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[Intervention Review]

Micronutrient supplementation in adults with HIV infection

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ABSTRACT

Background

Micronutrient deficiencies are common among adults living with HIV disease, particularly in low-income settings where the diet may be low in essential vitamins and minerals. Some micronutrients play critical roles in maintenance of the immune system, and routine supplementation could therefore be beneficial. This is an update of a Cochrane Review previously published in 2010.

Objectives

To assess whether micronutrient supplements are effective and safe in reducing mortality and HIV-related morbidity of HIV-positive adults (excluding pregnant women).

Search methods

We performed literature searches from January 2010 to 18 November 2016 for new randomized controlled trials (RCTs) of micronutrient supplements since the previous review included all trials identified from searches prior to 2010. We searched the CENTRAL (the Cochrane Library), Embase, and PubMed databases. Also we checked the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) and the ClinicalTrials.gov trials registers. We also checked the reference lists of all new included trials.

Selection criteria

We included RCTs that compared supplements that contained either single, dual, or multiple micronutrients with placebo, no treatment, or other supplements. We excluded studies that were primarily designed to investigate the role of micronutrients for the treatment of HIV-positive participants with metabolic morbidity related to highly active antiretroviral therapy (HAART). Primary outcomes included all-cause mortality, morbidity, and disease progression.

Data collection and analysis

Two review authors independently selected trials for inclusion, and appraised trial quality for risk of bias. Where possible, we presented results as risk ratios (RR) for dichotomous variables, as hazard ratios (HRs) for time-to-event data, and as mean differences (MD) for continuous variables, each with 95% confidence intervals (CIs). Since we were often unable to pool the outcome data, we tabulated it for each comparison. We assessed the certainty of the evidence using the GRADE approach.

Main results

We included 33 trials with 10,325 participants, of which 17 trials were new trials. Ten trials compared a daily multiple micronutrient supplement to placebo in doses up to 20 times the dietary reference intake, and one trial compared a daily standard dose with a high daily dose of multivitamins. Nineteen trials compared supplementation with single or dual micronutrients (such as vitamins A and D, zinc, and selenium) to placebo, and three trials compared different dosages or combinations of micronutrients.

Multiple micronutrients

We conducted analyses across antiretroviral therapy (ART)-naive adults (3 trials, 1448 participants), adults on antiretroviral therapy (ART) (1 trial, 400 participants), and ART-naive adults with concurrent active tuberculosis (3 trials, 1429 participants). Routine multiple micronutrient supplementation may have little or no effect on mortality in adults living with HIV (RR 0.91, 95% CI 0.72 to 1.15; 7 trials, 2897 participants, *low certainty evidence*).

Routine supplementation for up to two years may have little or no effect on the average of mean CD4+ cell count (MD 26.40 cells/mm^3, 95% CI −22.91 to 75.70; 6 trials, 1581 participants, *low certainty evidence*), or the average of mean viral load (MD −0.1 $\log_{10}$viral copies, 95% CI −0.26 to 0.06; 4 trials, 840 participants, *moderate certainty evidence*). One additional trial in ART-naïve adults did report an increase in the time to reach a CD4+ cell count < 250 cells/mm^3 after two years of high dose supplementation in Botswana (HR 0.48, 95% CI 0.26 to 0.88; 1 trial, 439 participants). However, the trial authors reported this effect only in the trial arm that received multiple micronutrients plus selenium (not either supplementation alone), which is inconsistent with the findings of other trials that used similar combinations of micronutrients and selenium.

In one additional trial that compared high-dose multiple micronutrient supplementation with standard doses in people on ART, peripheral neuropathy was lower with high dose supplements compared to standard dose (incidence rate ratio (IRR) 0.81, 95% CI 0.7 to 0.94; 1 trial, 3418 participants), but the trial was stopped early due to increased adverse events (elevated alanine transaminase (ALT) levels) in the high dose group.

Single or dual micronutrients

None of the trials of single or dual micronutrient supplements were adequately powered to assess for effects on mortality or morbidity outcomes. No clinically significant changes in CD4 cell count (data not pooled, 14 trials, 2370 participants, *very low or low certainty evidence*) or viral load (data not pooled, seven studies, 1334 participants, *very low or low certainty evidence*), were reported. Supplementation probably does increase blood concentrations of vitamin D and zinc (data not pooled, vitamin D: 4 trials, 299 participants, zinc: 4 trials, 484 participants, *moderate certainty evidence*) and may also increase blood concentrations of vitamin A (data not pooled, 3 trials, 495 participants, *low certainty evidence*), especially in those who are deficient.

Authors' conclusions

The analyses of the available trials have not revealed consistent clinically important benefits with routine multiple micronutrient supplementation in people living with HIV. Larger trials might reveal small but important effects.

These findings should not be interpreted as a reason to deny micronutrient supplements for people living with HIV where specific deficiencies are found or where the person's diet is insufficient to meet the recommended daily allowance of vitamins and minerals.

12 April 2019

Up to date

All studies incorporated from most recent search

All eligible published studies found in the last search (18 Nov, 2016) were included and six ongoing studies have been identified (see 'Characteristics of ongoing studies' section)

PLAIN LANGUAGE SUMMARY

Micronutrient supplements for non-pregnant adults with HIV infection

Cochrane researchers conducted a review of the effects of micronutrient supplements for people living with HIV. This is an update of a Cochrane Review previously published in 2010. After searching for relevant trials up to 18 November 2016, the review authors included 33 trials. Thirteen of these trials included people not on HIV treatment and were conducted in Thailand, Peru, and eight African countries. Nineteen trials included people on HIV treatment and were conducted in North America, Europe, Brazil, Singapore, Thailand, Botswana, and Uganda. One trial from China did not state whether people living with HIV were on treatment or not. Some trials looked at the effects of taking supplements with multiple micronutrients whereas others looked at supplementation with single vitamins or minerals.

What are micronutrient supplements and how might they help people living with HIV?

Micronutrient supplements contain vitamins or minerals, or both, that are essential to good health. Many of these vitamins play important roles in maintaining the human immune system, which helps to fight off infections.

Infection with HIV causes a progressive destruction of the immune system, which leaves people vulnerable to frequent infections. Many people living with HIV, especially in low-income countries, are also undernourished and many consume diets deficient that these essential micronutrients. Supplementation could therefore help people living with HIV to stay healthy for longer by strengthening their immune system or assisting recovery from infections.

What the research says

Multiple micronutrients

Providing a daily supplement that contains multiple vitamins and minerals may have little or no effect on reducing deaths in people living with HIV, whether they are taking antiretroviral drugs or not (*low certainty evidence*). Daily supplements may have little or no effect on HIV disease progression as measured by CD4 cell count (*low certainty evidence*) or HIV viral load (*low or moderate certainty evidence*).

Single or dual micronutrients

We do not know whether supplements that contain single vitamins or minerals reduce deaths (*very low certainty evidence*) or slow disease progression (*very low/low certainty evidence*) in people living with HIV. Supplementation with vitamin A, D, zinc, or selenium may improve the level of each vitamin in a person's blood, especially those with low levels before supplementation (*low/moderate certainty evidence*).

These findings do not mean that an adequate dietary intake for people living with HIV is not important. It is also not a reason to deny micronutrient supplements for those in whom a deficiency has been clinically demonstrated, or who are unlikely to meet the recommended daily allowance of vitamins and minerals.