

Vitamin A and human immunodeficiency virus infection

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By the year 2000 there will be an estimated twenty-six million individuals infected with human immunodeficiency virus (HIV) (Quinn, 1996). About four to five million cumulative cases are expected among children by the year 2000. The areas hardest-hit by the acquired immune deficiency syndrome (AIDS) epidemic are sub-Saharan Africa, south Asia, and south-east Asia, where the prevalence of micronutrient deficiencies is generally higher. More than 90 % of new HIV infections are now occurring in developing countries. Although HIV infection is characterized by a variety of micronutrient deficiencies and wasting (Beach *et al.* 1992; Kotler & Grunfeld, 1995), the relationship between nutritional status and clinical outcome in HIV infection is not well understood. Vitamin A plays a major role in normal immune function (Semba, 1994), and as early as the 1960s it was acknowledged that 'no micronutrient deficiency is more synergistic with infection than that of vitamin A' (Scrimshaw *et al.* 1968). The present review focuses on the relationship between vitamin A, immunity, and HIV infection.

VITAMIN A AND IMMUNITY

Vitamin A deficiency is a nutritionally-acquired immunodeficiency disorder characterized by widespread pathological alterations of mucosal epithelia of the respiratory, gastrointestinal, and genito-urinary tracts, impaired antibody responses to protein antigens, altered cell-mediated immunity, and alterations in T-cell subsets (Semba *et al.* 1992, 1993b; Wiedermann *et al.* 1993; Zhao & Ross, 1995; Cantorna *et al.* 1996; Ross, 1996). Vitamin A, through its active metabolite, all-*trans* retinoic acid, regulates genes through nuclear receptors in the steroid and thyroid hormone superfamily (Ross & Ternus, 1993). The genes relevant to immunity which are regulated by vitamin A have not been completely characterized, but probably include those for interleukin-4, interferon- γ (Cantorna *et al.* 1996), interleukin-2 receptor (Sidell *et al.* 1993), and others. Growth and activation of T and B cells are dependent on vitamin A (Buck *et al.* 1990; Garbe *et al.* 1992), and vitamin A supplementation is associated with increases in circulating lymphocytes, including CD4 T-cells and natural killer cells, suggesting that lymphopoiesis is enhanced by vitamin A (Semba *et al.* 1993b; Ross, 1996).

The potential consequences of the immunodeficiency associated with vitamin A deficiency have been shown in longitudinal studies of preschool children which were conducted in Indonesia in the late 1970s. These studies demonstrated that children with mild vitamin A deficiency were at higher risk of respiratory and diarrhoeal disease and higher mortality (Sommer *et al.* 1983, 1984). A series of community-based clinical trials of vitamin A supplementation for preschool children soon followed in Indonesia, India, Nepal, Sudan, and Ghana, which showed overall that vitamin A supplementation or fortification reduced child mortality by about 20–30 % (Beaton *et al.* 1993). Further analysis showed that vitamin A reduces the severity of diarrhoeal disease but seems to have little effect on respiratory disease (The Vitamin A and Pneumonia Working Group, 1995). High-dose vitamin A supplementation was also shown to reduce morbidity and mortality in

children with acute, complicated measles (Hussey & Klein, 1990; Coutsooudis *et al.* 1991). These clinical trials demonstrate that vitamin A is an immune enhancer and suggest that vitamin A may have other therapeutic applications as a therapy for HIV infection.

PATHOGENESIS OF VITAMIN A DEFICIENCY

Factors which may contribute to the development of vitamin A deficiency include: low intake of vitamin A-containing foods, anorexia of chronic disease, diarrhoea and malabsorption, concomitant protein–energy malnutrition, liver disease, abnormal urinary losses of vitamin A during infections, the acute-phase response, and accelerated utilization of vitamin A. In many developing countries where HIV infection is common, the intake of vitamin A-containing foods may be marginal. Oesophageal candidiasis, cryptococcal meningitis, and progressive multifocal leukoencephalopathy during HIV infection are associated with anorexia and wasting (Nahlen *et al.* 1993). Diarrhoea and malabsorption syndromes are common during HIV infection and can be caused by a wide variety of pathogens, including cryptosporidiosis and isosporiasis. Fat malabsorption has been reported in HIV-infected individuals and may interfere with vitamin A absorption and metabolism.

Protein–energy malnutrition increases the risk of developing vitamin A deficiency (Smith *et al.* 1973), probably because vitamin A transport relies on a carrier-protein complex of retinol-binding protein and transthyretin. Hepatitis appears to interfere with the metabolism of vitamin A (Smith & Goodman, 1971), and hepatitis B and C are common in many HIV-infected populations. During the acute-phase response, retinol-binding protein may break off from the carrier complex of transthyretin and retinol, allowing abnormal glomerular losses of vitamin A which may reach several times the required daily allowance for vitamin A (Stephensen *et al.* 1994; Alvarez *et al.* 1995). Individuals with HIV infection and AIDS have been shown to have higher abnormal urinary losses of vitamin A compared with controls (Silveira *et al.* 1996). Whether infections accelerate the utilization of vitamin A is not clear; however, the depletion of hepatic vitamin A was shown to be increased in children who incidentally contracted chickenpox during a vitamin A dosing study (Campos *et al.* 1987). It is unknown whether the virulence of HIV itself may influence vitamin A status.

PREVALENCE OF VITAMIN A DEFICIENCY DURING HUMAN IMMUNODEFICIENCY VIRUS INFECTION

The prevalence of vitamin A deficiency may vary widely, depending upon the population. Serum or plasma vitamin A levels have been used as the main indicator of vitamin A status in most of these investigations. In a hospital-based, cross-sectional study of fifty-nine adults with AIDS in New York City who were not taking vitamin supplements, 20 % had serum vitamin A levels $< 0.70 \mu\text{mol/l}$ (Karter *et al.* 1995). A study of 100 asymptomatic, HIV-infected homosexual men in Miami showed that 18 % had serum vitamin A levels $< 1.23 \mu\text{mol/l}$, which were considered to be in the marginal range (Beach *et al.* 1992). In forty-seven HIV-infected adults with wasting syndrome in Portland, Oregon, 14 % had serum vitamin A levels $< 1.75 \mu\text{mol/l}$ (Coodley *et al.* 1993). A study of seventy-four HIV-infected pregnant women in Thailand showed mean vitamin A levels of $1.23 \mu\text{mol/l}$. Direct comparisons of the vitamin A status in these various studies is problematic because of the different cut-offs of serum or plasma vitamin A used to define vitamin A deficiency in adults.

We investigated the vitamin A status of different HIV-infected populations which included injection drug users, homosexual men, adults in Uganda, pregnant women in Malawi, pregnant women in the USA, and lactating women in Haiti. Comparison of vitamin A levels in these different populations is useful because it may provide clues to the epidemiology and pathogenesis of vitamin A deficiency during HIV infection. Plasma vitamin A levels were measured in 284 HIV-infected injection drug users from a cohort study in Baltimore, Maryland (AIDS Linked to Intravenous Experiences, ALIVE study; Vlahov *et al.* 1991). The frequency distribution of vitamin A levels is shown in Fig. 1. In our studies in adults we have defined vitamin A deficiency as consistent with serum or plasma vitamin A levels $< 1.05 \mu\text{mol/l}$, a level at which some individuals may have impairment of biological function (Pilch, 1987). Using this criterion, about 29 % of HIV-infected injection drug users had plasma vitamin A levels consistent with deficiency in adults. Data from the first National Health and Nutrition Examination Survey show that in the normal adult population in the USA, 1–3 % of adults have serum vitamin A levels $< 1.05 \mu\text{mol/l}$ (Pilch, 1987). In a study of 311 HIV-infected homosexual men (Study to Help the AIDS Research Effort, SHARE) in Baltimore and Washington, DC, the frequency distribution of plasma vitamin A levels suggested that this population was replete in vitamin A (Fig. 2). The frequency distribution is flatter and shifted to the right in this population of homosexual men. Serum vitamin A levels were measured in 522 HIV-infected adults followed in a large cohort study in an outpatient clinic at Old Mulago Hospital, Kampala, Uganda (Fig. 3). The adults in Uganda were HIV seropositive and purified-protein-derivative positive or negative with no radiological evidence of tuberculosis.

Pregnant and lactating women are generally at higher risk of vitamin A deficiency. The frequency distribution of serum vitamin A levels in 474 HIV-infected pregnant women followed in the antenatal clinic at Queen Elizabeth Central Hospital, Blantyre, Malawi is shown in Fig. 4. Of these women 63.3 % had serum vitamin A levels consistent with vitamin A deficiency. In comparison, serum vitamin A levels from 513 HIV-infected pregnant women from the Womens and Infants Transmission Study (WITS), a multicentre study in the USA are shown in Fig. 5 (S. Landesman, D. Burns, D. Cotton, G. Fitzgerald, M. G. Fowler, R. Hershow, J. Pitt, R. D. Semba and C. Zorilla, unpublished results). Of the women in WITS, 22 % had serum vitamin A levels consistent with vitamin A deficiency.

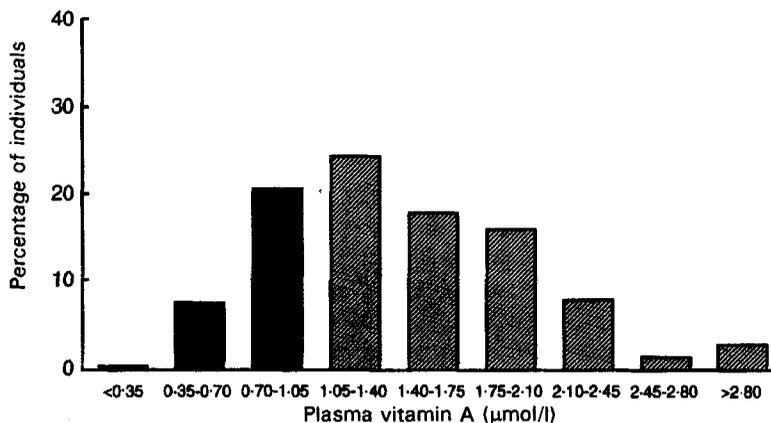


Fig. 1. Frequency distribution of vitamin A levels in 284 HIV-seropositive injection drug users in Baltimore, Maryland. (■), Proportion of individuals with vitamin A levels $< 1.05 \mu\text{mol/l}$.

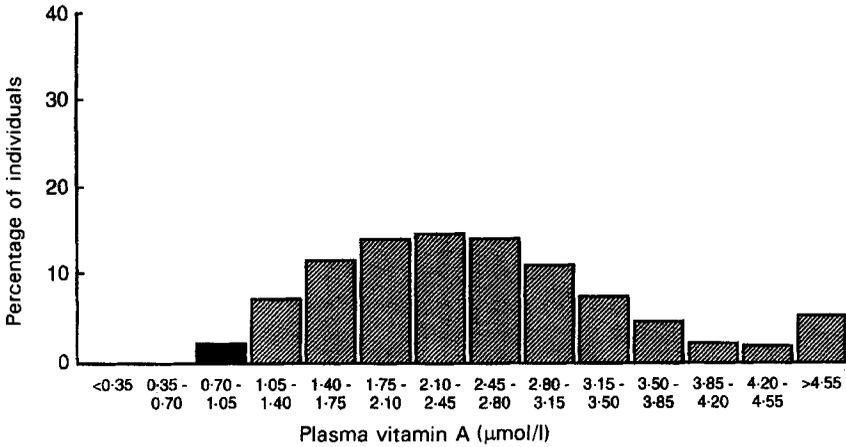


Fig. 2. Frequency distribution of vitamin A levels in 311 HIV-seropositive homosexual men in a cohort from Baltimore, Maryland and the Washington, DC area. (■), Proportion of individuals with vitamin A levels < 1.05 μmol/l.

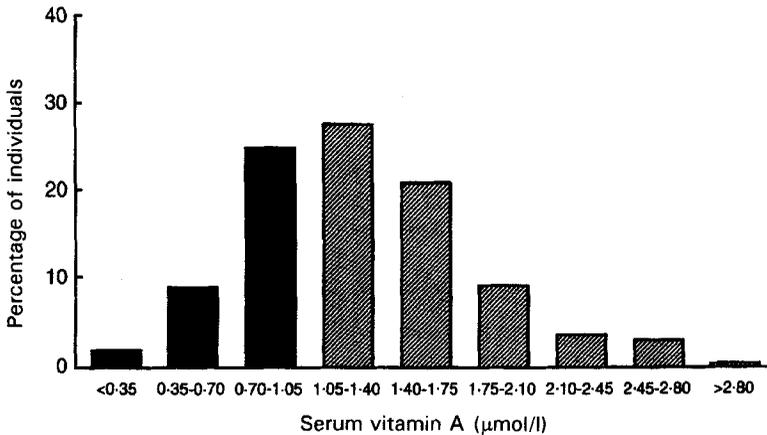


Fig. 3. Frequency distribution of vitamin A levels in 522 HIV-seropositive adults from an outpatient clinic of the Old Mulago Hospital, Kampala, Uganda. (■), Proportion of individuals with vitamin A levels < 1.05 μmol/l.

Overall, the vitamin A status of HIV-infected pregnant women in the USA was better than that in Africa. Vitamin A levels were measured in 126 HIV-infected lactating women at 6 months post-partum who were being followed in an outpatient clinic in Cite Soleil, Port Au Prince, Haiti (J. S. Coberly, R. D. Semba, N. Halsey, J. Desormeaux, D. Jules-Joseph, P. A. Carrenard, M. McBrien, R. Boulous and A. J. Ruff, unpublished results; Fig. 6). Over 75 % of these lactating women had vitamin A levels consistent with vitamin A deficiency.

Comparison of the frequency distributions of vitamin A levels in these six different populations allows some possible generalizations. First, HIV-infected adults from developing countries had lower vitamin A levels than HIV-infected adults in the USA. Such an observation might be expected because the intake of vitamin A-rich or vitamin A-fortified foods is lower in developing countries. Second, HIV-infected injection drug users from inner city Baltimore had lower vitamin A levels than HIV-infected homosexual men

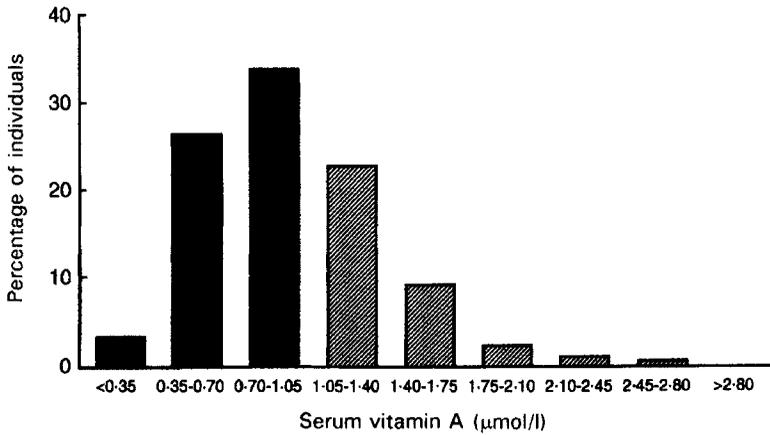


Fig. 4. Frequency distribution of vitamin A levels in 474 HIV-seropositive women seen in the antenatal clinic of the Queen Elizabeth Central Hospital, Blantyre, Malawi. (■), Proportion of individuals with vitamin A levels < 1.05 μmol/l.

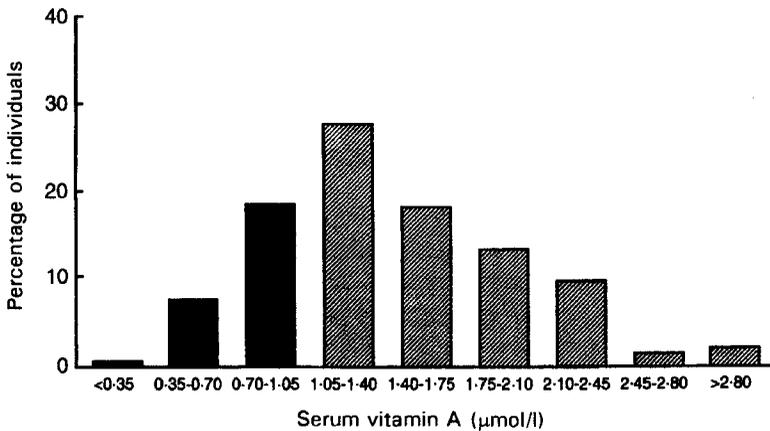


Fig. 5. Frequency distribution of vitamin A levels in 513 HIV-seropositive women in a multicentre cohort study in the USA (Women and Infants Transmission Study). (■), Proportion of individuals with vitamin A levels < 1.05 μmol/l.

from the same region. Dietary and socio-economic factors probably account for these differences. Third, many of the homosexual men were taking vitamin supplements (Tang *et al.* 1993), which suggests that supplementation reduces the risk of having a low vitamin A level, in spite of opportunistic infections associated with HIV infection. Finally, it is well known that pregnancy and lactation are high-risk periods for vitamin A deficiency in women, and these findings show an alarmingly high prevalence of vitamin A deficiency among HIV-infected pregnant and lactating women.

VITAMIN A DEFICIENCY AND MORTALITY

Vitamin A deficiency and HIV infection constitute a combined immunodeficiency syndrome which might be expected to have adverse clinical consequences. Vitamin A

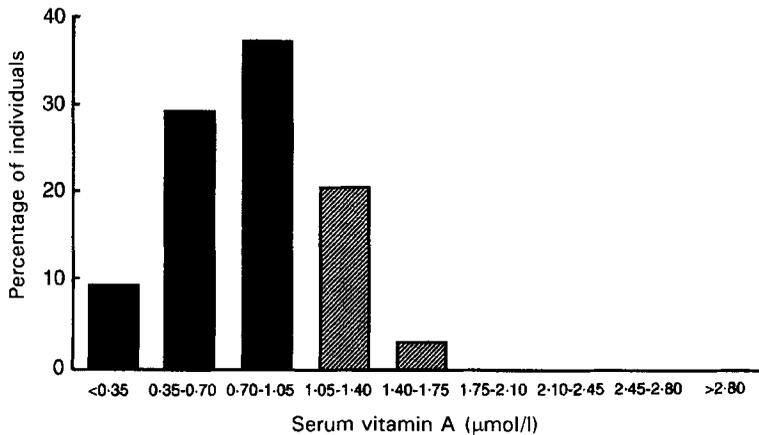


Fig. 6. Frequency distribution of vitamin A levels in 126 HIV-seropositive lactating women from Cite Soleil, Port Au Prince, Haiti. (■), Proportion of individuals with vitamin A levels < 1.05 µmol/l.

deficiency was shown to be associated with increased mortality in a longitudinal study of injection drug users in Baltimore (Semba *et al.* 1993a). Adults with vitamin A deficiency had decreased survival by about 1 year. This was corroborated by a larger nested case-control study within the ALIVE study which showed that vitamin A deficiency was an independent risk factor for mortality and was associated with a four-fold increased risk of death (Semba *et al.* 1995a). Three other studies from Haiti (Rwangabwoba *et al.* 1996), Uganda, and Miami have recently confirmed the association between vitamin A deficiency and increased mortality during HIV infection, with relative risks for mortality estimated between 2 and 4 in these different studies. In addition, further follow-up in the cohort of HIV-infected women in Malawi shows that women in the lowest quartiles of serum vitamin A levels had significantly higher mortality (Semba, 1997). Although data from five different study populations around the world now demonstrate a similar relationship between vitamin A deficiency and increased mortality in adults, it is unknown whether vitamin A supplementation will reduce mortality in HIV-infected adults.

VITAMIN A DEFICIENCY AND VERTICAL TRANSMISSION OF HUMAN IMMUNODEFICIENCY VIRUS

The period of highest risk for vitamin A deficiency in women is during pregnancy, when there are increased demands for vitamin A because of the growing fetus. Epidemics of nightblindness, the earliest clinical manifestation of vitamin A deficiency, were common among pregnant women in Europe in the nineteenth century and early part of this century before dietary improvements (Birnbacher, 1928). Nightblindness was so common in pregnant women near Bombay, India, that it was considered to be a normal symptom of pregnancy, along with morning sickness (Dixit, 1966). It has been shown recently in a case-control study in Nepal that pregnant women with nightblindness have significantly higher infectious disease morbidity than matched controls without nightblindness (Christian *et al.* 1996). As shown in Figs. 4 and 6, vitamin A deficiency has the highest prevalence among pregnant and lactating women. The major factor contributing to the high prevalence of nightblindness during pregnancy is probably insufficient intake of vitamin A-rich foods.

The rates of vertical transmission (mother-to-child transmission) of HIV generally are estimated to be 10–40 %, with rates being higher in developing countries. Prolonged duration of breast-feeding in developing countries was generally thought to account for the higher rates in areas such as sub-Saharan Africa, because HIV may be present in breast milk. Other known risk factors for vertical transmission include prolonged duration of rupture membranes at delivery (Landesman *et al.* 1996), high maternal HIV viral load (Dickover *et al.* 1996), low maternal CD4 count, and chorioamnionitis (Temmerman *et al.* 1995).

Given the potential effects of vitamin A deficiency on immunity, and the high prevalence of vitamin A deficiency during pregnancy, we investigated the relationship between vitamin A deficiency and vertical transmission. HIV-infected pregnant women in Malawi who were vitamin A-deficient were three to four times more likely to transmit HIV to their infants (Semba *et al.* 1994). There was a strong association between low maternal vitamin A levels and increased vertical transmission after controlling for CD4 count, maternal age, and maternal BMI. Infant mortality was higher among those born to vitamin A-deficient HIV-infected pregnant women, reaching 93 % mortality among infants born to the most-severely-vitamin A-deficient women (Semba *et al.* 1995b). Further studies in Malawi (Semba, unpublished results) have recently shown that HIV-seronegative pregnant women with serum vitamin A levels consistent with deficiency also have significantly higher infant mortality. Thus, the findings of maternal vitamin A deficiency and increased infant mortality are consistent among both HIV-seropositive and -seronegative women.

Whether low serum vitamin A levels are a 'marker' for increased vertical transmission or are causally involved is unknown. In experimental animal models, vitamin A deficiency during pregnancy is associated with chorioamnionitis (Noback & Takahashi, 1978), a placental infection which is a known risk factor for vertical transmission. In addition, animals made deficient in vitamin A during pregnancy have low birth weight and high mortality of offspring, which is consistent with the findings from human studies. Vitamin A deficiency may have serious consequences for immune function in the mother as well as immune development in the fetus, but these biological mechanisms have not been characterized. The association between maternal vitamin A deficiency and vertical transmission has been confirmed in Rwanda (Semba, unpublished results), Haiti (J. S. Coberly, R. D. Semba, N. Halsey, J. Desormeaux, D. Jules-Joseph, P. P. Carrenard, M. McBrien, R. Boulos and A. J. Ruff, unpublished results), and in Baltimore and New York City (Greenberg *et al.* 1996). A recent study from Kenya shows that HIV-infected women with vitamin A deficiency have a greatly increased risk of HIV load in breast milk, which suggests a possible mechanism for increased transmission through breast-feeding (Nduati *et al.* 1995).

VITAMIN A DEFICIENCY AND VIRAL LOAD

High circulating HIV viral load has been shown to be a risk factor for HIV progression (Ferre *et al.* 1995) and vertical transmission (Dickover *et al.* 1996). The relationship between serum vitamin A levels and viral load is of potential importance, because the HIV genome contains a retinoic acid response element in the long terminal repeat (Orchard *et al.* 1993), and all-*trans* retinoic acid, the active metabolite of vitamin A, has been shown to influence HIV replication (Poli *et al.* 1992; Turpin *et al.* 1992). In a cross-sectional study of 284 HIV-infected injection drug users from the ALIVE cohort, no relationship was found between plasma vitamin A levels and viral load (Semba, unpublished results). In a study of homosexual men from the Multicentre AIDS Cohort Study, there was no relationship

between serum vitamin A levels and viral load (Semba, unpublished results). A randomized, double-masked, placebo-controlled clinical trial of high-dose vitamin A supplementation for 120 HIV-infected adults shows that vitamin A supplementation has no effect on viral load (Semba, unpublished results). In a related study, a phase I/II trial of all-*trans* retinoic acid treatment for Kaposi's sarcoma showed no effect of retinoic acid on HIV p-24 antigenaemia, suggesting that retinoic acid had no effect on viral load (Bailey *et al.* 1995).

These studies suggest that vitamin A levels and viral load are independent risk factors during HIV infection, and that vitamin A deficiency is not a marker for viral load. High-dose vitamin A supplementation does not seem to have an effect on viral load levels, and this finding has implications for clinical trials of antenatal supplementation of vitamin A as a strategy to reduce mother-to-child transmission of HIV. These findings refute the idea that vitamin A supplementation would work in the same manner as an anti-retroviral medication, although some clinical trials are designed as if this were an expected biological effect. Perhaps it is more important that these findings show that vitamin A supplementation does not seem to up-regulate the expression of HIV, a theoretical consideration raised by *in vitro* studies. Should clinical trials of vitamin A therapy to reduce mother-to-child transmission show a beneficial clinical effect, these studies suggest that the biological mechanism(s) would probably be mediated through some other means, such as reduction in chorioamnionitis or improvement of immune development in mother and infant.

VITAMIN A AS THERAPY IN HUMAN IMMUNODEFICIENCY VIRUS INFECTION

The community- and hospital-based clinical trials of vitamin A for child survival and treatment of acute measles provide compelling rationale for investigating the use of vitamin A as therapy in HIV infection. Epidemiological studies demonstrate that vitamin A deficiency is common in HIV-infected pregnant women, injection drug users in the inner city, and in adult populations in developing countries. In sub-Saharan Africa, where anti-retroviral and prophylactic therapies may be prohibitively expensive, the optimization of micronutrient status may be among the affordable strategies available for potentially prolonging survival and reducing vertical transmission of HIV. Two recent clinical trials of vitamin A therapy for HIV-infected children suggest that vitamin A supplementation reduces diarrhoeal morbidity (Coutsoudis *et al.* 1995) and improves immunity (Hussey *et al.* 1996). Four clinical trials are currently in progress in Tanzania, South Africa, Malawi, and Zimbabwe to determine whether antenatal vitamin A supplementation can reduce vertical transmission and infant mortality. A large clinical trial in Uganda is addressing the question of whether periodic vitamin A supplementation can improve survival for HIV-infected children. A recent World Bank (1993) analysis has shown that vitamin A supplementation has the second-highest cost-benefit effect of forty-seven major health interventions studied. It remains to be determined whether vitamin A supplementation will have therapeutic benefit in reducing vertical transmission of HIV, infant mortality, and mortality of young children.

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