

Macronutrients and HIV/AIDS: a review of current evidence

*Jean W-C. Hsu, Paul B. Pencharz, Derek Macallan and
Andrew Tomkins*

*Consultation on Nutrition and HIV/AIDS in Africa:
Evidence, lessons and recommendations for action*

*Durban, South Africa
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Department of Nutrition for Health and Development

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Contents

1. Introduction	1
2. Energy metabolism.....	1
2.1. Resting metabolic rate	1
2.2. Energy intake.....	2
3. Energy malabsorption.....	3
4. Protein metabolism	4
4.1. Protein intake.....	4
4.2. Loss of body protein.....	5
4.3. Consequences of protein depletion in HIV/AIDS	7
4.4. Intermediary metabolism of protein	8
4.5. Muscle protein.....	10
4.6. Acute phase proteins.....	10
5. Body composition	11
5.1. Clinical features.....	11
5.2. Lipids.....	12
5.3. Endocrine factors.....	13
6. Effect of nutritional therapy.....	13
6.1. The effects of Protein/Energy supplementation	16
6.2. Pharmacologic promotion of protein anabolism.....	17
6.3. Non pharmacologic promotion of protein anabolism.....	17
7. The future	17
8. Research gaps	18
9. Summary.....	19

1. Introduction

Weight loss and malnutrition are common in patients with HIV infection or AIDS (1,2) and are likely to accelerate disease progression, increase morbidity and reduce survival because of the well documented impact of malnutrition on immunity (3). Several patterns of weight loss are seen (4). Even in the current era of highly active antiretroviral therapy (HAART), weight loss and muscle wasting remain significant clinical problems (5). Malnutrition and weight loss are likely to accelerate disease progression, increase morbidity and reduce survival. Three key factors contribute to malnutrition in patients with HIV/AIDS: inadequate intake, malabsorption and increased energy expenditure (6). Changes in whole-body protein turnover are now well described (7). Recently, the importance of endocrine dysfunction and the metabolic cost of inflammation, including the metabolic cost of producing cytokines, have been suggested as additional factors contributing to loss of body weight and changes in body composition (8). This review examines the effects of HIV/AIDS on energy and protein requirements and metabolism and describes the abnormal patterns of body composition and metabolism that occur in patients with HIV/AIDS. The effect of some treatments for patients with HIV/AIDS is also reviewed.

2. Energy metabolism

2.1. Resting metabolic rate

As with many infections increased resting metabolic rate (RMR) is often suggested as an important factor for energy imbalance in HIV/AIDS. There are differences in energy expenditure between children and adults with HIV/AIDS. Most studies in adult patients show that RMR is around 10% higher than in control groups (9-16). RMR is highest in those with the most severe disease. In particular those with secondary infection had higher RMRs (3) than did patients without secondary infection (17,18). Unlike adults, most studies in children show no difference in RMR between infected and uninfected children, though studies do show a raised energy expenditure in children with opportunistic infections (19-25). The different results in children and adults may be due to differences in nutritional status, dietary intake or disease severity. It is important to recognise that the effects of energy imbalance is more serious in children than adults because a high proportion of energy is

required for growth in healthy children and for catch up growth by children recovering from an opportunistic infection . Thus, despite the generally consistent finding that RMR is increased by 10% among adults with HIV/AIDS, change in RMR alone does not account for weight loss in adults and hardly contributes to weight loss in children. Other factors that contribute to total daily energy expenditure (TDEE) include physical activity, growth and diet-induced thermogenesis; these are not taken into account in measurement of RMR. (26-29). Variation in results of measurements of energy expenditure are likely due to differences in dietary intake, nutritional status, physical activity, and severity of opportunistic infection. However overall RMR is increased by about 10% in HIV/AIDS and is especially high during acute severe episodes of opportunistic infection

Total Daily Energy Expenditure

TDEE includes three components: RMR, physical activity and diet-induced thermogenesis in adults and an additional allowance for growth in children. The different components of TDEE can vary between each other. Thus, while RMR is often increased in HIV/AIDS TDEE does not necessarily increase because physical activity may be reduced because the patient feels too ill to get up and work. Indeed TDEE was decreased among men with HIV/AIDS during rapid weight loss, mainly because physical activity was reduced (30,31). TDEE studies have not been performed in HIV-infected children. However, ill children are usually less active and have a poor appetite so a lower TDEE might be expected in paediatric HIV/AIDS. TDEE is therefore not a major explanatory factor for energy imbalance in patients with HIV/AIDS.

2.2 Energy intake

Loss of appetite leading to reduced energy intake is the main reason why people lose weight in HIV/AIDS (32). Reduction in dietary intake leads to growth failure in HIV-positive children (33) and wasting in HIV-positive adults (34). Poor dietary intake is due to the metabolic processes which reduce appetite in many infections (35). Both systemic infections such as TB and intestinal infections including *Cryptosporidium* and oesophageal candidiasis are especially important (6). Poor dietary intake as a result of severe underlying infection may account for slow rates of recovery among children with severe malnutrition (36-38). Anorexia may also be caused by certain anti-retroviral

drugs (ARVS) and conversely as patients with HIV/AIDS start to improve clinically once they get established on ARVs they can develop a voracious appetite. Unless food is available the benefits of ARVs are not achieved; this is discussed in a separate review. Overall anorexia leading to a reduced nutrient intake is the most important cause of weight loss in HIV-positive patients. Encouraging severely malnourished children to eat is often difficult until their infections are adequately treated (39). This is especially so if severely malnourished children are infected with HIV/AIDS; encouraging children to eat when they have HIV/AIDS associated diarrhoea is a major challenge (40-43) Among many patients with HIV/AIDS, poor dietary intake occurs in a background of poverty and lack of food in the household. Things may get even worse because HIV/AIDS prevents people from feeling well enough to work - either to grow enough or to earn enough to buy food. Poor environmental conditions – especially contaminated water supplies and crowded living conditions, especially where TB and pneumocystis are rife, lead to frequent opportunities for colonisation by opportunistic infections that cause local pain and ulceration in the mouth, which together with fever and breathlessness lead to further reduction in appetite even when there is urgent need to replenish body nutrient stores. The complexities of metabolic responses in infection and their impact on appetite and body nutrient stores are discussed in detail during studies in other infections (44-49).

3. Energy malabsorption

Intestinal malabsorption leading to nutrient energy loss, is common in patient with HIV/AIDS (50,51). Chronic weight loss in HIV/AIDS often related to gastrointestinal disease and malabsorption (52). In addition to the damage to the intestinal villi caused by HIV, *Cryptosporidium*, one of the commoner and more serious opportunistic gut infections, for example, causes malabsorption and the degree of intestinal injury is related to the number of organisms infecting the intestine (53-57). Several studies have shown that those with more severe malabsorption have lower body mass index (58,59). Fast small bowel transit time. Children with HIV/AIDS can have devastating severity of diarrhoea, making it almost impossible to keep pace with rehydration therapy (60). Possible mechanisms responsible for malabsorption in HIV/AIDS include the impact of HIV on villi, specific enzyme deficiencies in intestinal mucosa, the effect of opportunistic infections and altered intestinal transit have all been considered but these are mainly conjectural and effective

treatments remain to be developed. The impact of nutritional interventions which are known to improve diarrhoea and nutrient absorption in non-HIV populations such as zinc (61-63), have not been evaluated in children HIV/AIDS but rather disappointing results were achieved in adults (64-70). Albendazole appears to improve absorption but the mechanisms are unclear (71). Carbohydrate malabsorption occurs in children with HIV/AIDS, even in those without bacterial or protozoal pathogens (72). High levels of faecal fat occur; one study showed that over 90% of HIV-positive patients had high faecal fat levels that were not related to dietary fat intake (73). Over 80% of HIV-positive patients in one study had faecal fat levels in the range of 20–30% of dietary fat intake (74). With these high levels of fat malabsorption, a negative energy balance will develop unless there is considerable increase in dietary energy. Fat malabsorption may be improved by use of pancreatic enzyme supplements (75,76) One study showed benefits from probiotics (77). Carbohydrate malabsorption is especially severe among children with immune depression (78,79). Malabsorption of iron also occurs (80). Despite the well documented evidence of fat malabsorption in HIV/AIDS it is possible to achieve nutritional rehabilitation using high fat diets (81), though whether alteration in the fat content of rehabilitation diets in severely malnourished children has not been investigated.

4. Protein metabolism

4.1. Protein intake

Protein deficiency is closely associated with energy deficiency; both are often deficient in HIV/AIDS and there is so much evidence of severe protein deficiency in HIV/AIDS that it has been proposed that children and adults with HIV/AIDS need much more protein than in their uninfected peer. Establishing the amount of protein which an individual needs to maintain body composition and function and, in the case of children, to grow is difficult. (38,82-88). Most studies have examined the metabolism of individual labelled amino acids as they become incorporated into pools of body protein or excreted as metabolic products. Thus a key question is frequently asked: Do HIV-positive individuals need to eat more protein or a different proportion of protein in their diet? A clinical state of protein depletion suggests that greater amounts of dietary protein are required. However much evidence from animal and human studies models in septic or catabolic states similar to HIV/AIDS shows that increased levels of amino acid or protein intake are not utilized adequately (89-91).

Several pro-inflammatory cytokines are produced during infection, which results in poor appetite and failure to grow or regain lost weight even when abundant nutrient supplies are provided (92,93).

There are informative examples of abnormal protein metabolism in infected children and adults (94-104) Several of these have involved providing considerable amounts of protein. Increasing dietary intake certainly changes protein metabolism and the balance between anabolism and catabolism but it does not appear that overall additional protein intake can replace lost protein stores until the infection is better managed. Thus, provision of additional protein does not in any way guarantee increased lean body mass and recovery of blood protein levels.. Indeed, clinical status can deteriorate if hyperalimentation is given in the presence of sepsis (105,106). Although weight gain often occurs in HIV-positive patients with active opportunistic infection who are treated with total parenteral nutrition, body composition analysis showed that the weight gained was predominantly fat (107).

Administration of excess dietary amino acids requires disposal processes including deamination and oxidation; these processes themselves require energy. The utilization of certain essential cellular cofactors may be deleterious to host metabolism. Thus modern nutritional support regimens for patients with sepsis tend to avoid hyperalimentation until the infection has been controlled. Direct evidence for specific clinical benefit from known increments of protein intake is largely lacking and will depend on the nutritional and inflammatory state of the patient. Dietary protein intake is often reduced in HIV/AIDS, especially during opportunistic infection; it is difficult to overcome this dietary reduction and doing so in the presence of opportunistic infection can be harmful.

4.2. Loss of body protein

Body protein loss is due to poor dietary intake, malabsorption and metabolic change. In the absence of adequate energy intake, body fat and protein are used as fuel sources, thus energy and protein metabolism cannot be separated within the context of clinical HIV/AIDS. During weight loss in HIV/AIDS the proportion of body stores that are lost, be they protein, fat or carbohydrate depends on the underlying nutritional state and the dietary intake. Thus the initial level of body protein and fat, together with the dietary intake and the severity of the inflammatory response will affect the rate of

weight loss (6,108,109). The proportion of loss of each compartment varies between individuals, possibly a result of genetic differences.

Fat is usually lost first and as body fat stores become progressively depleted, more lean body mass is lost per kilogram of total weight loss. The overall result is that protein depletion becomes more striking once fat reserves are lost. These changes are widely described in many wasting illnesses, but HIV seems to induce a special metabolic effect in the host involving a preferential loss of protein over fat (110-115). Evidence for preferential protein depletion in HIV comes largely from many cross-sectional body composition studies in which patients with AIDS wasting have been found to have proportionately greater loss of lean mass than fat (116-119). All studies do not support this hypothesis, however. In a longitudinal study of weight and body composition in HIV patients, the ratio of change in lean body mass to total body weight was similar to that found in dietary deprivation alone (120).

Patients with HIV/AIDS experience frequent experience episodes of clinical infection from repeated opportunistic pathogens infections, in between which they can rebuild nutrient stores. . . Repeated episodes of weight loss due to loss of fat and lean tissue followed by recovery appear to allow fat to be preferentially repleted and thus measurement of weight gain without assessment of body composition may lull clinician into a false sense of security. Indeed preferential fat repletion occurs elsewhere – in poststarvation refeeding (121), in TB (122) and in some severely malnourished children where they deposited more fat than protein if they were zinc deficient. (123,124). Preferential fat deposition was also noted during nutritional support in tuberculosis and may persist for least 6 months after the start of treatment (125). Whatever the metabolic mechanisms responsible for change in body composition in HIV/AIDS, they may be different from those present in chronic food insufficiency or loss of weight due to cancer. Loss of protein mass is markedly accelerated during opportunistic infections (126). It is not, however, clear why some patients experience a starvation-like metabolic response whereas others, especially those with *Pneumocystis carinii* infection, for example, may experience a hypermetabolic state (127,128).

Endocrine changes have been noted in chronic dietary deficiency and certain infections but their contribution to metabolism and changes in body composition seem particularly striking in

HIV/AIDS. Gonadal function is altered in HIV infection and hypotestosteronaemia may result in substantial loss of muscle mass (129). Screening for hypogonadism as part of the clinical assessment of HIV-infected subjects provides the potential for endocrine treatment as a means of enhancing lean body mass; this is discussed below. Loss of body protein during HIV/AIDS is therefore caused by poor diet, malabsorption, endogenous intestinal losses and altered metabolism; all are more striking during opportunistic infection.

4.3. Consequences of protein depletion in HIV/AIDS

Depletion of protein stores adversely affects many aspects of morbidity and mortality from infectious disease (130). Early studies of HIV suggested that mortality correlated with loss of lean tissue rather than overall weight loss (131). More recent studies support these findings (132-134). However, the close association between the immune suppression from HIV, changes in blood levels of nutrients as a result of inflammation (135), opportunistic infection and loss of lean body mass makes it difficult to determine how much the morbidity and mortality from an immunologically crippling disease are further contributed to by loss of body protein. The absence of carefully performed trials of nutritional supplementation makes it difficult to be absolutely certain as to how much nutrition interventions will improve the outcome of HIV/AIDS. However it is possible to extrapolate from the many studies of the effect of nutritional interventions in other diseases; there are many examples of benefits in terms of progression, severity and survival (136-141) among children with malnutrition and other diseases. There are many interventions possible to overturn the detrimental effect of severe malnutrition in other diseases in children and adults (142-144). It seems reasonable to assume that nutritional interventions in HIV/AIDS will enhance defence against infection, promote recovery and improve quality of life and survival despite the lack of properly conducted trials. In a cohort of relatively healthy HIV-positive adults, benefits of intervention in terms of well being and physical functioning score were rather small (145) but there are many anecdotal reports of considerable weight gain as patients become effectively treated with ARVs. Indeed the absence of food seriously impairs the ability to respond to ARVs effectively. Studies of nutritional therapy in TB show improved rates of growth and muscle power if they are given food rather than

advice alone. Such benefits may be of interest to a sedentary worker. They are likely to be saving for a manual worker and his/her family..

Several studies show the benefits of graded exercise schedules on body composition and well being (146). Those with severe HIV/AIDS associated wasting have profound fatigue and are unlikely to be able to maintain high levels of physical activity. However physical activity needs to be considered more positively as a means of rebuilding muscle protein stores. Many of the quality-of-life assessment instruments are specific to the cultures for which they were developed. Within the same country some who have lost weight will not feel able to work at their office or farm whereas others with similar body composition will be able to work. Globally, HIV-associated protein depletion is likely to have a major effect on work output and thus on the ability of an individual to generate income or produce food in economies without a well-developed welfare system. This will adversely affect the future nutritional state in a self-perpetuating spiral. Levels of lean body mass or body mass index at which function - whether physical activity, immune tolerance, recovery from illness or other measure - declines has not yet been determined for patients with HIV/AIDS. In the meantime there is enough evidence that overcoming even moderate malnutrition will have considerable benefits for health, development and survival (147,148). Loss of body protein plays a key role in reducing immunity, delaying tissue repair and slowing recovery after opportunistic infection. Recovering it requires a combination of improved infection control, increased food availability including items which are palatable for those with anorexia) and compassionate care and support.

4.4. Intermediary metabolism of protein

Protein metabolism in humans can only be measured in several ways (149,150). Whole-body protein turnover, an index of the rate at which amino acids are utilized from blood for protein synthesis and released from protein breakdown, is usually measured by using stable isotopes (150). A greater understanding of the flow of nutrients in HIV/AIDS will lead to more effective formulations of for treating people with HIV/AIDS and malnutrition. For this reason it is helpful to review the results of such studies even if they do not – for reasons of difference in study subjects and methodologies – produce consistent results. Asymptomatic HIV-positive subjects show faster release into the circulation of leucine and glutamine after an oral or intravenous dos. This indicates faster

rates of turnover of body protein, even without opportunistic infection and explains why some of the blood levels of “inflammatory” and “carrier” proteins change in early infection (151,152). Rates of protein turnover are usually increased in HIV/AIDS. These processes require extra energy. They may account for the extra 10% of energy that is required in HIV/AIDS, even in asymptomatic subjects. There is debate about how well metabolism responds to feeding in HIV/AIDS. Some studies indicate a normal response, even among those not receiving ARVs, (90) whereas other studies indicate reduced anabolism in HIV/AIDS (153,154). These differences may be due to differences in degree of disease, nutritional status, recent dietary intake or even type of ARV. Several mechanisms have been suggested (155). Skeletal muscle and visceral protein are the major components of body protein. Stable isotopes have been used to study the impact of HIV/AIDS on muscle protein as opposed to visceral protein.(156).

HIV/AIDS affects protein metabolism in different ways in different tissues (149). During an acute phase response there is a particular propensity to lose muscle protein (157-161). Studies on visceral protein during infection are few (162-164). Overall, protein loss occurs because of an imbalance between building up (anabolism) and breaking down (catabolism). There are many factors which influence whether an anabolic process can increase or a catabolic processes can decrease in the presence of infection. Defining and evaluating a series of formulations which are effective at improving muscle mass by means of reducing catabolism or increasing anabolism remains a research priority (6,165). In the meantime the overall evidence suggests that protein intake should be increased by 10% to match the increased intake of energy that is needed in HIV infected people. This should be continued to maintain body nutrient stores during the chronic asymptomatic phase of HIV. When immunity fails and an opportunistic infection occurs, encouragement should be given to the patient to keep going with the extra 10%. It is unlikely that they will be able to eat any more than this if they are feeling unwell. Indeed special, appetising formulations of food will be necessary, especially for children, to achieve their maintenance dietary intake. Once the opportunistic clinical infection has cleared, additional amounts of energy and protein up to 30 – 50% over the customary intake should be encouraged to achieve nutritional recovery.

4.5. Muscle protein

The metabolic mechanisms of muscle protein wasting in HIV-positive patients are not fully understood. Two key forces are at work – negative energy balance and the cellular effect of the virus and its opportunistic infections. It has been suggested that patients with AIDS who have increased whole-body protein synthesis cannot increase rates of muscle turnover to the same degree (47,48,56,83–84). This implies that protein turnover and synthesis in the viscera are markedly increased, and considerable evidence for this exists. Several studies show greatly increased metabolic activity in the liver (166,167). Studies using 3-methyl-histidine have given considerable insight into factors controlling muscle breakdown (168,169). The marked changes in plasma levels and turnover of acute phase proteins are striking. The rates of whole-body protein turnover in patients with HIV infection are generally increased (170). Considering the severity of the clinical sepsis, it is surprising that the rates are not even higher. Deficiencies of threonine and methionine were reported as rate limiting for whole-body protein synthesis in AIDS patients (171). Overall, most studies show that abnormal rates of whole-body protein turnover occur in HIV/AIDS and that they are considerably affected by energy balance, which is vital for maintaining normal protein metabolism.

4.6. Acute phase proteins

Plasma levels of most acute phase proteins are altered in HIV, even in asymptomatic cases (172-174). The role of these proteins in contributing to host immunity and carrying micronutrients in blood to tissues is increasingly recognized. Levels of acute phase proteins in the blood are controlled by changes in production in the liver and breakdown in the liver and other tissues together with alterations in the various pools of these proteins in the body. Measurement of some of these processes provides an understanding of how their levels in blood and tissues are controlled (175-177). The changes in acute phase proteins appear to be more related to severity of the infection and metabolic stress than to nutritional status or dietary intake (178). It is not yet clear how the changes in blood levels come about.

5. Body composition

5.1. Clinical features

The term “slim disease” was used to describe the marked wasting and loss of muscle mass in the early descriptions of HIV/AIDS and it still occurs as a striking clinical sign. Nevertheless more objective measurements are necessary for assessing and monitoring response to ARV and nutritional therapy. In adults the best measures are the body mass index (179) and mid-upper-arm circumference together with better definition and agreement on the characteristics of the facial appearance such that different observers can make a consistent assessment. Skin fold measurements can also be made but special training and great attention to detail are required because of the between-observer variation in measures. The easiest way to monitor nutritional recovery in adults is by measuring sequential weight gain but measures of weight gain do not distinguish whether the weight gain is due to fat or muscle so measurements of girth, skin fold thickness and morphology scores are necessary. With the increasing recognition that lipid abnormalities are frequent with the use of certain ARVs it is increasingly important to measure lipid profiles in an attempt to monitor and treat host nutrition.

Measurement of certain serum proteins such as albumin also gives useful information. Much has been published on the risks of morbidity and mortality due to the effect of malnutrition on host response independent of HIV (3,180-182) Among children, measurement of weight and height expressed as Z scores in comparison with median or percentage of international growth standards is useful. Linear growth as well as weight gain should be monitored. Measures of mid-upper-arm circumference are useful as they provide data on nutrition that are associated with increased risk of mortality independently of HIV but they are not so useful for monitoring increase in total body fat (183). Again, skin fold thicknesses can be measured to assess re accumulation of body fat but great care has to be taken to avoid observer error.

Recovery of weight loss usually occurs in patients with HIV/AIDS whose disease responds to ARV therapy, but a characteristic form of fat redistribution has been described (184,185). It includes loss of fat from the cheeks producing a clinically striking gaunt facial appearance together with accumulation of fat around the neck (the buffalo hump), waist and viscera—the lipodystrophy syndrome. This fat redistribution is remarkably different from what occurs in weight loss as a result of

poor dietary intake or metabolic disturbance. There is still disagreement on how to classify lipodystrophy, but the appearance of marked subcutaneous fat loss, development of buffalo humping of the fat between the shoulders, and the striking deposition of fat in the viscera are quite characteristic. Anthropometry, including waist-hip ratios, subcutaneous fat measurements and cross-sectional whole-body imaging are being used to define the morphological distribution of the fat more accurately (186,187).

The morphological appearances of lipodystrophy syndromes are often associated with insulin resistance, hypertriglyceridaemia and raised levels of high-density lipoproteins (98–100). Initially most cases of lipodystrophy and its associated metabolic disorders were noted in patients taking protease inhibitors (188). Treatment with non-protease-inhibitor ARVs is followed by some improvement in body fat distribution and the associated metabolic abnormality. However, cases of HIV-associated lipodystrophy have been noted with non-protease-inhibitor ARVs, and the mechanism for any association is not yet clear. In general, switching ARVs from one regimen to another has been more successful in improving metabolic disorders than it has been in improving fat distribution (189). Treatment with growth hormone and testosterone often improve the lipodystrophy (190)

In view of the considerable changes in lean body mass and subcutaneous fat that do not necessarily accompany each other, many investigators proposed that body composition studies should be done more intensively to monitor the progress of patients on ARVs (191-193). The clinical and biochemical patterns in lipodystrophy are striking and specific to HIV/AIDS and HAART. Their relationship to different ARV regimens and underlying nutritional status is discussed in more detail elsewhere (106).

5.2. Lipids

Abnormalities of lipid metabolism are also seen in HIV-positive patients, especially those receiving ARV therapy. Fat oxidation increases in HIV-positive patients but carbohydrate oxidation is suppressed in AIDS (19,195), suggesting that more fat than carbohydrate is used as fuel source. Lipodystrophy in HIV-positive patients with lipodystrophy syndrome is associated with accelerated lipolysis, which leads to futile cycling (196). In addition, lipodystrophy contributes to insulin resistance in HIV-positive patients (197,198), increasing the risk of diabetes mellitus. It is not known

whether patients who are undernourished at the time of HIV diagnosis are more or less susceptible to lipodystrophy development. Arguably, those on low-fat diets (such as most patients in developing countries) may have less endogenous fat production and therefore less low-density lipoprotein cholesterol. Some studies showed an increase in the prevalence of lipodystrophy among those with low body mass index and inferred that malnutrition may actually increase the susceptibility to side effects from ARV therapy (110,111). A greater understanding of what body tissues change in response to the disease and to the treatment will be necessary for developing better nutrition and ARV regimens for patients with HIV/AIDS. Marked changes in plasma lipids, attributable to HAART, require novel dietary and pharmacologic interventions.

5.3. Endocrine factors

Testosterone enhances muscle strength (199), oxandrolone enhances lean body mass (200), recombinant growth hormone reduces visceral fat and buffalo humps but has a lot of side effects (201), oxymetholone improves muscle mass (202) and metformin and rosiglitazone change fat distribution (203). Rather remarkably, the molecular basis for these actions, which are becoming more prevalent in patients taking ARVs for long periods, is almost completely unknown. Subcutaneous adipose tissue has been studied in HIV-positive subjects and glycerol release was noted to be higher in HIV-positive than -negative patients (204). Tumour necrosis factor release from subcutaneous adipose tissue and serum soluble tumour necrosis factor receptor 2 concentrations were also significantly higher in HIV-positive individuals with lipodystrophy (205). The absolute production of acylation-stimulating protein and the percentage conversion of the complementation protein to acylation-stimulating protein are significantly lower in HIV-positive subjects with lipodystrophy (204). Plasma adiponectin and leptin levels are altered in HIV but both elevated and depressed levels occur in lipodystrophy; adiponectin deficiency may play a role in the insulin resistance associated with HIV lipodystrophy (206). Endocrine treatment has a potential role in the management of the lipodystrophy syndrome and may stimulate a metabolic response in HIV infected adults and children.

6. Effect of nutritional therapy

The nutritional status of patients with HIV/AIDS depends on the availability of food and appropriate nutrient supplements, the severity of illness and access to treatment with ARVs and

prophylactic and therapeutic antibiotics and the presence of people to encourage them to eat and support them as they overcome their illness.

Nutritional Staging of HIV/AIDS A provisional scheme is shown below:-

Stage A – Where ARVs are available, additional food is available for the patient to respond to improved appetite once they go on ARVs, there is good quality dietary support to advise on best dietary ways of optimising effect of ARVs, there are special preparations to eat during illness from opportunistic infections and patient care and support is available – weight gain can be rapid, but may be more fat than protein.

Stage B – Where ARVs are available, additional foods are available for the patient to respond to improved appetite once they go on to ARVs, there are special preparations to eat during illness, but there are metabolic complications requiring dietary/ clinical advice – weight gain can be rapid but lipid and metabolic profiles are hazardous in the short and long term.

Stage C - Where ARVs are available but additional food is not available, even though patient care and support is. Nutritional recovery is frustratingly slow and opportunistic infections are more common and life threatening. Side effects of drugs may prevent compliance.

Stage D - Where ARVs are unavailable but additional food and patient care is. Nutritional support can achieve nutritional recovery and is likely to delay disease progression, decrease morbidity and improve survival. Nutritional recovery is slow depending on how much catch up/recovery can be achieved between infections.

Grade E - Where illness is severe, ARVs are unavailable, additional food is not available but patient care and support is available. Nutritional recovery is extremely difficult but possible.

Nutritional Interventions require designing according to the category of illness and environment.

Grade A – There are many helpful reports on the preparation of locally available foods suitable for people with difficulty in eating but no Random Controlled Trials (RCTs) showing the benefits of any one type as opposed to another among well nourished patients on ARVs have been performed.

Grade B – There is emerging recognition of metabolic problems and some studies of pharmacological ways of reducing the prevalence and severity of the hazardous profiles but no RCT of dietary approaches has been performed.

Grade C – There are many helpful reports describing the rate of weight gain as patients go on to ARVs but none defining the degree to which weight gain is affected by Household Food Security.

Grade D – There are reports and some papers, mainly among children with severe malnutrition, but no RCTS on how much one nutrition protocol compares with another.

Grade E – There are anecdotal reports on how people respond to provision of patient care and support including food gifts, but no assessment of their impact on nutrition, disease progression or survival.

Most studies have been among patients in Stage A or B in industrialised countries. Some patients benefit from dietary counselling and supplementation; others require tube feeding and even gastrostomy (1). Patients with HIV/AIDS and weight loss are metabolically analogous to patients with cystic fibrosis (207). Both groups have high levels of circulating cytokines and increased RMR during infective episodes. Nutritional support is largely ineffective until the infections are treated. However, there are window of opportunity between acute infective episodes. Supplemental energy and protein are largely effective in restoring body weight but their effect on achieving restoration of body protein as opposed to fat is not clear. These factors have been taken into account in the production off new

equations for calculating resting energy expenditure in patients with HIV/AIDS (208). It is hoped that these may be used to calculate a more tailored energy requirement for an individual. Anabolic hormones such as human growth hormone and androgens have been advocated (6,207) but no study has yet compared the effect of anabolic hormones with dietary supplements. Studies on growth hormone supplements have been limited to N. America. Few studies have examined the effect on body weight or composition of particular nutritional supplements (e.g. special preparations formulated with particular focus on certain amino acids) compared with conventional clinical supplements such as Sip Feeds. Despite a lot of problems in relation to diseases severity, availability of ARVs and the physical and socio-economic environment there are many things that can be done for patients with HIV/AIDS. At the every least, increasing their dietary and protein intakes in the period after recovery from opportunistic infection is likely to be beneficial in the short and long term.

6.1. The effects of Protein/Energy supplementation

Achieving Increased protein intake results in an increased body cell mass in HIV-positive men (209-211). Nutrition interventions combined with dietary counselling alter reduce loss of body protein by reducing whole-body protein breakdown. (212). An RCT compared nutritional counselling alone with supplements given for 6 weeks. There was increased energy intake but no discernible effect on body composition or quality of life (213). A longer 6-month study including supplements with arginine and omega-3 fatty acids failed to show significant benefit in terms of body composition compared with results observed in a group of control patients receiving dietary advice alone (214). Nevertheless, some studies have shown benefits from supplementation. Berneis et al. (124) gave supplements to 15 subjects in a small randomized trial lasting 3 months; supplements provided about 17% of energy from protein and resulted in an increase in protein intake of about 20 g/day. The subjects gained lean body mass (measured by bioimpedance analysis) and had slower rates of whole-body protein catabolism measured by [¹³C]leucine kinetics. One study sought to demonstrate rate-limiting amino acids for protein synthesis by looking for a lack of rise in plasma level when amino acids were administered as part of a complete amino acid–glucose mixture for 2.5 hours (171,215); the authors suggested that threonine and methionine may be rate limiting for whole-body protein synthesis in AIDS patients. A comparison of formula supplemented with α -linolenic acid, arginine

and RNA with a standard formula in a double-blind crossover study found greater weight gain with the supplemented formula (216). This was associated with modulation of pro inflammatory cytokines, including tumour necrosis factor, by the special formula.

Where dietary intake is already satisfactory, supplements are unlikely to be beneficial. Where the patients are relatively free from opportunistic infection, supplements can restore lean body mass. No evidence exists for advocating a particular formula; such data are needed. Different types of dietary protein preparation have been advised but there is insufficient evidence to recommend one regime over another

6.2. Pharmacologic promotion of protein anabolism

Anabolic steroids promote gain in lean body mass (217). The literature for recombinant human growth hormone is extensive and shows clear effects on nitrogen retention and improved physical functioning and quality of life but the side-effects and the cost implications are substantial (218). Discussion of the application of such treatments is beyond the scope of this review.

6.3. Non pharmacologic promotion of protein anabolism

A regular programme of resistance training was beneficial in terms of gain in lean body mass and strength among relatively well-nourished HIV-positive USA subjects (219). Other studies show that exercise and pharmacologic therapies with testosterone analogues act additively (220-223). While the value of exercise in maintaining muscle mass has been well established in experimental studies, its role for promoting nutrition among patients with HIV/AIDS in resource-poor situations has not been studied.

7. The future

The best way to achieve protein repletion in clinically severe HIV/AIDS is to establish effective ARV therapy. Despite intensive efforts, such therapy is currently only provided globally to a minority of people with HIV/AIDS. The provision of ARVs more widely often depends on government enthusiasm and donors resources. As more and more patients receive ARVs in the future, those caring for patients with HIV/AIDS will need to develop skills in managing the metabolic and nutritional side-effects of the drugs and in using nutritional interventions to improve the effectiveness and safety of ARVs. Present knowledge on nutrition and HIV now provides the start of an evidence

base for specific, focused nutritional guidelines for the improved management of HIV/AIDS. Now that HIV is prevalent among particular risk groups, including refugees, children with severe malnutrition and those living in poor environments with high rates of opportunistic infections including tuberculosis and diarrhoeal disease, evidence based guidelines for nutritional prophylaxis and treatment are especially important.

On present evidence it seems appropriate to provide an additional 10% of usual dietary recommendations for energy for those with asymptomatic HIV, keeping the proportion of protein in the diet the same as is usually recommended. Additional amounts of energy (say 20–50%) should be provided during convalescence between infective episodes. How to provide this food and encourage its intake in resource-poor situations needs much more innovation and evaluation. In many contexts increased energy and protein intake can only be achieved using locally available foodstuffs. In others the potential for prepared supplements is greater (224,225). There is, as yet, no evidence that particular supplements are more beneficial. Predictions for the next decade indicate that even if rates of HIV transmission are reduced, and even if ARVs become more widely available, many millions of people will become infected and malnourished. Nutritional guidelines should be developed in collaboration with guidelines for HAART; they are urgently needed.

8. Research gaps

Answers are needed for the following questions:

1. What is the impact of dietary supplements on prevention of progression of HIV/AIDS related illnesses – where ARVs are available and where they are not?
2. What is the impact of dietary supplements on slowing the decline in CD4+ count, especially in those whose count is as yet not sufficiently low that ARVs are indicated?
3. What are locally appropriate, sustainable ways of increasing dietary intake by 10% among adults and children who are HIV infected but as yet asymptomatic?
4. What are the best nutritional indicators for monitoring the clinical response of patients with HIV/AIDS to ARV and nutritional therapy?

5. How should the management protocols for moderately and severely malnourished children be modified if they are HIV infected?
6. What are the best nutritional support protocols for dietary management of complications of HIV/AIDS including diarrhoea and tuberculosis?
7. How can agricultural practices be improved to ensure that household food security is achieved in families where one or more adults are ill with HIV/AIDS?
8. What is the impact of Food Aid on nutritional status of individuals infected by HIV/AIDS and family members affected by HIV/AIDS?
9. What is the best dietary advice for those taking different types of ARVs?
10. What are the best combinations of macronutrient/micronutrient mixes in the prevention of progression of HIV/AIDS and maintenance of immunity?

9. Summary

Weight loss in adults and weight loss and growth failure in children are common in HIV/AIDS. Resting energy expenditure is increased by around 10% in adults with asymptomatic HIV. Nutritional requirements are increased by 20–50% during the convalescent catch-up period after an episode of opportunistic infection in both children and adults. The energy deficit in patients with HIV/AIDS results from a combination of reduced dietary intake, malabsorption, increased energy expenditure and abnormal utilization of substrates. Reduction in nutrient intake is the predominant factor causing weight loss in patients with HIV infection but malabsorption of fat is also important. Deficiency of protein stores and abnormal protein metabolism occur in HIV/AIDS but no evidence exists for increased protein intake over and above that necessary to accompany the required increase in energy. Dietary supplements using a range of palatable, affordable, available foodstuffs are needed to overcome anorexia during acute illness and convalescence. Particular formulations of nutritional supplements need to be developed and assessed for management of severe opportunistic infections such as persistent diarrhoea and tuberculosis. Nutritional status can be improved by adding endocrine supplements and physical exercise regimens; for many patients globally the real challenge is to grow enough or earn enough money to purchase food if the individual is too ill to work. New agricultural and social welfare policies are necessary to address deficiencies of household food security among

individuals with HIV/AIDS and families affected by HIV/AIDS. The short- and long-term benefits in terms of immune status, disease progression and physical function resulting from nutritional supplementation have not yet been determined. There is an urgent need to develop and test a series of nutritional supplements for the maintenance and improvement of nutritional status in HIV/AIDS.

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