Micronutrient supplementation in children and adults with HIV infection (Review)

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[Intervention Review]

Micronutrient supplementation in children and adults with HIV infection

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ABSTRACT

Background

Micronutrient deficiencies are widespread and compound the effects of HIV disease; micronutrient supplements may be effective and safe in reducing this burden.

Objectives

To assess whether micronutrient supplements are effective and safe in reducing mortality and morbidity in adults and children with HIV infection.

Search strategy

The CENTRAL, EMBASE, PubMed, and GATEWAY databases were searched for randomised controlled trials of micronutrient supplements using the search methods of the Cochrane HIV/AIDS Group.

Selection criteria

Randomised controlled trials were selected that compared the effects of micronutrient supplements (vitamins, trace elements, and combinations of these) with other supplements, placebo or no treatment on mortality, morbidity, pregnancy outcomes, immunologic indicators, and anthropometric measures in HIV-infected adults and children. Any adverse effects of supplementation were recorded.

Data collection and analysis

Two reviewers independently selected trials, appraised trial quality for risk of bias using standardised criteria, and extracted data using standardised forms.

Main results

Sixteen additional trials are included in this update to the original Cochrane review (Irlam 2005). Overall, 30 trials involving 22 120 participants are reviewed: 20 trials of single supplements (vitamin A, vitamin D, zinc, selenium) and 10 of multiple micronutrients. Eight trials were undertaken in child populations.

None of the six trials of vitamin A or beta-carotene supplementation in adults demonstrated any significant reduction in HIV disease progression. Vitamin A halved all-cause mortality in a meta-analysis of three trials in African children, had inconsistent impacts on diarrhoeal and respiratory morbidity, and improved short-term growth in one trial. No significant adverse effects of vitamin A in adults or children have been reported.

Zinc supplements reduced diarrhoeal morbidity and had no adverse effects on disease progression in a single safety trial in South African children. No significant clinical benefits were found from zinc supplementation of pregnant Tanzanian women or Peruvian adults with persistent diarrhoea.

Selenium reduced diarrhoeal morbidity in pregnant women in Tanzania, and reduced viral load in two separate small trials in American adults.

Single trials of vitamin D supplements in adults, and in adolescents and children, demonstrated safety but no clinical benefits.

Multiple micronutrient supplements conferred multiple clinical benefits to pregnant women and their offspring in a large Tanzanian trial. Supplementation in another Tanzanian trial reduced the recurrence of pulmonary TB and increased weight gain in co-infected patients. No significant adverse effects were reported.

Authors' conclusions

Multiple micronutrient supplements reduced morbidity and mortality in HIV-infected pregnant women and their offspring and also improved early child growth in one large randomised controlled trial in Africa. Additional research is needed to determine if these are generalisable findings. Vitamin A supplementation is beneficial and safe in HIV-infected children, but further evidence is needed to establish if supplementation confers similar benefits in HIV-infected adults. Zinc is safe in HIV-infected adults and children. It may have similar benefits in HIV-infected children and adults, and uninfected children with diarrhoea, as it does in HIV-uninfected children.

Further trials of single supplements (vitamin D, zinc, and selenium) are required to build the evidence base. The long-term clinical benefits, adverse effects, and optimal formulation of multiple micronutrient supplements require further investigation in individuals with diverse disease status.

PLAIN LANGUAGE SUMMARY

Micronutrient supplementation for children and adults with HIV infection

Multiple micronutrient supplements offer some benefits and are safe in HIV-infected pregnant women and their offspring. Vitamin A and zinc supplements are beneficial and safe in HIV-exposed and HIV-infected children. Further research is needed to build the evidence base for single supplements in adults and children in diverse settings.

BACKGROUND

Description of the condition

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 two thirds of all people living with HIV worldwide, an estimated 22.4 million in 2008, 1.8 million of whom are children under 15 years of age. The estimated prevalence of adult HIV in the region is 5.2% [4.9%; 5.4%] (UNAIDS 2009). It is estimated that HIV-related deaths account for about 14% of all child deaths in southern Africa (Black 2010).

Malnutrition takes many forms, but in sub-Saharan Africa it most commonly refers to inadequate protein and energy intake (protein energy malnutrition or PEM), usually with associated multiple

micronutrient insufficiency. Micronutrient deficiencies are common in HIV-infected children and adults, particularly in developing communities where diets are frequently inadequate to meet the recommended daily requirements. They are also 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 (ASSAf 2007).

Observational studies have suggested that both PEM and micronutrient deficiencies may hasten the progression of HIV infection, and that HIV worsens malnutrition. HIV infection and malnutrition therefore form a "vicious cycle" of immune dysfunction, infectious disease, and malnutrition (Piwoz 2000; Semba 1999).

Micronutrient supplements are either single or multiple formulations of vitamins and trace elements that have multiple functions including immune regulation and facilitating the body's utilisation of the macronutrients (carbohydrates, fats, and proteins) for energy and growth. It has been shown that supplementation can correct micronutrient deficiency states in malnourished HIV-infected individuals (Baeten 2002b; Fawzi 1998). Widespread supplementation may lessen the effects of concurrent micronutrient deficiency and help to reduce the morbidity and mortality due to HIV (Semba 1999), which is particularly significant for developing countries where nutritional deficiencies are common (ASSAf 2007; Micronutrient Initiative 2009).

Why it is important to do this review

A previous version of this Cochrane review included 16 trials in 7 countries based on a July 2004 search (Irlam 2005), and found no conclusive evidence that micronutrient supplementation effectively reduces or increases morbidity and mortality in HIV-infected adults. Vitamin A was found to be beneficial for HIV-infected children.

The HIV/AIDS pandemic has had a major impact on global health, nutrition, and overall socio-economic 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.

OBJECTIVES

To assess whether micronutrient supplements are effective and safe in reducing mortality and morbidity in adults and children with HIV infection.

METHODS

Criteria for considering studies for this review

Types of studies

All randomised controlled trials (RCTs) of micronutrient supplements compared with other supplements, placebo, or no treatment.

Types of participants

Adults and children with confirmed HIV infection (as reported in the trials) were included. No differentiation was made between HIV-exposed and HIV-infected infants.

HIV-infected pregnant women receiving vitamin A supplements were excluded as others have reviewed these trials (Kongnyuy 2009; Wiysonge 2005).

Types of interventions

Micronutrient supplements include 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), and combinations of the above only.

Types of outcome measures

Primary outcomes

The primary outcomes considered were mortality, morbidity, hospitalisations, and pregnancy outcomes.

Secondary outcomes

The secondary outcomes were indicators of HIV disease progression (viral load, T cell counts) and anthropometric measures.

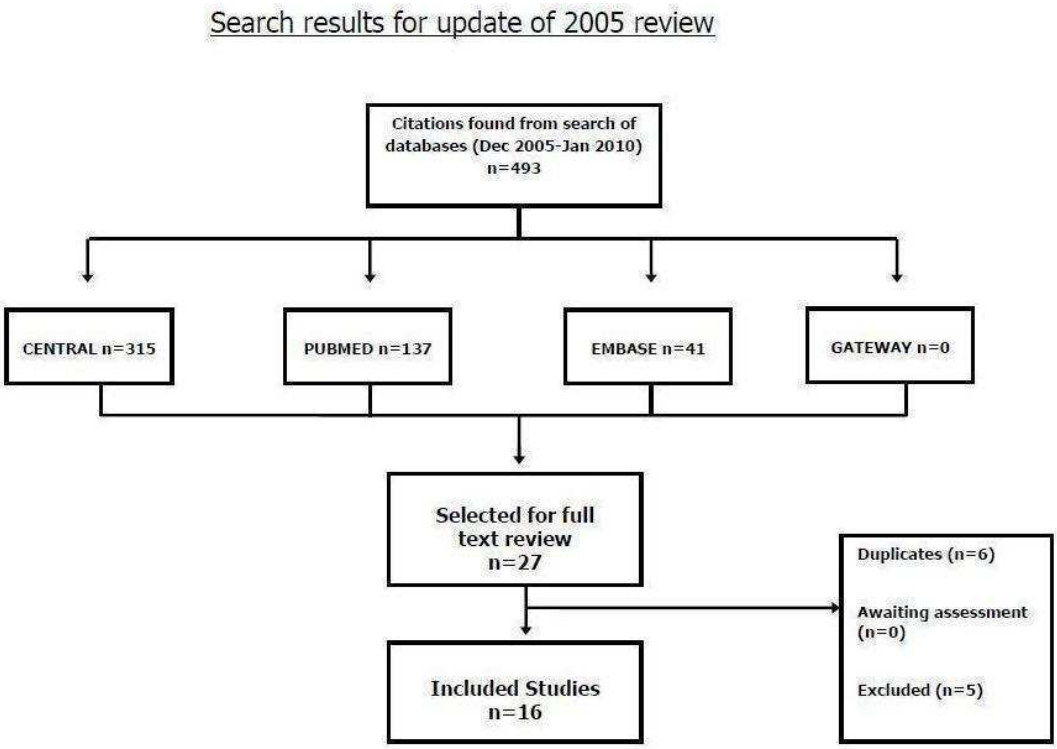
All adverse effects of supplementation were also considered.

Search methods for identification of studies

Periodic search updates to identify studies additional to the original review (Irlam 2005) were undertaken in December 2005, February 2007, April 2008, June 2009, and January 2010 of the CENTRAL, EMBASE, PUBMED, and GATEWAY databases, using the search methods of the Cochrane HIV/AIDS Group. Conference abstracts were not searched and no unpublished data were included. There were no language restrictions to the search.

The full search strategies for each of the databases above are presented in Appendices 1 to 4, and the flowchart of search results is in Figure 1.

Figure 1.



Data collection and analysis

Selection of studies

Three of the authors (JI, MV and NR) independently selected and appraised the papers for inclusion in the original review (Irlam 2005). JI and MV did the selection of studies for the review update.

Data extraction and management

Two of the authors (JI and MV) independently extracted data from the included studies using a data extraction form in the original review (Irlam 2005). Two of the authors (NS and NR) helped to resolve any queries about the papers. The extraction form was modified for the review update and completed independently by JI and CN for all studies in the original and updated review. Data were entered into the Review Manager 5 software.

Assessment of risk of bias in included studies

The risk of bias in the included studies was assessed independently by two authors (JI and NS) as high, low, or unclear using the six domains recommended by the Cochrane Collaboration 'Risk of bias' tool. These domains are sequence generation, allocation concealment (both described under Allocation below), blinding, incomplete outcome data, selective outcome reporting, and other potential sources of bias. The assessments are presented in the 'Risk of bias' tables and are summarised in Figure 2 and Figure 3.

Figure 2. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.

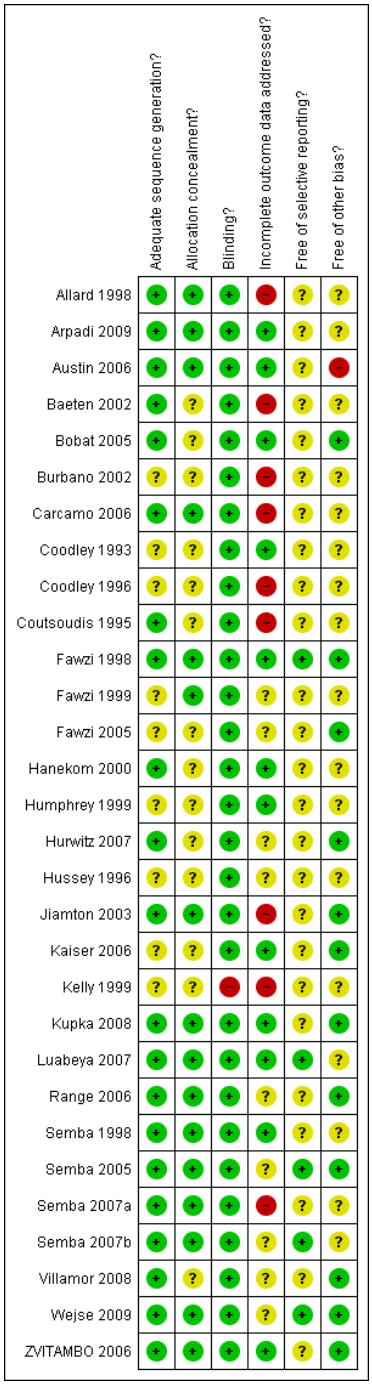
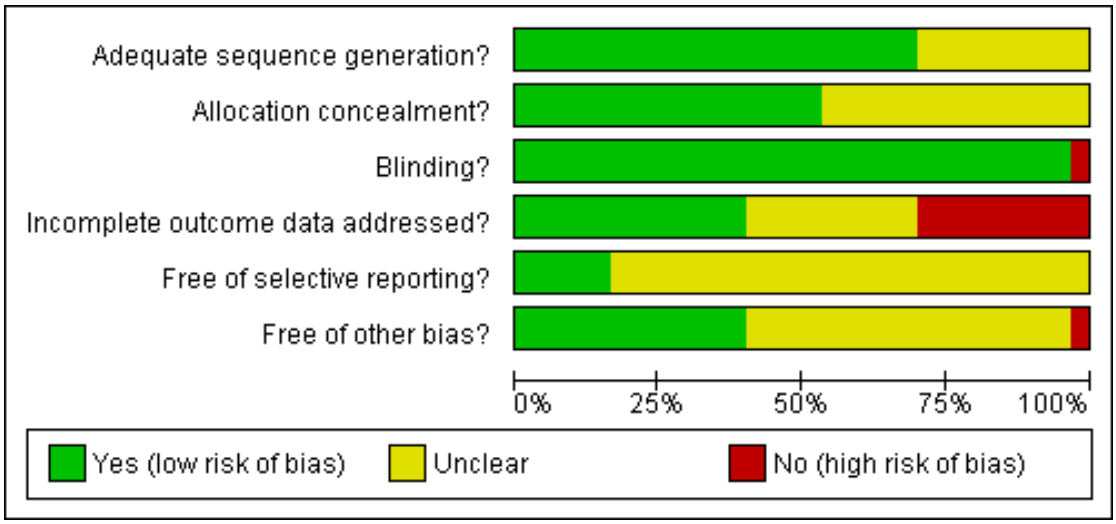


Figure 3. Methodological quality graph: review authors' judgements about each methodological quality item presented as percentages across all included studies.



Measures of treatment effect

The measures of treatment effect used were the risk ratio (RR) for dichotomous data, the weighted mean difference (WMD) for continuous data measured on the same scale, and the standardised mean difference (SMD) for continuous data measured on different scales, presented with 95% confidence intervals. Review Manager 5 and GradePro (GradePro 2008) software were used to produce Summary of Findings and Evidence Profile tables.

Dealing with missing data

Authors were not contacted for data that were missing from the included studies, with the exception of the ZVITAMBO study where clarity about the statistical analyses was sought.

Assessment of heterogeneity

Studies were first assessed for clinical heterogeneity by examining variability in the participants, interventions and outcomes. Statistical heterogeneity was assessed visually and by means of the chi-squared test for heterogeneity. Inconsistency across the studies in the meta-analysis was quantified by means of the I-squared statistic included in the Review Manager forest plots.

Data synthesis

Random effects meta-analyses were performed by JI and checked by a second author if it was agreed that the studies were sufficiently homogeneous.

Subgroup analysis and investigation of heterogeneity

Subgroup analyses were planned according to the intervention of interest (single supplements of vitamin A, D, zinc, or selenium, or multiple supplements) and whether it was performed in adults or children.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting classification.

Results of the search

The PRISMA flow diagram (Figure 1) summarises the results of the search.

Sixteen additional trials were included in this update to the original review (Irlam 2005). Overall, 30 trials involving 22 120 participants are included: 20 trials of single supplements (vitamin A, vitamin D, zinc, selenium) and ten of multiple micronutrients. Eight of the 30 trials were undertaken in child populations.

Included studies

Details of the included studies are reported in the table Characteristics of included studies.
They are grouped as follows by intervention in the description of the Effects of the interventions below:

- Vitamin A (6 trials in adults; 14 763 participants: Baeten 2002; Coodley 1993; Coodley 1996; Humphrey 1999; Semba 1998; ZVITAMBO 2006; 5 trials in children; 1120 participants: Coutsoudis 1995; Fawzi 1999; Hanekom 2000; Hussey 1996; Semba 2005)

- Vitamin D (1 trial in adults; 365 participants: Wejse 2009; 1 trial in children; 59 participants: Arpadi 2009)

- Zinc (2 trials in adults; 559 participants: Carcamo 2006; Fawzi 2005; 2 trials in children; 128 participants: Bobat 2005; Luabeya 2007)

- Selenium (3 trials in adults; 1361 participants: Burbano 2002; Hurwitz 2007; Kupka 2008)

- Multiple supplements (9 trials in adults; 2687 participants: Allard 1998; Austin 2006; Jiamton 2003; Kaiser 2006; Kelly 1999; Range 2006 (pulmonary tuberculosis patients); Semba 2007a (women injectable drug users); Semba 2007b (PTB patients); Villamor 2008 (PTB patients); 1 trial in pregnant and lactating women; 1078 participants: Fawzi 1998)

Excluded studies

Five studies were excluded due to inadequate methodological quality, use of interventions that were not exclusively micronutrients, or study outcomes that were not eligible for this review. See Characteristics of excluded studies.

Risk of bias in included studies

The Risk of Bias (ROB) tables (see Characteristics of included studies) provide the authors' judgements and comment on the risk of bias in each study (high, low, or unclear) with respect to each of the six domains described above. Figure 2 and Figure 3 present an overall graphical summary of the ROB assessments.

Allocation

Allocation refers to the generation of the random allocation sequence as well as concealment of the allocation code.
The methods of generating the random allocation sequence were sufficiently well described in three vitamin A trials in adults (Baeten 2002; Semba 1998; ZVITAMBO 2006) and judged to be at low risk of bias. The methods were too unclear in the remaining three studies (Coodley 1993; Coodley 1996; Humphrey 1999) to permit other than a judgement of "unclear" risk of bias. Allocation concealment was judged adequate in two studies (Semba 1998; ZVITAMBO 2006), and unclear in the remaining four (Baeten 2002; Coodley 1993; Coodley 1996; Humphrey 1999).
Three placebo-controlled vitamin A trials in children (Coutsoudis 1995; Hanekom 2000; Semba 2005) adequately described methods of randomisation. Two reported that allocation was adequately concealed (Fawzi 1999; Semba 2005).
One trial of vitamin D in adults and one of vitamin D in children were included. Both vitamin D trials used adequate random allocation to vitamin D or placebo; and allocation concealment was adequately described in both trials (Arpadi 2009; Wejse 2009).
Of the two trials of zinc in adults, random sequence generation was judged adequate in one (Carcamo 2006) and unclear in the other (Fawzi 2005). Allocation concealment was unclear in the Fawzi trial (Fawzi 2005) and adequate in the other trial (Carcamo 2006). Randomisation was adequately described in the two zinc trials in children; allocation concealment was judged unclear in one (Bobat 2005).
Of the three selenium studies, one (Burbano 2002) was unclear about the method of randomisation and allocation concealment, and another (Hurwitz 2007) was clear about randomisation but unclear about allocation concealment. The third trial was well reported and judged to have a low risk of bias in this domain (Kupka 2008).

Blinding

Blinding of patients, treatment providers and outcome assessors was judged adequate in all studies with the exception of one trial in adults with persistent diarrhoea (Kelly 1999). A multiple supplement was compared to a non-identical placebo, and it was unclear whether providers and assessors were blinded.

Incomplete outcome data

Four (Coodley 1993; Humphrey 1999; Semba 1998; ZVITAMBO 2006) of the six vitamin A trials in adults were judged to have adequately addressed incomplete outcome data. Incomplete outcome data was adequately addressed in one vitamin A trial (Hanekom 2000) in children, judged inadequate (i.e. at high risk of bias) in another (Coutsoudis 1995), and unclear in the remaining three trials (Fawzi 1999; Hussey 1996; Semba 2005).
One vitamin D trial (Arpadi 2009) adequately addressed incomplete outcome data while the other (Wejse 2009) did not.

Of the selenium studies, one trial (Kupka 2008) adequately addressed incomplete outcome data, one did not (Burbano 2002), and the judgment was "unclear" for the third (Hurwitz 2007).
Incomplete outcome data were adequately addressed in both zinc trials in children (Bobat 2005; Luabeya 2007), was unclear in one zinc trial in adults (Fawzi 2005), and not adequately addressed in the second zinc trial in adults (Carcamo 2006).
Incomplete outcome data was judged to be adequately addressed in two of the multi-nutrient supplement trials (Fawzi 1998; Kaiser 2006), judged "unclear" in another four (Austin 2006; Range 2006; Semba 2007b; Villamor 2008), and considered inadequately addressed in the remaining four (Allard 1998; Jiamton 2003; Kelly 1999; Semba 2007a).

Selective reporting

Insufficient information was provided to permit judgment of the extent of bias due to selective reporting of outcomes in all but 5 (Fawzi 1998; Luabeya 2007; Semba 2005; Semba 2007b; Wejse 2009) of the included studies.

Other potential sources of bias

Twelve trials (Bobat 2005; Fawzi 1998;Fawzi 2005; Hurwitz 2007; Jiamton 2003; Kaiser 2006; Kupka 2008; Range 2006; Semba 2005; Villamor 2008; Wejse 2009; ZVITAMBO 2006) were judged to be free of other biases, one trial (Austin 2006) was judged as not adequately free of other bias (stopped early due to interruption in the supply of medicine).
The judgement was "unclear" for the remaining seventeen trials; sixteen did not declare on potential conflicts of interest (Allard 1998; Arpadi 2009; Baeten 2002; Burbano 2002; Carcamo 2006; Coodley 1993; Coodley 1996; Coutsoudis 1995; Fawzi 1999; Hanekom 2000; Humphrey 1999; Hussey 1996; Kelly 1999; Semba 1998; Semba 2007a; Semba 2007b) and one (Luabeya 2007) experienced a delay in shipment which prevented 243 children from receiving their supplements for eleven weeks.
All but eleven trials (Allard 1998; Austin 2006; Burbano 2002; Coodley 1993; Coodley 1996; Hanekom 2000; Humphrey 1999; Hussey 1996; Jiamton 2003; Kaiser 2006; Kelly 1999) were funded either fully or partly from government sources; four were fully or partly funded by pharmaceutical companies (Coodley 1993; Kaiser 2006; Kelly 1999; Jiamton 2003); and the source of funding was not provided in two trials (Hanekom 2000; Hussey 1996).

Effects of interventions

Vitamin A in adults

Six trials of vitamin A in adults were included with a total of 14 763 participants, including both HIV-infected and uninfected subjects.
The majority of these came from a large Zimbabwean trial by the ZVITAMBO Study Group (ZVITAMBO 2006), which used a factorial design to compare the effect of four postpartum regimens of single large-dose maternal (400 000 IU) and infant (50 000 IU) vitamin A supplements versus placebo among 14 110 mother-infant pairs, which included 4495 HIV-infected mothers. Thirty percent of these mothers were vitamin A deficient, as indicated by serum retinol concentrations less than 1.05 micromol/L at 6 weeks.
This study found no effect on overall child mortality between baseline and 24 months. However, in HIV-exposed infants who were HIV-negative at baseline and HIV-infected at 6 weeks there was a 28% reduction in mortality (p=0.01); in HIV-exposed infants who were HIV-negative at 6 weeks of age there was approximately double the mortality in supplemented infants (p<=0.05).
There was no effect of vitamin A supplementation on morbidity among the HIV-positive women as measured by total number of sick clinic visits. Cause-specific visits for malaria, pelvic inflammatory disease, cracked and bleeding nipples, and vaginal infection were significantly reduced by between 16% and 40% depending on cause, compared to placebo.
High doses (180mg/ day or 600 000 IU) of beta-carotene for one month raised CD4 counts in a cross-over trial in 21 American outpatients (Coodley 1993), but not when given with multivitamins in an extended evaluation at 3 months (n=72); viral load was also unaffected (Coodley 1996). Vitamin A (10 000 IU) given daily for six weeks to 400 Kenyan women with a high prevalence of vitamin A deficiency (59% had serum retinol concentrations <30 microgram/dL) showed no effect on vaginal shedding of HIV-1, viral load, or CD4 counts (Baeten 2002).
Two small trials of short duration to test the safety of single high doses of vitamin A, 200 000 IU in 120 intravenous drug users for 4 weeks (Semba 1998), and 300 000 IU in 40 women of reproductive age for 8 weeks (Humphrey 1999), found no effect on CD4 counts or viral load.

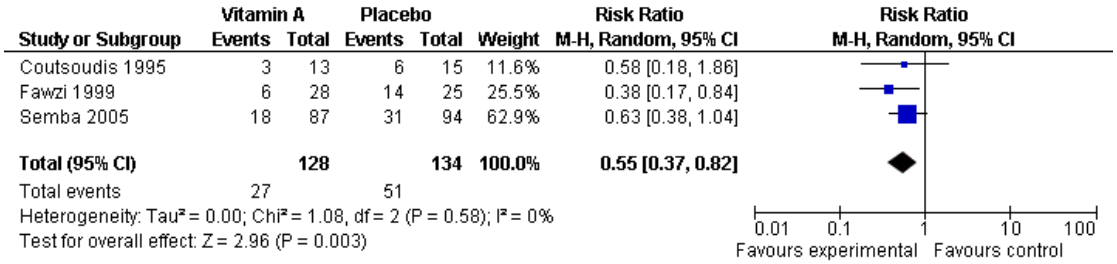
Vitamin A in children

Five small trials of vitamin A in children (n=1120) were included.
In Ugandan children (n=181), quarterly vitamin A supplementation (60mg RE or 200 000 IU) from 15 to 36 months reduced all-cause mortality by 46% (adjusted RR = 0.54; 95% CI: 0.30-0.98) after follow-up for a median of 17.8 months, a shorter period than planned due to early stopping of the trial . Morbidity effects were a halving of persistent cough (OR = 0.47; 95% CI: 0.23-0.96) , and reduction in the duration of ear discharge (p=0.03) (Semba 2005).
Periodic doses (100 000 IU to infants; 200 000 IU to 1-5 year olds) for 24 months to Tanzanian children (n=687) admitted with pneumonia halved all-cause mortality (RR = 0.51; 95% CI: 0.29-0.90) and significantly reduced the risk of severe watery diarrhoea (adjusted OR = 0.56; 95% CI: 0.32-0.99) (Fawzi 1999). In a subgroup of 58 HIV-infected children, all-cause mortality was reduced by 63% (RR = 0.37; 95% CI: 0.17-0.84) and AIDS-

related deaths by two-thirds (RR = 0.32; 95% CI: 0.1-0.99) (Fawzi 1999). There was a non-significant reduction in cough and rapid respiratory rate (RR = 0.54; 95% CI: 0.24-1.20) in this subgroup, and a non-significant increase in acute diarrhoea (RR = 1.55; 95% CI: 0.75-3.17) (Fawzi 1999). After four months of supplementation, there was a mean increase in height of 2.8 cm (95% CI: 1.0-4.6) of HIV-infected children under 18 months of age (Fawzi 1999; Villamor 2002a).

In South Africa, periodic vitamin A supplementation (50 000 IU at 1 and 3 months; 100 000 IU quarterly thereafter) of all children born to 118 HIV-infected women reduced all-cause morbidity by a third (OR = 0.69; 95% CI: 0.48-0.99) during 18 months of follow-up. In a subgroup of 28 children with HIV infection at birth, there was no effect on mortality but episodes of diarrhoea were halved (OR= 0.51; 95% CI: 0.27-0.99) (Coutsoudis 1995). A meta-analysis of the effect of vitamin A on mortality in 267 HIV+ children, based on the three trials above, showed an overall significant reduction of 50% (RR = 0.50; 95% CI: 0.31-0.79) (Figure 4).

Figure 4. Forest plot of comparison: 2 Vitamin A in children, outcome: 2.1 All-cause mortality.



A small trial (n=59) of 200 000 IU of vitamin A for two days in North American children receiving influenza vaccine decreased HIV viral load at 14 days from the time of vaccination, compared to an increase in the placebo group (p = 0.02) (Hanekom 2000). An identical regimen raised CD4 counts at four weeks in 75 South African children (p = 0.03) (Hussey 1996).

Vitamin D

Wejse et al (Wejse 2009) examined the effect of periodic vitamin D (100 000 IU cholecalciferol at baseline, and at 5 months and 8 months after inception) given supplementary to anti-TB treatment in 365 adults in Guinea-Bissau, 131 of whom were HIV-infected. They found no reduction in a clinical severity score (TB score) and no effect on 12-month mortality (HR = 1.8; 95% CI: 0.8-4.1) overall, or in the HIV-infected subgroup, compared to placebo.

A small trial (n=59) of vitamin D (100 000 IU cholecalciferol bi-monthly) and calcium versus double placebo to evaluate the effect on monthly serum vitamin D concentrations over 12 months in HIV-infected American children and adolescents, found significant increases in vitamin D levels (p< 0.0001) in the supplemented group, and no adverse effects on HIV disease progression, as measured by CD4 counts (p=0.18) and viral load (p=0.66) (Arpadi 2009).

Zinc

Daily zinc supplements (25mg) given to 400 pregnant Tanzanian women until 6 weeks after delivery had no effect versus placebo on foetal and neonatal mortality, duration of pregnancy, birth weight, maternal T cell counts, or viral load. The zinc supplements did appear to inhibit increases from baseline in haematological indicators compared to placebo, namely haemoglobin (p=0.03), packed cell volume (p=0.01), and red blood cell count (p<0.01). Zinc supplementation was also associated over 22 weeks' follow-up with a threefold increase in the risk of maternal wasting (risk of MUAC < 22 cm; p=0.03), and a 4 mm decline in MUAC during the second semester (p=0.02) (Fawzi 2005).

A placebo-controlled trial of 50 mg oral zinc twice daily for 14 days to 159 Peruvian adults with diarrhoea lasting for a week or more found no effect on the persistence and severity of diarrhoea at day 14 of treatment (Carcamo 2006). The participants were not on ART; those in the zinc group had median CD4 counts of 65 (0-909) versus 55 (2-2021) in the placebo group.

A placebo-controlled equivalence trial to determine the safety of zinc supplementation in HIV- infected children was conducted in 96 South African children aged 6 to 60 months (Bobat 2005). A daily dose of 10mg zinc sulphate for up to 6 months did not increase viral load. There was a significant reduction in the secondary outcome of diarrhoeal morbidity, as measured by the proportion of scheduled and illness clinic visits where a diagnosis of watery diarrhoea was made (p=0.001).

Diarrhoeal and respiratory morbidity in 341 HIV-uninfected and 32 HIV-infected rural South African children, aged 4 to 6 months, was measured by maternal report during home visits (pneumonia also confirmed by measurement of rapid respiratory rate) in a trial that compared supplementation for prophylaxis for a median of 14.9 months with 10 mg zinc plus vitamin A, or with zinc plus vitamin A and multiple supplements, to vitamin A alone. There were no differences between the treatment arms in either the HIV-uninfected or HIV-infected children on prevalent days or incidence density of diarrhoea (Luabeya 2007).

Selenium

Daily selenium supplements of 200 mg for 12 months in 186 American drug users versus placebo reduced the number of participants hospitalised for opportunistic infections and HIV-related conditions (RR = 0.40; 95% CI: 0.21-0.75), and lowered the risk of a CD4 decline of greater than 50 cells/mm^3 (Burbano 2002). Hurwitz et al evaluated an identical regimen for 9 months in a placebo-controlled trial of 262 HIV-infected adults, and found that supplements elevated serum levels (p<0.001), suppressed viral load (p<0.02), and increased CD4 counts (p<0.04) (Hurwitz 2007).

Kupka et al (Kupka 2008; Kupka 2009) randomised pregnant women in Tanzania (n=913) to 200µg daily selenium vs. placebo until 6 months post-delivery. The supplements did not improve maternal HIV disease progression or haemoglobin concentrations, but they did reduce maternal diarrhoeal morbidity by 40% (RR= 0.60; 95% CI: 0.42; 0.84). There was no significant effect on neonatal or overall child mortality, but a reduction in child mortality at 6 weeks was observed (RR=0.43; 95% CI: 0.19; 0.99).

Multiple supplements

A large trial was conducted in 1078 pregnant Tanzanian women, which employed a factorial design of daily multivitamins (mainly vitamins B, C and E in doses up to 22 times RDA) with and without vitamin A versus vitamin A only or placebo (Fawzi 1998). The supplementation commenced at enrollment (12-27 weeks gestation) and lasted throughout pregnancy and lactation. The median follow up with respect to survival was 71 months (IQR: 46-80 months). Significant delays in the progression to stage 4 disease or AIDS-related mortality (HR = 0.71; 95% CI: 0.51-0.98) and in progression to stage 4 disease alone (HR = 0.50; 95% CI: 0.28-0.90) were observed in women receiving multivitamin supplements, compared to placebo. Data were censored at the time of death when the cause of death could not be ascertained by means of standardised interviews and/or review of medical records, or was not deemed to be AIDS-related. Viral load and all signs of HIV-related complications in multivitamin-supplemented women were reduced relative to placebo, and CD4 and CD8 counts were raised, compared to vitamin A or placebo. Adding vitamin A to the multivitamin regimen reduced the beneficial effects on almost all maternal and infant outcomes to be generally comparable with the placebo.

Multivitamins improved mean maternal weight gain during the third trimester compared to no multivitamins (mean difference (MD) = 304 g; 95% CI: 17- 590), and reduced the risk of low weight gain (<= 100g per week; RR = 0.73; 95% CI: 0.58- 0.93) (Fawzi 1998; Villamor 2002b) and the risk of wasting (first episode of mid-upper arm circumference (MUAC) <22 cm; RR = 0.66; 95% CI: 0.47- 0.94) (Fawzi 1998; Villamor 2005b). Compared to vitamin A or placebo, multivitamins reduced the risk of hypertension during pregnancy (RR = 0.62; 95% CI: 0.40- 0.94) (Fawzi 1998; Merchant 2005), protected against depression (RR = 0.78; 95% CI: 0.66- 0.92) and improved quality of life (RR = 0.72; 95% CI: 0.59- 0.88 for social functioning) (Fawzi 1998; Smith Fawzi 2007).

Multivitamins reduced the risk of adverse pregnancy outcomes, including foetal deaths (RR = 0.61; 95% CI: 0.39-0.94), low birth weight (RR = 0.55; 95% CI: 0.38-0.81), severe preterm births (<34 weeks) (RR = 0.61; 95% CI: 0.38-0.95), and babies small for gestational age (RR = 0.57; 95% CI: 0.40-0.83) (Fawzi 1998).The mean birthweight of infants born to HIV-negative mothers in the supplemented group was significantly higher (MD = 94 g, p = 0.02) (Fawzi 2000). Child growth during the first two years of life was improved by maternal multivitamin supplementation, namely attained weight (MD = 459g; 95% CI: 35, 882), weight-for-age (MD = 0.42; 95% CI: 0.07, 0.77), and weight-for length (MD = 0.38; 95% CI: 0.07, 0.68) (Fawzi 1998; Villamor 2005a).

Maternal multivitamin supplementation also reduced the risk of child diarrhoea (RR = 0.83; 95% CI: 0.71-0.98 at 24 months), and improved children's CD4 counts (MD = 153 cells/µl; 95% CI: 67.6-238.4) (Fawzi 1998; Fawzi 2003) and micronutrient status during the first six months of age (Baylin 2005; Fawzi 1998). Vitamin A supplements reduced the risk in children of cough with rapid respiratory rate (RR = 0.69; 95% CI: 0.49-0.96) (Fawzi 1998; Fawzi 2003) and the incidence of clinical malaria by 71% (RR=0.29; 95% CI: 0.09-0.89) in children born to HIV-infected women (Fawzi 1998; Villamor 2007).

In multivitamin-supplemented women with low immunological or nutritional status, significant reductions were reported in the risk of child mortality by 24 months of age: 70% (RR = 0.30; 95% CI: 0.1-0.92) in women in the lowest quartile of lymphocyte counts (<1340/ mm^3); 60% (RR = 0.40; 95% CI: 0.17-0.98) in women with low baseline vitamin A (<20 µg/dl); and 69% (RR = 0.31; 95% CI: 0.13-0.73) in women with low baseline vitamin E (<9.7 µmol/l) (Fawzi 1998; Fawzi 2002).

In a trial of 481 Thai adults, twice-daily supplementation for 48 weeks with a commercial mix of 18 vitamins and minerals, some at doses up to 20 times higher than the recommended daily allowance (RDA), had no significant effect on overall mortality (p= 0.1), CD4 counts (p>0.3), or plasma viral load (p=0.4). Mortality was significantly reduced in those with low CD4 counts at baseline (CD4 <100: hazard ratio (HR) = 0.26; 95%CI: 0.07-0.97). A trend towards a reduced death rate in those with CD4 counts <200 at baseline was also reported (HR=0.37; 95% CI: 0.13, 1.06) (Jiamton 2003).

Daily supplementation with micronutrients and natural mixed carotenoids in a community randomised controlled trial of 331 Canadian adults with advanced AIDS had no effect on the primary outcome of time to new or recurrent AIDS-defining event or death (HR = 1.81; 95%CI: 0.95-3.42, p=0.07). A reduction in the secondary outcome of time to all-cause mortality was apparent in multivariate analysis (HR= 3.15; 95%CI: 1.10-8.98, p=0.03) and there was improved survival in those with higher baseline concentrations of serum carotene (p=0.04) or CD4 counts (p=0.005) (Austin 2006).

A small (n=40) randomised placebo-controlled trial of micronutrients given twice daily for 12 weeks in American adults on highly active antiretroviral therapy (HAART) reported a significant increase in the primary outcome of CD4 counts in the treatment group (p=0.029) (Kaiser 2006). There was no significant change in any of the secondary endpoints, namely virologic and metabolic parameters, neuropathy scores, and general health status.

The effects of multivitamin (MVM)/ zinc (Zn) supplementation during treatment of pulmonary tuberculosis (PTB) was tested by means of a two-by-two factorial trial in 499 PTB patients in Tanzania, 213 of whom were co-infected with HIV. There was a non-significant effect of MVM (RR 060; 95% CI 034, 105) and Zn (RR 063, 95% CI 037, 108) on mortality in co-infected patients when given separately but when MVM and Zn were given in combination there was a significant reduction in mortality of 71% (RR= 0.29; 95%CI: 0.10-0.80, p=0.016). The combined interventions did not however yield significant weight gain (237 kg; 95% CI 091, 383), irrespective of HIV status (Range 2006).

A trial in 1402 Malawian patients with PTB, 829 of them HIV-infected, of daily micronutrients, including zinc versus placebo for 24 months, did not reduce mortality in the HIV-infected subgroup (Semba 2007b). A placebo-controlled trial of daily micronutrients (retinol; vitamins B1, B2, B6, B12; niacin; vitamin C; vitamin E; folic acid; selenium) was conducted for 8 months among 887 Tanzanian adults with PTB, 471 of them with HIV infection (Villamor 2008). It found no effect on overall mortality, HIV disease progression, or nutritional indicators, but the risk of TB recurrence in HIV-infected patients was reduced (RR=0.37; 95%CI: 0.15;0.92).

In the USA, the effects of daily micronutrient and iron supplementation on iron status and anaemia were tested in 458 hepatitis C-positive female injection drug users, 138 of whom were HIV-infected. The daily supplement reduced anaemia and improved iron status in all women at 12 months versus those not receiving iron, without an adverse effect on viral load or CD4 counts (Semba 2007a).

Large daily doses of vitamins E and C for three months reduced measures of oxidative stress in a small (n = 49) Canadian trial, and showed a non-significant trend towards a reduction in viral load, but had no effect on HIV-associated morbidity. Vitamin C and E serum levels at three months were both significantly higher (p<0.005) in the treatment group than placebo, but levels of vitamin A, carotenoids, zinc and selenium were unchanged (Allard 1998).

Daily micronutrient (vitamins A, C, and E; selenium; zinc) supplementation in a trial of 135 Zambian adults with persistent diarrhoea, more than half of whom were classified vitamin A and vitamin E deficient, had no effects on mortality, diarrhoeal morbidity, CD4 counts, body mass index, quality of life scores, or vitamin A and E serum levels (Kelly 1999).

A trial of prophylactic zinc or multiple micronutrient supplementation to reduce diarrhoea and respiratory disease in young South African children is described above (Luabeya 2007). Neither intervention, alone or in combination, had an effect in either HIV-infected or uninfected children to support the prophylactic use of zinc or multiple micronutrients to reduce morbidity, although the sample size of HIV-infected children was very small.

Adverse effects of supplementation

No significant adverse effects of vitamin A in adults were reported. Adverse effects of vitamin A in children, irrespective of HIV status, included vomiting and bulging fontanelle (Coutsoudis 1995); and a small risk of acute diarrhoea in normally nourished (RR = 1.37; 95% CI: 1.06-1.79) and in growth-stunted children (RR = 1.84; 95% CI: 1.16-2.90) (Fawzi 1999) hospitalised with pneumonia. HIV-negative children who received vitamin A had a non-significant increased risk of cough and rapid respiratory rate compared to those on placebo (p = 0.07).

Vitamin A reduced the benefits of multivitamin supplementation in pregnant women in Tanzania (Fawzi 1998), and increased mortality in a sub-sample of infants who were HIV-negative at 6 weeks in a large trial of supplemented Zimbabwean mother-infant pairs (ZVITAMBO 2006).

Daily zinc supplements (25mg) to pregnant women in Tanzania inhibited increases in haematological indicators and increased the short-term risk of maternal wasting (Fawzi 2005).

DISCUSSION

Summary of main results

Vitamin A in adults

Despite strong evidence from observational studies (Tang 1993; Semba 1993; Semba 1995) of an association between low vitamin A levels and HIV disease progression and mortality in adults, none of the six trials reviewed demonstrated any significant reduction in HIV disease progression, or any significant adverse effects, associated with vitamin A or beta-carotene supplementation.

The ZVITAMBO trial of a single large dose of vitamin A given to Zimbabwean women and their infants during the postpartum period found a two-year mortality reduction in infants infected during the late intrauterine/ intrapartum/ early postnatal period, which supports existing evidence that vitamin A supplementation of HIV-infected infants and children is likely to prolong survival.

Mortality was higher, however, in a subgroup of infants who were not HIV-infected at 6 weeks of age. The authors suggest the possibility that priming with vitamin A may have increased viral load in babies subsequently infected during breastfeeding. This finding, together with the lack of effect on maternal mortality and the limited effect on maternal morbidity, leads the authors to raise concern about universal maternal postpartum vitamin A supplementation in HIV-endemic areas (ZVITAMBO 2006). This subgroup mortality effect is unique to this trial however, and further research is required to fully inform policy decisions.

Research is needed into the effect of smaller doses on maternal mortality in an HIV-prevalent population with a poorer vitamin A status than the women who participated in the ZVITAMBO trial. This issue is suggested by a large trial in a rural, undernourished, and presumably HIV-negative population in Nepal, which found that weekly vitamin A supplements halved maternal mortality up to 12 weeks postpartum (West 1999). Further research into other potential benefits of vitamin A supplementation is needed, such as reduced night-blindness in pregnant women where deficiency is common, irrespective of HIV status (van den Broek 2002). A systematic review of five trials has found no evidence however to support prenatal and postnatal vitamin A supplementation for reducing the risk of mother-to-child transmission (Kongnyuy 2009; Wiysonge 2005).

Vitamin A in children

Vitamin A is standard care in children without HIV infection who present with persistent diarrhoea and severe acute malnutrition (UNICEF 2007; WHO/UNICEF 2004). Six monthly regular supplements of vitamin A are also recommended for all children between 6 months and five years to support growth and development and to reduce all-cause mortality, irrespective of HIV status (Baeten 1993; WHO 2009).

There is strong evidence from a few African trials of clinical benefits of vitamin A on mortality in HIV-infected children, and moderate evidence for morbidity and growth benefits (Fawzi 1999; Villamor 2002a; Coutsoudis 1995; Semba 2005). A meta-analysis of three trials (Coutsoudis 1995; Fawzi 1999; Semba 2005) (Figure 4) shows that vitamin A halved all-cause mortality, although the HIV-infected children in two of the trials were small subgroups of the study populations. There is inconsistent evidence on the effects of vitamin A on morbidity, with some benefits and adverse effects on diarrhoeal and respiratory morbidity being reported, which may be due to the small sample sizes. The clinical benefits may be consequent to an improvement in immune function and to the rehabilitation of mucosal integrity, leading to a reduction in the severity and incidence of diarrhoeal infection, and an improvement in short-term growth.

Vitamin D

Vitamin D supplementation in HIV-infected individuals has not been substantially studied, but evidence from the two reviewed studies indicates that it does not have a deleterious effect on HIV disease progression. Wejse et al speculate that the lack of benefit in patients with TB in their study may have been due to suboptimal dosage, and that trials investigating prevention of latent TB infection with larger, perhaps daily, vitamin D doses may therefore be warranted (Wejse 2009). Arpadi et al recommend further research to determine what level of supplementation with vitamin D, together with daily calcium supplementation, will lead to clinically significant gains in bone mass accrual in children and adolescents with HIV, as well as other potential benefits (Arpadi 2009).

Zinc

In observational studies of HIV-infected adults, low levels of serum zinc have been related to HIV disease progression (Graham 1991), decreased CD4 cell counts (Baum 2003) and increased mortality (Baum 1997; Baum 2003), and low dietary intake has been associated with decreased survival (Baum 2003). An association has also been reported between self-prescribed zinc consumption above the recommended dietary allowance (RDA) and rapid progression to AIDS (Tang 1993) and mortality (Tang 1996), although this may have been due to reverse causality if adults with more advanced disease chose to take more supplements.

The authors of a trial in Tanzania concluded that there is no compelling evidence for the addition of zinc to antenatal supplements for pregnant HIV-infected women, as there were no reductions in adverse pregnancy outcomes, and increases in haemoglobin levels were inhibited (Fawzi 2005). This reported lack of benefit is consistent with trials in HIV-uninfected pregnant women in Nepal (Christian 2003) and Mexico (Ramakrishnan 2004) in which zinc was found to inhibit the absorption of iron and mitigate increases in haemoglobin levels.

A two-week course of 100 mg of elemental zinc daily to Peruvian adults presenting with diarrhoea had no effect on the persistence of diarrhoea (Carcamo 2006). Treatment benefit may have been concealed due to the short duration and high attrition rates however.

In children without HIV infection, zinc supplementation has been shown to reduce the risk and severity of diarrhoea and pneumonia in several studies (Baqui 2002; Bhandari 2002; Bhutta 1999; Bhutta 2000; Strand 2002; Zinc Investigators Collaborative Group 2000). The reported benefits in HIV-infected South African children on the secondary outcome of diarrhoeal morbidity (Bobat 2005) are consistent with the evidence from these earlier studies. The primary finding in the South African trial that HIV-1 viral load was not raised, suggests that zinc supplementation may be considered safe as a specific therapy in children with HIV infection who present with diarrhoea. A subsequent study by Luabeya et al (Luabeya 2007) did not provide support however, for the prophylactic use of zinc or multiple supplements to reduce diarrhoeal or respiratory morbidity in rural South African children, including 32 HIV-infected children. Further research in larger and diverse populations of HIV-infected children is therefore needed.

Selenium

Multiple observational studies have reported on the associations

between selenium and HIV disease. There have been few randomised trials directly assessing the relationship. Two trials that provided identical regimens of daily selenium supplements to North American adults reported a reduction in hospitalisations (Burbano 2002) and suppression of viral load and improved CD4 counts at 9 months, without any adverse effects (Hurwitz 2007). Mechanisms for the effect on viral load include an indirect effect of selenium via diminished oxidative stress, and a direct effect of the selenoproteins on viral replication. Both trials had small sample sizes however, and the significance of their findings need to be confirmed in other populations, especially in African settings where diets may be very different.

In the setting of Dar es Salaam, Tanzania, selenium supplements given during and after pregnancy did not delay HIV disease progression or improve pregnancy outcomes, but may improve child survival and decrease diarrhoeal morbidity (Kupka 2008) . Explanations offered for the lack of effect of selenium on maternal and pregnancy outcomes include a limiting effect of co-supplements; an effect restricted to patients with advanced HIV disease or those receiving HAART, which was not the case in this study; and the fact that selenium deficiency was probably uncommon. There is therefore good evidence from this large and rigorously designed trial of little to no benefit of providing selenium supplements to HIV-infected populations who are naÄ±ve to HAART, who receive high-dose multivitamin supplements, and who live in areas where selenium deficiency is uncommon.

Multiple supplements

Multivitamin supplements in pregnant and lactating women in a large Tanzanian trial with long-term follow-up were associated with a number of clinical benefits for mothers and their offspring (Fawzi 1998). The authors suggested that the supplements enhanced immunity, namely improved T-cell counts, reduced HIV viral replication and somehow protected oral and gastrointestinal epithelia and hence reduced HIV-related complications. Multivitamins reduced the risks of adverse pregnancy outcomes, improved child growth during the first two years of life, and reduced child mortality in the first two years of life among those born to immunologically- and nutritionally-compromised women. These benefits may have been due to improved quality of the mothers' breast milk, with consequent enhancement of the infants' micronutrient intake and immune function causing a reduction in mortality and morbidity from diarrhoeal disease and upper respiratory tract infections. It is also likely that the improvement in the mothers' health and nutritional status enabled them to provide better care for their children.

In evaluating the promising benefits of this trial, it is worth noting that the doses of some of the vitamins provided were far in excess of recommended daily requirements, and were based not on preliminary pharmacokinetic studies, but on the prevalence of deficiencies in relation to self-reported and self-prescribed intakes of HIV-infected American men (Baum 1994). It is possible that a micronutrient regimen with much lower doses could be equally effective.

In one trial the addition of vitamin A (both preformed retinol and high dose (30mg) beta carotene) reduced the benefits of the micronutrient supplement. This may have been due to beta carotene functioning as a pro-oxidant, rather than as an antioxidant as would be expected, on other micronutrients that were given as part of the supplement. The potential pro-oxidative effect of beta carotene is recognised and this reason has been speculated as the cause of adverse effects in certain cancer studies (ATBC 1994; ATBC 1996; Omenn 1996). In this trial the combination of high doses of beta carotene and iron may have accounted for some of the adverse outcomes in the Vitamin A groups. Finally, the reduced morbidity reported in this trial may not be specific to HIV-infected women, but may also apply to HIV-free women in other populations at risk of undernutrition and high maternal mortality. This needs to be determined in order to inform general recommendations.

Evidence of clinical benefit of multiple micronutrients has also been provided by a large trial in Thailand (n=481), although the reduction in mortality was restricted to those with the lowest CD4 count (CD4<100) at baseline. In contrast to the Tanzanian studies, there was no effect on CD4 counts, viral load or overall mortality, suggesting that the supplement reduced the risks of other infections or mediated its benefit by helping to maintain lean body mass (Jiamton 2003).

A trial of supplementation with micronutrients and natural mixed carotenoids in Canadian adults with advanced AIDS on antiretroviral therapy, observed a benefit in adjusted analyses of the secondary outcome of overall mortality (Austin 2006). The authors postulated that the treatment effect may be due the direct antioxidant action of the carotenoids, or to interactions with the ARVs that improve the drug response. Important limitations of the study were early termination due to interruptions in the supply of study medication, and a lack of uniformity in the formulated dose during the study.

In a trial of forty American adults on highly active antiretroviral therapy (HAART) who received multiple micronutrients an increase in CD4 count was also reported. The authors suggested that certain nutrients may enhance cellular immunity, and thereby decrease the rate of CD4 cell death (Kaiser 2006).

Two African trials of supplementation in pulmonary TB patients, some of whom were co-infected with HIV, evaluated the effect on mortality. Range et al found a significant reduction in deaths of co-infected HIV and TB patients when supplemented with MVM, but only when given in combination with zinc during PTB treatment; only marginal effects were observed when either MVM or Zn were given alone. Some of the benefit may have been secondary to the considerable increases in weight gain in the supplemented group (Range 2006).

Villamor also reported that daily supplementation with micronutrients reduced the recurrence of TB in HIV-infected adults not on antiretroviral treatment, and decreased complications among

HIV-negative adults (Villamor 2008). However, in a Malawian placebo-controlled trial that provided similar supplements but with lower levels of vitamins and minerals than those given in the Tanzanian study, there were no beneficial effects reported (Semba 2007a). This may have been because HIV-infected individuals require higher doses of micronutrients, either because of malabsorption states or increased utilization, to achieve clinical benefit. A meta-analysis of these two trials showed a non-significant reduction in mortality. Given the major contribution of TB to HIV-related mortality, it is important to conduct comparable studies in different settings to determine if these supplements may be effective adjuncts to antiretroviral drugs in preventing mortality.

Villamor et al reported that daily supplementation with micronutrients reduced the recurrence of TB in HIV-infected adults with TB not on antiretroviral treatment, and decreased complications among HIV-negative adults. Investigation of similar benefits is therefore required in HIV-infected patients receiving antiretroviral therapy in other settings, which could provide evidence for micronutrient supplementation as a useful and relatively inexpensive element of TB treatment regimens (Villamor 2008).

Semba et al have also studied the effects of daily micronutrient and iron supplementation in American female injection drug users with hepatitis C infection, a third of whom were HIV-infected. Although they found a reduction in anaemia and improved iron status compared to those not receiving iron, they caution against generalising these findings to other populations who were excluded from their study. The trial was also of short duration, and was underpowered to detect small but nevertheless significant adverse effects on HIV viral load in the long term (Semba 2007a).

A Zambian trial of multi-micronutrient supplements (vitamins A, C, and E, selenium, zinc) that was designed to test whether supplementation improves the clinical response to albendazole in the treatment of persistent diarrhoea in adults with HIV-wasting showed no effect on morbidity or mortality or serum vitamin levels (Kelly 1999). The absence of effect may have been real, or may have been due to inadequate duration of supplementation or to malabsorption of micronutrients.

Quality of the evidence

The quality of the evidence reviewed to date has some important limitations, as revealed in the summary assessment of the methodological quality of all included studies (Figure 3). Methods of random sequence generation and blinding were judged to be of low risk of bias in the majority of studies, but insufficient information about allocation concealment in many of the studies meant that the risk of bias is unclear. Fewer than half of the studies were judged to be of low risk of bias with respect to selective outcome reporting, or incomplete outcome data. The quality of evidence with respect to each of the interventions is presented below and summarised by study in Figure 2.

Vitamin A in adults

The method of randomisation was clearly described for three of six trials assessing vitamin A and not clearly described in the remaining three trials (Coodley 1993; Coodley 1996; Humphrey 1999). Allocation concealment was judged adequate in two (Semba 1998; ZVITAMBO 2006), and unclear in the remaining four (Baeten 2002; Coodley 1993; Coodley 1996; Humphrey 1999)

Placebo was given to participants, and treatment providers and assessors were blinded to the treatment assignments in all trials. Incomplete outcome data was deemed to be adequately addressed in four of the six trials, with the remaining two not clearly described (Baeten 2002; Coodley 1996). All six trials were judged to be unclear with respect to selective reporting. Only one trial (ZVITAMBO 2006) was judged to be free of other biases, while it was unclear for the remaining five.

Vitamin A in children

Five placebo-controlled trials in children (n= 1 120) were included (Coutsoudis 1995; Fawzi 1999; Hanekom 2000; Hussey 1996; Semba 2005), three with adequately described methods of randomisation and two with allocation concealment clearly described. All were blinded studies and incomplete outcome data was deemed to be adequately addressed in only one trial (Hanekom 2000), not described in another (Coutsoudis 1995) and inadequately addressed in the remaining three. Only one trial (Semba 2005) was judged to be free of selective reporting as well as free of other biases.

Vitamin D

One trial of vitamin D in adults (n= 365) (Wejse 2009) and one in children (n= 59) (Arpadi 2009) were included. Both were blinded, and used adequate random allocation to vitamin D or placebo. Allocation concealment was clearly described in both trials. Incomplete outcome data was adequately addressed in one trial (Arpadi 2009) and the other trial (Wejse 2009) was judged to be free of selective reporting as well as other biases.

Zinc

In the two trials of zinc in adults (Carcamo 2006; Fawzi 2005) (n=559), random generation was deemed to be adequate in one (Carcamo 2006). Allocation concealment was unclear in the Fawzi trial but clearly reported by Carcamo et al. Both trials were blinded placebo-controlled studies. Incomplete outcome data was inadequately addressed in one trial and not addressed in the other. It was unclear as to whether the trials were free of selective reporting but one trial was judged to be free of other biases (Fawzi 2005).

The two trials in children (Bobat 2005; Luabeya 2007) (n = 128) met most of the criteria for methodological quality with the exception of allocation concealment, which were not clearly described in the Bobat study. In addition, the Bobat trial was not judged free of selective reporting while the Luabeya trial was not deemed to be free of other biases.

Selenium

Three blinded placebo-controlled trials in adults (n= 1 361) were included (Burbano 2002; Hurwitz 2007; Kupka 2008). The Burbano trial was unclear about or failed to meet all but one of the

methodological quality criteria, whereas the Kupka trial met all but one of them. The Hurwitz trial was unclear about allocation concealment, did not adequately address incomplete outcome data and was not judged free of selective reporting.

Multiple supplements

Ten trials of multiple heterogeneous supplements in adults (n= 3 765) include a single large multi-factorial trial (n = 1 078) in pregnant and lactating women (Fawzi 1998) that has yielded multiple papers examining diverse outcomes at different time points. It meets all the criteria for methodological quality..

The remaining nine trials in adults (n= 2 687) (Allard 1998; Austin 2006; Jiamton 2003; Kaiser 2006; Kelly 1999; Range 2006 (pulmonary tuberculosis (PTB) patients); Semba 2007a (women injectable drug users or IDUs); Semba 2007b (PTB patients); Villamor 2008 (PTB patients) were generally well-reported trials, with the exception of the study by Kelly et al. The Kaiser trial did not adequately report on the method of randomisation and allocation concealment, and was not deemed to be free of selective reporting. Allocation concealment was not clearly described in the study by Villamor et al. Only two studies adequately addressed incomplete outcome data (Austin 2006; Kaiser 2006) while it was deemed to be unclear in three trials and inadequately addressed in the remaining four. Only one trial (Semba 2007b) was judged to be free of selective reporting, the remaining eight unclear. Four trials were judged free of other biases, one trial (Austin 2006) not free of other biases, and in the remaining four it was judged to be unclear.

Potential biases in the review process

Biases in the review process were minimised by performing a comprehensive search of the literature, independently selecting and appraising the studies, and extracting the data. Assessment of the risk of bias (RoB) of all studies was repeated for the studies in the original review (Irlam 2005) and for the newer studies using the updated RoB tool by JI and NS.

For the purpose of the review, the HIV status of children determined by each study was accepted as sufficient. In past years laboratory methods have improved and become more sensitive and specific, thereby reducing the likelihood of false positive or false negative attribution of HIV status. However, further analysis or validation of children's status was beyond the scope of this review.

Several studies have also reported on the increased morbidity and mortality of infants and children born to HIV-infected mothers compared to those born to HIV-uninfected mothers (Kuhn 2005; Newell 2004; Shapiro 2007, ZVITAMBO 2006). There are several possible mechanisms to explain this. First, the health and survival of HIV-infected mothers exert a major effect on child survival. Low maternal CD4 count or death increases child mortality by factors of 3.5 and 4 respectively, demonstrating the importance of basic care practices provided by a healthy mother. HIV-infected mothers also tend to breastfeed their infants for shorter intervals, which reduces the immune protection provided by breast milk and increases the risk of diarrhoea and malnutrition associated with other feeding practices. Lastly, infants born to HIV-infected mothers may have transient impairment of their immune systems that may increase susceptibility to non-HIV infectious diseases such as pneumonia. However there is insufficient basic evidence to determine which of these, or which combination, is most significant.

The effect of micronutrient supplements on HIV exposed but not infected infants and children was outside the scope of this review and was not formally evaluated. The few studies that did include these children in their reports (Luabeya 2007) did not suggest a differential response to micronutrient interventions of HIV exposed but uninfected children compared with children born to HIV-uninfected mothers.

Agreements and disagreements with other studies or reviews

In July 2007 the Academy of Science of South Africa (ASSAf) published *HIV/AIDS, TB and Nutrition*, a scientific inquiry into the nutritional influences on human immunity with special reference to HIV infection and active TB in South Africa (ASSAf 2007). The inquiry found a dearth of reliable and informative studies, and recommended improved nutritional policy and practice informed by high-quality research. It was recognised that nutritional interventions should be part of a comprehensive, integrated approach to HIV and TB, but are no substitute for anti-retroviral drugs in preventing transmission; that nutritional care should focus on diversified diets of available, affordable and culturally acceptable foods, as well as safe levels of macro- and micronutrients; and that priority should be accorded to HIV-infected pregnant women, lactating mothers and their babies.

Key recommendations of the ASSAf Scientific Panel with respect to micronutrient supplementation that were derived from the earlier version of this review (Irlam 2005) included:

- promoting adequate dietary intake of micronutrients at recommended INL98 levels
- providing elevated levels of micronutrients (at least 1-2 INL98s) through food fortification or supplements in settings where micronutrient deficiencies are endemic,
- offering multivitamin supplementation at INL98 levels to HIV-infected women
- better definition of the indicators of vitamin and mineral micronutrient levels in individuals and populations

A 2009 review (*Investing in the Future: A United Call to Action on Vitamin and Mineral Deficiencies*) prepared by the Micronutrient Initiative (an international not-for-profit organization) in partnership with UNICEF, WHO and others (Micronutrient Initiative 2009), reported that the 2008 Copenhagen Consensus, a group of world-renowned economists, ranked micronutrient supplements (high-dose vitamin A, and zinc supplements for children with di-

arrhoea) as the top development priority out of more than 40 interventions considered (Horton 2008). The benefit to cost ratio, as well as the feasibility and sustainability of the interventions, were considered. Vitamin A supplementation every 4 to 6 months for children from age 6 months to 5 years has been shown to reduce all-cause mortality by 23% (Baeten 1993), and 10 to14 days of therapeutic zinc supplementation for diarrhoea up to the age of 5 can halve diarrhoeal mortality (Baqui 2002).

Large scale vitamin A supplementation began in the late 1990's with mass polio immunization campaigns following WHO recommendations, and coverage has been adopted as an indicator of progress toward the Millennium Development Goal (MDG) of reducing child mortality by 2015 (Wagstaff 2004). There has been less progress in achieving universal post-partum vitamin A supplementation for breastfeeding mothers, which is recommended to boost the immune system of infants in the first months of life (UNICEF 2007). A review of recent research has suggested that neonatal mortality can be reduced by supplementing newborns within the first few days of life (Haider 2008), but there is as yet no international WHO recommendation on this. Low-dose supplementation of pregnant women with xerophthalmia, which may be due to systemic vitamin A deficiency, has also been recommended but not widely adopted (Horton 2008).

Strong evidence about the benefits of therapeutic zinc together with low osmolarity oral rehydration salts for reducing childhood diarrhoea (Baqui 2002; Bhutta 2000; Robberstad 2004; Zinc Investigators Collaborative Group 2000) resulted in a joint WHO/UNICEF recommendation in 2004 of 10 to 14 days of therapeutic zinc for children under 5 years of age (WHO/UNICEF 2004).

The WHO/UNICEF report concludes with a number of priority interventions by national governments, industry and international organizations for achieving the MDG on child mortality by 2015. These interventions include:

- six monthly vitamin A supplementation for children aged between 6 months and five years, to achieve at least 80% coverage on a recurrent basis
- zinc supplementation as part of national diarrhoea management policy
- multiple micronutrient supplements for children in non-malaria endemic regions
- improved iron intake by young children in malarial areas
- iron and folic acid supplementation for all women of childbearing age, with special focus on pregnant women
- testing the feasibility of providing women with multiple vitamin and mineral supplement

Although the international reviews above primarily refer to HIV-uninfected populations, their recommendations also apply to populations with HIV infection unless there is evidence of adverse effects.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence-base for the specific effect of micronutrient supplements in children and adults with HIV is limited, but is sufficient to make some recommendations for practice. In the absence of population-specific adverse effects, there is no reason to decline similar recommendations for HIV-infected populations.

- Periodic vitamin A supplementation of HIV-infected children over six months of age in resource-limited settings is supported by three African trials in this review, which is consistent with evidence of benefit that supports supplementation of HIV-uninfected children.

- Zinc supplements reduced diarrhoeal morbidity and had no adverse effects on disease progression in a single safety trial in South African children. Children with HIV should receive zinc supplements in the management of diarrhoea and severe acute malnutrition in the same way as HIV-uninfected children with the same conditions.

- Providing daily multivitamin supplements to HIV-infected pregnant and lactating women is supported by a large Tanzanian trial, although the optimal composition and dosage still needs to be established.

In keeping with WHO recommendations (WHO 2003), everything possible should be done to promote and support adequate dietary intake of micronutrients at Individual Nutrient Intake Level (INL98) levels, while recognising that this may not be sufficient to correct specific micronutrient deficiencies in all HIV-infected individuals.

In situations where micronutrient deficiencies are endemic, these nutrients should be provided through food fortification or micronutrient supplements where available that contain at least one to two INL98s. Importantly however, micronutrient deficiencies and immune dysfunction in HIV-infected adults and children may only be restored when there is effective suppression of viral replication of HIV.

Implications for research

Adequately powered studies are still required to determine the efficacy and safety of some single and multiple micronutrient supplements in people with HIV infection to determine their short-term and long-term benefits. In view of the potential significance of preliminary results in HIV-infected populations or the proven benefits in HIV-uninfected populations some specific micronutrients warrant particular investigation, namely selenium, vitamin D and zinc. The optimal composition and dosage of various supplements requires investigation, as these can vary considerably among commercial supplements and therefore may not have equivalent

effects. The cost-benefit or cost-effectiveness of nutritional interventions also requires evaluation.

Research participants should be diverse with respect to stage of disease, use of antiretroviral therapy, immune status, and nutritional status. The special needs of children, of HIV-exposed infants, and of pregnant and lactating women should be taken into account.

Future research should also determine the effect of lifelong antiretroviral therapy on micronutrient concentrations, independent of inflammatory markers, and whether micronutrient supplements affect HIV-related outcomes in HIV-infected persons receiving HAART.

Nutritional interventions to improve the health and well-being of persons living with HIV/AIDS need to be optimised and research into identifying optimal interventions and operational strategies is therefore required. Such research should not be to the detriment of antiretroviral treatment, 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 and children infected with HIV/AIDS.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Allard 1998

Methods	Country: Canada Setting: primary care physicians Duration of recruitment: Apr 1995 - Aug 1996 Design: Placebo-controlled, parallel group
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/d), vomiting, GI bleeding Participants randomised: 49 - 47 M and 2 F - mean age = 39 yrs Participants analysed: 49 Loss to follow-up/ withdrawal: 0 Exclusions post-randomisation: 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)
Notes	Number of patients on anti-retroviral therapy: Supplement group: 22/ 23 (85%) Control group: 18/ 26(78%) Controlled diet 2 weeks prior to randomisation and throughout study period, and dietary counselling. Source of funding: Canadian Foundation for AIDS Research

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table
Allocation concealment?	Yes	Allocation code not broken until post-analysis

Allard 1998 (*Continued*)

Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	No	High and unequal proportions of missing outcomes
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Unclear	Did not declare on conflict of interest

Arpadi 2009

Methods	Country: US Setting: 4 hospital-based HIV treatment programmes Duration of recruitment: 2004-2005 Design: Placebo-controlled, parallel group
Participants	INCLUSION CRITERIA: Perinatally-infected children and adolescents, aged 6-16 years. EXCLUSION CRITERIA: severe vitamin D deficiency Participants randomised: 59 - 26 M and 33 F - mean age = 10.4 yrs Participants analysed: 56 Loss to follow-up/ withdrawal: 6 Exclusions post-randomisation: 0
Interventions	INTERVENTION: 100 000 IU vitamin D bimonthly, and 1000 mg calcium (2 chews) per day CONTROL: double placebo DURATION: bimonthly/ daily for 12 months.
Outcomes	PRIMARY OUTCOMES: Serum 25 hydroxyvitamin D (25-OHD) concentrations Serum and urine calcium SECONDARY OUTCOMES: HIV disease progression (CD4 count, viral load, ARV failure)
Notes	Participants were perinatally infected. HIV disease was classified by using Centers for Disease Control and Prevention criteria Source of funding: National Institutes of Health

Risk of bias

Item	**Authors' judgement**	**Description**

Arpadi 2009 (*Continued*)

Adequate sequence generation?	Yes	Computerised randomisation
Allocation concealment?	Yes	Central allocation by study statistician
Blinding? All outcomes	Yes	Study personnel and participants were blinded
Incomplete outcome data addressed? All outcomes	Yes	Low attrition (3 of 59 failed to complete the study)
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Unclear	Did not declare on conflict of interest

Austin 2006

Methods	Country: Canada Setting: 22 outpatient clinics Duration of recruitment: Aug. 1997 - May 1999 Design: Placebo-controlled, parallel group
Participants	INCLUSION CRITERIA: HIV positive, at risk for HIV disease progression based on ART status, CD4, and viral load; >18 years EXCLUSION CRITERIA: Continuing CD4 improvement on ART, severe pre-existing hepatic dysfunction, acute opportunistic infection, missed 2 earlier clinic visits without prior arrangement Participants randomised:331 - 289 M and 42 F - median age = 40 yrs (21-65) in treatment, 39 (22-63) in control Participants analysed: 331 Loss to follow-up/ withdrawal/ death: 67 Discontinued intervention but remained in trial: 48 Exclusions post-randomisation: 0
Interventions	INTERVENTION: Multivitamins (incl. vitamin A and trace elements) + natural mixed carotenoids (equivalent to 120000IU beta-carotene daily) CONTROL: Multivitamins (incl. vitamin A and trace elements) without carotenoids DURATION: four capsules daily for mean (s.d.)13 (6) months.
Outcomes	PRIMARY OUTCOMES: Mortality (time to death from AIDS-defining illness or any cause); time to new or recurrent AIDS-defining illness. SECONDARY OUTCOMES: CD4 changes from baseline; viral load changes from baseline

Austin 2006 (*Continued*)

Notes	Study closed early at mean 13 mo. follow-up Number of patients on anti-retroviral therapy: Supplement group: 137/ 165 (83%) Control group: 148/ 166 (89%) Source of funding: Canadian HIV Trials Network Declared no conflicts of interest

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Centralised block randomisation
Allocation concealment?	Yes	Centralised sequential randomisation
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	Yes	Losses to follow up explained and survival analysis used
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	No	Study closed prematurely due to interruption in supply of medication

Baeten 2002

Methods	Country: Kenya Setting: hospital outpatient clinic Duration of recruitment: Sep 1998 - Jun 2000 Design: Placebo-controlled, parallel group
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 randomised: 400 - 400 F - median age = 28 yrs Participants analysed: 354 Loss to follow-up/ withdrawal: 46 Exclusions post-randomisation: 0

Baeten 2002 (*Continued*)

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
Notes	Number of patients on anti-retroviral therapy: Supplement group: 22/ 23 (85%) Control group: 18/ 26 (78%) Source of funding: Research grants from NIH, Univ of Washington, and Fogarty Int. Center; International AIDS Research and Training Program scholarships; Gen-Probe (reagents)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated block randomisation
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	No	Those lost to follow up had more advanced HIV disease and vitamin A deficiency
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Unclear	Did not declare on conflict of interest

Bobat 2005

Methods	Country: South Africa Setting: hospital outpatient clinic Duration of recruitment: Mar - Dec 2003 Design: Placebo-controlled, parallel group
Participants	INCLUSION CRITERIA: Children aged 6-60 months with HIV-1 infection attending hospital clinic in Pietermaritzburg, South Africa EXCLUSION CRITERIA: Children receiving ARVs Participants randomised: 96

Bobat 2005 (*Continued*)

	- 49 F and 46 M - median age (zinc group): 40.1 months (27.4 to 48.4) - median age (placebo group): 36.6 months (25 to 49.4) Participants analysed: 85 Losses to follow-up/ withdrawal: 11 Exclusions post-randomisation: 0
Interventions	INTERVENTION:10 mg zinc sulphate CONTROL: placebo DURATION: daily for 6 months
Outcomes	PRIMARY OUTCOME: Viral load SECONDARY OUTCOMES: % CD4 cells Haemoglobin concentrations Mortality Morbidity (Watery diarrhoea; Pneumonia; URTI; Ear infection)
Notes	Concentrations of HIV-1 RNA in plasma were measured with a reverse transcriptase-PCR assay (COBAS AmpliPrep/Cobas Amplicor HIV-1 Monitor version 1.5; Roche Molecular Systems, Branchburg, NJ, USA) at 1 month before randomisation, at the time of randomisation, and at 3, 6, and 9 months after the start of supplementation. Source of funding: WHO; Johns Hopkins; Global Health Bureau; USAID; commercial (tablets) Conflicts of interest: none

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computerised randomisation in blocks of size 8
Allocation concealment?	Unclear	Children allocated by investigator at hospital but concealment not explicitly stated
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	Yes	Small loss to follow up and reasons given
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Yes	Declared no conflict of interest

Burbano 2002

Methods	Country: USA Setting: community-based clinic Duration of recruitment: 1998 - 2000. Design: Placebo-controlled, parallel group
Participants	INCLUSION CRITERIA: confirmed HIV, past or present use of illegal drugs, >= 18 years, adequate selenium status (> 85 microgram/l) EXCLUSION CRITERIA: selenium deficient (< 85 microgram/l) Participants randomised: 259 - 112 F - median age = 40 yrs (range 24 to 54) Participants analysed: 186 Loss to follow-up/ withdrawal: 73 at 12 months Exclusions post-randomisation: 0
Interventions	200 microgram selenium or placebo daily for 12 months.
Outcomes	PRIMARY OUTCOMES: Number of hospital admissions Type of hospital admissions Risk of hospitalisation SECONDARY OUTCOMES: CD4 count Hospitalisation cost Plasma selenium
Notes	Number of patients on anti-retroviral therapy: 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

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	No	Exclusions from the analysis (28%) not reported by intervention group

Burbano 2002 (*Continued*)

Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Unclear	Did not declare on conflict of interest

Carcamo 2006

Methods	Country: Peru Setting: Tertiary hospitals Duration of recruitment: June 1998-Jan 2000 Design: Placebo-controlled, parallel group
Participants	INCLUSION CRITERIA: HIV-seropositive, persistent diarrhoea (>=7 days) without prior treatment EXCLUSION CRITERIA: None stated Participants randomised: 159 - 49 F and 110 M - median age = 30 yrs (range 19-57) in Zinc group - median age = 31 yrs (range 19-64) in placebo group Participants analysed: 159 Loss to follow-up/ withdrawal: 51 Exclusions post-randomisation: 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
Notes	Sulfamethoxazole-trimethoprim prescribed for patients with enteric bacterial pathogens (23 in zinc group and 12 in placebo) Source of funding:Fogarty IARTP grant; Univ. of Washington Center for AIDS Research; Centers for Disease Control and Prevention

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computer-generated blocked randomisation
Allocation concealment?	Yes	Assignment roll inaccessible to treatment allocators

Carcamo 2006 (*Continued*)

Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	No	High losses to follow up in both groups
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Unclear	Did not declare on conflict of interest

Coodley 1993

Methods	Country: USA Setting: Hospital outpatient clinics Duration of recruitment: not stated Design: Randomised 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 randomised: 21 - 20 M and 1 F - median age: not stated Participants analysed: 17 Loss to follow-up/ withdrawal: 4 Exclusions post-randomisation: 0
Interventions	INTERVENTION: 60mg Beta-carotene CONTROL: placebo DURATION: three times daily for 4 weeks
Outcomes	PRIMARY OUTCOMES: CD4 counts SECONDARY OUTCOMES: White blood cell count Lymphocyte count B-lymphocytes Serum beta-carotene
Notes	CD4 count data reported as means and ranges** 16 patients received anti-retroviral therapy. Source of funding: Hoffman La Roche Inc.
Risk of bias	

Coodley 1993 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	Yes	Low attrition at 1 month; reasons given
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Unclear	Did not declare on conflict of interest

Coodley 1996

Methods	Country: USA Setting: Hospital outpatient clinic and private practice Duration of recruitment: not stated Design: Placebo-controlled, parallel group
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 randomised: 72 - 63 M and 9 F - median age: not stated Participants analysed: 68 at 1 month; 50 at 3 months Loss to follow-up/ withdrawal: 4 at 1 month; 22 at 3 months Exclusions post-randomisation: 0
Interventions	INTERVENTION: 60mg Beta-carotene + multivitamins CONTROL: placebo + multivitamins DURATION: three 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

Coodley 1996 (*Continued*)

	Body weight Karnofsky scores
Notes	Number of patients on anti-retroviral therapy: Treatment group: 10 (28%) Control group: 17 (47%) Source of funding: research grant and commercial (materials)

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	No	High attrition at 3 months; reasons not given
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Unclear	Did not declare on conflict of interest

Coutsoudis 1995

Methods	Country: South Africa Setting: Tertiary hospital study clinic Duration of recruitment: April 1991-November 1993 Design: Placebo-controlled, parallel group
Participants	INCLUSION CRITERIA: Infants of HIV-infected women who had attended the antenatal clinic, delivered in hospital, and who lived within 10 miles of the hospital. EXCLUSION CRITERIA: Preterm infants Participants randomised: 118 - 28 HIV-infected (13 in vitamin A group) - 66 M and 52 F - mean maternal age = 25 yrs (vitamin A) vs. 24.8 yrs (placebo) Loss to follow-up: 17% (vitamin A) vs. 25% (placebo) at 6 months 36% (vitamin A) vs. 33% (placebo) at 12 months 58% (vitamin A) vs. 63% (placebo) at 18 months Exclusions post-randomisation: 0

Coutsoudis 1995 (*Continued*)

Interventions	INTERVENTION: Vitamin A CONTROL: placebo DURATION: Repeat doses of 50 000 IU retinyl palmitate at 1 and 3 months and 100 000 IU at 6, 9,12 and 15 months
Outcomes	PRIMARY OUTCOMES: Overall morbidity SECONDARY OUTCOMES: Acute diarrhoea Persistent diarrhoea (>=7 days) Hospitalised for diarrhoea Thrush Upper respiratory tract infection Lower respiratory tract infection (LRTI) Hospitalised for LRTI Rash
Notes	Monthly morbidity recall. Multiple episodes of same condition in a single month counted as one episode (per 100 months). Diagnosis of HIV infection in children based on positive HIV antibody test at 15 months (enzyme-linked immunosorbent assay [ELISA], Abbott, N Chicago, Ill). Children who had lost maternal antibody by 15 months or sooner were diagnosed as uninfected. Among the 11 deaths in children younger than 15 months, 9 were diagnosed as HIV-infected on the basis of the following criteria: at least one HIV-related sign or symptom when last seen and death from severe infection or persistent diarrhea beyond the first 4 weeks of life Source of funding: Medical Research Council; University of Natal; Fogarty International Center; National Institute of Mental Health

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table
Allocation concealment?	Unclear	The capsules looked identical and were placed in number-coded envelopes from which they were removed when appropriate.
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	No	Significant losses to follow up insufficiently explained

Coutsoudis 1995 (*Continued*)

Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Unclear	Did not declare on conflict of interest

Fawzi 1998

Methods	Country: Tanzania Setting: Hospital antenatal clinic Duration of recruitment: Apr 1995 - Jul 1997 Design: Randomised trial with two-by-two factorial design
Participants	INCLUSION CRITERIA: Pregnant women (12-27 weeks gestation) with confirmed HIV infection EXCLUSION CRITERIA: Non-resident in Dar es Salaam from recruitment until one year post-delivery Participants randomised: 1085 - mean age = 24.7 yrs Participants analysed: 1078 Loss to follow-up/ withdrawal: 54 Exclusions post-randomisation: 7 deaths
Interventions	INTERVENTION: Vitamin A alone (30 mg beta-carotene plus 5000 IU preformed vitamin A) OR vitamin A plus multivitamins (20mg vit B1, 20 mg vit B2, 25 mg vit B6, 100mg niacin, 50 microg vit B12, 500 mg vit C, 30 mg vit E and 0.8 mg folic acid) OR multivitamins without vitamin A At delivery, women in both vitamin A groups were given an additional 200 000 IU vitamin A, while the other 2 groups received placebo. CONTROL: placebo DURATION: Daily for the duration of follow-up i.e. from enrolment until end of study (Aug. 2003). Median follow-up was 71 months (IQR: 46 to 80) w.r.t. survival
Outcomes	PRIMARY OUTCOMES: Maternal outcomes: Mortality and disease progression from AIDS-related causes; HIV-related complications; viral load; T-cell counts Birth outcomes: Fetal death; low birth weight (< 2500g); preterm birth (< 37 weeks) SECONDARY OUTCOMES: Mortality among all live births and among HIV-infected infants Morbidity among infants (diarrhoea; respiratory tract infections) Morbidity among mothers (hypertension; depression; social functioning) Maternal weight gain during pregnancy Postnatal child growth and development CD4 counts of infants Micronutrient status of infants Haematologic status of children Psychomotor development index Mental development index

Fawzi 1998 (*Continued*)

Notes	All women received 400mg ferrous sulphate and 5 mg folate daily, plus weekly doses of chloroquine antenatally All infants received 100000 IU vitamin A at 6 months and 200000 IU every 6 months thereafter. Vitamin A dropped from two of the regimens in Sept. 2000 and replaced with placebo due to safety concerns. Source of funding: Fogarty International Center; National Institutes of Health; National Institute of Child Health and Human Development

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computerised factorial randomisation in blocks of 20
Allocation concealment?	Yes	Sequentially numbered bottles coded identically
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	Yes	Survival analysis used to impute missing outcome data
Free of selective reporting?	Yes	Rationale and design of study fully reported, and all outcomes were reported on
Free of other bias?	Yes	Declared no conflict of interest

Fawzi 1999

Methods	Country: Tanzania Setting: Hospital inpatient and outpatient follow-up Duration of recruitment: April 1993 - March 1997. Design: Placebo-controlled, parallel group
Participants	INCLUSION CRITERIA: Admitted to hospital for pneumonia; aged 6 - 60 months; no eye signs or symptoms of vitamin A deficiency EXCLUSION CRITERIA: treatment with vitamin A for 4 months prior to study entry; severe malnutrition; measles; pulmonary tuberculosis; diphtheria; whooping cough; xerophthalmia Participants randomised:687 - 58 HIV-infected of 648 with known status (9%) - 353 M and 295 F - mean maternal age = 25.6 yrs (vitamin A group) vs. 26.2 (placebo) Participants analysed: 648

Fawzi 1999 (*Continued*)

	Loss to follow-up/ withdrawal:76 Exclusions post-randomisation: 0
Interventions	INTERVENTION: vitamin A CONTROL: placebo DURATION: single dose on hospital admission, on day 2 and at 4 and 8 months after discharge (100,000 IU dose for infants; 200,000 IU for children)
Outcomes	PRIMARY OUTCOMES: All-cause mortality Cause-specific mortality (AIDS, diarrhoea, pneumonia, malaria, anaemia and other infections (measles, meningitis, dysentery, fever of unknown origin, malnutrition)) Diarrhoea Acute respiratory infection SECONDARY OUTCOMES: Hospitalisation Visits to health centre
Notes	Sera from children were tested for HIV antibodies by enzyme- linked immunosorbent assay and Western blot tests. For positive children <15 months of age, HIV infection was confirmed by amplified heat-denatured HIV-p24 antigen assays with confirmatory neutralization assays. Cause of death ascertained by review of hospital records and home verbal autopsy questionnaire by two physicians. Discrepancies resolved by third physician. Bi-weekly morbidity recall. No data provided on episodes of persistent diarrhoea or hospitalisation of HIV-infected children. Source of funding: Thrasher Research Fund; International Development Research Center

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomisation in blocks of 20 insufficiently described
Allocation concealment?	Yes	Vitamin A and placebo were dispensed out of a dropper from identical 25-ml opaque bottles that were labelled with one of four batch numbers. The batch number code was retained by the manufacturer until the end of the study
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	Unclear	Reasons for losses to follow up (n=76) not given

Fawzi 1999 (*Continued*)

Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Unclear	Did not declare on conflict of interest

Fawzi 2005

Methods	Country: Tanzania Setting: Tertiary hospital antenatal clinic Duration of recruitment: Sept 2000 - Oct 2002 Design: Randomised placebo-controlled trial
Participants	INCLUSION CRITERIA: Pregnant women (12-27 wk.), resident in Dar es Salaam for duration of study EXCLUSION CRITERIA: None Participants randomised: 400 - mean maternal age = 27 yrs Participants analysed: 397 Loss to follow-up/ withdrawal: 3 deaths; 18 left study area after delivery Exclusions post-randomisation: 3 left study area before delivery
Interventions	INTERVENTION: Zinc (25mg) CONTROL: placebo DURATION: daily until 6 weeks after delivery.
Outcomes	PRIMARY OUTCOMES: Maternal haematological indicators at 6 weeks postpartum Birth outcomes (duration, birthweight, birth length, head circumference, placental weight, preterm births, LBWs, SGAs, fetal loss, early child mortality Maternal T-cell counts
Notes	All women received weekly ferrous sulphate, folate, chloroquine phosphate, and multi-vitamin supplements (vitamins B, C, E). Source of funding: National Institute of Child Health and Human Development

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	A randomisation list was prepared in blocks of 20
Allocation concealment?	Unclear	At enrolment, each eligible woman was assigned to the next numbered bottle of regimen.
Blinding? All outcomes	Yes	Participants and investigators were blinded

Fawzi 2005 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	Low loss to follow up, but CD4 data missing without explanation for a high proportion of both groups
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Yes	Study sponsors had no role in study design and reporting

Hanekom 2000

Methods	Country: USA Setting: Hospital HIV clinic Duration of recruitment: Not stated Design: Randomised placebo-controlled trial
Participants	INCLUSION CRITERIA: Clinic patients who were eligible for non-primary annual influenza vaccination EXCLUSION CRITERIA: Hypersensitivity to eggs, acute febrile illness, recent receipt of intravenous gammaglobulin or vaccination. Participants randomised: 59 children - M : F ratio = 0.6 (vitamin A) and 1.3 (placebo) - median (range) age = 84 (31-209) months in vitamin A group; 77 months (25-142) in placebo group Participants analysed: 59 Loss to follow-up/ withdrawal: 1 Exclusions post-randomisation: 0
Interventions	INTERVENTION: vitamin A (200 000 IU retinyl palmitate) CONTROL: placebo DURATION: daily for 2 days.
Outcomes	PRIMARY OUTCOMES: Viral load changes after vaccination Antibody levels (H1N1, H3N2) after vaccination SECONDARY OUTCOMES: T-cell counts Vitamin A levels
Notes	HIV viral load (branch-chain DNA amplification, Chiton Corp, Emeryville, CA; lower limit of detection 500 copies/mL) measured on study days 0, 14, 28, and 42 All children received inactivated influenza vaccine on study day 14. All were receiving anti-retroviral therapy. An unknown number who had ARV changes were excluded from viral load analysis.
Risk of bias	

Hanekom 2000 (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated by pharmacy
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	Yes	One exclusion due to incomplete follow up
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Unclear	Did not declare on funding sources or conflicts of interest

Humphrey 1999

Methods	Country: USA Setting: HIV Clinic Duration of recruitment: Jan - July 1996. Design: Randomised placebo-controlled safety trial
Participants	INCLUSION CRITERIA: 18 to 45 years, CD4 > 200 EXCLUSION CRITERIA: pregnant or breastfeeding Participants randomised: 40 women - mean age (SD) in years = 36.2 (5.6) in vitamin A group and 33.2 (5.6) in placebo group Participants analysed: 39 Loss to follow-up/ withdrawal: 1 Exclusions post-randomisation: 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
Notes	Number of patients on anti-retroviral therapy: vitamin A group: 12 (60%) Control group: 7 (35%) Source of funding: Paediatric AIDS Foundation grant

Humphrey 1999 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	Yes	One lost to follow up
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Unclear	Did not declare on conflict of interest

Hurwitz 2007

Methods	Country: USA Setting: University clinic Duration of recruitment: June 2001 - July 2005 Design: Placebo controlled trial
Participants	INCLUSION CRITERIA: aged 18-55 years; no history of major systemic disorders related to HIV; pre-menopausal and non - pregnant EXCLUSION CRITERIA: on treatment for chronic conditions; selenium deficient Participants randomised: 310 - mean age = 40.5 yrs Participants analysed: 262 - 179 M and 86 F Loss to follow-up/ withdrawal: 88 Exclusions post-randomisation: 48 pre-treatment
Interventions	INTERVENTION:Selenium (200 micrograms) CONTROL: placebo DURATION: daily for 9 months
Outcomes	PRIMARY OUTCOMES: Viral load CD4 count Serum selenium
Notes	Patients on ARV: 105/141 (74%) in Se group; 87/121 (72%) in placebo group Preliminary analysis at 9 months of an 18-month trial Source of funding: National Institutes of Health

Hurwitz 2007 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computerised block randomisation
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	Unclear	High unexplained losses to follow up, balanced between groups. Imputational analyses conducted.
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Yes	Declared no conflict of interest

Hussey 1996

Methods	Country: South Africa Setting: HIV clinic at a children's hospital Duration of recruitment:1994-1995. Design: Randomised placebo-controlled trial. Lost to follow-up at 2 months: Total sample: 1 (3%) Intention-to-treat: not performed.
Participants	INCLUSION CRITERIA: Child attendees at HIV clinic EXCLUSION CRITERIA: Acute infections, fever Participants randomised: 75 - mean age = 17 mo. Participants analysed: 75 Loss to follow-up/ withdrawal: 0 Exclusions post-randomisation: 0.
Interventions	INTERVENTION: 200 000 IU vitamin A CONTROL: placebo DURATION: daily for 2 days.
Outcomes	PRIMARY OUTCOMES: T-Cell counts (absolute; CD4; CD56; CD29) SECONDARY OUTCOMES: Vitamin A levels

Hussey 1996 (*Continued*)

Notes	Conference abstract only Children who received vitamin A were more immuno-suppressed 50% of children had vitamin A < 20 microgram/dl.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	Participants and investigators
Incomplete outcome data addressed? All outcomes	Unclear	Insufficient information
Free of selective reporting?	Unclear	Insufficient information; study protocol and full report not available
Free of other bias?	Unclear	Did not declare on funding sources or conflicts of interest

Jiamton 2003

Methods	Country: Thailand Setting: Outpatient clinic Duration of recruitment: Mar 2000 - Jan. 2001 Design: Placebo-controlled trial Duration of recruitment: Mar 2000- Jan 2001.
Participants	INCLUSION CRITERIA: older than 18 years; 50<CD4<550; EXCLUSION CRITERIA: taking ARV or micronutrients for during month prior to enrollment Participants randomised: 481 - 189 M and 292 F - mean age = 32 yrs Participants analysed: 481 Loss to follow-up/ withdrawal: 79 at 48 weeks Exclusions post-randomisation: 0
Interventions	INTERVENTION: Micronutrient supplement (3000 micrograms vitamin A, 6mg beta-carotene, 20 micrograms vitamin D, 80 mg vitamin E , 180 micrograms vitamin K, 400 mg vitamin C, 24mg vitamin B1, 15 mg vitamin B2, 40 mg vitamin B6, 30 microg vitamin B12, 0.1 mg folic acid, 40 mg pantothenic acid , 10 mg iron, 200 mg magnesium, 8 mg manganese, 30 mg zinc, 300 micrograms iodine, 3 mg copper, 400 micrograms selenium, 150 micrograms chromium, 60 mg cysteine)

Jiamton 2003 (*Continued*)

	CONTROL: placebo DURATION: twice daily for 48 weeks.
Outcomes	PRIMARY OUTCOMES: Mortality Hospital admissions SECONDARY OUTCOMES: CD4 counts Viral load
Notes	Source of funding: Nestle Foundation; Vitabiotics

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Centralised randomisation in blocks of 10
Allocation concealment?	Yes	Interventions packaged in identical coded bottles
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	No	Those lost to follow-up were sicker than those who remained in the trial (baseline median CD4 counts among those lost did not differ between groups. Survival analysis used to address missing outcome data.
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Yes	Declared independence of study investigators declared

Kaiser 2006

Methods	Country: USA Setting: Four HIV study centres Duration of recruitment: Jan. 2002- May 2003 Design: Placebo-controlled trial
Participants	INCLUSION CRITERIA: On stable HAART regimen for >= 3 months; had developed symptoms of mitochondrial toxicity (distal symmetrical polyneuropathy (DSP)) from either stavudine and/or didanosine EXCLUSION CRITERIA: Pregnant; on treatment for active opportunistic infection or malignancy; vitamin B12

	deficient; already taking more than one micronutrient pill per day Participants randomised: 40 - 35 M and 5 F - mean age = 46 yrs Participants analysed: 40 Loss to follow-up/ withdrawal: 0 Exclusions post-randomisation: 0
Interventions	INTERVENTION: Micronutrient supplement (33 ingredients) CONTROL: placebo DURATION: 2x daily for 12 weeks
Outcomes	PRIMARY OUTCOMES: CD4 counts Viral load SECONDARY OUTCOMES: Metabolic parameters Neuropathy symptoms (DSP) score General health status
Notes	Source of funding:Bristol Myers-Squibb

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Unclear	Method of block randomisation method not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	Yes	No losses to follow up
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Yes	Declared no conflict of interest

Kelly 1999

Methods	Country: Zambia Setting: Home care service of tertiary hospital Duration of recruitment: not stated Design: 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 randomised: 135 - 79 M and 56 F - median age = 32.5 yrs (micronutrient); 34 (placebo) Participants analysed: 106 Loss to follow-up/ withdrawal: 29 Exclusions post-randomisation: 0
Interventions	INTERVENTION: Micronutrient supplement (10 500 IU vitamin A, 300mg vitamin C, 300mg vitamin E, 150 microg Selenium and 200mg Zinc sulphate) Both treatment groups also received 5mg folic acid and 800mg albendazole twice daily. CONTROL: placebo DURATION: daily for 2 weeks
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 Body Mass Index and 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
Notes	Source of funding: Smithkline Beecham

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Method not described
Allocation concealment?	Unclear	Not described
Blinding? All outcomes	No	Micronutrient and placebo capsules were not identical; unclear whether providers and assessors were blinded

Kelly 1999 (*Continued*)

Incomplete outcome data addressed? All outcomes	No	25% of patients were lost to follow-up due to death and the tradition of going back to the family home when terminally ill.
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Unclear	Did not declare on conflicts of interest.

Kupka 2008

Methods	Country: Tanzania Setting: antenatal clinics Duration of recruitment: Sept 2003 - July 2005 Design: Placebo-controlled, parallel group
Participants	INCLUSION CRITERIA: HIV-infected pregnant women (12-27 weeks gestation) seeking care EXCLUSION CRITERIA: Non-residents in Dar-es-Salaam or those not intending to stay until at least one year post-delivery Participants randomised: 915 - mean age = 27.5 yrs Participants analysed: 913 Loss to follow-up/ withdrawal: 0 Exclusions post-randomisation: 2
Interventions	INTERVENTION: Selenium (200 microgram selenomethionine) CONTROL: placebo DURATION: daily until 6 months post-delivery
Outcomes	PRIMARY OUTCOMES: Viral load; CD4 counts; genital shedding of HIV-infected cells; risk of mastitis; birth weight; adverse pregnancy outcomes; maternal and infant mortality SECONDARY OUTCOMES: Haemoglobin concentrations; maternal morbidity
Notes	Supported by the National Institute of Child Health and Human Development (NICHD R24 043555-05).

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computerised block randomisation

Kupka 2008 (*Continued*)

Allocation concealment?	Yes	Stickers used to conceal numeric allocation codes
Blinding? All outcomes	Yes	Participants and investigators
Incomplete outcome data addressed? All outcomes	Yes	Data on birth outcomes and birth weight missing for a low proportion of participants, and survival analysis used for mortality outcomes
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Yes	Declared no conflict of interest

Luabeya 2007

Methods	Country: South Africa Setting: Five rural primary care clinics Duration of recruitment: June 2003 - Oct 2004 Design: Controlled trial
Participants	INCLUSION CRITERIA: children 4-6 months old EXCLUSION CRITERIA: underweight for age; nutritional oedema; persistent diarrhoea; taking vitamin or micronutrient supplements in past month Participants randomised: 373 - 32 HIV-infected; 154 born to HIV-infected mothers; 187 born to HIV-uninfected mothers - 173 M and 162 F - mean age = 5.5 months Participants analysed: 335 Loss to follow-up/ withdrawal: 88 Exclusions post-randomisation: 0
Interventions	INTERVENTIONS: Zinc (10mg) and multiple micronutrients (B vitamins; vitamins C, D, E, K; copper, iron, iodine) vs. zinc and vitamin A (1250 IU) CONTROL: Vitamin A DURATION: daily for median duration of 14.9 months.
Outcomes	PRIMARY OUTCOMES: Percentage of days of diarrhoea per child SECONDARY OUTCOMES: Severity of diarrhoea

Luabeya 2007 (*Continued*)

	Percentage of weeks with upper respiratory symptoms Percentage of children who ever had pneumonia (maternal and field worker reports)
Notes	HIV testing of children was done between ages of 4 and 6 months using a quantitative HIV RNA assay (Nuclisens HIV-1 QT, Organon Teknika or Nuclisens EasyQ HIV-1, Biomerieux, Boxtel, The Netherlands) Source of funding: National Institute of Health; Wellcome Trust Declared no conflicts of interest

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computerised randomisation in blocks of 6
Allocation concealment?	Yes	Pre-packed sequentially numbered study supplements
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	Yes	Missing data addressed used appropriate statistical methods
Free of selective reporting?	Yes	All outcomes of interest were reported on
Free of other bias?	Unclear	Delay in shipment of supplements prevented 243 children from receiving supplements for 11 weeks

Range 2006

Methods	Country: Tanzania Setting: Five district health facilities Duration of recruitment: August 2001 to July 2002 Design: Placebo-controlled 2x2 factorial trial
Participants	INCLUSION CRITERIA: HIV-positive and HIV-negative persons aged >=15 years with sputum-positive pulmonary tuberculosis (new or relapsed cases) EXCLUSION CRITERIA: Patients who defaulted TB 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 randomised: 530 - 213 HIV-infected - 325 M and 205 F

Range 2006 (*Continued*)

	- mean age = 35.4 yrs Participants analysed: 499 Loss to follow-up/ withdrawal: 77 within 244 days post-treatment Exclusions post-randomisation: 31
Interventions	INTERVENTIONS: Micronutrient supplement contained vitamin A (1.5mg), vitamin B1 (20 mg), vitamin B2 (20 mg), vitamin B6 (25 mg), vitamin B12 (50mg), folic acid (08 mg), niacin (40 mg), vitamin C (200 mg), vitamin E (60 mg), vitamin D3 (5mg), selenium (02 mg) and copper (5 mg), and Zn tablets contained 45 mg elementary Zn CONTROL: placebo (2x2 factorial) DURATION: daily for 8 months. All patients received a standard 8 month TB chemotherapy regimen.
Outcomes	PRIMARY OUTCOMES: All-cause mortality at 8 months SECONDARY OUTCOMES: Viral load CD4 counts Weight gain
Notes	Source of funding: Danish International Development Assistance

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computerised randomisation
Allocation concealment?	Yes	Sealed envelopes, codes unbroken until post-analysis
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	Unclear	Survival analysis was done but there were significant imbalances in losses between intervention groups
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Yes	Declared no conflict of interest

Semba 1998

Methods	Country: USA Setting: Community-based clinic Duration of recruitment: Not stated Design: Placebo-controlled trial
Participants	INCLUSION CRITERIA: HIV-infected 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/mm3; pregnancy. Participants randomised: 120 - 89 M and 31 F - mean age = 38.2 yrs - 50% treatment group vs. 43% placebo group on ART Participants analysed: 120 Loss to follow-up/ withdrawal: 8.3% at 4 weeks Exclusions post-randomisation: 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
Notes	Source of funding: USAID

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Random number table in blocks of 10
Allocation concealment?	Yes	Sequentially numbered envelopes used to conceal allocation
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	Yes	Missing outcome data were balanced across groups
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Unclear	Did not declare on conflicts of interest.

Semba 2005

Methods	Country: Uganda Setting:Hospital clinic Duration of recruitment:Jan. 1995 - June 1998 Design: Placebo-controlled trial
Participants	INCLUSION CRITERIA: Children aged 6 months; resident near hospital for duration of trial EXCLUSION CRITERIA: Evidence of vitamin A deficiency Participants randomised: 181 at age 15 months - 90 M and 91 F - mean age = 15 months Participants analysed: 168 Loss to follow-up/ withdrawal: 0 Exclusions post-randomisation: 0
Interventions	INTERVENTION: 200 000 IU vitamin A CONTROL: placebo DURATION: every 3 months from 15 to 36 months.
Outcomes	PRIMARY OUTCOMES: Mortality SECONDARY OUTCOMES: Morbidity (diarrhoea, cough, fever, ear discharge, hospitalisation)
Notes	Infants of HIV-positive women were tested for HIV-1 infection by using a p24 antigen assay (Coulter Diagnostics, Hialeah, FL, USA) until June 1996, after which time infants were tested for HIV-1 by using a qualitative assay for HIV-1 DNA polymerase chain reaction (PCR; HIV-1 Amplicor, Roche Diagnostics, Indianapolis, IN, USA) or a quantitative assay for HIV-1 RNA PCR (Roche Amplicor Monitor, Roche Diagnostics, Branchburg, NJ, USA). All results were confirmed by serologic testing at ages 15 to 18 mo and by quantitative HIV-1 RNA PCR at age 15 mo (Roche Amplicor Monitor). All children received daily prophylactic sulfamethoxazole- trimethoprim therapy Source of funding: National Institutes of Health Declared no conflicts of interest

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated, random codes
Allocation concealment?	Yes	Sequentially numbered pill cards were used
Blinding? All outcomes	Yes	Participants, paediatrician and clinic staff were blinded

Semba 2005 (*Continued*)

Incomplete outcome data addressed? All outcomes	Unclear	Survival analysis used to account for differences in duration of follow up due to early termination of the trial
Free of selective reporting?	Yes	Study protocol not available but all stated outcomes of interest reported on
Free of other bias?	Yes	Trial stopped early due to change in national guideline on vitamin A supplementation

Semba 2007a

Methods	Country: USA Setting: Study clinic Duration of recruitment: Sept. 2002 - Aug. 2005 Design: Controlled trial
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 randomised: 458 - mean age = 40 yrs - 138 (30.1%) HIV-positive Participants analysed: 115 at 12 months Loss to follow-up/ withdrawal:151 (33%) Exclusions post-randomisation: 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
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

Semba 2007a (*Continued*)

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computerised randomisation
Allocation concealment?	Yes	Pre-packed sequentially numbered study supplements
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	No	High loss to follow up (27.7%) in both groups, and not reported by HIV status
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Unclear	Did not declare on conflicts of interest.

Semba 2007b

Methods	Country: Malawi Setting: Eight community health centres Duration of recruitment: July 1999 - 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 TB chemotherapy, prior vitamin supplements Participants randomised: 1148 - 829 HIV-positive - 336 M and 493 F - mean age = 34 yrs Participants analysed: 1148 Loss to follow-up: 103 in HIV-positive group (50 and 53 in micronutrient and placebo groups, respectively) Exclusions post-randomisation: 0
Interventions	INTERVENTION: Micronutrient supplement (vitamin A, C, D, E, B6, B12, Riboflavin, Thiamine, Niacin, folate, zinc, iodine, selenium) CONTROL: placebo DURATION: daily for 24 months.. All patients received a standard 8 month TB chemotherapy regimen.
Outcomes	PRIMARY OUTCOMES: All-cause mortality SECONDARY OUTCOMES:

Semba 2007b (*Continued*)

	Serum vitamin A, vitamin E and selenium	
Notes	Source of funding: National Institutes of Health and the Fogarty International Centre.	
Risk of bias		
Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Blocked randomisation
Allocation concealment?	Yes	pre-packed sequentially numbered study supplements
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	Unclear	High unexplained loss to follow up but survival analysis was used
Free of selective reporting?	Yes	Study protocol available; all outcomes of interest were reported on
Free of other bias?	Unclear	Did not declare on conflicts of interest.

Villamor 2008

Methods	Country: Tanzania Setting: Five outpatient TB clinics Duration of recruitment: April 2000 - April 2005 Design: Placebo-controlled
Participants	INCLUSION CRITERIA: age 18-65 years; non-pregnant; no anti-TB treatment for > 4 weeks in previous year; Karnofsky score >=40%; plan to stay in Dar es Salaam for 2 years EXCLUSION CRITERIA: none Participants randomised: 887 - 471 HIV-positive - 273 M and 198 F - mean age = 34 yrs Participants analysed: 1148 Loss to follow-up: 67 in HIV-positive group (33 and 34 in micronutrient and placebo groups, respectively) Exclusions post-randomisation: 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..

Villamor 2008 (*Continued*)

	All patients received DOTS anti-TB chemotherapy.
Outcomes	PRIMARY OUTCOMES: Culture negativity at 1 month after initiation of treatment; mortality during at least 24 months of follow-up; TB recurrences. SECONDARY OUTCOMES: Changes from baseline in viral load, CD4 cell counts, and body weight.
Notes	Source of funding: National Institute of Allergy and Infectious Diseases; US Department of Agriculture

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	computer-generated permuted blocks of 20, stratified by HIV status
Allocation concealment?	Unclear	All clinical and research staff were unaware of the subjects' treatment assignment, but insufficient information provided
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	Unclear	Reasons not given for losses to follow-up, although appropriate statistical analyses were used
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Yes	Declared no conflicts of interest

Wejse 2009

Methods	Country: Guinea-Bissau Setting: TB clinics in urban disease surveillance site Duration of recruitment: Nov 2003 - Dec 2005 Design: Placebo-controlled, parallel group
Participants	INCLUSION CRITERIA: TB patients starting anti-TB treatment, >=15 years. EXCLUSION CRITERIA: None Participants randomised: 367 - 222 M and 143 F - mean age = 37.5 yrs

Wejse 2009 (*Continued*)

	- 131 HIV-infected Participants analysed: 365 Loss to follow-up/ withdrawal: 84 Exclusions post-randomisation: 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 (TB score) SECONDARY OUTCOMES: 12-month mortality
Notes	Source of funding: Aarhus University Hospital; Danish Research Council for Developmental Research

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	Computer-generated sequence
Allocation concealment?	Yes	Identical, sequentially numbered containers were used.
Blinding? All outcomes	Yes	Patients, staff and researchers
Incomplete outcome data addressed? All outcomes	Unclear	Loss to follow up unknown in HIV+ subgroup; survival analysis used
Free of selective reporting?	Yes	Protocol available; all outcomes of interest reported on
Free of other bias?	Yes	HIV subgroup analyses not pre-specified but proportions were equally distributed; funder and provider had no role in study design

ZVITAMBO 2006

Methods	Country: Zimbabwe Setting:Maternity clinics and hospitals Duration of recruitment:Nov. 1997 - Jan. 2000 Design: Randomised trial with two-by-two factorial design

ZVITAMBO 2006 (*Continued*)

Participants	INCLUSION CRITERIA: Mother-infant pairs; HIV+ mothers; singleton infant with birthweight >=1500 g; resident in Harare after delivery EXCLUSION CRITERIA: Mother or infant with acute life-threatening condition Participants randomised: 4495 mothers - mean age = 25.6 yrs Participants analysed: 4495 infants of HIV+ mothers at baseline; 2582 infants assessable at 6 weeks for postnatal HIV infection Loss to follow-up/ withdrawal: 139 infants excluded from 24-month mortality analysis due to loss to follow-up, death from unnatural causes, or missing dates Exclusions post-randomisation: 0
Interventions	INTERVENTION:Single dose of maternal vitamin A (400 000 IU) and infant vitamin A (50 000 IU) OR maternal dose only OR infant dose only CONTROL: placebo DURATION: single dose <=96 hours after delivery
Outcomes	PRIMARY OUTCOMES: Postnatal mother-to-child transmission (MTCT) of HIV Child HIV-free survival Infant mortality up to 24 months
Notes	Follow-up period curtailed due to economic conditions in Zimbabwe Source of funding: Canadian International Development Agency, USAID, Gates Foundation; Rockefeller Foundation; BASF

Risk of bias

Item	**Authors' judgement**	**Description**
Adequate sequence generation?	Yes	Computerised factorial randomisation in blocks of 12
Allocation concealment?	Yes	Sealed envelopes and encrypted computer files
Blinding? All outcomes	Yes	Participants and investigators were blinded
Incomplete outcome data addressed? All outcomes	Yes	Survival analysis used to include censored data
Free of selective reporting?	Unclear	Insufficient information; study protocol not available
Free of other bias?	Yes	Declared no conflict of interest

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

Study	Reason for exclusion
Austin 2003	Trial terminated prematurely due to unstable intervention.
Constans 1996	Pilot study; vitamin A group had more advanced disease at baseline
Kennedy 2000	Included in Wiysonge 2005 review: Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection
Kumwenda 2002	Included in Wiysonge 2005 review: Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection
Mehta 2009	Observational analysis of perinatal outcomes and mortality vs. maternal vitamin D status in Tanzanian trial (Fawzi et al 1998)
Shor-Posner 2003	No outcomes of relevance to this review

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

Baum 2010

Methods	Country: USA Setting:hospital outpatient clinic Duration of recruitment:March 2002 - December 2005 Design: Placebo-controlled trial
Participants	INCLUSION CRITERIA: HIV-infected adults 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 study Participants randomised: 231 - 62 F and 169 M - mean age = 42.7 yrs Participants analysed:200 Loss to follow-up/ withdrawal:31 Exclusions post-randomisation: 0
Interventions	INTERVENTION:12 mg of elemental zinc for women; 15 mg for men CONTROL: placebo DURATION: 18 months
Outcomes	PRIMARY OUTCOMES:HIV disease progression, specifically immunological failure (CD4 < 200) SECONDARY OUTCOMES:HIV viral load, morbidity, and mortality
Notes	

CIGNIS 2010

Methods	Country: Zambia Setting:Public health sector clinic Duration of recruitment:October 2005 to July 2009 Design: Placebo-controlled trial
Participants	INCLUSION CRITERIA: healthy 6 month old infants EXCLUSION CRITERIA: no parental consent Participants randomised:743 - mean age = 6 months Participants analysed:576 Loss to follow-up/ withdrawal:167 Exclusions post-randomisation: 0
Interventions	INTERVENTION:micronutrient fortified porridge CONTROL: conventionally fortified porridge DURATION:12 months
Outcomes	PRIMARY OUTCOMES:stunting at age 18 months SECONDARY OUTCOMES:hospital referral; death
Notes	

Mda 2010

Methods	Country: South Africa Setting: academic hospital Duration of recruitment: November 2005 and May 2007 Design: Placebo-controlled trial
Participants	INCLUSION CRITERIA: HIV-infected children aged between 4 mo and 2 y; admitted with diarrhoea or pneumonia to the paediatric wards of an academic hospital EXCLUSION CRITERIA: diarrheal episode longer than 72 h on admission; pneumonia complicated by respiratory failure; children on ART or those who had received vitamin or micronutrient supplementation; children with chronic illness unrelated to HIV Participants randomised: - Participants analysed: Loss to follow-up/ withdrawal: Exclusions post-randomisation: 0
Interventions	
Outcomes	
Notes	

Ndeezi 2010

Methods	Country: Uganda Setting:Paediatric HIV clinics of the national referral hospital Duration of recruitment:June 2005-June 2008 Design: Placebo-controlled trial
Participants	INCLUSION CRITERIA: children aged 1 - 5 years whose mothers had attended the clinic at least once, and who adhered to a regular study follow-up schedule for one year. EXCLUSION CRITERIA: Children enrolled in other studies, those residing more than 15 kilometres from the clinic and those whose parents or caretakers were anticipating moving from the study area Participants randomised:847 - 56% were less than 36 months Participants analysed:695 Loss to follow-up/ withdrawal:152 Exclusions post-randomisation: 0
Interventions	INTERVENTION: 2xRDA of 14 micronutrients CONTROL: RDA of six multivitamins DURATION:6 months
Outcomes	PRIMARY OUTCOMES:Mortality at 12 months SECONDARY OUTCOMES:Growth (weight-for-height at 12 months); CD4 counts
Notes	

DATA AND ANALYSES

Comparison 1. Vitamin A in adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Maternal mortality	1		Hazard Ratio (Random, 95% CI)	Totals not selected
1.1 Twelve months	1		Hazard Ratio (Random, 95% CI)	Not estimable
1.2 Twenty four months	1		Hazard Ratio (Random, 95% CI)	Not estimable
2 Hospitalised at least once by 12 months post partum	1	4495	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.76, 1.22]
3 Infant death or HIV infection at 24 months	1	4495	Risk Ratio (M-H, Random, 95% CI)	1.02 [0.94, 1.10]
4 Infant HIV infection at 24 months	1	4495	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.91, 1.09]

Comparison 2. Vitamin A in children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	3	262	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.37, 0.82]
2 Morbidity rates	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 All-cause morbidity	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.2 Diarrhoea	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.3 Diarrhoea lasting a week or more	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2.4 Lower respiratory tract infection	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
3 Child growth at 12 months	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
3.1 Wasting	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
3.2 Stunting	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 3. Vitamin D in adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical severity score (TBscore) at 8 months	1	71	Mean Difference (IV, Random, 95% CI)	0.10 [-0.53, 0.73]
2 All cause mortality at 12 months	1	131	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.65, 2.02]

Comparison 4. Vitamin D in children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CD4 counts at 12 months	1	56	Mean Difference (IV, Random, 95% CI)	115.0 [-74.26, 304.26]
2 Viral load at 12 months	1	56	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.63, 0.43]

Comparison 5. Zinc in adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Newborn outcomes	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 Duration of pregnancy	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.2 Birth weight	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.3 Birth length	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.4 Head circumference	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
1.5 Placental weight	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
2 Low birth weight and prematurity	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Preterm < 37 wks	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Low birth weight < 2500 g	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Small for gestational age	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3 Fetal loss and early child mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Miscarriage	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.2 Stillbirth	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.3 Fetal death	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.4 Perinatal death	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.5 Neonatal death	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
4 Immune cell counts	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
4.1 CD4 counts at 6 weeks post partum	1		Mean Difference (IV, Random, 95% CI)	Not estimable
4.2 CD8 counts at 6 weeks postpartum	1		Mean Difference (IV, Random, 95% CI)	Not estimable
4.3 CD3 counts at 6 weeks postpartum	1		Mean Difference (IV, Random, 95% CI)	Not estimable
5 Viral load at 6 weeks postpartum	1	100	Mean Difference (IV, Random, 95% CI)	-0.32 [-0.69, 0.05]
6 Anthropometric outcomes	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
6.1 Overall weight gain during pregancy	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
6.2 Rate of weight gain during pregancy	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
6.3 Total change in MUAC durng pregnancy	1		Mean Difference (IV, Fixed, 95% CI)	Not estimable
7 Persistent diarrhoea at 2 weeks	1	104	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.76, 1.44]

Comparison 6. Zinc in children

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at 9 months	1	96	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.07, 1.42]
2 Scheduled and illness visits	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 Scheduled visits; watery diarrhoea	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.2 Scheduled visits; pneumonia	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.3 Scheduled visits; URI	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.4 Scheduled visits; ear infection	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.5 All visits; watery diarrhoea	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.6 All visits; URI	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.7 All visits; pneumonia	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2.8 All visits; ear infection	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3 Viral load at 9 months	1	85	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.40, 0.20]
4 CD4 % at 9 months	1	85	Mean Difference (IV, Random, 95% CI)	1.0 [-2.87, 4.87]

Comparison 7. Selenium in adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Adverse pregnancy outcomes	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 Low birth weight < 2500 g	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.2 Very low birth weight < 2000 g	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.3 Preterm birth < 37 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.4 Preterm birth < 34 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.5 Low birth weight and preterm birth	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.6 Low birth weight and term birth	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.7 Small for gestational age	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
2 Adverse pregnancy outcomes	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
2.1 Mean birth weight (g)	1		Mean Difference (IV, Random, 95% CI)	Not estimable
3 Perinatal mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 Miscarriage before 28 wks.	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.2 Stillbirth between 28 wk and delivery	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.3 Fetal loss	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
3.4 Perinatal death	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
4 Infant mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Neonatal death	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
4.2 Infant death	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable

4.3 Neonatal or infant death	1		Risk Ratio (M-H, Random, 95% CI)	Not estimable
5 Adult mortality	1	913	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.51, 1.98]
6 Viral load change 0-9 months	1	130	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.51, -0.15]
7 CD4 count change from 0- 9 months	1	130	Mean Difference (IV, Random, 95% CI)	65.0 [56.80, 73.20]
8 Hospitalised for all conditions	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Hospitalised for OIs and HIV-related conditions	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Comparison 8. Multiple supplements in non-pregnant adults

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Mortality (all cause) by 48 weeks	1		Hazard ratio (Random, 95% CI)	Totals not selected
2.1 New Subgroup	1		Hazard ratio (Random, 95% CI)	Not estimable
3 Mortality by 48 weeks (baseline CD4 < 200)	1		Hazard ratio (Random, 95% CI)	Subtotals only
4 Mortality by 48 weeks (baseline CD4 >= 200)	1		Hazard ratio (Random, 95% CI)	Totals not selected
5 Mortality by 48 weeks (baseline CD4 < 100)	1		Hazard ratio (Random, 95% CI)	Totals not selected
6 Mortality by 48 weeks (baseline CD4 >=100)	1		Hazard ratio (Random, 95% CI)	Totals not selected
7 New AIDS -defining infections	1	16	Risk Ratio (M-H, Random, 95% CI)	3.11 [0.44, 22.00]
8 New HIV-associated infections	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9 Recurrent HIV-associated infections	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
10 New other infections	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
11 Recurrent other infections	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
12 Viral load at 12 months	5	401	Mean Difference (IV, Fixed, 95% CI)	-1.07 [-1.25, -0.90]
13 CD 4 counts at 12 months	4	358	Mean Difference (IV, Fixed, 95% CI)	1.31 [-86.14, 88.76]
14 CD 8 counts at 12 months	2	222	Mean Difference (IV, Fixed, 95% CI)	18.0 [-219.65, 255.65]
15 CD 3 counts (entire period)	1	172	Mean Difference (IV, Fixed, 95% CI)	Not estimable
16 Weight gain at 7 months	1	192	Mean Difference (IV, Fixed, 95% CI)	Not estimable
17 Viral load change : Baseline to 2 months	1	96	Mean Difference (IV, Fixed, 95% CI)	Not estimable
18 CD4 cell count change: Baseline to 2 months	2	136	Mean Difference (IV, Fixed, 95% CI)	24.0 [5.75, 42.25]
19 Change in weight: Baseline to 7 months	1	192	Mean Difference (IV, Fixed, 95% CI)	Not estimable
20 Treatment failure after 1 month	1	322	Odds Ratio (M-H, Fixed, 95% CI)	0.73 [0.39, 1.37]

Comparison 9. Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Progression to stage 4 disease / death from AIDS-related causes	1		Hazard ratio (Random, 95% CI)	Totals not selected
2 Death from AIDS-related causes	1		Hazard ratio (Random, 95% CI)	Totals not selected
3 Progression to stage 4 disease	1		Hazard ratio (Random, 95% CI)	Totals not selected
4 Progression to stage 3 disease or higher	1		Hazard ratio (Random, 95% CI)	Totals not selected
5 HIV-related complications: thrush	1		Hazard ratio (Random, 95% CI)	Totals not selected
6 HIV-related complications: gingival erythema	1		Hazard ratio (Random, 95% CI)	Totals not selected
7 HIV-related complications: angular cheilitis	1		Hazard ratio (Random, 95% CI)	Totals not selected
8 HIV-related complications: oral ulcer	1		Hazard ratio (Random, 95% CI)	Totals not selected
9 HIV-related complications: reported mouth and throat ulcers	1		Hazard ratio (Random, 95% CI)	Totals not selected
10 HIV-related complications: painful tongue or mouth	1		Hazard ratio (Random, 95% CI)	Totals not selected
11 HIV-related complications: difficult or painful swallowing	1		Hazard ratio (Random, 95% CI)	Totals not selected
12 HIV-related complications: nausea and vomiting	1		Hazard ratio (Random, 95% CI)	Totals not selected
13 HIV-related complications: diarrhoea	1		Hazard ratio (Random, 95% CI)	Totals not selected
14 HIV-related complications: dysentery	1		Hazard ratio (Random, 95% CI)	Totals not selected
15 HIV-related complications: fatigue	1		Hazard ratio (Random, 95% CI)	Totals not selected
16 HIV-related complications: rash	1		Hazard ratio (Random, 95% CI)	Totals not selected
17 HIV-related complications: acute upper respiratory tract infection	1		Hazard ratio (Random, 95% CI)	Totals not selected
18 CD4 difference (baseline up to 3 months)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
19 CD4 difference (baseline to over 3 months)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
20 CD8 difference (baseline up to 3 months)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected
21 CD8 difference (baseline to over 3 months)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Comparison 10. Multiple supplements in pregnant and lactating women [child outcomes]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Foetal death (miscarriage+stillbirth)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2 Total mortality by 24 months including foetal deaths	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3 Mortality by 24 months among all live births	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4 Mortality by 24 months among HIV-infected live births	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5 Mortality by 24 months among HIV-infected infants at 6 weeks of age	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6 Mean birthweight	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
7 Birthweight < 2000 g	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8 Birthweight < 2500 g	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
9 Preterm birth (<37 weeks)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10 Severe preterm birth (<34 weeks)	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
11 Small for gestational age	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
12 CD4 count >= 3 months	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

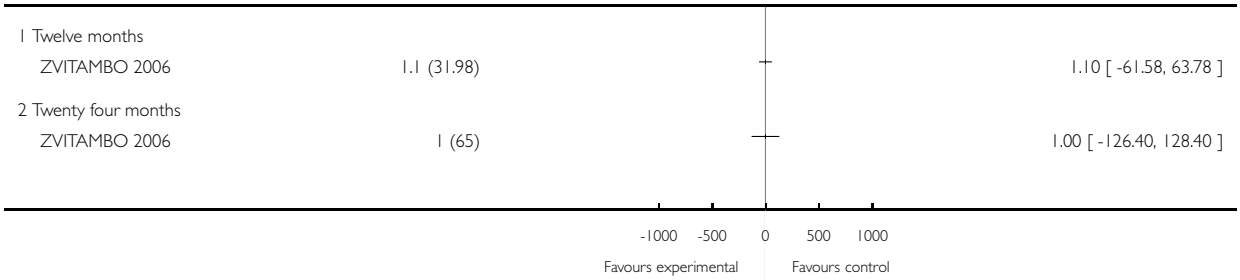
Analysis 1.1. Comparison 1 Vitamin A in adults, Outcome 1 Maternal mortality.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 1 Vitamin A in adults

Outcome: 1 Maternal mortality

Study or subgroup	Hazard Ratio (SE)	Hazard Ratio IV,Random,95% CI	Hazard Ratio IV,Random,95% CI
1 Twelve months			
ZVITAMBO 2006	1.1 (31.98)		1.10 [-61.58, 63.78]
2 Twenty four months			
ZVITAMBO 2006	1 (65)		1.00 [-126.40, 128.40]



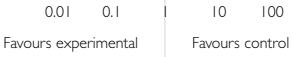
Analysis 1.2. Comparison 1 Vitamin A in adults, Outcome 2 Hospitalised at least once by 12 months post partum.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 1 Vitamin A in adults

Outcome: 2 Hospitalised at least once by 12 months post partum

Study or subgroup	Vitamin A n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
ZVITAMBO 2006	126/2229	133/2266		100.0 %	0.96 [0.76, 1.22]
Total (95% CI)	**2229**	**2266**		**100.0 %**	**0.96 [0.76, 1.22]**
Total events: 126 (Vitamin A), 133 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.31 (P = 0.76)					



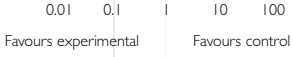
Analysis 1.3. Comparison 1 Vitamin A in adults, Outcome 3 Infant death or HIV infection at 24 months.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 1 Vitamin A in adults

Outcome: 3 Infant death or HIV infection at 24 months

Study or subgroup	Vitamin A (Aa+Ap) n/N	Placebo (Pa+Pp) n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
ZVITAMBO 2006	780/2229	781/2266		100.0 %	1.02 [0.94, 1.10]
Total (95% CI)	**2229**	**2266**		**100.0 %**	**1.02 [0.94, 1.10]**
Total events: 780 (Vitamin A (Aa+Ap)), 781 (Placebo (Pa+Pp))					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.37 (P = 0.71)					



Analysis 1.4. Comparison 1 Vitamin A in adults, Outcome 4 Infant HIV infection at 24 months.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 1 Vitamin A in adults

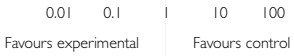
Outcome: 4 Infant HIV infection at 24 months

Study or subgroup	Vitamin A (Ap+Aa) n/N	Placebo (Pa+Pp) n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
ZVITAMBO 2006	643/2229	657/2266		100.0 %	0.99 [0.91, 1.09]
Total (95% CI)	**2229**	**2266**		**100.0 %**	**0.99 [0.91, 1.09]**

Total events: 643 (Vitamin A (Ap+Aa)), 657 (Placebo (Pa+Pp))

Heterogeneity: not applicable

Test for overall effect: Z = 0.11 (P = 0.91)



Analysis 2.1. Comparison 2 Vitamin A in children, Outcome 1 All-cause mortality.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 2 Vitamin A in children

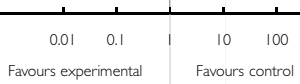
Outcome: 1 All-cause mortality

Study or subgroup	Vitamin A n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Coutsoudis 1995	3/13	6/15		11.6 %	0.58 [0.18, 1.86]
Fawzi 1999	6/28	14/25		25.5 %	0.38 [0.17, 0.84]
Semba 2005	18/87	31/94		62.9 %	0.63 [0.38, 1.04]
Total (95% CI)	**128**	**134**		**100.0 %**	**0.55 [0.37, 0.82]**

Total events: 27 (Vitamin A), 51 (Placebo)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.08$, df = 2 (P = 0.58); $I^2 = 0.0\%$

Test for overall effect: Z = 2.96 (P = 0.0031)



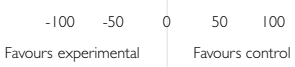
Analysis 2.2. Comparison 2 Vitamin A in children, Outcome 2 Morbidity rates.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 2 Vitamin A in children

Outcome: 2 Morbidity rates

Study or subgroup	Vitamin A N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 All-cause morbidity						
Coutsoudis 1995	97	0 (0)	97	0 (0)		0.0 [0.0, 0.0]
2 Diarrhoea						
Coutsoudis 1995	97	0 (0)	97	0 (0)		0.0 [0.0, 0.0]
3 Diarrhoea lasting a week or more						
Coutsoudis 1995	97	0 (0)	97	0 (0)		0.0 [0.0, 0.0]
4 Lower respiratory tract infection						
Coutsoudis 1995	97	0 (0)	97	0 (0)		0.0 [0.0, 0.0]



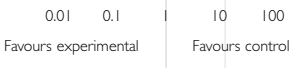
Analysis 2.3. Comparison 2 Vitamin A in children, Outcome 3 Child growth at 12 months.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 2 Vitamin A in children

Outcome: 3 Child growth at 12 months

Study or subgroup	Vitamin A n/N	Placebo n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
1 Wasting				
Fawzi 1999	2/22	7/19		0.25 [0.06, 1.05]
2 Stunting				
Fawzi 1999	6/13	11/16		0.67 [0.34, 1.32]



Analysis 3.1. Comparison 3 Vitamin D in adults, Outcome 1 Clinical severity score (TBscore) at 8 months.

Review: Micronutrient supplementation in children and adults with HIV infection

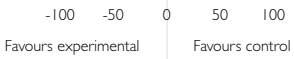
Comparison: 3 Vitamin D in adults

Outcome: 1 Clinical severity score (TBscore) at 8 months

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Wejse 2009	39	1.3 (1.4)	32	1.2 (1.3)		100.0 %	0.10 [-0.53, 0.73]
Total (95% CI)	**39**		**32**			**100.0 %**	**0.10 [-0.53, 0.73]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.31 (P = 0.76)



Analysis 3.2. Comparison 3 Vitamin D in adults, Outcome 2 All cause mortality at 12 months.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 3 Vitamin D in adults

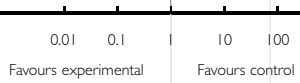
Outcome: 2 All cause mortality at 12 months

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Wejse 2009	21/72	15/59		100.0 %	1.15 [0.65, 2.02]
Total (95% CI)	**72**	**59**		**100.0 %**	**1.15 [0.65, 2.02]**

Total events: 21 (Treatment), 15 (Control)

Heterogeneity: not applicable

Test for overall effect: Z = 0.48 (P = 0.63)



Analysis 4.1. Comparison 4 Vitamin D in children, Outcome 1 CD4 counts at 12 months.

Review: Micronutrient supplementation in children and adults with HIV infection

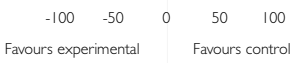
Comparison: 4 Vitamin D in children

Outcome: 1 CD4 counts at 12 months

Study or subgroup	Vitamin D N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Arpadi 2009	29	776 (359)	27	661 (363)		100.0 %	115.00 [-74.26, 304.26]
Total (95% CI)	**29**		**27**			**100.0 %**	**115.00 [-74.26, 304.26]**

Heterogeneity: not applicable

Test for overall effect: Z = 1.19 (P = 0.23)



Analysis 4.2. Comparison 4 Vitamin D in children, Outcome 2 Viral load at 12 months.

Review: Micronutrient supplementation in children and adults with HIV infection

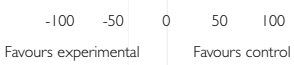
Comparison: 4 Vitamin D in children

Outcome: 2 Viral load at 12 months

Study or subgroup	Vitamin D N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Arpadi 2009	29	2.4 (0.9)	27	2.5 (1.1)		100.0 %	-0.10 [-0.63, 0.43]
Total (95% CI)	**29**		**27**			**100.0 %**	**-0.10 [-0.63, 0.43]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.37 (P = 0.71)



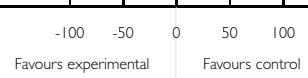
Analysis 5.1. Comparison 5 Zinc in adults, Outcome 1 Newborn outcomes.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 5 Zinc in adults

Outcome: 1 Newborn outcomes

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Duration of pregnancy						
Fawzi 2005	180	39.6 (2.9)	186	39.5 (3.2)		0.10 [-0.53, 0.73]
2 Birth weight						
Fawzi 2005	174	3071 (526)	184	3085 (507)		-14.00 [-121.12, 93.12]
3 Birth length						
Fawzi 2005	153	48.6 (2.5)	162	48.5 (3.1)		0.10 [-0.52, 0.72]
4 Head circumference						
Fawzi 2005	154	34.4 (1.5)	162	34.6 (1.4)		-0.20 [-0.52, 0.12]
5 Placental weight						
Fawzi 2005	141	517 (111)	147	515 (115)		2.00 [-24.10, 28.10]



Analysis 5.2. Comparison 5 Zinc in adults, Outcome 2 Low birth weight and prematurity.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 5 Zinc in adults

Outcome: 2 Low birth weight and prematurity

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Preterm < 37 wks				
Fawzi 2005	31/180	29/186		1.10 [0.70, 1.76]
2 Low birth weight < 2500 g				
Fawzi 2005	19/174	19/184		1.06 [0.58, 1.93]
3 Small for gestational age				
Fawzi 2005	25/176	34/184		0.77 [0.48, 1.23]

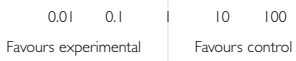
Analysis 5.3. Comparison 5 Zinc in adults, Outcome 3 Fetal loss and early child mortality.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 5 Zinc in adults

Outcome: 3 Fetal loss and early child mortality

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Miscarriage				
Fawzi 2005	5/198	3/199		1.68 [0.41, 6.91]
2 Stillbirth				
Fawzi 2005	13/198	10/199		1.31 [0.59, 2.91]
3 Fetal death				
Fawzi 2005	18/198	13/199		1.39 [0.70, 2.76]
4 Perinatal death				
Fawzi 2005	23/198	17/199		1.36 [0.75, 2.47]
5 Neonatal death				
Fawzi 2005	10/180	7/186		1.48 [0.57, 3.79]



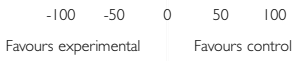
Analysis 5.4. Comparison 5 Zinc in adults, Outcome 4 Immune cell counts.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 5 Zinc in adults

Outcome: 4 Immune cell counts

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 CD4 counts at 6 weeks post partum						
Fawzi 2005	142	500 (251)	150	525 (290)		-25.00 [-87.11, 37.11]
2 CD8 counts at 6 weeks postpartum						
Fawzi 2005	142	1004 (452)	150	965 (389)		39.00 [-57.97, 135.97]
3 CD3 counts at 6 weeks postpartum						
Fawzi 2005	142	1610 (630)	150	1588 (557)		22.00 [-114.68, 158.68]



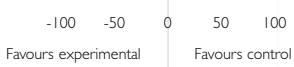
Analysis 5.5. Comparison 5 Zinc in adults, Outcome 5 Viral load at 6 weeks postpartum.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 5 Zinc in adults

Outcome: 5 Viral load at 6 weeks postpartum

Study or subgroup	Zinc N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Fawzi 2005	50	4.26 (1.01)	50	4.58 (0.89)		100.0 %	-0.32 [-0.69, 0.05]
Total (95% CI)	**50**		**50**			**100.0 %**	**-0.32 [-0.69, 0.05]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.68 (P = 0.093)							



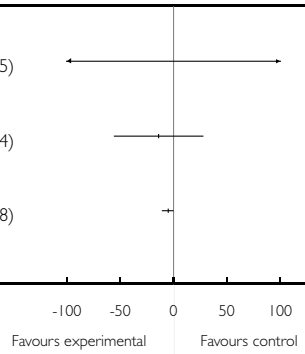
Analysis 5.6. Comparison 5 Zinc in adults, Outcome 6 Anthropometric outcomes.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 5 Zinc in adults

Outcome: 6 Anthropometric outcomes

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
1 Overall weight gain during pregancy						
Fawzi 2005	183	4354 (3060)	193	4700 (3015)		-346.00 [-960.40, 268.40]
2 Rate of weight gain during pregancy						
Fawzi 2005	183	316 (203)	193	330 (208.4)		-14.00 [-55.59, 27.59]
3 Total change in MUAC durng pregnancy						
Fawzi 2005	183	-6 (27.1)	193	-0.7 (27.8)		-5.30 [-10.85, 0.25]



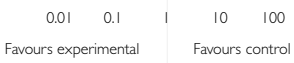
Analysis 5.7. Comparison 5 Zinc in adults, Outcome 7 Persistent diarrhoea at 2 weeks.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 5 Zinc in adults

Outcome: 7 Persistent diarrhoea at 2 weeks

Study or subgroup	Zinc n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Carcamo 2006	30/50	31/54		100.0 %	1.05 [0.76, 1.44]
Total (95% CI)	**50**	**54**		**100.0 %**	**1.05 [0.76, 1.44]**
Total events: 30 (Zinc), 31 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.27 (P = 0.79)					



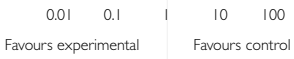
Analysis 6.1. Comparison 6 Zinc in children, Outcome 1 Mortality at 9 months.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 6 Zinc in children

Outcome: 1 Mortality at 9 months

Study or subgroup	Zinc n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Bobat 2005	2/46	7/50		100.0 %	0.31 [0.07, 1.42]
Total (95% CI)	**46**	**50**		**100.0 %**	**0.31 [0.07, 1.42]**
Total events: 2 (Zinc), 7 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.51 (P = 0.13)					



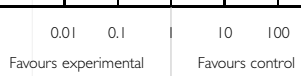
Analysis 6.2. Comparison 6 Zinc in children, Outcome 2 Scheduled and illness visits.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 6 Zinc in children

Outcome: 2 Scheduled and illness visits

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Scheduled visits; watery diarrhoea				
Bobat 2005	24/360	39/370		0.63 [0.39, 1.03]
2 Scheduled visits; pneumonia				
Bobat 2005	39/360	47/370		0.85 [0.57, 1.27]
3 Scheduled visits; URI				
Bobat 2005	141/360	165/370		0.88 [0.74, 1.04]
4 Scheduled visits; ear infection				
Bobat 2005	39/360	52/370		0.77 [0.52, 1.14]
5 All visits; watery diarrhoea				
Bobat 2005	30/407	65/447		0.51 [0.34, 0.76]
6 All visits; URI				
Bobat 2005	57/407	83/447		0.75 [0.55, 1.03]



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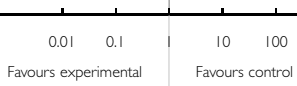
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
7 All visits; pneumonia				
Bobat 2005	164/407	202/447		0.89 [0.76, 1.04]
8 All visits; ear infection				
Bobat 2005	46/407	65/447		0.78 [0.55, 1.11]



Analysis 6.3. Comparison 6 Zinc in children, Outcome 3 Viral load at 9 months.

Review: Micronutrient supplementation in children and adults with HIV infection

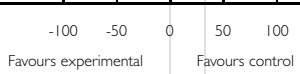
Comparison: 6 Zinc in children

Outcome: 3 Viral load at 9 months

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bobat 2005	44	5.4 (0.61)	41	5.5 (0.77)		100.0 %	-0.10 [-0.40, 0.20]
Total (95% CI)	**44**		**41**			**100.0 %**	**-0.10 [-0.40, 0.20]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.66 (P = 0.51)



Analysis 6.4. Comparison 6 Zinc in children, Outcome 4 CD4 % at 9 months.

Review: Micronutrient supplementation in children and adults with HIV infection

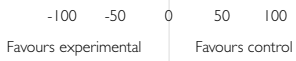
Comparison: 6 Zinc in children

Outcome: 4 CD4 % at 9 months

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Bobat 2005	44	20 (9.3)	41	19 (8.9)		100.0 %	1.00 [-2.87, 4.87]
Total (95% CI)	**44**		**41**			**100.0 %**	**1.00 [-2.87, 4.87]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.51 (P = 0.61)



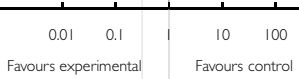
Analysis 7.1. Comparison 7 Selenium in adults, Outcome 1 Adverse pregnancy outcomes.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 7 Selenium in adults

Outcome: 1 Adverse pregnancy outcomes

Study or subgroup	Selenium n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Low birth weight < 2500 g				
Kupka 2008	42/407	66/435		0.68 [0.47, 0.98]
2 Very low birth weight < 2000 g				
Kupka 2008	15/407	27/435		0.59 [0.32, 1.10]
3 Preterm birth < 37 weeks				
Kupka 2008	66/407	70/435		1.01 [0.74, 1.37]
4 Preterm birth < 34 weeks				
Kupka 2008	22/407	22/431		1.06 [0.60, 1.88]
5 Low birth weight and preterm birth				
Kupka 2008	25/407	34/435		0.79 [0.48, 1.29]
6 Low birth weight and term birth				
Kupka 2008	17/340	32/360		0.56 [0.32, 0.99]
7 Small for gestational age				
Kupka 2008	72/391	73/417		1.05 [0.78, 1.41]



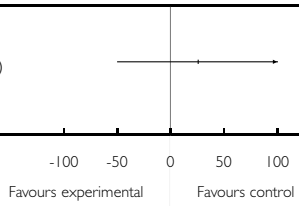
Analysis 7.2. Comparison 7 Selenium in adults, Outcome 2 Adverse pregnancy outcomes.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 7 Selenium in adults

Outcome: 2 Adverse pregnancy outcomes

Study or subgroup	Selenium N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
1 Mean birth weight (g)						
Kupka 2008	407	3008 (543)	435	2982 (588)		26.00 [-50.39, 102.39]



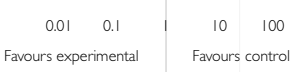
Analysis 7.3. Comparison 7 Selenium in adults, Outcome 3 Perinatal mortality.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 7 Selenium in adults

Outcome: 3 Perinatal mortality

Study or subgroup	Selenium n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Miscarriage before 28 wks.				
Kupka 2008	6/442	2/450		3.05 [0.62, 15.05]
2 Stillbirth between 28 wk and delivery				
Kupka 2008	29/446	21/467		1.45 [0.84, 2.50]
3 Fetal loss				
Kupka 2008	35/449	23/469		1.59 [0.95, 2.65]
4 Perinatal death				
Kupka 2008	38/427	30/454		1.35 [0.85, 2.13]



Analysis 7.4. Comparison 7 Selenium in adults, Outcome 4 Infant mortality.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 7 Selenium in adults

Outcome: 4 Infant mortality

Study or subgroup	Selenium n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
1 Neonatal death				
Kupka 2008	11/407	12/414		0.93 [0.42, 2.09]
2 Infant death				
Kupka 2008	8/364	19/380		0.44 [0.19, 0.99]
3 Neonatal or infant death				
Kupka 2008	19/404	31/413		0.63 [0.36, 1.09]

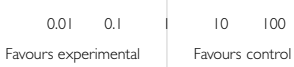
Analysis 7.5. Comparison 7 Selenium in adults, Outcome 5 Adult mortality.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 7 Selenium in adults

Outcome: 5 Adult mortality

Study or subgroup	Selenium n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Kupka 2008	16/456	16/457		100.0 %	1.00 [0.51, 1.98]
Total (95% CI)	**456**	**457**		**100.0 %**	**1.00 [0.51, 1.98]**
Total events: 16 (Selenium), 16 (Placebo)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.01 (P = 0.99)					



Analysis 7.6. Comparison 7 Selenium in adults, Outcome 6 Viral load change 0-9 months.

Review: Micronutrient supplementation in children and adults with HIV infection

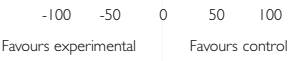
Comparison: 7 Selenium in adults

Outcome: 6 Viral load change 0-9 months

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hurwitz 2007	50	-0.05 (0.15)	80	0.28 (0.8)		100.0 %	-0.33 [-0.51, -0.15]
Total (95% CI)	**50**		**80**			**100.0 %**	**-0.33 [-0.51, -0.15]**

Heterogeneity: not applicable

Test for overall effect: Z = 3.59 (P = 0.00033)



Analysis 7.7. Comparison 7 Selenium in adults, Outcome 7 CD4 count change from 0- 9 months.

Review: Micronutrient supplementation in children and adults with HIV infection

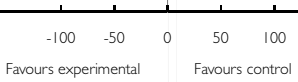
Comparison: 7 Selenium in adults

Outcome: 7 CD4 count change from 0- 9 months

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Hurwitz 2007	50	30 (25)	80	-35 (20)		100.0 %	65.00 [56.80, 73.20]
Total (95% CI)	**50**		**80**			**100.0 %**	**65.00 [56.80, 73.20]**

Heterogeneity: not applicable

Test for overall effect: Z = 15.54 (P < 0.00001)

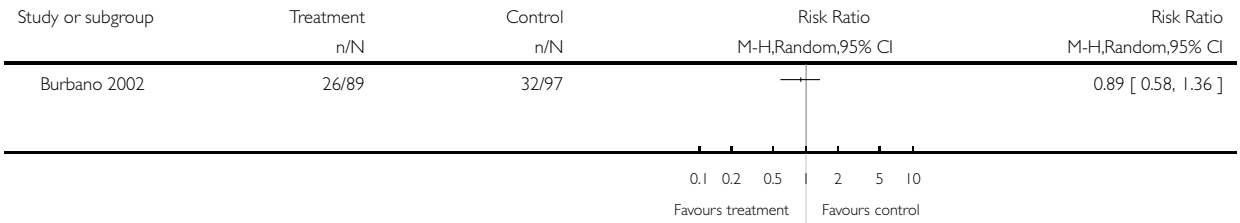


Analysis 7.8. Comparison 7 Selenium in adults, Outcome 8 Hospitalised for all conditions.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 7 Selenium in adults

Outcome: 8 Hospitalised for all conditions

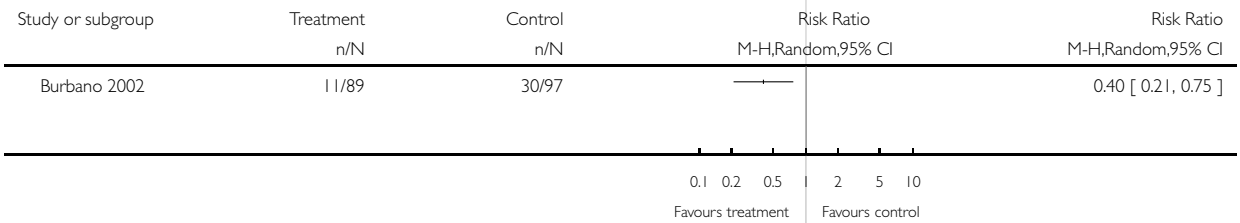


Analysis 7.9. Comparison 7 Selenium in adults, Outcome 9 Hospitalised for OIs and HIV-related conditions.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 7 Selenium in adults

Outcome: 9 Hospitalised for OIs and HIV-related conditions



Analysis 8.1. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 1 Mortality.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 1 Mortality

Study or subgroup	Multi-micronutrient n/N	Placebo n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Range 2006	4/42	14/42		0.29 [0.10, 0.80]
Semba 2007a	157/406	171/423		0.96 [0.81, 1.13]
Villamor 2008	74/200	66/204		1.14 [0.87, 1.50]

Analysis 8.2. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 2 Mortality (all cause) by 48 weeks.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 2 Mortality (all cause) by 48 weeks

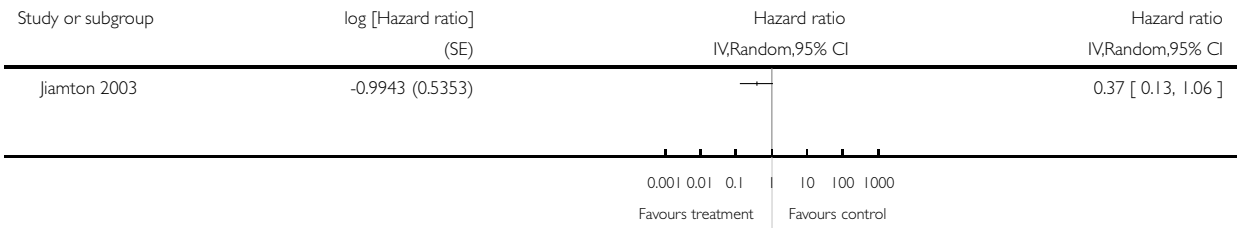
Study or subgroup	log [Hazard ratio] (SE)	Hazard ratio IV,Random,95% CI	Hazard ratio IV,Random,95% CI
1 New Subgroup			
Jiamton 2003	-0.6349 (0.4432)		0.53 [0.22, 1.26]

Analysis 8.3. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 3 Mortality by 48 weeks (baseline CD4 < 200).

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 3 Mortality by 48 weeks (baseline CD4 < 200)

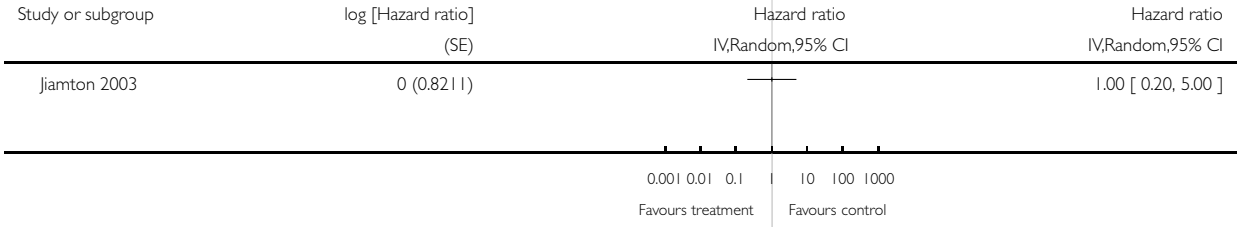


Analysis 8.4. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 4 Mortality by 48 weeks (baseline CD4 >= 200).

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 4 Mortality by 48 weeks (baseline CD4 >= 200)

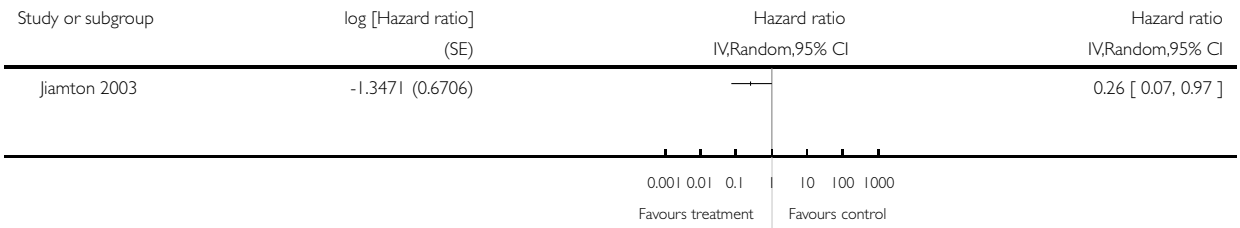


Analysis 8.5. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 5 Mortality by 48 weeks (baseline CD4 < 100).

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 5 Mortality by 48 weeks (baseline CD4 < 100)

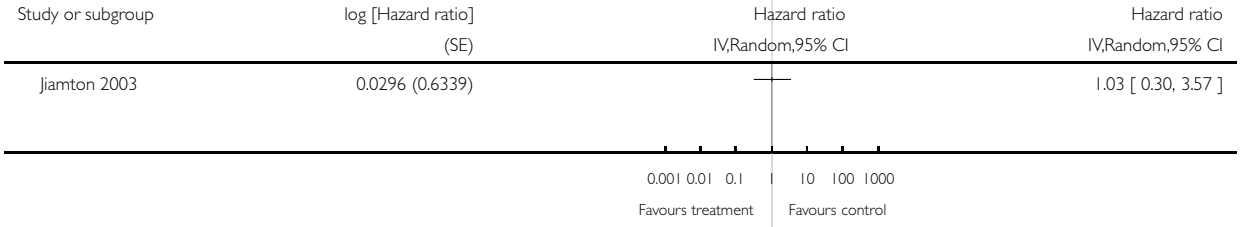


Analysis 8.6. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 6 Mortality by 48 weeks (baseline CD4 >=100).

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 6 Mortality by 48 weeks (baseline CD4 >=100)

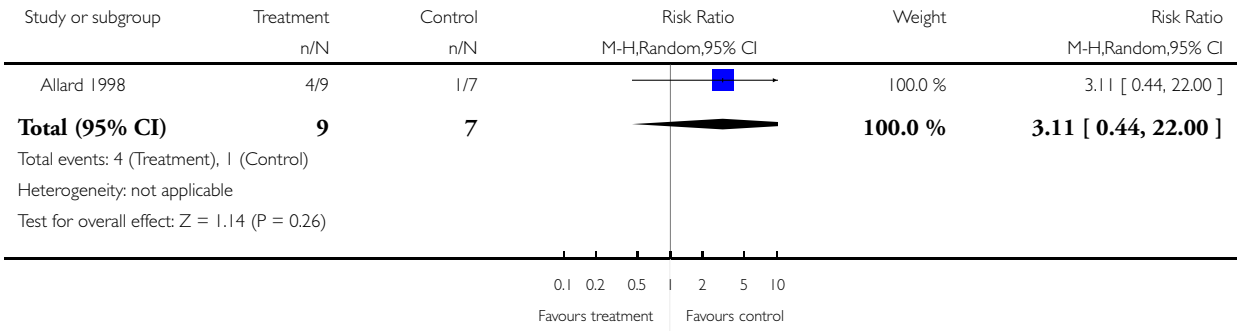


Analysis 8.7. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 7 New AIDS -defining infections.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 7 New AIDS -defining infections

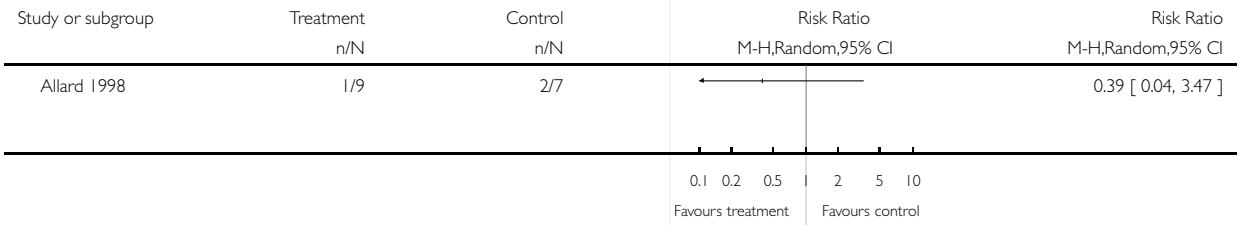


Analysis 8.8. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 8 New HIV-associated infections.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 8 New HIV-associated infections



Analysis 8.9. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 9 Recurrent HIV-associated infections.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 9 Recurrent HIV-associated infections

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Allard 1998	2/9	3/7		0.52 [0.12, 2.30]
Villamor 2008	6/130	14/111		0.37 [0.15, 0.92]

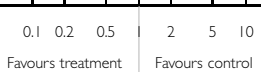
Analysis 8.10. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 10 New other infections.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 10 New other infections

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Allard 1998	2/9	0/7		4.00 [0.22, 72.01]



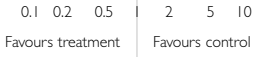
Analysis 8.11. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 11 Recurrent other infections.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 11 Recurrent other infections

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Allard 1998	0/9	1/7		0.27 [0.01, 5.70]



Analysis 8.12. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 12 Viral load at 12 months.

Review: Micronutrient supplementation in children and adults with HIV infection

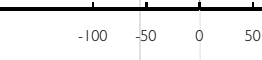
Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 12 Viral load at 12 months

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Allard 1998	20	3.67 (0.4)	20	4.92 (0.19)		-1.25 [-1.44, -1.06]
Kaiser 2006	18	2.3 (0.9)	22	2.4 (1)		-0.10 [-0.69, 0.49]
Range 2006	48	3.85 (0)	48	4.1 (0)		0.0 [0.0, 0.0]
Semba 2007a	27	3.7 (1.2)	26	4.1 (1)		-0.40 [-0.99, 0.19]
Villamor 2008	90	4.66 (0)	82	4.74 (0.83)		0.0 [0.0, 0.0]
Total (95% CI)	**203**		**198**			**-1.07 [-1.25, -0.90]**

Heterogeneity: Chi^2 = 18.60, df = 2 (P = 0.00009); I^2 =89%

Test for overall effect: Z = 11.94 (P < 0.00001)



Analysis 8.13. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 13 CD 4 counts at 12 months.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 13 CD 4 counts at 12 months

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Kaiser 2006	18	422 (161)	22	461 (254)		-39.00 [-168.60, 90.60]
Range 2006	48	423 (0)	48	403 (0)		0.0 [0.0, 0.0]
Semba 2007a	24	313 (181)	26	278 (244)		35.00 [-83.49, 153.49]
Villamor 2008	90	335 (0)	82	340 (240)		0.0 [0.0, 0.0]
Total (95% CI)	**180**		**178**			**1.31 [-86.14, 88.76]**

Heterogeneity: Chi² = 0.68, df = 1 (P = 0.41); I² =0.0%

Test for overall effect: Z = 0.03 (P = 0.98)

Analysis 8.14. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 14 CD 8 counts at 12 months.

Review: Micronutrient supplementation in children and adults with HIV infection

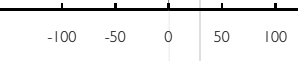
Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 14 CD 8 counts at 12 months

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Semba 2007a	24	746 (361)	26	728 (491)		18.00 [-219.65, 255.65]
Villamor 2008	90	987 (0)	82	929 (397)		0.0 [0.0, 0.0]
Total (95% CI)	**114**		**108**			**18.00 [-219.65, 255.65]**

Heterogeneity: Chi² = 0.0, df = 0 (P = 1.00); I² =0.0%

Test for overall effect: Z = 0.15 (P = 0.88)



Analysis 8.15. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 15 CD 3 counts (entire period).

Review: Micronutrient supplementation in children and adults with HIV infection

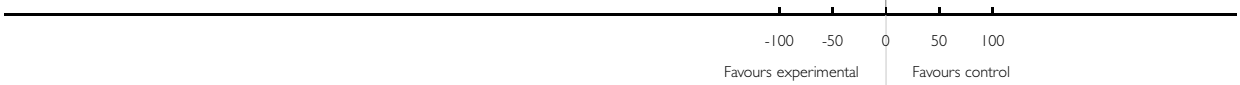
Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 15 CD 3 counts (entire period)

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Villamor 2008	90	1421 (0)	82	1361 (561)		0.0 [0.0, 0.0]
Total (95% CI)	**90**		**82**			**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)



Analysis 8.16. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 16 Weight gain at 7 months.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 16 Weight gain at 7 months

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Range 2006	95	59.4 (0)	97	57.9 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**95**		**97**			**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Analysis 8.17. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 17 Viral load change : Baseline to 2 months.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 17 Viral load change : Baseline to 2 months

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Range 2006	48	-0.01 (0)	48	0.08 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**48**		**48**			**0.0 [0.0, 0.0]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.0 (P < 0.00001)

Analysis 8.18. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 18 CD4 cell count change: Baseline to 2 months.

Review: Micronutrient supplementation in children and adults with HIV infection

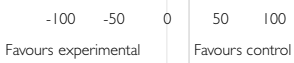
Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 18 CD4 cell count change: Baseline to 2 months

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Kaiser 2006	18	124 (36)	22	100 (18)		24.00 [5.75, 42.25]
Range 2006	48	-45 (0)	48	-104 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**66**		**70**			**24.00 [5.75, 42.25]**

Heterogeneity: Chi^2 = 0.0, df = 0 (P = 1.00); I^2 =0.0%

Test for overall effect: Z = 2.58 (P = 0.010)



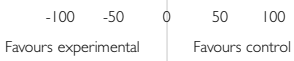
Analysis 8.19. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 19 Change in weight: Baseline to 7 months.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 19 Change in weight: Baseline to 7 months

Study or subgroup	Experimental N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Mean Difference IV,Fixed,95% CI
Range 2006	95	8.65 (0)	97	6.28 (0)		0.0 [0.0, 0.0]
Total (95% CI)	**95**		**97**			**0.0 [0.0, 0.0]**
Heterogeneity: not applicable						
Test for overall effect: Z = 0.0 (P < 0.00001)						



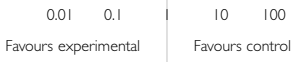
Analysis 8.20. Comparison 8 Multiple supplements in non-pregnant adults, Outcome 20 Treatment failure after 1 month.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 8 Multiple supplements in non-pregnant adults

Outcome: 20 Treatment failure after 1 month

Study or subgroup	Experimental n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Villamor 2008	21/165	26/157		100.0 %	0.73 [0.39, 1.37]
Total (95% CI)	**165**	**157**		**100.0 %**	**0.73 [0.39, 1.37]**
Total events: 21 (Experimental), 26 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.97 (P = 0.33)					

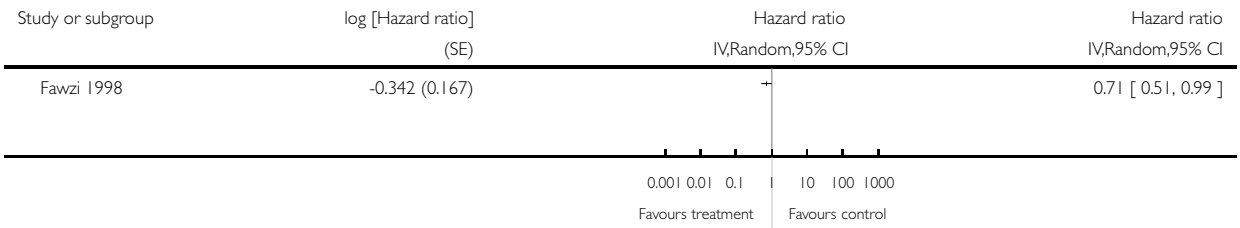


Analysis 9.1. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 1 Progression to stage 4 disease / death from AIDS-related causes.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 1 Progression to stage 4 disease / death from AIDS-related causes

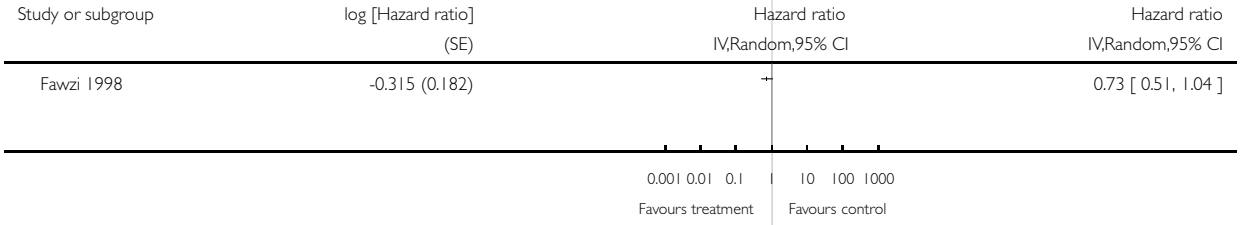


Analysis 9.2. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 2 Death from AIDS-related causes.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 2 Death from AIDS-related causes

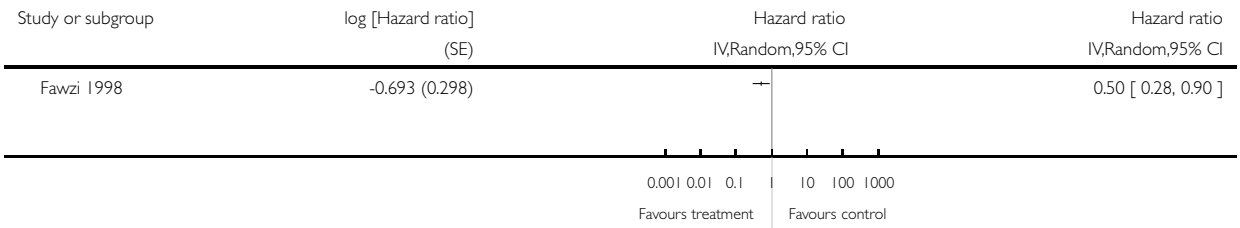


Analysis 9.3. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 3 Progression to stage 4 disease.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 3 Progression to stage 4 disease

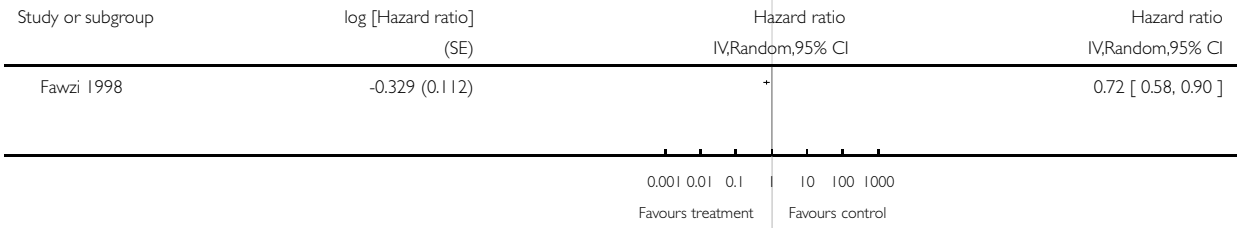


Analysis 9.4. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 4 Progression to stage 3 disease or higher.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 4 Progression to stage 3 disease or higher

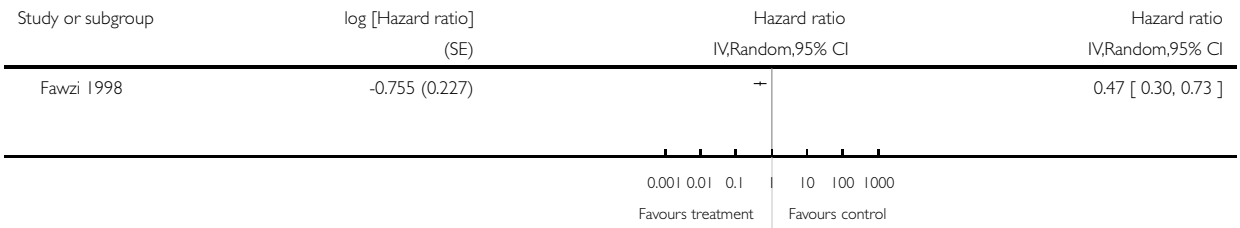


Analysis 9.5. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 5 HIV-related complications: thrush.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 5 HIV-related complications: thrush

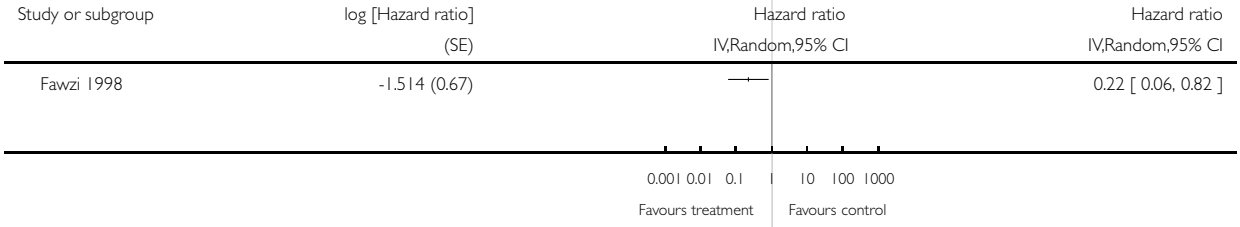


Analysis 9.6. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 6 HIV-related complications: gingival erythema.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 6 HIV-related complications: gingival erythema

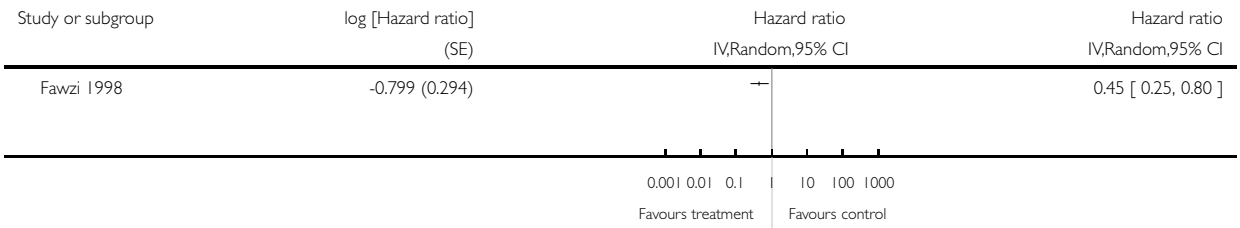


Analysis 9.7. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 7 HIV-related complications: angular cheilitis.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 7 HIV-related complications: angular cheilitis

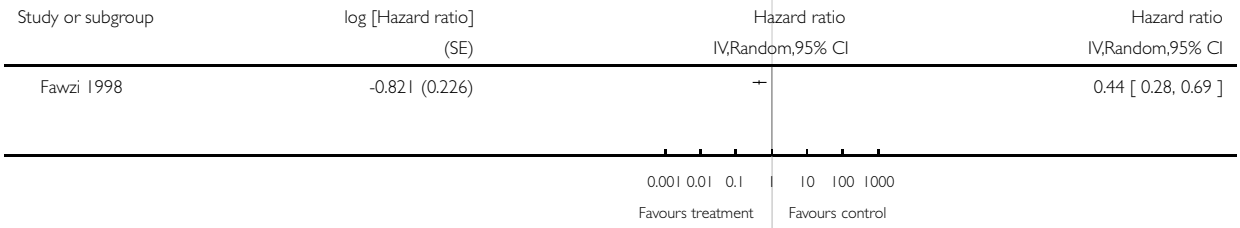


Analysis 9.8. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 8 HIV-related complications: oral ulcer.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 8 HIV-related complications: oral ulcer

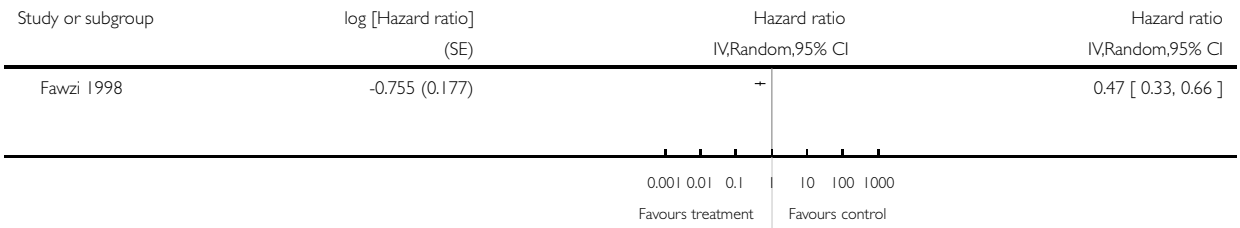


Analysis 9.9. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 9 HIV-related complications: reported mouth and throat ulcers.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 9 HIV-related complications: reported mouth and throat ulcers

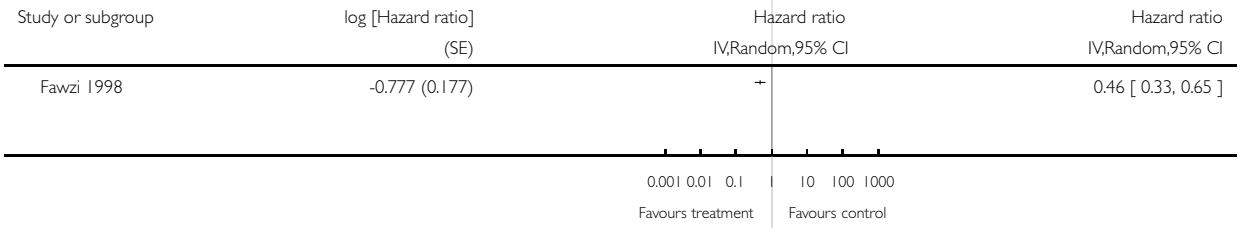


Analysis 9.10. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 10 HIV-related complications: painful tongue or mouth.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 10 HIV-related complications: painful tongue or mouth

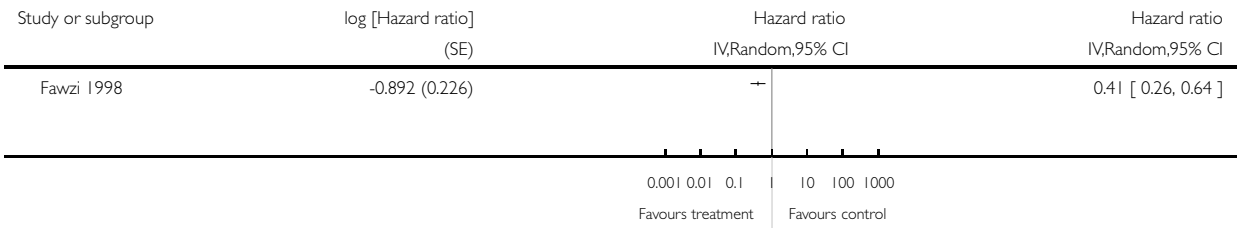


Analysis 9.11. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 11 HIV-related complications: difficult or painful swallowing.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 11 HIV-related complications: difficult or painful swallowing

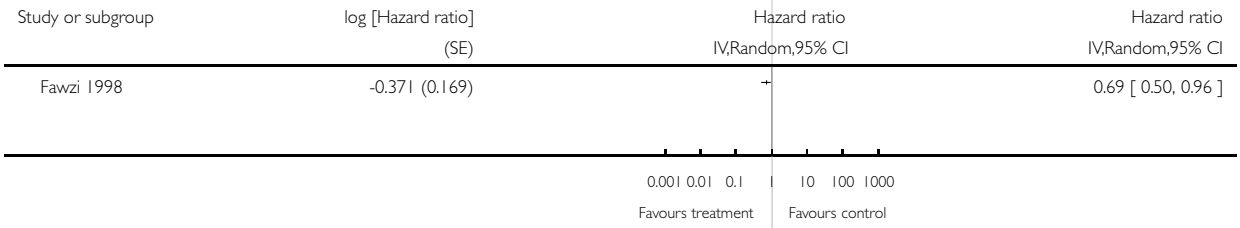


Analysis 9.12. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 12 HIV-related complications: nausea and vomiting.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 12 HIV-related complications: nausea and vomiting

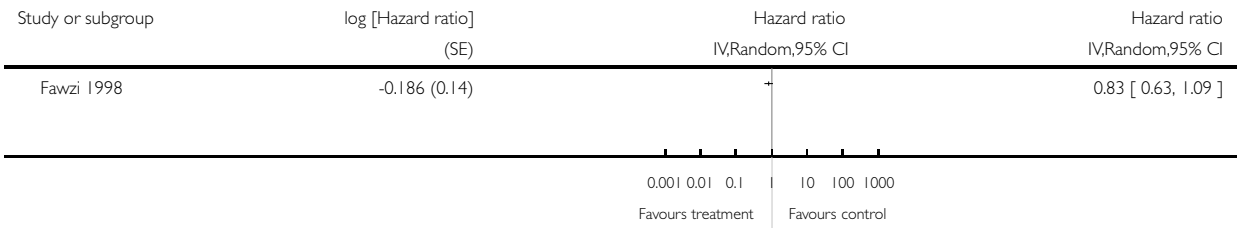


Analysis 9.13. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 13 HIV-related complications: diarrhoea.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 13 HIV-related complications: diarrhoea

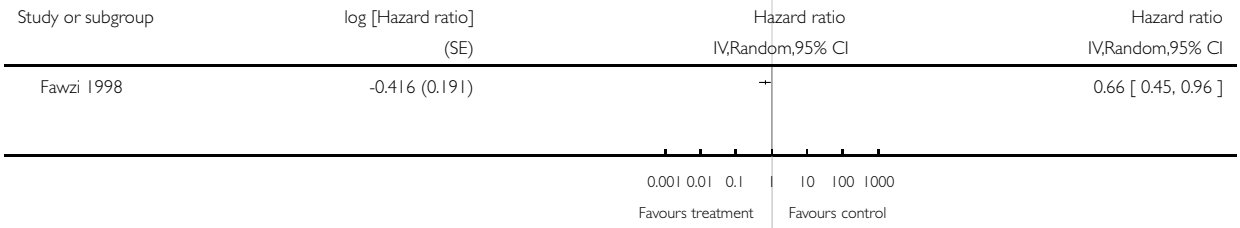


Analysis 9.14. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 14 HIV-related complications: dysentery.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 14 HIV-related complications: dysentery

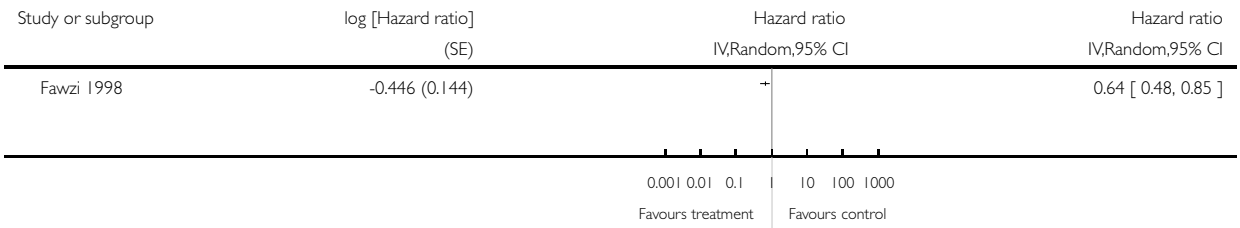


Analysis 9.15. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 15 HIV-related complications: fatigue.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 15 HIV-related complications: fatigue

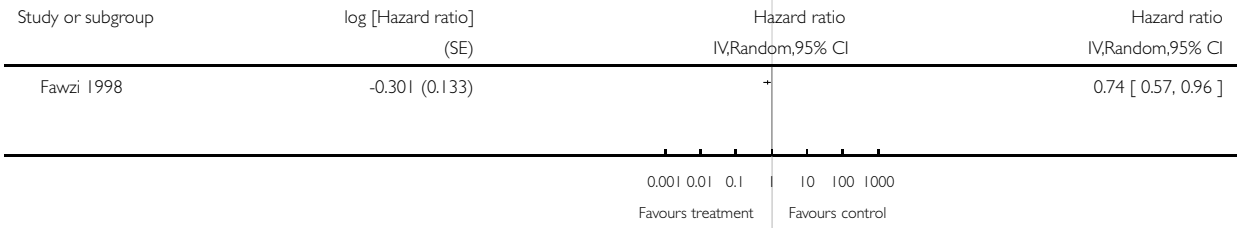


Analysis 9.16. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 16 HIV-related complications: rash.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 16 HIV-related complications: rash



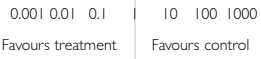
Analysis 9.17. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 17 HIV-related complications: acute upper respiratory tract infection.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 17 HIV-related complications: acute upper respiratory tract infection

Study or subgroup	log [Hazard ratio] (SE)	Hazard ratio IV,Random,95% CI	Hazard ratio IV,Random,95% CI
Fawzi 1998	-0.236 (0.096)		0.79 [0.65, 0.95]



Analysis 9.18. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 18 CD4 difference (baseline up to 3 months).

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 18 CD4 difference (baseline up to 3 months)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Fawzi 1998	373	167 (210)	349	112 (268)		55.00 [19.72, 90.28]

Analysis 9.19. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 19 CD4 difference (baseline to over 3 months).

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 19 CD4 difference (baseline to over 3 months)

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Fawzi 1998	261	99 (208)	246	59 (167)		40.00 [7.25, 72.75]

Analysis 9.20. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 20 CD8 difference (baseline up to 3 months).

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 20 CD8 difference (baseline up to 3 months)

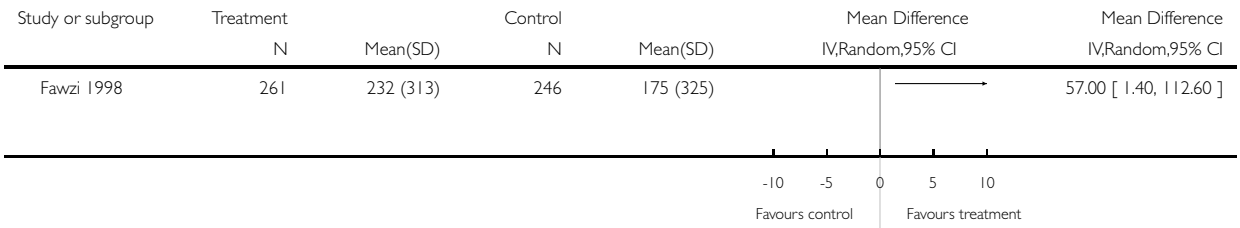
Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Fawzi 1998	373	385 (450)	349	289 (404)		96.00 [33.69, 158.31]

Analysis 9.21. Comparison 9 Multiple supplements in pregnant and lactating women [maternal outcomes], Outcome 21 CD8 difference (baseline to over 3 months).

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 9 Multiple supplements in pregnant and lactating women [maternal outcomes]

Outcome: 21 CD8 difference (baseline to over 3 months)

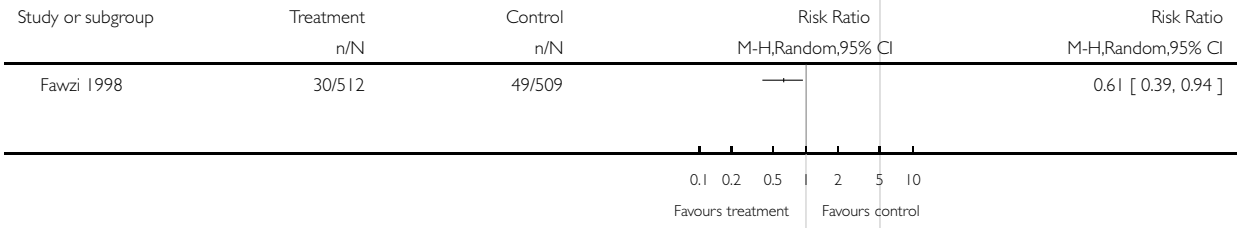


Analysis 10.1. Comparison 10 Multiple supplements in pregnant and lactating women [child outcomes], Outcome 1 Foetal death (miscarriage+stillbirth).

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 10 Multiple supplements in pregnant and lactating women [child outcomes]

Outcome: 1 Foetal death (miscarriage+stillbirth)



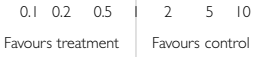
Analysis 10.2. Comparison 10 Multiple supplements in pregnant and lactating women [child outcomes], Outcome 2 Total mortality by 24 months including foetal deaths.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 10 Multiple supplements in pregnant and lactating women [child outcomes]

Outcome: 2 Total mortality by 24 months including foetal deaths

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Fawzi 1998	149/521	173/520		0.86 [0.72, 1.03]



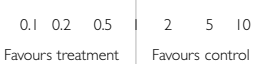
Analysis 10.3. Comparison 10 Multiple supplements in pregnant and lactating women [child outcomes], Outcome 3 Mortality by 24 months among all live births.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 10 Multiple supplements in pregnant and lactating women [child outcomes]

Outcome: 3 Mortality by 24 months among all live births

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Fawzi 1998	121/501	126/483		0.93 [0.75, 1.15]

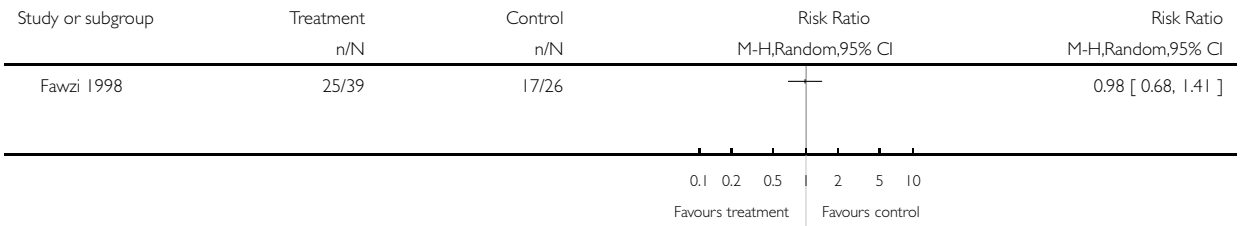


Analysis 10.4. Comparison 10 Multiple supplements in pregnant and lactating women [child outcomes], Outcome 4 Mortality by 24 months among HIV-infected live births.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 10 Multiple supplements in pregnant and lactating women [child outcomes]

Outcome: 4 Mortality by 24 months among HIV-infected live births

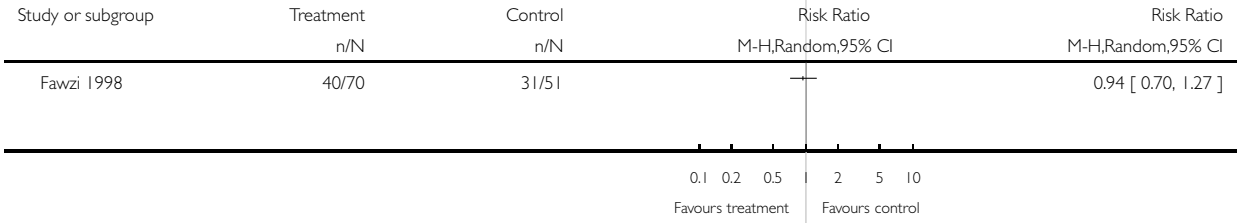


Analysis 10.5. Comparison 10 Multiple supplements in pregnant and lactating women [child outcomes], Outcome 5 Mortality by 24 months among HIV-infected infants at 6 weeks of age.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 10 Multiple supplements in pregnant and lactating women [child outcomes]

Outcome: 5 Mortality by 24 months among HIV-infected infants at 6 weeks of age



Analysis 10.6. Comparison 10 Multiple supplements in pregnant and lactating women [child outcomes], Outcome 6 Mean birthweight.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 10 Multiple supplements in pregnant and lactating women [child outcomes]

Outcome: 6 Mean birthweight

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Fawzi 1998	410	3048 (484)	390	2948 (522)		100.00 [30.15, 169.85]

Analysis 10.7. Comparison 10 Multiple supplements in pregnant and lactating women [child outcomes], Outcome 7 Birthweight < 2000 g.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 10 Multiple supplements in pregnant and lactating women [child outcomes]

Outcome: 7 Birthweight < 2000 g

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Fawzi 1998	7/410	16/390		0.42 [0.17, 1.00]

Analysis 10.8. Comparison 10 Multiple supplements in pregnant and lactating women [child outcomes], Outcome 8 Birthweight < 2500 g.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 10 Multiple supplements in pregnant and lactating women [child outcomes]

Outcome: 8 Birthweight < 2500 g

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Fawzi 1998	36/410	62/390		0.55 [0.38, 0.81]

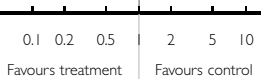
Analysis 10.9. Comparison 10 Multiple supplements in pregnant and lactating women [child outcomes], Outcome 9 Preterm birth (<37 weeks).

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 10 Multiple supplements in pregnant and lactating women [child outcomes]

Outcome: 9 Preterm birth (<37 weeks)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Fawzi 1998	96/455	106/433		0.86 [0.68, 1.10]



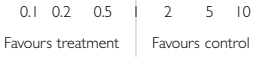
Analysis 10.10. Comparison 10 Multiple supplements in pregnant and lactating women [child outcomes], Outcome 10 Severe preterm birth (<34 weeks).

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 10 Multiple supplements in pregnant and lactating women [child outcomes]

Outcome: 10 Severe preterm birth (<34 weeks)

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Fawzi 1998	28/455	44/433		0.61 [0.38, 0.95]



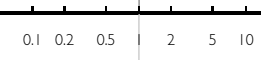
Analysis 10.11. Comparison 10 Multiple supplements in pregnant and lactating women [child outcomes], Outcome 11 Small for gestational age.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 10 Multiple supplements in pregnant and lactating women [child outcomes]

Outcome: 11 Small for gestational age

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H,Random,95% CI	Risk Ratio M-H,Random,95% CI
Fawzi 1998	39/390	66/378		0.57 [0.40, 0.83]



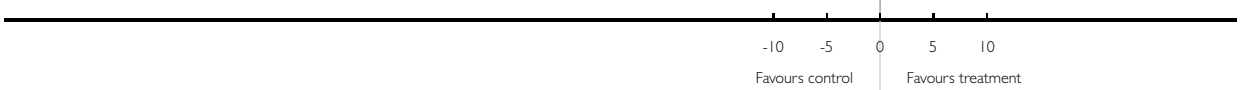
Analysis 10.12. Comparison 10 Multiple supplements in pregnant and lactating women [child outcomes], Outcome 12 CD4 count >= 3 months.

Review: Micronutrient supplementation in children and adults with HIV infection

Comparison: 10 Multiple supplements in pregnant and lactating women [child outcomes]

Outcome: 12 CD4 count >= 3 months

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)	Mean Difference IV,Random,95% CI	Mean Difference IV,Random,95% CI
Fawzi 1998	400	1711 (646)	388	1558 (576)		153.00 [67.60, 238.40]



APPENDICES

Appendix 1. Clib search strategy

ID	Search	Hits
#1	MeSH descriptor HIV Infections explode all trees	5951
#2	MeSH descriptor HIV explode all trees	1861
#3	hiv OR hiv-1* OR hiv-2* OR hiv1 OR hiv2 OR HIV INFECT* OR HUMAN IMMUNODEFICIENCY VIRUS OR HUMAN IMMUNEDEFICIENCY VIRUS OR HUMAN IMMUNE-DEFICIENCY VIRUS OR HUMAN IMMUNO-DEFICIENCY VIRUS OR HUMAN IMMUN* DEFICIENCY VIRUS OR ACQUIRED IMMUNODEFICIENCY SYNDROME OR ACQUIRED IMMUNEDEFICIENCY SYNDROME OR ACQUIRED IMMUNO-DEFICIENCY SYNDROME OR ACQUIRED IMMUNE-DEFICIENCY SYNDROME OR ACQUIRED IMMUN* DEFICIENCY SYNDROME	8801
#4	MeSH descriptor Lymphoma, AIDS-Related, this term only	21
#5	MeSH descriptor Sexually Transmitted Diseases, Viral, this term only	17

(*Continued*)

#6	(#1 OR #2 OR #3 OR #4 OR #5)	8933
#7	trace elements OR carotenoids OR vitamins	10040
#8	(#6 AND #7)	216
#9	(#6 AND #7), from 2009 to 2010	64

Appendix 2. PubMed search strategy

Search	Most Recent Queries	Time	Result
#5	Search ("2009/06/01"[Publication Date] : "2010/01/29"[Publication Date]) AND (#1 AND #2 AND #3)	04:12:51	15
#4	Search #1 AND #2 AND #3	04:10:19	802
#3	Search trace elements OR carotenoids OR vitamins	04:09:59	469770
#2	Search (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])	04:09:22	2198940
#1	Search HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw] OR ((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency	04:09:00	253650

(*Continued*)

	syndrome[tw])) OR "sexually transmitted diseases, viral"[MESH:NoExp]		

Appendix 3. EMBASE search strategy

No.	Query	Results	Date
#5	#1 AND #2 AND #3 AND [humans]/lim AND [embase]/lim AND [2009-2010]/py	2	29 Jan 2010
#4	#1 AND #2 AND #3	68	29 Jan 2010
#3	trace AND ('elements'/de OR 'elements') OR 'carotenoids'/de OR 'carotenoids' OR 'vitamins'/de OR 'vitamins'	65263	29 Jan 2010
#2	random*:ti OR random*:ab OR factorial*:ti OR factorial*:ab OR cross?over*:ti OR cross?over:ab OR crossover*:ti OR crossover*:ab OR placebo*:ti OR placebo*:ab OR (doubl*:ti AND blind*:ti) OR (doubl*:ab AND blind*:ab) OR (singl*:ti AND blind*:ti) OR (singl*:ab AND blind*:ab) OR assign*:ti OR assign*:ab OR volunteer*:ti OR volunteer*:ab OR 'crossover procedure'/de OR 'crossover procedure' OR 'double-blind procedure'/de OR 'double-blind procedure' OR 'single-blind procedure'/de OR 'single-blind procedure' OR 'randomized controlled trial'/de OR 'randomized controlled trial' OR allocat*:ti OR allocat*:ab	954892	29 Jan 2010
#1	'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus'/exp OR hiv:ti OR hiv:ab OR 'hiv-1':ti OR 'hiv-1':ab OR 'hiv-2':ti OR 'hiv-2':ab OR 'human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab OR 'human immunodeficiency virus':ti OR 'human immunodeficiency virus':ab OR 'human immunedeficiency virus':ti OR 'human im-	300319	29 Jan 2010

(*Continued*)

	munedeficiency virus':ab OR 'human immune-deficiency virus':ti OR 'human immune-deficiency virus':ab OR 'acquired immune-deficiency syndrome':ti OR 'acquired immune-deficiency syndrome':ab OR 'acquired immunedeficiency syndrome':ti OR 'acquired immunedeficiency syndrome':ab OR 'acquired immunodeficiency syndrome':ti OR 'acquired immunodeficiency syndrome':ab OR 'acquired immuno-deficiency syndrome':ti OR 'acquired immuno-deficiency syndrome':ab		

Appendix 4. Gateway search strategy

Search Number	Search	Items Found
#4	Search: (("HIV Infections"[MeSH] OR "HIV"[MeSH] OR hiv [tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw]) OR (((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "Sexually Transmitted Diseases, Viral"[MeSH:NoExp])) AND ((randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups) NOT (animals [mh] NOT humans [mh])) AND (trace elements OR carotenoids OR vitamins) Limit: 2009/06/01:2010/01/29	250
#3	Search: trace elements OR carotenoids OR vitamins	505930
#2	Search: (randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups) NOT (animals [mh] NOT humans [mh])	3008540

(*Continued*)

#1	Search: ("HIV Infections"[MeSH] OR "HIV"[MeSH] OR hiv [tw] OR hiv-1*[tw] OR hiv-2*[tw] OR hiv1[tw] OR hiv2[tw] OR hiv infect*[tw] OR human immunodeficiency virus[tw] OR human immunedeficiency virus[tw] OR human immuno-deficiency virus[tw] OR human immune-deficiency virus[tw]) OR (((human immun*) AND (deficiency virus[tw])) OR acquired immunodeficiency syndrome[tw] OR acquired immunedeficiency syndrome[tw] OR acquired immuno-deficiency syndrome[tw] OR acquired immune-deficiency syndrome[tw] OR ((acquired immun*) AND (deficiency syndrome[tw])) OR "Sexually Transmitted Diseases, Viral"[MeSH:NoExp])	367979

WHAT'S NEW

Last assessed as up-to-date: 24 February 2010.

Date	Event	Description
9 November 2010	New search has been performed	Substantial update.
9 November 2010	New citation required and conclusions have changed	Substantial update of the review.

HISTORY

Protocol first published: Issue 4, 2003

Review first published: Issue 4, 2005

Date	Event	Description
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

J. Irlam (JI) initiated the review and contributed to all stages of the initial and updated review.

M. Visser (MV) assisted with all stages of the initial review.

N. Rollins (NR) assisted with study selection and commented on the report of the initial and updated review.

N. Siegfried (NS) mentored JI and MV and assisted with study selection, assessment of risk of bias, and commented on the report of the initial and updated review.

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- SACC HIV/AIDS Mentoring Programme, South Africa.
- South African Cochrane Centre, South Africa.
- Medical Research Council, South Africa.
- UCT Primary Health Care Directorate, South Africa.
- UCT Child Health Unit, South Africa.

External sources

- Cochrane Child Health Field, Canada.

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; beta Carotene [*administration & dosage]

MeSH check words

Adult; Child; Female; Humans; Pregnancy