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The Interrelationship Between Nutrition and the Immune System in HIV Infection: A Review

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Abstract: Available scientific evidence has revealed that macronutrients and micronutrients are critical for fighting HIV-infection, because they are required by the immune system and major organs to attack infectious pathogens, HIV inclusive. It is believed that weight gain or maintenance might be achieved through good nutrition and has helped to reduce the consequences of wasting in people living with HIV/AIDS. Nutrition has helped to strengthen the immune system and reduce the severity and impact of opportunistic infections in people living with HIV/AIDS. It is known that an immune dysfunction as a result of HIV/AIDS leads to malnutrition and this in turn leads to further immune dysfunction. Various research studies have confirmed that nutrient deficiencies are associated with immune dysfunction and accelerated progression to AIDS. In this review, the interrelationship between nutrition and immune system in HIV infection is presented.

Key words: Nutrition, malnutrition, human immunodeficiency virus, immune system

INTRODUCTION

It is generally accepted that nutrition is an important determinant of immune responses (Chandra, 1997). Results from epidemiological and clinical studies suggest that nutritional deficiencies alter immuno-competence and increase the risk of infection. It is agreed that poor sanitation and personal hygiene, overcrowding, contaminated food, water and inadequate knowledge of nutrition contribute to susceptibility to infection. Previous research findings have confirmed that impaired immunity is a critical adjunct factor in malnutrition-associated infection. This concept does not only apply to people in developing countries but to people (all age groups) in all countries (Chandra, 1991, 1996, 1997; Bell *et al*., 1997; Bogden *et al*., 2000).

Adherence of bacteria to epithelial cells is an essential first step before invasion and infection can take place. The number of bacteria adhering to respiratory epithelial cells has been shown to increase in malnutrition as documented by Chandra (1997).

Role of micronutrients in the immune system: Several trace elements and vitamins have essential roles in metabolic pathways and immune cell functions. The deficiencies of these micronutrients have been noted and are known to complicate malnutrition and other systemic diseases. Likewise, human malnutrition is usually a composite syndrome of multiple nutrient deficiencies (Bendich and Chandra, 1990; Baum and Shor-Posner, 1998; Dannhauser *et al*., 1999; Bogden *et al*., 2000). Five general concepts have been advanced: (1) Alterations in immune responses occur early in the course of reduction in micronutrient intake. (2) The extent of immunological impairment depends on the type of nutrient involved, its interactions with other essential nutrients, the severity of the deficiency, the presence of concomitant infection and the age of the person concerned. (3) Immunological abnormalities predict outcome, particularly the risk of infection and mortality. (4) For many micronutrients, excessive intake is associated with impaired immune responses. (5) Tests of immuno-competence are useful in titration of physiological needs and in assessment of safe lower and upper limits of micronutrient intake (Chandra, 1997; Dannhauser *et al*., 1999). An established effect of nutrition on immunity has led to several practical applications and its usefulness is still relevant today.

Nutrition and HIV infection: The relationship between nutrition and HIV/AIDS is well recognized. In fact, in Africa AIDS was initially known as Slim Disease because of the classical wasting typically experienced by persons with the disease (Piwoz and Preble, 2000). HIV infection compromises the nutritional status of infected persons and in turn poor nutritional status can affect the progression of HIV infection (Friis and Michaelsen, 1998; Niyongabo *et al*., 1999; Piwoz and Preble, 2000; Fawzi, 2003).

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From a clinical view, infections may affect the nutritional status of an individual suffering from HIV/AIDS in various ways, such as a reduction in food intake and nutrient absorption and by increasing the utilization and excretion of proteins and micronutrients (Semba and Tang, 1999). It has also been observed that HIV infection accelerates the release of pro-oxidants, cytokines and other reactive oxygen species, leading to the increased utilization of antioxidants such as vitamin E, C, beta-carotene and micronutrients such as iron, zinc, selenium, manganese and copper (Friis and Michaelsen, 1998). An imbalance between these pro-oxidants and antioxidants causes oxidative stress which further damages the cells, proteins and enzymes, thus accelerating HIV replication (Schwartz, 1996).

It has been shown that deficiencies of nutrients may affect the immune function in ways that may influence viral expression and replication, which further affect progression of HIV disease and mortality of the patient (Semba and Tang, 1999). Hormones such as glucagons, insulin, epinephrine and cortisol which are involved in the metabolism of protein, carbohydrate and fat, have been reported to be affected by HIV infection (Macallan, 1999). Increased levels of these hormones is believed to contribute to weight loss and the wasting syndrome seen in HIV/AIDS patients (Macallan, 1999; Piwoz and Preble, 2000). Research studies have confirmed that nutrient deficiencies are associated with immune dysfunction and accelerated progression to AIDS (Fawzi and Hunter, 1998; Macallan, 1999). Furthermore, deficiencies of protein and essential fatty acids interfere with immune function.

Diet and nutrition in Africa: Certain foods are preferentially utilized in specific African countries and communities (Watson, 1994). The important staple foods eaten by Africans and the protein-energy percentages of these staples are: wheat (11%), millet (12%), rice (8%), maize (10%), yam (6%), plantain (4%) and cassava (3%) (Watson, 1994). The major meals are bulky and the amount of staple food usually consumed per average person per day does not provide the recommended daily allowance (RDA) of energy, protein and other essential nutrients (Enwonwu, 1992; Kotler, 1992; Moore *et al*., 1998).

These traditional foods are often prepared and served under poor hygienic conditions, thus setting the stage for repeated episodes of diarrhoea, thus aggravating the poor nutritional status (Abrams *et al*., 1993; Anyanwu and Enwonwu, 1995). For most African countries, the first decade of the HIV/AIDS epidemic was a period of severe economic crisis characterized by an unsustainable foreign debt burden, monetary devaluation and ten-to twenty-fold rise in consumer price indices. Reports have linked malnutrition with HIV infection and AIDS, hence it is appropriate to examine malnutrition in Africa and its relationship with HIV infection and AIDS.

Malnutrition: Improving the nutrition situation in Africa has been a challenge for decades, complicated by a combination of individual, household, community, national and international factors, including, in the last two decades, the emergence of HIV infection and AIDS (Castetbon *et al*., 1997; Piwoz and Preble, 2000). It has been reported that disease, cultural beliefs and customs, high fertility rates, poor economic status and limited access to health and other social services also contribute to chronic, endemic malnutrition on this continent (Ndure *et al*., 1999). Malnutrition is said to take many forms. These include protein-energy malnutrition (measured in terms of body size) and micronutrient malnutrition, which in its mild and moderate forms is not always recognized and is often referred to as hidden hunger (Ndure *et al*., 1999).

Ndure *et al*. (1999) reported that deficiencies in vitamins and minerals such as vitamin A, B complex, iron and iodine, that are vital for the body's normal function and immune system, occur in populations with high infectious disease burdens. These deficiencies have been associated with poor quality diets characterized by limited consumption of animal products and seasonal or periodic food insecurity. Recent data suggest that little or no progress has been made in reducing the malnutrition in sub-Saharan Africa in the last twenty years (Watson, 1994; Niyongabo *et al*., 1999; Piwoz and Preble, 2000). It is also indicated that, in several countries, malnutrition is increasing as a result of armed conflicts, deteriorating health systems, shrinking economies and HIV/AIDS (Murray and Lopez, 1996).

Malnutrition among African people and especially among women of childbearing age is also a serious problem, with an estimated 42% of African women as a whole and half of the pregnant women suffering from anaemia (ACC/SCN, 2000). Between 10 and 20% of Africans between the ages of 20 to 49 years are underweight and nearly 50% of the African population is at risk of developing micronutrient deficiency diseases (Baker *et al*., 1996; Mocroft *et al*., 1999). The consequences of malnutrition include acquisition of some kinds of infections as well as reduced labour productivity (Baker *et al*., 1996).

Pathogenesis of malnutrition in HIV/AIDS: Food intake is inhibited indirectly in patients with malabsorption, resulting from different diseases or systemic infections

due to the release of specific factors that inhibit appetite at the central nervous system level (Wheeler *et al*., 1998; Kotler *et al*., 1999). These problems may be exacerbated by economic factors or other impediments to obtaining food (Kotler, 1992).

Localized pathology and nutrient malabsorption: Watson (1994) indicated that oesophageal ulcers of viral, mycobacterial and neoplastic varieties were known to affect food intake. Anorexia may be a side effect of various medications. It is also known that neurological disease may impair appetite or produce swallowing disorders. There is also evidence that unabsorbed micronutrients such as vitamin A, zinc and iron in the lower bowel (ileum and colon) are associated with signals that decrease appetite (Hecker and Kotler, 1990).

Repletion of body cell mass through effective treatment of disease and by proper nutrition is an important consideration, although repletion is difficult, if not impossible, in patients with untreated serious disease complications (Watson, 1994).

Weight loss and lean body mass: The importance of this progressive condition has been reinforced by the expansion of the AIDS case definition to HIV Wasting Syndrome by the Centers for Disease Control and Prevention (Watson, 1994). Weight loss as well as low serum albumin levels are predictive of an increased risk of morbidity and mortality in hospitalized patients. Studies have established that the frequency of complications from malnutrition increases sharply when serum albumin levels fall below 30 g L^{-1} (Trujillo *et al*., 1992; Babamento *et al*., 1994; Macallan, 1998).

HIV/AIDS patients typically lose 46% of their potassium by the time of death and this potassium is lost over the last nine months of life. The patients also lose 34% of their ideal body weight during the last 4 to 5 months prior to death (Babamento *et al*., 1994).

In a study reported by Watson (1994), lean body mass (estimated from the potassium pool) was greater than the loss in body weight. The amount of lean body mass is sufficient in itself to be the cause of death. World War 2 era starvation studies point out that loss of less than 40% of body weight resulted in death (Watson, 1994). Studies of body composition in AIDS patients demonstrate that body cell mass depletion is out of proportion to losses of body weight or fat and findings indicated that nutritional support can improve the nutritional status of HIV/AIDS patients (Watson, 1994; Piwoz and Preble, 2000).

Relationship between HIV/AIDS and malnutrition: The epidemiology of malnutrition and of infectious diseases is intermingled particularly in impoverished communities in the Third World (Maletnlema, 1991; Scrimshaw and SanGiovanni, 1997). The relationship between HIV/AIDS and malnutrition presents a classical example of the well-recognized vicious cycle of immune dysfunction, infectious diseases and malnutrition. Changes in the immune function due to malnutrition are strikingly similar to those induced by HIV/AIDS. In fact, for many years, the impairment to immune function caused by malnutrition has been referred to as the Nutritional Acquired Immune Deficiency Syndrome or NAIDS (Savage and Burgess, 1995; Piwoz and Preble, 2000). Since normal immune function is dependent on good nutritional status, some researchers have come forward with the hypothesis that malnutrition is the predominant underlying cause for the full clinical expression of AIDS in HIV-seropositive persons (Maletnlema, 1991; Piwoz and Preble, 2000). According to these authors, inadequate nutrition may influence specific systems involved in the progression from asymptomatic HIV infection to the full-blown condition of AIDS, as well as intensify the susceptibility to opportunistic infections and may also contribute to the severity of HIV-related disease (Kelly *et al*., 1999). Malnutrition has clinical and social implications and is thus examined below.

Clinical implication: Long before the AIDS epidemic emerged in Africa in the early 1980s, the synergistic interactions between infections, nutritional status and immune function were recognized. Infectious diseases, no matter how mild, influence nutritional status and conversely, almost any nutrient deficiency, if sufficiently severe, will impair resistance to infection (Scrimshaw and SanGiovanni, 1997). The physical environments contain infectious microbes including viruses, bacteria and fungi. These are often more prevalent in Africa than in industrialized countries. In healthy individuals, the immune system protects the body from damage by these microbes. It has been noted that people with HIV/AIDS, whose immune systems are compromised, have difficulty in resisting a variety of serious infections (Piwoz and Preble, 2000). HIV acts by replicating inside host cells. To eliminate the infection, the immune system must recognize and destroy these infected cells. The cells that mediate immunity include lymphocytes. Among the lymphocytes, $CD4^+$T-cells (also called T4 cells and T-helper cells) are critical to the immune system functioning. HIV infection destroys $CD4^+$T-cells and leads to a deterioration of the overall immune system (Chandra, 1997; Martin, 2000; Bouic *et al*., 2001; Fawzi, 2003).

Infections affect nutritional status by reducing dietary intake and nutrient absorption and by increasing the utilization and excretion of protein and micronutrients

as the body mounts its acute phase response to invading pathogens (Maletnlema, 1991; Chandra, 1997). Infections also result in the release of pro-oxidant cytokines and other reactive oxygen species. This leads to the increased utilization of anti-oxidant vitamins, for example vitamins E, C and beta-carotene as well as sequestration of several minerals that are used to form anti-oxidant enzymes (Friis and Michaelsen, 1998).

Social implication: Malnutrition associated with HIV infection has serious and direct implications for the quality of life of people living with HIV and AIDS (Watson, 1994; Chandra, 1997). Weight loss is often the event that begins a vicious cycle of increased fatigue and decreased physical activity, including the inability to prepare and consume food (Norse, 1991; Babamento and Kotler, 1997; Fawzi and Hunter, 1998).

Malnutrition associated with HIV/AIDS affects entire families and their dependants and they require continuous care during bouts of illness. In parts of Africa where farming is a primary occupation and nutritional requirements are usually met through local food production, HIV/AIDS among agricultural workers is affecting farm incomes, food productivity and nutritional status (Babamento and Kotler, 1997).

Nutritional consequences of HIV infection in HIV/AIDS patient: To understand the relationship between nutrition and HIV/AIDS, one must consider the effect of the disease on the body size and composition (weight, lean body mass and body cell mass) as well as the effect on the functioning of the immune system. Nutrition plays a role in each of these conditions. One must also keep in mind that malnutrition may be a contributor to HIV disease progression as well as a consequence of the disease (Baum *et al*., 1995; Babamento *et al*., 1994; Beck, 2000; Piwoz and Preble, 2000). In populations in which malnutrition is endemic, body size and composition changes associated with protein-energy malnutrition may always be associated with deficiencies in vitamins and minerals which are important for the functioning of the immune system.

The wasting syndrome typically found in adult AIDS patients in Africa is a severe nutritional manifestation of the disease (Babamento *et al*., 1994). It has been noted that weight loss typically follows two patterns in people living with HIV/AIDS: slow and progressive weight loss from anorexia and gastrointestinal disturbances and rapid, episodic weight loss from secondary infections. Observations have also shown that even relatively small losses in weight (5%) have been associated with decreased survival in individuals with AIDS (Boelaert *et al*., 1996; Castaldo *et al*., 1996; Macallan, 1999). Research studies have shown that weight loss and wasting in HIV/AIDS patients may develop as a result of three major overlapping processes (Babamento *et al*., 1994; Keating *et al*., 1995; Macallan, 1999). These major overlapping processes are discussed below.

Reduction in food intake: This may be due to painful sores in the mouth, pharynx and oesophagus. Some data have shown that fatigue and depression, including changes in mental state, may also play a significant role by affecting appetite and interest in food (Babamento *et al*., 1994). Reductions in food intake are believed to be an important cause of slow and progressive weight loss (Abrams *et al*., 1993; Macallan, 1999).

Nutrient malabsorption: Malabsorption that accompanies frequent bouts of diarrhoea due to intestinal parasites and other pathogens has been reported in people with HIV/AIDS. Some HIV-infected individuals have demonstrated increased intestinal permeability and other intestinal defects in early infection (Keating *et al*., 1995; Macallan, 1999). Malabsorption of fats and carbohydrates has been found to be common at all stages of HIV infection in both adults and children (Semba and Tang, 1999). It has been pointed out that fat malabsorption, in turn, affects the absorption and utilization of fat-soluble vitamins.

Metabolic alterations: Changes in metabolism occur during HIV infection from severe reduction in food intake as well as from the immune system's response to the infection. When food is restricted, the body responds by altering insulin and glucagon production that regulate the flow of sugar and other nutrients in the body (Cimoch, 1997). Over time, the body uses up its carbohydrate stores from muscle and liver tissue and then begins to break down body protein to produce glucose. This process could cause protein loss and muscle wasting (Grimble, 1990; Babamento and Kotler, 1997; Cimoch, 1997).

Existing studies suggest that infections result in a loss of 0.6 to 1.2 g of protein per kilogram body weight per day in adults when amino acids are mobilized from skeletal muscle for gluconeogenesis, synthesis of immune proteins and enzymes in response to the release of cytokines (Fawzi and Hunter, 1998). For these reasons, protein requirements are substantially higher in HIV-infected individuals than in non-HIV-infected persons (Fawzi and Hunter, 1998; Scrimshaw and SanGiovanni, 1997).

Relevance of nutritional factors to the progression of HIV infection: The host's response to infection and inflammatory stimuli is mediated by cytokines (Haynes *et al*., 1996; D'Souza and Harden, 1996). Cytokines are a range of polypeptides that have multiple biological activities including enhancing the attraction, proliferation, activation and differentiation of white blood cells, as well as mediating a wide range of metabolic alterations (Grimble, 1990). Cytokine production and actions are affected by malnutrition (Grimble, 1990; Cimoch, 1997; Moore *et al*., 1997). Abnormalities in cytokine production characterize HIV infection. Impaired cellular anti-oxidant status has been identified as a consistent prominent feature of protein-energy malnutrition and other forms of malnutrition. This may play a key role in the rapid replication of HIV in malnourished individuals (Enwonwu, 1992; Semba *et al*., 1998; Piwoz and Preble, 2000). It has been demonstrated that in a chronically HIV-infected T lymphocyte cell line, non-toxic concentrations of ascorbate in the cell culture medium reduces the level of extra-cellular reverse transcriptase by 99% and the expression of p24 antigen by 90% (Harakeh *et al*., 1990).

The role of vitamins and minerals in HIV/AIDS patients: Many vitamins and minerals (also referred to as micronutrients) are important to the HIV/nutrition relationship due to their critical roles in cellular differentiation, enzymatic processes, immune system reactions and other body functions (Fawzi and Hunter, 1998). The role of micronutrients in other infectious diseases such as measles, diarrhoea and respiratory infections has been extensively studied and it is known that several vitamins and minerals are required by the immune system and major organs to fight infectious pathogens (Fawzi and Hunter, 1998; Semba and Tang, 1999). Persons with inadequate intakes, blood levels or body stores of these micronutrients have difficulty in resisting infection. As a result, the role of micronutrients in HIV/AIDS is of special importance in individuals and populations with marginal or low micronutrient intakes (Friis and Michaelson, 1998). This applies to most AIDS-affected Africans and, as already noted, micronutrient deficiency is endemic (Piwoz and Preble, 2000).

Studies in both industrialized and developing countries have confirmed that HIV-infected individuals have decreased absorption, excessive urinary losses and low blood concentrations of vitamins A, B_1, B_2, B_6, B_{12}, C, E, as well as of folate, beta-carotene, selenium, zinc and magnesium (Tang and Smit, 1998). At present, it is not known whether these deficiencies are independent markers of disease progression resulting from a compromised immune system, or whether they are causally related to the development or exacerbation of symptoms of HIV/AIDS. This distinction is important in order to determine whether nutritional therapy and management can retard or alter the course of the disease.

Selected micronutrients and HIV disease progression and mortality: Review studies published by Tang and Smit (1998), Fawzi and Hunter (1998), Baum and Shor-Posner (1998) and Semba and Tang (1999), have concluded that micronutrient deficiencies associated with HIV infection vary across populations and according to the disease stage are associated with an accelerated progression of HIV infection to AIDS and are predictive of AIDS related mortality. Micronutrient supplementation, unlike many other AIDS treatments, has the potential in Africa to be an affordable and relatively easy way to deliver a public health measure. The roles of specific micronutrients in HIV disease progression and mortality and findings from published intervention trials are summarized below.

Vitamin A: Of all the micronutrients, the role of vitamin A in HIV infection has received the greatest attention in Africa. This is because of its well-known role in affecting child morbidity and mortality as well as early observations that vitamin A status was associated with increased risks of mother-to-child-transmission (MTCT) of HIV (Semba *et al*., 1994); with HIV viral load in breast-milk and vaginal secretions (Nduati *et al*., 1995; John *et al*., 1997) with progression to AIDS (Tang *et al*., 1993, 1996); with adult survival (Semba *et al*., 1994; Semba, 1997) and with infant morbidity (Coutsoudis *et al*., 1995) and mortality (Dushiminana *et al*., 1992). The potential for vitamin A supplementation to impact positively the course of HIV/AIDS is worth pursuing since vitamin A is beneficial in HIV-negative populations, is inexpensive and is relatively easy to administer with minimal side effects, however megadose can be dangerous to health (Semba *et al*., 1994; Nduati *et al*., 1995).

Vitamin A deficiency may be caused by insufficient dietary intake of vitamin A-rich food, malabsorption, impaired storage (because of liver disease) and/or increased utilisation or urinary loss of vitamin A during acute and chronic infection (Semba, 1997). Vitamin A deficiency causes growth retardation and xeropthalmia and increases the incidence and/or severity of many infections. While vitamin A deficiency is relatively rare among HIV-negative adults in industrialized countries, up to one-third of HIV-positive adults in industrialized

countries may be vitamin A deficient (Kennedy *et al*., 2000). The percentage incidence of vitamin A deficiency in HIV-positive people in developing countries, including Africa, is reported to be higher (Nimmagadda *et al*., 1998).

Vitamin E: Vitamin E is necessary for the proper functioning of the immune system and it increases humoral and cell-mediated immune responses, including antibody production, phagocytic and lymphocytic responses and resistance to viral and infectious diseases (Odeleye and Watson, 1991; Watson, 1994). The oxidative stress created by HIV and related opportunistic infections increase the utilization of antioxidant vitamin E, possibly leading to deficiency. Vitamin E deficiency, in turn, further debilitates the immune system because of its role in immune stimulation and functioning, leaving people with HIV/AIDS more susceptible to opportunistic infections (Piwoz and Preble, 2000).

Studies in the USA found that high baseline serum vitamin E levels were associated with decreased HIV progression after taking into account HIV-related symptoms, $CD4^+$T cell count, age and other confounding variables (Tang *et al*., 1997). Individuals with serum vitamin E levels greater than or equal to 23.5 mmol L^{-1} took 34% longer time to develop AIDS compared with those with low serum vitamin E levels (Tang *et al*., 1997). Another study in Canada found that three months of supplementation with vitamin E (800 IU) and vitamin C (1000 mg) significantly reduced oxidative stress and HIV viral load (Allard *et al*., 1998). A study in Zambia among AIDS patients suffering from persistent diarrhea found that vitamin E deficiency at enrolment predicted mortality in the following month (Kelly *et al*., 1999).

Vitamin C: Research studies have suggested that at high doses (greater than 1000 mg), vitamin C has a unique pharmacological function, displaying the potential to serve as an antioxidant and primary source of electrons under conditions of drug-induced glutathione (GSH) deficiency or severe free-radical toxicity (Cathcart, 1991; Martenson and Meister, 1991; Semba and Tang, 1999). Due to the fact that antioxidant depletion and a chronic scorbutic-like state are associated with HIV/AIDS, metabolic functions of vitamin C essential for preventing these conditions in healthy subjects are potentially relevant to the control and management of such conditions in persons with HIV infection and AIDS (Watson, 1994).

HIV/AIDS patients manifest striking GSH deficiencies and often exhibit symptoms of acute-induced scurvy characterized by life-threatening weight loss, brittle bones and swollen glands (Cathcart, 1991). It has been reported that GSH deficiency can result from changes in dietary vitamin C intake. Volunteers fed controlled diets containing vitamin C at levels lower than the recommended daily allowance (60 mg dL^{-1}) had decreased concentrations of GSH in blood plasma (Watson, 1994). Administration of an ascorbate repletion diet (250 mg dL^{-1}) in the same study resulted in restoration of the plasma GSH level (Martensson and Meister, 1991; Watson, 1994). It has been pointed out that at high concentrations (obtained through supplementation), vitamin C can act directly to scavenge free radicals as well as convert oxidized forms of non-enzymatic scavengers (tocopherol and GSH disulphide) to their reduced states. Under these conditions, vitamin C functions as a direct source of high energy electrons, saves GSH and acts as an essential antioxidant in the presence of GSH deficiency (Watson, 1994; Martensson and Meister, 1991). Cycles of reactive oxygen intermediate production in HIV-infected persons may induce them to consume free-radical scavengers at an increased rate, leading to the depletion of vital antioxidants in the body.

Vitamin C: Immune function and antibacterial effects: Vitamin C has been found to affect immune function in several ways. It can stimulate the production of interferons, the proteins that protect cells against viral attack. It can stimulate the positive chemotactic and proliferative responses of neutrophils. It has also been shown that vitamin C can stimulate the synthesis of the humoral thymus factor and antibodies of the IgG and IgM classes (Flodin, 1988). Vitamin C deprivation reduces overall complement activity as adequate vitamin C has been found to play an important role in stimulating the C1q biosynthesis. Watson (1994) showed that vitamin C was effective in the inactivation of a wide range of pathogenic bacteria including *Staphylococcus aureus*, *Escherichia coli* and haemolytic *Streptoccoccus* species.

Antiviral action of vitamin C: A striking property of vitamin C is its ability to inactivate viruses and inhibit viral growth in their host cells. Vitamin C has been shown to suppress the human retrovirus expression in immortalized and transformed lymphocytic cell lines (Watson, 1994). It has been further proved that vitamin C is capable of inhibiting HIV replication in both chronically and acutely infected T cell lines in the absence of inducing agents, indicating that the compound (vitamin C) can directly interfere with specific steps in retrovirus replication in differentiated lymphocytic cells (Watson, 1994).

Vitamin B_{12}: Vitamin B_{12} deficiency is relatively uncommon in healthy, non-vegetarian populations. However, many studies of people with HIV in the USA reported low serum B_{12} levels even among asymptomatic persons. Low serum B_{12} levels are associated with neurological abnormalities, for example, neuropathy, myelopathy; impaired cognition; reduced $CD4^+$T-cell counts, increased bone marrow toxicity and increased mortality (Tang and Smit, 1998). A 9-year study among homosexual and bisexual men with HIV/AIDS in the USA found that men with low serum B_{12} at enrolment (<120 pmol L^{-1}) had significantly shorter AIDS-free survival times than men with adequate B_{12} (Tang *et al*., 1997). Another study of USA men found that improvements in B_{12} levels were associated with increases in $CD4^+$T cell count. No studies of vitamin B_{12} and HIV/AIDS in Africa have been identified (Baum *et al*., 1995).

Folic acid (folate): Folic acid works closely with vitamin B_{12}, but its role in HIV/AIDS remains unclear. Folic acid is required for the enzymes that produce DNA for replicating and growing cells, including those of the gastrointestinal (GI) tract, blood and growing foetus. Deficiency results in impaired cell division and protein synthesis, causing megaloblastic anaemia. If the GI tract is damaged as is common in HIV-related diarrhoea, folic acid reabsorption may be impaired, setting off a cycle in which deficiency results in further GI tract deterioration and malabsorption of other nutrients (Piwoz and Preble, 2000).

Nutritional support for HIV-positive/AIDS patients: As already pointed out, the nutritional status of HIV-positive/AIDS patients is frequently compromised. There is documented evidence that malnutrition will occur at some point in the disease process for more than 95% of patients (Levy, 1989; Fawzi and Hunter, 1998). About 65% will experience malabsorption; 95% will have significant weight loss, while about 90% will have oral or oesophageal infections. This may affect food intake (Levy, 1989). Molina (1989) reported a significant reduction in the life-span of HIV-infected patients who had a serum albumin level below 2.5 mg dL^{-1}, whereas a serum albumin level of greater than 3.0 mg dL^{-1} has been associated with prolonged life span and decreased morbidity. Although data to date, especially in Africa, are limited in this aspect, retrospective data support the role of improved nutritional status and prolonged life with reduced morbidity.

Many HIV-infected patients have demonstrated improved quality of life (increased activity, increased ability to perform activities of daily living, prolonged employment) after adequate provision of nutritional support (Rosenberg and Fauci, 1990; Oguntibeju *et al*., 2004a, b). The corner-stone of nutritional support is the nutritional status assessment. The impact of nutritional interventions usually depends on the underlying nutritional status of the individual concerned. If a nutritional supplement is given to correct a deficiency, it is more likely to have an impact than when it is given to persons who are nutritionally replete (Watson, 1994).

Nutritional intervention in early HIV disease: The Physicians Association for AIDS Care (1992) and Task Force on nutritional support in AIDS (1989), have established guidelines for nutritional support in early HIV infection which focus on improving oral intake by means of nutrient-dense food supplements and vitamin supplementation. It is suggested that counselling on nutrient selection and food preparation should begin and be periodically reinforced. This, it is believed, will establish a strong link between nutrition and HIV infection in the mind of the patient and health personnel that will alert both parties to more aggressive nutritional intervention when needed later. An optimal strategy would include measurements of energy expenditure and body composition to further the awareness of nutritional changes (Watson, 1994).

Nutritional interventions in latent HIV disease: During this stage of the illness, HIV is deceptively dormant in lymphoid and macrophage reservoirs (Pantaleo *et al*., 1993). However, evidence of ongoing viral replication and immune dysfunction is abundant, as follicular dendritic cells trap HIV particles and follicular lymph hyperplasia proceeds with subsequent activation of germinal B-cells and elaboration of interferon alpha (Pantaleo *et al*., 1993).

It is documented that $CD4^+$ T-cell levels fall at this stage by apoptosis and more rapid progression may occur by syncytia formation (Pantaleo *et al*., 1993). At this stage the Nutritional Task Force on AIDS (1992) and the Physicians Association for AIDS Care (1989) have established that enteral feeding supplementation be initiated with an intact formula. Although this present study does not focus directly on enteral feeding, it does agree with other authors on the importance of nutrition in the management of HIV infection. If augmented intake cannot be achieved or if weight loss continues despite enteral supplementation, assessment of the mucosal absorptive function must be undertaken. Efforts to stimulate the appetite with mesgesterol acetate or other stimulating agents have led to an increase mainly of fat

weight. Again, a multiple strategy may be needed at this stage that provides adequate nutrients along with pharmacological interventions aimed at modifying the metabolic abnormalities driven by cytokines (Vonroenn *et al*., 1998).

Nutritional intervention in late HIV disease: As viral replication continues in lymphoid and macrophage reservoirs, destruction of the follicular dendritic cells in the germinal center occurs, leading to lymphocyte depletion and massive viraemia as the antigen presentation FDC cells degenerate in an accelerated mode related to a lack of cytotoxic activity (Pantaleo *et al*., 1993). It is known that cytokine activity continues but is propelled by the appearance of opportunistic pathogens. Opportunistic or secondary infections abound and account for most of the digestive and nutritional malfunction (Lahdevirta *et al*., 1998). It is not until this very advanced stage that too many clinicians finally appreciate that there are nutritional problems with the patients. Body weight falls below its usual pre-illness weight by 20% and lean body mass simultaneously loses proportionately by another 10-15% (Kotler *et al*., 1989). Kotler *et al*. (1989) have established that death in these patients occurs from malnutrition. Although the Kotler *et al*. (1989) observation is subjective, it does point to the fact that malnutrition plays a significant role in HIV disease progression and death of the patients.

Importance of supplementation in HIV/AIDS patients: The provision of sufficient food and nutrition to meet people's basic needs for health, growth and development has been a long-standing challenge for African people. This challenge is further exacerbated by the emergence of HIV/AIDS. Several vitamins and minerals are critical for fighting HIV infection because they are required by the immune system and major organs to attack infectious pathogens. Research has shown that in the early period of HIV infection, weight gain or maintenance might be achieved through nutrition and has helped to reduce the consequences of wasting in people living with HIV/AIDS (Friis and Michaelsen, 1998; van Staden *et al*., 1998; Oguntibeju *et al*., 2005a, b).

With HIV/AIDS, being a disease of the immune system, new strategies, including specific dietary nutrients to improve immune functions, quality of life and prolong survival in infected individuals, could provide additional or alternative approaches for improving the health of HIV infected individuals. This strategy could also be used in establishing immunity in healthy uninfected persons (Fawzi and Hunter, 1998).

The aims of nutritional intervention in HIV/AIDS patients are: (a) to minimize loss of lean body mass; (b) to prevent vitamin and mineral deficiencies; (c) to surmount obstacles to nutrient intake and absorption and (d) to prevent or moderate the use of nutritional approaches that may not enhance the well-being of the patients (Woznicki and D'Alessandro, 1997). It is important for healthcare professionals caring for HIV-infected individuals to understand the relationship between nutrition, HIV infection and the immune system. Many clinicians support the use of dietary supplements by people living with HIV/AIDS (Baum, 1992; Abrams *et al*., 1993; Fawzi and Hunter, 1998; Oguntibeju *et al*., 2003b).

Studies have shown that even people who eat good food are likely to have vitamin and mineral deficiencies when infected with HIV (Cimoch, 1997). For instance, zinc, selenium, magnesium, carotenoids, vitamins A, E, C, B_2, B_6 and B_{12} have all been found to be low in HIV-infected subjects. This can happen before visible sickness and the development of AIDS (Woznicki and D'Alessandro, 1997; Oguntibeju *et al*., 2003c). The recommended daily allowance of vitamins and minerals is most often not sufficient for people living with HIV/AIDS. Supplementation has been shown to slow disease progression significantly (Semba and Tang, 1999).

In the developing world, in which the majority of the people cannot afford antiretroviral therapy, good nutrition, combined with minerals and vitamins form a strategy to improve the overall health of HIV infected individuals. From the mid 1980s until 1990, multiple deficiencies of vitamins and minerals were documented in people living with HIV/AIDS (Macallan, 1999). Although at this time no aggressive supplementation was recommended, a report by FDA, USA (1995), suggested that supplementation of vitamins and trace minerals once or twice the recommended daily allowance (RDA) might offset possible deficits and contribute to meeting increased requirements during hypermetabolic states. In addition, Dwyer *et al* (1998) reported that multivitamin supplements might be helpful for debilitated AIDS patients who suffer from malabsorption. Malnutrition is almost universal among people living with HIV/AIDS, hospitalized or not, largely because of AIDS-related malabsorption. Malnutrition favours opportunistic infections and contributes to wasting (Cimoch, 1997; Macallan, 1999), making supplementation an important aspect in the management of people living with HIV/AIDS.

There have been an increasing number of reports documenting multiple micronutrient deficiencies in HIV-infected/AIDS persons in the absence of proper and

adequate supplementation. There have also been increasing recommendations for supplementation in this group of people (Watson, 1994; Macallan, 1999; Oguntibeju *et al*., 2005c). In pursuance of this goal, members of the Physicians Association for AIDS Care have repeatedly emphasized the importance of supplementation. They carried their concern and objectives with emphasis to the third international symposium on nutrition and HIV/AIDS where they reiterated the importance of supplementation for people living with HIV/AIDS. Research has indicated that HIV-related dementia may be prevented or controlled through good nutrition. Observations from published research studies suggest that many of the negative effects of protein calorie malnutrition (PCM) may be directly or indirectly related to a deficiency of trace elements (Piwoz and Preble, 2000; Young, 1997). Baum (1992) recommended supplementation with vitamins A, C, E, the B vitamins and minerals such as zinc, magnesium and selenium. It was also at about this time that further research documenting the benefits of supplementation became available.

Abrams *et al.* (1993) published the results from two-six year epidemiological studies, one of which was a study of 296 men: a prospective study of dietary intake and AIDS in homosexual men. The authors observed that higher intake of all eleven micronutrients investigated was associated with a higher $CD4^+$T-cell count; daily use of multivitamin was associated with a reduced risk of AIDS and a significantly reduced risk of a low $CD4^+$T-cell count. In addition, there is increasing evidence that micronutrient supplementation is associated with the absence of, or reduced deficiencies and promotes clinical stability (Oguntibeju *et al*., 2006).

CONCLUSIONS

It is known that malnutrition acting in concert with other factors including viral replication and host genetic factors influence disease progression, therefore, nutritional intervention to prevent or reverse weight loss and wasting with HIV infection may help to preserve independence, improve quality of life and prolong survival. Micronutrient intervention may help to strengthen the immune system and reduce the severity and impact of opportunistic infections in people living with HIV/AIDS. Some nutritional imbalances may directly affect HIV viral replication. Correcting these imbalances may also help to slow HIV disease progression and prolong survival.

More research is essential to determine the dosage of various micronutrients for use by HIV/AIDS patients. Likewise, more defined roles of nutritional supplementation in immune response and in the management of HIV/AIDS patients need to be examined. Research studies are particularly needed in Africa to examine in detail the relationship between nutrition and immune system and the role of nutritional intervention in the management of HIV/AIDS. Africa is experiencing HIV crisis especially with the inability of most African government to provide antiretroviral therapy for the citizens who are less affluent economically.

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