REVIEW ARTICLE

Nutrition and HIV infection

Julie R. Lustig

Senior Research Fellow, Nutrition and HIV Project, Monash University Department of Medicine, Monash Medical Centre, Melbourne, Australia.

Nutritional status may have an impact at all stages of HIV disease. Many of the clinical features of HIV infection cause nutritional problems and may also be exacerbated by the presence of malnutrition. Inadequate food intake, due to a wide variety of aetiologies, malabsorption and altered metabolism, may all contribute to malnutrition. Additionally, factors in food, including micronutrients, can modulate immune function. Reduced micronutrient levels are documented at all stages of HIV infection although the significance of these findings and how they may relate to HIV disease severity and prognosis are still unclear. Body composition changes in adults include loss of weight with proportionately greater loss of lean mass. Paediatric HIV infection has received far less research attention, but growth failure is a significant nutritional complication seen clinically. Clinical experience suggests that early nutritional intervention may improve prognosis as well as quality of life. Nutritional management in HIV disease depends on the clinical state of the patient. Definition of the benefits of particular food factors and diets, as well as the most appropriate nutrition support modalities, would allow rational nutritional counselling. Better definition of the contribution food makes to health through its social role, and the opportunities this provides in patient care, would complement the biomedical research effort.

Introduction

Nutritional abnormalities are a frequent and characteristic feature of infection with human immunodeficiency virus (HIV) and represent a major determinant of survival[1–3] Nutritional status may have an impact at all stages of HIV disease from initial acquisition of infection, clinical manifestations, progression of the disease and palliation of advanced disease. Factors such as dietary intake, metabolic changes and absorptive capacity may all contribute to nutritional problems, as can factors such as psychological state, social supports and ethnicity.

HIV infection: an overview

HIV is a retrovirus that targets cell-mediated immunity by destroying a subset of T-lymphocytes with a CD4 molecule on the cell surface. HIV is transmitted by contact with infected body fluids which may occur by unprotected sexual contact, sharing contaminated injecting equipment, transfusion of contaminated blood or blood products or occupational exposure such as a needle-stick injury. Vertical transmission may occur from mother to child during pregnancy, childbirth or breast-feeding[4].

Following infection, progressive decline in immune function leads to the development of the manifestations of acquired immune deficiency syndrome (AIDS). The Centers for Disease Control[5] have defined a staging system for the classification of HIV infection in adults (Table 1).

Table 1. Classification of HIV infection*

• Group I	Acute infection
• Group II	Asymptomatic
• Group III	Persistent generalized lymphadenopathy
• Group IV	Subgroup A – constitutional disease
	Subgroup B – neurological disease
	Subgroup C – secondary infectious diseases
	Subgroup D – secondary cancers
	Subgroup E – other conditions

Source: Centres for Disease Control, USA 1987[5]
*Group IVA is also referred to as AIDS-Related Complex (ARC) and Group IVB, C, D, E may be referred to as Acquired Immune Deficiency Syndrome (AIDS).

It is currently unclear how many people infected with HIV will eventually develop AIDS. The San Francisco Clinic Cohort Study suggested that 48% of those infected with HIV would develop AIDS within 10 years[6]. Since that study was published, the widespread use of antiretroviral medications and more effective prophylactic regimes has probably lengthened that time span considerably[7]. Cofactors that influence the progression of asymptomatic HIV infection to development of AIDS are poorly understood. Cofactors that have been suggested include co-infection with cytomegalovirus[8] or other sexually transmitted diseases (particularly ulcer-

Correspondence address: Dr Julie Lustig, Department of Medicine, Monash Medical Centre, 246 Clayton Road, Clayton, Victoria, Australia 3168. Fax 61–3–550 5524

ative diseases)[9]. Lifestyle factors such as stress[10], drug use[11] and nutritional factors could also be important cofactors in progression.

As the AIDS pandemic enters its second decade and case numbers continue to increase, no definitive cures have been found nor has an effective vaccine been developed. It is time to examine other approaches to reducing the illness burden. Improvement in nutritional status may be one such approach.

Nutritional factors in the expression of HIV

The interaction between nutritional status and increased disease susceptibility is well known[12]. Many of the immunological abnormalities seen in HIV infection are very similar to those seen in malnutrition and in single nutrient deficiencies[13,14]. An interaction between nutrient deficiencies and HIV-induced immune deficiency has been proposed[13]. Reduced mucosal defences secondary to zinc deficiency has been suggested as one way in which malnutrition may interact with HIV acquisition[15]. There has been no formal study of such hypotheses to date.

Pathogenesis of wasting

The mechanisms that cause wasting in HIV infection are complex. They include: inadequate intake (due to anorexia, pain, other many factors), altered metabolism (increased energy expenditure or a maladaptive response to hypocaloric state), and malabsorption (failure to absorb ingested nutrients).

Inadequate intake

Anorexia. Anorexia (reduced desire to eat) is an important factor in weight loss and is a common symptom in HIV infection. However, when actual food intake is measured, there are conflicting reports of the adequacy of nutrient intake[16-19]. Other factors which may be involved in reduction in food intake include:

Gastrointestinal manifestations. Infection or malignancy in HIV infection can affect any organ in the gastrointestinal tract. Oral and oesophageal lesions (*Candida sp; Herpes simplex; Cytomegalovirus*, Kaposi's sarcoma; lymphoma, aphthous ulceration) may cause pain, haemorrhage or obstructive lesions[20,21]. Diarrhoea is a common gastrointestinal symptom in AIDS, reported in up to 90% of all AIDS patients[22]. Fear of exacerbation of symptoms is commonly cited as a cause for decreased food intake in those with diarrhoea.

Pharmacotherapy. Most of the medications used in treatment or prophylaxis of HIV infection can affect food intake by causing nausea, anorexia and taste changes as well as causing side-effects, such as sedation or pancreatitis, which can adversely affect nutritional state[23,24] (Table 2).

Psychosocial effects. Depression and anxiety can adversely affect food intake, as can reduced financial resources for those unable to work[25]. Illness may affect the physical ability to prepare and purchase food and lack of social support may further exacerbate these problems.

Table 2. Drugs with side-effects adversely affecting nutritional status

• Abdominal pain (pancreatitis)	Didanosine (ddI); dideoxycytidine (ddC)
• Drowsiness	Benzodiazepinies, morphine, codeine, haloperidol, amitryptyline, metoclopramide
• Dry Mouth	Amitryptyline, diphenoxylate with atropine, prochlorperazine
• Fever	Amphotericin, bleomycin, sulphamethoxazole-trimethoprim
• Hyper/hypoglycemia	Pentamidine
• Hypokalaemia	Amphotericin, piperacillin
• Hypomagnesemia	Amphotericin
• Nausea, Vomiting	Aminosalicylic acid, amphotericin, bleomycin, clindamycin, clotrimazole, dapsone, didanosine (ddI), doxorubicin, ethambutol, 5-flucytosine, ganciclovir, isoniazid, ketoconazole, loperamide, metronidazole, nystatin, pyrimethamine, sulphamethoxzole-trimethoprim, opiates, vinblastine, zidovudine (AZT)
• Paralytic ileus	Vincristine
• Retrograde amnesia	Benzodiazepines
• Sore throat	Aminosalicylic acid
• Stomatitis	Bleomycin, doxorubicin, vinblastine, ddC
• Taste alterations	Clotimazole, pentamidine, metronidazole, nystatin

(Adapted from: Bowden[23], Wong[24])

The social support systems of an HIV-infected individual are often fragmented, with many potential supporters being HIV-infected themselves. This may further undermine the practical support that can be provided.

Central nervous system manifestations of AIDS. Pathologic abnormalities in the CNS have been reported in 75–90% of patients who died of AIDS[26,27]. Cognitive dysfunction is also common[28]. Immune deficiency may result in opportunistic infections of the CNS and malignancies causing specific neurologic dysfunction. Direct involvement of the brain with HIV can result in AIDS dementia complex[29], typically causing problems of psychomotor slowing, poor concentration, forgetfulness and social withdrawal. All of these symptoms may undermine the ability of the person to maintain adequate nutrition.

Micronutrient deficiencies such as thiamin or vitamin B_{12} may conceivably contribute to cognitive dysfunction in HIV infection[30-32]. These may represent treatable causes of so-called dementia, though no research has been done in this area.

The role of cytokines. The cytokines interleukin-1 (IL-1) and tumour necrosis factor (TNF) have been shown to be anorexigenic in rats[33]. Elevated levels of TNF have also been measured in patients with AIDS[34], but no relationship between the degree of weight loss and the levels of circulating TNF was found. The elevations in TNF may have been related to intercurrent infections: subsequent studies have failed to demonstrate elevated TNF in AIDS[35,36].

Intriguingly, it has been suggested that not only is cytokine release altered in HIV infection, but that TNF and possibly other cytokines can themselves activate HIV replication[37]. Cytokines may thus occupy a central role not only in the pathogenesis of AIDS, but also in the

wasting and inflammatory response often seen in HIV disease.

Altered metabolism

Hypermetabolism (raised basal energy expenditure – BEE) is commonly found in the cachexia of fever or malignancy[38]. As febrile illnesses and malignancies are common in infection with HIV, an elevation in BEE would be expected in people with this disease. Even in the absence of sepsis or malabsorption, studies have demonstrated elevated BEE in both asymptomatic and advanced HIV infection[35,39-41]. An undetermined role for cytokines in this phenomenon has been suggested[35,39,40]. Grunfeld's group[41] postulated that some of the elevation in BEE could be explained by undetected opportunistic infections, but as elevated BEE was also present in asymptomatic subjects, they suggested that some of the BEE elevation could be related to the underlying HIV infection itself.

In contrast to the homeostatic adaptations to energy deficiency states observed in normal subjects, there is a maladaptive response seen in infection and inflammation[19]. Responses such as inhibition of ketosis, increased pyruvate oxidation, and failure to decrease the percentage of energy expenditure represented by protein oxidation, have been observed in septic catabolic states. In HIV infection, alterations in lipid metabolism have been observed[42]. No correlations were found between elevated triglyceride levels and body cell wasting. Several metabolic changes appear to contribute to the hypertriglyceridaemia seen in HIV infection. Firstly, there is an increase in de novo hepatic lipogenesis[42] and secondly, clearance of triglycerides is reduced due to inhibition of lipoprotein lipase activity[43]. These changes in lipid metabolism probably only account for a small amount of inappropriate energy use and do not fully explain wasting in HIV infection[43].

Notwithstanding the studies reviewed here, the role of hypermetabolism remains poorly understood. Many HIV-infected individuals are able to maintain constant body weight for long periods of time without significant increases in food intake. Clearly in some patients an adaptation occurs compensating for metabolic changes. The mechanisms whereby this can occur still need to be explored.

Adrenal insufficiency is an uncommon, but treatable, cause of wasting in AIDS patients. It has mostly been described as a consequence of cytomegalovirus infection of the adrenals[44].

Malabsorption

Malabsorption is common in HIV infection. Aetiologies include infections, malignancy, pancreatic disease and pharmacotherapy.

Infectious causes. HIV has been demonstrated in the small and large intestinal mucosa of patients with AIDS[45–48]. Detection of the virus does not necessarily imply a pathogenic role: AIDS enteropathy remains a diagnosis of exclusion[49]

A gastropathy with decreased acid secretion has been reported in AIDS. Its cause is not clear, but it has been speculated that the resultant hypochlorhydria could contribute to the entry of enteropathogenic organisms through the gastric mucosa[50]. Impaired absorptive function can occur in HIV-infected patients, even when no pathogens are detected. At a morphological level, partial villous atrophy has been reported[51–53]. Whether this is due to HIV infection itself, or to an as yet unidentified pathogen, is still unclear. Involvement of the intestinal autonomic nervous system by HIV may also contribute to gastrointestinal dysfunction by impairing motility and absorption[54].

Many pathogens causing diarrhoea and malabsorption have been isolated in HIV-infected patients[49,55] (Table 3). Clinical syndromes produced by these infections include diarrhoea, colitides and specific malabsorption syndromes. Any infectious agent that causes diarrhoea is also capable of producing malabsorption of both macro- and micronutrients.

Table 3. Enteric pathogens causing diarrhoea and malabsorption in HIV infection.

Pathogen
Viruses
• *Cytomegalovirus* (CMV)
• *Herpes simplex virus* (HSV)
Bacteria
• *Salmonella* sp.
• *Shigella* sp.
• *Campylobacter* sp.
• *Chlamydia trachomatis*
• *Vibrio parahaemolyticus*
• *Clostridium difficile*
Protozoa
• Cryptosporidium sp.
• *Microsporidium* sp.
• *Giardia Lamblia*
• *Entamoeba histolytica*
• *Isospora belli*
No infective agent found
• AIDS enteropathy

(Adapted from Simon et al[49], Keusch GT & Farthing MJG[55])

Non-infectious causes: malignancy. Kaposi's Sarcoma (KS) lesions have been detected throughout the gastrointestinal tract. Gastrointestinal KS is most likely to cause symptoms when it occurs in the oro-pharynx and oesophagus. Occasionally, the tumour has been associated with a protein-loosing enteropathy in the lower bowel, as well as massive haemorrhage and bowel obstruction[56,57]. Non-Hodgkin's lymphoma occurs in the intestinal tract of HIV-infected patients, but is far less common than KS in homosexual men. The tumours are almost all of B-cell origin[58]. Clinical symptoms include diarrhoea, haemorrhage, pain and intestinal obstruction. *Pancreatic insufficiency* resulting in malabsorption has occasionally been described in HIV infection. It may result from either chronic pancreatitis unrelated to HIV infection, opportunistic infection of the pancreas, or be drug-induced. Pancreatitis is a recognized adverse effect of didanosine (ddI)[59,60]. *Antibiotic use:* broad spectrum antibiotic use may result in bacterial overgrowth in the gut. Infections with bacteria such as *Clostridium difficile* are well documented in this context and may cause malabsorption[49].

Anthropological aspects of nutrition

Nutritional status has many determinants. The pathological manifestations of an illness such as HIV infection, are but one of these. Sociocultural aspects have profound influences on food intake, behaviour and beliefs, and hence nutritional status, in both health and illness. *Ethnic groups* have evolved particular systems of food and health beliefs and religious beliefs may also determine food intake. *Economic status* is important in determining food choice. Poverty affects the ability to purchase food as well as the type of food purchased. *Nutritional education* may be lacking in lower socioeconomic groups. There are good correlates between the prevalence of diseases such as obesity and socioeconomic and educational status[61]. *Food economics and politics* may be the main factors in the development of malnutrition, particularly in developing countries. Indigenous peoples in developed nations must not only deal with poor economic conditions, but also face a multitude of other factors such as dispossession, poor sanitary conditions and lack of education. *Low social activity* has been shown to be strongly predictive for premature death. It has been postulated that as many social activities in our society revolve around eating, it is the meal that determines the outcome[62]. Certainly, social isolation, such as the single parent or single homosexual may experience, may influence food intake behaviour. *Skills in food preparation* are important determinants of nutritional status. Male gender is still an important contributor to lack of food preparation skills in our society[63]. This may also apply to many individuals in the gay community.

HIV disease is largely a disease of young people, and the nutritional beliefs peculiar to young people will influence nutritional status and response to interventions. Young people may be particularly concerned with maintaining a culturally desirable body image. Loss of this body image (real or imagined) can be a major source of anxiety to HIV positive individuals as well as adversely affecting efforts to increase body weight[64]. *Children's food choices* have many determinants. Young people may use food for many purposes other than sustenance, such as to underline their own identity as children and to defy the adult world[63]. This may be particularly true for the child who is chronically ill and has reduced opportunity to assert themselves in other areas. *Recreational drugs and alcohol* may influence nutritional status in their own right. The infections or organ failure associated with abuse of these substances can lead to adverse nutritional consequences. In addition, the intoxicated person is unlikely to be capable of maintaining a nutritious diet being neither able to prepare food not to eat it.

Nutritional consequences of HIV infection

Changes in body composition

The body composition changes associated with the wasting of HIV infection have been reported in several papers. Weight loss is commonly documented in HIV infection[39,65,66]. There have been several more sophisticated descriptions of body composition changes in HIV infection. Kotler et al[67] studied a group of male and female patients with AIDS. Depletion of body cell mass, derived by measurement of total body potassium (TBK), was present in all subjects. Body fat content, measured by anthropometry (skin-fold thickness), was also diminished although the value of percentage body fat in patients was not significantly different from those obtained in healthy male homosexuals. Depletion of relative fat mass was more marked in the small group of female AIDS patients. While the pattern of body composition changes seen in the males resembled the wasting seen in sepsis or injury, the pattern in women, where fat depletion was greater than loss of lean body mass, resembled the pattern of wasting seen in starvation. The women studied suffered from reduced food intake due to severe upper gastrointestinal candidiasis, but had fewer serious complications of AIDS than the males. Their body composition changes thus appeared to reflect starvation rather than changes inherent to infection with HIV.

Kotler et al[3] subsequently studied the relationship of depletion of body cell mass and survival time. They found that whilst reduction in body weight paralleled body cell mass depletion, the regression line for TBK/height was a better predictor of death. The calculated body fat content showed no correlation with survival time and varied considerably in individual patients.

In a cohort of asymptomatic patients followed prospectively for 12 months[68], individuals were unable to demonstrate changes in protein stores as measured by in vivo neutron activation analysis (IVNAA) when weight and CD4 count remained stabled. As it has been postulated that loss of lean body mass may occur early in HIV infection, these findings were surprising.

In a recently reported study of both asymptomatic HIV-positive and AIDS patients bioelectrical impedance (BEI) was evaluated as a measure of body cell mass[69]. BEI compared favourably with deuterium and $^{22}NaCl$ dilution techniques in the AIDS patients who had significantly lower body weights than the asymptomatic individuals. The decrease in body weight was attributed to a decrease in both body cell mass and fat mass. Bioelectrical impedance was used to assess lean body mass in the Australian HIV Community Study[64], a cross-sectional study in which more advanced stages of infection were correlated with reduction in lean body mass.

Summary of body composition changes. The various body composition techniques used in research described above have been used to quantify some of the changes that occur in HIV infection. Table 4 summarizes the findings.

Table 4. Summary of body composition changes.

• Asymptomatic*:	Weight loss
	LBM reduced
	Relative fat mass reduced
• AIDS:	Weight loss
	LBM reduced (proportionately > simple starvation)
	Relative fat mass reduced
	Increased ECW and decreased ICW:
	Overall decreased total body water

*The term 'asymptomatic' is used here to imply 'otherwise asymptomatic', as clearly weight loss can be a symptom itself.

Table 5. Altered micronutrient levels in HIV infection.

Micronutrient	*commentary*	*Source*
Zinc	• ↓ serum Zn(?reflects body stores when Alb. ↓ in AIDS)	Falutz et al 1988[71] Malcolm et al 1992[76]
	• Wide variation	Moraglia et al[78]
	• Asymptomatic: ↓ serum Zn	Beach et al 1992[75] Graham et al[79]
Selenium	• ↓ serum	Dworkin et al 1986[72]
	• ↓ cardiac muscle	Dworkin et al 1989[83]
Vitamin B_{12}	• ↓ serum	Harris & Candeloro[31] Herbert 1988[32] Mantero-Atienza 1991[84] Beach et al 1992[75]
Folate	• ↓ .. ↑ serum/erythrocyte	Beach et al 1992[75] Bogden et al 1990[70]
Vitamin B_6	• ↓ serum (asymptomatic)	Baum et al 1991[81]
	• ↓ serum (AIDS)	Karter et al 1992[88]
Vitamin E	• ↓ (mixed asymptomatic & AIDS)	Bogden et al 1990[70]

(Adapted from Hyder & Oliver[111])

Changes in micronutrient status

Micronutrients are important for maintaining normal immune function. Reduced levels of many micronutrients have been documented in HIV infection. These include zinc, selenium, ascorbate, pyridoxine, carotenes, vitamin B_{12}, calcium and magnesium[70-75] (see Table 5).

The significance of these reduced levels is not clear and does not necessarily imply deficiency at a cellular level. A decreased blood level may, for example, reflect reduced carrier protein levels rather than true deficiency of the micronutrient. This has been demonstrated in the case of zinc levels in HIV infection: lowered plasma zinc was not associated with reduced cellular zinc. Cellular zinc was better correlated with disease severity than plasma levels[76]. Another suggestion has been that the reduced levels of micronutrients documented in HIV infection may reflect an acute phase response rather than true deficiency[77]. Thus interpretation of reduced levels of micronutrients should be viewed with caution. Such levels do not necessarily reflect deficiency states. Few researchers have acknowledged this and the literature abounds with rigid acceptance of deficiencies. Further research is clearly required in this area so as better to define micronutrient status in HIV infection and the role that micronutrient supplementation might play.

Zinc

Falutz et al[71] found significant reductions in serum zinc in AIDS patients and postulated that the aetiology was multi-factorial. But they questioned the validity of measuring of serum zinc as a reflection of body stores of zinc in patients who commonly also have reduced serum albumin, which may contribute to low levels of serum zinc. Additionally, acute infection itself may cause an apparent decrease in serum zinc concentration by intrahepatic sequestration mediated by interleukin-1[77]. Similarly, Malcolm et al[76] questioned the significance of plasma zinc levels, as described above.

In asymptomatic individuals, studies are conflicting. Moraglio et al[78] found a wide variance in the zinc status of their asymptomatic subjects. However, Beach et al[75] found significantly greater prevalence of reduced zinc levels in HIV positive subjects compared to controls. In another study, reduced levels of serum zinc (and copper) were found to predict progression to AIDS independent of CD4 counts and dietary intake of these nutrients[79].

Even when interpretation of reduced plasma levels is questioned, it has been suggested that zinc replacement can improve immunological function in early infection[75,80]. If cellular turnover is increased in HIV infection, zinc requirements may be increased and supplementation could be helpful, despite these caveats on interpretation of test results[76].

Selenium

Selenium has been studied in only a few small studies. Reduced selenium was reported in plasma, whole blood and red blood cells in patients with AIDS and ARC[72,73]. Selenium supplementation has been reported to result in increased levels of whole blood selenium as well as improvement in subjective well-being[73]. Kavanaugh-McHugh et al[82] reported a case of selenium deficiency associated with cardiomyopathy in a child with AIDS where cardiac function improved with selenium supplementation. Dworkin et al[89] reported reduced selenium in cardiac muscle biopsies.

There have not been clinical trials to support the routine use of selenium replacement or the use of large doses of selenium, as advocated by many alternative therapists.

Vitamin B_{12} and folate

Reduced levels of serum vitamin B_{12} were found in a study of 27 HIV-infected patients with megaloblastic anaemia and normal serum folate levels[31]. Interestingly, three of these patients were found to have intrinsic factor antibodies. Whilst the authors cited several explanations for reduced vitamin B_{12} levels, including malabsorption due to HIV terminal ileitis or hypochlorhydria and subsequent bacterial overgrowth, they postulated that intrinsic factor auto-antibodies represent a pathogenic mechanism resulting in B_{12} deficiency in AIDS. Herbert[32] similarly documented reduced levels of vitamin B_{12} in approximately one-third of their sample of 80 HIV positive patients who were already being supplemented with transcobalamin II, presumably reflecting malabsorption. Other studies[75,84] have similarly documented reduced levels of serum vitamin B_{12}.

Reduced cerebrospinal folate levels have been found in AIDS patients even when serum and erythrocyte levels were normal[74]. Tilkian[85] postulated mechanisms including co-existent B_{12} deficiency and significant catabolism to explain the lack of documented folate deficiency in the literature.

Vitamin B_6 (pyridoxine)

Vitamin B_6 deficiency has been reported in asymptomatic subjects[81]. In this study, all the subjects met the RDA for vitamin B_6 intake, although those consuming the lowest amounts of dietary vitamin B_6 had levels in the deficient range. In contrast, all the subjects consuming >20 mg/day (approximately ten times the USA RDA) had B_6 levels that are normally considered adequate. There were significant associations between reduced vitamin B_6 levels and parameters of immune function in

his study. In a related study, Fordyce-Baum et al[86] reported the complete dietary assessments of these HIV positive subjects. Multiple micronutrient supplementation was prevalent, often at doses far in excess of the RDA. Similar findings have been reported in other studies[87]. Many of the micronutrients taken have impact on immune status in their own right, so that evaluation of the effect of a single nutrient deficiency, such as vitamin B_6, on immune function can only be interpreted cautiously.

Vitamin A and beta-carotene

Reduced vitamin A (retinol) levels have been reported in a study of patients with AIDS[88]. They were not taking any vitamin A supplements and, compared to healthy controls, had a significantly lower mean serum retinol level. Even when dietary intake of retinol equivalents was normal, 27% had hyporetinaemia. Malabsorption may be deemed to contribute to the risk of vitamin A deficiency in those with advanced HIV infection population. Beach et al[75] found significantly reduced vitamin A levels in their study of asymptomatic subjects. High intake of vitamin A has been proposed as an immune-modulator in HIV infection. An early study demonstrated that high intake of vitamin A enhanced survival in murine AIDS[89]. Beta-carotene is a carotenoid that is metabolized to retinol and vitamin A and has been associated with immune modulation in both animal and human models[90]. In HIV infection, beta-carotene has been undergoing preliminary clinical trials[91]. Eleven subjects with HIV infection of various clinical stages were supplemented with 60 mg daily of beta-carotene for 4 months. Increases in the percentage of cells expressing Leu 11 (natural killer cells), Ia antigen and transferrin receptor (activated lymphocytes) were observed.

Vitamin E

In their group of HIV positive subjects with a range of stages of infection, Bogden et al[92] found reduced levels of vitamin E, but in Beach's study of asymptomatic subjects[75], vitamin E was in the normal range. As vitamin E is a fat-soluble vitamin, and may not be well absorbed in HIV infection, it would be expected that the prevalence of reduced levels would be similar to that found for vitamin A. The conflicting reports above probably reflect the small samples used as well as variability dependent on clinical manifestations of HIV infection.

Summary of micronutrient changes. There is considerable literature that documents reduced micronutrient levels in HIV infection. However, there is still a poor understanding of the significance of such reduced levels: they may well not reflect deficiency states at a cellular or, indeed, functional level.

Further research is required to establish recommended intake of micronutrients in HIV infection. Such research needs especially to consider some of the caveats to describing reduced levels of micronutrients in HIV infection and thus also to describing clinically significant changes with supplementation.

It is also important to recognize the potential of other factors in food, besides micronutrients, which may interact with immune status. There is evidence that components such as glutathione[93] enhance or omega-6 fatty acids[94] may suppress immune function. There has been little literature examining these factors in HIV infection.

Children

Childhood HIV infection: epidemiology

The World Health Organization states that, worldwide, over one million children are infected with HIV, half of whom have already developed AIDS. It is predicted that over 10 million children will be infected with HIV by the year 2000[94].

In Australia, the prevalence of HIV infection in children is low. To September 1992, there were 136 children under 13 years old (at time of diagnosis) with HIV infection in Australia[96]. Initially the predominant mode of HIV transmission in Australian children was via HIV-infected transfusions but this mode of transmission has ceased since HIV testing of blood and blood products began in 1985[97] and the major source of HIV transmission to Australian children is now vertical transmission[96].

Nutrition in childhood HIV infection

Paediatric HIV infection often leads to growth retardation, marked failure to thrive and multiple nutritional deficiencies, particularly protein-energy malnutrition[98].

The aetiology of nutritional problems in children with HIV infection is probably similar to the pathogenic mechanisms in adults, although there has been far less research in the paediatric population. A wide variety of problems such as poor appetite secondary to chronic disease, easy tiring, depression, respiratory distress, mouth infections, food inappropriate for a child's developmental level, neurologic impairment, psychosocial problems and food refusal may contribute to inadequate energy intake[99].

Gastrointestinal dysfunction is a major problem in paediatric HIV infection, as it is in the adult population. Enteric infections are common and include a similar spectrum of pathogens. An eneropathy occurring in the absence of an identifiable pathogen has been described in HIV-infected children[100] and may result in malabsorption and in increased gastrointestinal nutrient loss. Carbohydrate malabsorption has been reported in several papers[101,102].

Specific studies of micronutrient status in children with HIV infection are rare. Mantero-Atienza et al[103] have studied selenium status in infected infants and found a high prevalence of reduced selenium levels, similar to findings in adult populations. The same caveats to interpretation of lowered micronutrient levels apply equally to children as they do to adults (see Micronutrient status above). Paediatric guidelines on micronutrient supplementation have relied on extrapolations from adults[98].

Nutritional support may be indicated when growth fails, or during an acute infectious episode. Oral supplements have been recommended in the American Guidelines for Nutritional Support of HIV-Infected Children[98]. In the convalescent stage following an illness when 'catch-up' growth is usual, oral supplements have

also been recommended.

When enteral or parenteral nutrition support is utilized it is suggested that this should be accompanied where possible by oral intake, so as to maintain oral motor capabilities[98].

Perinatal infection: breast-feeding

The European Collaborative Study suggests that the overall risk of vertical transmission via breast-feeding (over and above transmission in utero or during delivery) is 14.4% (95% confidence interval 12–17%) for infants born to women known to be HIV positive prenatally[104]. When maternal HIV infection has occurred in the postnatal period, the estimated risk of vertical transmission is 29%[4].

The recent WHO/UNICEF Consensus Statement on HIV Transmission and Breast-Feeding[105] has clarified the situation regarding recommendations for breast-feeding in HIV infection (see Table 6).

Table 6. Summary of the WHO/UNICEF Consensus Statement on HIV Infection and Breast-feeding.

- Where infectious causes are not the primary cause of death in infancy, HIV-infected pregnant women should be advised not to breast-feed. Women whose infection status is unknown should be advised to breast-feed.
- When a baby is to be artificially fed, the choice of substitute feeding method and product should not be influenced by commercial pressures.
- Where the primary causes of infant mortality are infectious diseases and malnutrition, breast-feeding should remain the standard advice to pregnant women, including those known to be HIV-infected, as their baby's risk of becoming infected through breast milk is likely to lower than than its risk of dying in infancy of other causes if deprived of breast-feeding.
- In all countries, prevention of women of child-bearing age becoming infected with HIV in the first place is the over-riding priority in preventing HIV transmission from mother to child.
- Breast-feeding should continue to be promoted and supported in all populations, irrespective of HIV infection rates.

Nutritional management in HIV infection

Although guidelines for nutritional management of HIV infection have been published[106], there is little research in the literature of the outcome of nutritional interventions. Most recommendations are based on the existing data that identify the pathogenesis and consequences of malnutrition in HIV infection as well as on clinical experience.

Specific therapies

Treatment with zidovudine (AZT) may contribute to weight gain, presumably by improving immune function and reducing the frequency of opportunistic infections[107]. Conversely, many side-effects of anti-retrovirals (for example nausea caused by zidovudine or pancreatitis caused by didanosine) may have adverse effects on nutritional state. It appears that treatment of secondary infections in patients with AIDS may modify the wasting process, a very careful search for a treatable cause must be sought when assessing patients with weight loss[43].

A number of therapies has been used experimentally in the management of wasting in AIDS. Mostly these agents have proved to be disappointing in clinical practice. No single agents has been found to be especially useful, presumably reflecting the multifactorial and poorly understood underlying aetiologies.

Megesterol acetate has been used to promote weight gain in AIDS patients. Flynn et al[10] compared megesterol acetate with a placebo in a study of 65 subjects with AIDS. After 12 weeks treatment, the subjects receiving megesterol acetate gained significantly more weight (comprising increases in both lean and fat mass), had improved appetite and improved assessments of well-being.

Dronabinol (delta-9-THC), a derivative of cannabis, has been used in the USA for management of HIV-related anorexia and weight loss. A short double-blind crossover trial of dronabinol in patients with AIDS or ARC produced improved appetite and dietary energy intake, as well as reduction in nausea[109]. The changes were not significantly different in the active group, but this may have been due to the small sample size that was studied. Dronabinol has recently been approved for use in Australia.

Physical exercise may be an effective intervention as a means of preserving or increasing lean body mass. A 54-year-old male with AIDS undertook a physical training programme over a one-year period. Body composition measurements showed preservation of body cell mass (as measured by total body potassium)[110]. In another randomized, controlled study, regular exercise was shown to correlate with more stable T4 cell counts and fewer opportunistic infections. Body composition was not measured in this study and no attempt at explaining underlying mechanisms was made[111]. It could be speculated on the basis of suggestions that preservation of lean mass might be an important determinant of disease modulation, that regular exercise is beneficial because it maintains or promotes lean body mass.

Growth hormone may be another therapy which could promote weight gain. To date, it has only been investigated in very small study[112].

Nutrition support

In HIV-positive asymptomatic patients, the nutritional recommendations are[106,113]: (1) maintenance of an adequate intake of essential nutrients from a variety of foods, and (2) essential micronutrient supplementation (recommended by some groups). Clinicians have suggested that early nutritional intervention appears to be beneficial. Not only is severe nutritional depletion (and its concomitant debility) prevented, but suggestions have been made that early intervention could slow disease progression. Whilst no formal research is available to support these impressions, many clinicians currently advocate such intervention: improved quality of life is cited as an important and tangible benefit.

The small amount of research carried out on micronutrient interventions has concentrated on single nutrient supplementation. Some of this research suggests that deficiencies can be corrected and that some immunological abnormalities can be improved[73,75]. There are no clear guidelines on routine supplementation as research is not yet available to support any particular regimen. Clinicians' prescribing practices cover a wide

range from no micronutrient supplementation through to extensive supplementation[15,64].

In patients with AIDS, nutrition support will depend on clinical symptoms at a given time. Applications of general principles of nutritional management have been used, for example, in developing guidelines for the nutritional management of diarrhoea. Strategies such as restriction of fat or lactose or use of formula supplements containing medium-chain triglycerides have been utilized[112]. One study has reported reduction in frequency of diarrhoea in patients on a low-fat elemental diet[114]. Bulk-forming agents including Metamucil™[114], bran[115] and soluble fibres[112] may be effective treatments.

Enteral and parenteral nutrition support has been used in patients with AIDS. The route of administration will depend, in the main, on the clinical problems of an individual patient. Enteral nutrition (either via a nasogastric tube or via an enterostomy for more long-term support) was assessed in a recent study. Kotler et al[116] prospectively studied eight severely malnourished AIDS patients who were treated with enteral feeding. They found significant repletion in body cell mass, as measured by total body ^{40}K, as well as marked improvement in mental well-being and functional capacity. All but one of their previously bed-ridden patients was able to be discharged from hospital. One limiting factor in the use of enteral feeding in AIDS patients is the presence of severe malabsorption.

A comparative trial to assess the most appropriate enteral formula for patients with AIDS is in progress[117]. In part, the most appropriate formula will depend on the clinical status of the gastrointestinal tract. The use of parenteral nutrition in AIDS patients is not universally accepted, often for reasons which do not have a valid basis. The theoretical risk of catheter sepsis in immunocompromized patients is often raised by clinicians. In clinical practice this is not viewed as any more of a problem in HIV disease than in other immunocompromized states such as haematological malignancies. Catheter sepsis rates are determined predominantly by how the patients are cared for, not in whom they are used. The use of peripheral intravenous lines for parenteral nutrition infusions significantly lessens the risk of catheter sepsis and is viewed by many as the preferred method of administration of parenteral nutrition for all clinical indications including those found in HIV infection.

Other arguments against the use of parenteral nutrition in HIV infection could be seen as discriminatory. They include citing the 'terminal nature' of the infection. When parenteral nutrition is clinically indicated, such arguments alone are not considered in the management of other medical conditions and the same should be true for HIV infection.

In advanced and terminal stages of AIDS, management shifts towards palliation[118]. The emphasis should be on maintaining dignity and comfort for the individual. Nutrition support (in its various forms) continues to play a role in these stages of HIV disease.

Conclusion

There has been speculation that nutritional status is one of the cofactors which determine whether the HIV will become established and cause infection when an individual is exposed to it. Many of the clinical syndromes associated with HIV infection have profound nutritional consequences. These, in turn, have adverse effects on disease progression and ultimate survival.

Early management of nutritional problems may well improve prognosis, but further research is required in this area. Current guidelines for nutritional management in HIV infection rely on extrapolation from other disease states, clinical experience and the small body of knowledge gained from research work.

Further research is needed in the many aspects of nutrition and HIV infection. Such research will contribute to a better understanding of pathogenesis and progression. Definition of the effects of food and diet, nutritional formulate and micronutrients, on HIV infection will provide information for the rational development of nutritional guidelines and may provide the potential to enhance quality and length of life for those with HIV infection.

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Nutrition and HIV infection: a review

Julie R. Lustig

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摘要
營養與人類免疫缺陷病毒（HIV）傳染：評論

營養狀況也許對愛滋病毒的各個時期都有影響，人類免疫缺陷病毒（HIV）傳染的許多臨床特征會引起營養問題，同時由于營養不良也許會使病情惡化，由于廣泛的病因，吸收不良和新陳代謝改變引起的進食不足，均可致營養不良。此外，食物中的因素，包括微觀營養素可調節免疫功能。雖然這些發現的臨床意義和它們與愛滋病的嚴重程度和預后的關系仍未明確，但是已經證實人類免疫缺陷病毒傳染的各個時期，微觀營養素的水平下降。成人身體組成的改變，包括體重下降和較多喪失非脂肪組織。兒童的人類免疫缺陷病毒傳染研究更少，但生長障礙是一種明顯的營養合并症。臨床經驗指出早期營養干預也許可以改變預后和生活素質。愛滋病的營養處理取决于病人的臨床狀態。確定特別的食物因素，膳食和最適合營養支持方式的效益，考慮合理的營養計劃是重要的。同時，考慮食物在社會活動中對健康的效益，提供病人護理也是重要的，它將有助于生物醫學的研究。