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Vitamin A supplementation for the reduction of the risk of mother-to-child transmission of HIV

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Although advances in HIV prevention and treatment suggest the possibility of creating an AIDS-free generation, many areas of the world still suffer from high rates of mother-to-child transmission (MTCT) of HIV. Interventions proven to significantly decrease rates of MTCT of HIV are often unavailable in resource-limited settings due to lack of reliable clean water, low numbers of hospital deliveries and inconsistent availability of antiretroviral medications. Vitamin A, with its multiple roles in epithelial, reproductive and immune function, has been evaluated as a possible intervention for preventing MTCT. Early observational studies suggested an association between vitamin A deficiency and increased rates of MTCT of HIV; however, the controlled studies that followed did not find a benefit for vitamin A in decreasing MTCT rates. Although vitamin A has some benefits for infants postpartum, it is not recommended for the reduction of the risk of MTCT of HIV.

In the fight against HIV, prevention of mother-to-child transmission (MTCT) of HIV is critically important. Ninety percent of HIV-infected women live in Africa [1], and in 2013 alone, approximately 1.5 million HIV-infected women gave birth [2]. In the absence of treatment, infant HIV transmission rates are estimated to be between 15 and 45% [3]. MTCT encompasses any transmission that occurs during pregnancy, delivery or while breastfeeding. With appropriate interventions, such as Caesarean section delivery, formula feeding, and – most importantly – antiretroviral treatment (ART) in the peri-partum period, the rate of transmission can be reduced below 1% in industrialized nations [4]. Before ART was made widely available in 1999, clinicians and researchers struggled to identify interventions to help prevent MTCT of HIV. Micronutrient supplementation was an inexpensive and rapidly scalable intervention that many hoped would be an effective solution. Vitamin A has been studied over the last two decades as a possible intervention to decrease MTCT. Our objective is to review the current evidence available regarding the potential effect of vitamin A supplementation on MTCT of HIV.

Vitamin A is a fat-soluble vitamin found naturally in many foods, such as dairy products, green leafy vegetables, some fruits and fish and organ meats, such as liver [5]. It comes in two forms, preformed vitamin A (retinol and retinyl ester) and provitamin A carotenoids. Both must be metabolized intracellularly to active forms of vitamin A in order to function in the body [5]. Vitamin A is well-known for its role in human vision; however, it also plays a major role in cellular growth, maintenance of epithelial integrity, reproduction and immune function [6,7]. Pregnant women and children have the highest rates of vitamin A deficiency because these populations have increased needs for this micronutrient [5]. Global data indicate that vitamin A deficiency is also most prevalent in areas with higher prevalence of HIV and MTCT, including sub-Saharan Africa and Southeast Asia [8]. Children born to HIV-infected mothers have been found to benefit from receiving vitamin A

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supplementation in various outcome measures. A study from Tanzania showed a significantly smaller risk of severe watery diarrhea (odds ratio: 0.56; 95% CI: 0.32–0.99; p = 0.04) in children who took vitamin A compared with placebo [9]. Vitamin A supplementation in infants has also been associated with a reduction in mortality of 49% (relative risk: 0.51; 95% CI: 0.29–0.90; p = 0.02) [10]. HIV-infected mothers who received vitamin A supplementation while pregnant had babies with significantly improved birth weights and reduced anemia [11].

Several studies suggested that vitamin A deficiency may contribute to MTCT of HIV [12–15]. Greensberg focused on 133 HIV-infected women living in the USA [15]. In a multivariate logistic regression model, severe vitamin A deficiency was associated with increased MTCT of HIV [15]. Semba *et al.* found a statistically significant correlation between vitamin A deficiency and MTCT rates in 338 HIV-infected women in Malawi [12]. The authors speculated that vitamin A deficiency may compromise the epithelial integrity of tissues in the vaginal mucosa and mammary glands [12]. This was supported by a study by Mostad *et al.*, in which vitamin A deficiency was highly predictive of vaginal HIV-1 DNA shedding, as well as animal models looking at vitamin A deficiency and increased incidence of mastitis [16,17]. Thus, these studies suggested a link between vitamin A deficiency and an increased risk of infant exposure to HIV during vaginal delivery and in breast milk.

Over the years that followed, further studies did not consistently support these conclusions. In research focused on vaginal shedding of HIV, French *et al.* showed no association between HIV-1 RNA in cervicovaginal lavage and retinol levels [18]. Two interventional studies did not show any decrease in HIV infectivity with vitamin A supplementation [19,20]. Moreover, Fawzi *et al.* showed significantly more women in the vitamin A intervention arm had detectable levels of HIV-1 in cervicovaginal lavage compared with the control arm [19]. Further observational studies did not consistently support an association between vitamin A deficiency and MTCT of HIV. A study in the USA which enrolled 95 HIV-infected women found that vitamin A deficiency was rare and retinol levels were not associated with a risk of MTCT of HIV [21]. Another larger study in the USA of 449 HIV-infected women also found no statistically significant association between vitamin A levels and MTCT of HIV [22]. Both these studies took place in a resource-rich country and had relatively small sample sizes. Further randomized controlled trials were necessary to provide compelling evidence.

A Cochrane Review on vitamin A supplementation and MTCT of HIV was published in 2011, including all studies performed till September 2010. The authors found five randomized, placebo-controlled studies for inclusion. Four of the studies focused on antenatal vitamin A supplementation, and they enrolled a total of 3033 HIV-infected women [11,23–25]. The fifth study focused on post-natal vitamin A supplementation and enrolled 4495 HIV-infected women [26]. The included studies were conducted in Zimbabwe, South Africa, Malawi and Tanzania, and rates of vitamin A deficiency were 31–51% [11,23–26]. In these studies, women were either not on ART [23,24] or ART use was not documented [11,25,26]. One of the antenatal interventional studies did not analyze rates of MTCT of HIV due to high loss to follow-up rates [24], but two studies found no difference in MTCT between the vitamin A supplementation group and placebo [11,23]. One study, performed in Tanzania, found evidence that antenatal supplementation may increase the risk of MTCT of HIV [25]. In meta-analysis, the combined relative risk of MTCT of HIV with antenatal vitamin A supplementation compared with placebo (3 trials, 2022 women) was 1.05 (95% CI: 0.78–1.41) [11,23,25]. For the trial focused on postpartum supplementation in Zimbabwe, the relative risk was 1.04 (95% CI: 0.87–1.24) [26]. The type of vitamin A supplementation and frequency of dosing were variable among the included studies. Two studies used a combination of retinyl palmitate and β-cartonene as vitamin A supplementation [23,25], and three studies did not specify the type of retinol equivalent used in supplementation [11,24,26]. Most studies used daily supplementation for the intervention group, with only one study using a single large dose of vitamin A as an intervention [26]. However, in another study, the intervention group received daily dosing while both the intervention and control group received one dose of vitamin A at 6 weeks postpartum per their country's health policy [11]. It is unclear what effect this degree of variability of supplementation type and dosing would have on outcomes. However, despite this variability, these data suggest that even in regions where vitamin A deficiency is a public health concern, vitamin A supplementation for prenatal MTCT is not recommended.

One reason for the mixed impact of vitamin A supplementation seen between observational studies and interventional trials may be due to fluctuations in vitamin A levels from the virus itself. A review by Mehta and Fawzi outlines some possible mechanisms by which this would occur [27]. They note that advanced HIV disease may suppress release of vitamin A from the liver, which would make serum vitamin A levels low when there is actually sufficient vitamin A stored in the liver [27]. They also note that the HIV genome has a retinoic acid receptor element, which may lead to vitamin A supplementation actually increasing HIV replication and thus increasing the risk of MTCT of HIV [27]. Another study comparing HIV-infected and HIV-uninfected Kenyan women found that serum vitamin A deficiency was independently associated with both HIV-1 infection and the acute phase response [28]. Interestingly, HIV-infected women with acute phase responses had no increase in vitamin A levels with supplementation, which differed from their HIV-uninfected cohorts [28]. Thus, the authors speculated that the serum vitamin A concentrations might be more reflective of more active infection and the acute phase response rather than an intrinsic vitamin A deficiency [28].

Although there is not sufficient evidence to support the use of vitamin A supplementation for MTCT of HIV, supplementation may have other benefits in populations that are deficient in this nutrient. As mentioned previously, vitamin A supplementation may improve outcomes in infants born to HIV-infected mothers, such as mortality, birth weight, diarrhea and

anemia. However, limiting supplementation to those populations who are deficient is essential. As it is a fat-soluble nutrient, levels can accumulate in the body and dose-related toxicities may occur. Among the health risks from excessive vitamin A, the one most concerning for HIV-infected pregnant women is an increased incidence of congenital birth defects [29]. When considering vitamin A supplementation, judicious use should be considered. Any future studies related to MTCT of HIV should focus on the impact of vitamin A supplementation for HIV-infected women who are also on ARTs. The studies included in the Cochrane Review either had no antiretroviral therapy available to their participants or the study design did not clarify whether ART was available or not. This is a critical variable to consider to better understand the MTCT process and effective interventions.

We must continue to find ways to decrease new child HIV infections. With ARTs more widely available, the elimination of MTCT of HIV and the possibility of an AIDS-free generation is becoming a realistic public health goal. Resource-limited settings should focus on improving timely diagnosis of HIV in this population, linkage to care, access to ART, acceptability of ART for life and adherence, even as we search for additional interventions. Formula feeding is also recommended to help combat MTCT of HIV. However, when resources are limited and water sources are unreliable, formula feeding comes with increased risks of diarrhea and mortality. Thus, breastfeeding is still recommended for HIV-infected mothers in these settings.

It is clear that accessing and maintaining therapy with ART remains the most effective strategy to prevent MTCT. The WHO 2010 guidelines on HIV prenatal MTCT has two key focuses: lifelong ART for HIV-infected women in need of treatment, which is also safe and effective in reducing MTCT, and anti-retroviral prophylaxis to prevent MTCT during pregnancy, delivery and breastfeeding for HIV-infected women [30]. They report that once implemented, these recommendations could reduce the risk of MTCT of HIV to <5% in breastfeeding populations with a background risk of 35% and to <2% in non-breastfeeding populations with a background risk of 25% [30]. Future research should focus on impact, safety and efficacy of various methods of both ART and anti-retroviral prophylaxis during breastfeeding, particularly after 6 months, as few studies have looked at treatment during that time period.

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