

# COCHRANE COLUMN

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Prevention of mother-to-child transmission (MTCT) of HIV forms a key component of HIV/AIDS prevention programmes. This month we highlight the Cochrane Review by Wiysonge *et al.*, which evaluated the effects of vitamin A supplementation in preventing MTCT of HIV.

The aim of the Column is to highlight Cochrane systematic reviews of relevance to public health and to stimulate debate

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on relevance, feasibility, and acceptability. The Cochrane Collaboration (<http://www.cochrane.org>) is an international, non-profit organization that prepares and disseminates up-to-date systematic reviews on the effects of healthcare interventions in order to help people make well-informed decisions. Systematic reviews aim to answer focused health-care questions by systematically identifying and evaluating all relevant research studies and synthesizing their results.

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## Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection: Cochrane systematic review

Charles Shey Wiysonge, Muki Shehu Shey, Jonathan Sterne and Peter Brocklehurst

Mother-to-child transmission (MTCT) of HIV is the dominant mode of acquisition of HIV infection for children, currently resulting in more than 2000 new paediatric HIV infections each day worldwide. Observational studies have found significant associations between low serum vitamin A levels and increased risk of MTCT of HIV. We systematically reviewed currently available randomized controlled trials (RCTs) to evaluate the efficacy of vitamin A supplementation in preventing MTCT of HIV and other adverse pregnancy outcomes.

### Methodology

RCTs published between January 1980 and September 2005 were identified by searching the Cochrane Controlled Trials Register, PubMed, EMBASE, AIDSearch and conference proceedings, and contacting researchers. At least two authors independently assessed trial eligibility, and quality, and extracted data. We conducted meta-analysis using a fixed effects method, assessed heterogeneity between study results using the  $\chi^2$  test of homogeneity, and used Higgins'  $I^2$  to quantify the heterogeneity.

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### Results

Four trials, involving 3033 participants, met the inclusion criteria. There was no evidence of an effect of vitamin A supplementation on MTCT of HIV infection (Table 1). However, there was evidence of heterogeneity between the three trials with information on MTCT of HIV ( $\chi^2$ [df = 2] = 8.22,  $P = 0.02$ ,  $I^2 = 75.7\%$ ). While the trials conducted in South Africa [OR 0.98, 95% confidence interval (95% CI) 0.67–1.42 at 3 months] and Malawi (OR 0.78, 95% CI 0.53–1.15 at 24 months) did not find evidence that the effect of Vitamin A supplementation was different from that of placebo, the trial in Tanzania found evidence that vitamin A supplementation increased the risk of MTCT of HIV (OR 1.53, 95% CI 1.15–2.04 at 24 months) compared with placebo and multivitamins (excluding vitamin A).

Vitamin A supplementation significantly improved birth weight, but there was no evidence of an effect of vitamin A supplementation on still births, pre-term delivery, and infant mortality (Table 1).

### Discussion and conclusions

Vitamin A was postulated to prevent MTCT of HIV by affecting several risk factors for transmission, including the clinical, immunological, or viral stage of HIV disease among

**Table 1** Summary of meta-analysis results

Outcome	Number of trials	Number of participants	Pooled effect measure	95% CI	Heterogeneity
<b>Binary variables (The effect measure is the odds ratio)</b>					
MTCT of HIV	3	2022	1.14	0.93–1.38	$I^2 = 75.7%$ $P = 0.02$
Still births	4	2885	0.99	0.67–1.46	$P = 0.74$ $I^2 = 0%$
Pre-term delivery	3	2110	0.89	0.71–1.11	$I^2 = 56.6%$ $P = 0.10$
Death by 24 months among live births	2	1578	1.11	0.88–1.40	$I^2 = 0%$ $P = 0.89$
<b>Continuous variable (The effect measure is the weighted mean difference)</b>					
Birth weight	3	1809	89.78	84.73–94.83	$I^2 = 33.0%$ $P = 0.22$

pregnant women; the integrity of the epithelial lining of the placenta, vagina, or breast, prematurity and low birth weight, and the status of the systemic and digestive mucosal immune systems of the foetus and the child.

However, synthesis of the currently available data does not show evidence of an effect of vitamin A supplementation on the risk of MTCT of HIV, though there is an indication that vitamin A supplementation improves birth weight. The data suggest that the association between low serum vitamin A levels and increased risk of MTCT of HIV, seen in observational studies, could have alternative explanations, for example, low serum vitamin A levels may be a marker of

advanced HIV infection and not causally related to MTCT of HIV.

The full text of the Cochrane Review is available in *The Cochrane Library*: Wiysonge CS, Shey MS, Sterne JAC, Brocklehurst P. Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection. *The Cochrane Database of Systematic Reviews* 2005, Issue 4. Art. No.: CD003648. DOI: 10.1002/14651858.CD003648.pub2.

The first version of the Cochrane review published in Issue 3, 2002, was supported by the 2001 Aubrey Sheiham Public Health and Primary Care Scholarship to Dr C S Wiysonge.

## Commentary: Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection

Jennifer S Read

Worldwide, an estimated 2.3 million children are HIV-1-infected, and most acquired the infection through mother-to-child transmission (MTCT). In resource-rich settings, elimination of such transmission is considered within reach. However, in resource-poor settings, immense challenges remain in preventing MTCT of HIV-1.

The observation that maternal vitamin A deficiency was associated with MTCT of HIV-1<sup>1</sup> was important, in that it

suggested that vitamin A supplementation (a relatively simple and inexpensive intervention already utilized for other indications<sup>2</sup>) for HIV-1-infected pregnant women might prevent MTCT of HIV-1. To test this hypothesis, clinical trials of vitamin A supplementation among HIV-1-infected pregnant women were conducted.<sup>3–6</sup>

Wiysonge *et al.*<sup>7</sup> have performed a systematic review of all but the most recent of these trials. Overall, there was no evidence of an effect of vitamin A supplementation on MTCT of HIV-1 (OR = 1.14; 95% CI 0.93–1.38). The results of a trial in South Africa (daily supplementation with 5000 IU of retinyl palmitate and 30 mg of  $\beta$ -carotene during the third trimester of pregnancy with 200 000 IU of retinyl

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palmitate at delivery)<sup>3</sup> as well as of a trial in Malawi [daily antenatal supplementation with 3 mg retinol (10 000 IU of vitamin A)]<sup>4</sup> did not demonstrate any effect on MTCT of HIV-1. However, one trial in Tanzania (daily supplementation with 5000 IU of vitamin A and 30 mg of  $\beta$ -carotene throughout pregnancy and lactation, with 200 000 IU vitamin A at delivery) indicated a 38% increased risk of MTCT of HIV-1.<sup>5</sup> Of note, the systematic review indicated that vitamin A supplementation significantly improved birth weight.

The results of a final trial were published in early 2006.<sup>6</sup> Mother–infant pairs were randomized  $\leq$ 96 h after delivery to one of four treatment groups [vitamin A supplementation to mothers (400 000 IU) only, neonates (50 000 IU) only, both, or neither]. Neither maternal nor neonatal vitamin A supplementation had an effect upon post-natal MTCT of HIV-1. Furthermore, such supplementation did not significantly affect overall mortality by 24 months.

Thus, the available data do not provide support for the use of vitamin A supplementation of HIV-1-infected women and/or their neonates to prevent MTCT of HIV-1. And, at this time, the risks of such supplementation appear to outweigh benefits.

## References

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- 2 WHO/UNICEF/IVAGG Task Force. Vitamin A supplements: a guide to their use in the treatment and prevention of vitamin A deficiency and xerophthalmia. Geneva: WHO, 1998.
- 3 Coutsooudis A, Pillay K, Spooner E, Kuhn L, Coovadia HM. Randomized trial testing the effect of vitamin A supplementation on pregnancy outcomes and early mother-to-child transmission of HIV-1 in Durban, South Africa. *AIDS* 1999;**13**:1517–24.
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- 6 Humphrey JH, Iliff PJ, Marinda ET *et al.* Effects of a single large dose of vitamin A, given during the postpartum period to HIV-positive women and their infants, on child HIV infection, HIV-free survival, and mortality. *J Infect Dis* 2006;**193**:860–71.
- 7 Wiysonge CS, Shey MS, Sterne JAC, Brocklehurst P. Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection. *Cochrane Database Syst Rev* 2005;(4):CD003648.

# Commentary: Vitamin A supplementation for reducing the risk of mother-to-child transmission of HIV infection

Muhammad Ali Dhansay

In over 70 countries in the developing world, vitamin A deficiency (VAD) continues to be an important public health problem. It affects about 127 million preschool-aged children, of whom 1.2–3 million die unnecessarily while 4.4 million suffer from xerophthalmia that may lead to blindness. Other effects of VAD may be sub-clinical (impaired iron mobilization, disturbed cellular differentiation, and depressed immune response) or clinical (increased infectious morbidity, growth retardation, and anaemia).

Vitamin A supplementation (VAS) constitutes a major intervention strategy in combatting VAD. It has proven to be a simple, affordable, and effective child survival strategy. Considering the role of VAS in infection and immunity, it was natural that its role in HIV infection, and specifically in the prevention of mother to child HIV transmission, would be

investigated. The review by Wiysonge *et al.* is very relevant since almost all HIV infection among children results from mother-to-child transmission (MTCT), either during pregnancy and birth or with breastfeeding. It has, however, not provided a definitive answer. Disturbingly, the review raises the question of negative effects in the infant and child of VAS given to the HIV positive mother. We are further referred to the expected results of a large study of VAS in HIV positive women and their infants in Zimbabwe.<sup>1</sup>

It may be prudent to revisit the policy on post-partum VAS, as reflected in the editorial on the now published Zimbabwe study: ‘For now, the evidence available . . . raise concerns about the safety of maternal vitamin A supplementation programs as recommended by the World Health Organization . . . particularly in settings where HIV infection is prevalent.’<sup>2</sup> This has regional implications in particular since the epidemic of HIV infection is most obvious in sub-Saharan Africa, with southern Africa having the highest HIV prevalence in the world.

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The importance of evaluating the efficacy and safety of low-cost interventions that are often presumed to be beneficial cannot be emphasized enough. The role of randomized controlled trials to evaluate VAS in the context of MTCT of HIV is paramount. The trials included in the review by Wiysonge *et al.*, however, demonstrate the disparate results that can occur. This inconsistency in results from various studies is likely to be due to differences in nutritional, social, and morbidity backgrounds between and within countries and regions. The response of the scientific and public health community to the

Wiysonge review and the study by Humphrey *et al.* is eagerly awaited!

## References

- <sup>1</sup> Humphrey JH, Iliff PJ, Marinda ET *et al.* Effects of a single large dose of vitamin A, given during the postpartum period to HIV-positive women and their infants, on child HIV-infection, infection-free survival, and mortality. *J Infect Dis* 2006;**193**:860–71.
- <sup>2</sup> Fawzi WW. The benefits and concerns related to vitamin A supplementation. *J Infect Dis* 2006;**193**:756–59.

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# Response to Read and Dhansay

Charles Shey Wiysonge

As noted by JS Read and MA Dhansay in their respective commentaries, the results of the ZVITAMBO (Zimbabwe Vitamin A for Mothers and Babies) trial were published in early 2006.<sup>1</sup> The study randomly allocated 4495 HIV-positive women and their newborns within 96 h of delivery (in a 2 × 2 factorial design) to a large single dose of vitamin A for mother only, newborn only, both mother and newborn, or neither. Including this randomized placebo-controlled trial in our systematic review does not show evidence of an effect of vitamin A supplementation on mother-to-child transmission of HIV [OR 1.04, 95% confidence interval (95% CI) 0.91–1.19,  $I^2 = 68.8\%$ ] and death by 2 years of age in HIV-exposed children (OR 1.18, 95% CI 0.97–1.43). Thus, the conclusion of our review remains valid despite the newly available data; that is, currently available evidence does not

support the use of maternal and neonatal vitamin A supplementation for preventing mother-to-child transmission of HIV. And, we are not aware of any further trials investigating this issue.

## Reference

- <sup>1</sup> Humphrey JH, Iliff PJ, Marinda ET *et al.* Effects of a single large dose of vitamin A, given during the postpartum period to HIV-positive women and their infants, on child HIV infection, HIV-free survival, and mortality. *J Infect Dis* 2006;**193**:860–71.

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