervention and control groups with fixed-effects or random effects models. Sensitivity analyses were applied to further evaluate heterogeneity. Multiple micronutrient supplementation decreased the mortality and morbidity of HIV-infected adults nonstatistically significantly (RR=0.90; 95% CI, 0.80 to 1.02; $p=0.09$). Sensitivity analyses revealed that multiple micronutrient supplementation decreased the mortality and morbidity of adults infected with HIV alone statistically significantly (RR=0.75; 95% CI, 0.58 to 0.95; $p=0.02$), but not adults infected with both HIV and pulmonary tuberculosis (RR=0.97; 95% CI, 0.84 to 1.11; $p=0.65$). Multiple micronutrient consumption was correlated with reduction of the mortality and morbidity of HIV-infected adults, at least those in developing countries and infected with HIV alone, and should be prescribed by local doctors for those in earlier stages especially.

Key Words multiple micronutrient supplementation, mortality, HIV, meta-analysis, Randomized controlled trial

It is estimated that 33 million people worldwide are infected with human immunodeficiency virus (HIV), many of whom have symptoms of the acquired immunodeficiency syndrome (AIDS). From its discovery in 1981 to 2006, AIDS killed more than 25 million people. Over 95% of the global total of AIDS cases are in the developing world, especially in sub-Saharan Africa, with prevalence among adults at more than 10% in several African countries. The “Treat 3 million by 2005” plan of World Health Organization (WHO) demonstrated that patients with advanced disease will receive antiretroviral treatment, while those in earlier stages will be monitored and given supportive care (1). It is therefore reasonable and cost-effective to find some inexpensive ways to retard the progression to AIDS and death of HIV-infected patients.

When referring to the mechanisms of progression to AIDS, previous preclinical studies have revealed that oxidative stress may play an important role in the stimulation of HIV replication, the reduction in the number of circulating T lymphocytes and the development of immunodeficiency (2, 3). Antioxidant micronutrients, cheap and easily tolerated agents, have been revealed to

be correlated to not only antioxidant function but also the enhancement of immunity, and several observational studies have reported that a lot of micronutrient deficiencies among HIV-infected patients are associated strongly with the progression to AIDS and death (4–6).

Previous meta-analyses have demonstrated that micronutrient supplementation may be associated with reduction of mortality and morbidity among oxidative-injury related diseases, such as cardiovascular disease and cancer (7–9), but meta-studies on its relationship with infectious diseases are still scarce. Thus, we conducted a meta-analysis of randomized controlled trials to further illuminate whether multiple micronutrient supplementation was effective in reducing mortality and morbidity among HIV-infected adults.

METHODS

Search strategy and study assessment. PubMed/MEDLINE (September 2011), EMBASE (September 2011), and Cochrane Library (issue 9 2011) were searched for all randomized controlled trials (RCTs) on micronutrient supplementation and HIV-infected adults. The following Medical Subject Heading (MeSH) items and free-text words were variously combined to identify all RCTs as far as possible: micronutrient, multiple micronutrient, antioxidant, HIV, AIDS, mortality, morbidity, clinical

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Fig. 1. Flowchart of trial selection.

cal trial, randomized controlled trial, controlled clinical trial, and placebo controlled trial. Reference lists of relevant review articles were reviewed, and RCTs meeting the inclusion criteria discussed below were recruited in our meta-analysis. Two investigators (S. Jiang and J. He) independently manipulated the electronic search and assessed the title and abstract of every retrieved RCT, and if necessary, full articles were retrieved for further assessment to determine articles which met the inclusion criteria. The frequently used Jadad scale for assessing quality and risk of bias of RCTs has been discouraged by the Cochrane Collaboration; therefore, the same two investigators evaluated the quality of these studies applying the Jadad criteria. Only studies with a Jadad score of 3 or higher were included in our review. Discrepancies were resolved by consulting the third investigator (X. Zhao).

Study selection criteria. The titles and abstracts of all articles identified by the search strategy were retrieved for further review. Inclusion criteria were then applied to all potentially relevant RCTs. The inclusion criteria for the meta-analysis were as follows: (1) only RCTs evaluating the efficacy of multiple micronutrients on mortality and morbidity of HIV-infected adults; (2) study samples limited to adults infected with HIV; (3)

trials with double-blinding and placebo-control.

Data extraction. Two investigators (X. Zhao and H. Li) extracted the data of all included trials using a standardized protocol. Data extracted were as follows: (1) number of participants enrolled in each trial; (2) number of participants in intervention and control arms; (3) population of participants in each trial; (4) mean age of participants; (5) types and dosages of micronutrient intake; (6) concomitant diseases in each trial; (7) follow-up year; (8) dropout numbers in each trial; (9) publication year.

Statistical analyses. All statistical analyses but Begg's rank correlation test were performed using Review Manager 5.0 software programs (Cochrane Collaboration) for the performance of meta-analysis. Dichotomous data were expressed as relative risk (RR) with 95% confidence intervals (95% CI). In pooling the data from these included trials, a fixed-effects model was applied using the method of Mantel-Haenszel (M-H) when there was no statistically significant heterogeneity. A random effects model was employed using the method of DerSimonian and Laird (DL) if statistically significant heterogeneity was detected. The χ^2 test was employed to assess whether or not any clinical, methodological, or statistical heterogeneity existed among

Table 1. Characteristics of included trials.

Study, year (reference)	Country	Participants	Mean age, y	Micronutrients	Follow-up, y
Jiamton et al., 2003 (11)	Bangkok, Thailand	402 HIV-infected individuals living in and around Bangkok with CD4 count in the range of 50×10^6 – 550×10^6	32	vitamin A 3,000 μ g, betacarotene 6 mg, vitamin D 20 μ g, vitamin E 80 mg, vitamin K 180 μ g, vitamin C 400 mg, vitamin B ₁ 24 mg, vitamin B ₂ 15 mg, vitamin B ₆ 40 mg, vitamin B ₁₂ 30 μ g, folacin 100 μ g, panthothenic acid 40 mg, iron 10 mg, magnesium 200 mg, manganese 8 mg, zinc 30 mg, iodine 300 μ g, copper 3 mg, sele- nium 400 μ g, chromium 150 μ g, and cys- tine 66 mg	0.923
Fawzi et al., 2004 (12)	Dar es Salaam, Tanzania	806 pregnant women infected with HIV	25	20 mg of vitamin B ₁ , 20 mg of vitamin B ₂ , 25 mg of vitamin B ₆ , 100 mg of niacin, 50 μ g of vitamin B ₁₂ , 500 mg of vitamin C, 30 mg of vitamin E, and 0.8 mg of folic acid	5.9
Range et al., 2006 (13)	Mwanza, Tanzania	181 HIV-positive patients aged ≥ 15 y with sputum-positive pulmonary tuberculosis	35	Vitamin A 1.5 mg, vitamin B ₁ 20 mg, vitamin B ₂ 20 mg, vitamin B ₆ 25 mg, vitamin B ₁₂ 50 mg, folic acid 0.8 mg, niacin 40 mg, vitamin C 200 mg, vitamin E 60 mg, vitamin D ₃ 5 mg, selenium 0.2 mg, copper 5 mg, and Zn 45 mg	0.67
Semba et al., 2007 (14)	Zomba and Blantyre, Malawi	328 HIV-positive patients with pulmonary tuberculosis	micronutrients group: 34 placebo group: 33.1	vitamin A 2.4 mg, vitamin C 500 mg, vitamin D 10 μ g, vitamin E 181.8 mg, vitamin B ₆ 2 mg, vitamin B ₁₂ 6 μ g, riboflavin 1.7 mg, thiamin 1.5 mg, niacin 20 mg, folate 0.4 mg, zinc 10 mg, iodine 175 μ g, and selenium 65 μ g	1.04
Kelly et al., 2008 (15)	Misisi, Lusaka, Zambia	136 individuals infected with HIV	34	β -carotene 4.8 mg, vitamin C 70 mg, vitamin D 5 μ g, vitamin E 10 mg, vitamin B ₁ 1.4 mg, vitamin B ₂ 1.4 mg, niacin 18 mg, vitamin B ₆ 1.9 mg, vitamin B ₁₂ 2.6 μ g, folic acid 400 μ g, iron 30 mg, zinc 15 mg, copper 2 mg, selenium 65 μ g, and iodine 150 μ g	3.3
Villamor et al., 2008 (16)	Dar es Salaam, Tanzania	471 individuals infected with HIV and pulmonary tuberculosis	34	5,000 IU of retinol, 20 mg of vitamin B ₁ , 20 mg of vitamin B ₂ , 25 mg of vitamin B ₆ , 100 mg of niacin, 50 μ g of vitamin B ₁₂ , 500 mg of vitamin C, 200 mg of vitamin E, 0.8 mg of folic acid, and 100 μ g of sele- nium	2

these included trials. Statistical significance of the test for heterogeneity was set at 0.05. Sensitivity analysis was applied to further evaluate the heterogeneity. The potential publication bias in the meta-analysis was examined by checking the relationship between the intervention effects and the standard error of the estimate by applying a funnel plot visually. Begg's rank correlation test was conducted using Stata version 11.0 to evaluate the publication bias quantitatively.

RESULTS

Literature search

The detailed search step was summarized in a flow-

chart illustrating the process of exclusion for certain studies according to the Quality of Reporting of Meta-analysis (QUOROM) recommendations (10) (Fig. 1). We initially identified 205 potentially relevant articles. One hundred sixty-eight references were excluded because of study design based on titles and/or abstracts, and then 37 HIV-related RCTs were retained for further assessment. Of all these RCTs, 7 trials with single micronutrient supplementation, 7 trials evaluating the effect of micronutrient supplementation on mortality and morbidity of mother-to-child HIV-infected infants or children, 2 trials with fewer than 10 deaths, 2 trials evaluating the relationship between micronutrient

Table 2. Quality assessment of included trials.

Study, year	Randomization	Blinding	Placebo-controlled	Dropout (n)	Jadad score
Jiamton et al., 2003	adequate	double-blind	yes	79	5
Fawzi et al., 2004	unclear	double-blind	yes	0	4
Range et al., 2006	adequate	double-blind	yes	not stated	3
Semba et al., 2007	adequate	double-blind	yes	103	5
Kelly et al., 2008	adequate	double-blind	yes	not stated	4
Villamor et al., 2008	adequate	double-blind	yes	0	5

Adequate, if the allocation sequence was generated by a computer or random number table. Unclear, if the trial was described as randomized, but the method used for the allocation sequence generation was not described.

Fig. 2. Efficacy on mortality and morbidity of HIV-infected adults. CI, confidence interval.

Fig. 3. Funnel plot for the publication bias of all 6 included trials. p -value is derived from Begg's rank correlation test.

serum status and HIV and 1 trial with a placebo containing multiple micronutrients were also excluded. At last, we included 6 RCTs in the meta-analysis (11–16) (Table 1).

Description of included RCTs

The quality of included studies is shown in Table 2. All trials were randomized, double-blinded and placebo-controlled, and received Jadad scores of 3 ($n=1$), 4 ($n=2$), or 5 ($n=3$) points. All but one trial reported nonstatistically significant reduction or increase in mortality and morbidity of HIV-infected adults. The included trials were reported between 2003 and 2008, and their sample sizes varied between 136 and 806

participants. The numbers of micronutrient types ranged from 8 to 21, and 7 kinds of micronutrients, namely vitamin B1, vitamin B2, vitamin B6, vitamin B12, vitamin C, vitamin E and folic acid, were common to the 6 included trials. The dosages used in these supplements were about six to ten times higher than the recommended daily allowances (RDA) (17) for healthy individuals in 4 of the 6 trials (11–13, 16), and the other 2 trials administered the dosages approximately equal to RDA except for the higher dosages of vitamin A, C and E in 1 of the 2 trials (14, 15). All of these supplements were prescribed daily. The mean ages of included trials ranged from 25 to 35, and the average

Fig. 4. Efficacy on mortality and morbidity of pregnant women (A) and non-pregnant adults (B). CI, confidence interval.

Fig. 5. Efficacy on mortality and morbidity of adults infected with HIV alone (A) and infected with HIV and pulmonary tuberculosis (B). CI, confidence interval.

follow-up years ranged from 0.67 to 5.9 y. Participants in 3 trials were infected with pulmonary tuberculosis concomitantly.

Effect of multiple micronutrient supplementation on mortality and morbidity in HIV-infected adults

Overall, multiple micronutrient supplementation nonstatistically significantly decreased the mortality and morbidity of HIV-infected adults. The pooled relative risk (RR) comparing intervention with control groups was 0.90 (95% CI, 0.80 to 1.02; $p=0.09$) when applying the fixed-effects model (Fig. 2). The funnel plot

showed an asymmetric pattern, but Begg's rank correlation test suggested no publication bias in the meta-analysis ($p=0.133$) (Fig. 3).

Sensitivity analysis

Firstly, these included trials were divided into trials of pregnant women and trials of non-pregnant adults. The pooled RR of pregnant women was 0.80 (95% CI, 0.56 to 1.13; $p=0.20$), and the pooled RR of non-pregnant adults was 0.75 (95% CI, 0.50 to 1.12; $p=0.16$) (Fig. 4). they provided similar estimations of the RR, which indicated that the pregnant condition did not alter the

effect of multiple micronutrient supplementation.

Then we disaggregated these included trials into trials of participants infected with HIV alone and infected with pulmonary tuberculosis concomitantly. The pooled RR of those infected with HIV alone was 0.75 (95% CI, 0.58 to 0.95; $p=0.02$), and the pooled RR of trials of participants infected with pulmonary tuberculosis concomitantly was 0.97 (95% CI, 0.84 to 1.11; $p=0.65$) (Fig. 5).

DISCUSSION

Many previous and ongoing preclinical studies have demonstrated that micronutrient supplementation can enhance the immune function and decrease oxidative damage, and thus can retard or inhibit the progression of some infectious and oxidative injury-related diseases (18–21). When evaluating in an epidemic view, however, the effects of micronutrient supplementation on immune function and oxidative damage were disappointing, and even conflicting (22–24). One plausible explanation is the limitation of sample size in some observational studies. AIDS, which progressed from HIV infection, was characterized by the dysfunction of the immune system—a reduction in the CD4+ cell count. In recent two decades, oxidative stress was reported to be correlated with a faster progression of AIDS (25–27). Thus, clinical trials evaluating the effect of micronutrient supplementation on prognosis of HIV infection and AIDS were enforced extensively in recent years.

This is a meta-analysis to evaluate the efficacy of multiple micronutrient supplementation on the mortality and morbidity of HIV-infected adults. Our assessment was based on six included RCTs that were published within the past 10 y. The results of the meta-analysis revealed that adults infected with HIV could benefit from multiple micronutrient supplementation, which could decrease the mortality and morbidity, especially those infected with HIV alone. Wasting, which is characterized by an involuntary, progressive loss of lean and fat mass, is one of the strongest independent predictors of mortality in HIV-infected adults according to the results of studies carried out in developing and developed countries (28–30). The oral and gastrointestinal manifestations, nausea, vomiting and diarrhea, which are largely correlated with wasting and are more likely to be observed in advanced stages of HIV disease could influence the appetite and nutrition absorption of patients in addition to decreasing their quality of life (31). Many previous studies have revealed that supplementation of micronutrients could maintain the integrity of oral and gastrointestinal epithelia and thus decrease episodes of oral and gastrointestinal symptoms to improve local and systemic immunity (32, 33). Consequently, multimicronutrient supplementation may prolong survival time through reducing the incidence of wasting and favorably affect the prognosis of AIDS patients.

The results of sensitivity analysis revealed that although both patients infected with and without

tuberculosis were supplemented with multiple micronutrients, only those who are infected with HIV alone can benefit from multiple micronutrient supplementation with a favorably decreased and statistically significant RR of 0.75. Those who are infected concomitantly with tuberculosis cannot benefit from multiple intake of micronutrients with a RR approximately equal to 1, indicating that these patients may have progressed to a more severe situation of immune dysfunction and oxidative stress injury which can not be reversed by multimicronutrient consumption. This result was in accordance with a previous observational study which assessed the differences of clinical symptom incidences between AIDS patients infected and uninfected with tuberculosis (34). It demonstrated that AIDS patients infected with tuberculosis were more likely to develop fever, weight loss and lymphadenopathy. As has been discussed in the previous paragraph, similar to wasting, weight loss may be attributed to oral and gastrointestinal symptoms. The influence of fever and oxidative stress may be reciprocal. Riedel and Maulik revealed that fever is an integrated response of the central nervous system to oxidative stress (35), and several other studies indicated that fever can increase the lipid peroxidation parameters, decrease the cell antioxidant system (36) and induce oxidative stress (37). Lymphadenopathy was reported to be correlated with immune dysfunction (38). All this evidence supported our conjecture that patients infected with both HIV and tuberculosis may have progressed to a more severe situation of immune dysfunction and oxidative stress when compared with those infected with HIV alone. Nevertheless, the probable decreasing effect of multiple micronutrient supplementation on mortality and morbidity of total HIV-infected patients cannot be ruled out (Fig. 2).

Intervention of the meta-analysis was restricted within multiple micronutrient supplementation. Previous preclinical studies have revealed that multiple intake of micronutrients can improve their respective roles in strengthening immune system function and antioxidation reciprocally. For example, the antioxidant efficacy of vitamin E can be strengthened by vitamin C (39), β -carotene and selenium (40, 41), and vitamin E can play an analogous biochemical role to that of zinc in stabilizing membrane structure and reducing peroxidative damage (42). In several observational studies assessing the efficacy of only one or two kinds of micronutrients on progression of HIV infection, the results are even opposite (43, 44). One of the included RCTs evaluating the efficacy of both multivitamins and vitamin A revealed that multivitamin supplementation can significantly delay the progression of HIV-infection; however, supplementation with vitamin A alone had weaker effects that for the most part were not significantly different from those produced by the placebo (12). We all know fruits and vegetables are rich in multiple micronutrients, and Winkler et al. reported that HIV-infected patients can benefit from supplementation with fruit juices (45). Therefore, the cooperative interactions among these micronutrients may play a partial

role in the reduction of the mortality and morbidity of HIV-infected patients, and more meta-analyses assessing the effect of a single micronutrient should be carried out in the future.

There is a weakness which may limit the generalizability of the meta-analysis. All of the six included trials were carried out in developing countries, four of which were in sub-Saharan Africa. Trials in Europe, America and Oceania could not be found through our search strategy. Most of the advanced countries are on these three continents. Moreover, micronutrient deficiencies are more likely to happen in residents of developing countries, especially in sub-Saharan Africa, but not in developed countries. Thus, the effect of multiple micronutrient supplementation on residents of advanced countries should be considered cautiously, and there is a need for more double-blinded RCTs from these countries. Another limitation was the different formulations and dosages of micronutrients in the six trials, which might be inevitable in meta-analysis, an analytical approach based on published literature. Anyhow, all of the intaken micronutrients in each trial were included in the recommended daily allowance, and the strengthened effects among them cannot be ruled out. Only trials published in English were included, so there might also be a language bias.

In conclusion, our study demonstrates that multiple micronutrient consumption can decrease the mortality and morbidity of HIV-infected patients, at least those in developing countries. Based on the synthesized treatment methods of the 6 included RCTs, we suggest that multiple micronutrients, including the 7 types of common micronutrients (vitamin B group, vitamin C, vitamin E and folic acid) and several frequently prescribed ones (vitamin A, vitamin D, zinc, selenium and niacin), should be administered daily between the equivalent dosages of RDA and six to ten times the dosages of RDA, depending on the varying stages of AIDS, by local doctors. In the future, recently completed and other ongoing trials will provide more precise answers on the relationship between multimicronutrient intake and prognosis of HIV infection.

Acknowledgments

This study was funded by the Natural Science Foundation of China (No. 30771863 and No. 81172616), and not funded by any pharmaceutical company.

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