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The importance of micronutrient status in the vertical transmission of HIV and pregnancy outcome

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## Introduction

In the world today, over 40 million people are estimated to be living with HIV/AIDS of which approximately 43% are women (1). There are an estimated 1.3 million children infected with HIV, 92% of whom were infected through vertical (mother to child) transmission. Each year, approximately 590,000 infants acquire HIV-1 infections from their mothers (2). The majority of the people living with HIV/AIDS (over 95%) live in the developing world where access to treatment is limited if not impossible to obtain (1). Despite the fact that vertical transmission rates of HIV-1 have been significantly decreased in the United States and other developed nations through a combination of antiretroviral therapy, caesarian section and other delivery techniques, the global incidence of vertical transmission continues to increase at the alarming rate of about 1600 new infections each day. Vertical transmission rates in African studies approach 30-45%, while rates in developed nations are much lower, 7-30% (5). Vertical transmission may occur in utero, during delivery or through breastfeeding. Investigations into new strategies for combating the transmission of HIV from mother to infant that are possible to implement in developing regions are being conducted with positive results. These strategies include single doses of an antiretroviral drug nevirapine (6), micronutrient supplementation (7), and alternatives to breastfeeding (8). Micronutrient supplementation has been shown to have a positive effect on outcome measures in several studies centered on vertical transmission of HIV in developing countries. The majority of studies have focussed on either vitamin A or multi-vitamin supplements as a means of preventing infant HIV-1 infection.

## Nutrition, Immune Function and HIV

There is a complex interrelationship between the immune system, nutritional status and HIV infection (3). Each of these factors has deleterious effects on the other two factors creating a downward spiral towards HIV disease progression. The most notorious of these effects is wasting in HIV disease progression. Symptoms of AIDS will often lead to a suppression of appetite and the subsequent development of malnutrition. Malnutrition leads to a decreased immune response (lower CD4 cell counts), which in turn leaves the host more susceptible to opportunistic infection (14). Micronutrients have also been shown to be important determinants in immune function and the progression of HIV disease (4,3). Deficiency of vitamins A, B1, B2, B6, B12, C, D and E are common among persons infected with HIV (14). All of these have been shown to have important influences on the immune system (5). Deficiencies in these micronutrients may lead to alterations in lymphocytes such as the CD4, CD8, T and Ig cells. HIV disease progression may be inhibited through several mechanisms that are mediated by the above micronutrients. These include increasing humoral and cellular immunity, supporting the integrity of epithelial cells, inhibiting opportunistic infections and decreasing the proinflammatory cytokines and blood HIV viral load (5). In general, HIV infected persons receiving a multi-vitamin experienced higher numbers and increased function of NK and T cells (including CD4), higher antibody response, increased interleukin 2 production and a correlated 30% reduction in HIV disease progression in some studies. Other studies have shown that increased intake of B6, B12 and A are associated with improved survival of HIV positive persons (14)

Vitamin A has been associated with enhancement of cellular immunity, increased Natural Killer cells, total WBC counts, CD4/CD8 ratios, and improved humoral immunity (5, 14). It has also been implicated as essential to the maintenance and integrity of epidermal and mucosal tissue. This is particularly important in HIV/AIDS because opportunistic infections can cross the epithelial lining of the lungs and infect the immune compromised host (9). Deficiency of Vitamin A in HIV positive hosts results in decreased CD4 lymphocytes, increased disease progression, increased mortality and high vertical transmission rates of HIV (15).

## Clinical Trials Linking Vertical Transmission of HIV with micronutrient status

Vitamin A deficiency was first correlated with increased vertical transmission of HIV among an African cohort by Semba, et. al. in 1994 (10). The implications for potential clinical importance of this finding, particularly in developing regions where access to other forms of treatment are virtually impossible, prompted several subsequent studies with varied results. A fourfold increase in transmission risk in women with severe vitamin A deficiency was found in a study of women in metropolitan areas of the United States (11). Similar studies more recently did not find increased transmission rates in women with severe vitamin

A deficiency (13). This same study did find that low maternal vitamin A levels correlated with the delivery of low birth weight infants. In another study among African women, vitamin A supplementation was not associated with decreased HIV transmission, but did have positive effects on pregnancy outcomes such as decreasing preterm births, lowering the transmission rate in preterm babies and reducing the incidence of low birth weight deliveries (12). This has important public health implications because preterm delivery rates of HIV-1 infected mothers can range from 15% in Europe to 42% in Rwanda and are associated with increased mortality and morbidity. More recently, a study in Tanzania evaluated the effect of multivitamin and vitamin A supplementation on pregnancy outcomes (7). This study found that multivitamins decreased the risk of low birthweight, severe preterm birth, and fetal death while increasing CD4, CD8 and CD3 lymphocytes. Vitamin A alone was not found to have any effects. Several trials are currently underway in Malawi, South Africa and Nepal (7). The results from these trials will be important in determining vitamin A's role in HIV vertical transmission and pregnancy outcomes.

#### Vertical Transmission of HIV: possible mechanisms of micronutrients in prevention

Vertical transmission of HIV is defined as the transmission of the virus from mother to fetus or infant. This can occur in utero, during delivery or through breastfeeding, with 40-80% of these infections occurring during delivery (13,16). The mechanisms through which micronutrients may act in preventing the vertical transmission of HIV are best described for vitamin A, although the role of other vitamins in supporting the immune system as described above may also be important. Analysis of individual vitamin effect has been complicated by the use of multi-vitamins in most studies thus far. This subject merits further investigation, however, because multi-vitamin supplementation has been shown to be quite effective in reducing negative pregnancy outcomes and because they are affordable worldwide, ethical considerations dissuade trials in which single or no vitamin supplementation is a treatment. These trials continue at the present, but multivitamin supplementation should become a standard of care in the near future.

Intrauterine transmission rates have been difficult to determine and there is limited research available to assess this risk independently. In vitro studies recently have linked retinoic acid with an inhibition of HIV transcription, which would affect both viral load and transmission rate to the fetus. Vitamin A may also be important for maintaining the integrity of the placenta and protecting the developing fetus from infection. Multivitamins may act synergistically to enhance immune function in the mother and developing fetus, preventing viral expression and transmission (9).

Transmission risk during delivery may be increased by factors that affect the shedding of HIV-1 in cervical and vaginal secretions or by mechanisms that result in increased contact of maternal and infant fluids. In a clinical study in Mombassa, Kenya, cervical and vaginal shedding of HIV-1 infected cells was highly correlated to CD4 lymphocyte depletion as well as to vitamin A deficiency (16). Serum vitamin A concentration was slightly, although not significantly related to CD4 count, suggesting that vitamin A's effect could not be completely explained by higher CD4 cell counts. Severe Vitamin A deficiency resulted in as high as a 12-fold increase in odds of vaginal shedding. The mechanism by which vitamin A acts may be multi-factorial. Vitamin A plays a central role in the maintenance of epithelial cells (9). Deficiency of vitamin A may result in increased abrasions of the cervix and/or vaginal epithelium, leading to increased probability of transmission during birth (16). Similarly, vitamin A deficiency in the fetus may result in decreased epithelial integrity of the infant and an increased susceptibility to HIV infection during delivery. Other factors to consider are the incidence of prematurity and low birthweight, both of which are associated with increased HIV infection rates and with low micronutrient serum levels.

The final mechanism through which HIV may be vertically transmitted is breastfeeding. According to a meta-analysis of several clinical studies, the frequency of HIV transmission in breast milk may be as high as 29% during acute maternal HIV infection(8). The Center for Disease Control recommends that women infected with HIV should not breastfeed their infants and this has been implemented in developed nations. This is a very complicated and important issue in the developing world because breast milk is the most important element of child survival. It provides inexpensive nutrition and immunity to infectious diseases to the newborn infant while their own immune system is developing. Without this support, infant mortality and morbidity increases significantly. In light of these factors, the World Health Organization recommends that in regions where malnutrition and infectious diseases are prevalent, or where clean water is not

accessible, infants should continue to be breastfed despite HIV transmission risk. Additional studies into this matter are needed and low cost alternative feeding strategies should be developed. Several studies have shown that Vitamin A supplementation to lactating mothers reduces viral shedding in breast milk, increases the retinol levels in the milk and results in enhanced development of the infant's immune system (5).

## Conclusion

HIV disease status and vertical transmission are intimately related to the immune function and nutritional state of the host. Maintaining an appropriate level of micronutrient serum levels and stores should be a mainstay of support for HIV infected individuals. This is particularly important for pregnant mothers who have an increased physiological demand as a result of both HIV infection and pregnancy. In regions of the world where antiretroviral therapy is not accessible, supplementation with micronutrients provides an affordable and effective mechanism in reducing the prevalence of negative pregnancy outcomes and/or vertical transmission of HIV. Although the evidence is far from conclusive, the results thus far are promising for the role of vitamin supplementation in preventing vertical transmission and negative pregnancy outcomes. The negative side effects of this treatment are negligible although possible at extremely high doses. In addition, vitamin supplementation confers other health advantages to women and their children and is inexpensive to produce and deliver. Whenever possible, multivitamins, including vitamin A, should be administered to HIV positive pregnant and lactating mothers.

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