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Micronutrient supplementation in adults with HIV infection (Review)

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Visser ME, Durao S, Sinclair D, Irlam JH, Siegfried N.
Micronutrient supplementation in adults with HIV infection.
Cochrane Database of Systematic Reviews 2017, Issue 5. Art. No.: CD003650.
DOI: 10.1002/14651858.CD003650.pub4.

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[Intervention Review]

Micronutrient supplementation in adults with HIV infection

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Editorial group: Cochrane Infectious Diseases Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 5, 2017.

Citation: Visser ME, Durao S, Sinclair D, Irlam JH, Siegfried N. Micronutrient supplementation in adults with HIV infection. *Cochrane Database of Systematic Reviews* 2017, Issue 5. Art. No.: CD003650. DOI: 10.1002/14651858.CD003650.pub4.

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/mm³, 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/mm³ 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.

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.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON *[Explanation]*

Multiple micronutrients compared to placebo for adults with HIV infection

Participant or population: adults with HIV infection (with and without concurrent tuberculosis, with and without ART)
Settings: all settings
Intervention: multiple micronutrient supplementation (standard or high dose daily)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Micronutrients				
Mortality Follow-up: 8 to 24 months	**100 per 1000**	**91 per 1000** (72 to 115)	**RR 0.91** (0.72 to 1.15)	2897 (7 trials)	⊕⊕◯◯ **low**[1,2,3,4] due to indirectness and imprecision	Multiple micronutrients may have little or no effect on mortality
Hospital admissions Follow-up: 11 to 18 months	**139 per 1000**	**120 per 1000** (85 to 170)	**RR 0.86** (0.61 to 1.22)	881 (2 trials)	⊕◯◯◯ **very low**[1,4,5] due to indirectness and imprecision	We don't know if multiple micronutrients have any effect on hospital admissions
CD4 cell count Follow-up: 6 weeks to 2 years	The mean in the placebo groups ranged from **147 to 483 cells/mm^3**	The mean in the multiple micronutrient group was **26.40 cells/mm^3 higher** (22.91 lower to 75.70 higher)	-	1581 (6 trials)	⊕⊕◯◯ **low**[1,3,6] due to indirectness and inconsistency	Multiple micronutrients may have little or no effect on CD4 cell count
Viral load Follow-up: 6 weeks to 2 years	The mean in the placebo groups ranged from **4.1 to 5.4 $\log_{10}$copies/mL**	The mean in the multiple micronutrient groups was **0.10 $\log_{10}$copies/mL lower**	-	840 (4 trials)	⊕⊕⊕◯ **moderate**[1,7] due to indirectness	Multiple micronutrients probably have little or no effect on viral load

		(0.26 lower to 0.06 higher)				
Nutritional status Follow-up: 4 weeks to 1.9 years	-	-	Not pooled	1007 (3 trials)	⊕◯◯◯ **very low**[1,8,9] due to indirectness and imprecision	We don't know if multiple micronutrients have any effect on nutritional status parameters

The basis for the assumed risk is the median control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Abbreviations: ART: antiretroviral therapy; BMI: body mass index; CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[1]No serious risk of bias: most trials were at low risk of selection bias and used placebos to prevent performance or detection bias.
[2]No serious heterogeneity: none of the trials found statistically significant effects overall (although one small subgroup from one trial in Tanzania did find a statistically significant difference this is probably a chance finding).
[3]Downgraded by 1 for serious indirectness: although most trials reported this outcome, only one of these (from Uganda using standard dose micronutrients) included a substantial number of adults on ART in line with current recommendations. The other trials used standard or high dose micronutrients and were conducted in ART-naive adults (in Botswana, Zambia, and Thailand), and adults with concurrent tuberculosis (in Tanzania and Malawi).
[4]Downgraded by 1 for serious imprecision: the 95% CI is wide and includes both clinically important effects and no effect. The overall meta-analysis remains underpowered to confidently exclude effects.
[5]Downgraded by 2 for very serious indirectness: these two trials were conducted in Thailand (high dose micronutrients in ART-naive adults) and Uganda (standard dose micronutrients in adults on ART). The finding of no effect may not apply to all populations and settings.
[6]Downgraded by 1 for serious inconsistency: in total eight trials reported a measure of CD4+ cell count although we could only include six trials in this meta-analysis. Of note, one recent trial in Botswana among ART-naive adults (not included in the meta-analysis) reported a reduced risk of reaching a CD4+ cell count of less than 250 cells/mm^3 after two years of high dose supplementation. This finding is inconsistent with other trials that used similar combinations of micronutrients and selenium.
[7]Downgraded by 1 for serious indirectness: in total four trials in ART-naive adults, with concurrent TB (in Tanzania and Malawi) or without TB (in Kenia and Thailand), reported viral load. The finding of no effect may not apply to people on ART or other populations and settings.

[8]Downgraded by 2 for serious indirectness: only three trials (from Uganda, Zambia, and Tanzania) reported measures of nutritional status (BMI, weight, mid-upper arm circumference (MUAC), lean body mass). The finding of no effect may not apply to all populations and settings.

[9]Downgraded by 1 for serious imprecision: we were unable to pool data but the 95% CIs of the individual trials were wide and included clinically important effects and no effect.

BACKGROUND

Description of the condition

Despite a substantial decrease in the number of new HIV infections during the past decade, recent estimates from the United Nations Joint Programme on HIV/AIDS (UNAIDS) indicate that 35 million people were still living with HIV worldwide in 2013 (UNAIDS 2014). The HIV/AIDS pandemic has severely affected sub-Saharan Africa, more than any other part of the world. With about a tenth of the world's population, the region is home to more than two-thirds of all people living with HIV worldwide, an estimated 24.7 million adults and children (UNAIDS 2014). Globally, more than one-third of HIV-positive adults receive antiretroviral therapy (ART) (UNAIDS 2014). Earlier initiation of ART, in line with recent recommendations, is a challenge to implement in many countries, especially those in resource-limited settings (WHO 2015).

Adults living with HIV may also have micronutrient deficiencies, particularly those from communities at high risk of food insecurity since diets are frequently inadequate to meet the recommended daily requirements (Gebrehiwot 2014). A recent review reported that people living with HIV who experience food insecurity tended to have lower CD4 counts than their counterparts (Aibibula 2016). Deficiencies of micronutrients are more pronounced in individuals with advanced disease, as a consequence of reduced nutrient intake due to AIDS and opportunistic infections, and excessive losses due to diarrhoea, malabsorption, and parasitic infections. Furthermore, in sub-Saharan Africa, a region severely affected by the HIV/AIDS pandemic, protein energy malnutrition (PEM) is common. PEM refers to inadequate protein and energy intake and is usually associated with multiple micronutrient insufficiency (Irlam 2007).

Description of the intervention

Micronutrient supplements are either single or multiple formulations of vitamins and trace elements.

How the intervention might work

Micronutrients play a critical role in the maintenance of a functional immune system. The interactions between micronutrients and the components of the immune response are multifaceted and complex Chandra 1997; Raiten 2015). Several observational studies have suggested that micronutrient deficiencies may hasten clinical disease progression in HIV-positive adults. Low blood levels of vitamin A, B12, zinc, and selenium have been related to increased HIV progression (Graham 1991; Kupka 2004; Tang 1997) or death in this population (Baum 1997; Baum 2003; Semba 1993). Most participants in these earlier studies were not receiving ART at the time. More recently, vitamin D deficiency, which is assessed by low 25-hydroxy vitamin D levels, has been associated with increased disease progression of untreated (Mehta 2010) or treated HIV disease (Sudfeld 2012; Viard 2011), and impaired CD4 cell count recovery of HIV-positive men and women on antiretroviral therapy (ART) (Aziz 2013; Ross 2011).

Widespread micronutrient supplementation may lessen the effects of concurrent micronutrient deficiency and help to reduce the morbidity and mortality due to HIV (Semba 1999). It has also been suggested that micronutrient supplementation may enhance the CD4 cell responses of individuals on ART who demonstrate adequate viral suppression (Tang 2005).

Assessing the effectiveness of micronutrient supplementation in participants with inflammation requires special consideration. Acute inflammation results in the redistribution of micronutrients due to changes in plasma proteins and may therefore impact on the validity of nutrient biomarkers, such as serum micronutrient concentrations (Raiten 2015).

Why it is important to do this review

A previous version of this Cochrane review included 30 trials: 20 trials of single micronutrient supplements (vitamin A, vitamin D, zinc, and selenium) and 10 of multiple micronutrient supplements. Eight trials were undertaken in child populations and four trials were conducted among pregnant and lactating women (Irlam 2010). The review found no conclusive evidence that micronutrient supplementation effectively reduces or increases morbidity or mortality in HIV-positive adults.

The HIV/AIDS pandemic has had a major impact on global health, nutrition, and overall socioeconomic development. An update of the review based on recent, valid research is therefore important. Micronutrient supplements have potential benefit for people living with HIV infection. However, in order to understand the magnitude of this benefit and how supplements should be positioned alongside the proven advantages of antiretroviral drugs, a robust evidence-base to guide policy and practice is required.

At the request of the World Health Organization (WHO), two separate Cochrane Reviews on the role of micronutrient supplementation were published for HIV-positive pregnant women (Siegfried 2012) and children (Irlam 2013). The primary focus of this Cochrane review is therefore on the role of micronutrient supplementation in HIV-positive non-pregnant adults.

OBJECTIVES

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

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) of micronutrient supplements compared with placebo, no treatment, or other supplements (including variations in quantity or formulation).

Types of participants

HIV-positive adults, defined as people ≥ 15 years of age who were HIV-positive (WHO 2007). Two other Cochrane reviews have addressed micronutrient supplementation for HIV-positive children and pregnant women (Irlam 2013; Siegfried 2012). We included trials that recruited both HIV-positive adults and children if 80% or more of the participants were HIV-positive adults.

We included trials that recruited antiretroviral therapy (ART)-naive participants, as well as those that recruited participants on ART. Since the objective of this Cochrane Review is on the adjunctive role of micronutrients on mortality and HIV-related morbidity, 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 ART. A Cochrane review on treatment for dyslipidaemia in HIV infection is in progress (Martí-Carvajal 2010).

We included trials conducted in populations with and without HIV infection if outcome data were available for HIV-positive participants.

We included trials that involved participants with tuberculosis with and without HIV infection if outcome data were available for participants with HIV, regardless of whether the trial authors stratified the randomization of trial participants according to HIV infection status. We excluded studies that did not report outcome data for HIV-positive participants.

Types of interventions

We included trials of micronutrient supplementation that included vitamins (A, D, E, C, B1, B2, niacin, B6, B12, K, folate, beta-carotene), trace elements (zinc, selenium, magnesium, iron, iodine, copper, manganese, chromium, cobalt, molybdenum), or combinations of the above only. We described a supplement as a standard dose supplement if the trial provided a single micronutrient, or a combination of micronutrients, at the level of the Recommended Daily Intake (RDA). We described any supplement containing a single micronutrient, or a combination of micronutrients in multiples of the RDA, as a high-dose supplement. We excluded studies that assessed the effect of adding micronutrients to foods (food fortification).

Types of outcome measures

Primary outcomes

- All-cause mortality
- Morbidity (frequency, types, and duration of episodes of opportunistic infections; incidence of AIDS as defined by each trial; hospital admissions; and other types of illnesses related to HIV infection as reported in each study)
- Disease progression according to either the World Health Organization (WHO 2007), or the Centers for Disease Control and Prevention (CDC) clinical staging system (Schneider 2008), as reported in each included trial

Secondary outcomes

- Virological response: proportion of participants who maintained an undetectable viral load and change in HIV-RNA levels (mean relative change (percent) or mean absolute change, compared with baseline, and standard deviation (SD))
- Virological failure: proportion of participants who discontinued or switched ART due to virological failure, as defined by each included trial
- Markers of immune response, such as change in absolute CD4+ T lymphocyte count (mean relative change (percent) or mean absolute change, compared with baseline, and SD)
- Nutritional status, including measurements such as bodyweight, Body Mass Index (BMI), and body composition
- Biochemical markers, such as serum micronutrient concentrations

We excluded studies that only reported data that related to biochemical markers from this review.

Adverse events

We extracted data on all adverse events that we judged to be associated with micronutrient supplementation, as reported by each included trial. If the trial authors had classified these events according to the Adverse Event Toxicity Scale, we extracted the data accordingly: grade 1 or 2 (mild to moderate symptoms), grade 3 (serious symptoms), or grade 4 symptoms (denotes life-threatening events that require a significant clinical intervention) (DAIDS 2014).

Search methods for identification of studies

Electronic searches

We searched the CENTRAL (Appendix 1), PubMed (Appendix 2), and Embase (Appendix 3) databases from January 2010 up to 18 November 2016. We limited the search date from January

2010, since Irlam 2010 included all trials identified from searches prior to and including January 2010. In addition we checked the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (Appendix 4) and the ClinicalTrials.gov trial register (Appendix 5). We also searched the reference lists of the included trials.

Searching other resources

For this update, we searched the reference lists of all the included trials. We also contacted investigators of ongoing studies that have been completed by email to enquire about any new or imminent publications.

Data collection and analysis

Selection of studies

Two review authors (MV and SD) independently screened the titles and abstracts identified through the electronic searches for potentially eligible citations for full-text screening. In the case of uncertainty regarding eligibility, we screened the full-text article(s). Two review authors (MV and SD) screened full-text articles using a standardized eligibility form based on the inclusion criteria of the review. In the case of disagreement or uncertainty, a third review author (NS) provided their opinion. We listed all studies that we excluded after full-text assessment and their reasons for exclusion in a 'Characteristics of excluded studies' table. We constructed a PRISMA diagram to illustrate the study selection process.

Data extraction and management

Two review authors (MV and SD) independently extracted data from the included trials for the review update using an updated standardized electronic data extraction form. We extracted the following information from each trial.

- Administrative details: trial identification number; author(s); published or unpublished; year of publication
- Details of the trial: country and location of trial, trial design, duration and completeness of follow-up; informed consent and ethics approval, source of funding
- Details of participants: age, gender, disease progression according to clinical staging, relevant baseline characteristics including CD4 count and viral load
- Details of intervention and control group: type, dosage, and frequency of micronutrient(s); additional co-interventions (such as ART, tuberculosis treatment, or other management of opportunistic infections)
- Details of outcomes: all prespecified outcomes and any additional outcomes reported in the study; adverse events and toxicity
- Details of data analysis: numbers and reported statistics for each reported outcome. Where trial outcomes were reported in more than one reference, we used all the trial reports to extract data as comprehensively as possible

We entered data into the Review Manager 5 (RevMan 5) software (Review Manager 5). The trial ID for each included trial consisted of the name of the first trial author followed by the date of publication and the country code where the study was conducted (see Appendix 6).

Assessment of risk of bias in included studies

Two review authors (MV and SD) independently assessed the risk of bias of each new included trial using the Cochrane 'Risk of bias' assessment tool (Higgins 2011). Please see Appendix 7 for the additional assessment of risk of bias in included cluster-randomized trials.For each trial we assessed the following domains as either at high, low, or unclear risk of bias: sequence generation, allocation concealment, blinding (participants, personnel, and outcome assessor), incomplete outcome data, selective outcome reporting, and other sources of bias.

Measures of treatment effect

For the measures of treatment effect, we used the risk ratio (RR) for dichotomous data, the weighted mean difference (WMD) for continuous data measured on the same scale, and the standardized mean difference (SMD) for continuous data measured on different scales, presented with 95% confidence intervals (CIs). For time-to-event data we extracted the hazard ratio (HR). We used RevMan 5 for data analysis (Review Manager 5).

Unit of analysis issues

We included two trials with factorial designs (Baum 2013 BWA; Range 2006 TZA). For Range 2006 TZA, we halved the number of events and participants in the placebo group for dichotomous outcomes and the number of participants for continuous outcomes in our meta-analysis in order to avoid double counting. Since Baum 2013 BWA reported time-to-event data we were unable to incorporate the data into a meta-analysis.
We described the outcome data narratively for the cross-over trial by Coodley 1993 USA, since the study authors did not report outcome data before trial cross-over. For Kelly 2008 ZMB we did not include the data after trial cross-over as the trial authors did not clearly describe the wash-out period.

Dealing with missing data

We contacted the authors of three published conference abstracts in order to obtain further information regarding the trial protocol and study outcomes (Baum 2010 USA; Sales 2010; Scrimgeour 2010). We also contacted other trial authors in order to clarify data

or statistical analysis where needed. Where possible, we conducted a complete-case analysis. For trial outcomes where this was unclear, we used the number of participants randomized to each trial arm. We documented the attrition rate for each included trial in the 'Risk of bias' table.

Assessment of heterogeneity

First we assessed trials for clinical heterogeneity by examining variability in the participants, interventions, and outcomes. We assessed statistical heterogeneity visually and by means of the Chi² test for heterogeneity and the I² statistic. We classified heterogeneity according to the I² statistic values as follows (Higgins 2002).

- 0% to 40%: might not be important
- 30% to 60%: may represent moderate heterogeneity
- 50% to 90%: may represent substantial heterogeneity
- 75% to 100%: considerable heterogeneity

Assessment of reporting biases

To prevent reporting biases we searched multiple sources and searched for unpublished studies in trials registers. We did not examine funnel plots to assess the likelihood of publication bias as there were an insufficient number of trials per outcome.

Data synthesis

In view of the anticipated heterogeneity between trial populations and interventions, we used a random-effects model. When we were unable to pool data due to differences in the statistical methods and measures the study authors used, we presented the data in tables with a narrative summary.

Subgroup analysis and investigation of heterogeneity

We conducted stratified analyses according to whether participants were taking ART or not, and whether they were on concurrent treatment for tuberculosis or not. We stratified outcome data, such as CD4+ cell count and viral load, by time points (baseline and at longest time follow-up) in order to demonstrate changes over time.

Certainty of the evidence

Two review authors (MV and SD) independently assessed the certainty of the evidence for the outcomes under each comparison (type of micronutrient intervention) using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach. According to this approach the certainty rating of evidence for each outcome is determined by an assessment of the available study data in terms of its risk of bias, inconsistency, indirectness, imprecision, and publication bias. We used GRADEpro Guideline Development Tool (GDT) software to create 'Summary of findings' tables for each comparison (GRADEpro 2014).

Sensitivity analysis

We could not perform a sensitivity analysis to assess the robustness of the results against the 'Risk of bias' domains as there were too few studies for each comparison.

RESULTS

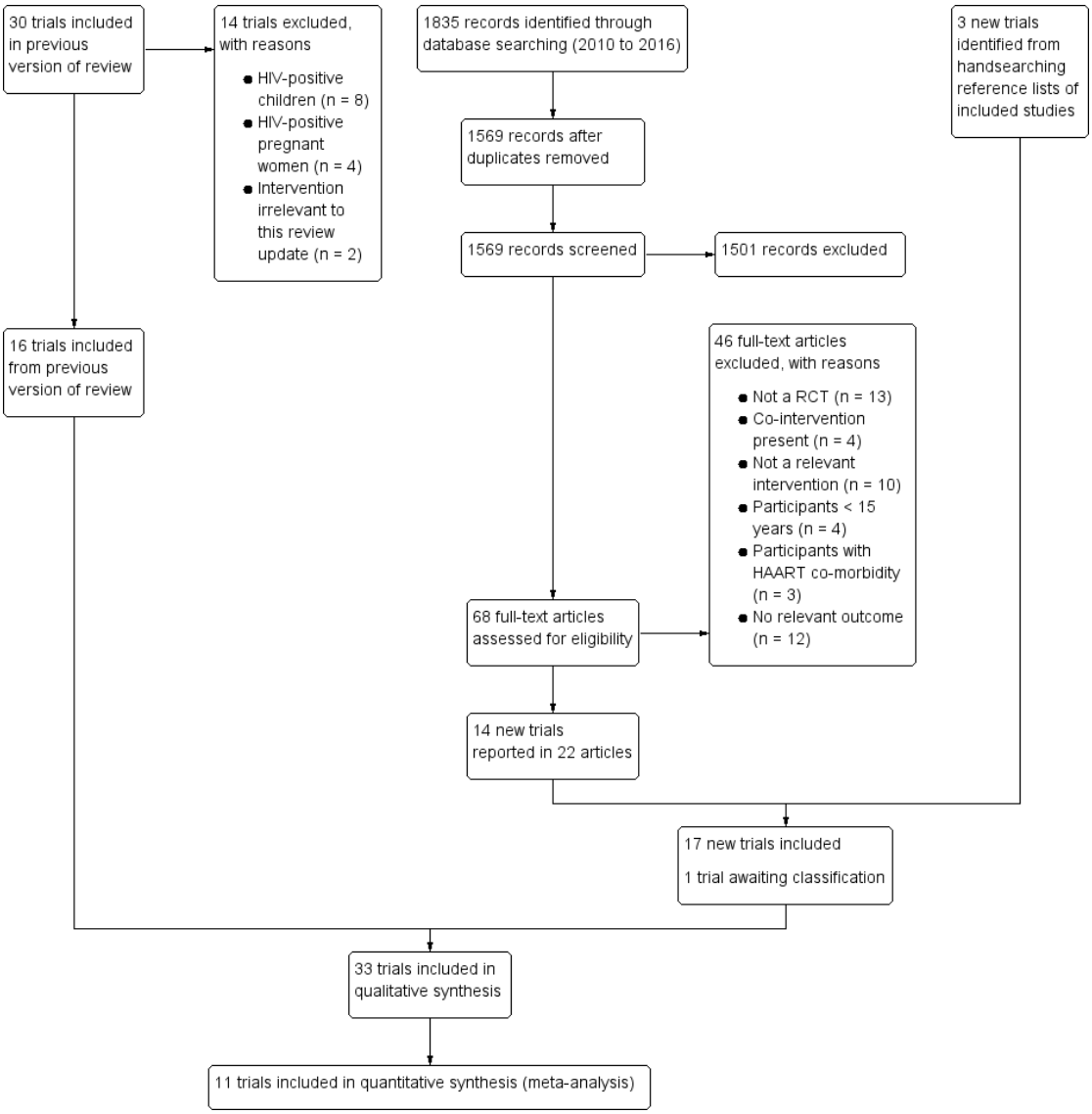
Description of studies

Results of the search

The previous version of this review, which included pregnant women and children, included 30 trials (Irlam 2010). Only 16 of these were eligible for inclusion in this Cochrane Review.

The PRISMA flow diagram summarizes the results of the searches for this update (Figure 1). Electronic database searches identified 1835 records, of which there were 1572 records after we removed duplicates. After we screened these records by title/abstract, we identified 68 articles for full-text assessment. Handsearching identified three new trials. Seventeen new trials met the inclusion criteria of this review, which gave a total of 33 included trials. Of the new included trials, four reported outcome data in two articles (Asdamongkol 2013 THA; Bang 2012 DEN; Baum 2010 USA; Baum 2013 BWA), and two letters of correspondence were related to one included trial (Isanaka 2012 TZA). Two included trials published their trial protocols (Guwatudde 2015 UG; Kamwesiga 2015 RWA). We identified one additional trial from our most recent search (18 November 2016), which we included in the 'Characteristics of studies awaiting classification' section. We identified six ongoing trials from searching trial registries.

Figure 1. Study flow diagram



Included studies

Participants

Thirteen trials, which included 4493 participants, were conducted in antiretroviral therapy (ART)-naive participants (Baeten 2002 KEN; Baum 2013 BWA; Cárcamo 2006 PER; Jiamton 2003 THA; Kamwesiga 2015 RWA; Kelly 1999 ZMB; Kelly 2008 ZMB; Lawson 2010 NIG; McClelland 2004 KEN; Range 2006 TZA; Semba 2007 MWI; Villamor 2008 TZA; Wejse 2009 GNB). One small trial did not state whether participants received ART or not (Zhao 2010 CHN).

The remaining 19 trials included 5730 participants, with most receiving either mono- or combination ART (Allard 1998 CAN; Coodley 1993 USA; Coodley 1996 USA; Humphrey 1999 USA; Semba 1998 USA), or highly active antiretroviral therapy (HAART) (Asdamongkol 2013 THA; Bang 2012 DEN; Baum 2010 USA; Burbano 2002 USA; Dougherty 2015 USA; Giacomet 2013 ITA; Guwatudde 2015 UG; Green 2005 SGP; Grigoletti 2013 BRA; Hurwitz 2007 USA; Isanaka 2012 TZA; Overton

2015 USA; Semba 2007 USA; Stallings 2014 USA). Many of these trials were small with fewer than 100 participants, with the exception of Isanaka 2012 TZA which had more than 3000 participants.

In five trials participants were on concurrent treatment for active tuberculosis (Lawson 2010 NIG; Range 2006 TZA; Semba 2007 MWI; Villamor 2008 TZA; Wejse 2009 GNB).

Trial site

Trials were undertaken in the following places.

- Africa: Botswana (Baum 2013 BWA), Kenya (Baeten 2002 KEN; McClelland 2004 KEN), Guinea-Bissau (Wejse 2009 GNB), Malawi (Semba 2007 MWI), Nigeria (Lawson 2010 NIG), Rwanda (Kamwesiga 2015 RWA), Tanzania (Range 2006 TZA; Isanaka 2012 TZA; Villamor 2008 TZA), Uganda (Guwatudde 2015 UG), and Zambia (Kelly 1999 ZMB; Kelly 2008 ZMB)
- Asia: China (Zhao 2010 CHN), Singapore (Green 2005 SGP), and Thailand (Asdamongkol 2013 THA; Jiamton 2003 THA)
- North America: Canada (Allard 1998 CAN) and USA (Baum 2010 USA; Burbano 2002 USA; Coodley 1993 USA; Coodley 1996 USA; Dougherty 2015 USA; Humphrey 1999 USA; Hurwitz 2007 USA; Overton 2015 USA; Semba 1998 USA; Semba 2007 USA; Stallings 2014 USA)
- South America: Brazil (Grigoletti 2013 BRA) and Peru (Cárcamo 2006 PER)
- Europe: Denmark (Bang 2012 DEN) and Italy (Giacomet 2013 ITA)

Interventions

Twenty-nine placebo-controlled studies met the inclusion criteria. Of these, two had factorial designs (Baum 2013 BWA; Range 2006 TZA). For both of these trials we extracted data for two treatment comparisons. Trials assessed the effectiveness of the supplementation of the following.

- Multiple micronutrients (10 trials; 3533 participants: Baum 2013 BWA; Guwatudde 2015 UG; Jiamton 2003 THA; Kelly 1999 ZMB; Kelly 2008 ZMB; McClelland 2004 KEN; Range 2006 TZA; Semba 2007 MWI; Villamor 2008 TZA; Zhao 2010 CHN)
- Vitamin A (4 trials; 581 participants: Baeten 2002 KEN; Coodley 1993 USA; Humphrey 1999 USA; Semba 1998 USA)
- Vitamin D (5 trials; 447 participants: Bang 2012 DEN; Giacomet 2013 ITA; Overton 2015 USA; Stallings 2014 USA; Wejse 2009 GNB)
- Vitamin E combined with vitamin C (1 trial, 49 participants: Allard 1998 CAN)
- Folinic acid (1 trial, 30 participants: Grigoletti 2013 BRA)
- Zinc (6 trials, 826 participants: Asdamongkol 2013 THA; Baum 2010 USA; Cárcamo 2006 PER; Green 2005 SGP; Lawson 2010 NIG, Range 2006 TZA)
- Selenium (4 trials, 1308 participants: Baum 2013 BWA; Burbano 2002 USA; Hurwitz 2007 USA; Kamwesiga 2015 RWA)

In addition, we identified four trials that assessed the effectiveness of the supplementation of the following.

- High dose versus standard dose multiple micronutrients (Isanaka 2012 TZA)
- 4000 IU vitamin D versus 7000 IU vitamin D (Dougherty 2015 USA)
- Multiple micronutrients with iron versus multiple micronutrients (Semba 2007 USA)
- β-carotene with multivitamins versus multivitamins (Coodley 1996 USA)

The follow-up periods of these trials ranged from two weeks to 24 months.

Sample size

Trials were generally underpowered to demonstrate effects on mortality. For example, to demonstrate a 25% reduction in deaths of HIV-positive participants not on ART 2412 trial participants would be required, and to identify the same reduction for those on ART 7314 trial participants would be required (Table 1). This far exceeds the number of participants in the three included trials that reported on this outcome (Isanaka 2012 TZA; Jiamton 2003 THA; Villamor 2008 TZA). Isanaka 2012 TZA based their sample calculation of 3000 participants on the basis of a 25% reduction in the composite outcome of death and disease progression (any new or recurrent AIDS-defining illness). We have provided the optimal information sizes for nutritional outcomes in Table 2. For full details of the included studies refer to the 'Characteristics of included studies' section.

Excluded studies

We excluded 14 trials that were included in the previous version of this review, Irlam 2010, from the current version. Eight trials were in HIV-positive children; four trials were in HIV-positive pregnant women; and in two trials the study participants received micronutrient supplements that did not contain micronutrients exclusively (Austin 2006; Kaiser 2006).

We excluded 46 records after full-text assessment, 13 of which were not RCTs. We excluded the remaining studies because they addressed interventions that were not exclusively micronutrients (n = 10), had a co-intervention (n = 4), involved trial participants aged less than 15 years (n = 4) or those with HAART co-morbidity (n = 3), or reported study outcomes not relevant to this review (n = 12) (Figure 1).

See the 'Characteristics of excluded studies' table.

Risk of bias in included studies

We evaluated the risk of bias of included studies for each of the six domains in the Methods section above (see the 'Characteristics of included studies' table). Figure 2 and Figure 3 present a graphical summary of the 'Risk of bias' assessments.

Figure 2. 'Risk of bias' graph: review authors' judgements about each 'Risk of bias' item presented as percentages across all included studies.

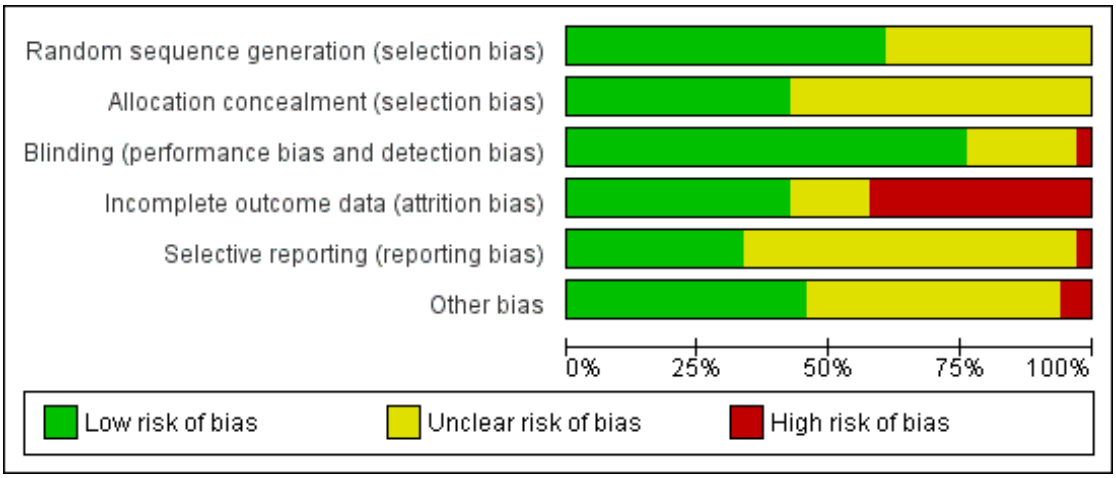
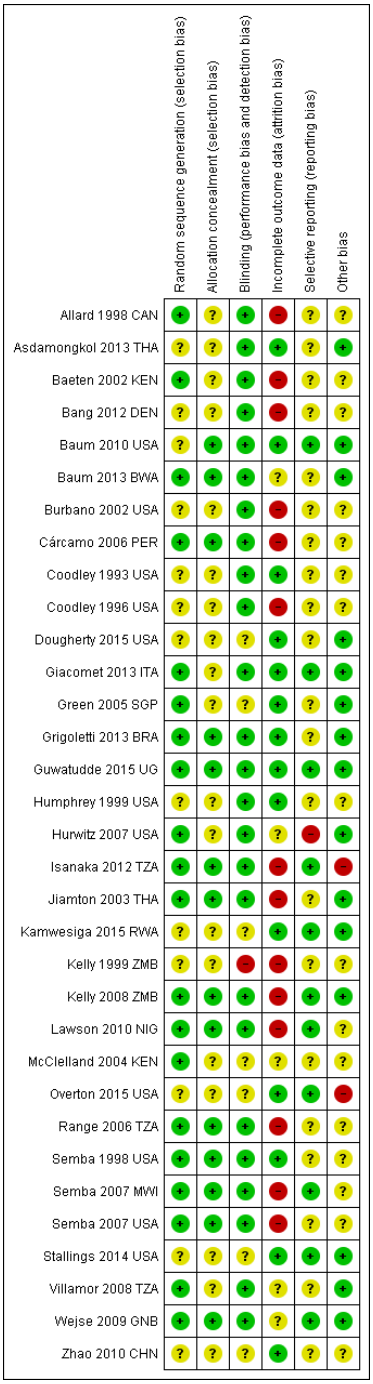


Figure 3. 'Risk of bias' summary: review authors' judgements about each 'Risk of bias' item for each included study.



Allocation

Overall 20 trials adequately described a low risk method of random sequence generation. In 13 trials the methods were unclear. Fourteen trials adequately described a method of allocation concealment, and in 19 the methods were unclear.

Blinding

Blinding of participants, treatment providers and outcome assessors was well described in 25 trials, which we judged to be at low risk of detection and performance bias. The remaining trials were at unclear risk except Kelly 1999 ZMB, which we considered to be high risk due to the use of a non-identical placebo. The main reason for trials being at unclear risk was that no information was provided about the blinding of the investigators or outcome assessors.

Incomplete outcome data

We judged 14 trials to be at high risk of attrition bias due to incomplete outcome data. In two trials this risk only applied to the measures of viral load which were only reported on a subset of trial participants (Isanaka 2012 TZA; Jiamton 2003 THA). Eleven trials had high attrition overall or differential attrition, or both (Allard 1998 CAN; Bang 2012 DEN; Burbano 2002 USA; Cárcamo 2006 PER; Coodley 1996 USA; Kelly 1999 ZMB; Kelly 2008 ZMB; Lawson 2010 NIG; Range 2006 TZA; Semba 2007 MWI; Semba 2007 USA), and in Baeten 2002 KEN participants lost to follow-up had more advanced HIV disease and vitamin A deficiency. Thus we considered these trials to be at high risk for attrition bias.

Selective reporting

Insufficient information was available to permit judgment about the extent of bias due to selective outcome reporting in all but 11 included studies. We judged 10 of these as at low risk (Baum 2010 USA; Giacomet 2013 ITA; Guwatudde 2015 UG; Isanaka 2012 TZA; Kamwesiga 2015 RWA; Lawson 2010 NIG; Overton 2015 USA; Semba 2007 MWI; Stallings 2014 USA; Wejse 2009 GNB), and one as at high risk of reporting bias (Hurwitz 2007 USA).

Other potential sources of bias

One trial was stopped early due to evidence of increased alanine transaminase (ALT) levels with the intervention (Isanaka 2012 TZA).

Fourteen trials did not declare potential conflicts of interest (Allard 1998 CAN; Asdamongkol 2013 THA; Baeten 2002 KEN; Bang 2012 DEN; Burbano 2002 USA; Cárcamo 2006 PER; Coodley 1993 USA; Coodley 1996 USA; Humphrey 1999 USA; Kelly 1999 ZMB; Lawson 2010 NIG; McClelland 2004 KEN; Semba 1998 USA; Semba 2007 MWI).

All but 19 trials were funded either fully or partly from government sources (Allard 1998 CAN; Asdamongkol 2013 THA; Baeten 2002 KEN; Baum 2010 USA; Baum 2013 BWA; Burbano 2002 USA; Coodley 1993 USA; Coodley 1996 USA; Green 2005 SGP; Grigoletti 2013 BRA; Humphrey 1999 USA; Hurwitz 2007 USA; Isanaka 2012 TZA; Jiamton 2003 THA; Kelly 1999 ZMB; McClelland 2004 KEN; Semba 1998 USA; Stallings 2014 USA; Villamor 2008 TZA); five were fully or partly funded by pharmaceutical companies (Bang 2012 DEN; Coodley 1993 USA; Jiamton 2003 THA; Kelly 1999 ZMB; Overton 2015 USA); and one trial did not provide the source of funding (Zhao 2010 CHN).

Effects of interventions

See: **Summary of findings for the main comparison** Multiple micronutrients compared to placebo for adults with HIV infection; **Summary of findings 2** Vitamin A compared to placebo; **Summary of findings 3** Vitamin D compared to placebo; **Summary of findings 4** Zinc compared to placebo; **Summary of findings 5** Selenium compared to placebo

Comparison 1: Multiple micronutrients versus placebo

Ten trials compared a daily multiple micronutrient supplement to placebo, given for between two weeks and two years (see Table 3). Most participants were ART-naive HIV-positive adults, and in three trials all participants were on treatment for active pulmonary tuberculosis. Only Guwatudde 2015 UG recruited people already taking ART (49.8% of trial participants), and the remaining participants were commenced on ART at the start of this trial. Trials were conducted in Africa (Baum 2013 BWA; Guwatudde 2015 UG; Kelly 1999 ZMB; Kelly 2008 ZMB; McClelland 2004 KEN; Range 2006 TZA; Semba 2007 MWI; Villamor 2008 TZA), Thailand (Jiamton 2003 THA), and China (Zhao 2010 CHN).

Four trials evaluated multiple micronutrient supplements in doses consistent with the Recommended Daily Intake (RDA) (standard dose supplements), and six trials used substantially higher doses (high dose supplements). In summary, high dose supplements included: vitamin A (2 to 3 x RDA), B vitamins (6 to 20 x RDA), vitamin C (3 to 5 times x RDA), vitamin D (1 x RDA), Vitamin E (2 to 20 x RDA), selenium (2 to 7 x RDA), and zinc (2 to 4 x RDA) (see Table 4).

Of the ten trials, we judged four to be at low risk of selection bias (Baum 2013 BWA; Guwatudde 2015 UG, Isanaka 2012 TZA; Jiamton 2003 THA), and we considered seven to be at low risk

of performance and detection bias as they adequately described blinding (Baum 2013 BWA; Guwatudde 2015 UG; Jiamton 2003 THA; Kelly 2008 ZMB; Range 2006 TZA; Semba 2007 MWI; Villamor 2008 TZA).

Mortality

Overall, statistically significant differences on mortality were not demonstrated, but the trials were substantially underpowered to confidently detect or exclude small but clinically important effects (risk ratio (RR) 0.91, 95% confidence interval (CI) 0.72 to 1.15; 7 trials, 2897 participants, Analysis 1.1).

- In three trials in ART-naive adults, although the proportion of deaths was lower with supplementation, the 95% confidence interval (CI) was wide and included the possibility of both clinically important effects and no effect (RR 0.60, 95% CI 0.31 to 1.15; 3 trials, 1068 participants; I^2 statistic = 0%). One additional small trial from Zambia, with only four weeks follow-up, also reported no difference in mortality but did not present data that we could include in the meta-analysis (Kelly 1999 ZMB).
- In the only trial in adults on ART, Guwatudde 2015 UG, the proportion of deaths was similar in both treatment arms, and the 95% CI was very wide (RR 1.25, 95% CI 0.50 to 3.10; 1 trial, 400 participants).
- In three trials in adults on treatment for active tuberculosis (and also not on ART), although the CI was narrower, there was no effect of supplementation on mortality (RR 0.92, 95% CI 0.69 to 1.23; 3 trials, 1429 participants; I^2 statistic = 54%). One small factorial trial from Tanzania, Range 2006 TZA, found a statistically significant effect in a subgroup of HIV-positive participants who received multiple micronutrients plus zinc, but the CI was wide and the trial was underpowered (RR 0.29, 95% CI 0.09 to 0.87; 1 trial, 84 participants). A positive result in an underpowered study is not likely to reflect a true result (low positive predictive value (PPV)) and the magnitude of the effect estimate may also be exaggerated (Button 2013). Furthermore, the trial authors reported differential attrition between treatment groups.

Morbidity and clinical disease progression

Two trials reported the risk of hospital admission, and although this was lower with multiple micronutrient supplementation, the CIs were wide and included both clinically important benefits and harms (RR 0.86, 95% CI 0.61 to 1.22; 2 trials, 881 participants, Analysis 1.2). In one trial, Guwatudde 2015 UG, participants commenced ART at the start of the trial and in the second trial, Jiamton 2003 THA, participants were not on ART.

One additional trial in people on treatment for tuberculosis reported no difference in the risk of clinical disease progression (hazard ratio (HR) 1.08 95% CI 0.72 to 1.62; 1 trial, 313 participants, Analysis 1.3).

Virological and immunological outcomes

Nine trials reported changes in CD4+ count over periods from four weeks to two years (see Table 5). We could not incorporate one additional trial from Botswana that reported time-to-event analyses (time to reach CD4+ count < 250 cells/mm^3) into the meta-analyses (Baum 2013 BWA).

- Six trials reported data as means with standard deviation (SD) and the pooled effect had a wide 95% CI including modest benefits and harms (mean difference (MD) 24.79, 95% CI −23.54 to 73.12; 6 trials, 1581 participants; Analysis 1.4, Analysis 1.5). Only one small trial from China administering multiple micronutrients at around the daily recommended intake, reported a statistically significant effect with supplementation after six months (1 trial, 99 participants, Zhao 2010 CHN). The other much larger trials that administered higher doses of multiple micronutrients found no suggestion of effects; including 808 participants with HIV alone, and 674 participants with HIV plus active tuberculosis
- Three trials reported data as medians and interquartile range (IQR), and neither found a statistically significant result (3 trials, 911 participants, data not pooled, Table 5)
- One additional trial from Botswana reported data as the HR of reaching a CD4+ count of less than 250 cells/mm^3. The hazard was lower with high dose supplements of multivitamins plus selenium for two years (HR 0.48, 95% CI 0.26 to 0.88; 1 trial, 439 participants) and with multivitamins alone (HR 0.54; 95% CI 0.3 to 0.98; 1 trial, 436 participants) However, the trial authors reported that this effect was only apparent with supplementation of both multivitamins and selenium after adjustment for multiple confounders (HR 0.46, 95% CI 0.25 to 0.85; 1 trial, 439 participants) (Baum 2013 BWA)

Five trials of high dose multiple micronutrients reported changes in viral load at time points from six weeks to two years (see Table 6).

- Four trials reported data as means with SDs and the pooled estimate was close to no effect with a CI which included a modest benefit and no effect (MD −0.10, 95% CI −0.25 to 0.05; 4 trials, 1064 participants; Analysis 1.6,Analysis 1.7)
- The fifth trial reported no effect on viral load in a multivariable random-effects regression model (1 trial, 437 participants, P = 0.4) (Baum 2013 BWA)

Nutritional status and blood micronutrient concentrations

Three trials reported changes in measures of body composition (BMI, weight, mid-upper arm circumference (MUAC), fat mass or lean body mass) with no statistically significant differences between groups (see Table 7).

Three trials reported changes in blood concentrations of vitamin A, vitamin E, or selenium (see Table 7), with statistically significant increases after 48 weeks supplementation in Thailand (Jiamton 2003 THA), and eight months supplementation in

Malawi (Semba 2007 MWI). The third small trial from Zambia reported no change in serum vitamin A or vitamin E concentrations after four weeks supplementation, despite many being deficient in one or both at baseline (1 trial, 135 participants, Kelly 1999 ZMB).

Adverse events associated with supplementation

One trial with high dose micronutrient supplements reported no differences in serious adverse events such as acute diarrhoea, vomiting, or severely elevated ALT levels (Baum 2013 BWA). Genital HIV-shedding was increased after six weeks, following high dose supplements in another trial (McClelland 2004 KEN). A third trial of high dose supplementation reported discolouration of urine more frequently in the intervention group, but no differences for other minor adverse events such as nausea, headache, dizziness, drowsiness, or rash (Jiamton 2003 THA). Three trials that involved high dose supplementation did not report any adverse events (Kelly 1999 ZMB; Range 2006 TZA; Villamor 2008 TZA).

High dose supplements was associated with a decrease in peripheral neuropathy in one trial, although this was not reported for just the subgroup with HIV (RR 57%, 95% CI 41% to 69%; 1 trial, 887 participants) (Villamor 2008 TZA). Participants in this trial were taking isoniazid for active tuberculosis which is a known vitamin B6 antagonist and may cause neuropathy without supplementation.

One trial with standard dose supplements reported no differences in adverse events such as nausea and vomiting (Guwatudde 2015 UG). A cluster-randomized trial with standard dose supplements reported four cases of pellagra in the placebo group (three were associated with high ethanol intakes) (Kelly 2008 ZMB). Two trials that involved standard dose supplementation did not report any adverse events (Semba 2007 MWI; Zhao 2010 CHN).

Certainty of the evidence

For a critical appraisal of the summary of evidence, see the 'Summary of findings for the main comparison' table (Summary of findings for the main comparison) and Additional tables 8, 9, and 10 for the stratified analyses (participants taking ART or not, and whether they were on concurrent treatment for tuberculosis or not) (Table 8; Table 9; Table 10).

Comparison 2: High-dose versus standard dose multivitamins

One large Tanzanian trial, Isanaka 2012 TZA, investigated the effects of a standard versus a high-dose daily multivitamin supplement for 24 months among participants starting HAART (see Table 4).

Mortality

There were no statistically significant differences in all-cause mortality (RR 1.06, 95% CI 0.89 to 1.26; 1 trial, 3418 participants; Analysis 2.1), or AIDS-related mortality (RR 1.14, 95% CI 0.82 to 1.58; 1 trial, 3418 participants; Isanaka 2012 TZA).

Morbidity and clinical disease progression

There was no difference in clinical disease progression events combined with death from any cause (RR 1.00, 95% CI 0.96 to 1.04; 1 trial, 3418 participants).

Immunological and virological outcomes

There was a small difference between groups in mean CD4+ cell count at baseline (MD −7.00 cells/mm^3, 95% CI −13.74 to −0.26), and a similar difference at 15 months (MD −12.00 cells/mm^3, 95% CI −24.00 to −0.00; 1 trial, 3418 participants, Analysis 2.2). No differences were demonstrated in mean viral load at baseline or end of follow-up (MD −0.20 $\log_{10}$copies/mL, 95% CI −0.51 to 0.11; 1 trial, 236 participants, Analysis 2.3; Isanaka 2012 TZA).

Nutritional status and blood micronutrient concentrations

There was no difference in BMI between the two groups (MD 0 kg/m^2; 95% CI −0.2 to 0.2; 1 trial, 3418 participants). Blood concentrations of micronutrients were not reported.

Adverse events associated with supplementation

This trial was stopped early with a median length of follow-up of 15 months due to an increased risk of elevated ALT levels (greater than 40 IU/L) among trial participants who received high dose multivitamin supplements (incidence rate ratio (IRR) 1.44, 95% CI 1.11 to 1.87; one trial, 2921 participants). No differences were observed for other adverse events such as fatigue, nausea or vomiting, diarrhoea, severe anaemia, and rashes or lesions. The incidence of peripheral neuropathy was lower with high dose supplements (IRR 0.81, 95% CI 0.7 to 0.94; 1 trial, 3418 participants).

Comparison 3: Vitamin A versus placebo

Four trials compared a vitamin A supplement to placebo (see Table 11). Participants from two trials in the USA received a single high dose of vitamin A (200,000 IU to 300,000 IU) and were followed up for four to eight weeks (Humphrey 1999 USA; Semba 1998 USA). ART-naive women in one trial from Kenya received a daily dose of vitamin A (10,000 IU) for six weeks (Baeten 2002 KEN). The trial authors of a small cross-over trial of daily supplements containing a vitamin A precursor (β-carotene) did not report data before cross-over (Coodley 1993 USA).

Of the four trials, we judged one to be at low risk of selection bias (Semba 1998 USA), and all four that adequately described blinding and were at low risk of performance and detection bias.

Mortality, morbidity, and clinical disease progression

The trials did not report these outcomes.

Immunological and virological outcomes

Two trials reported changes in CD4+ count at four and six weeks follow-up, and neither reported statistically significant changes (2 trials, 464 participants, data not pooled, see Table 12). One trial did report that mean CD4+ count was higher in the supplemented group after six weeks (P = 0.04), but the difference was no longer statistically significant after multivariate linear regression analysis (Baeten 2002 KEN).

Three trials reported changes in viral load, with no statistically significant differences at four to eight weeks (3 trials, 495 participants, data not pooled, see Table 13).

Nutritional status and blood micronutrient concentrations

Three trials reported changes in blood retinol concentrations (data not pooled, see Table 14). In the only trial with a significant proportion of participants with vitamin A deficiency at baseline (59% < 1.05 µmol/L), median serum concentrations were higher after six weeks of supplementation compared to placebo (P = 0.03) (Baeten 2002 KEN). In the other two trials, in which most participants were not deficient, average blood retinol concentrations remained unchanged after follow-up periods of four and eight weeks, respectively (Humphrey 1999 USA; Semba 1998 USA).

Note: one further trial from the USA evaluated supplementation with a vitamin A precursor, β-carotene (60 mg) three times daily (Coodley 1996 USA). This trial reported an increase in blood concentrations of β-carotene at three months but no statistically significant effects on CD4+ cell count.

Adverse events associated with supplementation

Signs or symptoms of toxicity (headache, nausea, vomiting, diarrhoea, fever) were similar in the intervention and control groups at 24 hours and one week after administration in one trial (Humphrey 1999 USA). No adverse events were reported in the other two trials of vitamin A supplementation (Baeten 2002 KEN; Semba 2007 USA). Slight skin discolouration was reported by the participants in the intervention group of a one small trial of β-carotene supplementation (Coodley 1993 USA).

Certainty of the evidence

For a critical appraisal of the summary of evidence, see 'Summary of findings' table 2 (Summary of findings 2).

Comparison 4: Vitamin D versus placebo

Five trials compared a vitamin D supplement, with or without a calcium supplement, to placebo (see Table 15). Participants in two trials received a total of three or four doses of vitamin D (100,000 IU), given every three to five months (Giacomet 2013 ITA; Wejse 2009 GNB). Two trials from the USA used a daily supplement containing 7000 IU vitamin D or 4000 IU vitamin D plus calcium (1000 mg), respectively, for 12 months (Overton 2015 USA; Stallings 2014 USA). A fifth trial from Denmark combined a single dose of vitamin D (100,000 IU) at study entry with a daily vitamin D supplement (1200 IU) plus calcium (1200 mg) for 16 weeks (Bang 2012 DEN).

In one trial from Guinnea-Bissau participants did not receive ART and were on treatment for active pulmonary tuberculosis (Wejse 2009 GNB). In the other trials most participants were on ART (see Table 15).

We considered only one of the five trials to be at low risk of selection bias (Wejse 2009 GNB), but three trials adequately described blinding and we considered them to be at low risk of detection and performance bias (Bang 2012 DEN; Giacomet 2013 ITA; Wejse 2009 GNB).

Mortality, morbidity, and clinical disease progression

Only a single trial reported mortality in people with active tuberculosis, which was significantly underpowered to evaluate mortality (RR 1.15, 95% CI 0.65 to 2.02; 1 trial, 131 participants, Analysis 3.1). The effect estimate has wide CIs which include both important effects and no effect.

Immunological and virological outcomes

Four trials reported changes in the mean or median CD4+ cell counts, over periods from four to 12 months and found no statistically significant effects (4 trials, 288 participants, data not pooled; see Table 16).

One very small study from the USA reported a reduction in viral load over time in those participants with a detectable viral load, using a multi-level regression model (1 trial, 28 participants, P < 0.05) (Stallings 2014 USA).

Nutritional status and blood micronutrient concentrations

Four trials reported changes in serum concentrations of 25-hydroxy vitamin D for periods that ranged from four to 12 months. Both single dose supplements and daily supplements resulted in a significant increase in mean or median blood concentrations (ng/mL) (4 trials, 305 participants, data not pooled; see Table 17).

Note: one further trial from the USA compared supplementation with 4000 IU vitamin D to 7000 IU vitamin D daily in participants on ART (Dougherty 2015 USA). This trial reported an increase in blood concentrations of 25-hydroxy vitamin D with

both doses at three months, but no statistically significant effects on viral load.

Adverse events associated with supplementation

One trial reported one case of hypercalcaemia in a trial participant who received a single high dose of vitamin D, followed by daily administration (Bang 2012 DEN). The other four trials of vitamin D supplementation did not report any cases of hypercalcaemia (Giacomet 2013 ITA; Overton 2015 USA; Stallings 2014 USA; Wejse 2009 GNB).

Certainty of the evidence

For a critical appraisal of the summary of evidence, see 'Summary of findings' table 3 (Summary of findings 3).

Comparison 5: Zinc versus placebo

Six trials compared a zinc supplement to placebo, given for between two weeks and 18 months (see Table 18). Two trials provided daily supplements at the level of the RDA (Asdamongkol 2013 THA; Baum 2010 USA), with one being a small trial from Thailand in participants with immunological discordance on ART (Asdamongkol 2013 THA).

Higher doses of zinc (50 mg to 100 mg) were given to ARV-naive participants with persistent diarrhoea for 14 days in one trial in Peru (Cárcamo 2006 PER) and to participants on ART from Singapore for four weeks (Green 2005 SGP). In another two trials, participants were on treatment for active pulmonary tuberculosis, and received either a high daily dose of zinc (45 mg) or a weekly dose (90 mg) for six to eight months (Lawson 2010 NIG; Range 2006 TZA).

We considered only one of the six trials to be at low risk of selection bias (Cárcamo 2006 PER), but five trials adequately described blinding and we judged them to be at low risk of performance or detection bias.

Mortality

All three trials that reported deaths were substantially underpowered to confidently detect or exclude effects. None of the trials found statistically significant results and the 95% CI for the overall effect was wide, including both important effects and no effect (RR 1.24, 95% CI 0.53 to 2.86; 3 trials, 433 participants, Analysis 4.1).

Morbidity and clinical disease progression

One trial from Peru in ART-naive adults with persistent diarrhoea reported that a high daily dose of zinc (100 mg) had no effect on the persistence of diarrhoea after two weeks (HR 0.91, 95% CI 0.5 to 1.66; 1 trial, 104 participants, Analysis 4.2; Cárcamo 2006 PER).

One trial from the USA reported that daily zinc supplementation at the level of the DRI for 18 months significantly reduced the proportion of participants with diarrhoea over time (odds ratio (OR) 0.4, 95% CI 0.18 to 0.87; 1 trial, 231 participants, Analysis 4.3; Baum 2010 USA). However, the 95% CI was wide and the trial was also underpowered to have confidence in this result.

Immunological and virological outcomes

Three trials reported changes in CD4+ cell count over periods from 28 days to six months (3 trials, 192 participants, data not pooled, see Table 19) . One trial reported a statistically significant difference in one small subgroup (Asdamongkol 2013 THA). This subgroup is substantially underpowered and therefore a positive result is not likely to reflect a true result (low PPV) (Button 2013). However, one additional trial from the USA in adults on ART reported a statistically significant reduction in the risk of reaching a CD4+ count less than 200 cells/mm³ after supplementation for 18 months (RR 0.24, 95% CI 0.10 to 0.56; 1 trial, 231 participants; Table 19; Baum 2010 USA).

Three trials reported changes in viral load over periods from 28 days to 18 months, and all three trials (including Baum 2010 USA) reported no statistically significant differences with supplementation (3 trials, 400 participants, data not pooled, see Table 20).

Nutritional status and blood micronutrient concentrations

Two trials reported blood zinc concentrations at the trial endpoints of 28 days and 6 months, respectively (two trials, data not pooled, see Table 21) (Asdamongkol 2013 THA; Green 2005 SGP). No difference in zinc concentrations were reported, except for a small number of participants from one trial in Thailand who were deficient in zinc at baseline (Asdamongkol 2013 THA).

In addition, the authors of one trial from Peru in adults with persistent diarrhoea reported a smaller proportion of supplemented participants with low blood zinc levels after 14 days (1 trial, 159 participants, P = 0.01, see Table 21) (Cárcamo 2006 PER). Another trial from the USA reported significantly higher blood zinc concentrations in the supplemented group at the study endpoint of 18 months, adjusted for C-reactive protein levels (1 trial, 231 participants, ß = 0.04; P = 0.047) (Baum 2010 USA).

Adverse events associated with supplementation

In one trial one participant in the intervention group developed an erythematous rash after taking a standard dose supplement for one month, which resolved when the supplement was discontinued (Asdamongkol 2013 THA). Two trials of high dose supplementation reported similar numbers of participants in the intervention and control groups with gastrointestinal symptoms such

as vomiting, diarrhoea or abdominal pain (Cárcamo 2006 PER; Green 2005 SGP).

Certainty of the evidence

For a critical appraisal of the summary of evidence, see 'Summary of findings' table 4 (Summary of findings 4).

Comparison 6: Selenium versus placebo

Four trials compared a daily selenium supplement (200 µg) to placebo, given for between nine and 24 months (see Table 22). Two trials recruited only ART-naive participants (Baum 2013 BWA; Kamwesiga 2015 RWA), and two recruited both ART-naive people and people on ART (Burbano 2002 USA; Hurwitz 2007 USA).

Of the four trials, we only judged one to be at low risk of selection bias (Baum 2013 BWA), and three to be at low risk of performance and detection bias as they adequately described blinding (Baum 2013 BWA; Burbano 2002 USA; Hurwitz 2007 USA).

Mortality

Not reported.

Morbidity and clinical disease progression

One trial in HIV-positive injection drug users in the USA reported a statistically significant reduction in the risk of hospital admissions for opportunistic infections and HIV-related conditions after supplementation for 12 months (RR 0.40, 95% CI 0.21 to 0.75; 1 trial, 186 participants, Analysis 5.1). However, the trial authors stated that fewer participants in the placebo group compared to the selenium group were on ART at baseline ($P < 0.05$) which may have influenced this result (Burbano 2002 USA).

Immunological and virological outcomes

All four trials reported measures of change in CD4+ cell count with mixed findings and poor reporting of baseline and end values (see Table 23). In people not taking ART we observed the following.

- Baum 2013 BWA reported no significant reduction in the risk of reaching a CD4+ count < 250 cells/mm³ with selenium supplements for two years in people not on ART (HR 0.83 95% CI: 0.48 to 1.42; 1 trial, 437 participants), and Kamwesiga 2015 RWA reported no significant reduction in the risk of reaching a CD4+ count of less than 350 cells/mm³ (RR 0.81 95% CI 0.61 to 1.09; 1 trial, 300 participants)
- However, Kamwesiga 2015 RWA reported a reduction in the monthly rate of CD4 cell depletion (MD 1.74, 95% CI 0.31 to 3.17; 1 trial, 300 participants)

In populations with mixed exposure to ART, we observed the following.

- Burbano 2002 USA reported that fewer trial participants in the supplemented group experienced a CD4 cell decline of greater than 50 cells/mm³ ($P = 0.01$; authors' own figures)
- Hurwitz 2007 USA reported a multiple regression model that found higher selenium levels predicted a greater increase in CD4+ cell counts at 9 months ($P < 0.04$; authors' own figures). However, this trial is at high risk of selective reporting as the statistically significant results are only for a subgroup of participants classified as 'selenium responders'. It is unclear if this classification or analysis was planned a priori

Only three trials reported effects on viral load and statistically significant benefits were only reported from the multiple regression model used by Hurwitz 2007 USA.

Nutritional status and blood micronutrient concentrations

Three trials reported statistically significant increases in blood selenium concentrations of participants after supplementation for 6 to 12 months (527 participants, data not pooled, see Table 24)

Adverse events associated with supplementation

One trial reported no differences in symptoms such as nausea, vomiting and skin and hair changes of participants, but those in the intervention group were more likely to report anxiety ($P = 0.04$) and sleep symptoms ($P = 0.01$). (Kamwesiga 2015 RWA). Another trial stated that all serious adverse events reported (which included acute diarrhoea, vomiting, or severely elevated ALT levels) were adjudicated as having a remote relationship to the intervention (Baum 2013 BWA). Two other selenium supplementation trials reported no adverse events (Burbano 2002 USA; Hurwitz 2007 USA).

Certainty of the evidence

For a critical appraisal of the summary of evidence, see 'Summary of findings' table 5 (Summary of findings 5).

Comparison 7: Vitamin E plus vitamin C versus placebo

One small Canadian trial compared high daily doses of vitamins E (800 IU) and C (1000 mg) to placebo in adults on combination ART for three months. Participants were followed up for six months because of a possible carry-over effect of the intervention (Allard 1998 CAN).

Allocation concealment was not well described and so the risk of selection bias was unclear, but the trial was adequately blinded.

Mortality

Not reported.

Morbidity and clinical disease progression

Allard 1998 CAN reported that high daily doses of vitamin E and C for three months had no effect on the risk of new AIDS defining infections after six months (RR 3.54, 95% CI 0.43 to 29.43; 1 trial, 49 participants).

Immunological and virological outcomes

Allard 1998 CAN reported no effect on viral load (log_{10}copies/mL) after three months supplementation of high daily doses of vitamin E and C (MD 0.95 log_{10} copies/mL, 95% CI 0.14 to 2.04; 1 trial, 49 participants).

Nutritional status and blood micronutrient concentrations

This trial reported that high daily doses of vitamins E and C for three months increased blood concentrations of vitamin E (µmol/L) (MD 28.70, 95% CI 20.01 to 37.39; one trial, 49 participants) and vitamin C (µmol/L) (MD 27.30, 95% CI 12.88 to 41.72; 1 trial, 49 participants) of adults on ART (Allard 1998 CAN).

Adverse events associated with supplementation

Two participants in the intervention group reported epigastric discomfort (Allard 1998 CAN).

Comparison 8: Folinic acid versus placebo

One small Brazilian trial compared the effect of a daily folinic acid supplement (5 mg) to placebo on the vascular response of 30 HIV-positive adults on ART (Grigoletti 2013 BRA). This trial was at low risk of selection bias, and detection and performance bias.

Mortality

Not reported.

Morbidity and clinical disease progression

Not reported.

Immunological and virological outcomes

This trial reported no difference in median CD4 cell counts after daily supplementation of folinic acid for four weeks (1 trial, 30 participants, P = 0.994) (Grigoletti 2013 BRA).

Nutritional status and blood micronutrient concentrations

This trial reported increases in blood concentrations of folate and vitamin B12 after supplementation of folinic acid for four weeks (1 trial, 30 participants, P < 0.001) (Grigoletti 2013 BRA).

Adverse events associated with supplementation

No adverse events were reported (Grigoletti 2013 BRA).

Comparison 9: Iron versus no iron

One trial in the USA compared the effect of a daily micronutrient supplement containing iron to a supplement without iron in female injection drug users for 12 months. Of the trial participants who were HIV-positive, approximately one-third were on HAART at baseline and during the study (Semba 2007 USA).

Mortality

Not reported.

Morbidity and clinical disease progression

Not reported.

Immunological and virological outcomes

This trial reported no difference in CD4 cell counts or viral load measurements in participants who received the micronutrient plus iron supplement compared to those who received the supplement without iron for 12 months (CD4 cell count (cells/mm^3): MD 35, 95% CI −83.5 to 153.5; viral load (log_{10}copies/mL): MD −0.4, 95% CI −0.99 to 0.19; 1 trial, 103 participants; Semba 2007 USA).

Adverse events associated with supplementation

No adverse events were reported (Semba 2007 USA).

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Vitamin A compared to placebo for adults with HIV infection currently taking ART or not

Participant or population: adults with HIV infection
Settings: any
Intervention: vitamin A (single dose or daily dose)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Vitamin A				
Mortality	-	-	-	(0 trials)	-	-
Morbidity	-	-	-	(0 trials)	-	-
CD4 cell count (cells/mm^3) Follow-up: 6 to 8 weeks	-	-	Not pooled	464 (2 trials)	⊕⊕◯◯ **low**[1,2,3,4] due to risk of bias and indirectness	Vitamin A may have little or no short-term effect on CD4 cell count
Viral load ($\log_{10}$ copies/mL) Follow-up: 6 to 8 weeks	-	-	Not pooled	495 (3 trials)	⊕⊕◯◯ **low**[1,2,3,4] due to risk of bias and indirectness	Vitamin A may have little or no short-term effect on viral load
Change in vitamin A concentrations (µmol/L) Follow-up: 6 to 8 weeks	-	-	Not pooled	495 (3 trials)	⊕⊕◯◯ **low**[1,3,4,5] due to risk of bias and indirectness	Vitamin A may increase blood concentrations of persons with HIV with low baseline concentrations

*The basis for the assumed risk (for example, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Abbreviations: ART: antiretroviral therapy; CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[1]Downgraded by 1 for serious risk of bias: one trial in Kenya with 400 participants reported high attrition overall (11.5%) and the trial authors stated that participants who were lost to follow-up had more advanced HIV disease and were more likely to be vitamin A deficient (Baeten 2002 KEN).
[2]No serious heterogeneity: none of the trials found statistically significant effects.
[3]Downgraded by 1 for serious indirectness: trials were conducted in the USA and Kenya, and most participants were not on antiretroviral therapy (ART). This may not completely exclude the possibility of effects in some settings or populations.
[4]No serious imprecision: no statistically significant differences were seen. Although two trials were underpowered, one trial in Kenya with 400 participants was adequately powered to reliably detect a clinically beneficial effect on CD4 cell count, viral load, and blood vitamin A concentrations (Baeten 2002 KEN).
[5]No serious heterogeneity: a statistical significant increase in blood vitamin concentrations was reported in one trial from Kenya with 400 participants. Baseline blood vitamin concentrations of these participants were much lower than the 95 participants in the other two trials in the USA.

Vitamin D compared to placebo for adults with HIV infection

Participant or population: adults with HIV infection
Settings: any
Intervention: vitamin D (repeated single doses or daily dose with or without additional calcium)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Vitamin D				
Mortality Follow-up: 12 months	**254 per 1000**	**292 per 1000** (165 to 513)	**RR 1.15** (0.65 to 2.02)	131 (1 trial)	⊕◯◯◯ **very low**[1,2,3] due to indirectness and imprecision	We don't know if vitamin D supplements have any effect on mortality
Morbidity	-	-	-	(0 trials)	-	-
CD4 cell count (cells/mm^3) Follow-up: 16 weeks to 12 months	-	-	Not pooled	288 (4 trials)	⊕⊕◯◯ **low**[1,4] due to indirectness	Vitamin D supplements may have little or no effect on CD4 cell count
Viral load (log$_{10}$ copies/mL) Follow-up: 12 months	The mean in the placebo group was **3.78**	The mean in the multiple micronutrient groups was **0.66 lower** (1.37 lower to 0.05 higher)	-	28 participants (1 trial)	⊕◯◯◯ **very low**[1,5,6] due to indirectness and imprecision	We don't know if vitamin D supplements have an effect on viral load

Change in 25(OH) vitamin D concentrations (ng/mL) Follow-up: 16 weeks to 12 months	-	-	Not pooled	299 (4 trials)	⊕⊕⊕◯ **moderate**[1,7,8] due to indirectness	Vitamin D supplements probably increase blood 25(OH) vitamin D levels

*The basis for the assumed risk (for example, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; RR: risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[1]No serious risk of bias: the included trials were generally at low risk of bias.
[2]Downgraded by 2 for serious indirectness: only a single trial from Guinea-Bissau reports the number of deaths after 12 months follow-up in HIV-positive participants on treatment for active tuberculosis (Wejse 2009 GNB).
[3]Downgraded by 1 for serious imprecision: the 95% CI is wide and includes both a relative risk reduction and relative risk increase of greater than 25%.
[4]Downgraded by 2 for serious indirectness: no changes in mean or median CD4 cell counts were reported from these four small trials from Italy (Giacomet 2013 ITA), the USA (Overton 2015 USA), Guinea-Bissau (Wejse 2009 GNB), or Denmark (Bang 2012 DEN). This doesn't exclude the possibility of effects in some populations.
[5]Downgraded by 2 for very serious indirectness: this is a single very small trial from the USA.
[6]Downgraded by 1 for serious imprecision: the trial is very small, and the 95% CI is wide and includes no effect.
[7]No serious heterogeneity: all four studies report a statistical significant increase in blood 25(OH) vitamin D concentrations (ng/mL).
[8]Downgrade by 1 for serious risk of indirectness: all studies were conducted in high income countries (Italy, Canada, Denmark, and the USA).

Zinc compared to placebo for adults with HIV infection

Participant or population: adults with HIV infection
Settings: any
Intervention: zinc (daily or weekly dose)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Zinc				
Mortality Follow-up: 6 to 18 months	**110 per 1000**	**135 per 1000** (58 to 315)	**RR 1.24** (0.53 to 2.86)	433 (3 trials)	⊕◯◯◯ **very low**[1,2,3] due to indirectness and imprecision	We don't know if zinc supplements have any effect on mortality
Rate of diarrhoea Follow-up: 18 months	-	-	**OR 0.40** (0.18 to 0.87)	231 (1 trial)	⊕◯◯◯ **very low**[1,4,5] due to indirectness and imprecision	We don't know if zinc supplements have any effect on the frequency of diarrhoea
Change in CD4 cell count (cells/mm^3) Follow-up: 1 to 18 months	-	-	Not pooled	431 (4 trials)	⊕⊕◯◯ **low**[1,2,6] due to indirectness and inconsistency	Zinc supplements may have little or no effect on CD4 cell count
Change in viral load (log_{10}copies/mL) Follow-up: 1 to 18 months	-	-	Not pooled	400 (3 trials)	⊕⊕◯◯ **low**[1,2,7] due to indirectness and imprecision	Zinc supplements may have little or no effect on viral load

Change in blood zinc concentrations Follow-up: 1 to 18 months	-	-	Not pooled	484 (4 trials)	⊕⊕⊕◯ **moderate**[1,2,8] due to indirectness	Zinc supplements probably increase blood zinc concentrations of persons with HIV with low baseline concentrations

*The basis for the assumed risk (for example, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; RR: risk ratio; OR: odds ratio; HR: hazard ratio

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[1]No serious risk of bias: the included studies were generally at low risk of bias.
[2]Downgraded by 1 for serious indirectness: the available data is from limited settings and populations. The findings are not easily generalized to other populations.
[3]Downgraded by 2 for serious imprecision: the 95% CI around the absolute effect is very wide and crosses 1. The overall meta-analysis is underpowered to confidently exclude effects.
[4]Downgraded by 2 for very serious indirectness: this finding is from a single study in the USA and may not be applicable to other settings.
[5]Downgraded by 1 for serious imprecision: although the 95% CI does not cross the line of no effect this trial is underpowered to detect or exclude clinically important differences.
[6]Downgrade by 1 for serious inconsistency: one very small trial from Singapore reports a marginal improvement in median CD4 count after 6 months of standard dose supplements (Asdamongkol 2013 THA), and one study reports a significant reduction in the risk of decline of CD4+ to < 200 in those taking standard supplements (Baum 2010 USA). Two other small studies using high dose supplements report no statistically significant difference (Green 2005 SGP; Range 2006 TZA).
[7]Downgraded by 1 for serious imprecision: all three trials were underpowered to include or exclude clinically important effects (Baum 2010 USA; Green 2005 SGP; Range 2006 TZA).
[8]No serious inconsistency: three trials report an increase in blood zinc concentrations over time. The participants in one trial that did not report an increase in blood concentrations after supplementation, were not deficient in zinc at baseline (Green 2005 SGP).

Selenium compared to placebo for adults with HIV infection

Participant or population: adults with HIV infection
Settings: all settings
Intervention: selenium (daily dose)
Comparison: placebo

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Placebo	Selenium				
Mortality	-	-	-	(0 trials)	-	-
Hospital admissions Follow-up: 12 months	**309 per 1000**	**124 per 1000** (65 to 232)	**RR 0.4** (0.21 to 0.75)	186 (1 trial)	⊕◯◯◯ **very low**[1,2,3] due to risk of bias, indirectness, and imprecision	We don't know if selenium supplements reduce hospital admissions
Change in CD4 cell count (cells/mm^3) Follow-up: 9 to 24 months	-	-	Not pooled	1187 participants (4 trials)	⊕⊕◯◯ **low**[4,5] due to risk of bias and imprecision	Selenium supplements may have little or no effect on CD4 cell count
Change in viral load (log_{10}copies/mL) Follow-up: 24 months	-	-	Not estimable	439 participants (1 trial)	⊕⊕◯◯ **low**[6,7]	Selenium supplements may have little or no effect on viral load
Change in selenium concentrations (µg/L) Follow-up: 6 to 12 months	-	-	Not pooled	527 (3 trials)	⊕⊕◯◯ **low**[4,8,9]	Selenium supplements may increase blood selenium concentrations

*The basis for the assumed risk (for example, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Abbreviations: ART: antiretroviral therapy; CI: confidence interval; RR: risk ratio; HR: hazard ratio

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[1]Downgraded by 1 for serious risk of bias: high attrition due to participants with incomplete medical records. In addition, fewer participants in the placebo group compared to the selenium group were on antiretroviral therapy (ART) at baseline (Burbano 2002 USA).
[2]Downgraded by 1 for serious indirectness: only a single trial is available from the USA in HIV-positive intravenous drugs users. This is not easily generalized to other HIV-positive populations.
[3]Downgraded by 1 for serious imprecision: this trial is underpowered to detect clinically important differences.
[4]Downgraded by 1 for serious risk of bias: two of the three trials reported high attrition rates (Burbano 2002 USA; Hurwitz 2007 USA). In one trial fewer participants in the placebo group compared to the selenium group were on ART at baseline (Burbano 2002 USA).
[5]Downgraded by 1 for serious imprecision: three of the four trials were underpowered to include or exclude clinically important effects (Burbano 2002 USA; Hurwitz 2007 USA; Kamwesiga 2015 RWA). One trial from Botswana was adequately powered and reported no effect on the decline in CD4 cell counts of ART-naive participants (Baum 2013 BWA).
[6]No serious risk of bias: the included trial was at low risk of selection and performance bias (Baum 2013 BWA). The trial authors performed multiple imputation of viral load data. The trial authors did not provide details.
[7]Downgraded by 2 for serious indirectness: only a single trial is available from Botswana in participants not on ART (Baum 2013 BWA).
[8]No serious heterogeneity: all three trials reported either an increase in the mean blood selenium concentration of participants or the proportion of participants with selenium concentrations above a certain threshold level.
[9]Downgraded by 1 for indirectness: participants in two of the three included trials were not deficient in selenium at baseline (Burbano 2002 USA; Hurwitz 2007 USA). The third trial reported data on participants who were selenium deficient at baseline; however it was a small subsample of the main trial from Botswana (Sales 2010).

DISCUSSION

Summary of main results

Multiple micronutrients

Routine multiple micronutrient supplementation may have little or no effect on mortality in adults living with HIV, but the pooled analysis remains underpowered to confidently exclude small effects (*low certainty evidence*). Trials were conducted in antiretroviral therapy (ART)-naïve adults (3 trials, 1068 participants, *low certainty evidence*), adults on ART (1 trial, 400 participants, *very low certainty evidence*), and adults with concurrent active tuberculosis (3 trials, 1429 participants, *low certainty evidence*).

Routine supplementation for up to two years, has also not been shown to have consistent benefits on either mean CD4+ cell count (*low certainty evidence*) or mean viral load (*moderate certainty evidence*). One recent trial in ART-naïve adults reported a reduction in the risk of reaching a CD4+ cell count of less than 250 cells/mm³ after two years of high dose supplementation in Botswana. However, this effect was only robust in the trial arm receiving multiple micronutrients plus selenium (not either supplementation alone) and is inconsistent with the findings of other trials using similar combinations of micronutrients and selenium.

In one additional trial that compared high dose multiple micronutrient supplementation with standard doses in people on antiretroviral therapy (ART), peripheral neuropathy was reduced with high dose supplements compared to standard dose, but the trial was stopped early due to increased adverse events 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 such as hospital admissions and persistence or rate of diarrhoea. Clinically important effects on CD4+ cell count or viral load were not reported. Supplementation probably does increase blood concentrations of vitamin D and zinc, and may also increase blood concentrations of vitamin A, especially in those who are deficient at baseline.

Overall completeness and applicability of evidence

The included trials of multiple micronutrient supplements were predominantly conducted in people who either were not taking ART or were on concurrent treatment for tuberculosis. In these populations, routine supplementation has not been shown to consistently improve disease progression as measured by average CD4+ cell count. One recent well-conducted trial, from Botswana detected a benefit in the group receiving multivitamins with selenium but not with multivitamins alone. However, the lack of demonstrable benefit in other trials with similar selenium content, suggest that this effect should be repeated before reliable conclusions can be drawn.

The trials of single or dual micronutrient supplements included more participants on ART, and several were conducted in populations with proven micronutrient deficiencies. Despite this the only demonstrable benefits were improvements in serum levels of some micronutrients. However, these effects may be enough for some to recommend routine supplementation in similar populations.

There are several possible explanations for the lack of benefit seen in many of these trials.

- The period of supplementation may have been insufficient to demonstrate effects, with benefits only accruing over prolonged periods of supplementation. Supplementation ranged from as little as four weeks up to two years.
- The prevalence of micronutrient deficiencies may have been too low in some of these populations to demonstrate an effect. Baseline micronutrient status was poorly assessed in many of the included trials, particularly those evaluating multiple micronutrients, so it is difficult to determine which populations these negative results should be applied to. Only one trial reported adjustment of their analysis of blood micronutrient concentrations for the effect of inflammation, an important confounder.
- The doses supplemented varied considerably. Many trials evaluated doses significantly higher than the daily recommended intake, and one trial of multiple micronutrients directly compared high doses with standard doses to investigate this. However, it should be noted that the high doses were not well-tolerated in this trial.
- The trials may simply be too small to demonstrate effects. Certainly there is insufficient evidence to say that micronutrients could never have effects.

Given the lack of benefit in those not on ART, it seems unlikely that large effects would be seen in those who are taking ART, but adequately powered trials may still be justifiable to explore this. There may be a number of ways by which specific micronutrients may impact on or interact with ART, including aspects of drug pharmacokinetics. However, the clinical significance of these interactions remains to be determined (Raiten 2011).

Quality of the evidence

We considered the certainty of the evidence for most of the outcomes in this review to be low or very low, meaning that we can have only minimal confidence in these effects. We downgraded the certainty of the evidence mainly for the following reasons.

- Indirectness: since micronutrient deficiencies differ widely among populations it is difficult to generalize the findings of a single trial, or even a few trials, to all settings, and all populations.
- Imprecision: most included trials were small and well below the optimal information size for the outcomes that were being measured and therefore not able to reliably detect or exclude an effect.

Potential biases in the review process

We tried to minimize any biases in the review process by performing a comprehensive search of the literature, and by independently selecting studies, appraising studies, and extracting data. Two review authors, MV and SD, assessed the risk of bias of the new included studies using the updated 'Risk of bias' tool (Higgins 2011).

This review included outcome data for HIV participants from four RCTs that included both HIV-positive and HIV-negative participants without stratified randomization (Kelly 2008 ZMB; Lawson 2010 NIG; Range 2006 TZA; Semba 2007 MWI).

Agreements and disagreements with other studies or reviews

In the previous version of this Cochrane Review, Irlam 2010 concluded that further trials of single supplements (vitamin D, zinc, and selenium) were required to build the evidence base for adults and that the long-term clinical benefits, adverse effects, and optimal formulation of multiple micronutrient supplements required further investigation.

Forrester 2011 conducted a narrative review to investigate whether the 2003 WHO recommendations for micronutrient intake in HIV-positive adults should change. This review focused primarily on the results of nine trials of multiple micronutrient supplementation; seven trials in non-pregnant HIV-positive adults, and two in pregnant HIV-positive women. The authors noted that "five of the six trials that used high-dose multiple micronutrients showed benefits in terms of either improved CD4 cell counts or survival", but also that "many of these trials were small and of short duration, and the long-term risks and benefits of high-dose multiple micronutrients are not established". Our analysis and appraisal of the evidence agrees that there is currently insufficient evidence to make firm conclusions about the effects of supplementation.

For the effects of micronutrient supplementation in pregnant women and children with HIV, see the separate Cochrane reviews by Siegfried 2012 and Irlam 2013.

AUTHORS' CONCLUSIONS

Implications for practice

To date trials of routine multiple micronutrient supplementation have not demonstrated consistent clinically important benefits on HIV disease progression or mortality. However, the trials are generally too small to confidently exclude the possibility of important effects.

These findings should not be interpreted as a reason to deny supplementation where specific deficiencies have been demonstrated (such as vitamin D, zinc, and selenium), or where the person's diet is unlikely to meet the recommended daily allowance of vitamins and minerals.

Implications for research

Furthermore, adequately powered studies with sufficient follow-up periods are still required to confidently prove or exclude any long-term clinical benefit of routine supplementation.

Such research should not be to the detriment of ART, as this remains the one intervention to date that has consistently been shown to reduce morbidity and mortality, and improve the nutritional status of adults living with HIV/AIDS.

ACKNOWLEDGEMENTS

We are grateful to Cochrane South Africa and the editorial base of the Cochrane Infectious Diseases Group, for assistance and support in preparing this review update. We also thank the following individuals.

- Tamara Kredo, Cochrane SA, for providing advice and guidance throughout the review process
- Joy Oliver, Cochrane SA, for conducting the searches for this update
- Tonya Esterhuizen, Centre for Evidence-based Health Care, Stellenbosch University, for providing statistical advice
- Xuan Hui, a methodologist of the Cochrane Eyes and Vision Group, for the translation of the included Chinese article into English
- Nigel Rollins, who was an author on the previously published versions of this review (Irlam 2002; Irlam 2005; Irlam 2010)

The editorial base of the Cochrane Infectious Diseases Group is funded by UK aid from the UK Government for the benefit of developing countries (Grant: 5242). David Sinclair and Solange Durao were partly supported by the Effective Health Care Research Consortium. This Consortium is funded by UK aid from the UK Government for the benefit of developing countries (Grant: 5242).

The views expressed in this review do not necessarily reflect UK government policy.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Allard 1998 CAN

Methods	Country: Canada Setting: primary care physicians Duration of recruitment: April 1995 to August 1996 Duration of follow-up: 6 months Design: randomized placebo-controlled trial
Participants	Inclusion criteria: patients of participating physicians with stable HIV-infection Exclusion criteria: active opportunistic infection, smoking, prior antioxidant therapy, hyperlipidaemia, kidney/liver dysfunction, intractable diarrhoea (≥ 6 liquid stools/day) , vomiting, gastrointestinal (GI) bleeding Participants randomized: 49; 47 males and 2 females; mean age = 39 years Loss to follow-up/withdrawal: 0 Exclusions postrandomization: 0
Interventions	Intervention: 800 IU vitamin E and 1000 mg vitamin C Control: placebo Duration: daily for 3 months
Outcomes	Primary outcomes • Viral load, oxidative stress (lipid peroxides, malondialdehyde, breath pentane) Secondary outcomes • Plasma micronutrients (vitamin E, C, A carotenoids, zinc, selenium); new and recurrent infections (AIDS-defining, HIV-associated, and other)
Adverse events	Two participants in the intervention group reported epigastric discomfort
Notes	Number of participants on antiretroviral therapy (ART) • Supplement group: 22/23 (85%). • Control group: 18/26(78%). Controlled diet 2 weeks prior to randomization and throughout study period, and dietary counselling Source of funding: Canadian Foundation for AIDS Research

Risk of bias *Risk of bias*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial authors used a random number table to perform randomization
Allocation concealment (selection bias)	Unclear risk	The trial authors did not adequately describe allocation concealment

Allard 1998 CAN (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	The trial authors blinded the participants and investigators to treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	There were high and unequal proportions of missing outcomes (3/23 intervention group versus 6/26 control group)
Selective reporting (reporting bias)	Unclear risk	There was insufficient information; the trial protocol was unavailable
Other bias	Unclear risk	The trial authors did not declare their conflicts of interest, if any

Asdamongkol 2013 THA

Methods	Country: Bangkok, Thailand Setting: HIV Clinic, Ramathibodi Hospital, Mahidol University Duration of recruitment: May 2011 to April 2012 Duration of trial: 6 months Duration of follow-up: 6 months Design: randomized placebo-controlled trial, stratified according to baseline blood zinc levels Follow-up: monitoring of clinical condition, adverse events, and adherence every 3 months
Participants	Inclusion criteria: HIV-positive people aged ≥ 18 years who were on ART for at least 12 months, with complete viral suppression (HIV RNA 40 copies/mL), and having $CD4_+$ cell count < 200 cells/mm³ that increased < 30% from baseline after achieving undetectable HIV RNA after 12 months of ART Exclusion criteria: pregnancy or women planning to become pregnant, and participants who previously received zinc supplements (duration not stated) Participants screened: 70 Participants eligible for randomization: 31 Participants randomized: 31 (low blood zinc levels (N = 12); normal blood zinc levels (N = 19)) Mean age at randomization: 45 ± 11 years 21 female/10 male 62.3% (144/231) of participants were receiving ART at baseline The trial authors reported that the distribution of the ART regimens was similar between the 2 groups at baseline
Interventions	InterventionS: 15 mg chelated zinc daily Control: placebo daily Duration: 6 months Compliance: participants were asked to return any unused study medication every 3 months and pill counts were conducted. The trial authors did not report compliance rates

Asdamongkol 2013 THA (*Continued*)

Outcomes	Primary • Blood zinc levels Secondary • CD4 count, CD4 %
Adverse events	One participant in the zinc group developed an erythematous rash after supplementation for 1 month, which resolved when the participants discontinued taking the zinc supplement
Notes	Links to other studies (study ID): Asdamongkol 2012 under Asdamongkol 2013 THA Source of funding: research grant of Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand Conflict of interest: None Ethics: Ramathibodi Hospital, Mahidol University Institutional Ethics committee but type of consent not stated Trial registration: not stated

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial randomized participants to receive zinc supplements or placebo in a 1:1 ratio in blocks of 4. However, the trial authors did not clearly describe the process of selecting the blocks
Allocation concealment (selection bias)	Unclear risk	Although the trial authors stated that the pharmacy bottled the supplements, they did not provide any information on whether the bottles were prelabelled in a sequential order
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial authors stated that the zinc or placebo pills were indistinguishable in shape, size, and colour. Outcome measures (laboratory assays) were unlikely to have been affected by detection bias
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participant in the zinc group was withdrawn from the trial during the follow-up period
Selective reporting (reporting bias)	Unclear risk	The trial protocol was unavailable.
Other bias	Low risk	The trial authors declared that they had no conflicts of interest

Baeten 2002 KEN

Methods	Country: Kenya Setting: hospital outpatient clinic Duration of recruitment: September 1998 to June 2000 Median duration of follow-up: 42 days (32 to 445 days) Design: randomized placebo-controlled trial
Participants	Inclusion criteria: HIV-1 seropositive women attending Coast Provincial General Hospital outpatient clinics in Mombasa, Kenya Exclusion criteria: age < 18 or > 45; pregnancy, or use of vitamin supplements or oral contraceptive pills Participants randomized: 400; 400 females; median age = 28 years Loss to follow-up/withdrawal: 46 Exclusions postrandomization: 0
Interventions	Intervention: vitamin A (10,000 IU retinyl palmitate) Control: placebo Duration: daily for 6 weeks
Outcomes	Primary outcomes: • Vaginal HIV DNA and RNA Secondary outcomes • Plasma viral load CD4 and CD8 counts
Adverse events	None reported
Notes	Source of funding: research grants from NIH, University of Washington, and Fogarty International Center; International AIDS Research and Training Program scholarships; Gen-Probe (reagents)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The trial authors used computer-generated block randomization
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe how they performed allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	The participants and investigators were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition in both treatment groups (vitamin A group: 12%; placebo group: 11%) . The trial authors stated that those lost to follow-up had more advanced HIV disease and were more likely to be vitamin A-defi-

Baeten 2002 KEN (*Continued*)

		cient
Selective reporting (reporting bias)	Unclear risk	There was insufficient information regarding selective reporting; the trial protocol was not available
Other bias	Unclear risk	The trial authors did not declare whether or not they had conflicts of interest

Bang 2012 DEN

Methods	Country: Denmark Setting: outpatient clinic, Department of Infectious Diseases, Hvidovre Hospital Duration of recruitment: July 2008 to September 2009 Duration of trial: 15 months Duration of follow-up: 16 weeks Design: randomized placebo-controlled trial with 3 intervention arms Follow-up: at baseline, a medical history and assessment of total calcium intake was performed for each participant At baseline and at 16 weeks, bloods were taken to measure immunological parameters, HIV-viral load, parathyroid hormone, calcium, vitamin D, and biochemical bone markers. The trial assessed quality of life of each participant at baseline and at 16 weeks (Medical Outcomes Study (MOS) 36-item Short Form Health Survey (SF-36) questionnaire)
Participants	Inclusion criteria: HIV-positive males aged ≥ 18 years who were receiving highly active antiretroviral therapy (HAART) Exclusion criteria: previous bone disease, tuberculosis, sarcoidosis, active malignancy with bone metastasis, elevated serum calcium Participants randomized: 61 Mean age at randomization: 48 ± 9 years No reported baseline differences between treatment groups in terms of time since HIV diagnosis, type of HAART, CD4 and CD8 cell counts, HIV viral load, calcium intake Treatment assignment of 2 participants who used vitamin D supplementation prior to the study not reported
Interventions	InterventionS: calcitriol and vitamin D: 100,000 IU vitamin D at study entry; tablets containing 1200 mg calcium plus 1200 IU vitamin D and 0.5 µg to 1.0 µg calcitriol daily Vitamin D: 100,000 IU vitamin D at study entry; tablets containing 1200 mg calcium plus 1200 IU vitamin D and placebo daily Control: placebo at trial entry; tablets containing 1200 mg calcium and placebo daily Duration: 16 weeks Compliance: participants were asked to return any unused trial medication after 16 weeks. Compliance rates with the daily study tablets were not reported for each treatment group. According to the trial authors, 77% and 67% of participants achieved a satisfactory compliance (defined by the trial authors as ≥ 80% of the number of tablets dispensed) for the calcitriol/placebo tablet and cholecalciferol/placebo tablet, respectively

Bang 2012 DEN (*Continued*)

Outcomes	Primary outcome • Changes in absolute CD4 and CD8 count, changes in % CD4 and % CD8 Secondary outcome: • Changes in HIV viral load and blood concentrations of parathyroid hormone (PTH), calcium, 25 hydroxyvitamin D (25-OHD), and 1,25 hydroxyvitamin D 1,25 (OH)D2 • Changes in quality of life • Changes in biochemical bone markers of bone formation (P1NP) and bone resorption (CTx)
Adverse events	Hypercalcaemia (calcitriol + vitamin D group (2 events); vitamin D group (1 event), constipation (8 events)) 11 adverse events were only reported as unrelated to the study medication (calcitriol + vitamin D group (6 events); vitamin D group (3 events); control group (2 events))
Notes	Source of funding: Pharma-Vinci, Roche (sponsorship of trial supplements) Conflict of interest: nothing declared Ethics: regional ethics committee and the National Board of Health Trial registered at clinicaltrials.gov (NCT00990678)

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It is unclear how the trial generated randomization codes.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not provide any information regarding allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial authors reported that participants and investigators were blinded throughout the trial. For the outcomes of CD4/CD8 cell counts and viral loads, lack of blinding of outcome assessors was unimportant
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was not similar across treatment groups: (19/20 (95%) for calcitriol and vitamin D group; 17/19 (89%) for vitamin D group, and 15/22 (68%) for control group) . The reasons for attrition in each group were unclear
Selective reporting (reporting bias)	Unclear risk	The trial protocol from clinicaltrials.gov states the measurement of all outcomes at baseline and at 2, 4, 8, 12, and 16 weeks. However, the trial authors reported data for baseline and 16 weeks only. Although the

Bang 2012 DEN (*Continued*)

		trial authors reported T lymphocyte subsets (CD4, CD8) as the primary outcome, the trial protocol describes blood vitamin D concentrations as the primary outcome
Other bias	Unclear risk	The trial authors did not include any statement on conflicts of interest. It was unclear whether study sponsors played any role in the study design or reporting of study findings

Baum 2010 USA

Methods	Country: USA Setting: primary health care clinic, Miami Duration of recruitment:March 2002 to December 2005 Duration of trial: 46 months Duration of follow-up: 18 months Design: randomized placebo-controlled trial Follow-up: a nurse practitioner performed a physical examination, medical history, urine toxicology, and took bloods (CD4 count, HIV viral load, C-Reactive protein, zinc) from participants at baseline and every 6 months. The trial assessed participants' morbidity during monthly visits to clinic by means of a questionnaire, which was confirmed by information recorded in medical charts. Cause of death was determined by means of authorized contacts, medical records, and death certificates
Participants	Inclusion criteria: HIV-positive people aged ≥ 18 years with low plasma zinc levels (< 0.75 mg/L) and no history of endocrine or psychiatric disorders Exclusion criteria: premenopausal women who were pregnant or had an intention to become pregnant; plasma zinc levels ≤ 0.35 mg/L at any time during the trial Participants screened: 557 Participants eligible for randomization: 246 Participants randomized: 231; 62 female and 169 male Mean age at randomization: 42.7 ± 7 years 62.3% (144/231) of participants were receiving ART at baseline There were no reported baseline differences in demographic characteristics, clinical disease stage, CD4 cell count, HIV viral load, adherence to ART, drug or alcohol use, cigarette use, or plasma zinc levels
Interventions	Intervention: 12 mg of elemental zinc for women; 15 mg for men daily Control: placebo daily Duration: 18 months Compliance: assessed monthly with questionnaires and pill counts. 3.65 ± 0.31 pills returned out of a possible 4 pills per month After completion of the trial it is reported that participants who received zinc had higher blood zinc concentrations over time compared to those who received placebo, after controlling for C-Reactive protein concentrations (data not provided)

Baum 2010 USA (*Continued*)

Outcomes	Primary outcomes: • Immunological failure (CD4 count < 200 cells/mm³) Secondary outcomes: • HIV viral load • Morbidity (incidence of diarrhoea, upper and lower respiratory infections, and other health events (not specified)) • Prevalence of hypertension • Mortality
Adverse events	None
Notes	Source of funding: National Institute on Drug Abuse Conflict of interest: none Ethics: Florida International University Institutional Review Board Trial registered at clinicaltrials.gov (NCT00149552)

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	It was unclear how the trial generated randomization codes.
Allocation concealment (selection bias)	Low risk	A pharmacist bottled and precoded the trial supplements for each participant for the entire trial period according to the randomization code
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial authors reported that the clinical and study personnel and participants were blinded. Only the pharmacist and statistician were aware of treatment assignments during the trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	There was low attrition. However, the uneven numbers, deaths, plasma zinc, and dropouts may be related to main outcome
Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes as reported are consistent with the trial protocol from www.clinicaltrials.gov.
Other bias	Low risk	The trial authors declared that they had no conflicts of interest. An independent company that was not involved in the design or implementation of the study, or the analysis and reporting of the findings. manufactured the trial supplements

Baum 2013 BWA

Methods	Country: Botswana Setting:Princess Marina Hospital, Gaborone, Botswana Duration of recruitment: Duration of trial: 4 years and 7 months (December 2004 to July 2009) Duration of follow-up: 24 months Design: randomized placebo-controlled factorial trial with 3 intervention arms Follow-up: a monthly questionnaire was administered about acceptability of the supplement, adherence, adverse effects, and intercurrent morbidity (health events occurring between the trial visits; confirmed by documentation in medical record) Every 3 months: physical examination and medical history performed by a nurse or physician, blood sample taken for CD4 cell count Every 6 months: HIV viral load, plasma micronutrient levels (20% subsample), and blood chemistries
Participants	Inclusion criteria: HIV-positive participants aged 18 years and older, ART-naive and CD4 cell count > 350 /µL Exclusion criteria: pregnancy Participants screened: 1003 Participants eligible for randomization: 922 Participants randomized: 878 Median age at randomization: 31 to 33 years The trial authors reported no statistically differences in baseline CD4 cell count, HIV viral load, Body Mass Index (BMI), haemoglobin, albumin, total cholesterol, and HDL-cholesterol levels
Interventions	Intervention (multivitamins group): thiamin 20 mg, riboflavin 20 mg, vitamin B6 25 mg, niacin 100 mg, vitamin B12 50 µg, folic acid 0.8 mg, vitamin C 500 mg, vitamin E 30 mg Intervention (selenium group): 200 µg daily Intervention (multivitamins plus selenium group): as above Control: placebo daily Administered as 1 pill daily. Pills were indistinguishable in shape, size, and colour Duration: 24 months Compliance: pill counts at each follow-up visit, Adherence reported as 96% (no standard deviation (SD) stated) The trial measured plasma micronutrient levels (subsample of participants) but the trial authors did not report this information All participants received isoniazid (INH) prophylaxis
Outcomes	Primary outcome • Time from randomization to reaching CD4 cell count of 200 cells/µL or less. In March 2008, this outcome was changed to reaching a CD4 cell count of 250/µL or less due to change in ART policy Secondary outcomes: • HIV viral load • Composite of time from randomization to reaching CD4 cell count of 200/ µL or less or AIDS defining conditions or AIDS-defining death • Time from randomization to reaching CD4 cell count of 350/ µL or less • Composite of time from randomization to reaching CD4 cell count of 350/ µL or less or AIDS defining conditions or AIDS-defining death

Baum 2013 BWA (*Continued*)

Adverse events	The trial authors reported a total of 79 adverse events which they judged as having a remote relationship with the trial intervention Acute diarrhoea/vomiting: 5 events (3 in multivitamins plus selenium group; 2 placebo group) Severely elevated alanine transaminase (ALT) (> 5 times normal range): 3 events (1 in multivitamins group; 2 in placebo group)
Notes	Links to other trials (trial ID): Sales 2010 Source of funding: National Institute on Drug Abuse Conflict of interest: none Ethics: Florida International University Institutional Review Board, Harvard School of Public Health IRB, Botswana Health Research Unit of the National Ministry of Health Trial registration: not reported

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	A statistician generated block randomization in blocks of 20
Allocation concealment (selection bias)	Low risk	Participants were assigned into one of the trial groups using the next sequential number from the randomization list generated by the data centre. The pharmacist prelabelled the pills for the entire trial with the identification number according to the assignment list
Blinding (performance bias and detection bias) All outcomes	Low risk	Pills were indistinguishable in shape, size, and colour; also the trial authors stated that trial personnel and participants were blinded. Outcome measures (laboratory assays) were unlikely to be affected by detection bias
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The trial authors reported the number of participants who withdrew from the trial due to pregnancy; however, other reasons for lost-to follow-up were not stated. There were similar levels of attrition across treatment groups (selenium group: 17% (38/220); multivitamins plus selenium group: 19% (42/220); placebo group: 15% (21/219)) For the measures of viral load, the trial authors performed multiple imputation, but did not provide any details in terms of the

Baum 2013 BWA (*Continued*)

		proportion of data that was missing
Selective reporting (reporting bias)	Unclear risk	The trial protocol was unavailable.
Other bias	Low risk	The trial authors declared no conflicts of interest. The trial was funded by a non-conflicting funding source

Burbano 2002 USA

Methods	Country: USA Setting: community-based clinic Duration of recruitment: 1998 to 2000 Duration of follow-up: 12 months Design: randomized placebo-controlled trial
Participants	Inclusion criteria: confirmed HIV, past or present use of illegal drugs, ≥ 18 years, adequate selenium status (> 85 µg/L) Exclusion criteria: selenium deficient (< 85 µg/L) Participants randomized: 259 112 female Median age = 40 years (range 24 to 54) Loss to follow-up/withdrawal: 73 at 12 months Exclusions postrandomization: 0
Interventions	200 microgram selenium or placebo daily for 12 months.
Outcomes	Primary outcomes • Number of hospital admissions • Type of hospital admissions • Risk of hospitalization Secondary outcomes • CD4 count • Hospitalization cost • Plasma selenium
Adverse events	None reported
Notes	Number of participants on ART: Selenium group: 64 (76%) Control group: 60 (53%) Number, type, and duration of hospital admissions recorded 2 years prior and during study period. Medical records reviewed by team of physicians Source of funding: research grant and commercial (materials)

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**

Burbano 2002 USA (*Continued*)

Random sequence generation (selection bias)	Unclear risk	The trial authors did not describe how they performed sequence generation
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe how they performed allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Exclusions from the analysis (73/259 (28%)) not reported by treatment group
Selective reporting (reporting bias)	Unclear risk	Insufficient information; the trial protocol was unavailable
Other bias	Unclear risk	The trial authors did not declare on any conflicts of interest, if any

Coodley 1993 USA

Methods	Country: USA Setting: hospital outpatient clinics Duration of recruitment: not stated Duration of follow-up: 8 weeks Design: randomized cross-over trial; no washout period
Participants	Inclusion criteria: HIV-seropositive Exclusion criteria: on other forms of vitamin A supplementation; significant hepatic or renal dysfunction; active opportunistic infection or fever Participants randomized: 21 20 male and 1 female Median age: not stated Loss to follow-up/withdrawal: 4 Exclusions postrandomization: 0
Interventions	Intervention: 60 mg beta-carotene Control: placebo Duration: 3 times daily for 4 weeks
Outcomes	Primary outcomes • CD4 counts Secondary outcomes • White blood cell count • Lymphocyte count • B-lymphocytes • Serum beta-carotene

Coodley 1993 USA (*Continued*)

Adverse events	No toxicity; skin discolouration in treatment group
Notes	CD4 count data reported as means and ranges 16 participants received ART. Source of funding: Hoffman La Roche Inc.

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial authors did not describe the method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe the method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Low attrition at 1 month; the trial authors provided reasons
Selective reporting (reporting bias)	Unclear risk	There was insufficient information; the trial protocol was unavailable
Other bias	Unclear risk	The trial authors did not declare on conflict of interest, if any

Coodley 1996 USA

Methods	Country: USA Setting: hospital outpatient clinic and private practice Duration of recruitment: not stated Duration of follow-up: 3 months Design: randomized controlled trial (RCT)
Participants	Inclusion criteria: HIV-seropositive; > 21 years Exclusion criteria: other forms of vitamin A supplementation 30 days prior to study; ART 60 days prior to study; significant hepatic or renal dysfunction; CD4 < 50 or > 600 Participants randomized: 72 63 male and 9 female Median age: not stated Loss to follow-up/withdrawal: 4 at 1 month; 22 at 3 months Exclusions postrandomization: 0

Coodley 1996 USA (*Continued*)

Interventions	Intervention: 60 mg beta-carotene + multivitamins Control: placebo + multivitamins Duration: 3 times daily for 3 months
Outcomes	Primary outcomes • CD4 counts Secondary outcomes • T-cell counts • White blood cell counts • Natural killer cells • HIV p-24 antigen • Serum beta-carotene • Body weight • Karnofsky scores
Adverse events	None reported
Notes	Number of participants on ART: treatment group: 10 (28%); control group: 17 (47%) Source of funding: research grant and commercial (materials)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial authors did not describe the method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe the method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	High attrition at 3 months (22/72 participants were lost to follow-up); the trial authors did not provide reasons
Selective reporting (reporting bias)	Unclear risk	Insufficient information; the trial protocol was unavailable
Other bias	Unclear risk	The trial authors did not declare on conflict of interest, if any

Cárcamo 2006 PER

Methods	Country: Peru Setting: tertiary hospitals Duration of recruitment: June 1998 to Jan 2000 Duration of follow-up: 2 weeks Design: randomized placebo-controlled trial
Participants	Inclusion criteria: HIV-seropositive, persistent diarrhoea (≥ 7 days) without prior treatment Exclusion criteria: none stated Participants randomized: 159 49 female and 110 male Median age = 30 years (range 19 to 57) in zinc group Median age = 31 years (range 19 to 64) in placebo group Loss to follow-up/withdrawal: 51 Exclusions postrandomization: 0
Interventions	Intervention: zinc sulphate (100 mg) Control: placebo Duration: daily for 14 days
Outcomes	Primary outcomes • Persistence of diarrhoea • Time until cessation of diarrhoea Secondary outcomes: • Plasma zinc and copper levels
Adverse events	Gastrointestinal symptoms attributable to the medication (nausea, vomiting, abdominal pain) similar in both treatment groups
Notes	Sulfamethoxazole-trimethoprim prescribed for participants with enteric bacterial pathogens (23 in zinc group and 12 in placebo) Source of funding: Fogarty IARTP grant; University of Washington Center for AIDS Research; Centers for Disease Control and Prevention (CDC)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The trial authors used computer-generated blocked randomization
Allocation concealment (selection bias)	Low risk	The trial authors stated that the treatment allocators were unable to access the assignment roll
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and investigators were blinded.

Cárcamo 2006 PER (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	High risk	There were high losses to follow-up in both groups (34.6% intervention group versus 29.5% control group)
Selective reporting (reporting bias)	Unclear risk	There was insufficient information; the trial protocol was unavailable
Other bias	Unclear risk	The trial authors did not declare on conflict of interest, if any

Dougherty 2015 USA

Methods	Country: USA Setting: 2 outpatient clinics, Philadelphia Design: RCT (safety trial) Duration of recruitment: January 2010 to January 2011 Duration of follow-up: 12 weeks Follow-up: participants were followed up at 6 and 12 weeks. Blood and urine measurements were also performed for vitamin D (25-hydroxy vitamin D, 1,25-dihydroxy vitamin D), calcium, metabolic parameters, and immunological parameters
Participants	Inclusion criteria: participants with perinatally acquired HIV (PHIV) and behaviorally-acquired HIV (BHIV) Exclusion criteria: participation in another study impacting 25(OH) vitamin D, pregnant or lactating females, and other conditions affecting growth, dietary intake, or nutritional status. People who were taking supplements that contained vitamin D were not eligible. Those willing to discontinue supplementation with approval of their medical provider were eligible after a 2-month washout period Participants screened: 240 Participants eligible for randomization: 146 Randomization was stratified by HIV acquisition (PHIV/BHIV) and season of the year Participants randomized: 44 Mean age at randomization: 18.4 ± 4.7 years (4000 IU vitamin D group) and 19.1 ± 5.0 yrs (7000 IU vitamin D group) 30 male and 14 female Clinical characteristics, growth status, ART regimen similar at baseline
Interventions	Intervention: 7000 IU vitamin D group One gelatin capsule containing one 2000 IU capsule and one 5000 IU softgel (over-encapsulated) daily Control: 4000 IU vitamin D group One gelatin capsule containing two 2000 IU capsules (over-encapsulated) daily Duration: 12 weeks Compliance: residual tablets or volumes recorded at the 12-week visit. Adherence also assessed by questionnaire at 6,12 weeks and telephonically at weeks 1, 3, 5, 8, and 10. The trial authors did not report the mean adherence during the trial period

Dougherty 2015 USA (*Continued*)

Outcomes	Primary outcomes • Serum 25 (OH) vitamin D and calcium concentrations Secondary outcomes • Immunological and virological parameters
Adverse events	No evidence of any adverse biochemical, haematological, immunological, or virological event
Notes	Source of funding: National Institutes of Health Conflict of interest: none Ethics: Children's Hospital of Philadelphia IRB Trial registration: NCT01092338

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	It was unclear how the randomization codes were generated.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not provide any information regarding the method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding not specified except for participants who received a single capsule which was identical in size, shape, and colour
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was due to migration (n = 1) and loss to follow-up (n = 1)
Selective reporting (reporting bias)	Unclear risk	The trial protocol was not available.
Other bias	Low risk	The trial authors declared no conflicts of interest. A non-conflicting funding source funded the trial

Giacomet 2013 ITA

Methods	Country: Italy Setting: outpatient clinic, Milan Duration of recruitment: April 2011- Duration of trial: 15 months Duration of follow-up: 12 months Design: randomized placebo-controlled trial Follow-up: blood samples were taken from each participant (vitamin D, immunological parameters) at baseline and at 3, 6, 9, 12 months
Participants	Inclusion criteria: HIV-positive people aged ≤ 30 years, low blood vitamin D concentrations (25(OH)D < 30 ng/mL) Exclusion criteria: participants of African descent, hyperparathyroidism, vitamin D supplementation during the 12 month period prior to study entry, use of any medication known to alter vitamin D (excluding ARV) in the previous 6 months, concomitant severe illness Participants screened: 90 Participants eligible for randomization: 57 Participants randomized: 52 Median age at randomization: vitamin D group: 20 (interquartile range (IQR) 18 to 23) yrs; placebo group: 18 (15 to 23) years 86% (43/50) of participants on HAART No reported baseline differences in clinical disease stage, type of antiretroviral therapy (ART), CD4 cell count, blood vitamin D, calcium, Parathyroid hormone (PTH) concentrations. Undetectable viral load (< 37 copies/mL) was recorded for 72% (18/25) and 84% (21/25) of participants in the vitamin D and placebo group, respectively at baseline
Interventions	Intervention: single dose of 100,000 IU vitamin D (oral dose in oil suspension) at baseline and at 3, 6, and 9 months Control: single dose of placebo (oral dose in oil suspension) at baseline and at 3, 6, and 9 months Compliance: directly observed
Outcomes	Primary outcomes • Serial mean changes in 25(OH)D; 1,25 (OH)2D concentrations Secondary outcomes • Serial mean changes in absolute CD4 cell count, % CD4
Adverse events	Reported no adverse events during the trial period
Notes	Source of funding: Italian Ministry of Health Conflict of interest: none Ethics: Luigi Sacco Hospital Ethical Committee Trial registered at clinicaltrialsregister.eu (2011-00059354)

Risk of bias		***Risk of bias***
Bias	**Authors' judgement**	**Support for judgement**

Giacomet 2013 ITA (*Continued*)

Random sequence generation (selection bias)	Low risk	The trial used block randomization in blocks of 4.
Allocation concealment (selection bias)	Unclear risk	The trial used matching sealed plastic syringes labelled with unique identification numbers, but it is unclear if these numbers were sequentially labelled or not
Blinding (performance bias and detection bias) All outcomes	Low risk	All the trial participants, outcome assessors (laboratory technicians and immunologists) and personnel, except the paediatrician who administered the treatment, were blinded to it
Incomplete outcome data (attrition bias) All outcomes	Low risk	The trial authors did not provide any reasons for lost to follow-up of 2 participants in the placebo group at 3 and 6 months. The trial authors performed ITT analyses
Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes as reported are consistent with the trial protocol from www.clinicaltrialsregister.eu
Other bias	Low risk	The trial authors declared that they had no conflicts of interest

Green 2005 SGP

Methods	Country: Singapore Setting: outpatient clinic at national HIV referral centre, Tan Tock Seng Hospital Duration of trial: January 2003 to July 2003 (7 months) Duration of follow-up: 28 days Design: randomized placebo-controlled trial Follow-up: medical history, physical examination, adverse events at 14 and 28 days. Bloods taken in fasted state at baseline and after 28 days for immunological parameters and zinc levels
Participants	Inclusion criteria: HIV-positive participants > 18 years with CD4 count < 200 cells/mm^3, no opportunistic infections 6 months prior and stable ART for 3 months prior to study entry Exclusion criteria: pregnancy, intravenous drug users, on immunomodulatory therapy, oral zinc supplementation Participants screened: 420 Participants eligible for randomization:189 Participants randomized: 66 Mean age at randomization: 40 ± 7.8 yrs (zinc group) versus 40 ± 8.3 yrs (placebo group) 61 male and 5 female 77% of participants were on HAART. Demographic, clinical characteristics, and an-

Green 2005 SGP (*Continued*)

	tiretroviral drug regimes were similar in both treatment groups at baseline
Interventions	Intervention: 220 mg zinc sulphate (50 mg elemental zinc) administered as a capsule daily along with ART Control: placebo Supplement and placebo capsules were identical in appearance Duration: 28 days Compliance: adherence was reported as the proportion of participants in each treatment group who took ≥ 90% of scheduled doses (zinc group: 93.5% (30/32); control group: 94% (32/34))
Outcomes	Primary outcome: immune response to tuberculosis Secondary outcomes: CD4, CD8 cell counts, naive T cells, blood zinc levels
Adverse events	Nausea or vomiting (3 participants in both groups), diarrhoea (4 participants in intervention group versus 1 participant in control group) One participant from the zinc group developed Indinavir-related renal colic on day 7 One participant from the placebo group developed fever on day 28 and was diagnosed with *M. fortuitum* infection. One participant from the placebo group developed a *Staphylococcus aureus* soft tissue abscess on day 23.
Notes	Conflict of interest: none Source of funding: National Health Group Singapore Ethics:Tan Tock Seng Hospital

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The trial used a computer-generated randomization sequence in blocks of 6
Allocation concealment (selection bias)	Unclear risk	It was unclear how the trial organized the process of treatment allocation
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not specified, except for participants who received identical capsules
Incomplete outcome data (attrition bias) All outcomes	Low risk	The trial withdrew one participant due to an adverse event. This was unlikely to have influenced the results
Selective reporting (reporting bias)	Unclear risk	The trial protocol was not available.
Other bias	Low risk	The trial authors included a statement regarding no conflicts of interest

Grigoletti 2013 BRA

Methods	Country: Brazil Setting: outpatient clinic, Hospital de Clínicas de Porto Alegre, Porto Alegre Duration of recruitment: August 2009 to September 2011 Duration of trial: 25 months Duration of follow-up: 4 weeks Design: randomized placebo-controlled trial Follow-up: blood samples and vascular measurements taken at baseline and again at 4 weeks
Participants	Inclusion criteria: HIV-positive adults on HAART (at least 6 months) with undetectable HIV viral load (<50 copies/mL) and CD4 count > 200 cells/mm^3 Exclusion criteria: diabetes mellitus, active infection, liver or renal disease, history of cardiovascular disease, uncontrolled hypertension, pregnancy, use of illicit drugs, mental illness, current tobacco use, women on hormone replacement therapy and current intake of dietary supplements (such folic acid, antioxidants) Participants screened: 1332 Participants eligible for randomization: 175 Participants randomized: 30 participants stratified according to sex Mean age at randomization: 45 ± 2 years 14 male and 16 female All participants were on HAART. Clinical characteristics and antiretroviral drug regimes were similar at baseline
Interventions	Intervention: 1 capsule containing 5 mg folinic acid daily (in the morning) Control: 1 placebo capsule, indistinguishable in appearance, daily (in the morning) Duration: 4 weeks Compliance: no details provided, but an increase in blood folic acid concentrations was demonstrated in the intervention group
Outcomes	Primary outcome • Brachial artery vascular response Secondary outcomes • CD4 cell counts, blood concentrations of folate, vitamin B12, lipid profiles, homocysteine
Adverse events	No adverse events were reported
Notes	Conflict of interest: none Source of funding: research grants and scholarship (Hospital de Cl nicas de Porto Alegre Fund for Research (FIPE- HCPA), Coordination for the Development of Higher Education (CAPES), Brazil) Ethics: Hospital de Clínicas de Porto Alegre Ethics review board

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The trial used computer-generated randomization in blocks of 10

Grigoletti 2013 BRA (*Continued*)

Allocation concealment (selection bias)	Low risk	A person not affiliated to the trial precoded and sequentially numbered bottles
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial authors reported blinding of participants and investigators
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up occurred.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information, and the trial protocol was not available
Other bias	Low risk	The trial authors declared that they had no conflicts of interest

Guwatudde 2015 UG

Methods	Country: Uganda Setting: outpatient clinic, Mackerere University College, Kampala Design: placebo-controlled trial Duration of recruitment: April 2010 to June 2012 Duration of follow-up: 18 months Follow-up: at baseline and at 3, 6, 12, and 18 months participants underwent a full clinical examination. In addition, assessments of the following was performed: complete blood counts, CD4 cell count, presence of syphilis, malaria, intestinal parasites, and nutritional status
Participants	Inclusion criteria: HIV-positive adults ≥ 18 yrs, initiation of ART at the time of randomization or on HAART for at least 6 months, intention to stay within 20 km of study site Exclusion criteria:Pregnancy, participants who were very ill Participants screened: 1134 Participants eligible for randomization: 421 Participants randomized: 400 Mean age at randomization: 36.9 ± 9.6 years (intervention group) 34.7 ± 8.1 years (control group) 123 male and 277 female Clinical characteristics, duration of ART, and multivitamin use similar at baseline
Interventions	Intervention (multivitamin group): daily tablet providing the following vitamins at the RDA level 1.4 mg vitamin B1, 1.4 mg vitamin B2, 1.9 mg vitamin B6, 2.6 µg vitamin B12, 18 mg niacin, 0.4 mg folic acid, 70 mg vitamin C, 10 mg vitamin E Control: daily tablet consisting of placebo Duration: 18 months Compliance: assessed by research staff every month by recording participant self reported compliance and conducting pill counts. The trial authors did not report mean compliance

Guwatudde 2015 UG (*Continued*)

Outcomes	Primary: changes in CD4 cell count and weight, quality of life Secondary: changes in haemoglobin, blood ALT concentrations, development of a new or recurrent disease progression event including all-cause mortality, hospitalization events, changes in ART from first- to second-line therapy
Adverse events	A total of 550 adverse events were reported mostly related to nausea and vomiting, with no differences between treatment arms The trial authors also reported 1 event of severe anaemia (Hb < 7 g/dL) in the multivitamin group and 3 events of high ALT concentrations (> 200 IU/L) (1 in multivitamin arm, 2 in placebo arm)
Notes	Conflict of interest: none Source of funding: Eunice Kennedy Shriver National Institute of Child Health and Human Development of the National Institutes of Health research grant Ethics: Scientific Review Committee of the Infectious Diseases Institute at Makerere University College of Health Sciences and Institutional Review Boards of Harvard School of Public Health and Makerere University School of Public Health Trial registered at clinicaltrials.gov (NCT 1228578)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Prior to initiation of the trial, a staff member at Harvard School of Public Health (HSPH) who was not associated with trial implementation generated serial numbers from 1 to 400 and randomly assigned participants to intervention or placebo groups, in blocks of 10
Allocation concealment (selection bias)	Low risk	Trial regimen bottles were labelled with serial numbers only. The trial pharmacist at the trial site dispensed the assigned regimen bottles to participants in sequential order of enrolment. The list that showed the trial arm linked to each serial number remained with the trial statistician at HSPH and was not accessible to trial staff in Uganda
Blinding (performance bias and detection bias) All outcomes	Low risk	Trial participants, staff, and investigators were blinded. The size, colouring, and packaging of the placebo was identical to the multivitamin tablet
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall attrition was low (8%) and was due to death (18/400), migration (7/400), withdrawal of consent (2/400), and loss to

Guwatudde 2015 UG (*Continued*)

		follow-up (6/400)
Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes were as reported, and were consistent with the trial protocol (Guwatudde 2015 UG).
Other bias	Low risk	The trial authors declared they had no conflicts of interest. A non-conflicting funding source funded the trial

Humphrey 1999 USA

Methods	Country: USA Setting: HIV clinic Duration of recruitment: January to July 1996 Duration of follow-up: 8 weeks Design: randomized placebo-controlled safety trial
Participants	Inclusion criteria: 18 to 45 years, CD4 > 200 cells/mm³ Exclusion criteria: pregnant or breastfeeding Participants randomized: 40 women Mean age (SD) in years = 36.2 (5.6) in vitamin A group and 33.2 (5.6) in placebo group Loss to follow-up/withdrawal: 1 Exclusions postrandomization: 0
Interventions	Intervention: 300,000 IU vitamin A Control: placebo Duration: single dose
Outcomes	Primary outcomes • Viral load • T-cell subsets (%CD4; % CD8 which are CD38+) Secondary outcomes: • Vitamin A status
Adverse events	Signs or symptoms of toxicity (headache, nausea, vomiting, diarrhoea, fever) similar in the intervention and control groups at 24 hours and 1 week after administration
Notes	Number of participants on ART • Vitamin A group: 12 (60%) • Control group: 7 (35%) Source of funding: Paediatric AIDS Foundation grant

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

Humphrey 1999 USA (*Continued*)

Random sequence generation (selection bias)	Unclear risk	The trial authors did not describe the method of random sequence generation used
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe the method of allocation concealment used
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant was lost to follow-up.
Selective reporting (reporting bias)	Unclear risk	Insufficient information; the trial protocol was not available
Other bias	Unclear risk	The trial authors did not declare on conflicts of interest, if any

Hurwitz 2007 USA

Methods	Country: USA Setting: university clinic Duration of recruitment: June 2001 to July 2005 Duration of follow-up: 9 months Design: randomized placebo controlled trial
Participants	Inclusion criteria: aged 18 to 55 years; no history of major systemic disorders related to HIV; premenopausal and not pregnant Exclusion criteria: on treatment for chronic conditions; selenium deficient Participants randomized: 310 Mean age = 40.5 years 179 male and 86 female Loss to follow-up/withdrawal: 88 Exclusions postrandomization: 48 pretreatment
Interventions	Intervention: selenium (200 µg) Control: placebo Duration: daily for 9 months
Outcomes	Primary outcomes • Viral load • CD4 count • Serum selenium
Adverse events	None

Notes	Participants on ART: 105/141 (74%) in selenium group; 87/121 (72%) in placebo group Preliminary analysis at 9 months of an 18-month trial Source of funding: National Institutes of Health

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The trial used computerized block randomization.
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe the method of allocation concealment used
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	There were high unexplained losses to follow-up, which were balanced between groups. The trial authors performed imputational analyses
Selective reporting (reporting bias)	High risk	The trial only reported data on main study outcomes for subgroups of participants (selenium responding versus non-responding participants)
Other bias	Low risk	The trial authors declared they had no conflicts of interest

Isanaka 2012 TZA

Methods	Country: Tanzania Setting: outpatient HAART clinics Duration of recruitment: November 2006 to November 2008 Median duration of follow-up: 15 months (IQR 6 to 19) Design: RCT Follow-up: full clinical examination and HIV disease staging (WHO staging criteria) of participants conducted at baseline and thereafter monthly by trial physicians. Occurrence of any illness in the previous month recorded by trial nurses at baseline and thereafter monthly. They also performed anthropometric measurements (height, weight, waist, hip, mid-thigh, mid-arm circumference) at baseline and monthly thereafter. Bloods were taken from participants at baseline and every 4 months for T cell counts, full blood count, and ALT. HIV viral load was determined at the same time intervals, but was subject to the availability of reagents. Dietary intake was assessed at baseline and every 12 months Participants were followed up monthly until the date of death, loss to follow-up, or early study closure (refer to section on adverse events). Cause of death was determined by the use of medical records and standard verbal autopsy techniques by 2 HIV clinicians who had to reach consensus
Participants	Inclusion criteria: men and women with HIV-infection initiating ART (WHO Stage 4 HIV disease and CD4 count < 200; WHO Stage HIV infection and CD4 count < 350) , intention to stay in Dar es Salaam for at least 2 years Exclusion criteria: pregnant or lactating women Participants randomized: 3418 Mean age at randomization: 37.8 ± 8.6 years (high-dose group) versus 38.4 ± 8.6 years (standard-dose group) 1141 female, 569 male (high-dose group) versus 1181 female, 527 male (standard-dose group)
Interventions	Intervention (high-dose group): micronutrient tablet daily containing 8 different micronutrients at multiple levels of the Recommended Daily Allowance (RDA): thiamine 20 mg, riboflavin 20 mg, vitamin B6 25 mg, niacin 100 mg, vitamin B12 50 µg, folic acid 0.8 mg, vitamin C 500 mg, vitamin E 30 mg Control (standard-dose group): micronutrient tablet daily containing 8 different micronutrients at single level of the RDA: thiamin 1.2 mg, riboflavin 1.2 mg, vitamin B6 1.3 mg, niacin 15 mg, vitamin B12 2.4 µg, folic acid 0.4 mg, vitamin C 80 mg, vitamin E 15 mg The intervention and control tablets were indistinguishable in terms of appearance and taste Duration: minimum of 24 months Compliance: determined by the number of tablets absent from the returned bottles every month divided by the number of the tablets the participant should have taken. Mean compliance was reported as 90% for both treatment groups (no variance reported) Co-intervention: cotrimoxazole prophylaxis if CD4 count < 200 in all participants
Outcomes	Primary: all-cause mortality, HIV disease progression (new or recurrent episode of HIV disease according to the WHO Clinical Staging system) Secondary: AIDS-related mortality (due to *Pjiroveci* pneumonia, pulmonary tuberculosis, extrapulmonary tuberculosis, Kaposi sarcoma, wasting, HIV/AIDS with opportunistic infection, invasive cervical carcinoma), changes in CD4 count, HIV viral load,

Isanaka 2012 TZA (*Continued*)

	BMI, haemoglobin
Adverse events	Preliminary data analysis after 1 year after the start of the trial (November 2008) indicated an increased mortality risk with high-dose supplementation. Subsequently, all participants received standard dose supplements up to March 2008 when it was determined that the increased mortality risk was restricted to severely malnourished participants (BMI < 16) These participants were subsequently excluded from enrolment and those who had been enrolled received standard dose supplementation. Since 612 participants enrolled in this period did not fulfil the eligibility criteria of the trial protocol, the sample size was increased However, the trial was terminated prematurely in March 2009 because of evidence of increased ALT levels among participants receiving the high-dose supplement Other adverse events reported include during the trial included fatigue, nausea or vomiting, diarrhoea, severe anaemia, peripheral neuropathy, rashes or lesions and genital discharge or sores
Notes	Source of funding: National Institute of Child Health Conflict of interest: none Ethics: Harvard School of Public Health, Muhimbili University of Health and Allied Sciences, Tanzania Food and Drugs Authority, and National Institute of Medical Research Trial registered at clinicaltrials.gov (NCT00383669)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The trial used a computer-generated randomization sequence in blocks of 20
Allocation concealment (selection bias)	Low risk	Independent pharmacists performed sequential numbering of trial supplements. At each research site participants were allocated to the next numbered bottle at that site
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial authors reported the participants and research staff as blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Overall loss to follow-up was not reported. The trial authors only analysed viral load for a subset (7%) of trial participants and therefore this outcome was judged to be at high risk of attrition bias

Isanaka 2012 TZA (*Continued*)

Selective reporting (reporting bias)	Low risk	The primary and secondary outcomes as reported, as well as the reported changes to the trial protocol, are consistent with the trial protocol at www.clinicaltrials.gov.
Other bias	High risk	Trial was stopped early due to evidence of increased levels of ALT in the high-dose group

Jiamton 2003 THA

Methods	Country: Thailand Setting: outpatient clinic Duration of recruitment: March 2000 to January 2001 Duration of follow-up; 48 weeks Design: randomized placebo-controlled trial
Participants	Inclusion criteria: older than 18 years; 50 < CD4 < 550 Exclusion criteria: taking ARV or micronutrients for during month prior to enrolment Participants randomized: 481 (stratified according to CD4 cell count < 200 cells/mm^3 and ≥ 200 cells/mm^3) 189 male and 292 female Mean age = 32 years Loss to follow-up/withdrawal: 79 at 48 weeks Exclusions postrandomization: 0
Interventions	Intervention: micronutrient supplement (3000 µg vitamin A, 6 mg beta-carotene, 20 µg vitamin D, 80 mg vitamin E, 180 µg vitamin K, 400 mg vitamin C, 24 mg vitamin B1, 15 mg vitamin B2, 40 mg vitamin B6, 30 µg vitamin B12, 0.1 mg folic acid, 40 mg pantothenic acid, 10 mg iron, 200 mg magnesium, 8 mg manganese, 30 mg zinc, 300 µg iodine, 3 mg copper, 400 µg selenium, 150 µg chromium, 60 mg cysteine) Control: placebo Duration: twice daily for 48 weeks.
Outcomes	Primary outcomes • Mortality • Hospital admissions Secondary outcomes • CD4 counts • Viral load
Adverse events	A total of 137 minor adverse events such as dizziness, drowsiness, nausea, and rash reported, with more participants in the intervention arm who reported urine discolouration (P < 0.001)
Notes	Source of funding: Nestle Foundation; Vitabiotics

Jiamton 2003 THA (*Continued*)

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The trial authors used centralized randomization in blocks of 10
Allocation concealment (selection bias)	Low risk	Interventions were packaged in identical coded bottles.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	Attrition was low overall (12/242 in the treatment group and 3/239 in the placebo group). Similar baseline median CD4 cell counts among participants from both treatment groups who were lost to follow-up. The trial authors used survival analysis to address missing outcome data. However, the trial authors only analysed viral load for a subset (29%) of trial participants and so we judged this trials to be at high risk of attrition bias for this outcome
Selective reporting (reporting bias)	Unclear risk	Insufficient information; the trial protocol was not available
Other bias	Low risk	The trial authors provide a declaration on no conflicts of interest

Kamwesiga 2015 RWA

Methods	Country: Rwanda Setting: 2 outpatient facilities Design: placebo-controlled trial Duration of recruitment: not stated Duration of follow-up: 24 months Follow-up: trained nursing practitioners will collect clinical, nutritional, and psychosocial data at baseline and at 6, 12, 18, and 24 months. Blood samples will also be taken for CD4 cell count and viral load measurements at these time intervals
Participants	Inclusion criteria: HIV-positive adults aged ≥ 21 years, ART-naive with CD4 cell counts 400 to 650 cells/mm^3, HIV-positive women willing to practice barrier method of birth control, intention to remain in clinic catchment area for study period Exclusion criteria: pregnancy Participants screened: 2680

Kamwesiga 2015 RWA (*Continued*)

	Participants eligible for randomization: 300 Participants randomized: 300 Mean age at randomization: 33 years (median) IQR 28 to 39 years (intervention group) ; 35 years (median) IQR 28 to 41 years (control group) 98 male and 202 female Sociodemographic characteristics, CD4 cell count, HIV viral load, BMI similar at baseline
Interventions	Intervention: 1 tablet containing 200 µg selenium (in the form of selenomethionine) daily Control: 1 placebo tablet daily Duration: 24 months Compliance: adherence counselling provided at baseline and every month. The trial authors did not report mean compliance data
Outcomes	Primary: composite of the following: reduction in CD4 cell count < 350 cells/mm³ or start of ART or development of AIDS-defining illness Secondary: viral load at 6, 12, 18, and 24 months, quality of life, weight gain, presence of opportunistic infections, mortality
Adverse events	Most participants did not report any symptoms. Self-reported symptoms included nausea, vomiting, skin or hair changes or both, and changes in emotional status. Participants in the selenium group were more likely to report anxiety (41 events versus 16 events in the placebo group; P = 0.04) and sleep symptoms (36 events versus 15 events in the placebo group, P = 0.01)
Notes	Source of funding: Global Benefit, Canada. Micronutrient supplement supplied by a nutraceutical company (CanAlt labs and Seroyal) Conflict of interest: none Ethics: institutional review boards of the Canadian College of Naturopathic Medicine and Wilfred Laurier University in Canada, and the National Ethics Committee (NEC) in Rwanda

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The research department of the manufacturing company prepared the randomization schedule using a simple randomization block design, but the trial authors did not specify the method of sequence generation
Allocation concealment (selection bias)	Unclear risk	The trial authors stated that each participant was assigned to a unique study identification number. Sequential numbering and allocation was not explicitly stated. They also stated that an unblinded allocation list was provided to the treatment

Kamwesiga 2015 RWA (*Continued*)

		provider and an independent statistician for the purpose of conducting an interim analyses
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial authors did not specify whether blinding was performed, except for participants who received identical supplements
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition was 6% in both treatment groups (9/151 in the selenium group and 9/149 in the placebo group). Reasons for attrition included death (n = 2), migration (n = 9) and loss to follow-up (n = 7). The trial authors stated that 10 participants (4 in the selenium group and 6 in the placebo group) were not included in their primary analyses
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes are consistent with the trial protocol (Kamwesiga 2015 RWA).
Other bias	Low risk	Although the pharmaceutical industry provided the trial supplements, the trial authors included a statement of no conflicts of interest

Kelly 1999 ZMB

Methods	Country: Zambia Setting: home care service of tertiary hospital Duration of recruitment: not stated Duration of follow-up: 4 weeks Design: randomized placebo-controlled trial
Participants	Inclusion criteria: adults with persistent diarrhoea for more than 1month Exclusion criteria: < 18 years, pregnancy, administration of antibiotics in the week prior to recruitment, Karnofsky scores > 80 or < 50 Participants randomized: 135 79 male and 56 female Median age = 32.5 years (micronutrient); 34 (placebo) Loss to follow-up/withdrawal: 29 Exclusions postrandomization: 0
Interventions	Intervention: micronutrient supplement (10,500 IU vitamin A, 300 mg vitamin C, 300 mg vitamin E, 150 µg selenium and 200 mg zinc sulphate) Both treatment groups also received 5 mg folic acid and 800 mg albendazole twice daily Control: placebo Duration: daily for 2 weeks

Kelly 1999 ZMB (*Continued*)

Outcomes	Primary outcomes
	• Recovery from diarrhoea
	  ○ Patient weeks with and without diarrhoea during 12 weeks' follow-up
	  ○ Remission at 4 weeks
	• All-cause mortality during first 4 weeks
	• Change in BMI and mid-upper arm circumference (MUAC)
	• Change in Karnofsky score
	Secondary outcomes
	• Changes in CD4 and CD8 counts at 4 weeks
	• Changes in serum vitamin A and E after 4 weeks

Adverse events	None
Notes	Source of funding: Smithkline Beecham

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial authors did not describe the method of random sequence generation used
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe the method of allocation concealment used
Blinding (performance bias and detection bias) All outcomes	High risk	Micronutrient and placebo capsules were not identical; it was unclear whether providers and assessors were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	High risk	25% of participants were lost to follow-up due to death and the tradition of going back to the family home when terminally ill
Selective reporting (reporting bias)	Unclear risk	There was insufficient information; the trial protocol was not available
Other bias	Unclear risk	The trial authors did not provide a declaration on conflicts of interest

Kelly 2008 ZMB

Methods	Country: Zambia Setting: Misisi township, Lusaka, Zambia Duration of trial: August 2003 to December 2006 (41 months) Duration of follow-up: 38 months Design: cluster randomized cross-over trial (cluster randomization by household) Follow-up: trained nurses recorded episodes of diarrhoea and cough every 2 weeks. Nutritional status (height, weight, MUAC, body impedance) and household hygiene (score) were assessed at 6, 14, 22, and 38 months
Participants	Inclusion criteria: all adult (≥ 18 years) residents HIV status: HIV-positive (n = 136); HIV negative (n = 224), and unknown HIV-status (n = 140)
Interventions	Members of the same household received the same treatment allocation Intervention: multiple micronutrient tablet once daily (β-carotene 4.8 mg; 1.4 mg vitamin B1, 1.4 mg vitamin B2, 1.9 mg vitamin B6, 2.6 µg vitamin B12; 18 mg niacin; 70 mg vitamin C; 10 mg vitamin E; 0.4 mg folic acid; 30 mg iron; 15 mg zinc; 2 mg copper; 65 µg selenium and 150 µg iodine) Control: placebo tablet once daily (supplement and placebo tablets identical in appearance and taste Duration: 1.9 years to trial cross-over; thereafter 1.5 years Adherence: unused trial supplements were retrieved monthly. Median compliance reported as > 95% (variance not reported) at the crossover point
Outcomes	Primary outcome • Incidence of diarrhoea Secondary outcomes • Incidence of severe diarrhoeal episodes • Incidence of respiratory infection (cough) • Changes in CD4 count of HIV-positive participants • Changes in nutritional status • Mortality
Adverse events	Four cases of pellagra occurred in the placebo group; 3 of whom were associated with high ethanol intakes
Notes	Source of funding: Wellcome trust Ethics: University of Zambia Research Ethics Committee; London School of Hygiene and Tropical Medicine Research Ethics Committee Trial registration: ISRCTN 31173864 Conflict of interest: declared no conflict of interest. None of the authors had any financial interest in manufacturing or licensing of any micronutrient formulation

Risk of bias		*Risk of bias*
Bias	**Authors' judgement**	**Support for judgement**

Random sequence generation (selection bias)	Low risk	The trial statistician generated the random number sequence for the selection of households
Allocation concealment (selection bias)	Low risk	Only the statistician and manufacturers had access to the trial code. The supplements were supplied in precoded, sealed plastic bottles
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, investigators, and assessors were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	There were high rates of attrition (30% before cross-over; 42% at trial completion); the trial authors did not state the attrition rates for each treatment group
Selective reporting (reporting bias)	Low risk	All the outcomes as reported are consistent with the trial protocol from www.controlled-trials.com, except for all-cause mortality.
Other bias	Low risk	The trial authors declared that they had no conflicts of interest Recruitment bias: households were randomized, all participating members of each household received the same treatment allocation Baseline imbalance: randomization was stratified by household size Loss of clusters: attrition of clusters was not reported.

Lawson 2010 NIG

Methods	Country: Nigeria Setting: 8 district hospitals, Abuja, Nigeria Duration of recruitment: September 2003 to June 2005 Duration of trial:Not stated Duration of follow-up: 6 months Design: randomized placebo-controlled factorial trial with three intervention arms Follow-up :Blood samples (complete blood count, erythrocyte sedimentation rate (ESR) and biochemical tests) and three sputum samples and a chest X-ray, were conducted at enrolment. Sputum specimens were collected weekly for the first 8 weeks of therapy and again at 12, 16, 20 and 24 weeks. Blood samples and chest X-rays were repeated at 2 and 6 month follow-up
Participants	Inclusion criteria: HIV-positive and HIV-negative adults aged > 15 years with sputum positive pulmonary tuberculosis Exclusion criteria: previous antituberculous therapy, pregnancy, lactation, use of corticosteroids or zinc in the previous month, major surgery in the previous month, diabetes, severe cardiovascular or hepatic disease, currently taking oral contraceptives, unable to return Participants screened: 1321 (399 smear-positive) Participants eligible for randomization: 350 Participants randomized: 350 (155 HIV-positive participants not stratified) Mean age at randomization: 29 to 34 years The mean BMI was greater in the zinc group at baseline:21.3 ± 4.7 versus 19.6 ± 3.5 (zinc and vitamin A group) versus 19.8 ± 3.3 (placebo group)
Interventions	Intervention: 90 mg elemental zinc plus retinol (5000 IU) weekly or 90 mg elemental zinc plus placebo weekly Control: duel placebo (similar in appearance) weekly Duration: 6 months Adherence: all participants received their supplements under direct observation for the first 2 months together with standard antituberculous treatment (2RHZE/4HE). Monthly supplies were then given for the following 4 months
Outcomes	Primary outcomes: sputum conversion, CXR scores Secondary outcomes: clinical symptoms, BMI, Karnofsky score, deaths, ESR, haemoglobin
Adverse events	Two major adverse events (participants withdrawn from trial)
Notes	Source of funding: none stated Conflict of interest: no statement included Ethics: Liverpool School of Tropical Medicine Research Ethics Committee, Zankli Medical Centre Institutional Review Board Trial registration: ISRCTN36636609

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

Lawson 2010 NIG (*Continued*)

Random sequence generation (selection bias)	Low risk	Treatment allocation into three supplement groups was performed at the Liverpool School of Tropical Medicine using permuted block randomization with 4 different block sizes. Random numbers generated by Minitab with block randomization using 4 different block sizes
Allocation concealment (selection bias)	Low risk	An investigator who was not on site prepared the allocation sequence. Treatment assignments were prepared in serially numbered sealed envelopes. Sequentially numbered packets were assigned consecutively to participants according to allocation sequence
Blinding (performance bias and detection bias) All outcomes	Low risk	Investigators, participants, and the laboratory staff were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Loss to follow-up of HIV-positive participants at 6 months was not balanced between treatment groups: zinc group 16 % (8/56); zinc and vitamin A group 23% (11/47); and placebo group: 30% (16/52)
Selective reporting (reporting bias)	Low risk	Primary outcomes reported were consistent with the trial protocol (ISRCTN36636609)
Other bias	Unclear risk	The trial authors did not provide any conflict of interest statement

McClelland 2004 KEN

Methods	Country: Kenya Setting: outpatient clinics at Coast Provincial General Hospital, Mombasa Duration of recruitment: September 1998 to June 2000 Duration of trial: 22 months Duration of follow-up: 6 weeks Design: randomized placebo-controlled trial Follow-up: at the 6 week follow-up visit participants underwent a physical examination and bloods and genital tract specimens were collected (as before at baseline)
Participants	Inclusion criteria: women (18 to 45 years) with HIV-1 infection Exclusion criteria: women who were pregnant or the use of vitamin supplements or oral contraceptives during 3-month period before study entry Participants screened: 2021

McClelland 2004 KEN (*Continued*)

	Participants eligible for randomization: 650 Number randomized: 400 (plus 200 participants in vitamin A arm) Mean age: 29 ± 7 years (micronutrient group) versus 29 ± 6 years (placebo group) No participant received ART. It is reported that CD4 cell count and vaginal HIV shedding were higher in the micronutrient group (statistical significance not shown)
Interventions	Intervention: micronutrient supplement (20 mg vitamin B1, 20 mg vitamin B2, 25 mg vitamin B6, 50 µg vitamin B12; 100 mg niacin; 500 mg vitamin C; 30 mg vitamin E; 0.8 mg folic acid; 200 µg selenium) administered as a hard gel capsule daily Control: placebo (supplement and placebo capsules identical in appearance) Duration: daily for 6 weeks Compliance: reported as the proportion of participants in each treatment group who took 95% of scheduled doses (micronutrient group: 93.7% (168/179); control group: 92.1% (164/178). Supplements were dispensed with an electronic alarm vial
Outcomes	Primary outcomes: vaginal and cervical HIV-1 shedding Secondary outcomes: CD4, CD8 cell count, viral load
Adverse events	Multivitamin supplementation increased cervical and vaginal shedding of HIV-positive cells
Notes	Source of funding: National Institutes of Health and University of Washington Clinical Nutrition Research Unit Conflict of interest: statement not included Ethics: University of Nairobi, University of Washington Trial registration: not specified

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The trial used computer-generated randomization sequence in blocks
Allocation concealment (selection bias)	Unclear risk	It was unclear who was responsible for the allocation of treatment (sequential numbering of medication bottles not specified)
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding was not specified except for participants who received identical capsules
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Twenty-one(10.5%) and 22(11%) participants were lost to follow-up from the multivitamin and placebo groups respectively. However, the trial authors did not state the reasons for loss to follow-up. Participants who were lost to follow-up had lower CD4 cell counts compared to those who com-

McClelland 2004 KEN (*Continued*)

		pleted the trial, but cell counts were not reported for each treatment group
Selective reporting (reporting bias)	Unclear risk	The trial protocol was not available
Other bias	Unclear risk	The trial authors did not provide any statement regarding conflicts of interest

Overton 2015 USA

Methods	Country: USA Setting:39 AIDS Clinical trials network research units Duration of recruitment: September 2011 to February 2012 Duration of trial: 48 weeks Duration of follow-up: 48 weeks Design: randomized placebo-controlled trial Follow-up: blood samples at enrolment, 24 and 48 weeks; DXA scan at enrolment and again at 48 weeks
Participants	Inclusion criteria: HIV-positive people who were not on ART with viral load > 1000 copies/mL and blood 25 (OH) vitamin D level ≥ 10 and < 75 ng/mL, creatinine clearance ≥ 60 mL/min and serum calcium < 10.5 mg/dL Exclusion criteria: participants taking daily supplements containing calcium and vitamin D exceeding 500 mg and 800 IU respectively, any biphosphonate therapy, recent steroid or chemotherapy treatment, thyroid disease, substance or alcohol abuse, a history of fragility fracture, osteoporosis or nephrolithiasis or weight > 300 lb. Pregnant and lactating women were also excluded Participants screened: 218 Participants eligible for randomization: 183 Number randomized: 167 Mean age: 36 years (IQR 28 to 47) (vitamin D/calcium group) versus 31 years (IQR 25 to 44) (placebo group) Two participants from the vitamin D/calcium group had protocol violations due to the incorrect screening vitamin D assay being performed. The trial authors did not include this data in the analyses
Interventions	Intervention: 4000 IU vitamin D3 daily plus 500 mg calcium carbonate twice daily with food Control: placebo daily plus placebo twice daily with food (identical in appearance) Duration: daily for 48 weeks Compliance: all participants were initiated on first line ART (EFV/FTC/TDF)
Outcomes	Primary: change in total hip bone mineral density (BMD) Secondary: changes in lumbar spine BMD, 25(OH) vitamin D levels, parathyroid hormone (PTH), markers of bone turnover, and other inflammatory biomarkers and CD4 cell counts at 24 and 48 weeks

Adverse events	No differences were observed between the treatment groups in terms of reported adverse events during the study period. Vitamin D/calcium group (33 Grade 1-2 events, 15 Grade 3 events, and 2 Grade 4 events) and placebo group (33 Grade 1-2 events, 15 Grade 3 events, and 5 Grade 4 events). No cases of hypercalcaemia were reported. One death in the Vitamin D/calcium group was reported in the context of rapid HIV disease progression
Notes	Source of funding: National Institute of Allergy and Infectious Diseases. The pharmaceutical industry provided supplements and placebos Conflict of interest: none Ethics: Institutional Review Boards of all participating research sites Trial registration: NCT 01403051

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial authors reported block randomization stratified for baseline 25(OH) vitamin D levels (≤ 20 and > 20 ng/mL), but the trial authors did not specify the method of generation randomization sequence
Allocation concealment (selection bias)	Unclear risk	The trial authors did not report the details regarding the allocation of study supplements
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Blinding not specified except for participants who received identical supplements
Incomplete outcome data (attrition bias) All outcomes	Low risk	Overall attrition was 9% (15/167). Reasons for attrition include death (n = 1), nonadherence to treatment/study visits (n = 2), withdrew consent (n = 1), or lost to follow-up (n = 11)
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes reported were consistent with trial protocol (NCT 01403051)
Other bias	High risk	The pharmaceutical industry sponsored ARTs and supplements, industry representatives served on the study team and reviewed manuscript prior to publication, thus there was a potential conflict of interest

Range 2006 TZA

Methods	Country: Tanzania Setting: 5 district health facilities Duration of recruitment: August 2001 to July 2002 Design: placebo-controlled 2 x 2 factorial trial
Participants	Inclusion criteria: HIV-positive and HIV-negative people aged ≥15 years with sputum-positive pulmonary tuberculosis (new or relapsed cases) Exclusion criteria: participants who defaulted tuberculosis chemotherapy or those who remained smear-positive on chemotherapy (failure cases) and those with serious tuberculosis or other disease unlikely to survive; pregnant and lactating women Participants randomized: 530 213 HIV-positive 325 male and 205 female Mean age = 35.4 years Participants analysed: 499 Loss to follow-up/withdrawal: 77 within 244 days post-treatment Exclusions postrandomization: 31
Interventions	InterventionS: micronutrient supplement contained vitamin A (1.5 mg), vitamin B1 (20 mg), vitamin B2 (20 mg), vitamin B6 (25 mg), vitamin B12 (50mg), folic acid (0·8 mg) , niacin (40 mg), vitamin C (200 mg), vitamin E (60 mg), vitamin D3 (5 mg), selenium (0·2 mg) and copper (5 mg), and zinc tablets contained 45 mg elementary zinc Control: placebo (2 x 2 factorial) Duration: daily for 8 months. All participants received a standard 8 month tuberculosis chemotherapy regimen
Outcomes	Primary outcomes • All-cause mortality at 8 months Secondary outcomes • Viral load • CD4 counts • Weight gain
Adverse events	None reported
Notes	Source of funding: Danish International Development Assistance

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computerized randomization.
Allocation concealment (selection bias)	Low risk	Sealed envelopes, codes unbroken until post-analysis

Range 2006 TZA (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and investigators were blinded
Incomplete outcome data (attrition bias) All outcomes	High risk	Differential attrition rates between treatment groups > 10% [Zinc group: 10.3% (6/58); Multivitamin/mineral group: 23.7% (14/59); Multivitamin/mineral plus zinc group: 12.5 % (6/48) Placebo group: 12.5% (6/48)]
Selective reporting (reporting bias)	Unclear risk	Insufficient information; study protocol not available
Other bias	Unclear risk	Randomization was not stratified by HIV-status of participants. Declared no conflict of interest

Semba 1998 USA

Methods	Country: USA Setting: community-based clinic Duration of recruitment: not stated Duration of follow-up: 4 weeks Design: randomized placebo-controlled trial
Participants	Inclusion criteria: HIV-positive intravenous drug users participating in ALIVE (AIDS Linked to Intravenous Experiences) Cohort (N = 630); ≥ 18 years; not taking vitamin A supplements Exclusion criteria: CD4 > 500 cells/mm^3; pregnancy. Participants randomized: 120 89 male and 31 female Mean age = 38.2 years 50% treatment group versus 43% placebo group on ART Loss to follow-up/withdrawal: 8.3% at 4 weeks Exclusions postrandomization: 0
Interventions	Intervention: single dose of 200 000 IU vitamin A Control: placebo
Outcomes	Primary outcomes • Viral load • CD4 count Secondary outcomes • Serum vitamin A
Adverse events	None reported

Semba 1998 USA (*Continued*)

Notes	Source of funding: USAID

Risk of bias ***Risk of bias***

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial used a random number table in blocks of 10.
Allocation concealment (selection bias)	Low risk	The trial used sequentially numbered envelopes to conceal allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Missing outcome data were balanced across groups.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information; the trial protocol was not available
Other bias	Unclear risk	The trial authors did not provide any declaration regarding conflicts of interest

Semba 2007 MWI

Methods	Country: Malawi Setting: 8 community health centres Duration of recruitment: July 1999 to October 2004 Design: placebo-controlled
Participants	Inclusion criteria: HIV-positive and HIV-negative adults with smear-positive pulmonary tuberculosis (new cases) Exclusion criteria: prior or current tuberculosis chemotherapy, prior vitamin supplements Participants randomized: 1148 829 HIV-positive 336 male and 493 female Mean age = 34 years Participants analysed: 1148 Loss to follow-up: 103 in HIV-positive group (50 and 53 in micronutrient and placebo groups, respectively) Exclusions postrandomization: 0
Interventions	Intervention: micronutrient supplement (vitamin A, C, D, E, B6, B12, riboflavin, thiamine, niacin, folate, zinc, iodine, selenium) Control: placebo

Semba 2007 MWI (*Continued*)

	Duration: daily for 24 months. All participants received a standard 8-month tuberculosis chemotherapy regimen
Outcomes	Primary outcomes • All-cause mortality Secondary outcomes • Serum vitamin A, vitamin E, and selenium
Adverse events	Not reported
Notes	Source of funding: National Institutes of Health and the Fogarty International Centre

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The trial used blocked randomization.
Allocation concealment (selection bias)	Low risk	The trial used prepacked sequentially numbered supplements.
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	The attrition rates were greater than 10% and the trial authors did not report the reasons for loss to follow-up (supplement group 12.3%; placebo group 12.5%)
Selective reporting (reporting bias)	Low risk	The trial protocol was available; the trial authors reported on all outcomes of interest
Other bias	Unclear risk	The trial authors did not stratify randomization by HIV status of participants. The trial authors did not declare their conflicts of interest, if any

Semba 2007 USA

Methods	Country: USA Setting: study clinic Duration of recruitment: September 2002 to August 2005 Design: controlled trial

Semba 2007 USA (*Continued*)

Participants	Inclusion criteria: women ≥ 18 years; history of injection drug use (IDU) within past 10 years; hepatitis C (HCV) antibody-positive; Karnofsky status > 80%; serum ferritin < 200 ng/mL Exclusion criteria: pregnant; history of liver failure, renal disease, interferon therapy for HCV; haemochromatosis; blood disorders Participants randomized: 458 Mean age = 40 years 138 (30.1%) HIV-positive Participants analysed: 115 at 12 months Loss to follow-up/withdrawal:151 (33%) Exclusions postrandomization: 0
Interventions	Intervention: micronutrients with iron (18 mg) Control: micronutrients only Duration: daily for 12 months
Outcomes	Primary outcomes • Haemoglobin • Iron status • Plasma HCV • Viral load • Liver enzymes
Adverse events	Not reported
Notes	On HAART: 27/69 (intervention) and 23/69 (control) Trial stopped early due to slow recruitment. Source of funding: National Institute on Drug Abuse; National Institute on Nursing Research

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The trial used computerized randomization.
Allocation concealment (selection bias)	Low risk	The trial used prepacked sequentially numbered study supplements
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	High risk	There was high loss to follow-up (27.7%) in both groups, and the trial authors did not report this information by HIV status

Semba 2007 USA (*Continued*)

Selective reporting (reporting bias)	Unclear risk	There was insufficient information; the trial protocol was not available
Other bias	Unclear risk	The trial authors did not provide a declaration on conflicts of interest

Stallings 2014 USA

Methods	Country: USA Setting: Children's Hospital of Philadelphia, Philadelphia Duration of recruitment: July 2011 to June 2013 Duration of follow-up: 12 months Design: randomized placebo-controlled trial Follow-up: participants were followed up at 3, 6, and 12 months. At each visit adverse events and compliance were recorded. Blood and urine measurements were also performed for vitamin D (25-Hydroxy vitamin D, 1,25 Dihydroxy vitamin D), calcium, metabolic parameters, and immunological parameters
Participants	Inclusion criteria: perinatally acquired HIV infection (PHIV), 5.0 to 24.9 year or behaviorally-acquired HIV infection (BHIV), 15.0 to 24.9 years; usual state of good health 2 weeks before study entry Exclusion criteria: other adverse growth, dietary intake, or nutritional status conditions, pregnancy, lactation, and use of vitamin D3 supplements. If Vitamin D3 supplements were discontinued, participants underwent a 2-week wash-out period before trial entry Participants screened: 121 Participants eligible for randomization: 58 Participants randomized: 58 (stratified by PHIV/BHIV) Mean age at randomization: 20.7 ± 3.7 years 76% of participants on HAART (vitamin D group:23/30 (77%); placebo group 21/28 (75%)) The trial authors reported no statistically differences in baseline disease characteristics, vitamin D status, dietary intake, or metabolic parameters
Interventions	Intervention: 7000 IU vitamin D3 daily (those unable to swallow capsules took 0.49 mL daily of 400 IU vitamin D3 drops) Control: placebo capsules (those unable to swallow capsules took 0.49 mL daily of placebo drops) Duration: 12 months Compliance: residual capsules or volume (in the case of drops) were recorded at follow-up visits. Mean adherence was 92 ± 8% over 12 months with no differences between groups
Outcomes	Primary: blood 25-Dehydroxy vitamin D levels Secondary: HIV load (among participants with a detectable viral load), CD4%
Adverse events	Four participants in the placebo group were withdrawn from the study after 6 months according to prespecified criteria (3 consecutive 25 (OH) vitamin D values < 11 ng/mL) . No participant experienced the predefined serious adverse event of 25 (OH) vitamin

	D levels > 80 ng/mL at any time during the follow-up period. Serum calcium levels increased from 9.5 ± 0.4 to 9.6 ± 0.4 mg/dL after 12 months in the vitamin D group
Notes	Source of funding: NIH/National Center for Complementary and Alternative Medicine, National Center for Research Resources, National Center for Advancing Translational Sciences Conflict of interest: the trial authors declared no conflict of interest Ethics: Children's Hospital of Philadelphia Institutional Review Board Trial registration: clinicaltrials.gov (NCT 01475890)

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial authors stated that participants were randomized in parallel (1:1 ratio) to receive the intervention of the placebo
Allocation concealment (selection bias)	Unclear risk	The trial authors did not provide any information in terms of how study supplements were numbered and allocated to participants
Blinding (performance bias and detection bias) All outcomes	Unclear risk	The trial authors referred to a "double blind" study but it was unclear who was blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Attrition rates were 10% (3/30) in vitamin D group versus 17% (5/28) in placebo group. Three participants were lost to follow-up (without reasons) in the vitamin D group and 1 participant in the placebo group. Four participants from the placebo group were withdrawn from study (according to prespecified withdrawal rules)
Selective reporting (reporting bias)	Low risk	The primary outcomes as reported were consistent with the trial protocol from www.clinicaltrials.gov.
Other bias	Low risk	The trial authors declared no conflicts of interest.

Villamor 2008 TZA

Methods	Country: Tanzania Setting: 5 outpatient tuberculosis clinics Duration of recruitment: April 2000 to April 2005 Median duration of follow-up: 30 months (IQR 15 to 41) Design: randomized placebo-controlled trial
Participants	Inclusion criteria: HIV-positive and HIV-negative adults aged 18 to 65 years with positive sputum smears for acid-fast bacilli who planned to stay in Dar es Salaam for 2 years Exclusion criteria: pregnancy, antituberculosis treatment for > 4 weeks in previous year, Karnofsky score < 40% HIV-positive participants randomized: 471 273 male and 198 female Mean age = 34 years Loss to follow-up: 67 in HIV-positive group (33 and 34 in micronutrient and placebo groups, respectively) Exclusions postrandomization: 0
Interventions	Intervention: micronutrient supplement (retinol; vitamins B1, B2, B6, B12; niacin; vitamin C; vitamin E; folic acid; selenium) Control: placebo Duration: daily for 24 months. All participants received DOTS antituberculosis chemotherapy
Outcomes	Primary outcomes • Culture negativity at 1 month after initiation of treatment; mortality during at least 24 months of follow-up; tuberculosis recurrences. Secondary outcomes • Changes from baseline in viral load, CD4 cell counts, and body weight.
Adverse events	None reported
Notes	Source of funding: National Institute of Allergy and Infectious Diseases; US Department of Agriculture

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The trial authors used computer-generated permuted blocks of 20. Randomization was stratified by HIV status of participants
Allocation concealment (selection bias)	Unclear risk	All clinical and research staff were unaware of the participants' treatment assignment, but the trial authors provided insufficient information

Villamor 2008 TZA (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Low risk	Participants and investigators were blinded.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The trial authors did not provide reasons for losses to follow-up, although they used appropriate statistical analyses
Selective reporting (reporting bias)	Unclear risk	Insufficient information; the trial protocol was not available
Other bias	Low risk	The trial authors declared that they had no conflicts of interest

Wejse 2009 GNB

Methods	Country: Guinea-Bissau Setting: tuberculosis clinics in urban disease surveillance site Duration of recruitment: November 2003 to December 2005 Duration of follow-up: 12 months Design: placebo-controlled, parallel group
Participants	Inclusion criteria: tuberculosis participants starting antituberculosis treatment, ≥ 15 years Exclusion criteria: none Participants randomized: 222 male and 143 female; mean age 37.5 yrs; 131 HIV-positive Participants analysed: 365 Loss to follow-up/withdrawal: 84 Exclusions postrandomization: 2
Interventions	Intervention: 100,000 IU cholecalciferol (vitamin D) Control: placebo Duration: at inclusion; 5 and 8 months after inclusion
Outcomes	Primary outcomes: Reduction in a clinical severity score (tuberculosis score) Secondary outcomes: 12-month mortality
Adverse events	Minor adverse events reported; no difference between groups. There were no reported cases of hypercalcaemia
Notes	Source of funding: Aarhus University Hospital; Danish Research Council for Developmental Research

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**

Wejse 2009 GNB (*Continued*)

Random sequence generation (selection bias)	Low risk	The trial authors used a computer-generated sequence when performing randomization
Allocation concealment (selection bias)	Low risk	The trial used identical, sequentially numbered containers to perform allocation concealment
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, staff, and researchers were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Loss to follow-up was unknown in the HIV-positive subgroup.
Selective reporting (reporting bias)	Low risk	The trial protocol was available; the trial authors reported on all outcomes of interest
Other bias	Low risk	The trial authors did not prespecify the HIV subgroup analyses but proportions were equally distributed; the trial funder and provider had no role in trial design

Zhao 2010 CHN

Methods	Country:China Setting: village in Huaiyang county, Henan province Design: randomized placebo-controlled trial Duration of recruitment: June 2008 to November 2008 Duration of follow-up: 6 months
Participants	Inclusion criteria: HIV-positive people aged 25 to 49 years with BMI 18-25kg/m2 and CD4 count > 200 with no clinical symptoms of AIDS Exclusion criteria: not stated Number randomized: 102 Mean age at randomization: micronutrient group:37.8 ± 2.9 years; placebo group: 37.3 ± 2.3 years 50 male and 49 female No baseline differences between treatment groups in terms of gender, weight, height
Interventions	Intervention: tablet containing: vitamin A 200 µg, β-carotene 200 µg, vitamin D 5 µg, thiamin 1 mg, riboflavin 1 mg, vitamin B6 1 mg, folic acid 0.15 mg, vitamin C 100 mg, vitamin E 15 mg, iron 6 mg, zinc 5 mg, selenium 30 µg, calcium 400 mg Control: identical placebo daily Duration: 6 months Compliance: not reported

Zhao 2010 CHN (*Continued*)

Outcomes	Primary: change in absolute CD3, CD4, and CD8 counts and of markers of humoral immunity (IgA, IgG, IgM, and C3)
Adverse events	Not reported
Notes	Source of funding: not specified Conflict of interest: not specified Ethics: review board not specified Trial registration: not specified

Risk of bias ***Risk of bias***

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial authors did not describe the method of random sequence generation
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe the method of allocation concealment
Blinding (performance bias and detection bias) All outcomes	Unclear risk	There was no information from the trial authors on blinding of participants, investigators, or outcome assessors
Incomplete outcome data (attrition bias) All outcomes	Low risk	Three participants, out of a total number of 102 randomized, were lost to follow-up
Selective reporting (reporting bias)	Unclear risk	The trial protocol was not available.
Other bias	Unclear risk	The study authors did not provide conflict of interest statements

Abbreviations: ALT: alanine aminotransferase; ALP: alkaline phosphate; ART: antiretroviral therapy; AST: aspartate aminotransferase; BMI: Body Mass Index; CXR: Chest X-Ray; ESR: erythrocyte sedimentation rate ; GFR: glomerular filtration rate; HAART: highly active antiretroviral therapy; IDU: injection drug user; HCV: Hepatitis C; INH: isoniazid; IQR: interquartile range; MUAC: mid-upper arm circumference; NSAIDS: non-steroidal anti-inflammatory drugs; PTH:Parathyroid hormone; SD: standard deviation.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Aghdassi 2010	Trial participants had highly active antiretroviral therapy (HAART)-related co-morbidity
AIDS Policy Law 2012	Not a randomized controlled trial (RCT)
Arpadi 2012	Most trial participants were under 15 years of age
Austin 2006	The trial intervention was irrelevant to this review
Balasubramanyam 2011	Co-intervention present
Balfour 2014	The trial intervention was irrelevant to this review
Brown 2015	This study did not report any relevant outcomes
Chow 2010	Trial participants had HAART-related co-morbidity
Coelho 2015	Not a RCT
Currier 2010	Not a RCT
Daneshpajouhnejad 2011	This study did not report any relevant trial outcomes
Etminani-Esfahani 2012	Not a RCT
Gharakhanian 2011	Not a RCT
Groleau 2013	This study did not report any relevant trial outcomes
Havens 2012a	This study did not report any relevant trial outcomes
Havens 2012b	This study did not report any relevant trial outcomes
Havens 2012c	This study did not report any relevant trial outcomes
Havens 2012d	This study did not report any relevant trial outcomes
Hemsworth 2012	The trial intervention was irrelevant to this review
Hummelen 2011	The trial intervention was irrelevant to this review
Kaiser 2006	The trial intervention was irrelevant to this review
Kakalia 2011a	Most trial participants were less than 15 years of age
Kakalia 2011b	Most trial participants were less than 15 years of age

(*Continued*)

Lachmann 2014	Not a RCT
Ladep 2010	Co-intervention present
Lange 2009	The trial intervention was irrelevant to this review
Lange 2011	The trial intervention was irrelevant to this review
Lescoat 2012	Not a RCT
Lin 2013	Trial participants had HAART-related co-morbidity
Longenecker 2011	This study did not report any relevant trial outcomes
Madrid 2012	Not a RCT
Mandal 2011	This study did not report any relevant trial outcomes
Martineau 2013	Not a RCT
Mascitelli 2011	Not a RCT
Mburu 2010	The trial intervention was irrelevant to this review
Mehta 2010	Not a RCT
Morgan 2010	Co-intervention present
Motswagole 2013	The trial intervention was irrelevant to this review
Pasquet 2011	Not a RCT
PrayGod 2011	The trial intervention was irrelevant to this review
Schall 2016	The study did not report any relevant outcomes
Scrimgeour 2010	The study did not report any relevant outcomes
Singhal 2010	The trial intervention was irrelevant to this review
Steenhoff 2015	More than 20% of the trial participants were less than 15 years of age
Stewart 2011	Co-intervention present
Sudarsanam 2011	The trial intervention was irrelevant to this review
Visser 2011	The study did not report any relevant trial outcomes

(*Continued*)

Welz 2011	Not a RCT

Abbreviations: HAART: highly active antiretroviral therapy; RCT: randomized controlled trial.

Characteristics of studies awaiting assessment *[ordered by study ID]*

Odunukwe 2016

Methods	Country: Nigeria Setting: HIV treatment centre, Lagos
Participants	Inclusion criteria: HIV-positive men and women who were eligible for highly active antiretroviral therapy (HAART) and who were HBsAg positive (Hepatitis B virus or HBV)
Interventions	Intervention: 200 µg selenium daily plus HAART Control: HAART Duration: 18 months
Outcomes	Changes in HBV load, HIV load, CD4 cell count, and alanine transaminase (ALT)
Notes	

Abbreviations: HAART: highly active antiretroviral therapy; HBV: hepatitis B.

Characteristics of ongoing studies *[ordered by study ID]*

Lebouché 2014

Trial name or title	The role of extended-release niacin on immune activation and neurocognition in HIV-positive patients treated with antiretroviral therapy (CTN PT006)
Methods	Country: Canada Setting: Chronic Viral Illness Service, Montreal Chest Institute of the McGill University Health Centre (MUHC), and the Cliniquemédicale l'Actuel, Montreal Design: randomized cross-over trial
Participants	Inclusion criteria: 21 years or older, viral load < 50 copies/mL for the last 3 months, CD4+ T-cell count ≤ 350 cells/μL; and on stable ART (ART unchanged for treatment failure (rebound in viral load)) for more than 12 months Exclusion criteria: prior history of hypersensitivity reaction to niacin or any other component of the study drug; prior history of flushing; liver disease (including coinfection with hepatitis B or C virus) or unexplained persistent elevations of serum transaminases; alanine aminotransferase (ALT) or aspartate aminotransferase (AST) or alkaline phosphatase > 2.5 times the upper limit of normal ; active duodenal or gastric peptic ulcer;

Lebouché 2014 (*Continued*)

	active bleeding disorders; history of gout; active AIDS events in the last 3 months as determined by the treating physician; unstable angina or acute phase myocardial infarction; diabetic or potentially diabetic with hypercholesterolaemia; renal dysfunction; co-enrolment in another study involving neurocognitive evaluation; or pregnant or nursing or planning to become pregnant
Interventions	Immediate versus deferred use of ER niacin for 24 weeks. The administration of ER niacin will be titrated (weeks 0 to 4: 500 mg, weeks 5 to 12: 1000 mg, weeks 12 to 24: 2000 mg). All participants will receive ART
Outcomes	Primary outcome: T cell activation (change in percentage of CD8+ CD38+ HLA-DR+ T-cells) Secondary outcomes: change in total CD4 cell count
Starting date	February 2012
Contact information	bertrand.lebouche@mcgill.ca
Notes	

NCT 01295034

Trial name or title	Vitamin D supplements for HIV-positive patients on cART (NCT01295034)
Methods	Country: USA Setting: Mount Sinai Medical Center, New York Design: controlled trial
Participants	Inclusion criteria: HIV-positive adults ≥ 18 to 70 yrs, stable highly active antiretroviral therapy (HAART) regimen (at least 12 months) with undetectable viral load (at least 6 months), not consuming more than 2 g calcium and 800 IU vitamin D daily Exclusion criteria: receiving vitamin D, current treatment for bone disease, receiving medications known to affect bone mineralization, medical conditions known to affect vitamin D, calcium and phosphate levels, kidney disease, unstable medical condition likely to preclude participation in a 12-month trial, pregnancy
Interventions	Intervention: oral dose of 50,000 IU vitamin D2 weekly for 8 weeks, thereafter 1000 IU vitamin D2 daily for 48 weeks Control: oral dose of 2000 to 4000 IU vitamin D3 daily for 12 months, with dose titration as necessary Duration: 12 months
Outcomes	Primary: 25 (OH) vitamin D levels (% of participants who have levels in the range of 30 to 60 ng/mL) Secondary: change in CD4 cell count
Starting date	March 2011
Contact information	andrea.branch@mssm.edu
Notes	

NCT 01798680

Trial name or title	Trial of Vitamin D in HIV progression (TOV4)
Methods	Country: Tanzania Setting: Dar es Salaam Design: placebo-controlled trial
Participants	Inclusion criteria: HIV-positive adults ≥ 18 yrs, initiation of HAART at the time of randomization, 25(OH) vitamin D concentration < 30 ng/mL Exclusion criteria:pregnancy, participation in another micronutrient trial
Interventions	Intervention: oral dose of 50000 IU vitamin D3 weekly for 4 weeks, thereafter 2000 IU vitamin D3 daily up to 12 months Control: oral dose of placebo weekly for 4 weeks, thereafter 2000 IU vitamin D3 daily up to 12 months Duration: 12 months
Outcomes	Primary: All-cause death, pulmonary tuberculosis within 12 months of randomization Secondary: CD4 cell count, clinical diagnosis of co-morbidities, weight, calcium, Parathyroid hormone (PTH) and alkaline phosphate (ALP) concentrations
Starting date	February 2014
Contact information	mina@hsph.harvard.edu fmugusi@muhas.ac.tz
Notes	

NCT 02810275

Trial name or title	Folinic Acid: Supplementation and Therapy (NCT02810275)
Methods	Country: Brazil Setting: Hospital de Clinicas de Porto Alegre
Participants	Inclusion criteria: HIV infected and HIV-HCV co-infected men and women aged 18 to 50 years receiving HAART with undetectable viral load for more than 6 months Exclusion criteria: diabetes mellitus, previous CVD: acute myocardial infarction, myocardial revascularization, or stroke,creatinine > 1.5 mg/dL,clinical diagnosis or ultrasound, endoscopic, or laboratory evidence of liver cirrhosis, on treatment with: statins, fibrates, hormone replacement therapy, sulfonamides, vitamin supplements, or folinic acid in the last 30 days and pregnant women
Interventions	Intervention: 5 mg folinic acid daily Control: placebo daily Duration: 4 weeks
Outcomes	Changes in flow mediated dilatation. serum homocysteine levels
Starting date	October 2012

NCT 02810275 (*Continued*)

Contact information	Sandra Costa Fuchs, Hospital de Clinicas de Porto Alegre
Notes	

NCT 02827643

Trial name or title	Vitamin D and Calcium Supplement Attenuate Bone Loss Among HIV- Infected Patients Receiving Tenofovir Disoproxil Fumarate, Lamivudine or Emtricitabine and Efavirenz (NCT02827643)
Methods	Country: Thailand Setting: Ramathibodi Hospital, Mahidol University, Bangkok
Participants	Inclusion criteria: HIV-1-infected patients aged 18 to 50 years who start 3TC or FTC, TDF, and EFV within 3 months before enrolment Exclusion criteria: CrCl < 60 mL/min/1.73 m^2, $CaCO_3$ supplement > 500 mg/day or vitamin D supplement > 800 IU/day, steroid use (equivalent to prednisolone> 5 mg/day more than 3 months), osteoporosis treatment, serum calcium > 10.5 g/dL clinical history of fragility fracture, pregnancy, or breastfeeding, secondary amenorrhoea, hyperthyroidism, history of kidney stone or current active opportunistic infection
Interventions	Intervention: once daily calcium carbonate 1,250 mg (600 mg elemental calcium) and weekly vitamin D2 (20,000 IU) plus TDF/3TC or FTC/EFV therapy Control: TDF/3TC or FTC/EFV therapy Duration: 24 weeks
Outcomes	Changes in bone mineral density, 1,25 (OH) vitamin D concentrations
Starting date	June 2016
Contact information	pataweeb44@gmail.com
Notes	

NCT 02856269

Trial name or title	Zinc Supplementation and Cardiovascular Risk in HIV (NCT02856269)
Methods	Country: USA Setting: University Hospitals Cleveland Medical Center
Participants	Inclusion criteria: HIV-1 infected adults aged ≥ 18 years with blood zinc level ≤ 0.75 mg/L that are receiving a stable antiretroviral regimen with no plans to change during study with HIV-1 RNA level of ≤ 400 copies/mL and no diarrhoea or nausea/vomiting for the last month Exclusion criteria: pregnancy/lactation,presence of inflammatory condition, regular use of agents that may affect inflammation in the last 3 months. regular use of NSAIDS, aspirin, or statins will be allowed as long as dose has been stable for the last 3 months and is not expected to change during the study Presence of active neoplastic diseases requiring chemotherapy and use of immunosuppressive drugs, known cardiovascular disease, uncontrolled diabetes, allergy or intolerance to zinc sulfate. AST, and ALT > 2.5 x

NCT 02856269 (*Continued*)

	upper normal limit, haemoglobin < 9.0 g/dLor GFR < 50 mL/min
Interventions	Intervention: 45 mg zinc gluconate daily Control: 90 mg zinc gluconate daily Duration: 12 weeks
Outcomes	Changes in blood zinc concentrations
Starting date	September 2016
Contact information	mccomsey.grace@clevelandactu.org
Notes	

Abbreviations: ALT: alanine aminotransferase; ALP: alkaline phosphate; ART: antiretroviral therapy; AST: aspartate aminotransferase; GFR: glomerular filtration rate; HAART: highly active antiretroviral therapy; NSAIDS: non-steroidal anti-inflammatory drugs; PTH: parathyroid hormone.

DATA AND ANALYSES

Comparison 1. Multiple micronutrients versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	7	2897	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.72, 1.15]
1.1 People with HIV not on ART	3	1068	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.31, 1.15]
1.2 People with HIV on ART or initiating ART	1	400	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.50, 3.10]
1.3 People with HIV not on ART and on treatment for active tuberculosis	3	1429	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.69, 1.23]
2 Hospital admissions	2	881	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.61, 1.22]
2.1 People with HIV not on ART	1	481	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.42, 1.49]
2.2 People with HIV on ART	1	400	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.59, 1.36]
3 Clinical disease progression	1		Hazard Ratio (Random, 95% CI)	1.08 [0.72, 1.62]
3.1 People with HIV not on ART and on treatment for active tuberculosis	1		Hazard Ratio (Random, 95% CI)	1.08 [0.72, 1.62]
4 CD4+ cell count	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
4.1 At baseline	5	1209	Mean Difference (IV, Random, 95% CI)	-18.27 [-55.97, 19.42]
4.2 At longest follow-up	6	1533	Mean Difference (IV, Random, 95% CI)	26.40 [-22.91, 75.70]
5 CD4+ cell count at longest follow-up; subgrouped by participant characteristics	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
5.1 People with HIV not on ART	2	441	Mean Difference (IV, Random, 95% CI)	30.36 [-7.13, 67.84]
5.2 People with HIV on ART or initiating ART	1	367	Mean Difference (IV, Random, 95% CI)	-6.0 [-35.87, 23.87]
5.3 People with HIV not on ART and on treatment for active tuberculosis	2	626	Mean Difference (IV, Random, 95% CI)	-5.77 [-55.80, 44.25]
5.4 People with HIV - Not stated if they are taking ART	1	99	Mean Difference (IV, Random, 95% CI)	106.0 [77.23, 134.77]
6 Viral load	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
6.1 At baseline	4	1166	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.16, 0.07]
6.2 At longest follow-up	4	792	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.26, 0.06]
7 Viral load at longest follow-up; sub-grouped by participant characteristics	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
7.1 People with HIV not on ART	2	497	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.27, 0.07]

7.2 People with HIV not on ART but in treatment for active tuberculosis	2	295	Mean Difference (IV, Random, 95% CI)	-0.09 [-0.45, 0.26]

Comparison 2. High dose multivitamins versus standard dose

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1	3418	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.89, 1.26]
1.1 People with HIV on ART or initiating ART	1	3418	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.89, 1.26]
2 CD4+ cell count	1	6186	Mean Difference (IV, Fixed, 95% CI)	-8.20 [-14.08, -2.32]
2.1 At baseline	1	3418	Mean Difference (IV, Fixed, 95% CI)	-7.0 [-13.74, -0.26]
2.2 At follow-up	1	2768	Mean Difference (IV, Fixed, 95% CI)	-12.0 [-22.00, -0.00]
3 Viral load	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 Baseline	1	3418	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.05, 0.05]
3.2 At follow-up	1	236	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.51, 0.11]

Comparison 3. Vitamin D versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 People with HIV not on ART and on treatment for active tuberculosis	1	131	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.65, 2.02]

Comparison 4. Zinc versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	3	433	Risk Ratio (M-H, Random, 95% CI)	1.24 [0.53, 2.86]
1.1 People with HIV on ART	1	231	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.58, 3.32]
1.2 People with HIV not on ART and on treatment for active tuberculosis	2	202	Risk Ratio (M-H, Random, 95% CI)	1.62 [0.22, 11.89]
2 Persistence of diarrhoea	1	104	Hazard Ratio (Random, 95% CI)	0.91 [0.50, 1.66]
2.1 People with HIV not on ART	1	104	Hazard Ratio (Random, 95% CI)	0.91 [0.50, 1.66]
3 Rate of diarrhoea	1	231	Odds Ratio (Random, 95% CI)	0.40 [0.18, 0.87]
3.1 People with HIV on ART	1	231	Odds Ratio (Random, 95% CI)	0.40 [0.18, 0.87]

Comparison 5. Selenium versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Hospital admissions	1	186	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.21, 0.75]
1.1 People with HIV on ART	1	186	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.21, 0.75]

ADDITIONAL TABLES

Table 1. Optimal information size calculations (dichotomous outcomes)

Outcome	Power	Two-sided significance level	Risk in control group	Relative risk reduction	Risk in intervention group	Sample size (total)
Death	80%	95%	15.5%[1]	25%	11.6%	2412
Death	80%	95%	8.3%[2]	25%	6.2%	4782
Death	80%	95%	5.5%[3]	25%	4.1%	7314
CD4 cell count $\leq$ 350 cells/mm^3[4]	80%	95%	10%	60%	55%	2312
CD4 cell count $\leq$ 350 cells/mm^3[4]	80%	95%	25%	60%	44%	314
CD4 cell count $\leq$ 350 cells/mm^3[4]	80%	95%	50%	60%	29%	76

[1]Estimated annual risk of death of antiretroviral naive HIV-infected persons ($\geq$10 years after seroconversion) (Collaborative Group on AIDS Incubation 2000).

[2]Estimated annual risk of death of antiretroviral naive HIV-infected persons (5 to 9 years after seroconversion) (Collaborative Group on AIDS Incubation 2000).

[3]Estimated risk of death of HIV-infected persons after receiving first-line antiretroviral therapy regimens for 12 months (Mbuagbaw 2010).

[4]Antiretroviral naive HIV-infected participants who experience a decline in CD4 count (Kamwesiga 2011a, which is under Kamwesiga 2015 RWA).

Table 2. Optimal information size calculations (continuous outcomes)

Outcome	Power	Two-sided significance level	Ratio of group 1: group 2	Mean in control group	SD	Mean in supplement group	SD	Mean difference	Sample size (total)
Mean blood 25 (OH) vitamin D level at 12 months[1]	80%	95%	1	17 ng/ml	9	28 ng/ml	9	11.5	22
Mean blood 25 (OH) vitamin D level at 12 months[1]	80%	95%	1	17 ng/ml	20	28 ng/ml	20	11.5	104
Mean BMI at 24 months[3]	80%	95%	1	21 kg/m^2	3	22 kg/m^2	3	1 kg/m^2	284
Mean BMI at 24 months[4]	80%	95%	1	21 kg/m^2	3	23 kg/m^2	3	2 kg/m^2	72

Abbreviations: BMI: body mass index; SD: standard deviation.
[1]This example is based on data from Stallings 2014 USA. This example uses the SD from the control group.
[2]This example is based on data from Stallings 2014 USA. This example uses the SD from the supplemented group.
[3]This example uses the SD from Villamor 2008 TZA, but uses a 1 kg/m^2 mean difference for illustrative purposes.
[4]This example uses the SD from Villamor 2008 TZA, but uses a 2 kg/m^2 mean difference for illustrative purposes.

Table 3. Characteristics of trials evaluating multiple micronutrients versus placebo

Trial ID	Country	Participants	Baseline HAART use (%)	Mean baseline CD4+ cell count (cells/mm^3)	Mean baseline viral load (copies/ml or log$_{10}$ copies/mL)	MMN dose[1]	Duration of supplementation
Baum 2013 BWA	Botswana	HIV-positive	0	423 (median)	11,800 (median)	High	24 months
Guwatudde 2015 UG	Uganda	HIV-positive	49.8[2]	145 (median) 137 (median)	N/A	Standard	18 months
Jiamton 2003 THA	Thailand	HIV-positive	0	244 (median)	3.9 (1.0)	High	48 weeks

Table 3. Characteristics of trials evaluating multiple micronutrients versus placebo (*Continued*)

Kelly 1999 ZMB	Zambia	HIV-positive plus chronic diarrhoea	0	291 (median)	N/A	High	2 weeks
Kelly 2008 ZMB	Zambia	HIV-positive	0[3]	N/A	N/A	Standard	1.9 years[4]
McClelland 2004 KEN	Kenya	HIV-positive	0	294 (209)	5.3 (0.9)	High	6 weeks
Zhao 2010 CHN	China	HIV-positive	Not stated	417 (69)	Not stated	Standard	6 months
Range 2006 TZA	Tanzania	HIV-positive plus active TB	0	363 (275)	4.02 (0.98)	High	8 months
Semba 2007 MWI	Malawi	HIV-positive plus active TB	0	Not stated	5.4 (median)	Standard	24 months[5]
Villamor 2008 TZA	Tanzania	HIV-positive plus active TB	0	305 (227)	4.6 (1.0)	High	24 months

Abbreviations: HAART: highly active antiretroviral therapy; MMN: multiple micronutrient; TB: Tuberculosis

[1]Standard dose supplements provided most of the micronutrients at the level of the Dietary Recommended Intake (DRI). High-dose supplements provided most of the micronutrients in multiples of the DRI.

[2]Guwatudde 2015 UG: participants who received ART for no longer than 6 months. The rest of the trial participants were initiated on ART at baseline.

[3]Kelly 2008 ZMB: we excluded participants taking HAART from the analysis of CD4 and viral load.

[4]Kelly 2008 ZMB was a cross-over trial, with cross-over at the end of 1.9 years. We did not include the outcome data for the period after cross-over.

[5]Semba 2007 MWI: the median duration of follow-up was 12.5 months, due to the introduction of ART programme.

Table 4. Composition of multiple micronutrient supplements

Micronutrient	RDA male aged 19 to 70 years	Standard doses[1]				High doses[2]						Standard dose	High dose
		Kelly 2008 ZMB	Zhao 2010 CHN	Semba 2007 MWI	Guwatu 2015 UG	Baum 2013 BWA	Kelly 1999 ZMB	Jiamton 2003 THA	McCleland 2004 KEN	Range 2006 TZA	Villamor 2008 TZA	Isanaka TZA	2012
Vitamin A	900 µg (3000 IU)	-	200 µg (660 IU)	2424µg (8000	-	-	3182 µg (10500	3027 µg (9990	-	1500 µg (5000	1515 µg (5000	-	-

Table 4. Composition of multiple micronutrient supplements (*Continued*)

				IU)			IU)	IU)		IU)	IU)		
B-carotene	-	4.8 mg	-	-	-	-	-	6 mg	-	-	-	-	-
Vitamin B1 (Thiamine)	1.2 mg	1.4 mg	1 mg	1.5 mg	1.4 mg	20 mg	-	24 mg	20 mg	20 mg	20 mg	1.2 mg	20 mg
Vitamin B2 (riboflavin)	1.3 mg	1.4 mg	1 mg	1.7 mg	1.4 mg	20mg	-	15 mg	20 mg	20 mg	20 mg	1.2 mg	20 mg
Vitamin B3 (niacin)	16 mg	18 mg	-	20 mg	18 mg	100 mg	-	54 mg	100mg	40 mg	100 mg	15 mg	100 mg
Vitamin B6 (pyridoxine)	1.3 to 1.7 mg	1.9 mg	1 mg	2 mg	1.9 mg	25 mg	-	40mg	25 mg	25 mg	25 mg	1.3mg	25 mg
Vitamin B9 (folinic acid)	400 µg	400 µg	150 µg	400 µg	400 µg	800 µg	5000 µg	100 µg	800 µg	800 µg	800 µg	400 µg	800 µg
Vitamin B12	2.4 µg	2.6 µg		6 µg	2.6 µg	50 µg	-	30µg	50 µg	50 µg	50 µg	2.4 µg	50 µg
Panthothenic acid	5 mg	-	-	-	-	-	-	40 mg	-	-	-	-	-
Vitamin E	15 mg	10 mg	15 mg	133 mg	10 mg	30 mg	300 mg	80 mg	30 mg	60 mg	200 mg	15 mg	30 mg
Vitamin D	5 to 15 µg (200 to 600	5 µg (200 IU)	5 µg (200 IU)	10 µg (400 IU)	-	-	-	20 µg (800 IU)	-	5 µg (200 IU)	-	-	-

Table 4. Composition of multiple micronutrient supplements (*Continued*)

	IU)												
Vitamin K	120 µg	-	-	-	-	-	-	180 µg	-	-	-	-	-
Vitamin C	90 mg	70 mg	100 mg	500 mg	70 mg	500 mg	300 mg	400 mg	500 mg	200 mg	500 mg	80 mg	500 mg
Selenium	55 µg	65 µg	30 µg	65 µg	-	200 µg	150 µg	400 µg	200 µg	200 µg	100 µg	-	-
Iron	8 mg		6 mg	-	-	-	-	10 mg	-	-	-	-	-
Zinc	11 mg	15 mg	5 mg	10 mg	-	-	200 mg	30 mg	-	45 mg	-	-	-
Copper	0.9 mg	-	-	-	-	-	-	3 mg	-	5 mg	-	-	-
Iodine	150 µg	-	-	175 µg	-	-	-	300 µg	-	-	-	-	-
Chromiu	35 µg	-	-	-	-	-	-	150 µg	-	-	-	-	-
Manganese	2.3 mg	-	-	-	-	-	-	8 mg	-	-	-	-	-
Calcium	1000 mg	-	400 mg	-	-	-	-	-	-	-	-	-	-

Abbreviations: IU: International units; RDA:Recommended Daily Allowance

[1]Standard dose supplements provided most of the micronutrients at the level of the RDA.

[2]High-dose supplements provided most of the micronutrients in multiples of the RDA.

Table 5. Change in CD4 cell count (cells/mm^3): multiple micronutrients versus placebo

Trial ID	Statistical measure	Intervention			Control			Timing of endpoint	Difference between groups at endpoint (as reported by trial authors)
		Baseline	Endpoint	N[1]	Baseline	Endpoint	N[1]		
Guwatudde 2015 UG	Median (IQR)	145 (86 to 215)	Not reported	200	137 (68 to 192)	Not reported	200	18 months	MD -6.17 (95% CI -29.3 to 16.9)[2]

Table 5. Change in CD4 cell count (cells/mm^3): multiple micronutrients versus placebo (*Continued*)

Jiamton 2003 THA	Median (IQR)	244 (52 to 544)	200 (66 to 358)	192	261 (50 to 550)	232 (73 to 377)	184	48 weeks	"Did not differ"
Kelly 1999 ZMB	Median (IQR)	292	Not reported	66	282	Not reported	69	4 weeks	"Not different"[3]
Kelly 2008 ZMB	Mean (SD)	370 (190)	415 (242)	41	365 (212)	409 (192)	43	1.9 years[3]	P = 0.55
McClelland 2004 KEN	Mean (SD)	294 (209)	300 (205)	179	262 (202)	265 (189)	178	6 weeks	Adjusted regression co-efficient 23 (95% CI 3 to 43); P = 0.03
Zhao 2010 CHN	Mean (SD)	417 (69)	589 (85)	50	466 (72)	483 (59)	49	6 months	P < 0.05
Range 2006 TZA	Mean (SD)	460 (391)	423 (373)	48	460 (385)	403 (460)	48	8 weeks	P = 0.18
Villamor 2008 TZA	Mean (SD)	305 (277)	Not reported	200	339 (256)	340 (240)	204	2 years[5]	MD -5 (−37 to 26); P = 0.74
Baum 2013 BWA	Median (IQR)	428 (336 to 555)	Not reported	220	411 (327 to 545)	Not reported	217	2 years	Not reported[7]

Abbreviations: IQR: Interquartile range; MD: Mean difference; SD: Standard deviation

[1]The number of participants stated is the number assessed for end-point data.

[2]Guwatudde 2015 UG: the trial authors reported a mean difference which is different to our calculation. The reasons for this are unclear.

[3]Kelly 1999 ZMB: the trial authors did not report data that we could include in a meta-analysis.

[4]Kelly 2008 ZMB was a cross-over trial, with cross-over at the end of 1.9 years. CD4+ counts were recorded during the second year of follow-up. The data for the period after cross-over is not included in this table.

[5]Range 2006 TZA: data shown are for multiple micronutrients plus zinc versus placebo. There were also no differences for micronutrients without zinc versus placebo.

[6]Villamor 2008 TZA also reported outcomes at 8 months, with no significant difference between groups.

[7]Baum 2013 BWA: data shown are for multivitamins plus selenium versus placebo. The trial authors reported reductions in the risk of CD4+ falling to < 250 cells/μL for multivitamins plus selenium versus placebo (HR 0.48, 95% CI 0.26 to 0.88) and for multivitamins alone versus placebo (HR 0.54, 95% CI 0.3 to 0.98). Multivariate analysis showed that this effect was only apparent with supplementation of both multivitamins and selenium (HR 0.46, 95% CI 0.25 to 0.85).

Table 6. Change in viral load (log_{10} copies/mL): multiple micronutrients versus placebo

Trial ID	Statistical measure	Intervention			Control			Timing of endpoint	Difference between groups at endpoint (as reported by trial authors)
		Baseline	Endpoint	N[1]	Baseline	Endpoint	N[1]		
Baum 2013 BWA	Median (IQR)	4.0 (3.3-4.7)	Not reported[2]	220	4.3 (3.6 to 4.8)	Not reported[2]	217	24 months	P = 0.4[3]
Jiamton 2003 THA	Mean (SD)	3.9	4.4 (1.4)	71[4]	4.2	4.5 (1.54)	69	48 weeks	P = 0.4
McClelland 2004 KEN	Mean (SD)	5.3 (0.9)	5.3 (0.9)	179	5.4 (0.9)	5.4 (0.9)	178	6 weeks	P = 0.4
Range 2006 TZA	Mean (SD)	3.72 (1.18)	3.85 (1.4)	48	3.9 (1.33)	4.1 (1.54)	48	8 weeks	"Not significant"[5]
Villamor 2008 TZA	Mean (SD)	4.6 (1.0)	Not reported	71	4.6 (0.9)	4.74 (1.54)	69	2 years[6]	MD −0.08 (−0.22 to 0.05) ; P = 0.23

Abbreviations: CI: Confidence interval; IQR: Interquartile range; MD: Mean difference; SD: Standard deviation
[1]The number of participants stated is the number assessed for end-point data.
[2]Baum 2013 BWA: multiple imputation of viral load data was performed. The trial authors did not provide details.
[3]Baum 2013 BWA: data shown are for multivitamins plus selenium versus placebo. There were also no differences for multivitamins without selenium versus placebo.
[4]Jiamton 2003 THA: viral load analyses was conducted on the first 140 consecutive participants (29% of participants).
[5]Range 2006 TZA: data shown are for multiple micronutrients plus zinc versus placebo. There were also no differences for micronutrients without zinc versus placebo.
[6]Villamor 2008 TZA also reported outcomes at 8 months, with no significant difference between groups.

Table 7. Change in nutritional status parameters: multiple micronutrients versus placebo

Trial ID	Nutritional parameter	Statistical measure	Intervention	Control	Timing of endpoint	Difference between groups at endpoint (as reported by trial authors)

Table 7. Change in nutritional status parameters: multiple micronutrients versus placebo (*Continued*)

			Baseline	End-point	N[1]	Baseline	End-point	N[1]		
Villamor 2008 TZA	BMI (kg/m^2)	Mean (SD)	19.3 (2.8)	Not reported	233	19.6 (2.9)	21.2 (3.3)	238	2 years[2]	MD -0.1 (−0.4 to 0.2); P = 0.37
Guwatudde 2015 UG	Weight (kg) Haemo-globin (g/dL)	Not reported Median (IQR)	Not reported 12.2 (11.2 to 13.2)	Not reported Not reported	200 200	Not reported 12.3 (11.3 to 13.5)	Not reported Not reported	200 200	18 months 18 months	MD 0.54 (−0.40 to 1.48); P = 0.691 MD 0.16 (−0.21 to 0.16); P = 0.977
Jiamton 2003 [12]	Blood vitamin E (µmol/L)[3]	Mean (SD)	22 (9)	Not reported	Not reported	19 (7)	Not reported	Not reported	48 weeks	MD 10.7 (7.0 to 14.3)[4]; P < 0.001
	Blood selenium (µmol/L)[5]	Mean (SD)	1.6 (0.2)	Not reported	Not reported	1.6 (0.2)	Not reported	Not reported	48 weeks	MD 0.16 (0.0 to 0.34)[6]; P = 0.04
Kelly 1999 ZMB[12]	Blood vitamin A (µmol/L)[7,8]	Mean	0.63	Not reported	66	0.65	Not reported	69	4 weeks	P = 0.21
	Blood vitamin E (µmol/L)[3,8]	Mean	11.4	Not reported	66	11.7	Not reported	69	4 weeks	"No difference"
Kelly 2008 ZMB	BMI (kg/m^2) MUAC (cm) Fat mass (kg) Lean body mass (kg) Grip strength (kg)	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	1.9 years[9]	"No significant differences at any time point"

Table 7. Change in nutritional status parameters: multiple micronutrients versus placebo (*Continued*)

Semba 2007 MWI[12]	Blood vitamin A (µmol/L)[7,11]	Geometric mean	0.59	Reported in a graph	383	0.59	Reported in a graph	397	8 months	"Significantly higher"
	Blood selenium (µmol/L)[10,11]	Geometric mean	0.66	Reported in a graph	392	0.64	Reported in graph	405	8 months	

Abbreviations: BMI: Body Mass Index; IQR: Interquartile range; MUAC: Mid-upper arm circumference; MD: Mean difference; SD: Standard deviation

[1]The number of participants stated is the number assessed for endpoint data.

[2]Villamor 2008 TZA also reported outcomes at 8 months, with no significant difference between groups (MD 0, 95% CI −0.2 to 0.3; P = 0.74).

[3]Reference value for vitamin E sufficiency ≥ 11.6 µmol/L.

[4]Jiamton 2003 THA: the trial authors reported endpoint data on a subset of 44 participants. The trial authors did not state the number of participants for each treatment group. Baseline vitamin E levels (µmol/L) reported for 112 participants.

[5]Reference value for selenium sufficiency: ≥ 0.95 µmol/L.

[6]Jiamton 2003 THA: the trial authors reported endpoint data on a subset of 54 participants. The number of participants for each treatment group is not stated. Baseline selenium levels (µmol/L) reported for 129 participants.

[7]Reference value for vitamin A deficiency: < 0.7 µmol/L.

[8]Kelly 1999 ZMB: the trial authors reported that 67% and 55% of participants were deficient in vitamins A and E, respectively, at baseline.

[9]Kelly 2008 ZMB was a cross-over trial, with cross-over at the end of 1.9 years.

[10]Reference value for selenium sufficiency: ≥ 0.75 µmol/L.

[11]Semba 2007 MWI: the trial authors reported that 60% and 75% of participants were deficient in vitamin A and selenium respectively, at baseline.

[12]Analysis of blood micronutrient concentrations did not include adjustment for biomarkers of inflammation.

Table 8. Multiple micronutrients compared to placebo for adults with HIV infection not currently taking ART

Multiple micronutrients compared to placebo for adults with HIV infection not currently taking ART						**Multiple micron currently taking**
Participant or population: adults with HIV infection not currently taking ART **Settings:** all settings **Intervention:** multiple micronutrient supplementation (standard or high dose daily) **Comparison:** placebo						**Participant or p** **Settings:** all setti **Intervention:** m **Comparison:** pl
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (trials)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				

Table 8. Multiple micronutrients compared to placebo for adults with HIV infection not currently taking ART (*Continued*)

	Placebo	Micronutrients				
Mortality Follow-up: 12 to 24 months	**45 per 1000**	**26 per 1000** (14 to 52)	**RR 0.60** (0.31 to 1.15)	1068 (3 trials)	⊕⊕◯◯ **low**[1,2,3,4] due to indirectness and imprecision	Multiple micronutrients may reduce mortality
Hospital admissions Follow-up: 48 weeks	**84 per 1000**	**66 per 1000** (35 to 125)	**RR 0.79** (0.42 to 1.49)	481 (1 trial)	⊕◯◯◯ **very low**[1,4,5] due to indirectness and imprecision	We don't know if multiple micronutrients have any effect on hospital admissions
CD4 cell count Follow-up: 6 weeks to 2 years	The mean in the placebo groups ranged from **265 to 409 cells/mm^3**	The mean in the multiple micronutrient group was **30.36 cells/mm^3 higher** (7.13 lower to 67.84 higher)	-	441 (2 trials)	⊕⊕◯◯ **low**[1,6,7] due to indirectness and inconsistency	Multiple micronutrients may have little or no effect on CD4+ cell count
Viral load Follow-up: 6 to 48 weeks	The mean in the placebo groups ranged from **4.4 to 5.3 $\log_{10}$copies/mL**	The mean in the multiple micronutrient groups was **0.10 $\log_{10}$copies/mL lower** (0.27 lower to 0.07 higher)	-	497 (2 trials)	⊕⊕⊕◯ **moderate**[1,8] due to indirectness	Multiple micronutrients probably have little or no effect on viral load
BMI (kg/m^2) Follow-up: 1.9 years	-	-	-	84 (1 trial)	⊕◯◯◯ **very low**[1,9,10] due to indirectness and imprecision	We don't know if multiple micronutrients have any effect on BMI

The basis for the assumed risk is the median control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Abbreviations: ART: antiretroviral therapy; BMI: body mass index; CI: confidence interval; MUAC: mid-upper arm circumference; RR: risk ratio

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Table 8. Multiple micronutrients compared to placebo for adults with HIV infection not currently taking ART (*Continued*)

Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. **Very low certainty:** we are very uncertain about the estimate.	on our confidenc **Low certainty:** f our confidence i **Very low certain**

[1]No serious risk of bias: all trials were at low risk of selection bias. Appropriate methods of blinding were used.
[2]No serious heterogeneity: none of the trials found statistically significant effects.
[3]Downgraded by 1 for serious indirectness: the three trials were conducted in Botswana (Baum 2013 BWA), Zambia (Kelly 2008 ZMB) and Thailand (Jiamton 2003 THA).The finding of no effect may not apply to all populations.
[4]Downgraded by 1 for serious imprecision: the 95% CI is wide and includes both clinically important effects and no effect. The overall meta-analysis is substantially underpowered to confidently exclude effects.
[5]Downgraded by 2 for very serious indirectness: only a single trial is available from Thailand (Jiamton 2003 THA). The finding of no effect is not easily generalized to other settings.
[6]Downgraded by 1 for serious inconsistency: One trial in Botswana among ART-naive adults (not included in the meta-analysis) reported a reduced risk of reaching a CD4+ cell count of less than 250 cells/mm³ after two years of high dose supplementation. This finding is inconsistent with other trials that used similar combinations of micronutrients and selenium.
[7]Downgraded by 1 for serious indirectness: these two trials both used high-dose multiple micronutrients and were conducted in Kenya (with 6 weeks follow-up) and Zambia (with 1.9 years follow-up). TThe finding of no effect may not apply to people on ART or other populations and settings.
[8]Downgraded by 1 for serious indirectness: these two studies both used high dose multiple micronutrients and were conducted in Kenya (with 6 weeks follow-up) and Thailand (with 48 weeks follow-up). The finding of no effect may not apply to people on ART or other populations and settings.
[9]Downgraded by 2 for very serious indirectness: only a single trial from Zambia (Kelly 2008 ZMB) reports measures of nutritional status. This does not exclude the possibility of effects in some populations.
[10]Downgraded by 1 for serious imprecision: this trial is underpowered to detect or exclude clinically important differences. The trial reported no difference in BMI, mid-upper arm circumference (MUAC), lean body mass or fat mass but did not present data.

Table 9. Multiple micronutrients compared to placebo for adults with HIV infection currently taking ART

Multiple micronutrients compared to placebo for adults with HIV infection currently taking ART						**Multiple micron rently taking AI**
Participant or population: adults with HIV infection currently taking ART **Settings:** any setting **Intervention:** multiple micronutrient supplementation (standard dose daily) **Comparison:** placebo						**Participant or p Settings:** any set **Intervention:** m **Comparison:** pl
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (trials)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Micronutrients**				

Table 9. Multiple micronutrients compared to placebo for adults with HIV infection currently taking ART (*Continued*)

Mortality Follow-up: 12 to 24 months	**40 per 1000**	**50 per 1000** (20 to 124)	**RR 1,25** (0.50 to 3.10)	400 (1 trial)	⊕◯◯◯ **very low**[1,2,3] due to indirectness and imprecision	We don't know if multiple micronutrients have any effect on mortality
Hospital admissions Follow-up: 48 weeks	**195 per 1000**	**176 per 1000** (115 to 265)	**RR 0.90** (0.59 to 1.36)	400 (1 trial)	⊕◯◯◯ **very low**[1,2,3] due to indirectness and imprecision	We don't know if multiple micronutrients have any effect on mortality
CD4 cell count Follow-up: 18 months	The mean change in the placebo group was **147 cells/mm^3**	The mean change in the multiple micronutrient group was **6.17 cells/mm^{3}lower** (29.3 lower to 16.9 higher)	_	367 (1 trial)	⊕◯◯◯ **very low**[1,2,4] due to indirectness and imprecision	We don't know if multiple micronutrients have any effect on CD4 cell count
Viral load	-	-	-	-	-	-
Weight (kg) Follow-up: 18 months	The mean change in the placebo group was **3.3 kg**	The mean change in the multiple micronutrient group was **0.54 kg higher** (0.40 lower to 1.48 higher)		400 (1 trial)	⊕◯◯◯ **very low**[1,2,4] due to indirectness and imprecision	We don't know if multiple micronutrients have any effect on weight

*The basis for the assumed risk (for example, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; HR: hazard ratio; RR: risk ratio.

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

[1]No serious risk of bias: this trial was at low risk of selection bias. The trial authors used appropriate methods of blinding.

[2]Downgraded by 2 for serious indirectness: this single trial was conducted in Uganda and administered standard dose multiple micronutrients for two years. The finding of no effect may not be applicable to higher dose or the populations or settings.
[3]Downgraded by 2 for serious imprecision: this single trial is significantly underpowered to confidently detect or exclude effects.
[4]Downgraded by 1 for serious imprecision: the 95% CI is wide and includes what may be clinically important effects and no effect.

Table 10. Multiple micronutrients compared to placebo for adults with HIV infection and concurrent active tuberculosis

Multiple micronutrients compared to placebo for adults with HIV infection and concurrent active tuberculosis not currently taking ART						**Multiple micron concurrent activ**
Participant or population: adults with HIV infection and concurrent active tuberculosis not currently taking ART **Settings:** any setting **Intervention:** multiple micronutrient supplementation (standard or high dose daily) **Comparison:** placebo						**Participant or p** currently taking **Settings:** any set **Intervention:** m **Comparison:** pl
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**Number of participants (trials)**	**Certainty of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Micronutrients**				
Mortality Follow-up: 8 to 24 months	**357 per 1000**	**328 per 1000** (246 to 439)	**RR 0.92** (0.69 to 1.23)	1429 (3 trials)	⊕⊕◯◯ **low**[1,2.3,4] due to indirectness and imprecision	Multiple micronutrients may have little or no effect on mortality
Clinical disease progression from stage 3 to stage 4 Follow-up: 24 months	-	-	**HR 1.08** (0.72 to 1.62	313 (1 trial)	⊕◯◯◯ **very low**[1,4,5] due to indirectness and imprecision	We don't know if multiple micronutrients have any effect on clinical disease progression
CD4 cell count Follow-up: 2 to 24 months	The mean in the placebo groups ranged from **340 to 403 cells/mm^3**	The mean in the multiple micronutrient group was **5.77 cells/mm^3 lower** (55.8 lower to 44.25 higher)	-	674 (2 trials)	⊕⊕◯◯ **low**[1,3,4] due to indirectness and imprecision	Multiple micronutrients may have no effect on CD4 cell count
Viral load Follow-up: 2 to 24 months	The mean in the placebo groups ranged from	The mean in the multiple micronutri-	-	343 (2 trials)	⊕⊕◯◯ **low**[1,3,4] due to indirect-	Multiple micronutrients may have no effect on

Table 10. Multiple micronutrients compared to placebo for adults with HIV infection and concurrent active tuberculosis (*Continued*)

	4.1 to 4.7 log_{10}copies/mL	ent groups was **0. 09 log_{10}copies/ mL lower** (0.45 lower to 0. 26 higher)			ness and imprecision	viral load
BMI Follow-up: 24 months	The mean BMI in the placebo group was **21.2 kg/m^2**	The mean BMI in the micronutrient group was **0.1 lower** (0.4 lower to 0.2 higher)	-	471 (1 trial)	⊕◯◯◯ **very low**[1,4,5] due to indirectness and imprecision	We don't know if multiple micronutrients have any effect on BMI

*The basis for the assumed risk (for example, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Abbreviations: ART: antiretroviral therapy; CI: confidence interval; HR: hazard ratio; RR: risk ratio

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RR: risk ratio

GRADE Working Group grades of evidence
High certainty: further research is very unlikely to change our confidence in the estimate of effect.
Moderate certainty: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low certainty: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low certainty: we are very uncertain about the estimate.

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[1]No serious risk of bias: the trials were at low risk of selection bias, except for two trials that recruited both HIV-positive and HIV-negative participants and did not stratify the randomization (Range 2006 TZA; Semba 2007 MWI). The trials used appropriate methods of blinding.
[2]No serious heterogeneity: one small subgroup of a trial in Tanzania did find a statistically significant difference (Range 2006 TZA), but larger trials did not.
[3]Downgraded by 1 for serious indirectness: the three trials were conducted in Tanzania and Malawi and most patients were not taking ART. The finding of no effect may not apply to people on ART or other populations and settings.
[4]Downgraded by 1 for serious imprecision: the 95% CI is wide and includes clinically important effects and no effect.
[5]Downgraded by 2 for serious indirectness: data is provided by a single trial from Tanzania and participants were not on antiretroviral therapy (ART).

Table 11. Characteristics of trials evaluating vitamin A supplements versus placebo

Trial ID	Country	Participants	Baseline ART use	Mean baseline blood vitamin A concentration (µmol/L)[1]	Mean baseline CD4+ cell count (cells/mm^3)	Mean baseline viral load (log_{10} copies/mL)	Dose[2]	Duration of supplementation
Baeten 2002 KEN	Kenia	HIV-positive women	0%	0.097 (median) 0.095 (median)	240 (median) 203 (median)	5.34 (median) 5.54 (median)	10,000 IU retinol daily	6 weeks
Humphrey 1999 USA	USA	HIV-positive women	49%	1.52 (0.42) 1.41 (0.31)	Not reported	Not reported	300,000 IU retinol	Single dose
Semba 2007 USA	USA	HIV-positive IDUs	46%	1.61 1.37	296 (median) 259 (median)	9.49 (median) 9.67 (median)	200,000 IU retinol	Single dose
Coodley 1993 USA[3]	USA	HIV-positive	94%	-	-	-	180 mg β-carotene	4 weeks

Abbreviations: IDUs: Injection drug users; IU: International units; RDA: Recommended Daily Allowance
[1]Reference value for vitamin A sufficiency: > 1.05 µmol/L.
[2]RDA for a male aged 19 to 70 years is 900 µg (3000 IU) daily.
[3]Coodley 1993 USA was a cross-over trial, with cross-over at the end of 4 weeks. The baseline and outcome data is not reported for the period before cross-over and therefore we could not include it.

Table 12. Change in CD4 cell count (cells/mm^3): vitamin A versus placebo

Trial ID	Statistical measure	Intervention			Control			Timing of end-point	Difference between groups at end-point (as reported by trial authors)
		Baseline	End-point	N[1]	Baseline	End-point	N[1]		
Semba 1998 USA	Median	296	Reported in a graph	Not reported[2]	259	Reported in a graph	Not reported[2]	4 weeks	P = 0.17
Baeten 2002 KEN	Median	240	272	176	203	225	178	6 weeks	P = 0.04 Adjusted regres-

Table 12. Change in CD4 cell count (cells/mm^3): vitamin A versus placebo (*Continued*)

									sion coefficient 0.34 (−0.22 to 0.90); P = 0.90

[1]The number of participants stated is the number assessed for endpoint data.
[2]Semba 1998 USA: the trial authors reported that 110 particpants completed the trial, but did not report the number of participants for each treatment group.

Table 13. Change in viral load (log_{10} copies/mL) : Vitamin A versus placebo

Trial ID	Statistical measure	Intervention			Control			Timing of endpoint	Difference between groups at endpoint (as reported by trial authors)
		Baseline	Endpoint	N[1]	Baseline	Endpoint	N[1]		
Semba 1998 USA	Median	9.49	Reported in a graph	Not reported[2]	9.67	Not reported	Not reported[2]	4 weeks	P = 0.17
Humphrey 1999 USA	Geometric mean	Reported in a graph	Reported in a graph	19	Reported in a graph	Reported in a graph	12	8 weeks	P = 0.56
Baeten 2002 KEN	Median	5.34	5.34	176	5.54	5.49	178	6 weeks	P = 0.1

[1]The number of participants stated is the number assessed for endpoint data.
[2]Semba 1998 USA: the trial authors reported that 110 particpants completed the trial, but do not report the number of participants for each treatment group.

Table 14. Change in nutritional status parameters: vitamin A versus placebo

Trial ID	Nutritional parameter	Statistical Measure	Intervention			Control			Timing of endpoint	Difference between groups at endpoint (as reported by trial authors
			Baseline	Endpoint	N[1]	Baseline	Endpoint	N[1]		
Baeten 2002 KEN[3]	Vitamin A (µmol/L)[2]	Median	0.97	1.03	Not reported	0.95	0.94	Not reported	6 weeks	P = 0.03. "No effect" reported for

Table 14. Change in nutritional status parameters: vitamin A versus placebo (*Continued*)

										those who were severely de-
Semba 1998 USA[3]	Vitamin A (µmol/L)[3]	Median	1.61	Presented in a graph	Not reported	1.37	Presented in a graph	Not reported	4 weeks	"Not different"
Humphrey 1999 USA[3]	Vitamin A (µmol/L)[3]	Median	1.56	1.54	20	1.37	1.30	15	4 weeks	"No change"

[1]The number of participants stated is the number assessed for endpoint data.
[2]Baeten 2002 KEN: Data converted from µg/dL to µmol/L.
[3]Analysis of blood micronutrient concentrations did not include adjustment for biomarkers of inflammation.

Table 15. Characteristics of trials evaluating Vitamin D supplements versus placebo

Trial ID	Country	Participants	Baseline ART use	Mean baseline blood 25(OH)$_2$ vitamin D concentration (ng/mL)[1]	Mean baseline CD4+ cell count (cells/mm^3)	Mean baseline viral load (log$_{10}$ copies/mL)	Dose[2]	Duration of supplementation
Bang 2012 DEN	Denmark	HIV-positive men	100%	27.2 (11.5) 29.2 (12.4)	507 (268) 463 (197)	Not reported	100,000 IU then 1200 IU	Single dose at baseline then daily for 16 weeks (plus 1200 mg calcium daily)
Giacomet 2013 ITA	Italy	HIV-positive; ≤ 30 years	86%	15 (median)[3]	663 (median) 673 (median)	Not reported	100,000 IU	Single dose at baseline and at 3, 6, and 9 months
Overton 2015 USA	USA	HIV-positive men and women	0%[4]	26.7 (median) 25.1 (median)	346 (median) 337 (median)	4.5	4000 IU	Daily for 48 weeks (plus 100 mg calcium)

Table 15. Characteristics of trials evaluating Vitamin D supplements versus placebo *(Continued)*

Stallings 2014 USA	USA	HIV-positive; ≤ 25 years	76%	18.2 (8.4) 17.7 (9)	Not reported[5]	3.17 (0.96)[6]	7000 IU	Daily for 12 months
Wejse 2009 GNB	Guinea-Bissau	HIV-positive plus active TB	0%	Not reported for HIV-positive participants	Not reported for HIV-positive participants	Not reported	100,000 IU	Single dose at baseline, 5, 8 months

Abbreviations: ART: antiretroviral therapy; IU: International units; TB: Tuberculosis
[1]Reference value for vitamin D sufficiency: 25 (OH) vitamin D ≥ 30 ng/mL.
[2]RDA for a male aged 19 to 70 years ranges between 5 to 15 µg (200 to 600 IU) daily.
[3]Giacomet 2013 ITA: only participants with low blood vitamin D concentrations were included in the trial (25(OH)D < 30 ng/mL).
[4]Overton 2015 USA: all trial participants were intiated on ART at baseline.
[5]Stallings 2014 USA: 62% of partcipants had a CD4 cell count > 500 cells/mm^3.
[6]Stallings 2014 USA: 44% of trial participants presented with a detectable viral load at baseline (vitamin D group:13, placebo group: 11).

Table 16. Change in CD4 cell count (cells/mm^3): vitamin D versus placebo

Trial ID	Statistical measure	Baseline			Endpoint			Timing of endpoint	Difference between groups at endpoint (as reported by trial authors)
		Intervention	Control	N[1]	Intervention	Control	N[1]		
Bang 2012 DEN	Mean (SD)	507 (268)	463 (197)	17	Not reported	Not reported	15	16 weeks	"No changes" in naïve or activated CD4+ cell counts
Giacomet 2013 ITA	Median	15	15	25	Not reported	Not reported	25	12 months	MD 58.1 (−114.5 to 230.7)[2]
Overton 2015 USA	Median	346	342	79	551[3]	526[3]	86	48 weeks	P = 0.90
Wejse 2009 GNB	Mean	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported	8 months	MD −22 (P = 0.17)[4]

Abbreviations: MD: Mean difference; SD: Standard deviation
[1]The number of participants stated is the number assessed for endpoint data.
[2]Giacomet 2013 ITA: the trial authors also reported no difference in CD4+ cell count at 3, 6, and 9 months.
[3]Overton 2015 USA: the trial authors reported an increase in CD4+ cell count within both treatment groups (P > 0.001).
[4]Wejse 2009 GNB: subset of 41 HIV-positive participants who had CD4+ cell counts at baseline and endpoint.

Table 17. Change in nutritional status parameters: vitamin D versus placebo

Trial ID	Nutritional parameter	Statistical Measure	Intervention			Control			Timing of endpoint	Difference between groups at endpoint (as reported by trial authors)
			Baseline	Endpoint	N[1]	Baseline	Endpoint	N[1]		
Bang 2012 DEN[2]	25 (OH) vitamin D (ng/mL)[2]	Mean (SD)	27.2 (11.5)	31.6 (9.9)	17	29.2 (12.4)	19.2 (13.9)	15	16 weeks	P < 0.001
Giacomet 2013 ITA[2]	25 (OH) vitamin D (ng/mL)[2]	Median	15	Not reported	25	15	Not reported	25	12 months	MD 12.5 (5.9 to 19) P < 0.001
Overton 2015 USA[2]	25 (OH) vitamin D (ng/mL)[2]	Median	26.7	56.4	79	25.1	26.2	86	48 weeks	P < 0.001
Stallings 2014 USA[2]	25 (OH) vitamin D (ng/mL)[2]	Mean (SD)	10.3 (6.4)	17 (13.1)	30	11.3 (7.6)	10.5 (6.2)	28	12 months	P < 0.001

Abbreviations: MD: Mean difference; SD: Standard deviation
[1]The number of participants stated is the number assessed for end-point data.
[2]Analysis of blood micronutrient concentrations did not include adjustment for biomarkers of inflammation.

Table 18. Characteristics of trials evaluating zinc supplements versus placebo

Trial ID	Country	Participants	Baseline ART use	Mean baseline blood zinc concentration (µg/L)[1]	Mean baseline CD4+ cell count (cells/mm^3)	Mean baseline viral load (copies/mL or $\log_{10}$ copies/mL)	Dose[2]	Duration of supplementation

Table 18. Characteristics of trials evaluating zinc supplements versus placebo (*Continued*)

Asdamongkol 2013 THA[3]	Thailand	HIV-positive	100% with immunological discordance	80 (median) 76 (median)	183 (median) 162 (median)	Not reported	15 mg daily	6 months
Baum 2010 USA	USA	HIV-positive	62%[4]	60 (10)[5]	373 (280)	4.0 (1.0)	12 mg (women) 15 mg (men)	18 months
Cárcamo 2006 PER	Peru	HIV-positive plus persistent diarrhoea	0%	66 (median) 65 (median)	65 (median) 55 (median)	Not reported	50 mg twice daily	14 days
Green 2005 SGP	Singapore	HIV-positive	95%	86.9 (15.0) 92.2 (18.3)	112 (62) 131 (65)	26 338 (38 335) 28 093 (41 056	50 mg daily	28 days
Lawson 2010 NIG	Nigeria	HIV-positive plus active TB	0%	Not reported	Not reported	Not reported	90 mg weekly[6]	6 months
Range 2006 TZA	Tanzania	HIV-positive plus active TB	0%	Not reported	406 (median) 460 (median)	3.83 (median) 3.90 (median)	45 mg daily	8 months

Abbreviations: ART: Antiretroviral therapy; RDA: Recommended Daily Allowance; TB: Tuberculosis

[1]Reference value for zinc sufficiency: > 70 µg/L.

[2]RDA for a male aged 18 to 70 years is 11 mg daily.

[3]Asdamongkol 2013 THA: the trial authors stratified participants with or without low blood zinc concentrations and randomized them to receive zinc or placebo.

[4]Baum 2010 USA: proportion of trial participants who were on ART and had an undetectable viral load at baseline: 30%

[5]Baum 2010 USA: the trial authors excluded participants with normal baseline blood zinc levels (≥ 75 µg/L)

[6]Lawson 2010 NIG: the trial authors randomized participants to receive either weekly doses of zinc (90 mg) and vitamin A (5000 IU), zinc (90 mg) and placebo, or a dual placebo.

Table 19. Change in CD4 count (cells/mm^3) : zinc versus placebo

Trial ID	Statistical measure	Intervention			Control			Timing of endpoint	Difference between groups at endpoint (as reported by trial authors)
		Baseline	Endpoint	N[1]	Baseline	Endpoint	N[1]		

Table 19. Change in CD4 count (cells/mm^3) : zinc versus placebo (*Continued*)

Asdamongkol 2013 THA	Median (IQR)	183 (151 to 213)	250 (190 to 286)	13	162 (139 to 182)	192 (162 to 254)	[17]	6 months	Supplementation increased median CD4+ in those with low zinc at baseline (P = 0.042) but not those with normal zinc (P > 0.05)
Baum 2010 USA	Mean (SD)	385 (285)	Not reported	104	361 (275)	Not reported	96	18 months	Reduced risk of CD4+ < 200 cells/μL [2] with intervention (RR 0.24, 95% CI 0.10 to 0.56)
Cárcamo 2006 PER	Median	66	Not reported	-	65	Not reported	-	-	Not reported
Green 2005 SGP	Mean (SD)	113 (61)	127 (73)	30	134 (63)	156 (75)	33	28 days	P = 0.91
Range 2006 TZA	Mean (95% CI)	406 (327 to 485)	422 (331 to 512)	58	460 (351 to 569)	403 (309 to 569)	48	2 months	"Not significant"

Abbreviations: CI: Confidence interval; IQR: Interquartile range; RR: Relative risk; SD: Standard deviation
[1]The number of participants stated is the number assessed for endpoint data.

Table 20. Change in viral load (copies/mL or log_{10} copies/mL): zinc versus placebo

Trial ID	Statistical measure	Intervention			Control			Timing of endpoint	Difference between groups at endpoint (as reported by trial authors)
		Baseline	Endpoint	N[1]	Baseline	Endpoint	N[1]		
Baum 2010 USA	Mean (SD)	4.0 (1.0)	Not reported	115	4.0 (1.1)	Not reported	116	18 months	"Not affected by supplementation"
Green 2005 SGP	Mean (SD)	24,740 (36,856)	27,652 (39,418)	30	26,286 (40,297)	24,551 (39,013)	33	28 days	P = 0.26

Table 20. Change in viral load (copies/mL or log_{10} copies/mL): zinc versus placebo (*Continued*)

Range 2006 TZA	Mean (95% CI)	3.83 (3.52 to 4.15)	4.28 (3.86 to 4.71)	58	3.9 (3.53 to 4.27)	4.1 (3.67 to 4.54)	48	2 months	"Not significant"

Abbreviations: CI: Confidence interval; SD: Standard deviation; TB: Tuberculosis
[1]The number of participants stated is the number assessed for endpoint data.

Table 21. Changes in nutritional status parameters: zinc versus placebo

Trial ID	Nutritional parameter	Statistical Measure	Intervention			Control			Timing of endpoint	Difference between groups at endpoint (as reported by trial authors)
			Baseline	Endpoint	N[1]	Baseline	Endpoint	N[1]		
Asdamongkol 2013 THA[2,3]	Blood zinc (µg/L)	Median (IQR)	80 (66 to 87)	82 (71 to 100)	13	76 (66 to 88)	74 (69 to 82)	17	6 months	"higher after zinc supplementation, particularly in patients with low plasma zinc levels at baseline"
Baum 2010 USA	Blood zinc (µg/L)	Mean (SD)	40 (10)	Not reported	Not reported	40 (11)	Not reported	Not reported	18 months	Adjusted [4] regression coefficient ß = 0.04; P = 0.0472
Cárcamo 2006 PER[5]	Blood zinc (µg/L)	Median	66	Not reported	Not reported	65	Not reported	Not reported	14 days	Not reported[5]
Green 2005 SGP[5]	Blood zinc (µg/L)	Mean (SD)	92.2 (18.3)	120.3 (68.0)	30	86.9 (15)	111.8 (37.9)	33	28 days	P = 0.67

Abbreviations: IQR: Interquartile range; SD: Standard deviation

[1]The number of participants stated is the number assessed for endpoint data.
[2]Asdamongkol 2013 THA: participants with or without low blood zinc concentrations were stratified and randomized to receive zinc or placebo.
[3]Analysis of blood micronutrient concentrations did not include adjustment for biomarkers of inflammation.
[4]Baum 2010 USA: regression coefficient adjusted for C-reactive protein levels (biomarker for inflammation).
[5]Cárcamo 2006 PER: the trial authors reported a smaller proportion of participants in the supplemented group with low zinc levels after 14 days of follow-up (65.6% versus 93.7%; P = 0.01).

Table 22. Characteristics of trials evaluating selenium supplements versus placebo

Trial ID	Country	Participants	Baseline ART use	Mean baseline blood selenium concentration (µg/l)[1]	Mean baseline CD4+ cell count (cells/mm^3)	Mean baseline viral load (copies/mL or $\log_{10}$ copies/mL)	Dose[2]	Duration of supplementation (months)
Baum 2013 BWA	Botswana	HIV-positive	0 %	65 (10) 70 (24)[3]	423 (median)	18 500 (median)	200 µg daily	24 months
Burbano 2002 USA	USA	HIV-positive IDUs	Combination therapy 21% HAART 46%[3]	Not reported [5]	427 (421) 378 (295)	55,257 (147, 152) 60,905 (144, 292)	200 µg daily	12 months
Hurwitz 2007 USA	USA	HIV-positive	73%	Not reported [6]	417 (264) 441 (266)	24,558 (87, 051) 10,491 (20, 251)	200 µg daily	9 months
Kamwesiga 2015 RWA	Rwanda	HIV-positive	0%[7]	Not reported	552 (median) 527 (median)	3.8 (median) 3.9 (median)	200 µg daily	24 months

Abbreviations: ART: antiretroviral therapy; HAART: Highly active antiretroviral therapy; IDUs: injection drug users.
[1]Reference values used to define selenium sufficiency: > 75 µg/L or > 85 µg/L
[2]RDA for a male aged 18 to 70 years is 55 µg daily.
[3]Sales 2010 BWA in Baum 2013 BWA: Baseline selenium concentrations reported for a sub-sample of 79 trial participants.
[4]Burbano 2002 USA: the trial authors reported fewer ARV naive participants in the selenium group (24%) compared to the placebo group (37%) at baseline.
[5]Burbano 2002 USA: participants with low baseline blood selenium levels (≤ 85 µg/L) were excluded from the trial.
[6]Hurwitz 2007 USA: participants with low baseline blood selenium levels (≤ 75 µg/L) were excluded from the trial.
[7]Kamwesiga 2015 RWA: participants who were eligible for ART were excluded from the trial.

Table 23. Change in CD4 cell count (cells/mm^3): selenium versus placebo

Trial ID	Statistical measure	Intervention			Control			Timing of endpoint	Difference between groups at endpoint (as reported by study authors)
		Baseline	Endpoint	N[1]	Baseline	Endpoint	N[1]		
Baum 2013 BWA	Median (IQR)	423 (347 to 539)	Not reported	220	411 (327 to 545)	Not reported	217	2 years	Not reported[2]
Burbano 2002 USA	Mean (SD)	427(421)	Not reported	Not reported	376(295)	Not reported	Not reported	12 months	Not reported[3]
Hurwitz 2007 USA	Mean (SD)	417 (264)	Not reported	Not reported	441 (266)	Not reported	Not reported	9 months	Not reported[4]
Kamwesiga 2015 RWA	Median (IQR)	552 (470 to 636)	Not reported	149	527 (465 to 610)	Not reported	151	24 months	Not reported[5]

Abbreviations: CI: confidence interval; HR: hazard ratio; IQR: interquartile range; RR: risk ratio; SD: standard deviation

[1]The number of participants stated is the number assessed for endpoint data.

[2]Baum 2013 BWA: the trial authors reported no reduction in risk of CD4+ falling to < 250 cells/μL^2 (HR 0.83, 95% CI 0.48 to 1.42).

[3]Burbano 2002 USA: the trial authors reported that 46% of participants in the placebo group versus 25% in the selenium group experienced a decline in CD4 cell count > 50 cells/mm^3 (P = 0.01).

[4]Hurwitz 2007 USA: the trial authors reported in a multiple regression model that increased selenium levels predicted a greater decrease in viral load (P < 0.02), which predicted a greater increase in CD4 counts (P < 0.04).

[5]Kamwesiga 2015 RWA: the trial authors reported a 44 % reduction in the rate of CD4+ cell decline per month (MD 1.74, 95% CI 0.31 to 3.17). No reduction in risk of CD4+ falling to < 350 cells/μL^2 (RR 0.81, 95% CI 0.61 to 1.09).

Table 24. Change in nutritional status parameters: selenium versus placebo

Trial ID	Nutritional parameter	Statistical measure	Intervention			Control			Timing of endpoint	Comment
			Baseline	Endpoint	N[1]	Baseline	Endpoint	N[1]		
Burbano 2002 USA[2]	Blood selenium (μg/L)	-	Not reported	Not reported	-	Not reported	Not reported	Not reported	12 months	Not reported [3]

Table 24. Change in nutritional status parameters: selenium versus placebo *(Continued)*

Hurwitz 2007 USA[2]	Blood selenium (µg/L)	-	Not reported	Not reported	83	Not reported	Not reported	91	9 months	MD 31.7 (27.4 to 36); P<0.001
Kamwesiga 2015 RWA	Blood selenium (µg/L)	-	Not reported	Not reported	-	Not reported	Not reported	-	24 months	-
Sales 2010[2]	Blood selenium (µg/L)[4]	Mean (SD)	65 (10)	147 (15.3)	33	70 (24)	69 (12.1)	46	6 months	P<0.001

Abbreviations: MD: Mean difference; SD: Standard deviation
[1]The number of participants stated is the number assessed for endpoint data.
[2]Analysis of blood micronutrient concentrations did not include adjustment for biomarkers of inflammation.
[3]Burbano 2002 USA: the trial authors reported proportions of participants with blood selenium levels < 135 µg/L at the end of the trial: 89% versus 47% (P = 0.001).
[4]Sales 2010: data reported on a subsample of trial participants from the trial by Baum 2013 BWA.

WHAT'S NEW

Last assessed as up-to-date: 18 November 2016.

Date	Event	Description
16 May 2017	New search has been performed	We included 17 new trials in this review update, and assessed the certainty of the evidence using the GRADE approach. Nigel Rollins stepped down from the review author team. Solange Durao and David Sinclair joined as review authors
16 May 2017	New citation required and conclusions have changed	The original protocol for this review included studies in both HIV-positive children and pregnant women (Irlam 2002) . Two separate reviews on the role of micronutrient supplementation for HIV-positive pregnant women, Siegfried 2012, and children, Irlam 2013, have been published. The primary focus of this review update was therefore on the role of micronutrient supplementation in HIV-positive men and women who were not pregnant

HISTORY

Protocol first published: Issue 4, 2003

Review first published: Issue 4, 2005

Date	Event	Description
3 June 2011	Amended	Paragraph added about the review being split into three reviews
19 January 2011	Amended	External source of support added.
9 November 2010	New citation required and conclusions have changed	Substantial update of the review.
9 November 2010	New search has been performed	Substantial update.
9 November 2010	Feedback has been incorporated	External reviewers' feedback incorporated into update
30 September 2010	New search has been performed	Inclusion of 16 additional trials, assessment of Risk of Bias using new ROB tool, and extensive updating of text

CONTRIBUTIONS OF AUTHORS

Marianne Visser (MV) initiated the review update and contributed to all stages of the review.

Solange Durao (SD) contributed to all stages of the review update.

David Sinclair (DS) contributed to the preparation of the review update for submission.

James Irlam (JI) commented on the report of the review update.

Nandi Siegfried (NS) assisted with study selection and commented on the review update.

DECLARATIONS OF INTEREST

Marianne Visser (MV) has no known conflicts of interest.

Solange Durao (SD) has no known conflicts of interest.

David Sinclair (DS) has no known conflicts of interest.

James Irlam (JI) has no known conflicts of interest.

Nandi Siegfried (NS) has provided consultancies to several World Health Organization (WHO) guidelines processes within the HIV department including nutritional interventions.

SOURCES OF SUPPORT

Internal sources

- SACC HIV/AIDS Mentoring Programme, South Africa.
- South African Cochrane Centre, South Africa.
- Medical Research Council, South Africa.
- Liverpool School of Tropical Medicine, UK.

External sources

- Department for International Development, UK.

Grant: 5242

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The original protocol for this review included studies in both HIV-positive children and pregnant women (Irlam 2002). Two separate reviews on the role of micronutrient supplementation for HIV-positive pregnant women, Siegfried 2012, and children, Irlam 2013, have been published. The primary focus of this review update was therefore on the role of micronutrient supplementation in HIV-positive men and women who were not pregnant.

INDEX TERMS

Medical Subject Headings (MeSH)

*Dietary Supplements; *HIV Infections [complications; mortality]; HIV-1; HIV-2; Micronutrients [*administration & dosage; deficiency]; Pregnancy Complications, Infectious [mortality]; Randomized Controlled Trials as Topic; Selenium [administration & dosage]; Vitamin A [administration & dosage]; Vitamin D [administration & dosage]; Vitamins [administration & dosage]; Zinc [administration & dosage]; beta Carotene [administration & dosage]

MeSH check words

Adult; Child; Female; Humans; Pregnancy