Vitamin supplements, socioeconomic status, and morbidity events as predictors of wasting in HIV-infected women from Tanzania

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ABSTRACT

Background: Wasting is a strong independent predictor of mortality in HIV-infected persons. Vitamin supplements delay the disease progression, but their effect on wasting is not known. Data are lacking on the risk factors for wasting in African HIV-infected persons.

Objectives: The objectives were to examine the effect of vitamin supplements on wasting in HIV-infected women and to assess the effects of sociodemographic characteristics, morbidity events, and immunologic progression on the risk of wasting.

Design: HIV-infected women (n = 1078) from Tanzania were randomly assigned to receive 1 of 4 daily oral regimens: multivitamins (B complex, C, and E), vitamin A plus β-carotene, multivitamins that included vitamin A plus β-carotene, or placebo. The endpoints of the study included first episodes of a midupper arm circumference <22 cm or a body mass index (BMI; in kg/m²) <18 and the incidence of weight loss episodes during a median 5.3 y of follow-up.

Results: Multivitamins alone significantly reduced the risk of a first episode of a midupper arm circumference <22 cm (relative risk: 0.66; 95% CI: 0.47, 0.94; P = 0.02). In multivariate-adjusted Cox models, the woman’s age, education level, and height were inversely related to the incidence of wasting. Episodes of diarrhea, nausea or vomiting, lower respiratory tract infections, oral ulcers, thrush, severe anemia, and low CD4⁺ cell counts were each significantly related to an increased risk of wasting.

Conclusions: Vitamins C and E and the vitamin B complex have a protective effect on wasting in HIV-infected women. Prevention of diarrhea, severe respiratory tract infections, and anemia are likely to decrease the burden of wasting. Am J Clin Nutr 2005;82:857–65.

KEY WORDS Wasting, HIV infection, multivitamins, vitamin A, diarrhea, anemia

INTRODUCTION

Wasting is an AIDS-defining condition (1) and is characterized by an involuntary, progressive loss of lean and fat body mass. According to the findings of studies conducted in developed (2–6) and in developing (7) countries, wasting is one of the strongest independent predictors of mortality in HIV-infected adults. The validity of wasting to predict mortality was recently found to be as high as that of low CD4⁺ cell counts, independent of other predictors of disease stage, such as viral load (7). The effect of wasting on survival is also independent of the administration of highly active antiretroviral treatment, which was shown in studies conducted in Germany (8) and the United States (9). In addition to an increased risk of death, wasting is also related to accelerated disease progression (5, 10–12), adverse pregnancy outcomes (13), and a higher risk of mother-to-child HIV transmission (14).

Although the exact sequence of events that leads to wasting has not been completely elucidated, some studies have implicated opportunistic infections as important intermediaries in the causal chain (15, 16). Gastrointestinal infections can lead to decreased intakes of nutrients because of swallowing pain and intestinal malabsorption and to increased use of nutrients because of inflammation and oxidative stress. In countries that have a high prevalence of HIV infection, evidence from large epidemiologic studies on the role of infection events on wasting is scarce. Furthermore, it is not known whether the predictors of wasting in HIV-infected persons in developing countries are the same as those in populations in more affluent regions. Knowledge of these predictors would provide insight for the development of interventions that are more accurately tailored to the prevailing risk factors in poor countries.

Pharmacologic treatments with recombinant growth hormone, testosterone, and anabolic agents are some of the few known treatments that are efficacious against wasting (17). Most of these options have prohibitively high costs that make them unappealing to policy makers in resource-limited countries, which have many competing public health priorities. It is therefore critical to find inexpensive interventions that improve clinical outcomes in HIV-infected persons who live in poor settings.

We have shown that supplementation with an inexpensive regimen of vitamin B complex and vitamins C and E effectively delays HIV disease progression, improves CD4⁺ cell counts, and reduces viral load in women from Tanzania (18). We hypothesized that these supplements also have beneficial effects against...
wasting, because the basic metabolic disturbances that lead to wasting appear to represent an adaptive response to a generalized inflammatory state (19, 20) and vitamins possess significant immunomodulating potential. In the present study, we examined the effects of vitamin supplements on wasting in women from the Tanzania trial. We also assessed the risk factors for wasting, which included sociodemographic characteristics, the incidence of morbidity events, and immunologic progression of the women during follow-up.

SUBJECTS AND METHODS

Study design and population

Between April 1995 and July 1997, we enrolled 1078 HIV-1–infected women who attended their first prenatal care visit in Dar es Salaam, Tanzania. The women were followed until August 2003, which was when the trial ended. Complete descriptions of the study have been reported previously (18, 21). Briefly, the women were randomly assigned to receive a daily oral dose of 1 of the following 4 regimens: 1) multivitamins (20 mg thiamine, 20 mg riboflavin, 25 mg B-6, 100 mg niacin, 50 µg B-12, 500 mg vitamin C, 30 mg vitamin E, and 0.8 mg folic acid), 2) vitamin A (5000 IU preferred) plus β-carotene (30 mg), 3) multivitamins with vitamin A plus β-carotene, or 4) placebo. All of the women received folic acid, iron, and malaria prophylaxis during pregnancy, according to the standard of care. At delivery, the women who received multivitamins alone or with vitamin A and β-carotene received an additional single 200 000 IU dose of vitamin A, whereas the women who received multivitamins alone or placebo alone received placebo. The active treatment and placebo tablets were identical in size and color.

At the first visit, trained research nurses obtained information from the women on age, education, socioeconomic and marital status, and obstetric history. The nurses also measured the women’s height to the nearest 0.1 cm using Seca Bodymeter 206 stadiometers (Seca, Hamburg, Germany), the women’s weight to the nearest 100 g using Seca 700 balance-beam scales, and the women’s left midupper arm circumference (MUAC) to the nearest 100 g using nonstretchable tailor’s tapes. Also at the first visit, study nurses measured the women’s height to the nearest 0.1 cm using Seca 700 balance-beam scales, and the women’s left midupper arm circumference (MUAC) to the nearest 100 g using nonstretchable tailor’s tapes. Also at the first visit, study nurses measured the women’s height to the nearest 0.1 cm using Seca 700 balance-beam scales, and the women’s left midupper arm circumference (MUAC) to the nearest 0.1 cm at the midpoint between the acromion and olecranon with nonstretchable tailor’s tapes. Also at the first visit, study physicians performed a complete medical examination on the women and collected specimens that were later used for laboratory analyses. The analyses included the following: complete blood cell counts and CD4+, CD8+, and CD3+ T cell subset counts (FACScount and FACSCAN systems; Becton-Dickinson, San Jose, CA); serum concentrations of selenium (measured by neutron activation analysis) and vitamins A and E (measured by HPLC); tests for malaria parasites in the peripheral blood; and tests for intestinal parasites or sexually transmitted diseases.

Follow-ups were conducted on the women at monthly clinic visits in which study physicians carried out a complete clinical examination and nurses measured weight and MUAC. The women were asked about their health status during the preceding period, including questions on the incidence of signs and symptoms of disease. Diarrhea was defined as ≥3 watery stools during a 24-h period, and dysentery was defined as an episode of diarrhea with mucus or blood. When the participants missed their scheduled clinic visits or traveled out of Dar es Salaam, a home visit was made and the woman’s neighbors or relatives were asked about her vital status. Neither anthropometric measurements nor information on morbidity were collected during these visits.

In September 2000, the data and safety monitoring board recommended that the vitamin A plus β-carotene supplement be dropped because it appeared to increase the transmission of HIV from mothers to their children (22). Subsequently, the women who had been randomly assigned to receive either vitamin A plus β-carotene alone or with multivitamins received either placebo alone or with multivitamins, respectively. Given earlier findings from the Tanzania trial that indicated that a multivitamin regimen reduced adverse gestational outcomes during initial pregnancies (21), the women who had subsequent pregnancies during the follow-up period were given open-label vitamins B, C, and E (ie, the same formulation given in the multivitamins arm of the study) throughout their pregnancies; these women reverted to their originally assigned blinded regimen after delivery. Antiretroviral medications were not available in the study setting at the time of the study. All participants gave informed consent to be included in the study. The institutional review boards of Muhimbili University College of Health Sciences, the Tanzanian National AIDS Control Program, and Harvard School of Public Health approved the study protocol.

Definition of endpoints

Several binary definitions of wasting were used according to changes in anthropometric status during the follow-up. MUAC, body mass index (BMI; in kg/m²), and body weight were evaluated at each visit, and wasting was defined dichotomously, with a MUAC < 22 cm and a BMI < 18 as the primary endpoints. The cutoff for MUAC was chosen according to the value recommended in women for the screening of malnutrition (23). A previous study showed an increased prevalence of a MUAC < 22 cm in HIV-positive compared with HIV-negative women in Tanzania (24). The cutoff for wasting according to BMI was selected on the basis of the findings of a recently published study of HIV-infected African adults, which showed that a BMI < 18 had comparable validity with a CD4+ cell count < 200 cells/mm³ in the prediction of mortality (7).

A weight loss >10% from the weight recorded at baseline was a secondary endpoint and was based on a conventional definition of HIV-related wasting (25, 26). An additional secondary endpoint was the incidence of weight-loss periods during follow-up; these periods were defined for each participant when the arithmetic difference of consecutive between-visit weight measurements was negative. Weight-loss periods were classified according to their duration and severity. Long periods of weight loss were those that lasted ≥4 mo, whereas short periods lasted ≤4 mo (15). Severe periods of weight loss were defined as weight loss >1 kg/mo and moderate periods were defined as weight loss ≤1 kg/mo.

Effect of vitamin supplements on wasting

We followed the intent-to-treat principle to examine the effect of vitamin supplements on wasting. To check the randomization assumption, we compared the distribution of baseline characteristics by treatment arm. Analyses that considered the first 2 and 4 y of follow-up and also the whole follow-up period were performed. To examine the effect of multivitamins, we compared the women who received either multivitamins alone or multivitamins and vitamin A plus β-carotene with the women who
received either vitamin A plus β-carotene alone or placebo. Similarly, to examine the effect of vitamin A plus β-carotene, we compared the women who received either vitamin A plus β-carotene alone or multivitamins and vitamin A plus β-carotene with the women who received either multivitamins alone or placebo. The cumulative incidence of each outcome was estimated as the number of first occurrences during follow-up divided by the number of people who were at risk (ie, the women who were free of the outcome at baseline). Next, Cox proportional hazards models were used to estimate hazard ratios (HRs) and 95% CIs. In these models, the time-to-first event for each of the endpoints was the dependent variable and an indicator variable for treatment assignment was the predictor. The participants who did not develop the outcome were censored (ie, were counted as not having the event) at their last available follow-up visit. The median follow-up was 63 mo (interquartile range: 16, 81). In supplemental analyses, we assessed the potential interaction between multivitamins and vitamin A plus β-carotene on wasting outcomes by testing the significance of a cross-product term in the Cox models and then using a partial-likelihood ratio test.

We also estimated the effect of treatment on the incidence of weight-loss periods by using proportional rates models for recurrent events (27, 28) with time-to-weight loss as the outcome and indicator variables for treatment as predictors; the 95% CIs around the relative risks were calculated with the robust sandwich covariance matrix estimate. Because large decreases in BMI or weight occur after delivery from pregnancies, all analyses were repeated excluding the person-time contributed during pregnancy and the results were virtually the same; therefore, we present the results that include all person-time available.

Compliance with the study regimen, which was evaluated as the number of tablets absent from bottles that were returned at the monthly visits divided by the total number of tablets the woman should have taken, was high: 79% of the women complied over the total period of follow-up, 83% at 2 y, and 80% at 4 y. Compliance was not significantly different between the groups.

Sociodemographic characteristics and the risk of wasting

We used Cox models to examine the associations between baseline characteristics, which included age, level of education, parity, whether the woman cohabited with a partner, height, serum selenium concentrations, and the risk of first wasting episodes at 2 and 4 y of follow-up and during the entire period. Because the results were not different for any length of follow-up considered, only the results that included the total follow-up are presented. The influence of these characteristics on the incidence of weight-loss periods was examined through proportional rates models for recurrent events. All estimates were adjusted for regimen assignment and for baseline CD4⁺ cell counts.

Morbidity during follow-up

We considered variables that were updated during follow-up as time-dependent predictors of first episodes of wasting. These variables included signs and symptoms of disease during the previous month that were reported from each nurse visit (ie, diarrhea, dysentery, and nausea or vomiting), physician diagnoses during clinic attendances (ie, oral ulcer, thrush, or respiratory tract infections), and results from laboratory tests, which included tests for malaria, hemoglobin concentrations, and CD4⁺ cell counts. We defined risk sets using the time interval between exposure assessments. For exposures that were updated monthly (ie, nurse and physician visits), we increased the length of the risk sets to 3 consecutive monthly periods and used the cumulative number of each morbidity episode during these intervals to assign the exposure status; the outcome was evaluated at the end of each period. HRs and 95% CIs, which were adjusted for treatment assignment and sociodemographic characteristics, were estimated with the use of Cox models.

To examine the associations between morbidity events and weight-loss periods of different duration and severity, we estimated the incidence rates of each event during short-moderate, short-severe, long-moderate, and long-severe weight-loss periods, as well as during periods without weight loss, using Poisson regression. The likelihood ratio test was used to ascertain whether the incidence of morbidity events varied across these periods. Incidence rate ratios were then estimated for each event in a comparison between the incidence rates during each of the 4 types of weight-loss periods and the rates during periods without weight loss. All analyses were carried out with the use of SAS version 9.0 (SAS Institute Inc, Cary, NC).

RESULTS

Of the 1078 women who were randomly assigned, 27 had only one anthropometric measurement during the follow-up and thus were excluded from the analyses. The mean (±SD) age of the women was 24.7 ± 4.8 y at recruitment; 20% of the women had symptomatic HIV disease [above stage 1 of the World Health Organization classification (29)], and 13% of the women had CD4⁺ cell counts <200 cells/mm³. The baseline characteristics did not differ significantly by treatment arm (Table 1). The correlation between BMI and MUAC at the first visit was 0.82 and did not vary significantly by CD4⁺ cell count categories. In the women without each outcome at baseline, the cumulative incidence rates of first episodes of a MUAC < 22 cm, a BMI < 18, and weight loss of >10% were 29%, 27%, and 63%, respectively, over a median 63 mo of follow-up. Five thousand seven hundred seventy-one periods of weight loss were reported, which encompassed 22 044 of the total 25 914 person-months of follow-up. The median rate of weight loss was 0.8 kg/mo (interquartile range: −1.7, −0.4). According to their duration and severity, 38% of the weight-loss episodes were short and moderate, 32% were short and severe, 23% were long and moderate, and 8% were long and severe.

Effect of vitamin supplements on wasting outcomes

Supplementation with vitamin B complex and vitamins C and E resulted in a 29% reduction in the risk of a first episode of a MUAC < 22 cm after 2 y of follow-up (P = 0.01), a 21% risk reduction after 4 y (P = 0.05), and a 17% risk reduction during the whole period (P = 0.10; Table 2). No apparent benefit of multivitamins on BMI or weight loss outcomes was observed.

Marginally significant negative interactions were found between the multivitamins and the vitamin A plus β-carotene regimens; the latter appeared to reduce the benefit of multivitamins alone on MUAC < 22 cm. Compared with placebo, multivitamins alone reduced the risk of a first episode of a MUAC < 22
cm by 41% during the first 2 y (95% CI: 13%, 60%; P = 0.008), by 39% during the first 4 y (95% CI: 12%, 57%; P = 0.008), and by 34% during the whole follow-up period (95% CI: 6%, 53%; P = 0.02). By contrast, the effects of multivitamins plus vitamin A plus β-carotene during the same respective periods were 23% (95% CI: −12%, 56%; P = 0.17; P for interaction: 0.19), 10% (95% CI: −24%, 36%; P = 0.51; P for interaction: 0.06), and 4% (95% CI: −32%, 30%; P = 0.82; P for interaction: 0.08).

### TABLE 2

Effect of vitamin supplements on wasting outcomes in HIV-1–infected women from Tanzania

<table>
<thead>
<tr>
<th>Outcome</th>
<th>MUAC &lt; 22 cm</th>
<th>Effect of MV</th>
<th>Effect of VA + βC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total n at risk</td>
<td>MV</td>
<td>No MV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUAC &lt; 22 cm</td>
<td></td>
<td>502</td>
<td>489</td>
</tr>
<tr>
<td>Total n at risk</td>
<td></td>
<td>502</td>
<td>489</td>
</tr>
<tr>
<td>First 2 y (no. of events)</td>
<td></td>
<td>96</td>
<td>125</td>
</tr>
<tr>
<td>First 4 y (no. of events)</td>
<td></td>
<td>121</td>
<td>143</td>
</tr>
<tr>
<td>Whole period (no. of events)</td>
<td></td>
<td>137</td>
<td>154</td>
</tr>
<tr>
<td>BMI &lt; 18 kg/m²</td>
<td></td>
<td>523</td>
<td>512</td>
</tr>
<tr>
<td>Total n at risk</td>
<td></td>
<td>523</td>
<td>512</td>
</tr>
<tr>
<td>First 2 y (no. of events)</td>
<td></td>
<td>91</td>
<td>93</td>
</tr>
<tr>
<td>First 4 y (no. of events)</td>
<td></td>
<td>122</td>
<td>120</td>
</tr>
<tr>
<td>Whole period (no. of events)</td>
<td></td>
<td>134</td>
<td>140</td>
</tr>
<tr>
<td>Weight loss &gt;10%</td>
<td></td>
<td>528</td>
<td>523</td>
</tr>
<tr>
<td>Total n at risk</td>
<td></td>
<td>528</td>
<td>523</td>
</tr>
<tr>
<td>First 2 y (no. of events)</td>
<td></td>
<td>283</td>
<td>266</td>
</tr>
<tr>
<td>First 4 y (no. of events)</td>
<td></td>
<td>316</td>
<td>299</td>
</tr>
<tr>
<td>Whole period (no. of events)</td>
<td></td>
<td>334</td>
<td>324</td>
</tr>
</tbody>
</table>

1. MV, multivitamins; VA, vitamin A; βC, β-carotene; MUAC, midupper arm circumference.
2. From Cox proportional hazards models with time-to-first event of each outcome as the dependent variable and treatment assignment as the predictor.
3. Comparison between the women who received MV, namely MV alone or MV and VA + βC, and the women who did not receive MV, namely those who received VA + βC alone or placebo.
4. Comparison between the women who received VA + βC, namely VA + βC alone or MV and VA + βC, and the women who did not receive VA + βC, namely those who received MV alone or placebo.
5. Events correspond to the first occurrence of each outcome during follow-up. Only the women without an outcome at the first visit were considered to be at risk.
6. The median follow-up time was 63 mo (5.3 y).
Baseline characteristics of HIV-infected women as predictors of wasting

We examined the risk of wasting according to the women’s characteristics at the first visit (Table 3). Age, level of education, stature, and CD4⁺ cell counts were inversely and significantly related to the risk of a first episode of a MUAC < 22 cm. After adjustment, women aged <20 y had a 1.8-fold greater risk of a MUAC < 22 cm than did the women aged 25–29 y (P = 0.002); also, women with ≥9 y of formal education had a 53% lower risk of wasting than did women with 5–8 y of formal education (P = 0.003) and a 60% lower risk than did women with no formal education (P = 0.004). Every 1 cm increase in height was related to an adjusted average 3% reduction in the risk of wasting (95% CI: 1.5; P = 0.002), whereas CD4⁺ cell counts <200 cells/mm³ were associated with a risk of wasting 3 times that associated with CD4⁺ cell counts ≥500 cells/mm³ (P < 0.0001). After an additional adjustment for baseline MUAC, the association of the risk of wasting and age was no longer evident, and the associations between the risk of wasting and education (adjusted HR for ≥9 compared with 5–8 y formal education: 0.55; 95% CI: 0.33, 0.91; P = 0.02; P for trend: 0.05) and stature (HR for height >150 cm compared with height ≤150 cm: 1.29; 95% CI: 0.95, 1.75; P = 0.11) were attenuated. This suggests that the associations between these variables and wasting were in part related to the fact that younger, less educated, and shorter women had low MUACs at the first visit. After adjustment for potential confounders, the level of education and the CD4⁺ cell count at baseline were each inversely associated with the risk of wasting when measured as a first episode of a BMI < 18. Variables that were not significantly associated with wasting after adjustment included the serum selenium concentration measured at the first visit, parity, the presence of intestinal parasites or sexually transmitted diseases, and whether the mother contributed to the household income or cohabited with a partner.

Time-varying morbidity events as predictors of wasting

We assessed the risk of wasting according to time-varying characteristics that comprised the incidence of signs and symptoms of infections, anemia, malaria parasites, and low CD4⁺ cell counts during follow-up. The incidence of diarrhea, nausea or vomiting, oral ulcers, thrush, or lower respiratory tract infection after adjustment for potential confounders was significantly related to an increased risk of a first episode of a MUAC < 22 cm or a BMI < 18 during the subsequent 3 mo (Table 4). For events that were reported >1 time during 3-mo intervals, such as diarrhea and nausea or vomiting, significant dose-response trends in the risk of wasting according to the number of events were found. Severe anemia (defined as a hemoglobin concentration <85 g/L) or CD4⁺ cell counts <200 cells/mm³ during the 6 mo before the start of the study were significantly and independently associated with a greater risk of wasting when measured as a MUAC < 22 cm or a BMI < 18.

Finally, we compared the incidence of morbidity episodes during periods of weight loss with those during periods with no weight loss (Table 5). The rates of diarrhea, dysentery, nausea or vomiting, oral ulcer or thrush, and lower respiratory tract infections were significantly higher during periods of weight loss than in periods with no weight loss. The rates of diarrhea, dysentery, and nausea were particularly high during short and long periods of severe weight loss. Oral ulcers and thrush were most frequent during long periods of weight loss and especially when the
weight loss was severe. The incidence of upper respiratory tract infections was not significantly increased during weight-loss periods; however, lower respiratory tract infections were significantly more common during long periods of any severity of weight loss and during short periods of moderate weight loss than during periods of no weight loss.

DISCUSSION

In the present randomized controlled trial, supplementation with vitamin B complex and vitamins C and E significantly reduced the risk of wasting when measured as a decline in MUAC. Given the randomized nature of the study, these results were not likely attributable to a confounding bias. The beneficial effect of vitamins on wasting is consistent with the previously reported effects of vitamins on HIV disease progression (18) and could be related to the actions of vitamins at various levels of immunity. Enhancement of specific aspects of immune function would result in fewer and less severe episodes of the opportunistic infections that lead to wasting. Several studies suggest that multivitamins could improve cellular immunity in HIV-infected subjects; in this population from Tanzania (18) and in women from Kenya (30), multivitamin supplementation increased the number of circulating CD4$^+$ cells. Supplementation with vitamin E alone improved T cell–dependent macrophage activation, as measured with the cutaneous delayed-type hypersensitivity response (31–33); it also increased the synthesis of interleukin 2 (31) and T cell–mediated antibody production (32). Lymphocyte
We also examined the associations between sociodemographic characteristics at recruitment and the risk of wasting. Age, stature, and the level of education were inversely related to the incidence of a MUAC < 22 cm. Baseline differences in MUAC between categories of these predictors could partly explain the results from the longitudinal analyses; however, the inverse association between education and wasting, when measured as either a MUAC < 22 cm or a BMI < 18, persisted after adjustments for baseline anthropometry and for other confounders. Previous studies in this population suggested that the woman’s level of education could play a key role in the occurrence of wasting during the course of HIV. In a large cross-sectional study of pregnant women, HIV infection was strongly associated with an increased prevalence of wasting in women with ≤ 4 y of education, but not in women with ≥ 9 y of education (24). Also, a monotonic positive association between the level of education and the rate of weight gain during pregnancy was reported in this group of HIV-infected women from Tanzania (40). Women who were better educated could have improved their nutritional and hygienic practices and may be empowered to reallocate limited resources to health care in the event of HIV-related complications. A long-term investment in improving access to formal education is likely to have a positive effect on the nutritional status of populations with a high prevalence of HIV-infection.

Associations between intercurrent illnesses and weight loss have been described mostly in clinical studies; however, evidence from large, population-based cohorts is scarce, particularly in sub-Saharan Africa. This closely monitored cohort provided us with a unique opportunity to examine the relations between morbidity events and the risk of wasting. Consistent
with the findings of studies that were conducted in England (15) and in the United States (16, 41), we found that events that interfere with nutrient intake (ie, oral ulcers, thirst, and vomiting) or absorption (ie, diarrhea) were significant risk factors for wasting when measured as a first episode of a low MUAC or BMI. In addition, we found that episodes of weight loss were more frequently accompanied by morbidity events than were episodes with no weight loss. Our results suggest that gastrointestinal and respiratory morbidity events could influence not only the incidence of weight loss but also the duration and severity of weight loss. Diarrhea and vomiting appeared to be particularly more frequent during severe weight-loss periods than during moderate weight-loss periods, whereas oral ulcers and thirst were more frequent during prolonged weight-loss periods. The interpretation of these findings is limited, because the precise timing of weight loss in relation to the occurrence of morbidity events was not known; it is conceivable that some morbidity events could have been the result rather than the cause of weight loss during the intervals considered. Another limitation of our study was that it was not possible to identify the specific agents that caused diarrhea or respiratory tract infections. In a study from Zambia, microsporidia accounted for most persistent diarrhea episodes in patients with AIDS (42), which suggests that diarrhea could be primarily the result of immunosuppression in HIV-infected adults from African settings. It will be relevant in future studies to ascertain whether characteristics of resource-limited settings, such as inadequate sanitary conditions and lack of safe water, contribute significantly to secondary infections in HIV-infected adults and children. Public health interventions to improve these specific conditions could have a significant effect in reducing morbidity and mortality in areas that are heavily affected by the HIV epidemic.

In the present longitudinal study, severe anemia was a predictor of wasting independent of CD4+ cell counts. Hemoglobin concentrations <140 g/L were related to the wasting syndrome in a small case-control study that was nested within the Multicenter AIDS Cohort Study and was conducted between 1991 and 1993 (43). Anemia has been identified as an important risk factor for mortality in HIV-infected women (44, 45), and resolution of anemia through erythropoietin administration seemed to be related to an increased survival in an observational study (46). It is not known whether the relation between anemia and survival is a causal one or whether anemia could represent an indicator of HIV disease progression. Our findings suggest that the causal relation between anemia and mortality could be mediated through an effect on wasting and HIV disease progression. The efficacy of interventions against anemia on clinical and immunologic outcomes needs to be assessed in clinical trials.

In conclusion, supplementation of HIV-infected women with vitamin B complex and vitamins C and E reduces the risk of wasting. This new finding adds to previously reported benefits of this formulation and provides additional support for the recommendation of long-term daily supplementation in HIV-infected persons at the doses used in the present trial. Whether supplementation at doses resembling the recommended dietary allowances has the same benefits of multiple recommended dietary allowances on the health and survival outcomes of HIV-infected persons needs to be urgently addressed in randomized trials. Similarly, the potential benefits of providing vitamin B complex and vitamins C and E to HIV-uninfected women who attend prenatal care need to be ascertained. The level of education is a robust predictor of wasting in this population from subSaharan Africa. This constitutes yet another argument for investing in increased access to formal education for girls in developing countries. Anemia, low CD4+ cell counts, and morbidity episodes that are likely to be the result of opportunistic infections are important risk factors for wasting in HIV-infected women who were not receiving antiretroviral treatment.

We are grateful to the women who made the study possible through their participation. We thank the study investigators, coordinator, physicians, and research assistants as well as laboratory technicians, nurses, midwives, and administrative staff in the field.

EV carried out the data analyses, interpreted the results, and wrote the initial draft of the manuscript. ES, GM, KM, and EV participated in the study implementation and supervision in the field. DJH contributed to the study design. WWF is the Principal Investigator of the Tanzania Trial of Vitamins. All authors participated in the data interpretation and in writing the final draft of the manuscript. None of the authors had any conflicts of interest.

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VITAMINS AND WASTING IN HIV-INFECTED WOMEN


