Nutritional aspects of HIV-associated wasting in sub-Saharan Africa[1–4]

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ABSTRACT

The twin global epidemics of HIV infection and food scarcity disproportionately affect sub-Saharan Africa, and a significant proportion of patients who require antiretroviral therapy (ART) are malnourished because of a combination of HIV-associated wasting and inadequate nutrient intake. Protein-calorie malnutrition, the most common form of adult malnutrition in the region, is associated with significant morbidity and compounds the immunosuppressive effects of HIV. A low body mass index (BMI), a sign of advanced malnutrition, is an independent predictor of early mortality (<6 mo) after ART initiation in several analyses, and recent studies show an association between early weight gain when receiving ART and improved treatment outcomes. The cause of the observed increase in mortality is uncertain, but it is likely due in part to malnutrition-induced immune system dysfunction, a higher burden of opportunistic infections, and metabolic derangements. In this article, we describe the epidemiology of HIV infection and malnutrition in sub-Saharan Africa, potential causes of increased mortality after ART initiation among patients with a low BMI, recent studies on post-ART weight gain and treatment outcome, and trials of macronutrient supplementation from the region. We close by highlighting priority areas for future research. *Am J Clin Nutr* 2010;91 (suppl):1138S–42S.

INTRODUCTION

The geographic and pathophysiologic overlaps of the malnutrition and HIV infection epidemics in sub-Saharan Africa complicate the treatment of either condition in isolation. Since 2002, access to antiretroviral therapy (ART) for the treatment of HIV infection has expanded rapidly across the region, and 2.1 million of an estimated 7 million people in need now receive care (1). Although clinical and programmatic success has been reported from many countries in the region (2–5), HIV-associated wasting and inadequate nutrition hasten disease progression and likely contribute to the strikingly high early mortality observed in several analyses (4, 6, 7).

HIV-associated wasting was recognized as a negative prognostic indicator and a major contributor to the development of malnutrition in HIV-infected individuals early in the epidemic. Untreated HIV infection increases energy requirements while it decreases appetite and, in more advanced stages, it limits the intake and absorption of nutrients. Malnutrition refers to a range of conditions that develop when the body does not receive optimal amounts of the vitamins, minerals, and other nutrients needed to maintain healthy tissues and organ function. Diagnosing malnutrition accurately in the field is difficult in many sub-Saharan African settings, and the contribution of malnutrition to early mortality when receiving ART is a matter of debate. However, demographic data from patients who enter HIV care indicate that weight loss is widespread in this population, and evidence suggests that malnutrition compounds immune suppression and contributes to metabolic dysfunction.

PREVALENCE OF HIV AND MALNUTRITION IN SUB-SAHARAN AFRICA

Sub-Saharan Africa is affected by a disproportionately high prevalence of both HIV infection and food scarcity (8). As of December 2007, there were an estimated 33 million persons with HIV-1 worldwide (9). Globally, the HIV-1 epidemic appears to have stabilized, but an estimated 1.9 million new infections occurred in sub-Saharan Africa in 2007, which brings the total to 22 million persons with HIV-1 in the region, and represents 67% of the global burden.

The prevalence of malnutrition in sub-Saharan Africa is influenced by a host of factors, which includes seasonal variation, droughts and floods, the prevalence of infectious and chronic diseases, variable sanitary conditions, and social and political events. Survey estimates of clinical malnutrition are complicated by large and dispersed rural populations, a lack of appropriate diagnostic modalities, and potential confounders of associated signs and symptoms (eg, weight loss, edema, and physical manifestations of vitamin and mineral deficiencies). However, a low body mass index (BMI; in kg/m^2) has emerged as a useful indicator of a poor nutritional state (8). The World Health Organization uses BMI to grade nutritional status in the following manner: mild malnutrition (BMI = 17.00–18.49), moderate malnutrition (BMI = 16.00–16.99), and severe malnutrition (BMI $<$ 16.00) (10).

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[2] Presented at the symposium "Cachexia and Wasting: Recent Breakthroughs in Understanding and Opportunities," held at Experimental Biology 2009, New Orleans, LA, 18 April 2009.

[3] Supported by a US National Institutes of Health grant (R21 AI 076430) and Fogarty International Center grants (R24-TW007988, K01-TW06670).

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First published online February 10, 2010; doi: 10.3945/ajcn.2010.28608D.

An analysis of demographic and health surveys from 11 sub-Saharan African countries estimated that 10.3% of HIV-infected women (aged 15–49 y) have BMIs <18.5; similar data are not available for men (11). However, the prevalence of wasting can be significant, especially in advanced stages of the disease: among 40,778 persons with advanced HIV disease who started ART in urban Lusaka, Zambia, 3624 (9%) had a BMI <16.0; 3097 (8%) had a BMI between 16.00 and 16.99; and 6910 (17%) had a BMI between 17.00 and 18.49 (12).

In resource-limited settings, the prevalence of undernourishment provides a useful estimate of the general risk of clinical malnutrition within a population, independent of additional factors such as HIV infection (13). Undernourishment occurs when average energy consumption is insufficient to meet energy requirements; persons who habitually do not meet the minimum norms within a population are considered underfed or undernourished. In sub-Saharan Africa, 212 million persons, or 25% of the global total, were estimated to be undernourished in 2005 (14). This represents an increase of 43 million persons since 1990, but much of this rise (31.6 million) occurred in the Democratic Republic of the Congo as a result of civil war. Southern Africa has the highest prevalence of undernourishment (37%), followed by East Africa (35%), Central Africa [30% (excludes Democratic Republic of the Congo)], and West Africa (14%). A rise in commodity prices since 2007 is estimated to have increased the number of undernourished persons in sub-Saharan Africa by ≈20 million (14).

CAUSES OF HIV-ASSOCIATED WEIGHT LOSS

Weight loss has been recognized as a significant prognostic factor in HIV infection since the the epidemic began (15), and a ≥10% decrease from usual body weight, with concomitant chronic diarrhea or chronic weakness and fever, was an early AIDS-defining condition (16). Decreased energy intake is thought to be the primary cause of weight loss in HIV-infected individuals, in part because of anorexia caused by elevated interleukin-1, interleukin-6, and tumor necrosis factor α (17, 18). Oral and gastrointestinal infections can make food ingestion painful or difficult; constitutional manifestations of advanced HIV disease (eg, fatigue, fever, dyspnea), contribute to progressive disability and interfere with an individual's ability to ingest or obtain food (19). Additionally, elevated proinflammatory cytokines in untreated HIV infection prevent weight gain despite sufficient intake of energy and protein (18).

Although work capacity, muscle strength, and physical activity may be decreased in advanced HIV disease, the total daily energy expenditure may rise because of an increase in the resting metabolic rate (RMR). In some studies, RMR increased 10–30% in HIV infection and was higher in the presence of secondary infections or elevated plasma viral load, but the data vary (20–23). Much of the increase in RMR is due to the metabolic expense of inflammation in response to untreated viremia and opportunistic infections, and an elevated rate of protein turnover (24, 25). Treatment with ART may decrease RMR without altering the rate of lipolysis, which suggests that the metabolic consequences of HIV infection persist despite viral suppression (26).

Malabsorption of nutrients due to infection by intestinal parasites and *Mycobacterium*, decreased small bowel transit time, decreased carbohydrate absorption, bowel wall edema secondary to hypoalbuminemia, and abnormally high fecal fat excretion further contribute to negative energy balance and weight loss (27). Even after the initiation of ART, the side effects of certain antiretroviral drugs (eg, nausea, insomnia) may prevent adequate intake [and paradoxically may be exacerbated if taken without food (28, 29)], and malnutrition and low body weight may potentiate drug toxicity (30, 31).

ASSOCIATION BETWEEN LOW BMI AND EARLY MORTALITY WHEN RECEIVING ART

In resource-limited settings, HIV-infected persons may present for evaluation after significant unmeasured weight loss, and BMI provides a useful indicator of a potentially poor nutritional state if more advanced diagnostic capacity is not available. Caution is warranted, however, because a low BMI can be indicative of conditions with various prognostic significance, which include normal anthropometric variation, chronic inadequate food intake, or wasting associated with HIV and other infections. For example, in HIV- and tuberculosis-coinfected individuals, the reduction in body cell mass and protein stores may be more extensive than in HIV-infected controls, but this disparity is not reflected in the BMI value because of an attendant increase in extracellular volume (32).

Although BMI at the time of presentation for medical care is an imperfect marker of nutritional status, a low BMI is an independent predictor of mortality and morbidity in HIV-infected patients in developed countries, even after the introduction of combination ART (33). Some data suggest an inverse relation between the risk of HIV disease progression and BMI. In a cohort of HIV-1–infected drug users in the United States, obesity was associated with slower disease progression and better survival, independent of $CD4^+$ lymphocyte count (34). However, the implication of this finding for resource-constrained settings is unclear; a report from Botswana showed a higher BMI to be a risk factor for lactic acidosis when receiving ART (35).

A low BMI at the start of ART was an independent predictor of early mortality (ie, in the first 90 d of therapy) in several analyses from sub-Saharan Africa. In Zambia, patients who started ART with a BMI <16.0 had 2-fold higher mortality when compared with those above this BMI threshold (4). In rural Malawi, patients who initiated ART with a BMI ≤15.9 had a 6-fold increased risk of death at 3 mo compared with those with a BMI ≥18.5, and those with a BMI between 16.0 and 16.9 had a >2-fold increased risk (6). In Tanzania, patients with a BMI <16.0 at ART initiation had a mortality rate double that of patients with a BMI ≥18.5 (7).

POTENTIAL CAUSES OF INCREASED EARLY MORTALITY WHEN RECEIVING ART

The cause of increased early mortality among patients with low BMI at ART initiation is likely multifactorial, the result of the aggregate effects of malnutrition-induced immune system dysfunction, a higher burden of opportunistic infections, and metabolic derangement. Protein-calorie malnutrition (PCM) is a common form of adult malnutrition in areas characterized by food scarcity, and results from the chronic insufficient intake of macronutrients (energy and protein), often in a setting of chronic or recurrent infections. Similar to AIDS, PCM is associated with

suppression of the antigen-specific arms of the immune system and several generalized host defense mechanisms (36). Persons with PCM are more susceptible to opportunistic infections and suffer greater morbidity (37, 38). PCM is associated with reactivation of viral infections and decreased T-cell primary antibody response and memory response (39), a reversal of the T-helper-to-suppressor ratio (40), and atrophy of the lymph tissues (41). Peripheral lymphocyte and eosinophil counts may be decreased and natural killer cells show decreased activity (42).

The presence of HIV-related opportunistic infections among low-BMI individuals may complicate immune recovery and increase early mortality when receiving ART. HIV- and tuberculosis-coinfected patients have a lower BMI, hemoglobin, and serum albumin concentration than HIV-infected individuals who do not have tuberculosis at the time of presentation for treatment (43). Helminth coinfection accelerates HIV disease progression, and a systematic review showed that helminth eradication can decrease plasma HIV-1 viral load and increase $CD4^+$ cell count (44). Malaria infection, a common illness in much of sub-Saharan Africa, increases HIV-1 viral load significantly and contributes to anemia and decreased functional capacity (45). Syphilis or herpes simplex virus infection can also increase HIV-1 viral load and decrease $CD4^+$ cell count in comparison to HIV-infected controls (46, 47). The loss of gut-associated lymphoid tissue during the initial phase of HIV infection can cause lasting impairment in the integrity of the gastrointestinal epithelial mucosal barrier (48), and can predispose toward bacterial translocation across the gut wall (49) and potential septicemia.

The rapid depletion of body cell mass, especially skeletal muscle, in advanced HIV may contribute to metabolic derangements. Studies have reported preferential depletion of muscle over adipose tissue in HIV-associated wasting (50, 51), but the data are inconsistent (52, 53). A reduction in muscle mass, if present, decreases the muscle phosphate stores available to replenish serum phosphate. In patients with wasting and anorexia, a low serum phosphate may be adequate for the relatively low turnover rate of metabolic intermediates (eg, ATP and 2,3-diphosphoglycerate), but with increased appetite and food intake after ART initiation, a precipitous decline can occur (54). This phenomenon, termed "refeeding syndrome," may be exaggerated in areas where staple foods contain a high ratio of carbohydrate to protein and fat (55). As a result of serum phosphate depletion, potassium, magnesium, and sodium homeostasis is disrupted, which may cause cardiac arrhythmias, seizures, coma, pulmonary edema, paralysis, and respiratory arrest (56, 57). This pathophysiology may be operative in some cases of early ART mortality (58).

Decreased intake of some micronutrients was associated with accelerated HIV disease progression in observational studies (59, 60), which suggests a role for vitamin supplementation in nutritional support programs. A randomized trial of supplementation with B-complex vitamins, vitamin C, and vitamin E in Tanzania delayed HIV disease progression or death significantly (61). Similarly, supplementation with B-complex vitamins was beneficial in HIV-infected black South Africans (62).

ASSOCIATION BETWEEN EARLY WEIGHT GAIN WHEN RECEIVING ART AND TREATMENT OUTCOME

Given the association between low BMI and early ART mortality reported from many resource-limited settings, a natural question is whether the promotion of weight gain should be a treatment priority in these patients. Two recent reports have described an association between early weight gain when receiving ART and improved outcomes 3–6 mo after ART initiation. A study in Zambia of 27,915 patients who survived >6 mo on ART showed an inverse relation between early weight gain and the risk of post–6-mo mortality (12). Among patients with a baseline BMI <16, a failure to gain weight at 6 mo was associated with a 10-fold hazard of death compared with patients who gained >10 kg (adjusted hazard ratio: 9.7; 95% CI: 4.7, 20.0). The magnitude of the increased hazard of death associated with a failure to gain weight diminished with increased baseline BMI. Similar trends were noted for percentage weight change.

A similar study of a combined cohort of patients in Kenya (n = 2681) and Cambodia (n = 2451) reported an association between weight gain at 3 and 6 mo and subsequent survival, which was more pronounced among lower baseline BMI values (63). Among patients with BMI ≤18.5, a weight gain of ≤5% at 3 mo, compared with those with a weight gain >10%, was associated with a nearly 5-fold increased risk of death during the period from 3 to 6 mo post-ART initiation (mortality rate ratio: 4.8; 95% CI: 2.3, 10.1). A comparison of the same weight gain thresholds at 6 mo showed a 6-fold increased risk of death in the period from 6 to 12 mo (mortality rate ratio: 6.0; 95% CI: 3.3, 10.7).

TRIALS OF SUPPLEMENTARY FEEDING FOR MALNOURISHED HIV PATIENTS IN SUB-SAHARAN AFRICA

The associations between weight loss and HIV disease progression and between weight gain and mortality during ART could simply reflect greater severity of HIV disease or lesser responses to ART, and do not prove a causal role of poor nutrient intake. However, the possibility that enhancing nutrient intake could improve ART outcomes should be investigated, and has served as the basis for randomized trials of macronutrient supplementation (ie, supplementary feeding). Trials in the United States and Europe among nonmalnourished HIV-infected adults (ie, BMI > 19.5 in all studies) have shown inconsistent improvements in weight but not in survival (64), but none were conducted in areas characterized by food scarcity.

In sub-Saharan Africa, only 2 randomized trials of supplementary feeding in HIV-infected adults have been published. A study in Zambia compared ART adherence among HIV-infected patients who received World Food Program rations and patients enrolled in HIV care at clinics that had not yet received food assistance (65). The criteria for food distribution were based on household food insecurity, not the patients' nutritional status, and the mean BMIs in the intervention and control groups were 21.0 and 20.8 (women), and 19.6 and 19.7 (men), respectively. Patients in the intervention group were more likely to achieve 95% monthly antiretroviral drug adherence than were patients in the control group (relative risk: 1.5; 95% CI: 1.2, 1.8), but there was no significant difference in weight gain, $CD4^+$ cell response, or survival. However, the study lacked sufficient power to detect small but potentially relevant weight change differences between groups (eg, 1–2 kg).

A recent trial in urban Malawi randomized 491 adults who initiated ART with BMI <18.5 to receive 1360 kcal/d of either

a corn-soya blend or a ready-to-use fortified spread (a peanut-based, high-energy supplement) for 3.5 mo (66). There was not a study arm without nutritional supplementation. After 3.5 mo, patients who received the ready-to-use fortified spread showed a significantly greater increase in BMI (2.2 ±1.9 compared with 1.7 ± 1.6) than those who received the corn-soya blend, but there were no significant differences in survival, HIV-1 viral load, CD4 count change, or quality of life.

Although a survival benefit has not been shown to date, the hope that supplementary feeding can improve medication adherence and patient retention has prompted some HIV programs in sub-Saharan Africa to incorporate nutritional programs for malnourished clients (67, 68).

FUTURE DIRECTIONS

Given the intersections between HIV disease progression and endemic undernourishment in sub-Saharan Africa, as well as the association between HIV-associated wasting and early ART mortality, significant potential exists to improve survival and other outcomes through the provision of nutritional supplements to individuals with advanced HIV disease and malnutrition. Prospective trials of nutritional supplementation are needed to determine whether undernourishment is causally related to poor outcomes when receiving ART or is merely associated. However, caution should be exercised in the provision of macronutrient support, to avoid the precipitation of refeeding syndrome or other metabolic derangements from supplementation regimens that are overaggressive, poorly timed, or improperly balanced.

The identification and correction of nutritional deficiencies in sub-Saharan Africa is limited by inadequate diagnostic modalities and priorities that compete for health-care resources. Improved methods are needed to distinguish malnutrition with HIV-associated wasting (characterized by preferential skeletal muscle depletion and attendant decreased phosphate stores) from chronic insufficient food intake. This distinction may be crucial for early patient evaluation and treatment, because of the potential for differing metabolic abnormalities. Finally, further study of the characteristics of weight gain after ART initiation is warranted, with particular emphasis on the association between body composition changes and subsequent immune reconstitution, virologic suppression, and survival.

Underweight individuals will continue to represent a significant proportion of patients who present for HIV care in sub-Saharan Africa. Regional food insecurity is likely to persist in the near term, especially with drought conditions that continue in much of southern Africa and a trend of commodity prices that have risen over the past decade. To address malnutrition as a component of HIV care will require a sustained shift in policy and funding priorities, but critical data are still needed for successful implementation.

The authors' responsibilities were as follows—JRK and DCH: literature review, organization, and revision of the manuscript; and JRK: initial manuscript draft. No conflicts of interest were reported.

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