Review

Effects of Antioxidants on CD4 and Viral Load in HIV-Infected Women in Sub-Saharan Africa – Dietary Supplements vs. Local Diet

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Received: January 24, 2011; Accepted: October 14, 2011

Abstract: In sub-Sahara Africa, micronutrient deficiency, especially of antioxidant micronutrients including vitamins A, C, and E, β-carotene, selenium, zinc, and polyphenols is very common in HIV-positive patients. Amongst adults, women are the most vulnerable. Antioxidants are known to play a vital role in the immune system, reducing oxidative stress. Oxidative stress is induced by excess production of reactive oxygen species (ROS), due to the HIV infection. Such damage may be prevented or moderated through adequate oral intake of antioxidants, scavenging ROS, as well as protecting cells and tissues against oxidative stress. Antioxidants can be provided to the body through locally available antioxidant rich-diets such as fruit-and-vegetable-based diets and/or dietary supplements. Provision of antioxidants through local diets or dietary supplements exercise beneficial effects on biological markers of the immune system (CD4 and viral load). However, while dietary supplements represent a costly and short-term strategy to limiting antioxidant deficiency, local diets, combined with adequate nutritional education, can provide a low-cost and long-term strategy to reduce oxidative stress, prevent micronutrient deficiency, and slow down HIV disease progression. The former can be applicable in countries around the West, Central, and South coast of Africa, which are rich in natural food resources. In contrast with significant evidence that dietary supplements confer benefits in HIV patients, fewer data are available relating to the benefits of local diets. Thus the need to do more research in this area arises. This review compares available data on effects of antioxidants on CD4 and viral load in HIV-positive women noneligible for antiretroviral therapy. Intake of antioxidants though dietary supplements and local diet, associated with nutritional education, is compared. Studies conducted in sub-Sahara Africa are considered.

Key words: micronutrient, dietary supplement, antioxidant, CD4, Viral load, local diet, HIV infection

Introduction

The human immunodeficiency virus (HIV) is one of the most important public health problems that have increased the mortality rate in sub-Sahara Africa [55]. According to the United Nations Development Program on HIV/AIDS, out of the 39.5 million adults and children estimated worldwide to be living with HIV, 24.7 million comes from sub-Saharan Africa. Of these, approximately 50 % are women [65].

Since the beginning of the HIV epidemic, major research efforts have been put in place to reduce the burden of HIV/AIDS on infected persons. This includes the discovery of antiretroviral therapy (ARV) and comprehensive health-care measures. ARV cannot cure HIV/AIDS but studies indicate that ARV can suppress the replication of HIV-virus, slowing down the HIV disease progression [37]. Amongst comprehensive health-care measures, nutrition is the most important. The major nutritional problem faced by HIV/AIDS patients in sub-Saharan Africa is malnutrition. The relation between malnutrition and HIV/AIDS has been well established and adequate nutrition has been recognized as part of comprehensive care for HIV-infected persons [18, 34, 36] (see Figure below). Micronutrient deficiency-induced malnutrition is a result of changes in body metabolism and inadequate nutrient intake due to conditions such as mouth sores, swallowing problems, loss of appetite, diarrhea and vomiting, and malabsorption [9, 27]. This results in weight loss and micronutrient deficiency, which in turn impairs the nutritional and immune status of HIV patients [6]. Of the micronutrients available, antioxidant micronutrients play a vital role in maintaining the integrity of immune cells.

The presence of the HIV virus in the body provokes the activation of phagocytic cells (macrophages and neutrophils), to destroy the microorganisms through the generation of reactive oxygen species (ROS). Common ROS are the hydroxyl radical hydrogen peroxide and the superoxide anion. ROS are known to play a critical role in the induction of oxidative stress and the degradation of immune cells [38]. Excess production of ROS can attack double bonds in polyunsaturated fatty acids, inducing lipid peroxidation that may result in more oxidative cellular stress. Oxidative stress is a condition when the balance between prooxidant and antioxidant is upset, and there is overproduction of ROS and resulting pathology [7]. Oxidative stress promotes the replication of the virus by up-regulating the activation of NF-Kappa B (NF-κB), a transcriptional promoter of proteins that are involved in the inflammatory and acute-phase response. NF-κB is bound to I-κB in the cytoplasm in its inactive form but tumor necrosis factor-α and ROS can cause the activation of NF-κB from I-κB. NF-κB then translocates to the nucleus and binds to the DNA, promoting transcription of HIV-1 [50]. To prevent such damage, adequate amounts of neutralizing antioxidants micronutrients are required. Antioxidants are substances or nutrients present especially in fruits and vegetables [2]. They are known for their beneficial effects on free radicals in biological systems, reducing oxidative stress on immune cells and reducing replication of HIV [17, 29]. Some common antioxidants include ascorbic acid, alpha-tocopherol, carotenoids, polyphenolic flavonoids, selenium, and zinc, which can be obtained directly from the local diet [29]. Previous studies have shown positive effects of antioxidant micronutrient supplement and/or antioxidant-rich diet on standard biological markers such as CD4 cells and viral load [19, 21, 28, 30, 37, 57, 67]. Meanwhile some studies have demonstrated the adverse effects of micronutrient supplementation on the immune system. The supplementation of vitamin E, for example, has been shown to increase expression of CCR5 (the major cell entry co-receptor for T-cell line-tropic and macrophage-tropic strains of HIV-1, respectively) by preventing the production of natural ligands of CCR5 [Regulated upon Activation, Normal T-cell Expressed, and Secreted (RANTES), macrophage inflammatory protein-1 alpha [MIP-1a], and macrophage inflammatory protein-1 beta [MIP-1b]), hence an increase infection of CD4 cells whence increase viral load [34, 47].

However, due to economic constraints in most sub-Saharan African countries, dietary supplements are beyond the reach of all but a privileged few. Thus the need to optimize the nutritional status of HIV patients through the available and cheap local diet arises [36]. This approach may be particularly profitable to HIV-asymptomatic patients, who in sub-Saharan African are not yet eligible to free ARV.

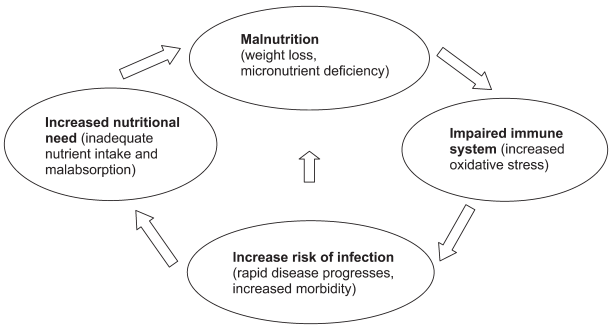

Figure 1: Effects of HIV on nutritional and immune status [42].

This article reviews published literature on the effects of antioxidant micronutrient intake on CD4 and viral load in HIV-asymptomatic women. Intake of antioxidants (AO) through dietary supplements is compared to intake through local diet. Studies conducted in sub-Sahara Africa are considered.

Method

For the review, literature was available in Pubmed, and Medline. The following key words were entered for the search: micronutrient deficiency, HIV/AIDS, sub-Sahara Africa, oxidative stress, antioxidant and fruits and vegetables, antioxidants, CD4, and viral load.

Inclusion criteria: Studies containing analysis of the effects of antioxidants either as dietary supplements or local diet, on CD4 and viral load in HIV-infected women in sub-Saharan Africa. Search was limited to HIV-asymptomatic patients and studies with sample size above 30, and studies performed between 1998 and 2010. Exclusion criteria were: HIV studies on pregnant women and children.

Results

Effects of common antioxidants on biological markers (CD4 cells and viral load)

Vitamin A

Of all the vitamins known, the role of vitamin A has been studied most extensively. Vitamin A plays an important role in the modulation of normal immune function through lymphopoiesis and cellular differentiation. Vitamin A deficiency is a result of a low serum level of vitamin A due to reduced dietary intake following the HIV-related conditions already mentioned [6, 9, 27]. Vitamin A deficiency can also be a result of increased urinary excretion due to acute infections [55]. Visser and co-workers also observed in resource-poor settings in South-Africa, an association between advanced disease and/or weight loss and lowered blood concentrations of vitamin A [67]. Vitamin A deficiency can lead to pathological changes in the mucosal surfaces, impaired antibody responses, decreased CD4 cell population, and altered T- and B-cell functions [52, 55]. Previous studies have shown that low vitamin A levels are also associated with increased risk of transmission of HIV from mother to child [10]. This finding is similar to that of Fawzi, who observed a low plasma vitamin A level and a decreased risk of mother-to-child transmission (MTCT) of HIV after supplementation with vitamin A [19, 20]. Later on, Fawzi and co-workers again attempted to explain the possible mechanisms for the observation, proposing that advanced HIV disease may suppress release of vitamin A from the liver, leading to low levels of vitamin A in the plasma despite the body having enough vitamin A liver stores. Also, advanced HIV disease is likely to increase the risk of MTCT, and hence it would appear that low serum vitamin A levels are associated with increased MTCT [22].

β-carotene

Carotenoids are amongst the most important dietary antioxidants found in the human plasma. Their concentrations in plasma are considered to be the most accurate indicator of dietary carotenoid intake. Many epidemiologic studies have associated high carotenoid intake with a decrease in the incidence of chronic disease. However, the biological mechanisms for such protection are currently unclear. Multiple possibilities exist: certain carotenoids can be converted to retinoids (i.e. have provitamin A activity), can modulate the enzymatic activities of lipoxygenases (proinflammatory and immunomodulatory molecules), and can have antioxidant properties. Beta-carotene amongst other carotenoids is known to have antioxidant properties, but the antioxidant activity of these compounds can shift into a prooxidant effect, depending on such factors as oxygen tension or carotenoid concentration. Mixtures of carotenoids alone or in association with other antioxidants can increase their activity against lipid peroxidation [75]. Contrary to expectations clinical trials found no benefit of supplementing Beta-carotene on CD4 counts [14, 42]. Meanwhile observational studies indicate its beneficial effects on disease progression [8, 20]. Baeten and co-workers observed in a multivariate analysis that, beta-carotene concentrations below the median were associated with elevated C-reactive protein (CRP) [>10 mg/L, adjusted odds ratio (aOR) 3.32, 95 % confidence interval (CI) 1.99–5.53, $p<0.001$ and higher HIV-1 plasma viral load (for each log(10) copies/mL increase, OR 1.38, 95 % CI 1.01–1.88, $p=0.04$] [4]. Baeten suggests that low beta-carotene concentrations reflect primarily more active HIV infection, rather than true deficiency amenable to intervention [4].

Table I: Antioxidative supplements and effect on clinical parameters (CD4 counts and viral load) and disease progression.

Author (reference number) and year	Location	Sample size	Study design	Duration (months)	Micronutrient type and dosage	Effects on CD4 and RNA Viral load
Graham. et al. 2007	Kenya	67	Prospective study	84 (7years)	Vitamin E	Low vitamin E level before infection does not influence disease progression
Visser M.E. et al. 2003	South Africa	132	Cross-sectional study	12	Vitamin A and Zinc	Patients with advanced disease were more likely to have low plasma vitamin A and Zn are common in HIV infected patients
Olaniyi JA and Arinola OG 2007	Nigeria	58				Significant correlation between Zn and CD4 status
Kassu et al. 2007	Ethiopia	110	Cross-sectional study	8	Vitamin A	Low vitamin A levels in HIV asymptomatic patients compared to healthy control
Baeten JM et al. 2007	Kenya	400	Cross-sectional study	22	β-carotene	Modest statistical correlation between β-carotene level and CD4, high viral load CRP and albumin
Djinhi et al. 2009	Cote d'Ivoire	30			Selenium	
Paul Kelly et al. 2008	Zambia	500	Cluster-randomized double blind placebo-controlled trial with mid pint cross-over	38	Multiple micronutrient (β-carotene, vitamin B-1, B-2, B-6, B-12, Niacin, Folic acid, C, D3, E, Iron, Zinc, Selenium, Iodine)	Rate of mortality and occurrence of diarrhoea dropped
Fawzi et al. 2007	Tanzania	1078	Randomized double blind placebo controlled trial	71	Vitamin A (performed vitamin A 5000 IU and B-carotene 30 mg) and multivitamin (B2 (20 mg), B6 (25 mg), Niacin (100 mg), B12 (50 μg) vitamin C (500 mg) and E (30 mg), folic acid (0.8 mg)	Increased CD4 and CD8 cell count and low viral load. Smaller effects of receiving vitamin A alone
Allard et al. 1998		49	Randomized double blind placebo controlled trial	3	Vitamin C (1000 mg) and vitamin E (800 IU)	Reduction in lipid peroxide and malondialdehyde. Trend towards reduction in viral load

Table II: Local diet based strategy accompanied by nutritional counseling. Effect on clinical parameters (CD4 counts and viral load) and disease progression.

Author and year	Location	Sample size	Study design	Duration (months)	Micronutrient type and dosage	Effects on CD4 and RNA Viral load
Zotor FB and Amuna P 2008	Accra Ghana	1039	N/A	5	Food Multimix- based on local food	≥ 40 % Daily nutritional needs of vulnerable groups including HIV/ AIDS patients met
Kuria EN 2009	Kenya	147 asymptomatic HIV, 265 unestablished HIV-status	Cross-sectional descriptive survey	/	Low nutrient diet	No significant effect on CD4 and/ or viral load
Vorster et al. 2004	South Africa	1766 216 asymptomatic HIV, 1550 control	Cross-sectional population-based survey	5	Animal rich diet and vegetables	Improved nutritional status of HIV-infected persons . Effect on CD4 and viral load not mentioned.

Vitamin C

Vitamin C, also known as ascorbic acid, is synthesized in the liver of most mammalian species but not by humans. Vitamin C is therefore essential and must be ingested by humans for survival.

Like most antioxidants, a study by Allard and co-workers indicate an increased utilization of vitamin C in HIV-infected persons compared to healthy controls [1]. Increased utilization coupled with low dietary intake of vitamin C can lead to vitamin deficiency during the HIV infection [1]. Meanwhile, previous studies give evidence that massive doses of vitamin C can suppress the symptoms of HIV disease and markedly reduce the occurrence of secondary infections [49]. Further, recent studies indicate that increased intakes of vitamin C during HIV infection can lead to a mild increase of CD4 counts, while helping to prevent oxidative damage and enhancing normal immune function and survival [1, 59]. Meanwhile Fawzi and co-workers also observed that supplementation of vitamin C in combination with vitamin E may provide protection to red blood cells from being destroyed by free radicals that are features of oxidative stress in HIV infection [22].

Vitamin E

Studies reveal low vitamin E levels in the plasma of HIV-infected persons [1, 6, 57, 58]. The low levels of vitamin E in HIV patients can be a result of increased utilization of vitamin E in quenching free radicals, thereby preventing peroxidation of polyunsaturated fatty acids [43]. Vitamin E deficiency in HIV patients can also be due to poor dietary intake, poor absorption, diarrhea, and impairment of the recycling mechanism of vitamin E through vitamin C [57]. In prospective studies of HIV-1 infected people, higher vitamin E levels and higher intake have been associated with lower risk of progression to AIDS [46, 58, 67]. Meanwhile in other studies, the supplementation of vitamin E influenced the production of RANTES, an important antiviral chemokine. In a small supplementation study, 500 mg of alpha-tocopherol given once daily for 2 months reduced RANTES production and increased the expression of CCR5 on the surface of CD4+ T-cells of HIV-1 infected persons. Endogenous production of antiviral factors like RANTES may significantly affect HIV-1 replication and the pace of disease progression [32, 34, 44].

Selenium

Selenium plays an important role in the selenoenzyme glutathione peroxidase that protects cells against free radical damage and oxidative stress. Evidence exists that the utilization of selenium increases in HIV patients, leading to low plasma selenium levels [6]. Low serum selenium levels exacerbate the oxidative stress induced by HIV, increasing the risk of mortality and the occurrence of AIDS-related opportunistic infections [5]. Previous studies showed an increase in lipid peroxidation (oxidative stress) in HIV-positive individuals with lower plasma concentrations of selenium. Further studies illustrated that supplementation with selenium in HIV-positive patients led to higher glutathione peroxidase levels [12, 15]. These studies do not indicate an improvement in the concentration of CD4 cells. Meanwhile, Hurwitz and co-workers [31] observed a suppression of the viral load in HIV patients after supplementation with selenium. However, most studies on selenium are small and observational study design, making confounding a possible explanation for contradictory results.

Zinc deficiency

Human zinc deficiency is thought to be prevalent worldwide, particularly in populations with diets poor in zinc and animal proteins, and rich in inhibitors of zinc absorption such as phytic acid. Studies indicate an association between zinc deficiency and impaired immune function, increasing infection risk [32]. Zinc is involved in the growth, development, and function of neutrophils, macrophages, natural killer cells, and T and B lymphocytes. Studies also show that zinc supplementation can reduce the rate of diarrheal diseases, reduce acute lower respiratory tract infections as well as increase levels of CD4 cells [43, 71]. However the reported relationships of zinc and HIV-related outcomes have not been consistent across studies. Meanwhile Abrams and co-workers [73], in a related study, also indicated a positive relationship between CD4 counts and dietary intake of zinc. However, in that study, no relation between dietary intake of zinc and HIV disease progression was evident. According to Fawzi and co-workers [28], confounding can be a possible explanation for these results.

Polyphenols

Polyphenols including flavonoids are a class of secondary plant substances that are widespread in plants. These include food grains such as sorghum, millet, barley, and dry beans, peas, and other legumes; fruits such as apples, blackberries, cranberries, grapes, oranges, pears, plums, raspberries, and strawberries; and vegetables such as cabbage, celery, onion, and parsley also contain a large quantity of polyphenols. Phenolic compounds are also present in tea and wine. They are known to exert a strong antioxidant effect *in vitro* [11, 25, 29, 45, 70]. Thus, by counteracting oxidative stress, they can boost immune function in HIV-infected persons [27]. Some studies however show no effect of polyphenols on CD4 and viral load after supplementation with fruit juices, although plasma antioxidant capacity is increased [2, 74]. This observation is contrary to findings from Müller and co-workers [39], where antioxidant treatment increased intracellular glutathione in T-cells (an indication of reduced intracellular oxidative stress) and increased proliferation of CD4 cell count. In the same study, a decrease in viral load was observed but only in the sub-groups with advanced immunodeficiency [29]. However, although some studies have shown that supplementation of polyphenol affects lymphocyte proliferation and apoptosis, it will be profitable to perform further research in this area, considering larger sample sizes and studies of longer duration. Also a variety of polyphenols should be considered for the calculation of polyphenol intake.

Discussion

One of the major comprehensive care concerns is the control of HIV-related malnutrition. Malnutrition and infection are both separate contributors to morbidity and mortality in HIV/AIDS [22]. The effects are most important in resource-limited settings, where the synergistic interaction between micronutrient malnutrition and infection is very common [24, 26]

Micronutrients, including antioxidants, constitute a major challenge in maintaining both a healthy nutritional and immune status in HIV-infected persons. Excessive immune activation due to HIV infection has a prooxidant effect, increasing oxidative stress, known in *in vitro* studies to increase HIV replication [31, 50] and antioxidant demand [43]. Antioxidant demand increases due to reduced dietary intake.

The present article reviews data illustrating the effects of antioxidant micronutrients on biological mark-

ers (CD4 and viral load) provided to HIV-positive asymptomatic women in sub-Sahara Africa. Antioxidant intakes through supplements and/or local diet are compared. There is no doubt that dietary supplements have their place in clinical management, but their overall efficacy, because of costs and the ability of poor communities to sustain supplementation programs, remains highly questionable. Although our search did not provide a good number of studies on the use of antioxidant-rich local diets, and their effect on CD4 and viral load, there are advantages in utilizing commonly accessible, affordable, and identifiable food sources that are familiar and culturally appropriate to poor communities and vulnerable groups [29]. Local diet, in spite of being readily available, is equally a rich source of essential nutrients such as antioxidants that can be profitable for HIV patients. Orange-fleshed sweet potatoes (OFSP), palm oil, and a multitude of fresh fruits just to name a few, are naturally rich in_β-carotene, and are an excellent food source of provitamin A, and vitamin E. These varieties can make a significant contribution to a viable, long-term, effective, and sustainable food-based approach to prevent vitamin A deficiency in developing countries [16, 29, 46, 54].

There is also evidence that nutrients from the local diet are better absorbed than synthetic supplements and provide a bright spectrum of other micronutrients (B-group vitamins, iron, magnesium, calcium, copper, etc.) and macronutrients (carbohydrates, protein, and fats), all important for maintaining the metabolic processes in the body and preventing weight loss [18, 36, 48, 53, 60].

Meanwhile Kuria in a cross-sectional survey discovered that most people living with HIV/AIDS consume food that is low in nutrients and without the variety necessary to build up the immune system and maintain adequate weight [34]. This indicates the need to combine local diet with adequate nutritional education of HIV-infected persons [48, 60, 62, 68]. Meanwhile, nutritional education can be profitable in limiting food contamination that can occur during preparation of local diet. It is therefore important during the implementation of interventions with local diet to educate participants on good hygiene practices, in order to avoid further infections in an already compromised immune system.

There is one important strength of this review. The study design of studies included in this review comprises both observational designs as well as randomized clinical trials, making it possible to compare results from both designs.

Limitations and recommendations

There are several limitations to this review. There are currently more data available for nutritional interventions conducted with dietary supplements compared to those conducted with local diet alone, thus a possible cause for publication bias. This problem may be linked to ethical considerations in conducting clinical trials with different diets in infected subjects. We are aware that setting criteria for the selection of literature could greatly limit this review.

In addition, results of findings were not always consistent between observational studies and clinical trials. Thus, larger and long-lasting clinical trials are needed to examine the efficacy of these micronutrients on clinical outcomes, both in dietary supplements and in local diets, to ascertain their potential benefits in HIV patients.

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