Nutrition and immune function in human immunodeficiency virus infection

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The triad of human immunodeficiency virus (HIV) infection, nutritional status and immune function are intimately related, each factor having effects on the others. The dominant effect in this three-way relationship is the effect of HIV infection on nutritional status, an effect which, until the advent of potent anti-retroviral drugs, has been manifest primarily as wasting. Recently, more complex metabolic abnormalities have become apparent, particularly fat redistribution syndromes, hyperlipidaemia and hypercholesterolaemia. For the converse effect, the effect of nutritional state on HIV disease progression, there is good evidence that clinical outcome is poorer in individuals with compromised nutrition. However, the beneficial effects of nutritional support have been more difficult to demonstrate. For macronutrients, effective macronutrient supply improves survival in severely-malnourished individuals and may have beneficial effects in less-severely-affected individuals. Micronutrient deficiencies appear to be involved in modifying clinical HIV disease and may also be associated with enhanced mother-to-child transmission of virus, particularly in developing countries. Intervention trials in this setting are currently under way. In conclusion, the interaction of HIV infection and nutrition is of great importance not just because of the major impact that HIV infection has on nutritional state, but also because strategies to improve nutritional status, both quantitatively and qualitatively, may have a beneficial effect on the clinical and immunological course of the disease.

HIV infection: AIDS: Nutritional status: Wasting: Micronutrients

The interaction between human immunodeficiency virus (HIV) infection, nutrition and immune function forms a very complex relationship in which most variables interact in a bidirectional manner with most other variables. This relationship is illustrated in Fig. 1. The dominant effect in this triangular model is the effect of HIV infection on nutritional state, and it is in this area that most information has become available (Macallan, 1998). Our understanding of the converse relationship, the impact of nutritional status on immune function and disease progression, is much less clear and the data in this area are more confusing.

I would first like to address the effect of HIV infection on nutritional state, and then consider issues relating nutritional state to HIV disease progression, particularly addressing the question as to whether alterations in nutritional state can influence clinical outcome.
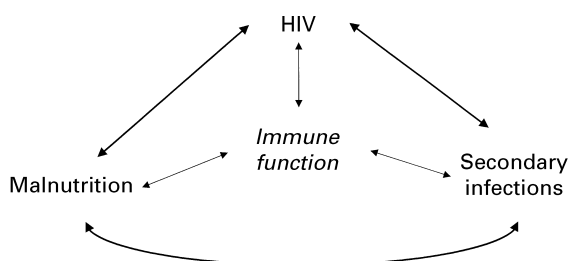
The impact of human immunodeficiency virus on nutritional state

Wasting in human immunodeficiency virus infection

Until a few years ago, when effective anti-retroviral treatment became available, the dominant clinical nutritional effect of HIV was wasting. In recognition of the clinical importance of wasting in HIV disease progression, unexplained weight loss was included as an acquired

Fig. 1. Model of interaction of human immunodeficiency virus (HIV) infection, nutritional state and immune function.

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immune deficiency syndrome (AIDS)-defining diagnosis in the Centers for Disease Control (1987) criteria for AIDS. In some individuals with HIV infection wasting occurs progressively over long periods of time, often over many years, and such chronic progressive wasting is often associated with chronic gastrointestinal disease (Macallan *et al.* 1993). In our experience, a more common pattern of wasting is characterized by acute intermittent episodes of weight loss lasting several weeks or months at a time. Such acute episodes of wasting are often associated with acute opportunistic infections (Fig. 2; Macallan *et al.* 1993). Fortunately, such infective episodes have become less common since the widespread introduction of prophylactic anti-infectives such as co-trimoxazole which has dramatically reduced the incidence of pneumocystis carinii pneumonia. From patterns of weight change similar to that seen in Fig. 2, one may make a number of observations regarding the pathophysiology of HIV-related wasting. First, HIV *per se* does not necessarily induce a wasting state. Infected subjects may remain weight stable for many years, even in the absence of anti-retroviral treatment. Second, opportunistic infections appear to be a major precipitant of weight loss, and their prevention, diagnosis and prompt treatment are therefore of major importance in preventing wasting. Third, anabolism or weight recovery is still possible in such patients with effective treatment of the secondary precipitating event (Macallan *et al.* 1993).

Underlying such wasting are a number of metabolic disorders which HIV appears to induce. All areas of intermediary metabolism appear to be affected, including energy balance, carbohydrate metabolism, protein metabolism and lipid metabolism, although the relative contributions of each remains unclear (Macallan, 1998). A full discussion is not possible here, but abnormalities such as accelerated whole-body protein turnover, altered carbohydrate metabolism and hyperlipidaemia are characteristic of infection (Hommes *et al.* 1991*a*,*b*; Grunfeld *et al.* 1992; Hellerstein *et al.* 1993; Macallan *et al.* 1995*a*). However, the final common denominator of wasting must be negative energy balance. Our studies of energy balance in HIV-infected individuals, albeit in the era before effective anti-retroviral treatment,

demonstrated that weight loss is the consequence not of accelerated or excessive energy expenditure but a consequence of reduced energy intake (Macallan *et al.* 1995*b*; LA Sheehan, DC Macallan & GE Griffin, unpublished results). Such observations demonstrate the importance of maintaining energy intake in managing patients with HIV infection (Fig. 3).

Anti-retroviral therapy and nutritional state

Recently there have been major changes in the clinical face of HIV infection, and we have now entered the era of so-called 'highly-active anti-retroviral therapy' (HAART). The full impact of such therapy on wasting is yet to be seen, but several early studies have been published. Weight recovery is frequently seen in patients responding to HAART (Force *et al.* 1997; Teixeira *et al.* 1997; Silva *et al.* 1998; Stricker & Goldberg, 1998). However, in most studies there are still some individuals who fail to gain weight or still continue to lose weight. For example, in a large study of patients commencing treatment with indinavir, after a median of 176 d on treatment, body weight had increased in 119 of 160 patients (74·4 %), had not changed in thirteen (8·1 %) and had fallen in twenty-eight (17·5 %), relative to baseline (Carbonnel *et al.* 1998). Furthermore, some investigators have found that cohorts of patients starting anti-retroviral therapy, including a protease inhibitor, fail to regain weight as a whole group (Fig. 4; Schwenk *et al.* 1999). This overall lack of a positive trend masks the observation that some individuals in the cohort did gain weight after commencing therapy. At 14 weeks 13 % (*n* 8) of the patients showed a positive weight gain trend (> 5 %/100 d) and at 28 weeks this percentage had risen to 21 (*n* 13). However, at the same time points 3 % (*n* 2) and 11 % (*n* 7) of the patients respectively demonstrated significant (> 5 %/100 d) negative weight trends (Schwenk *et al.* 1999).

Thus, it appears that even in the era of HAART wasting does continue to remain a clinical problem, albeit far less commonly than previously, and may become more of a problem if viral resistance to such drugs becomes an increasing clinical complication.
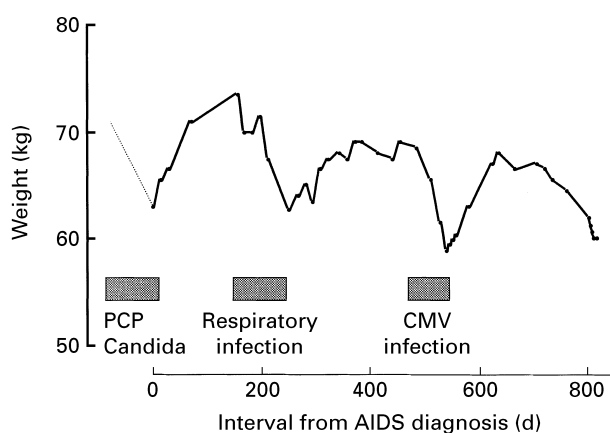
Fig. 2. Acute weight loss episodes in an individual with human immunodeficiency virus infection progressing to acquired immune deficiency syndrome (AIDS). PCP, pneumocystis carinii pneumonia; CMV, cytomegalovirus. (From Macallan *et al.* 1993.)
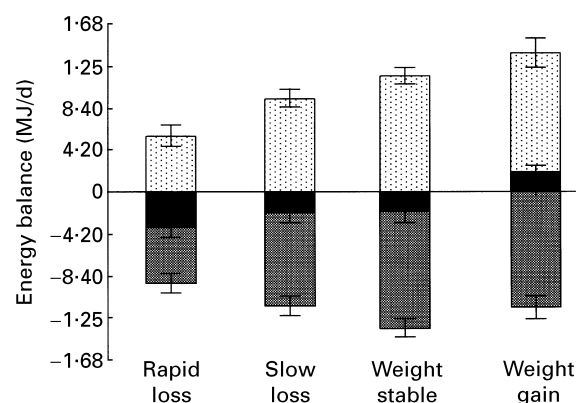
Fig. 3. Relationship between energy expenditure, energy intake and weight loss in patients with AIDS. (▨), Intake; (■), balance; (▨), expenditure. Values are means and standard deviations represented by vertical bars for the following no. of patients: rapid loss *n* 7, slow loss *n* 21, weight stable *n* 16, weight gain *n* 7. (From Macallan *et al.* 1995*b*.)
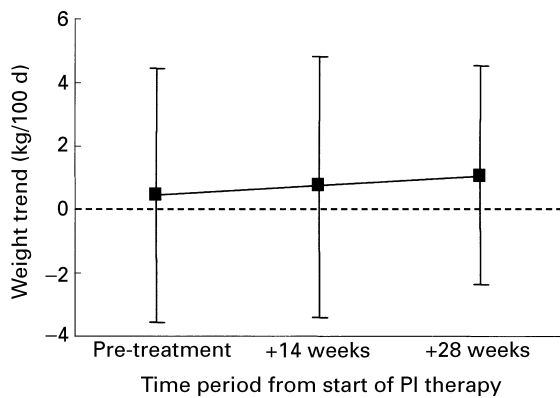
Fig. 4. Impact of initiation of highly-active anti-retroviral therapy on weight trend in patients with human immunodeficiency virus infection. PI, protease inhibitor. Values are means and standard deviations represented by vertical bars for twenty-four patients. (From Schwenk *et al.* 1999.)

Even when HAART does restore body mass, not all metabolic abnormalities are reversed. Recently a new constellation of metabolic abnormalities have been recognized in treated HIV patients, which have been collectively termed lipodystrophy (Carr *et al.* 1998*a*). The features of this syndrome include the redistribution of body fat away from subcutaneous areas, particularly facial fat deposits, with a concurrent accumulation of fat in the visceral compartment or in the dorso-cervical fat pad (Carr *et al.* 1998*b*; Lo *et al.* 1998; Miller *et al.* 1998). As a consequence, abdominal swelling may develop, whilst peripheral tissues such as limbs and face become grossly 'wasted'. At the same time, plasma triacylglycerols are often grossly increased, sometimes dramatically, to levels at which pancreatitis is likely (Henry *et al.* 1998*b*; Sullivan *et al.* 1998). In addition, there are reports of premature atherosclerosis in individuals on HAART (Behrens *et al.* 1998; Gallet *et al.* 1998; Henry *et al.* 1998*a*; Laurence, 1998; Vittecoq *et al.* 1998). Thus, it appears that, although anti-retroviral treatment does result in clinical improvement in overall nutritional state, not all metabolic abnormalities are reversed, and patients on therapy may still require further investigation and management of their metabolic syndrome.

The impact of nutrition on human immunodeficiency virus disease

Nutrition and human immunodeficiency virus disease progression

The impact of nutrition on HIV disease is a part of the model (Fig. 1) which is more difficult to define. In order to address this aspect, let us first consider whether an effect of malnutrition on HIV disease progression can be demonstrated. Early in the HIV epidemic Kotler *et al.* (1989) observed a relationship between loss of lean body mass and timing of death in patients with AIDS. They demonstrated that many patients with AIDS died at a level of malnutrition barely compatible with life, and speculated that the degree of malnutrition may have been key in determining the final clinical course and death of such patients. Such an impact of

nutritional state on survival was elegantly shown by Suttmann *et al.* (1995), who demonstrated an independent effect of loss of body cell mass on survival. More recently, the Community Programs for Clinical Research in AIDS have demonstrated that a weight-losing trend predicts subsequent mortality and susceptibility to opportunistic infections (Wheeler *et al.* 1998). Thus, there does appear to be evidence that impaired nutritional state adversely influences disease progression.

If malnutrition does accelerate the progress of HIV infection, it might be argued that improving nutritional state may improve clinical outcome. Although this situation appears to be implicitly true from the evidence mentioned previously, it has been much harder to demonstrate such an effect at the clinical level. There is a wide literature addressing this question, but many of the results are difficult to interpret as a result of having either poor or absent controls or inappropriate outcome measures. There are many difficulties associated with assessing the effect of nutritional intervention on HIV, not least because of the dramatic effects of other factors such as the presence or absence of opportunistic infections, the impact of drug treatment, and environmental, social and psychological factors. It is quite possible that even if a particular nutritional intervention had a major effect, it might not be 'visible' through the confounding 'smokescreen' of these many other factors. Despite this situation, several studies do address the question of whether nutrition intervention has an impact on clinical outcome, and I will cite examples to illustrate the findings.

Modification of the inflammatory response

One area of interest is whether nutrients can be used to modify the inflammatory response to HIV infection. n-3 Fatty acids are known to have an anti-inflammatory effect. One large clinical trial of such fatty acids in patients with AIDS had a disappointing impact on clinical outcome, having no effect on weight trend or serum cytokines, even though triacylglycerol concentrations were modified, as expected (Hellerstein *et al.* 1996).

Micronutrients and human immunodeficiency virus disease

The impact of micronutrients on HIV disease progression has also been an area of great interest. Several studies have shown an association between disease progression and micronutrient status. For example, Baum *et al.* (1995) showed an association between development of vitamin A or B_{12} deficiency with a reduction in CD4+ cell count; conversely they found that normalization of vitamin B_{12}, or indeed Zn, was associated with an increase in CD4+ cell count. However, there are difficulties in interpreting plasma vitamin levels, particularly since they are affected by the acute-phase response and are susceptible to changes in binding proteins. Similarly, there are difficulties in interpreting the impact on clinical outcome when surrogate markers such as CD4+ cell count are used as indices of efficacy. Some investigators have chosen to look at micronutrient intake rather than plasma levels. For example, Tang *et al.* (1993) demonstrated that high intakes of vitamin C, thiamin or

niacin were associated with a reduced relative risk of disease progression, whereas high intakes of Zn were associated with an increased risk of disease progression. Vitamin A intake appeared to have a 'U'-shaped relationship with outcome, both very high and very low intakes being associated with poorer outcome (Tang *et al*. 1993).

Certainly, it does appear that some individuals with HIV infection develop moderate to severe micronutrient deficiency, and that this deficiency affects their clinical state; such patients should clearly receive adequate vitamin supplementation. Extrapolating such selective use of vitamin supplements to universal supplementation for all HIV-infected individuals is a strategy which is more difficult to justify from the available evidence. However, large clinical studies designed to prove the value of universal supplementation are almost impossible to perform in the current changing clinical climate and are unlikely to be forthcoming. Micronutrients, of course, are normally ingested with macronutrients as part of food; wasting, which by definition is indicative of macronutrient deficiency, is therefore likely to be a useful marker of micronutrient deficiency and thus, in my opinion, it is wasting patients who should be selectively targeted for micronutrient supplementation.

Micronutrients and mother-to-child transmission of human immunodeficiency virus

One area of particular interest in terms of the place of micronutrients in HIV disease is their potential role in modifying mother-to-child transmission of HIV around the time of childbirth. This possibility is particularly pertinent in the developing world where vertical transmission is a common mode of transmission, and where such interventions are affordable compared with very expensive anti-retroviral therapy. A recent study from Africa showed that vitamin A deficiency was very common among pregnant women, and that the degree of deficiency correlated strongly with the risk of transmission from mother to baby (Fig. 5; Semba *et al*. 1994). Comparable results were observed in a similar study in two metropolitan areas in the USA (Greenberg *et al*. 1997). These observations have given rise to several interventional trials, the results of which are still awaited. One trial has now published the results of pregnancy

outcome (but not HIV transmission which requires a longer follow-up period; Fawzi *et al*. 1998). Groups received multivitamin supplementation and/or vitamin A supplementation. Surprisingly, vitamin A supplementation alone appeared to have no impact on pregnancy outcome, whereas multivitamin supplementation did have a major impact in terms of fetal death, low birth weight, preterm birth and low weight-for-age (Table 1). Hopefully, the role and relative contributions of different vitamin supplementation strategies (multivitamins, vitamin A, etc.) should become clearer as several studies in the developing world reach completion in the next few years.

Macronutrient supply in severe malnutrition

Although there are many exciting possibilities for ways in which nutritional intervention may impinge on HIV disease progression in a positive way, no consensus has yet emerged from the results of intervention studies to date, particularly those studies involving micronutrient supplementation.

However, one area where nutritional intervention can be shown to have clear benefit is in those individuals with severe malnutrition and wasting in whom provision of adequate nutrition may have a dramatic effect on survival. This benefit was recently demonstrated by a French study of severely-malnourished patients receiving total parenteral nutrition. In such patients survival was improved from 57 to 211 d (Melchior *et al*. 1997). Several other studies have
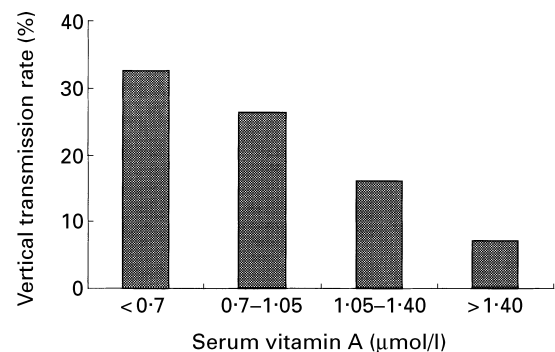
Fig. 5. Vitamin A status and risk of mother-to-child transmission of human immunodeficiency virus. (From Semba *et al*. 1994.)

Table 1. Effect of multivitamin (MV) and vitamin (vit) A supplementation during pregnancy in human immunodeficiency virus-infected women in Tanzania.* (from Fawzi *et al*. 1998)

	MV				
	Relative risk of adverse outcome	95 % CI	Statistical significance: *P*		Vit A
Child variables					
Fetal death	0·61	0·39–0·94	0·02		NS (*P* = 0·59)
Low birth weight (< 2500 g)	0·56	0·38–0·82	0·002		NS (*P* = 0·54)
Preterm birth (< 37 weeks)	0·61	0·38–0·96	0·03		NS (*P* = 0·70)
Small-for-gestational age	0·57	0·39–0·82	0·002		NS (*P* = 0·29)
Maternal variables	MV	no MV	*P*†	Vit A	No vit A	*P*†
Maternal CD4+						
Change at 6 weeks post partum	+ 167	+ 112	< 0·001	+ 142	+ 138	0·13

* The study included 1075 pregnant women randomized to four arms: placebo; multivitamin (no vitamin A); vitamin A; multivitamin with vitamin A.
† Statistical significance of difference.

demonstrated the importance of nutritional support in severe macronutrient deficiency, and this is an area which should not be neglected.

Conclusion

The interaction of nutrition, immunity and HIV is clearly both complex and important. The impact of HIV infection on nutritional state is marked and has been a major clinical feature of the disease for many years. The pattern of metabolic changes seen is altering, particularly with the advent of potent drugs active against HIV, which may have their own metabolic impact. Nutritional intervention represents one potential means to modify disease progression. In terms of micronutrients much of the evidence remains unclear, but the impact of vitamin A and multivitamins in the developing world is an area of great clinical importance, and new information is currently emerging. Where there is macronutrient deficiency there now appears to be no doubt that appropriate nutrition support can have a major impact on morbidity and mortality; such support may also result in improvements in immune function, as discussed earlier in this meeting (Chandra, 1991, 1997; RK Chandra, personal communication).

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