

Review article

Micronutrients and the pathogenesis of human immunodeficiency virus infection

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(Received 23 March 1998 – Revised 28 September 1998 – Accepted 2 October 1998)

Micronutrient deficiencies may be common during human immunodeficiency virus (HIV) infection. Insufficient dietary intake, malabsorption, diarrhoea, and impaired storage and altered metabolism of micronutrients can contribute to the development of micronutrient deficiencies. Low plasma or serum levels of vitamins A, E, B₆, B₁₂ and C, carotenoids, Se, and Zn are common in many HIV-infected populations. Micronutrient deficiencies may contribute to the pathogenesis of HIV infection through increased oxidative stress and compromised immunity. Low levels or intakes of micronutrients such as vitamins A, E, B₆ and B₁₂, Zn and Se have been associated with adverse clinical outcomes during HIV infection, and new studies are emerging which suggest that micronutrient supplementation may help reduce morbidity and mortality during HIV infection.

Human immunodeficiency virus: Malnutrition: Micronutrients

Human immunodeficiency virus (HIV) infection continues to increase worldwide, with over 90 % of new cases occurring in developing countries (Quinn, 1996). Although major advances have been made in understanding the biology of HIV infection and significant progress in therapy has occurred in the last few years, the basic role of host nutrition in the pathogenesis of HIV infection still remains a major lacuna in scientific knowledge. The idea that a malnourished host has a greater susceptibility to infections and a relatively worse prognosis is almost universally accepted, yet it is often difficult to demonstrate that specific nutritional deficiencies contribute to poor clinical outcomes. With the spread of the acquired immunodeficiency syndrome (AIDS) pandemic in developing countries where nutritional problems are commonplace and expensive drugs are generally unavailable, the identification and correction of micronutrient deficiencies may take on increasing importance. The purpose of the current review is to present the epidemiological and clinical evidence for the role of micronutrient deficiencies in the pathogenesis of HIV infection. The model for this discussion is a vicious cycle in which micronutrient deficiencies, nutritionally related immunosuppression, and oxidative stress lead to accelerated progression of HIV disease (Fig. 1).

Factors contributing to micronutrient deficiencies

Insufficient dietary intake

Micronutrient intake may be affected by anorexia, central nervous system disease, dysphagia, and odynophagia (painful swallowing) during HIV infection. Loss of appetite, aversion to food, and dysphagia were commonly reported by HIV-infected adults in Côte D'Ivoire (Castetbon *et al.* 1997). Oesophageal candidiasis is not infrequent during HIV infection and will usually cause dysphagia and odynophagia. Decreased food intake may occur even in asymptomatic HIV-infected adults and has been associated with significant weight loss (McCorkindale *et al.* 1990). Among patients with advanced HIV infection and AIDS, anorexia, nausea, and vomiting may be common and severe (Ysseldyke, 1991; Schwenk *et al.* 1993; Niyongabo *et al.* 1997). Chronic fatigue may interfere with shopping, cooking, and consumption of regular meals (Luder *et al.* 1995).

Many HIV-infected individuals do not consume at least the recommended dietary allowance (RDA) for some B-complex vitamins, vitamin E, and Zn (Abrams *et al.* 1993; Tang *et al.* 1993; Baum *et al.* 1994; Luder *et al.* 1995; Smit *et al.* 1996) (Fig. 2). The RDA is the level of intake of an essential nutrient that, on the basis of scientific knowledge, is

Abbreviations: AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus; IDU, injection drug users; NF- κ B, nuclear factor κ B; RDA, recommended dietary allowance; ROI, reactive oxygen intermediates.

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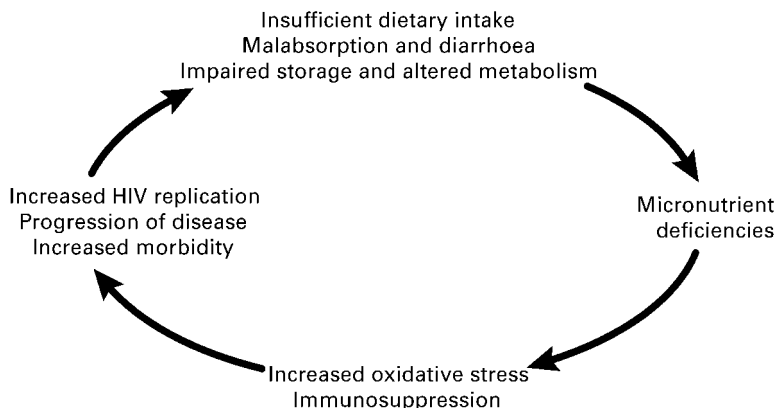


Fig. 1. Vicious cycle of micronutrient deficiencies and human immunodeficiency virus (HIV) pathogenesis.

considered to be adequate to meet the known nutrient needs of practically all healthy persons (National Research Council, 1989). Because the RDA is generally defined at a level which is two standard deviations above what is considered to be the average level of requirement for a nutrient, it is still possible for a healthy person to consume less than the RDA and have adequate intake. However, it is unclear whether the RDA can be applied to the nutrient needs of individuals with HIV infection. HIV-infected adults with dietary intakes greater than the RDA for different micronutrients have been reported to have low serum or plasma micronutrient levels consistent with deficiencies, suggesting that intakes at the level of the RDA may be insufficient for individuals with HIV infection (Baum *et al.* 1992).

Malabsorption and diarrhoea

Diarrhoea and malabsorption of fats, carbohydrates and vitamin B₁₂ appear to be common in all stages of HIV infection. *Cryptosporidia*, *Microsporidia*, cytomegalovirus, and *Mycobacterium avium-intracellulare*, are major causes of diarrhoea in patients with AIDS, and many pathogens are

resistant to treatment and lead to severe weight loss and death (Sharpstone & Gazzard, 1996). In London, 60% of HIV-infected homosexual men at all stages of infection had fat malabsorption (Miller *et al.* 1988). A study of sixty-one HIV-infected adults with or without diarrhoea showed that 50% had steatorrhoea (Koch *et al.* 1996a). Malabsorption of fat probably reduces absorption of fat-soluble vitamins such as vitamins A and E. Tests of gastrointestinal integrity such as the lactose H₂ breath test and D-xylose absorption test show that about 30% of symptomatic HIV-infected children have carbohydrate malabsorption (Miller *et al.* 1991; Castaldo *et al.* 1996). Abnormal D-xylose testing was found in nine out of twenty adults with pathogen-negative diarrhoea and weight loss (Gillin *et al.* 1985). Abnormal absorption of vitamin B₁₂ may be common during HIV infection, with abnormal Schilling tests described in a high proportion of adults with or without chronic diarrhoea (Harriman *et al.* 1989; Ehrenpreis *et al.* 1994) and in 87.5% of patients with cryptosporidiosis (Goodgame *et al.* 1995).

Jejunal and duodenal villous atrophy with or without crypt hyperplasia occurs in all stages of HIV disease (Kotler *et al.* 1984; Batman *et al.* 1989; Greenson *et al.*

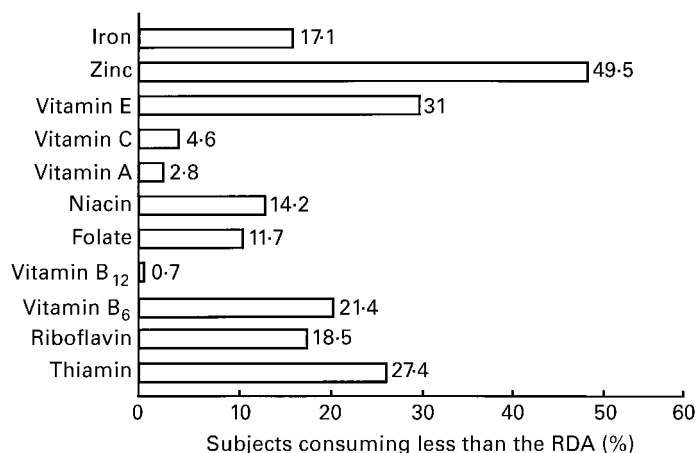


Fig. 2. Micronutrient intakes in the Baltimore–Washington cohort of the Multicenter AIDS Cohort Study. Percentage of subjects consuming less than the recommended dietary allowance (RDA).

1991; Keating *et al.* 1995). Increased intestinal permeability may occur in about one quarter of asymptomatic HIV-infected adults and may increase with HIV disease progression (Keating *et al.* 1995). Physiological studies of human duodenal biopsies show that HIV-infected patients with diarrhoea have epithelial barrier defects, suggesting that a passive leak of ions, substrates, and water could contribute to diarrhoea during HIV infection (Stockmann *et al.* 1998). Increased gut permeability has been associated with nutritional depletion in patients without HIV infection (van der Hulst *et al.* 1998).

Impaired storage and altered metabolism

The liver is a site for accumulation of many micronutrients, including vitamins A and E, and Fe. Hepatitis B and C are extremely common in HIV-infected adults and are associated with more rapid progression to cirrhosis and decreased survival (Ockenga *et al.* 1997; Soto *et al.* 1997). Although hepatitis and cirrhosis are known to interfere with metabolism of vitamin A and retinol-binding protein (Smith & Goodman, 1971), the relationship between liver disease and storage of vitamin A or other micronutrients during HIV infection has not been examined. There have been no necropsy studies that have examined micronutrient concentrations in the livers of individuals who have died with HIV infection.

HIV-infected patients are at higher risk of developing renal disease, including acute renal failure, fluid–electrolyte and acid–base disturbances, HIV-associated nephropathy and other glomerulopathies (D'Agati & Appel, 1997). A low-molecular-mass proteinuria appears to be common during HIV infection, even during asymptomatic infection, leading to losses of retinol-binding protein and albumin (Kabanda *et al.* 1996). In patients with AIDS and acute infection, there may be significant losses of retinol and retinol-binding protein in the urine, which may hasten the depletion of body stores of vitamin A (Jolley *et al.* 1997). During the acute-phase response, transthyretin can dissociate from the transthyretin–retinol-binding protein–retinol complex, thus allowing the 21 kDa retinol-binding protein–retinol complex to be easily lost into the urine (Ramsden *et*

al. 1978). A recent study from Brazil suggests that there is elevated urinary excretion of vitamin E among adults with HIV infection (Jordão *et al.* 1988). It is unknown whether renal disease hastens the excretion of other micronutrients.

Prevalence of micronutrient deficiencies

Before turning to the prevalence of micronutrient deficiencies in different HIV-infected populations, some caveats should be mentioned. Most studies addressing micronutrient status during HIV infection have employed serum or plasma levels of micronutrients, a widely used method for assessing status for many micronutrients (Gibson, 1990). Serum or plasma levels are sometimes considered to have their limitations, especially with a small sample size or with acutely ill patients. For some micronutrients, serum or plasma levels may not be the most sensitive indicators of micronutrient status. Children, injection drug users (IDU), pregnant women, heterosexual adults, and homosexual men might be epidemiologically distinct, yet some studies have lumped risk groups together when reporting micronutrient deficiencies. There is not always agreement as to which biochemical cut-off point defines 'deficiency'.

There is sufficient information from existing studies to make some general statements about micronutrient deficiencies during HIV infection. The prevalence of micronutrient deficiencies during HIV infection seems to vary widely, depending on study population and stage of disease (Table 1). In general, homosexual men and heterosexual adults in industrialized countries have the lowest prevalence of micronutrient deficiencies. IDU from large inner cities, pregnant women, and children seem to be at the highest risk of having micronutrient deficiencies. There is still a paucity of information from developing countries regarding micronutrient status during HIV infection.

Fat-soluble vitamins and carotenoids

Low vitamin A levels considered to be consistent with deficiency have been reported in 2–11% of homosexual men (Beach *et al.* 1992; Tang *et al.* 1997b), 15% of IDU (Semba *et al.* 1993), and 40–60% of pregnant women in

Table 1. Selected micronutrient levels in different human immunodeficiency virus-infected populations

Location	Risk group	<i>n</i>	Criteria used for deficiency*	% Deficient	Reference
New York City	heterosexual adults	64	vitamin A < 0.87 µmol/l	0	Skurnick <i>et al.</i> (1996)
			vitamin E < 14 µmol/l	4	
			vitamin B ₆ < 179 µmol/l	2	
			zinc < 10.7 µmol/l	4	
Baltimore/Washington	homosexual men	311	vitamin A < 1.05 µmol/l	3	Tang <i>et al.</i> (1997b)
			vitamin E < 11.6 µmol/l	11	
Miami	homosexual men	100	vitamin A < 1.05 µmol/l	11	Beach <i>et al.</i> (1992)
			vitamin E < 5 µmol/l	19	
			vitamin B ₆ †	30	
			zinc < 11.5 µmol/l	26	
Miami	adult men	70	selenium < 85 g/l	11	Mantero-Atienza <i>et al.</i> (1991)
Baltimore	injection drug users	126	vitamin A < 1.05 µmol/l	15	Semba <i>et al.</i> (1993)
Malawi	pregnant women	338	vitamin A < 1.05 µmol/l	65	Semba <i>et al.</i> (1994)
Kenya	pregnant women	205	vitamin A < 0.70 µmol/l	24	John <i>et al.</i> (1997)

* Measurements on serum or plasma.

† Erythrocyte transaminase assay, activity coefficient >1.85 for deficiency.

developing countries (Semba *et al.* 1994; Phuapradit *et al.* 1996). Frequency distributions of vitamin A levels from several different HIV-infected populations have been published (Semba, 1997). Abnormally low circulating provitamin A carotenoids occur in about 30–80 % of HIV-infected individuals (Bodgen *et al.* 1990; Ullrich *et al.* 1994; Phuapradit *et al.* 1996; Skurnick *et al.* 1996). HIV-infected children in Italy had lower β -carotene and vitamin E levels than healthy control children (Mastroiacovo *et al.* 1996). Low serum levels of 1,25-dihydroxycholecalciferol, the biologically active form of vitamin D, have been described in HIV-infected adults with normal levels of 25-hydroxycholecalciferol (Haug *et al.* 1994). The biological meaning of low 1,25-dihydroxycholecalciferol levels is unclear since 25-hydroxycholecalciferol levels are considered a more sensitive indicator of vitamin D status. Low vitamin E levels occur in 4 % of heterosexual adults and in 10–20 % of homosexual men and IDU (Bodgen *et al.* 1990; Beach *et al.* 1992; Baum *et al.* 1994, 1995). Most of these studies involving measurements of vitamin E levels have not measured the vitamin E:lipid ratio, which is considered to be a more accurate method for assessment of vitamin E status (Thurnham *et al.* 1986).

Vitamin C and B-complex vitamins

During HIV infection, abnormally low plasma or serum vitamin C levels have been reported in 7–27 % of homosexual men and IDU (Bodgen *et al.* 1990; Coodley & Girard, 1991; Beach *et al.* 1992) and 20 % of heterosexual adults (Skurnick *et al.* 1996). Normal blood thiamin and riboflavin levels have been reported in HIV-infected heterosexual adults, homosexual men, and IDU, although blood levels of thiamin and riboflavin may be insensitive indicators of status. Low blood niacin levels have been reported in about 5 % of HIV-infected adults (Bodgen *et al.* 1990; Skurnick *et al.* 1996). Abnormally low vitamin B₆ levels have been reported in 10–30 % of homosexual men and IDU (Beach *et al.* 1992; Tang *et al.* 1997a). About 20–30 % of homosexual men with AIDS have serum vitamin B₁₂ levels below the normal range (Burkes *et al.* 1987; Harriman *et al.* 1989; Paltiel *et al.* 1995). Folate deficiency has been reported in about 0–8 % of HIV-infected IDU and homosexual men (Bodgen *et al.* 1990; Coodley & Girard, 1991; Skurnick *et al.* 1996; Tang *et al.* 1997a), but one study reports that among HIV-infected adults who were not receiving folate supplements, 57–64 % had evidence of folate deficiency (Boudes *et al.* 1990). In contrast, others have reported that serum or erythrocyte folate levels are increased during early HIV infection (Beach *et al.* 1988; Tilkian *et al.* 1988).

Minerals and trace elements

Haematopoietic abnormalities are common during HIV infection. Antiretroviral therapy, malabsorption of Fe, and infection with HIV, cytomegalovirus, and *Mycobacterium avium intracellulare*, have been implicated as factors contributing to abnormal haematopoiesis (Mueller *et al.* 1996). Bone marrow biopsies and serum studies showed that over one-third of symptomatic, HIV-infected children had Fe

deficiency (Mueller *et al.* 1996). Fe deficiency in HIV-infected children is associated with intestinal Fe malabsorption and anaemia (Castaldo *et al.* 1996). During HIV infection, serum Cu levels consistent with deficiency were not found in heterosexual adults (Skurnick *et al.* 1996) but were noted in 3–11 % of homosexual men and IDU (Bodgen *et al.* 1990; Beach *et al.* 1992). Higher serum Cu levels were found in HIV-infected compared with HIV-seronegative homosexual men, and higher levels of Cu may reflect an increase in serum caeruloplasmin levels during the acute-phase response (Graham *et al.* 1991). In the same study, Cu and Zn levels in toenails were not significantly different between HIV seropositive and seronegative men (Graham *et al.* 1991). Serum Mg levels consistent with deficiency have been described in about 20–50 % of HIV-infected adults (Bodgen *et al.* 1990; Beach *et al.* 1992), but the significance of Mg deficiency during HIV infection is unknown. Zn deficiency, as measured by serum or plasma levels, has been reported in 26 % of asymptomatic homosexual men (Beach *et al.* 1992) and 29 % of hospitalized patients with AIDS (Koch *et al.* 1996b). Whole blood, erythrocyte, and plasma Se levels are lower in adults with AIDS (Dworkin *et al.* 1986). Low serum or plasma levels of Se consistent with deficiency (Cirelli *et al.* 1991; Mantero-Atienza *et al.* 1991) and low cardiac Se levels (Dworkin, 1994) have been described in HIV-infected adults.

Mechanisms by which micronutrient deficiency may influence HIV infection

There are many factors involved in the pathogenesis of HIV infection, including host genetic, immunological, and nutritional factors and viral factors such as virulence and strain. The premise that micronutrient deficiencies play a role in the pathogenesis of HIV infection is broadly based on two theories, the free-radical theory and the nutritional immunological theory, which have related and overlapping mechanisms.

Free-radical theory and HIV pathogenesis

Activated macrophages and neutrophils have important roles in the killing of micro-organisms through the generation of reactive oxygen intermediates (ROI) such as superoxide radicals (O₂⁻), hydrogen peroxide (H₂O₂), and hydroxyl radicals (HO). The ROI which are produced can also induce cellular injury and lysis, because free radicals have the potential to cause oxidation of nucleic acids, chromosomal breaks, peroxidation of lipids in cell membranes, and damage to collagen, proteins, and enzymes. ROI can damage bystander cells and induce pathology, and the generation of ROI by immune effector cells or injured tissue is balanced by the antioxidant defence system. Oxidative stress refers to the condition when the balance between prooxidants and antioxidants is upset and there is overproduction of ROI and resulting pathology (Baruchel & Wainberg, 1992).

Nuclear factor κ B (NF- κ B) is a transcriptional promotor of proteins which are involved in the inflammatory response and the acute-phase response. NF- κ B is bound to factor I κ B in the cytoplasm in its inactive form, but various factors,

such as tumour necrosis factor- α and ROI can cause the release of NF- κ B from factor I κ B, and NF- κ B translocates to the nucleus and binds to DNA (Duh *et al.* 1989; Schreck *et al.* 1991). Glutathione is a major intracellular thiol which acts as a free-radical scavenger and is thought to inhibit activation of NF- κ B (Staal *et al.* 1990; Kalebic *et al.* 1991). NF- κ B is involved in the transcription of HIV-1. Thus, free-radicals may potentially be involved in the pathogenesis of HIV infection through direct effects of cells and through interactions with NF- κ B and activation of HIV replication. HIV-infected adults with low levels of glutathione in their CD4⁺ lymphocytes have been shown to have decreased survival (Herzenberg *et al.* 1997), providing some rationale for clinical trials of *N*-acetylcysteine (an oral prodrug form of glutathione) during HIV infection.

Nutritional immunological theory and HIV pathogenesis

Some micronutrients play essential roles in maintaining normal immune function. According to this theory, micronutrient deficiencies compromise host immunity to HIV and associated infections, leading to clinical progression of disease. Vitamin A plays a central role in the growth and function of T and B cells, antibody responses, and maintenance of mucosal epithelia, including those of the respiratory, gastrointestinal, and genitourinary tracts (Semba, 1998). Vitamin A, through its active metabolites, all-*trans* and 9-*cis* retinoic acid, acts via nuclear receptors to regulate gene expression. There is some interaction between nuclear retinoic acid receptors, vitamin D, and thyroid hormone receptors (Chambon, 1996). Zn plays an important role in the growth, development, and function of neutrophils, macrophages, natural killer cells, and T and B lymphocytes (Shankar & Prasad, 1998). Vitamin E influences the function of T cells, B cells, and phagocytic cells and may protect immune effector cells against oxidative stress (Meydani & Beharka, 1998). Some evidence exists that vitamin B₆, Se, and folate may influence immune function (Dhur *et al.* 1991; Rall & Meydani, 1993; Roy *et al.* 1995), but much further work is needed to characterize the role of these specific deficiencies in immune function.

Clinical and epidemiological observations

Longitudinal studies suggest that deficiencies in certain micronutrients are associated with increased morbidity

and mortality during HIV infection. Low plasma or serum vitamin A levels are associated with accelerated HIV progression (Baum *et al.* 1995), increased mortality (Semba *et al.* 1993), higher vertical transmission of HIV (Semba *et al.* 1994; Greenberg *et al.* 1997), child growth failure (Semba *et al.* 1997), and increased HIV load in breast milk and the birth canal (Nduati *et al.* 1995; John *et al.* 1997; Mostad *et al.* 1997). A longitudinal study of over 300 HIV-infected homosexual men showed that individuals with high serum vitamin E levels had a 30% lower risk of progression to AIDS (Tang *et al.* 1997b). Low plasma vitamin B₆ levels are not associated with HIV disease progression (Baum *et al.* 1991; Tang *et al.* 1997a), however, intake of vitamin B₆ supplements at greater than twice the RDA has been linked with improved survival in HIV-infected homosexual men (Tang *et al.* 1996). The risk of progression to AIDS was increased twofold in homosexual men with vitamin B₁₂ deficiency (Tang *et al.* 1997a). The pathogenesis of anaemia during HIV infection is poorly understood, and low haemoglobin levels have been associated with increased immune activation, low transferrin, and high ferritin levels (Fuchs *et al.* 1993). Low serum Zn levels are associated with reduced secretory function of the thymus (Falutz *et al.* 1988) and HIV disease progression in homosexual men (Graham *et al.* 1991; Baum *et al.* 1995). Zn levels can decrease during the acute-phase response, and it has been suggested that these low Zn levels may reflect HIV replication (Graham *et al.* 1991). Although Se deficiency is rare in man, Se deficiency was noted to be common during HIV infection and was linked with increased mortality (Baum *et al.* 1997).

Micronutrient supplementation trials

There has been a paucity of clinical trials of micronutrient supplementation during HIV infection (Table 2). Most of the studies consist of pilot interventions with single micronutrients. The available pilot studies have been conducted in populations which are at different risk for micronutrient deficiencies, thus, it is difficult to make extrapolations to other populations from these findings. High-dose vitamin A supplementation seemed to reduce diarrhoeal morbidity in HIV-infected infants in an underprivileged population in Durban, South Africa (Coutsoudis *et al.* 1995). A clinical trial in children with AIDS in Cape Town showed that 60 mg retinol equivalents of vitamin A given on two consecutive

Table 2. Clinical trials of micronutrients for human immunodeficiency virus (HIV)-infected individuals

Location	Subjects	<i>n</i>	Intervention	Outcome	Reference
Durban	children	28	vitamin A, age-adjusted doses	↓ diarrhoeal morbidity	Coutsoudis <i>et al.</i> (1995)
Cape Town	children	75	vitamin A, 60 mg RE, two doses	↑ CD4 ⁺ lymphocytes	Hussey <i>et al.</i> (1996)
Baltimore	injection drug users	120	vitamin A, 60 mg RE	no change HIV load	Semba <i>et al.</i> (1998)
Portland	adults	72	β-carotene, 180 mg/d	no change in CD4 ⁺ lymphocytes	Coodley <i>et al.</i> (1996)
Italy	adults	35	zinc sulfate, 200 mg/d	↓ infectious morbidity	Mocchegiani <i>et al.</i> (1995)
Dar Es Salaam	pregnant women	1075	multivitamin + vitamin A/β-carotene, vitamin A/β-carotene, both, or neither	multivitamin ↓ fetal mortality, low birthweight	Fawzi <i>et al.</i> (1998)
Toronto	adults	49	vitamins C (1 g) and E (800 mg) daily	↓ lipid peroxidation, ↓ HIV load	Allard <i>et al.</i> (1998)

RE, retinol equivalents.

days could increase circulating CD4 and natural killer cell counts 1 month after supplementation (Hussey *et al.* 1996). In HIV-infected IDU in inner city Baltimore, a single high oral dose of vitamin A (60 mg retinol equivalents) did not seem to influence HIV load but may possibly have helped stabilize the decline in circulating CD4⁺ lymphocytes (Semba *et al.* 1998). Megadose β -carotene did not appear to have additional benefit for HIV-infected adults who were already on multivitamins in Portland, Oregon (Coodley *et al.* 1996). Daily Zn supplementation (200 mg/d) for 30 d reduced infectious disease morbidity in adults with AIDS in Italy (Mocchegiani *et al.* 1995). A reduction in oxidative stress and an apparent decrease in viral load were noted in a clinical trial of vitamins E (800 mg/d) and C (1 g/d) in HIV-infected adults in Toronto (Allard *et al.* 1998).

A recent large study from Tanzania suggests that micronutrient supplementation to HIV-infected pregnant women will greatly improve birth outcomes. Women who received daily multivitamin supplementation from the second trimester until delivery had about a 40% decrease in fetal deaths and low birth weight. The study involved a 2 × 2 factorial design in which mothers received either (1) a multivitamin (vitamins C, E, B₆, B₁₂, folate, thiamin, riboflavin, niacin), (2) vitamin A (1.5 mg retinol equivalents) plus β -carotene (30 mg), (3) a multivitamin, vitamin A, and β -carotene, or (4) placebo. All women in the study received daily Fe and folate. Vitamin A and β -carotene supplementation had no apparent effect on fetal deaths and low birth weight. Multivitamins were associated with a significant increase in CD3⁺, CD4⁺, and CD8⁺ lymphocyte counts. To date, this is the largest micronutrient clinical trial to be conducted among HIV-infected individuals, and shows that there may be great promise in using micronutrients to improve maternal and child health in developing countries.

Comment

The advent of highly active antiretroviral therapy has dramatically changed the therapeutics of HIV infection for the minority of individuals living in industrialized countries (Sepkowitz, 1998). Combination antiretroviral therapy alone may have an impact on increasing resistance to gastrointestinal microsporidiosis and cryptosporidiosis infections (Carr *et al.* 1998). Micronutrient supplementation has largely been relegated to the sphere of complementary therapies in industrialized countries (Kotler, 1998). Billions of dollars are spent each year on vitamin and mineral supplements in industrialized countries, and many individuals with HIV infection are taking supplements although there is a lack of clear data which show that such health expenditure is worthwhile.

For the other 90% of those infected with HIV in developing countries, it will be especially important to identify micronutrient deficiencies and to determine whether micronutrient supplementation will improve clinical outcomes. Micronutrient supplementation meets the criteria for sustainable health interventions in terms of cost, technology transfer, and lack of requirements for sophisticated monitoring. In least developed countries which have been hard hit by the AIDS pandemic, the main priorities include access to clean water and adequate sanitation. Micronutrient

interventions are compatible with this basic public health approach, and micronutrient supplementation has been shown in similar circumstances to have the highest cost-benefit ratio known for any health interventions (United Nations Children's Fund, 1998).

There are still many unanswered questions regarding nutrition and HIV infection. Which micronutrient deficiencies are common in HIV-infected populations in developing countries? What factors contribute to the development of micronutrient deficiencies? Do individuals with HIV infection have the same requirements as individuals without infection? Will micronutrients contained in supplements be absorbed well in patients with asymptomatic HIV infection? Does the content of micronutrient supplements need to be higher in HIV-infected individuals with diarrhoea and malabsorption? Will micronutrient supplementation reduce morbidity and mortality during HIV infection? These are some of the basic questions regarding micronutrient deficiencies which should be a high priority on the research agenda for nutrition and HIV infection in the near future.

Acknowledgements

This work was supported in part by the National Institutes of Health (HD30042, HD32247), the Fogarty International Center, and the United States Agency for International Development (Cooperative Agreement DAN-0045-A-5094-00).

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