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Vitamin A supplements for reducing mother-to-child HIV transmission (Review)

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TABLE OF CONTENTS

[Intervention Review]

Vitamin A supplements for reducing mother-to-child HIV transmission

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ABSTRACT

Background

Strategies to reduce the risk of mother-to-child transmission of the human immunodeficiency virus (HIV) include lifelong antiretroviral therapy (ART) for HIV-positive women, exclusive breastfeeding from birth for six weeks plus nevirapine or replacement feeding plus nevirapine from birth for four to six weeks, elective Caesarean section delivery, and avoiding giving children chewed food. In some settings, these interventions may not be practical, feasible, or affordable. Simple, inexpensive, and effective interventions (that could potentially be implemented even in the absence of prenatal HIV testing programmes) would be valuable. Vitamin A, which plays a role in immune function, is one low-cost intervention that has been suggested in such settings.

Objectives

To summarize the effects of giving vitamin A supplements to HIV-positive women during pregnancy and after delivery.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) up to 25 August 2017, and checked the reference lists of relevant articles for eligible studies.

Selection criteria

We included randomized controlled trials conducted in any setting that compared vitamin A supplements to placebo or no intervention among HIV-positive women during pregnancy or after delivery, or both.

Data collection and analysis

At least two review authors independently assessed study eligibility and extracted data. We expressed study results as risk ratios (RR) or mean differences (MD) as appropriate, with their 95% confidence intervals (CI), and conducted random-effects meta-analyses. This is an update of a review last published in 2011.

Main results

Five trials met the inclusion criteria. These were conducted in Malawi, South Africa, Tanzania, and Zimbabwe between 1995 and 2005 and none of the participants received ART. Women allocated to intervention arms received vitamin A supplements at a variety of doses (daily during pregnancy; a single dose immediately after delivery, or daily doses during pregnancy plus a single dose after delivery). Women allocated to comparison arms received identical placebo (6601 women, 4 trials) or no intervention (697 women, 1 trial). Four trials (with 6995 women) had low risk of bias and one trial (with 303 women) had high risk of attrition bias.

The trials show that giving vitamin A supplements to HIV-positive women during pregnancy, the immediate postpartum period, or both, probably has little or no effect on mother-to-child transmission of HIV (RR 1.07, 95% CI 0.91 to 1.26; 4428 women, 5 trials, *moderate certainty evidence*) and may have little or no effect on child death by two years of age (RR 1.06, 95% CI 0.92 to 1.22; 3883 women, 3 trials, *low certainty evidence*). However, giving vitamin A supplements during pregnancy may increase the mean birthweight (MD 34.12 g, 95% CI −12.79 to 81.02; 2181 women, 3 trials, *low certainty evidence*) and probably reduces the incidence of low birthweight (RR 0.78, 95% CI 0.63 to 0.97; 1819 women, 3 trials, *moderate certainty evidence);* but we do not know whether vitamin A supplements affect the risk of preterm delivery (1577 women, 2 trials), stillbirth (2335 women, 3 trials), or maternal death (1267 women, 2 trials).

Authors' conclusions

Antepartum or postpartum vitamin A supplementation, or both, probably has little or no effect on mother-to-child transmission of HIV in women living with HIV infection and not on antiretroviral drugs. The intervention has largely been superseded by ART which is widely available and effective in preventing vertical transmission.

PLAIN LANGUAGE SUMMARY

Vitamin A supplements for reducing mother-to-child transmission of HIV infection

What is the aim of this review?

The main aim of this Cochrane Review was to assess the effects of giving vitamin A supplements to HIV-positive women, during pregnancy or after delivery, or both, on the risk of mother-to-child transmission of HIV infection. Cochrane researchers collected and examined all relevant studies to answer this question and included five trials. This is an update of a review last published in 2011.

What is the key message of this review?

Giving vitamin A supplements to HIV-positive women, during pregnancy or after delivery, or both, probably makes little or no difference to the risk of mother-to-child transmission of HIV (*moderate certainty evidence*).

What are the main results of the review?

Five trials met the inclusion criteria of the review. Two trials were from South Africa and one trial each from Malawi, Tanzania, and Zimbabwe. The trials compared women receiving vitamin A supplements to women not receiving such supplements. None of the participants received antiretroviral therapy (ART).

The review shows that in women living with HIV infection and not on ART:

- giving vitamin A supplements to HIV-positive women during pregnancy, immediately after delivery, or both, probably has little or no effect on the risk of mother-to-child transmission of HIV (*moderate certainty evidence*) and may have little or no effect on child death by two years of age (*low certainty evidence*);

- giving vitamin A supplements to HIV-positive women during pregnancy may increase the mean birthweight (*low certainty evidence*) and probably reduces the number of low birthweight babies (*moderate certainty evidence*), but it is uncertain whether the intervention has an effect on the number of preterm births, stillbirths, or deaths among the women (*very low certainty evidence*).

The intervention has largely been superseded by ART, which is widely available and effective in preventing mother-to-child transmission of HIV.

How up-to-date is this review?

The review authors searched for studies up to 25 August 2017.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Population: HIV-positive women during pregnancy and immediate postpartum period
Settings: any setting
Intervention: vitamin A supplements
Comparison: placebo or no intervention

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	Number of participants (trials)	Certainty of the evidence (GRADE)	Comments
	Assumed risk with no vitamin A	Corresponding risk with vitamin A supplements				
HIV infection status of the child	27 per 100	29 per 100 (24 to 34)	RR 1.07 (0.91 to 1.26)	4428 (5 trials)	⊕⊕⊕◯ moderate[1] due to imprecision	Vitamin A supplements probably have little or no effect on mother-to-child transmission of HIV
Mean birthweight	2964 g	34 g higher (13 g lower to 81 g higher)	MD 34.12 (−12.79 to 81.02)	2181 (3 trials)	⊕⊕◯◯ low[2] due to imprecision	Vitamin A supplements may increase the mean birthweight
Low birthweight	17 per 100	13 per 100 (11 to 17)	RR 0.78 (0.63 to 0.97)	1819 (3 trials)	⊕⊕⊕◯ moderate[3] due to imprecision	Vitamin A supplements probably reduce the incidence of low birthweight babies
Child death by two years of age	14 per 100	15 per 100 (13 to 18)	RR 1.06 (0.92 to 1.22)	3883 (3 trials)	⊕⊕◯◯ low[2] due to imprecision	Vitamin A supplements may have little or no effect on child death by two years of age
Preterm delivery	20 per 100	17 per 100 (10 to 28)	RR 0.84 (0.52 to 1.37)	1577 (2 trials)	⊕◯◯◯ very low[2,4] due to imprecision and selective reporting	It is uncertain whether or not vitamin A supplements have an effect on preterm deliveries

Stillbirth	3 per 100	3 per 100 (2 to 5)	RR 1.13 (0.72 to 1.77)	2335 (3 trials)	⊕◯◯◯ very low[2,4] due to imprecision and selective reporting	It is uncertain whether or not vitamin A supplements have an effect on stillbirths
Maternal death	3 per 100	2 per 100 (1 to 4)	RR 0.71 (0.35 to 1.43)	1267 (2 trials)	⊕◯◯◯ very low[2,4] due to imprecision and selective reporting	It is uncertain whether or not vitamin A supplements have an effect on maternal deaths

*The basis for the assumed risk is the mean control group risk across studies. The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Abbreviations: CI: confidence interval; g: gram; MD: mean difference; RR: risk ratio

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

[1]We downgraded by 1 for imprecision, as the CI ranges from small benefits to a clinically important increase in harm.
[2]We downgraded by 2 for imprecision, as the CI ranges from clinically important benefits to a substantial increase in harm.
[3]We downgraded by 1 for imprecision, as the CI ranges from substantial benefits to no effect.
[4]We downgraded by 1 for possibility of selective reporting, because 1 or more eligible studies did not report this outcome.

BACKGROUND

Description of the condition

The Global Burden of Disease Study estimates that there were 38.8 million people living with the human immunodeficiency virus (HIV) worldwide in 2015, half of whom were women of childbearing age (Wang 2016). In addition, there are more than 600 new paediatric infections each day worldwide; most of which occur in sub-Saharan Africa (UNAIDS 2015). Children mostly acquire these infections from their mothers during pregnancy, delivery, or breastfeeding.

The high number of women who are of childbearing age and who are living with HIV makes the prevention of mother-to-child transmission of HIV a global health priority (UNAIDS 2015). Current strategies to reduce the risk of transmission include lifelong antiretroviral therapy (ART) to HIV-positive women, exclusive breastfeeding from birth for six weeks plus nevirapine, or replacement feeding plus nevirapine from birth for four to six weeks (WHO 2015), elective Caesarean section delivery (Read 2005), and avoiding giving children chewed food. Despite their benefits, these interventions are impractical in many resource-limited countries because they require the determination of the HIV status of pregnant women and are costly, complex, and require skilled personnel. Simple, inexpensive, and effective interventions that could potentially be implemented in the absence of prenatal HIV testing programmes would be valuable. Vitamin A supplementation during pregnancy is one low-cost intervention that has been suggested (Newell 2000).

Description of the intervention

Vitamin A refers to a group of unsaturated organic compounds that include preformed vitamin A and provitamin A carotenoids (Damodaran 2017). The vitamin exists as preformed retinol in animal food sources, retinyl esters in fortified foods, and provitamin A carotenoids in plant sources. Both preformed vitamin A and provitamin A are metabolized in cells to retinal and retinoic acid, the active forms of vitamin A, to upkeep the vitamin's multiple biological functions (Thorne-Lyman 2012).

The biological functions of vitamin A include the regulation and promotion of growth and differentiation of many cells, and maintenance of the integrity of the epithelial cells of the respiratory and digestive tracts. Vitamin A is necessary for formation of the photosensitive visual pigment in the retina, and reproductive functions (Wolf 2001; Tanumihardjo 2011). In the 1920s the vitamin was considered to be an anti-infective agent (Green 1928), and there is increasing evidence that it is essential for normal immune function (Ross 1996; Semba 1998).

Vitamin A deficiency is most prevalent in areas where diets lack preformed vitamin A, such as in South and Southeast Asia, and Sahel and sub-Saharan regions of Africa (West 2001). It has been estimated that about 19 million pregnant women in low-income countries are affected with vitamin A deficiency each year (West 2002; WHO 2009). Vitamin A deficiency in pregnant women is associated with night blindness, severe anaemia, wasting, malnutrition, reproductive and infectious morbidity (Christian 1998a), and increased risk of mortality one to two years following delivery (Christian 2000). About 10 million women suffer from night blindness during pregnancy as a result of Vitamin A deficiency, and this is associated with a constellation of adverse health and nutritional conditions among mothers and their infants (Christian 1998b; Christian 1998c; Christian 2001; WHO 2009).

How the intervention might work

In areas where poor diet and infection coexist, Vitamin A deficiency can increase the severity of infection, which in turn can reduce intake and accelerate body losses of vitamin A to exacerbate deficiency. Vitamin A deficiency and infection in vulnerable groups (notably young children and pregnant or lactating mothers) represent the most compelling consequences of vitamin A deficiency and underlie its significance as a public health problem around the world (WHO 2009).

Observational studies in sub-Saharan Africa have shown low serum vitamin A levels in HIV-positive women to be associated with significantly increased rates of mother-to-child transmission of HIV (Semba 1994) and infant mortality (Semba 1995). However, three observational studies in the USA provided conflicting results: low serum vitamin A was associated with a higher risk of mother-to-child transmission of HIV in one study (Greenberg 1997), but not the other two (Burger 1997; Burns 1999). These studies used different definitions for vitamin A deficiency: two studies used serum retinol levels of less than 30 mg/dL (Greenberg 1997; Burns 1999), and the other study used less than 20 mg/dL (Burger 1997). The studies also had small sample sizes; for example, in Burger 1997, only 4/95 (4.2%) of women had serum retinol levels of less than 20 mg/dL.

Vitamin A was hypothesized to decrease mother-to-child transmission of HIV by acting through several maternal, foetal, child risk factors for transmission, or all three. The proposed risk factors were the clinical, immunological, or viral stage of HIV disease among women; the integrity of the epithelial lining of the placenta, maternal lower genital tract, or breast; the occurrence of prematurity and low birthweight; and the status of the systemic and digestive mucosal immune systems of the foetus and the child (Fawzi 1998; Fawzi 2000).

Why it is important to do this review

Even though there have been dramatic reductions in the number of new HIV infections among children (UNAIDS 2015), the mag-

nitude of the paediatric HIV epidemic in resource-limited countries is still important. The simplicity and low cost of vitamin A supplementation makes the clarification of its role in mother-to-child transmission of HIV of considerable importance. We aimed to combine all high-quality randomized controlled trials (RCTs) conducted to date to estimate the effect of vitamin A supplementation on mother-to-child transmission of HIV. This is an update of a Cochrane Review published in 2011 (Wiysonge 2011).

OBJECTIVES

To summarize the effects of giving vitamin A supplements to HIV-positive women during pregnancy and after delivery.

METHODS

Criteria for considering studies for this review

Types of studies

RCTs.

Types of participants

Pregnant or breastfeeding women, confirmed HIV-positive by a validated laboratory test. The women could be of any age, at any clinical stage of HIV disease, and could be living in any setting.

Types of interventions

Intervention

Vitamin A supplementation, irrespective of formulation (retinol with or without beta-carotene), timing of supplementation (antepartum, postpartum, or both), dosing, or duration of supplementation. We conducted sensitivity analyses to investigate the robustness of the results to the inclusion of trials that used beta-carotene.

Control

Eligible comparison interventions included placebo or no intervention.

Types of outcome measures

Primary outcomes

- HIV infection status of the child.

Secondary outcomes

Child

- Mean birthweight.
- Low birthweight, defined as birthweight less than 2500 g.
- Child death by two years of age.
- Preterm delivery, defined as birth at less than 37 weeks of gestation.
- Stillbirth.

Mother

- Maternal death.
- Postpartum CD4 count.

Search methods for identification of studies

We attempted to identify all relevant trials regardless of language or publication status (published or unpublished) up to 25 August 2017 (Table 1).

The HIV Information Specialist, Joy Oliver, searched the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed, Embase, Clinicaltrials.gov, and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) using the search strategies shown in Table 1 and Table 2. We have also provided the search strategy for previous editions of the review in Table 3 and Table 4.

Data collection and analysis

Two review authors evaluated study eligibility, assessed risk of bias, and extracted data in duplicate. The two authors resolved any disagreements by discussion and consensus. The review authors involved in evaluating study eligibility, assessing risk of bias, and extracting data were not blinded to the names of the trial authors, their institutions, or journals of publication. We reported the data collection and analysis procedures of previous editions of this Cochrane Review in the previous published versions of this review (Wiysonge 2002; Wiysonge 2005; Kongnyuy 2009; Wiysonge 2011).

Selection of studies

Two review authors (either CSW and VNN or CSW and EJK) screened the literature search results by title and abstract for potentially relevant trials and retrieved the full-text articles as required. The two review authors then independently assessed trial eligibility and resolved differences by discussion and consensus. We considered a trial with multiple publications as one trial. We contacted the corresponding authors of two potentially eligible trials to obtain unpublished data (Chikobvu 2000; Friis 2004). We listed all

studies that we excluded after full-text assessment and the reasons for exclusion in the 'Characteristics of excluded studies' table. We constructed a PRISMA flow diagram to illustrate the study selection process.

Data extraction and management

Two review authors (CSW and VNN, CSW and EJK, or CSW and MSS) extracted information on study methods, participants, interventions, and outcomes from each included trial, and reported this information in the 'Characteristics of included studies' table.

Assessment of risk of bias in included studies

For each included trial, two review authors (CSW and VNN, CSW and EJK, or CSW and MSS) independently assessed the risk of bias by addressing seven prespecified domains (Higgins 2011): generation of the randomization sequence, concealment of the allocation of interventions, blinding of participants and personnel, blinding of outcome assessment, completeness of outcome data, completeness of outcome reporting, and any other concerns.
We described what the trial authors reported that they did for each domain and then decided the risk of bias for that domain by assigning a judgement of 'low', 'high', or 'unclear' risk of bias. We summarized the risk of bias for each trial as either low or high. We classified any trial that had a high risk of bias linked to allocation concealment, blinding of outcome assessment, or completeness of outcome data as having a high risk of bias. We considered all other trials to have low risk of bias.

Measures of treatment effect

We expressed each study result as the risk ratio (RR) for dichotomous data or the mean difference (MD) for continuous data, with 95% confidence intervals (CIs).

Unit of analysis issues

There were no unit of analysis issues in this Cochrane Review, as all eligible trials were individually randomized.

Dealing with missing data

We conducted a complete-case analysis such that we included all participants with a recorded outcome in the analyses. We have reported all missing data and trial dropouts (see the 'Characteristics of included studies' table). One trial reported results as means with their standard errors (SE) instead of standard deviations (SD) (Kumwenda 2002). We calculated the SD using the following formula: SD = (square root of N) x (SE).

Assessment of heterogeneity

We assessed the heterogeneity of effects across included trials by visually inspecting the graphical display of data in forest plots and using the Chi² test of homogeneity. In the presence of significant statistical heterogeneity, defined as $P < 0.1$, we first checked data accuracy to exclude data capturing errors. We quantified observed heterogeneity using the Higgins I^2 statistic.

Assessment of reporting biases

If we had 10 or more trials included in a meta-analysis, we would have used funnel plots to assess the risk of publication bias. In such circumstances, we would have assessed the funnel plot visually, followed by formal statistical tests to assess any observed funnel plot asymmetry (Egger 1997; Harbord 2006). Apart from reporting biases, potential causes of funnel plot asymmetry may include high risk of bias, true heterogeneity of effects, and chance (Higgins 2011).

Data synthesis

We used both unpublished (Chikobvu 2000), and published data (Coutsoudis 1999; Fawzi 2002; Kumwenda 2002; Humphrey 2006), to analyse trial participants in groups to which they were randomized, regardless of which or how much treatment they actually received.
Two trials used two-by-two factorial designs (Fawzi 2002; Humphrey 2006).
In the first trial, women and their newborns were recruited within four days of delivery and randomly assigned to four treatment groups: Aa, Ap, Pa, and Pp. "A" was maternal vitamin A supplementation, "P" was maternal placebo, "a" was infant vitamin A supplementation, and "p" was infant placebo (Humphrey 2006). In this Cochrane Review, we only used data from Ap (intervention) versus Pp (placebo).
In the second trial with a two-by-two factorial design, pregnant women were randomly assigned to receive either "vitamin A alone", "vitamin A plus multivitamins", "multivitamins without vitamin A", or "placebo" (Fawzi 2002). Although the trial authors stated that there was no evidence of clinical interaction between vitamin A and multivitamins, our plan was to consider only the "vitamin A alone" arm as the intervention. However, in the multiple publications from this trial, separate data for "vitamin A alone" were only available for low birthweight and maternal deaths. Thus, for the other outcomes we used data as reported by the trial authors, that is, vitamin A (a combination of "vitamin A alone" and "vitamin A plus multivitamins" arms) versus no vitamin A (consisting of "multivitamins without vitamin A" and "placebo" arms).
We conducted random-effects meta-analyses in RevMan 5 because of the diversity of study designs, type of intervention (that is, preformed vitamin A with or without beta-carotene), timing of intervention (that is, antepartum supplementation, postpartum sup-

plementation, or both), dosing of the supplements, and comparison groups (that is, placebo or no intervention) (RevMan 2014). We also calculated the optimal information size for the outcomes and presented this information in Table 5. In addition, we used the GRADE approach to assess the certainty of the evidence for the effect of vitamin A supplementation on each key outcome (Guyatt 2008). We constructed a 'Summary of findings' table using GRADEpro software (GRADEpro GDT 2015).

Subgroup analysis and investigation of heterogeneity

For the primary outcome, we conducted a subgroup analysis based on the timing of vitamin A supplementation, that is antepartum supplementation (Chikobvu 2000; Kumwenda 2002), postpartum supplementation (Humphrey 2006), or both (Coutsoudis 1999; Fawzi 2002).

Sensitivity analysis

We included trials that provided supplements containing only preformed vitamin A (Chikobvu 2000; Kumwenda 2002; Humphrey 2006), and trials that used both preformed vitamin A (retinol) and a provitamin A carotenoid (beta-carotene) (Coutsoudis 1999; Fawzi 2002).

Beta-carotene is easily converted to retinol, but also has antioxidative properties (Thorne-Lyman 2012). We therefore conducted sensitivity analyses to investigate the robustness of the results on the primary outcome to the type of intervention (that is, we omitted trials that used beta-carotene).

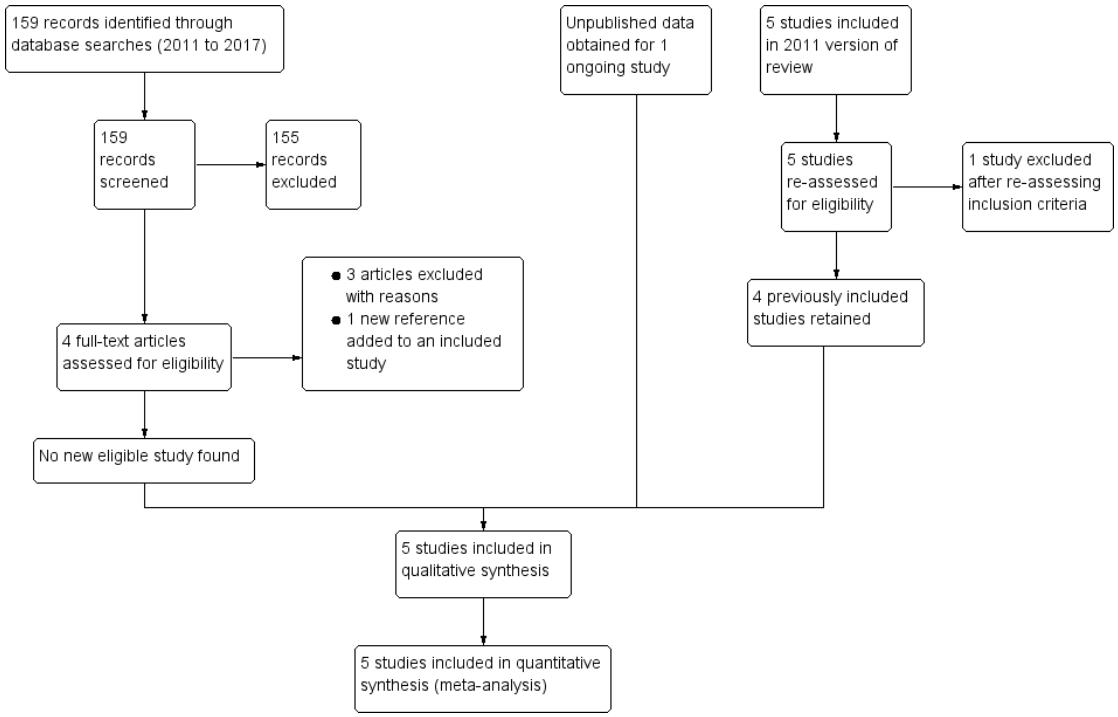
RESULTS

Description of studies

Results of the search

Figure 1 shows the search and study selection process for this Cochrane Review, in line with the PRISMA statement (Moher 2009).

Figure 1. PRISMA flow diagram



Of the five trials included in the previous version of this review, Wiysonge 2011, we retained four of the previously included trials (Coutsoudis 1999; Fawzi 2002; Kumwenda 2002; Humphrey 2006), and excluded one trial because further assessment revealed that it did not meet our inclusion criteria (Friis 2004). We obtained unpublished data for one ongoing trial (Chikobvu 2000). Of the 159 records identified from the updated literature search, we excluded 158 and identified one new article to add to an already included study.

Included studies

Five trials met the inclusion criteria (see Figure 1 and the 'Characteristics of included studies' table). These include a trial that we classified as ongoing in previous published versions of this review (Chikobvu 2000). The trial was conducted from September 1997 to December 2000 in South Africa, and the principal investigator of the trial has provided us with outcome data on mother-to-child transmission of HIV (Chikobvu 2000). We briefly describe below the designs, participants, interventions, comparisons, and outcome measures of the five included trials.

Period of study

These five included trials were conducted between 1995 and 2005, at the height of the HIV epidemic in sub-Saharan Africa.

Design

Three of the included trials were randomized trials (Fawzi 2002; Kumwenda 2002; Humphrey 2006). Two trials were described as randomized trials, but the trial authors did not describe the methods used to generate the randomization sequence (Coutsoudis 1999; Chikobvu 2000). Two trials had two-by-two factorial designs (Fawzi 2002; Humphrey 2006). All trials used participants as units of randomization. The proportion of participants lost to follow-up ranged from 3.2% (Humphrey 2006), to more than 48% (Chikobvu 2000). All trial authors excluded mother-infant pairs lost to follow-up from their analyses.

Location

The five trials were conducted in four countries in sub-Saharan Africa: Malawi (one trial; Kumwenda 2002), South Africa (two trials; Coutsoudis 1999; Chikobvu 2000), Tanzania (one trial; Fawzi 2002), and Zimbabwe (one trial; Humphrey 2006).

Population

In trials with antepartum vitamin A supplementation, participants consisted of HIV-positive pregnant women recruited during their first antenatal visit (Chikobvu 2000), 12 to 27 weeks' gestation (Fawzi 2002), 18 to 28 weeks' gestation (Kumwenda 2002), and 17 to 39 weeks' gestation (Coutsoudis 1999). For the single trial of postpartum vitamin A supplementation, HIV-positive women were recruited within 96 hours of delivery (Humphrey 2006).The prevalence of vitamin A deficiency among the women at baseline was 30.6% in Coutsoudis 1999, 34% in Fawzi 2002, and 51% in Kumwenda 2002; but was not reported in two trials (Chikobvu 2000; Humphrey 2006).

Interventions

Vitamin A supplements

Three trials used supplements that contained retinol alone (Chikobvu 2000; Kumwenda 2002; Humphrey 2006), and two trials used both retinol and beta-carotene (Coutsoudis 1999; Fawzi 2002).

Two trials provided vitamin A supplements to women only during pregnancy (Chikobvu 2000; Kumwenda 2002). One trial provided vitamin A during pregnancy, but did not report information on the type or dose of vitamin A used (Chikobvu 2000). The second trial provided pregnant women in the intervention arm with 10,000 IU daily oral doses of vitamin A (Kumwenda 2002).

One trial provided vitamin A supplements only after delivery (Humphrey 2006). This trial had a factorial design and the interventions consisted of a single oral dose of 400,000 IU vitamin A to the mother only; 50,000 IU single oral dose to the newborn only; or 400,000 IU to the mother and 50,000 IU to the newborn (Humphrey 2006). In our analyses, we considered only the group in which the mother alone received vitamin A supplements as the intervention arm.

In two trials, women received vitamin A supplements both during pregnancy and immediately after delivery (Coutsoudis 1999; Fawzi 2002). In the first trial, women in the intervention arm received 5000 IU retinyl palmitate and 30 mg beta-carotene daily during pregnancy. In addition, at delivery, women in the intervention arm received 200,000 IU of retinyl palmitate (Coutsoudis 1999). The second trial employed a two-by-two factorial design (Fawzi 2002). Women in the intervention arms received daily doses of vitamin A (30 mg beta carotene plus 5000 IU retinyl palmitate) alone; vitamin A plus multivitamins (20 mg vitamin B1, 20 mg vitamin B2, 25 mg vitamin B6, 100 mg niacin, 50 µg vitamin B12, 500 mg vitamin C, 30 mg vitamin E, and 0.8 mg folic); or multivitamins alone. At delivery, women receiving any vitamin A were given an additional 200,000 IU oral dose of vitamin A (Fawzi 2002).

Concomitant interventions

Two trials did not provide information on any concomitant interventions (Coutsoudis 1999; Chikobvu 2000). In the remaining three trials, the pregnant women received daily oral doses of iron and folic acid (Fawzi 2002; Kumwenda 2002; Humphrey 2006). One trial also reported providing weekly doses of chloroquine (Fawzi 2002), and another trial provided all women with

oral vitamin A (100,000 IU) at six weeks postpartum, according to national policy (Kumwenda 2002). In one trial all children, regardless of whether they were in the intervention or comparison arm, received 100,000 IU vitamin A at six months of age and 200,000 IU of vitamin A every six months afterwards (Fawzi 2002).

Antiretroviral therapy (ART)

None of the five included trials reported giving ART to participants.

Comparison interventions

In four trials, the comparison intervention was a placebo (Coutsoudis 1999; Chikobvu 2000; Fawzi 2002; Humphrey 2006). The fifth study used a "no intervention" comparison group (Kumwenda 2002). All women in this trial received iron and folic acid, and half of them were randomly assigned to receive vitamin A. Supplements that contained vitamin A, iron, and folic acid were indistinguishable from the ones that contained only iron and folic acid (Kumwenda 2002).

Outcome measures

Primary outcomes

HIV infection status of the child

We obtained data on children's HIV infection status at three months (Coutsoudis 1999; Chikobvu 2000), and at 24 months (Fawzi 2002; Kumwenda 2002; Humphrey 2006). A child was determined to be HIV-positive when a blood specimen tested positive using polymerase chain reaction (PCR) at any point or a plasma specimen obtained at 18 months of age or older tested positive using enzyme-linked immunosorbent assay (ELISA).

Secondary outcomes

Birthweight

Three trials reported data on mean birthweight (Coutsoudis 1999; Fawzi 2002; Kumwenda 2002).

Child death by two years of age

Three trials reported data on child death by 24 months of age (Fawzi 2002; Kumwenda 2002; Humphrey 2006).

Low birthweight

Three trials reported data on the occurrence of low birthweight, that is, children born with birthweight less than 2500g (Coutsoudis 1999; Fawzi 2002; Kumwenda 2002).

Preterm delivery

Two trials reported data on preterm deliveries, that is, births at less than 37 weeks of gestation (Coutsoudis 1999; Fawzi 2002).

Stillbirth

Three trials reported data on stillbirths (Coutsoudis 1999; Fawzi 2002; Kumwenda 2002).

Maternal death

One trial reported data on maternal deaths from any cause by three months after delivery (Coutsoudis 1999). The second trial reported data on maternal deaths from AIDS-related causes at two and four years (Fawzi 2002). We have used the two-year data in this review.

Postpartum CD4 count

One trial reported postpartum CD4 cell count at two and four years (Fawzi 2002). We have used the two-year data in this review.

Excluded studies

We included Friis 2004 in the previous version of this review (Wiysonge 2011), but excluded the study from this review update because the intervention consisted of multivitamins (including vitamin A) rather than vitamin A alone. We identified 159 records from literature searches. We excluded 155 records after screening by title/abstract. Of the four remaining studies, we excluded three studies after full-text assessment (Duggan 2012; Olofin 2016; Locks 2017), and identified one new reference to an already included study. We excluded the remaining three studies because they assessed the effects of multivitamins (and not vitamin A) and had as participants, children born to HIV-positive women (rather than the women themselves) (Duggan 2012; Olofin 2016; Locks 2017).

Risk of bias in included studies

We have provided detailed ' Risk of bias' assessments of the included trials in the ' Characteristics of included studies' table, and provided a summary in Figure 2 and Figure 3.

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

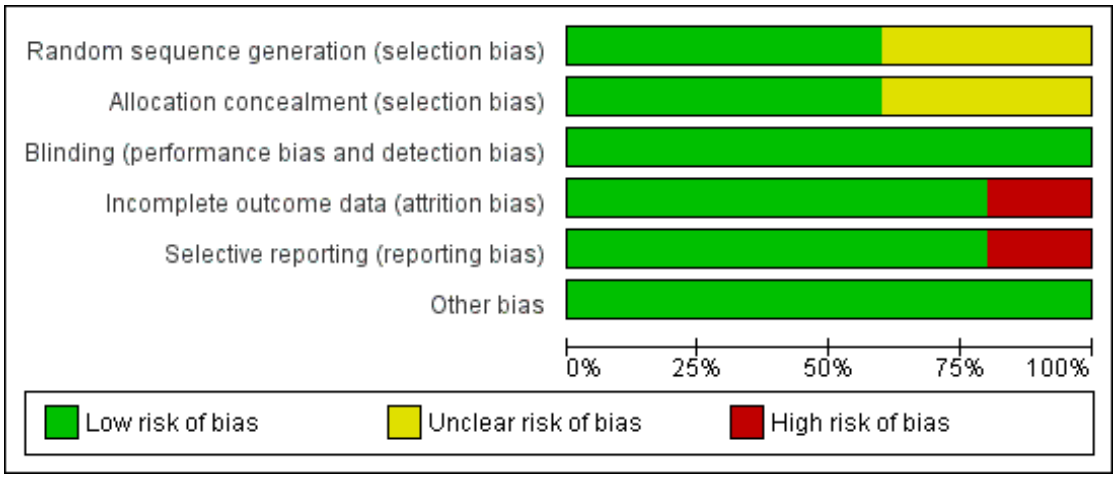
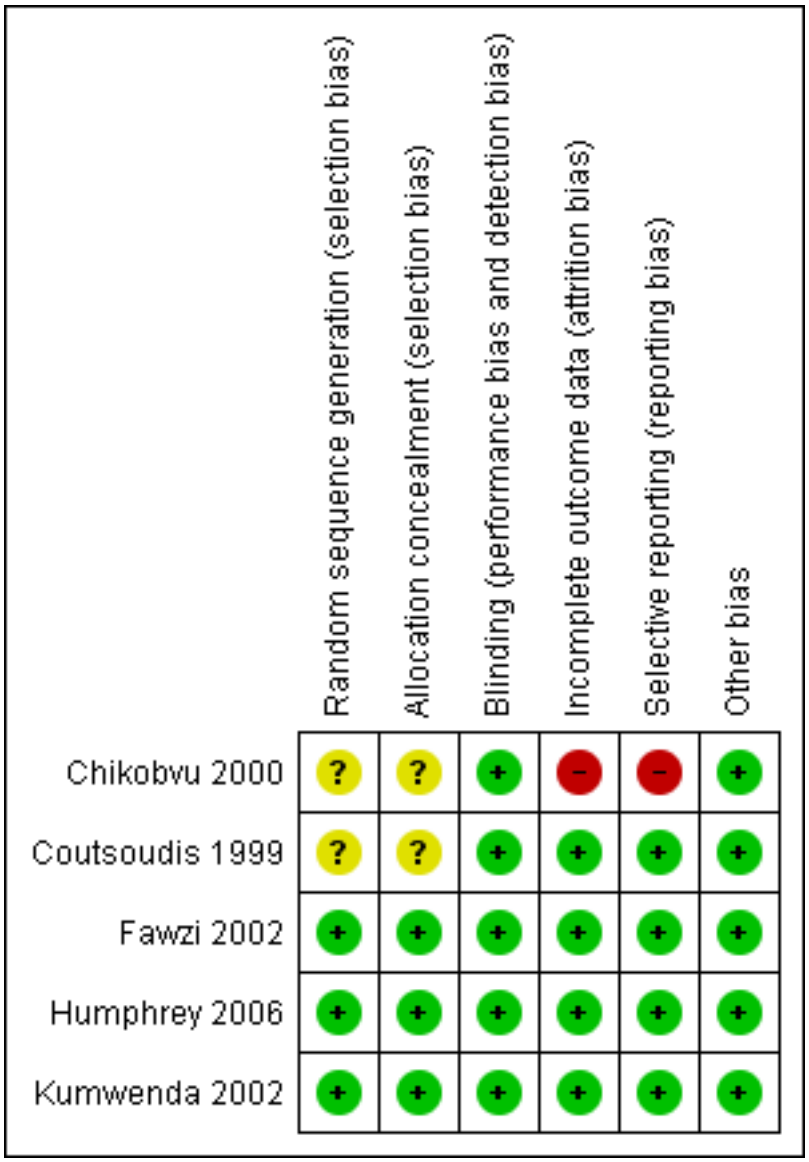


Figure 3. ' Risk of bias' summary: review authors' judgements about each ' Risk of bias' item for each included trial



Allocation

Sequence generation

Regarding sequence generation, three trials were at low risk of bias (Fawzi 2002; Kumwenda 2002; Humphrey 2006), and the risk of bias in two trials was unclear (Coutsoudis 1999; Chikobvu 2000). The authors of the latter trials did not clearly describe the methods used to generate the randomization sequence (Coutsoudis 1999; Chikobvu 2000).

Allocation concealment

Three trials were at low risk of bias as per allocation concealment (Fawzi 2002; Humphrey 2006; Kumwenda 2002). We judged two trials to have an unclear risk of bias (Coutsoudis 1999; Chikobvu 2000), as the trial authors did not describe the methods used to conceal allocation to intervention and comparison groups.

Blinding

All five trials were at low risk of performance bias because participants and care providers were blinded to treatment allocation.
The five included trials performed blinding of outcome assessors, thus we judged them to be at low risk of detection bias.

Incomplete outcome data

Four trials had low risk of bias in relation to completeness of outcome data (Coutsoudis 1999; Fawzi 2002; Kumwenda 2002; Humphrey 2006), but we judged one trial to be at high risk of bias (Chikobvu 2000). The proportion of participants lost to follow-up was 3.2% in Humphrey 2006, 5.0% in Fawzi 2002, 7.8% in Coutsoudis 1999, 9.0% in Kumwenda 2002, and more than 48% in Chikobvu 2000. Therefore, the proportion of randomized participants with evaluable data ranged from less than 52% (Chikobvu 2000), to 96.8% (Humphrey 2006).

Selective reporting

We judged the risk of reporting bias to be low in four trials (Coutsoudis 1999; Fawzi 2002; Kumwenda 2002; Humphrey 2006). However, we observed evidence of selective reporting in one trial, which we judged to be at high risk of reporting bias (Chikobvu 2000). The trial did not report data on mother-to-child transmission of HIV because of high loss to follow-up (Chikobvu 2000).

Other potential sources of bias

We observed no other potential sources of bias in included studies.

Summary of 'Risk of bias' assessment

Overall, four trials (with 6995 women) were at low risk of bias (Coutsoudis 1999; Fawzi 2002; Kumwenda 2002; Humphrey 2006), and one trial (with 303 women) was at high risk of bias (Chikobvu 2000).

Effects of interventions

See: **Summary of findings for the main comparison** Effects of giving vitamin A supplements to HIV-positive women during pregnancy or after delivery

We have summarized the effects of vitamin A supplementation of HIV-positive women during pregnancy, immediately after delivery, or both, on key outcomes in the 'Summary of findings' table (Summary of findings for the main comparison).

Primary outcome

HIV infection status of the child

The risk ratio for the effect of vitamin A supplementation during pregnancy on mother-to-child transmission of HIV was 0.85 (95% CI 0.67 to 1.09; 650 women, 2 trials) and for vitamin A supplementation immediately after delivery was 1.11 (95% CI 0.98 to 1.09; 2248 women, 1 trial). In the two trials that provided vitamin A supplementation to women during pregnancy and immediately after delivery, the RR was 1.17 (95% CI 0.86 to 1.59; 1530 women, 2 trials).

Overall, the trials show that vitamin A supplementation of HIV-positive women during pregnancy or the immediate postpartum period, or both, probably has little or no effect on the risk of mother-to-child transmission of HIV (RR 1.07, 95% CI 0.91 to 1.26; 4428 women, 5 trials, *moderate certainty evidence).* There were no substantial differences in effects across the three subgroups (heterogeneity P = 0.15, I^2 statistic = 48.1%; Analysis 1.1).

The effects were similar between studies that provided supplements containing only retinol (RR 1.00, 95% CI 0.81 to 1.22; 2898 women, 3 trials) and those that provided both retinol and beta-carotene (RR 1.17, 95% CI 0.86 to 1.59; 1530 women, 2 trials).

Secondary outcomes

Child

Birthweight

Vitamin A supplementation of HIV-positive women during pregnancy may increase the mean birth weight of babies (MD 34.12 g, 95% CI −12.79g to 81.02; 2181 women, 3 trials, *low certainty evidence)*. The effect was fairly consistent across the three trials (heterogeneity P = 0.34, I^2 statistic 8%; Analysis 1.2).

Low birthweight

Vitamin A supplementation of HIV-positive pregnant women probably reduces the incidence of low birthweight (RR 0.78, 95% CI 0.63 to 0.97; 1819 women, 3 trials, *moderate certainty evidence*). The effect was homogenous across the three included trials (heterogeneity P = 0.56; I^2 statistic = 0%; Analysis 1.3).

Child death by two years of age

Vitamin A supplementation of HIV-positive women during pregnancy or the immediate postpartum period, or both, may have little or no effect on child death by two years of age (RR 1.06, 95% CI 0.92 to 1.22; 3883 women, 3 trials, *low certainty evidence*). This finding was consistent across the three studies (heterogeneity P = 0.49, I^2 statistic = 0%; Analysis 1.4).

Preterm delivery

It is uncertain whether vitamin A supplementation of HIV-positive pregnant women has an effect on the risk of preterm deliveries (RR 0.84, 95% CI 0.52 to 1.37; 1577 women, 2 trials, *very low certainty evidence*). There was unexplained heterogeneity of effects between the two studies (heterogeneity P = 0.03, I^2 statistic = 79%; Analysis 1.5).

Stillbirth

It is uncertain whether vitamin A supplementation of HIV-positive pregnant women has an effect on the incidence of stillbirths (RR 1.13, 95% CI 0.72 to 1.77; 2335 women, 3 trials, *very low certainty evidence*). This uncertainty was consistent across the three trials (heterogeneity P = 0.80, I^2 statistic = 0%; Analysis 1.6).

Mother

Maternal death

It is uncertain whether vitamin A supplementation of HIV-positive women during pregnancy and immediate postpartum period has an effect on maternal deaths, as the certainty of the evidence was very low (RR 0.71, 95% CI 0.35 to 1.43; 1267 women, 2 trials). This finding was consistent between the two trials (heterogeneity P = 0.75, I^2 statistic = 0%; Analysis 1.7).

Postpartum CD4 count

It is uncertain whether vitamin A supplementation of HIV-positive women during pregnancy and immediate postpartum period has an effect on postpartum maternal CD4 levels, as the certainty of the evidence was very low (mean difference −13.00, 95% CI −60.46 to 34.46; 511 women, 1 trial; Analysis 1.8).

DISCUSSION

Summary of main results

Five randomized trials, which were conducted between 1995 and 2005 and included 7298 HIV-positive women in sub-Saharan Africa, met the inclusion criteria of this Cochrane Review. The included trials assessed the effects of vitamin A supplementation during pregnancy, immediately after delivery, or both. A synthesis of the results of the trials shows that vitamin A supplementation probably has little or no effect on mother-to-child transmission of HIV (*moderate certainty evidence*) and may have little or no effect on child death by two years of age (*low certainty evidence*). However, vitamin A supplements may increase the mean birthweight (*low certainty evidence*) and probably reduce the incidence of low birthweight (*moderate certainty evidence*). Due to very low certainty evidence it is uncertain whether vitamin A supplements have an effect on preterm delivery, stillbirth, or maternal death.

Overall completeness and applicability of evidence

By the end of the 20th century, HIV had produced a global epidemic that was far more extensive than was predicted when the infection emerged less than two decades earlier. Antenatal seroprevalence of HIV was more than 10% in many countries in sub-Saharan Africa, the risk of mother-to-child transmission of HIV was about 30% to 45% in the region, and the region was contributing more than 90% of the nearly 2000 new HIV infections in children each day worldwide (De Cock 2000; UNAIDS 2001).

In this context, it was estimated that even with a 3% reduction in transmission, vitamin A supplementation of HIV-positive women would be a cost-effective method of preventing mother-to-child transmission of HIV. Vitamin A supplements are easily provided through existing health services (Wiysonge 2006). It was thus necessary to clarify the effect of the vitamin on mother-to-child transmission of HIV. Such clarification was judged to be important to decision-makers considering affordable options for reducing mother-to-child transmission of HIV in resource-limited settings (Wiysonge 2002).

Despite our comprehensive search, we found only six potentially eligible trials on the topic, of which five trials met our inclusion criteria. Our review shows that vitamin A supplementation of HIV-positive women during pregnancy, after delivery, or both, probably has little or no effect on mother-to-child transmission of HIV.

Our data suggest that the association between low serum vitamin A levels and increased risk of mother-to-child transmission of HIV seen in observational studies (Semba 1994; Greenberg 1997), could have other explanations. Given the observational design of such studies, residual confounding by advanced HIV infection or other factors may explain the seemingly protective association (Fawzi 1998).

In high-income countries, the combination of (1) antiretroviral prophylaxis, (2) elective Caesarean section delivery, and (3) formula feeding in clinical practice, coupled with increased prenatal HIV counselling and testing, has essentially eliminated mother-to-child transmission of HIV in those settings (Mofenson 2000; Navér 2006; UNAIDS 2015). Due to cost and other constraints, many countries in sub-Saharan Africa had difficulties implementing these interventions (McIntyre 2002). However, in the last decade, there have been dramatic improvements. Antiretroviral drugs are now widely available in sub-Saharan Africa and other resource-constrained settings (UNAIDS 2015; WHO 2015; Wang 2016).

Vitamin A is teratogenic when consumed at high doses during early pregnancy, but none of the trials included in this review reported information on adverse events. However, the doses of vitamin A used in the trials were within the recommended safe low doses (WHO 1998).

Quality of the evidence

Due to the inconsistency of the effect of vitamin A supplementation on mother-to-child of HIV across included trials, we downgraded the certainty of this evidence to moderate. The GRADE Working Group classifies research evidence as being of moderate certainty if the true effect of the intervention is likely to be close to what was found in the research but there is a possibility that it is substantially different (Guyatt 2008). Therefore, this review does not completely exclude the possibility of a small beneficial or harmful effect of vitamin A supplementation on the risk of mother-to-child of HIV.

For most of the other outcomes assessed, we judged the certainty of the evidence to be very low (Summary of findings for the main comparison), implying that we are uncertain about the true effect of vitamin A supplementation on these outcomes. Our main concerns with the evidence were imprecision (as the CIs ranged from large benefits to clinically important increases in harm) and the possibility of publication bias (because two or more eligible trials did not report the outcomes).

Potential biases in the review process

We minimized bias in the process of conducting and reporting the review by adhering to the Methodological Expectations of Cochrane Intervention Reviews (MECIR) (Higgins 2016).

The ultimate goal of this review was to determine whether vitamin A supplementation of HIV-positive women could be recommended as a public health policy to reduce mother-to-child of HIV. We therefore considered overall mother-to-child of HIV, whether occurring during pregnancy, during delivery, or after birth. As such we pooled data from all studies, subgrouped by the timing of supplementation. We do not think that pooling data from these trials has introduced bias to the review.

Agreements and disagreements with other studies or reviews

We found that vitamin A supplements probably make little or no difference to the risk of mother-to-child transmission of HIV. This finding is consistent with the findings of previous reviews of maternal vitamin A supplementation by our team (Wiysonge 2002; Wiysonge 2005; Kongnyuy 2009; Wiysonge 2011), and others (Thorne-Lyman 2012).

Our review also shows that giving vitamin A supplements during pregnancy or the immediate postpartum period, or both, may have little or no effect on child death by two years of age. This finding is consistent with that of other authors (Gorgia 2010; Thorne-Lyman 2012). In a previous systematic review, Gorgia 2010 pooled data from six randomized trials and found little or no effect on infant mortality of giving synthetic vitamin A supplements to seemingly healthy mothers after delivery.

In another review, Thorne-Lyman 2012 pooled data from 17 trials among women of any HIV status and found little or no effect of antepartum retinol and beta-carotene supplements on infant mortality. As in this Cochrane Review, Thorne-Lyman 2012 found that antepartum supplementation was protective against low birthweight among HIV-positive women.

Vitamin A is important for embryogenesis; playing a vital role in the development of the foetal heart, embryonal circulatory system, and the regulation of heart asymmetry (Zile 1998). This role could

explain the substantial reduction in low birthweight in the vitamin A group compared to placebo or no intervention.

AUTHORS' CONCLUSIONS

Implications for practice

Antepartum or postpartum vitamin A supplementation, or both, probably makes little or no difference to the risk of mother-to-child transmission of HIV. The evidence from this Cochrane Review suggests that giving vitamin A supplements to pregnant HIV-positive women may have beneficial effects on birthweight.

Implications for research

Given that the currently available randomized trial data do not exclude the possibility that vitamin A supplementation could have small beneficial or harmful effects on mother-to-child transmission of HIV, there may be need for an appropriately powered randomized trial to assess the additive effect of the intervention in antiretroviral-treated women. However, with the current widespread use and success of antiretroviral therapy (ART) in reducing mother-to-child transmission of HIV, further research on the use of vitamin A supplements for this indication may not be warranted.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Chikobvu 2000

Methods	Randomized controlled trial (RCT)
Participants	303 HIV-positive pregnant women from metropolitan Bloemfontein, South Africa. Most participants (56%) lived in informal settlements and all attended public health facilities. For the trial, women were asked to volunteer for HIV testing during their first antenatal visit. Pretest counselling was done in groups, and post-test counselling was done individually. Women who were seropositive for HIV were asked to participate in the trial
Interventions	Vitamin A supplementation versus placebo
Outcomes	Mother-to-child transmission (MTCT) of HIV
Notes	All trial participants gave separate informed consent for the trial. All patients were recruited by one study physician and received verbal or written information (Sesotho, English, or Afrikaans information sheets)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The trial authors did not mention the method used to generate the randomization sequence
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe the method used to conceal the treatment allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	The trial used an identical placebo; HIV diagnosis was done in the laboratory
Incomplete outcome data (attrition bias) All outcomes	High risk	More than 48% of women were lost to follow-up and we do not know whether this was related to outcomes
Selective reporting (reporting bias)	High risk	Not all prespecified outcomes were reported in various publications from this trial
Other bias	Low risk	We do not believe that other biases were introduced, over and above the high loss to follow-up and the selective reporting

Coutsoudis 1999

Methods	Described as randomized double-blind. The trial authors lost eight per cent of mother-infant pairs during follow-up and excluded them from the analysis
Participants	728 HIV-positive women enrolled at 17 to 39 weeks' gestation in KwaZulu-Natal Province of South Africa; 30.6% of whom had serum retinol levels < 20 µg/dL
Interventions	Daily oral vitamin A (5000 IU retinyl palmitate and 30 mg beta-carotene) or placebo. At delivery, women in the vitamin A group received a dose of 200,000 IU of retinyl palmitate while the placebo arm received an identical placebo
Outcomes	Stillbirths, HIV infection in the child, neonatal deaths, preterm birth, birthweight, low birthweight
Notes	No woman received any antiretroviral therapy (ART). It is not stated in the trial reports whether the women also received iron or folic acid, or both

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The trial authors did not describe the method used to generate the randomization sequence
Allocation concealment (selection bias)	Unclear risk	The trial authors did not describe the method used to conceal the treatment allocation
Blinding (performance bias and detection bias) All outcomes	Low risk	Use of identical placebo; diagnosis of HIV was done in the laboratory
Incomplete outcome data (attrition bias) All outcomes	Low risk	Less than 10% of women were lost to follow-up and we do not believe that this was related to the outcome. We do not believe this introduced bias
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported in various publications from this trial
Other bias	Low risk	We do not believe that other biases were introduced that could have affected study findings

Fawzi 2002

Methods	Randomized, placebo-controlled, double-blind. The trial authors lost five per cent of mother-infant pairs during follow-up and excluded them from the analysis
Participants	1075 pregnant HIV-positive women enrolled at 12 to 27 weeks' gestation in Dar es Salam, Tanzania. Of 1085 women initially randomized, 10 were eventually excluded for either being HIV-negative (n = 7) or not pregnant (n = 3). The prevalence of vitamin A deficiency (< 0.70 µmol/L) was about 34% during the second trimester
Interventions	Daily oral dose of one of: vitamin A (30 mg beta carotene + 5000 IU retinyl palmitate) alone, multivitamins (20 mg vitamin B1, 20 mg vitamin B2, 25 mg vitamin B6, 100 mg niacin, 50 µg vitamin B12, 500 mg vitamin C, 30 mg vitamin E, and 0.8 mg folic) plus vitamin A, multivitamins without vitamin A, or placebo At delivery, women receiving any vitamin A were given an additional 200,000 IU oral dose of vitamin A while the others received an extra dose of placebo In this review, we used only data from the vitamin A only (intervention) and the placebo arms
Outcomes	Stillbirths, HIV infection in child, preterm delivery, low birthweight, postpartum CD4 levels
Notes	It is not mentioned in this trial whether any woman received ART. All women were given daily oral doses of iron and folic acid, and weekly doses of chloroquine. All children, regardless of which intervention group they were in, received 100,000 IU vitamin A at six months of age, and 200,000 IU of vitamin A every six months afterwards

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The trial used computer-generated randomization sequence.
Allocation concealment (selection bias)	Low risk	Block randomization; blocks of 20. At enrolment, the investigators assigned each eligible woman the next numbered bottle of study drug
Blinding (performance bias and detection bias) All outcomes	Low risk	At enrolment, each eligible woman was assigned the next numbered bottle of study drug. Active tablets and placebo were indistinguishable, so that neither the participants nor the investigators could identify which participants were randomized to the which regimen
Incomplete outcome data (attrition bias) All outcomes	Low risk	Fifty-four women (5.0%) were lost to follow-up, and we do not believe that this was related to the outcome. We do not believe

Fawzi 2002 (*Continued*)

		this introduced bias
Selective reporting (reporting bias)	Low risk	The trial authors reported on all outcomes specified in the goals of the study articles
Other bias	Low risk	We do not believe that other biases were introduced that could have affected the study findings

Humphrey 2006

Methods	Randomized, placebo-controlled trial.
Participants	4495 mother-infants pairs who were part of the Zimbabwe Vitamin A for Mothers and Babies (ZVITAMBO) trial in Harare Zimbabwe. Mother-infant pairs were enrolled at 96 hours (or less) after delivery
Interventions	A 2-by-2 factorial design with 4 treatment groups Aa, Ap, Pa, and Pp; where "A" was maternal vitamin A supplementation (400,000 IU), "P" was maternal placebo, "a" was infant vitamin A supplementation (50,000 IU), and "p" was infant placebo In this review, we used only data from Ap (intervention) versus Pp (placebo)
Outcomes	Primary outcome: breastfeeding-associated MTCT and HIV-free survival Secondary outcome: adverse effects in HIV-positive women or their infants
Notes	All but 4 mothers initiated breastfeeding, no information on ART or cotrimoxazole prophylaxis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The trial authors performed randomization using computer-generated blocks of 12
Allocation concealment (selection bias)	Low risk	Treatment assignment was concealed by prepacking study supplements in sequentially numbered series assigned to study identification numbers. Concealed envelopes with study number; link between number and treatment assignment kept at central location
Blinding (performance bias and detection bias) All outcomes	Low risk	Participants, care providers, and outcome assessors were blinded to the treatment allocation. Mothers were assigned an original study identification number at enrolment and were given the next sequentially numbered opaque bottle with supplements

Incomplete outcome data (attrition bias) All outcomes	Low risk	One hundred and forty-three (3.2%) mother-infant pairs were lost to follow-up. We do not believe that the loss to follow-up was related to the outcome
Selective reporting (reporting bias)	Low risk	The trial authors reported outcomes that were prespecified in the protocol (NCT00198718)
Other bias	Low risk	We do not believe that other biases were introduced that could have affected the study findings

Kumwenda 2002

Methods	RCT. Participants were assigned to treatment using computer-generated random numbers, and treatment was concealed by pre-packing study supplements in sequentially numbered series assigned to study identification numbers. Sixty-three women (9%) were lost to follow-up before delivery and excluded from the analyses. The 14 pairs of twins in the study were excluded from the birth weight and mortality analyses because twins are known to have lower birth weights and higher mortality rates
Participants	697 pregnant HIV-positive women enrolled at 18 to 28 week's gestation in Blantyre, Malawi. The prevalence of vitamin A deficiency (< 0.70 µmol/L) was 51% during the second trimester
Interventions	All women received orally administered daily doses of iron (30 mg of elemental iron) and folate (400 µg) from enrolment until delivery. One-half of the women were randomized to receive daily doses of orally administered vitamin A (10,000 IU)
Outcomes	Stillbirths, HIV infection in child, preterm delivery, low birthweight, postpartum CD4 levels
Notes	All women received oral vitamin A (100,000 IU) at 6 weeks postpartum, as per policy of the Malawi Ministry of Health

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	The trial authors determined treatment assignment by use of a computer random-number generator
Allocation concealment (selection bias)	Low risk	Treatment assignment was concealed by pre-packing study supplements in sequentially numbered series assigned to study identification numbers. Mothers were as-

Kumwenda 2002 (*Continued*)

		signed an original study identification number at enrolment and were given the next sequentially numbered opaque bottle with supplements
Blinding (performance bias and detection bias) All outcomes	Low risk	Supplements containing vitamin A, iron, and folate were identical in appearance to the supplements containing iron and folate
Incomplete outcome data (attrition bias) All outcomes	Low risk	Nine per cent of women were lost to follow-up and we do not believe that this was related to the outcome. We do not believe this introduced bias
Selective reporting (reporting bias)	Low risk	The trial authors reported on all outcomes specified in the goals of the study articles
Other bias	Low risk	We do not believe that other biases were introduced that could have affected the study findings

Abbreviations: ART: antiretroviral therapy; MTCT: mother-to-child transmission; RCT: randomized controlled trial.

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

Study	Reason for exclusion
Duggan 2012	The intervention consisted of multiple multivitamins (not vitamin A) and the participants were children born to HIV-positive women (rather than the women themselves)
Friis 2004	The intervention consisted of multiple multivitamins and not vitamin A
Locks 2017	The intervention consisted of multiple multivitamins (not vitamin A) and the participants were children born to HIV-positive women (rather than the women themselves)
Olofin 2016	The intervention consisted of multiple multivitamins (not vitamin A) and the participants were children born to HIV-positive women (rather than the women themselves)

DATA AND ANALYSES

Comparison 1. Vitamin A supplementation versus no vitamin A supplementation

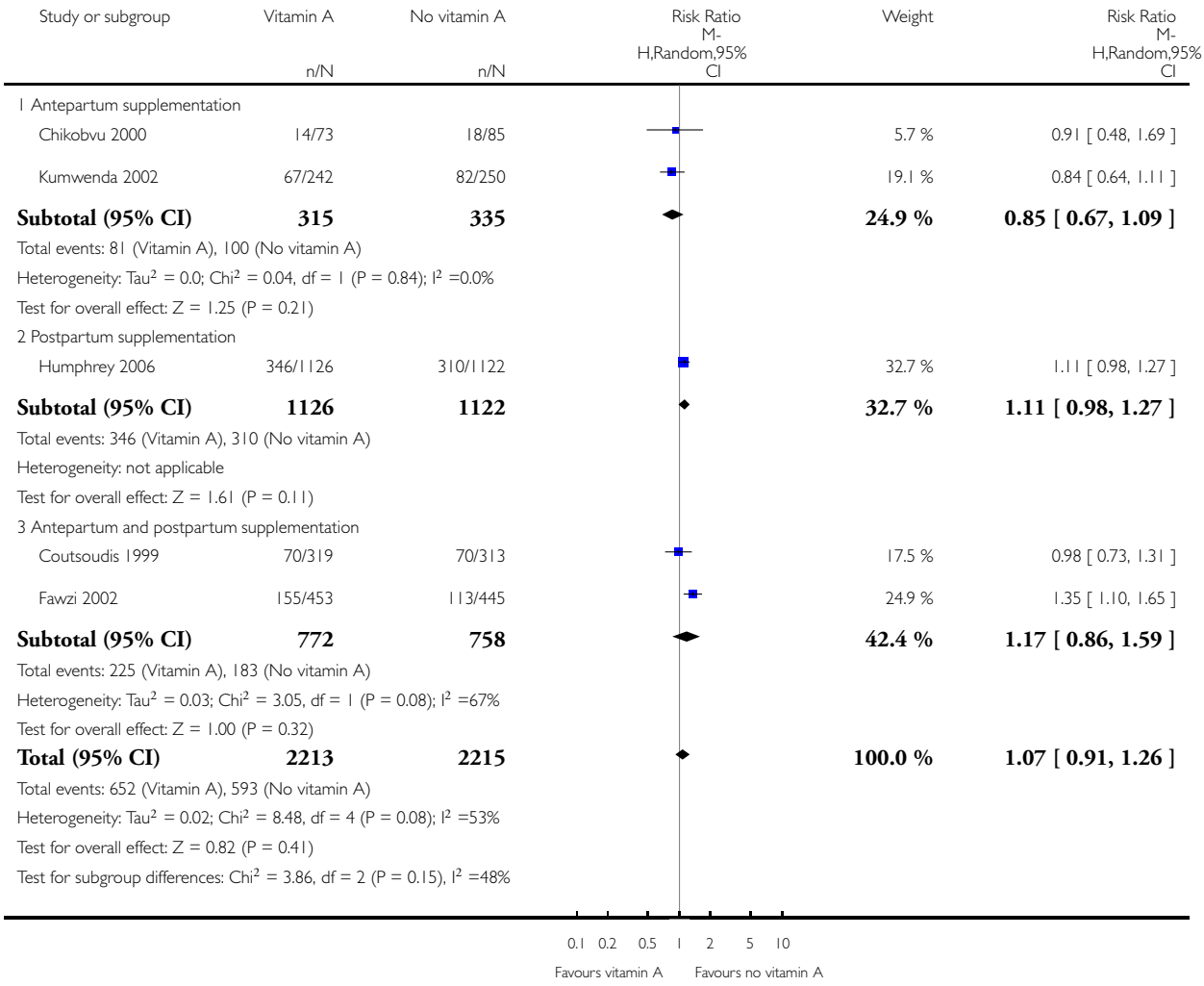
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 HIV infection status of the child	5	4428	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.91, 1.26]
1.1 Antepartum supplementation	2	650	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.67, 1.09]
1.2 Postpartum supplementation	1	2248	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.98, 1.27]
1.3 Antepartum and postpartum supplementation	2	1530	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.86, 1.59]
2 Mean birthweight	3	2181	Mean Difference (IV, Random, 95% CI)	34.12 [-12.79, 81.02]
3 Low birthweight	3	1819	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.63, 0.97]
4 Child death by two years of age	3	3883	Risk Ratio (M-H, Random, 95% CI)	1.06 [0.92, 1.22]
5 Preterm delivery	2	1577	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.52, 1.37]
6 Stillbirth	3	2335	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.72, 1.77]
7 Maternal death	2	1267	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.35, 1.43]
8 Postpartum CD4 count	1	511	Mean Difference (IV, Random, 95% CI)	-13.0 [-60.46, 34.46]

Analysis 1.1. Comparison 1 Vitamin A supplementation versus no vitamin A supplementation, Outcome 1 HIV infection status of the child.

Review: Vitamin A supplements for reducing mother-to-child HIV transmission

Comparison: 1 Vitamin A supplementation versus no vitamin A supplementation

Outcome: 1 HIV infection status of the child



Analysis 1.2. Comparison 1 Vitamin A supplementation versus no vitamin A supplementation, Outcome 2 Mean birthweight.

Review: Vitamin A supplements for reducing mother-to-child HIV transmission

Comparison: 1 Vitamin A supplementation versus no vitamin A supplementation

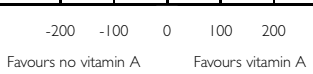
Outcome: 2 Mean birthweight

Study or subgroup	Vitamin A N	Mean(SD)	No vitamin A N	Mean(SD)	Mean Difference IV,Random,95% CI	Weight	Mean Difference IV,Random,95% CI
Coutsoudis 1999	346	3085 (562)	343	3069 (573)		28.4 %	16.00 [-68.76, 100.76]
Kumwenda 2002	285	2895 (523)	309	2805 (563)		26.9 %	90.00 [2.67, 177.33]
Fawzi 2002	453	3005 (507)	445	2993 (504)		44.7 %	12.00 [-54.13, 78.13]
Total (95% CI)	**1084**		**1097**			**100.0 %**	**34.12 [-12.79, 81.02]**

Heterogeneity: Tau^2 = 144.06; Chi^2 = 2.18, df = 2 (P = 0.34); I^2 =8%

Test for overall effect: Z = 1.43 (P = 0.15)

Test for subgroup differences: Not applicable



Analysis 1.3. Comparison 1 Vitamin A supplementation versus no vitamin A supplementation, Outcome 3 Low birthweight.

Review: Vitamin A supplements for reducing mother-to-child HIV transmission

Comparison: 1 Vitamin A supplementation versus no vitamin A supplementation

Outcome: 3 Low birthweight

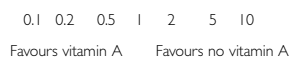
Study or subgroup	Vitamin A n/N	No vitamin A n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Coutsoudis 1999	42/346	48/343		32.0 %	0.87 [0.59, 1.28]
Fawzi 2002	39/269	46/267		31.1 %	0.84 [0.57, 1.24]
Kumwenda 2002	40/285	65/309		36.9 %	0.67 [0.47, 0.96]
Total (95% CI)	**900**	**919**		**100.0 %**	**0.78 [0.63, 0.97]**

Total events: 121 (Vitamin A), 159 (No vitamin A)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.16$, df = 2 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 2.23 (P = 0.026)

Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1 Vitamin A supplementation versus no vitamin A supplementation, Outcome 4 Child death by two years of age.

Review: Vitamin A supplements for reducing mother-to-child HIV transmission

Comparison: 1 Vitamin A supplementation versus no vitamin A supplementation

Outcome: 4 Child death by two years of age

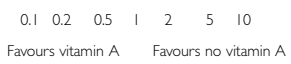
Study or subgroup	Vitamin A n/N	No vitamin A n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Fawzi 2002	163/527	159/514		60.6 %	1.00 [0.83, 1.20]
Kumwenda 2002	69/285	68/309		23.2 %	1.10 [0.82, 1.48]
Humphrey 2006	67/1126	53/1122		16.2 %	1.26 [0.89, 1.79]
Total (95% CI)	**1938**	**1945**		**100.0 %**	**1.06 [0.92, 1.22]**

Total events: 299 (Vitamin A), 280 (No vitamin A)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 1.41$, df = 2 (P = 0.49); $I^2 = 0.0\%$

Test for overall effect: Z = 0.83 (P = 0.41)

Test for subgroup differences: Not applicable

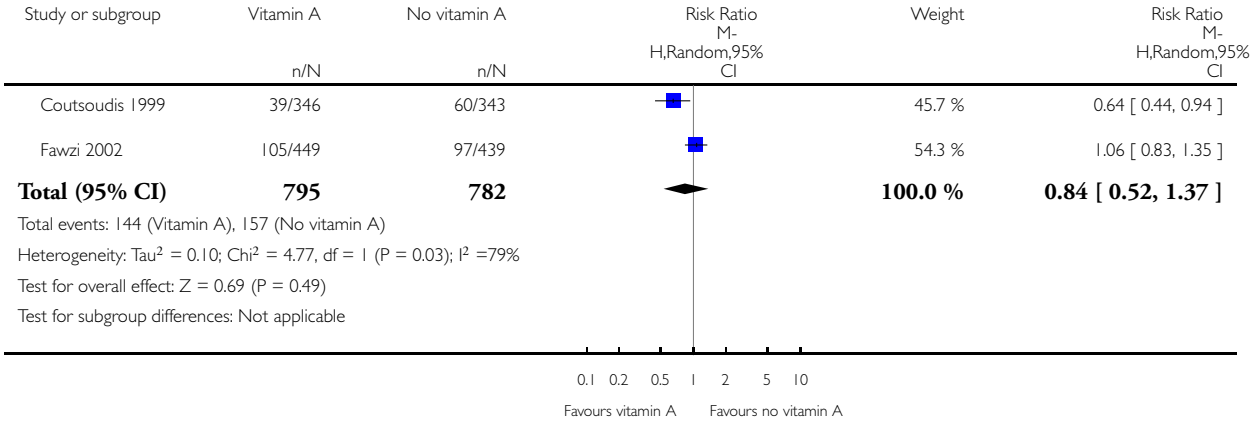


Analysis 1.5. Comparison 1 Vitamin A supplementation versus no vitamin A supplementation, Outcome 5 Preterm delivery.

Review: Vitamin A supplements for reducing mother-to-child HIV transmission

Comparison: 1 Vitamin A supplementation versus no vitamin A supplementation

Outcome: 5 Preterm delivery



Analysis 1.6. Comparison 1 Vitamin A supplementation versus no vitamin A supplementation, Outcome 6 Stillbirth.

Review: Vitamin A supplements for reducing mother-to-child HIV transmission

Comparison: 1 Vitamin A supplementation versus no vitamin A supplementation

Outcome: 6 Stillbirth

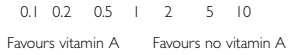
Study or subgroup	Vitamin A n/N	No vitamin A n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Coutsoudis 1999	6/341	4/330		13.0 %	1.45 [0.41, 5.10]
Kumwenda 2002	8/306	6/317		18.7 %	1.38 [0.48, 3.93]
Fawzi 2002	25/527	24/514		68.4 %	1.02 [0.59, 1.76]
Total (95% CI)	**1174**	**1161**		**100.0 %**	**1.13 [0.72, 1.77]**

Total events: 39 (Vitamin A), 34 (No vitamin A)

Heterogeneity: $Tau^2 = 0.0$; $Chi^2 = 0.44$, df = 2 (P = 0.80); $I^2 = 0.0\%$

Test for overall effect: Z = 0.52 (P = 0.60)

Test for subgroup differences: Not applicable

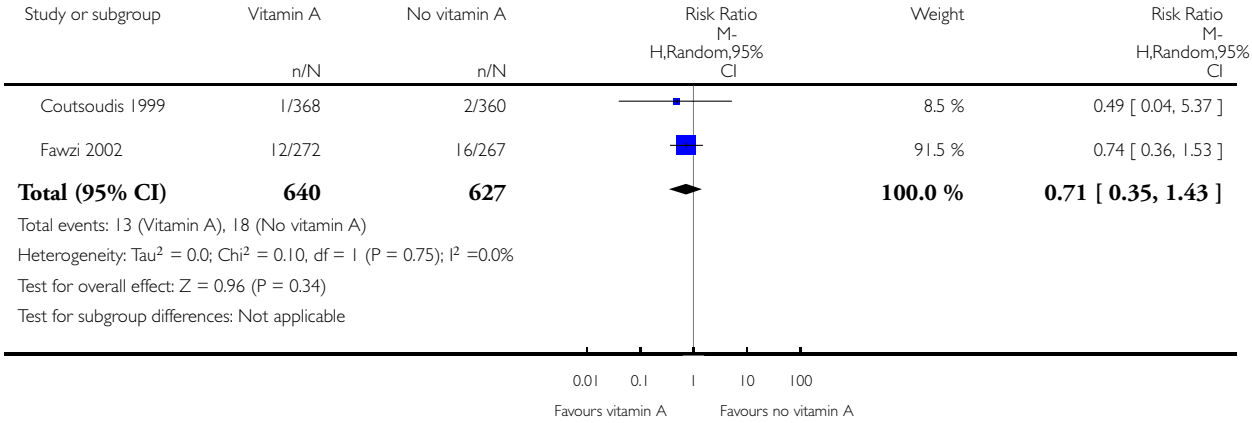


Analysis 1.7. Comparison 1 Vitamin A supplementation versus no vitamin A supplementation, Outcome 7 Maternal death.

Review: Vitamin A supplements for reducing mother-to-child HIV transmission

Comparison: 1 Vitamin A supplementation versus no vitamin A supplementation

Outcome: 7 Maternal death

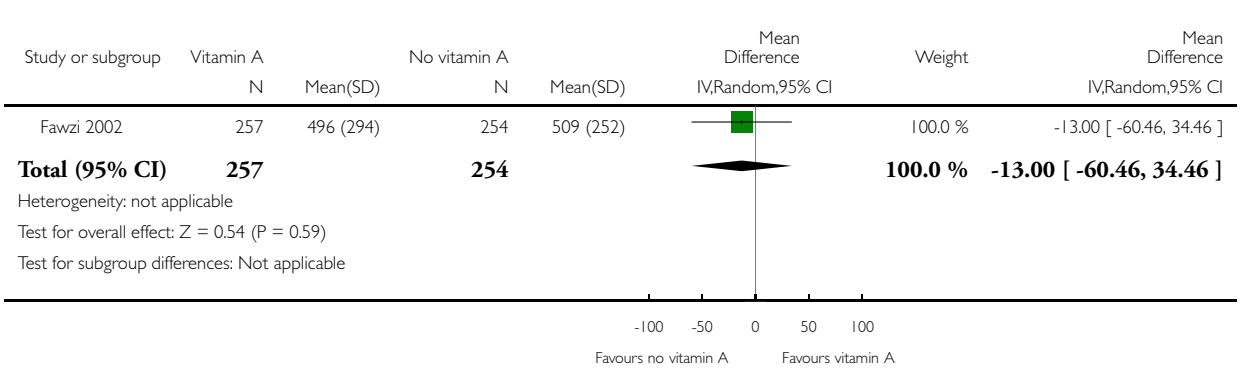


Analysis 1.8. Comparison 1 Vitamin A supplementation versus no vitamin A supplementation, Outcome 8 Postpartum CD4 count.

Review: Vitamin A supplements for reducing mother-to-child HIV transmission

Comparison: 1 Vitamin A supplementation versus no vitamin A supplementation

Outcome: 8 Postpartum CD4 count



ADDITIONAL TABLES

Table 1. Search strategy used on 25 August 2017

Search set	CENTRAL	PubMed	Embase	WHO ICTRP	ClinicalTrials.gov
#1	MeSH descriptor: [HIV Infections] explode all trees	Search ((HIV Infections[MeSH] OR HIV[MeSH] OR hiv[tiab] OR hiv-1*[tiab] OR hiv-2*[tiab] OR hiv1[tiab] OR hiv2[tiab] OR hiv infect*[tiab] OR human immunodeficiency virus[tiab] OR human immunedeficiency virus[tiab] OR human immunodeficiency virus[tiab] OR human immune-deficiency virus[tiab] OR ((human immun*[tiab]) AND (deficiency virus[tiab])) OR acquired immunodeficiency syndrome[tiab] OR acquired immunedeficiency syndrome[tiab] OR acquired immunodeficiency syndrome[tiab] OR acquired immune-deficiency syndrome[tiab] OR ((acquired immun*[tiab]) AND (deficiency syndrome[tiab])) OR "sexually transmitted diseases, Viral"[MeSH:NoExp]))	'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection'/de OR 'human immunodeficiency virus infection' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus'/de OR 'human immunodeficiency virus' OR 'human immunodeficiency virus:ab,ti' OR hiv:ab,ti OR 'hiv-1':ab, ti OR 'hiv-2':ab,ti OR 'human immunodeficiency virus':ab,ti OR 'human immunedeficiency virus':ab,ti OR 'human immune-deficiency virus':ab,ti OR 'human immunodeficiency virus':ab,ti OR 'acquired immunodeficiency syndrome':ab, ti OR 'acquired immuno-deficiency syndrome':ab,ti OR 'acquired immune-deficiency syndrome':ab, ti OR 'acquired immunedeficiency syndrome':ab,ti	hiv AND vitamin A OR hiv AND retinol OR hiv AND retinoic OR hiv AND micronutrients OR hiv AND carotene	HIV and "VITAMIN A" | Interventional Studies | Studies received from 05/20/2016 to 08/25/2017
#2	MeSH descriptor: [HIV] explode all trees	Search (randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized [tiab] OR placebo	'randomized controlled trial'/de OR 'randomized controlled trial' OR random*:ab,ti OR trial:ti OR allocat*:	-	-

Table 1. Search strategy used on 25 August 2017 (*Continued*)

		[tiab] OR "clinical trials as topic"[mesh: noexp] OR randomly [tiab] OR trial [tiab]) NOT (animals [mh] NOT humans [mh])	ab,ti OR factorial*:ab,ti OR placebo*:ab,ti OR assign*:ab,ti OR volunteer*:ab,ti 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 ((doubl* NEAR/3 blind*):ab,ti) OR (singl*: ab,ti AND blind*:ab,ti) OR crossover*:ab,ti OR cross+over*:ab,ti OR ((cross NEXT/1 over*):ab,ti)		
#3	hiv or hiv-1* or hiv-2* or hiv1 or hiv2 or (hiv near infect*) or (human immunodeficiency virus) or (human immunedeficiency virus) or (human immune-deficiency virus) or (human immuno-deficiency virus) or (human immune deficiency virus) or (human immuno 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) (Word variations have been searched)	Search (infectious disease transmission, vertical[mh] OR vertical transmission[tiab] OR vertical infect*[tiab] OR infection transmission[tiab] OR mother-to-child transmission[tiab] OR MTCT[tiab])	'animal'/de OR 'animal experiment'/de OR 'invertebrate'/de OR 'animal tissue'/de OR 'animal cell'/de OR 'nonhuman'/de	-	-

Table 1. Search strategy used on 25 August 2017 (*Continued*)

#4	MeSH descriptor: [Lymphoma, AIDS-Related] this term only	Search (vitamin A[mh] OR vitamin*[tiab] OR caroten*[tiab] OR retinol[tiab] OR retinoic[tiab] OR micronutrient*[tiab])	'human'/de OR 'normal human'/de OR 'human cell'/de	-	-
#5	MeSH descriptor: [Sexually Transmitted Diseases, Viral] this term only	Search (#1 AND #2 AND #3 AND #4)	#3 AND #4	-	-
#6	#1 or #2 or #3 or #4 or #5	Search (((#1 AND #2 AND #3 AND #4))) AND ("2016/05/20"[Date - Publication] : "2017/08/25"[Date - Publication])	#3 NOT #5	-	-
#7	[mh "infectious disease transmission, vertical"] or "vertical transmission":ti,ab,kw or vertical next infect*:ti,ab,kw or "infection transmission":ti,ab,kw or "mother-to-child transmission":ti,ab,kw or MTCT:ti,ab,kw (Word variations have been searched)	-	#2 NOT #6	-	-
#8	[mh "vitamin A"] or vitamin*:ti,ab,kw or caroten*:ti,ab,kw or retinol:ti,ab,kw or retinoic:ti,ab,kw or micronutrient*:ti,ab,kw (Word variations have been searched)	-	'vertical transmission'/de OR 'vertical transmission':ab,ti OR 'infectious disease transmission':ab,ti OR 'mother+to+child transmission':ab,ti OR mtct:ab,ti	-	-
#9	#6 and #7 and #8	-	caroten*:ab,ti OR retinoic:ab,ti OR 'retinol'/de OR	-	-

Table 1. Search strategy used on 25 August 2017 (*Continued*)

			retinol:ab,ti OR vitamin*:ab,ti OR 'vitamin a'/de OR micronutrient*:ab,ti		
#10	#6 and #7 and #8 Publication Year from 2016 to 2017	-	#1 AND #7 AND #8 AND #9	-	-
#11	-	-	#1 AND #7 AND #8 AND #9 AND [20-5-2016]/sd NOT [25-8-2017]/sd	-	-

Table 2. Search strategy used on 20 May 2016

Search set	CENTRAL	PubMed	Embase
#1	HIV Infections	HIV Infections OR HIV OR hiv OR hiv-1* OR hiv-2* OR hiv1 OR hiv2 OR hiv infect* OR human immunodeficiency virus OR human immunedeficiency virus OR human immunodeficiency virus OR human immunedeficiency virus OR (human immun* AND deficiency virus) OR acquired immunodeficiency syndrome OR acquired immunedeficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR (acquired immun* AND deficiency syndrome) OR "sexually transmitted diseases, Viral"	human immunodeficiency virus infection OR human immunodeficiency virus infection OR human immunodeficiency virus infection OR human immunodeficiency virus OR human immunodeficiency virus OR human immunodeficiency virus OR hiv OR hiv-1 OR hiv-2 OR human immunodeficiency virus OR human immunedeficiency virus OR human immunedeficiency virus OR human immunodeficiency virus OR acquired immunodeficiency syndrome OR acquired immuno-deficiency syndrome OR acquired immune-deficiency syndrome OR acquired immunedeficiency syndrome
#2	HIV	randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR "clinical trials as topic" OR randomly OR trial) NOT (animals NOT humans)	randomized controlled trial OR randomized controlled trial OR random* OR trial OR allocat* OR factorial* OR placebo* OR assign* OR volunteer* OR crossover procedure OR crossover procedure OR double-blind procedure OR double-blind procedure OR single-blind procedure OR single-blind procedure OR doubl* NEAR/3 blind* OR singl* AND blind* OR crossover* OR cross+over* OR cross NEXT/1 over*

Table 2. Search strategy used on 20 May 2016 (*Continued*)

#3	hiv or hiv-1* or hiv-2* or hiv1 or hiv2 or hiv near infect* or human immunodeficiency virus or human immunedeficiency virus or human immune-deficiency virus or human immuno-deficiency virus or human immune deficiency virus or human immuno 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	infectious disease transmission, vertical OR vertical transmission OR vertical infect* OR infection transmission OR mother-to-child transmission OR MTCT	animal OR animal experiment OR invertebrate OR animal tissue OR animal cell OR nonhuman
#4	Lymphoma, AIDS-Related	vitamin A OR vitamin* OR caroten* OR retinol OR retinoic OR micronutrient*	human OR normal human OR human cell
#5	Sexually Transmitted Diseases, Viral	1-4/AND	#3 AND #4
#6	1-5/OR	5 AND (2010/06/01 NOT 2016/05/20)	#3 NOT #5
#7	infectious disease transmission, vertical or vertical transmission or vertical next infect* or infection transmission or mother-to-child transmission or MTCT	-	#2 NOT #6
#8	vitamin A or vitamin* or caroten* or retinol or retinoic or micronutrient*	-	vertical transmission OR vertical transmission OR infectious disease transmission OR mother+to+child transmission OR mtct
#9	6-8/AND	-	caroten* OR retinoic OR retinol OR retinol OR vitamin* OR vitamin a OR micronutrient*
#10	Limit 9 to publication date 2010-2016	-	#1 AND #7 AND #8 AND #9
#11	-	-	#10 AND (2010/06/01 NOT 2016/05/20)

Table 3. Search strategy used in June 2010

Search set	CENTRAL	PubMed	Embase
#1	MeSH descriptor HIV Infections explode all trees	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]	'human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection'/de OR 'human immunodeficiency virus infection' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus'/de OR 'human immunodeficiency virus'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 immuno-deficiency virus':ti OR 'human immuno-deficiency virus':ab OR 'human immunedeficiency virus':ti OR 'human immunedeficiency 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
#2	MeSH descriptor HIV explode all trees	Search (randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised [tiab] OR placebo [tiab] OR drug therapy [sh] OR randomly [tiab] OR trial [tiab] OR groups [tiab]) NOT (animals [mh] NOT humans [mh])	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 allocat*:ti OR allocat*:ab OR volunteer*:ti OR volunteer*:ab OR 'crossover procedure'/exp OR 'crossover procedure'/de OR 'crossover procedure'OR 'double-blind procedure'/exp OR 'double-

Table 3. Search strategy used in June 2010 (*Continued*)

			blind procedure'/de OR 'double-blind procedure' OR 'single-blind procedure'/exp OR 'single-blind procedure'/de OR 'single-blind procedure' OR 'randomised controlled trial'/exp OR 'randomised controlled trial'/de OR 'randomised controlled trial'
#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 IMMUNODEFICIENCY VIRUS OR HUMAN IMMUN* DEFICIENCY VIRUS OR ACQUIRED IMMUNODEFICIENCY SYNDROME OR ACQUIRED IMMUNEDEFICIENCY SYNDROME OR ACQUIRED IMMUNO-DE- FICIENCY SYNDROME OR ACQUIRED IMMUNE-DEFICIENCY SYNDROME OR ACQUIRED IMMUN* DEFICIENCY SYNDROME	Search mother-to-child-transmission OR MTCT OR infectious disease transmission, vertical	'mother-to-child transmission' OR 'mother to child transmission' OR mtct OR 'vertical transmission'/de OR 'vertical transmission'
#4	MeSH descriptor Lymphoma, AIDS-Related, this term only	Search caroten* OR retinoic OR retinol OR vitamin* OR vitamin A OR micronutrient*	caroten* OR retinoicOR 'retinol'/de OR retinolOR vitamin*OR 'vitamin a'/de OR 'vitamin a'OR micronutrient*
#5	MeSH descriptor Sexually Transmitted Diseases, Viral, this term only	Search #1 AND #2 AND #3 AND #4 Limits: Publication Date from 2007/01/01 to 2010/06/08	#1 AND #2AND #3AND #4
#6	(#1 OR #2 OR #3 OR #4 OR #5)	-	#1 AND #2AND #3AND # 4AND [humans]/lim AND [embase]/lim AND [1-1-2007]/sd NOT [8-6-2010]/sd
#7	mother-to-child-transmission OR MTCT	-	-
#8	MeSH descriptor Infectious Disease Transmission, Vertical, this term only	-	-
#9	(#7 OR #8)	-	-

Table 3. Search strategy used in June 2010 (*Continued*)

#10	caroten* OR retinoic OR vitamin* OR vitamin A OR micronutrient*	-	-
#11	(#6 AND #9 AND #10)	-	-
#12	(#6 AND #9 AND #10), from 2007 to 2010	-	-

Table 4. Search strategy used in February 2008

Search set	PubMed	Embase	AIDSearch	GATEWAY
#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"[MH]	(('human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection') OR ('human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection')) OR (((('human immunodeficiency virus'/exp OR 'human immunodeficiency virus') OR ('human immunodeficiency virus'/exp OR 'human immunodeficiency virus'))) OR ((('b cell lymphoma'/exp OR 'b cell lymphoma') OR ('b cell lymphoma'/exp OR 'b cell lymphoma'))) 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 immunedeficiency virus':ti OR 'human immunedeficiency virus':ab) OR ('human	(HIV INFECTIONS) OR HIV OR HIV OR HIV-1* OR HIV-2* OR HIV1 OR HIV2 OR (HIV INFECT*) OR (HUMAN IMMUNOD-EFICIENCY VIRUS) OR (HUMAN IMMUNEDEFICIENCY VIRUS) OR (HUMAN IMMUNO-DE-FICIENCY VIRUS) OR (HUMAN IMMUNE-DEFICIENCY VIRUS) OR ((HUMAN IMMUN*) AND (DEFICIENCY VIRUS)) OR (ACQUIRED IMMUNODEFICIENCY SYNDROME) OR (ACQUIRED IMMUNEDEFICIENCY SYNDROME) OR (ACQUIRED IMMUNO-DEFICIENCY SYNDROME) OR (ACQUIRED IMMUNE-DEFICIENCY SYNDROME) OR ((ACQUIRED IMMUN*) AND (DEFICIENCY SYNDROME)) OR (SEXUALLY TRANSMITTED DISEASES, VIRAL)	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]) AND (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"[MH])

Table 4. Search strategy used in February 2008 (*Continued*)

#2	Search randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR (comparative study) OR (comparative studies) OR (evaluation studies) OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT human [mh])	(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'/exp OR 'crossover procedure') OR ('crossover procedure'/exp OR 'crossover procedure')) OR (('crossover procedure'/exp OR 'crossover procedure') OR ('crossover procedure'/exp OR 'crossover procedure')))) OR ((('double-blind procedure'/exp OR 'double-blind procedure') OR ('double-blind procedure'/exp OR 'double-blind procedure')) OR (('double-blind procedure'/exp OR 'double-blind procedure') OR ('double-blind procedure'/exp OR 'double-blind procedure')))) OR ((('single-blind procedure'/exp OR 'single-blind procedure') OR ('single-blind procedure'/exp OR 'single-blind procedure')) OR (('single-blind procedure'/exp OR 'single-blind procedure') OR ('single-blind procedure'/exp OR 'single-blind procedure')))) OR ((((('randomised controlled trial'/exp OR 'ran-	((RANDOMIZED CONTROLLED TRIAL) OR (CONTROLLED CLINICAL TRIAL) OR (RANDOMIZED CONTROLLED TRIALS) OR (RANDOM ALLOCATION) OR (DOUBLE-BLIND METHOD) OR (SINGLE-BLIND METHOD) OR (CLINICAL TRIAL) OR (CLINICAL TRIALS) OR ("CLINICAL TRIAL") OR ((SINGL* OR DOUBL* OR TREBL* OR TRIPL* AND (MASK* OR BLIND*)) OR PLACEBOS OR PLACEBO* OR RANDOM* OR (COMPARATIVE STUDY) OR (EVALUATION STUDIES) OR (FOLLOW-UP STUDIES) OR (PROSPECTIVE STUDIES) OR CONTROL* OR PROSPECTIV* OR VOLUNTEER*)) NOT (ANIMALS NOT HUMAN)	Search: (randomised controlled trial [pt] OR controlled clinical trial [pt] OR randomised controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw]))) OR ((placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR (comparative study) OR (comparative studies) OR (evaluation studies) OR follow-up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT human [mh]))

Table 4. Search strategy used in February 2008 (*Continued*)

		domised controlled trial') OR ('randomised controlled trial'/exp OR 'randomised controlled trial')) OR (('randomised controlled trial'/exp OR 'randomised controlled trial') OR ('randomised controlled trial'/exp OR 'randomised controlled trial')))) OR (allocat*:ti OR allocat*:ab) AND [2003-2008]/py		
#3	Search (DISEASE TRANSMISSION, VERTICAL) OR MTCT OR (MOTHER-TO-CHILD TRANSMISSION)	'mother-to-child transmission' OR mtct OR 'vertical disease transmission' AND [2003-2008]/py	(MOTHER-TO-CHILD TRANSMISSION) OR MTCT OR (VERTICAL DISEASE TRANSMISSION)	Search: (DISEASE TRANSMISSION, VERTICAL) OR MTCT OR (MOTHER-TO-CHILD TRANSMISSION)
#4	Search CAROTEN* OR RETINOIC OR RETINOL OR VITAMIN* OR MICRONUTRIENT*	caroten* OR retinoic OR ('retinol'/exp OR 'retinol') OR vitamin* OR micronutrient* AND [2003-2008]/py	CAROTEN* OR RETINOIC OR RETINOL OR VITAMIN* OR MICRONUTRIENT*	Search: CAROTEN* OR RETINOIC OR RETINOL OR VITAMIN* OR MICRONUTRIENT*
#5	Search PREGNANT OR PREGNANCY OR ANTEPARTUM OR PRENATAL OR ANTEPARTUM OR PRE-NATAL OR PREPART*	pregnant OR ('pregnancy'/exp OR 'pregnancy') OR antepartum OR ('ante partum') OR antenatal OR ('ante natal') OR prenatal OR ('pre natal') AND [2003-2008]/py	PREGNANT OR PREGNANCY OR ANTEPARTUM OR (ANTEPARTUM) OR ANTENATAL OR (ANTE-NATAL) OR PRENATAL OR (PRENATAL)	Search: PREGNANT OR PREGNANCY OR ANTEPARTUM OR PRENATAL OR ANTEPARTUM OR PRE-NATAL OR PREPART*
#6	Search #1 AND #2 AND # 3 AND #4 AND #5 Limits: Publication Date from 2003 to 2008	#1 AND #2 AND #3 AND #4 AND #5	#1 AND #2 AND #3 AND #4 AND #5	#1 and #2 and #3 and #4 and #5 Limit: 2003:2008

Table 5. Optimal information size calculation

Outcome	Assumed risk	Source	Clinically important relative improvement	Sample size required
HIV infection in child	27/100	Analysis 1.1	25%	1236
Mean birthweight	2964	Analysis 1.2	25%	6178

Table 5. Optimal information size calculation (*Continued*)

Low birthweight	17/100	Analysis 1.3	25%	2194
Still birth	3/100	Analysis 1.4	25%	14,264
Preterm birth	20/100	Analysis 1.5	25%	1806
Child death	14/100	Analysis 1.6	25%	2748
Maternal death	3/100	Analysis 1.7	25%	14,264

We based the sample size calculations: 2-sided tests, with ratio of 1:1, power of 0.8 and confidence level of 0.05.
We performed the sample size calculations using http://www.sealedenvelope.com/power/binary-superiority/

WHAT'S NEW

Last assessed as up-to-date: 25 August 2017.

Date	Event	Description
7 September 2017	New search has been performed	One new trial met the inclusion criteria of this review update. We excluded one trial that was included in the previous edition of the review, Wiysonge 2011, from this review update because it did not meet our inclusion criteria, and we re-extracted birthweight data. We amended the number of child-related and maternal secondary outcomes. In addition, there were changes to the review author team
7 September 2017	New citation required but conclusions have not changed	This is an update to a review published in 2011.

HISTORY

Protocol first published: Issue 2, 2002

Review first published: Issue 2, 1995

Date	Event	Description
18 January 2011	Amended	External source of support added.
7 September 2010	New citation required but conclusions have not changed	Review expanded to include postpartum supplementation; SOF table added
7 September 2010	New search has been performed	Updated, with GRADE Summary of Findings table.
14 May 2008	Amended	Converted to new review format.
14 May 2008	New search has been performed	Update of review.
11 January 2008	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Charles S Wiysonge led the conduct and writing of this update of the Cochrane Review, with substantial intellectual contributions from Valantine N Ndze, Eugene J Kongnyuy, and Muki S Shey. All review authors approved the final version of the review for submission.

DECLARATIONS OF INTEREST

Charles S Wiysonge has no known conflicts of interest.

Valantine N Ndze has no known conflicts of interest.

Eugene J Kongnyuy has no known conflicts of interest.

Muki S Shey has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- South African Medical Research Council, South Africa.
- Liverpool School of Tropical Medicine, UK.

External sources

- Effective Health Care Research Consortium, UK.

Grant: 5242

- National Research Foundation of South Africa, South Africa.

Grant: 108571

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Differences between 2011 review and this review update

Authorship

The 2011 review had five authors (Wiysonge CS, Shey MS, Kongnyuy EJ, Sterne JA, and Brocklehurst P), but the current update has four authors (Wiysonge CS, Ndze VN, Kongnyuy EJ, and Shey MS).

Primary outcome

There are no differences between the two versions of the review, as both have an identical primary outcome (HIV infection status of the child).

Secondary outcomes

The 2011 review had 12 secondary outcomes linked to the child (infant death, stillbirth, neonatal sepsis, neonatal admission to neonatal unit, death by 24 months of age, side effects in the child, preterm delivery, very preterm delivery, birth weight, low birth weight, very low birthweight, and long-term side effects in survivors) and five maternal secondary outcomes (maternal death, postpartum infection, side effects in the mother, cost of the intervention, and acceptability of the intervention). The current update has five child-related secondary outcomes (mean birthweight, low birthweight, child death by two years of age, preterm delivery, and stillbirth) and two secondary outcomes linked to the mother (maternal death and postpartum CD4 count).

Methods

In Wiysonge 2011, we used a fixed-effect method as our default method for meta-analysis, and only used a random-effects model when there was substantial statistical heterogeneity ($P < 0.1$). However, due to clinical heterogeneity, we used the random-effects method for all meta-analyses in this review update.

Included studies

We included five studies in the 2011 review (Coutsoudis 1999; Fawzi 2002; Kumwenda 2002; Friis 2004; Humphrey 2006), and five reviews in the current update (Coutsoudis 1999; Chikobvu 2000; Fawzi 2002; Kumwenda 2002; Humphrey 2006). We included Friis 2004 in the 2011 review but excluded it from this review update because further assessment revealed that the study did not meet our inclusion criteria. In addition, we included a new study in this update (Chikobvu 2000).

INDEX TERMS

Medical Subject Headings (MeSH)

*Pregnancy Complications, Infectious; HIV Infections [mortality; prevention & control; *transmission]; Infectious Disease Transmission, Vertical [*prevention & control]; Randomized Controlled Trials as Topic; Treatment Outcome; Vitamin A [*administration & dosage]; Vitamin A Deficiency [*complications; drug therapy]; Vitamins [*administration & dosage]

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy