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Self-reported dietary intake and appetite predict early treatment outcome among low-BMI adults initiating HIV treatment in sub-Saharan Africa

John R Koethe[1,2,*], Meridith Blevins[3,4], Claire Bosire[5,6], Christopher Nyirenda[1,7], Edmond K Kabagambe[5], Albert Mwango[3,8], Webster Kasongo[3,9], Isaac Zulu[1,7], Bryan E Shepherd[4] and Douglas C Heimburger[1,3,6]

[1]Centre for Infectious Diseases Research in Zambia, Lusaka, Zambia: [2]Division of Infectious Diseases, Department of Medicine, Vanderbilt University Medical Center, A2200-MCN, 1161 21st Avenue South, Nashville, TN 37232-2582, USA: [3]Institute for Global Health, Vanderbilt University, Nashville, TN, USA: [4]Department of Biostatistics, Vanderbilt University, Nashville, TN, USA: [5]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, USA: [6]Department of Nutrition Sciences, University of Alabama at Birmingham, Birmingham, AL, USA: [7]Department of Internal Medicine, University Teaching Hospital, Lusaka, Zambia: [8]Zambian Ministry of Health, Lusaka, Zambia: [9]Tropical Diseases Research Centre, Ndola, Zambia

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Abstract

Objective: Low BMI is a major risk factor for early mortality among HIV-infected persons starting antiretrovial therapy (ART) in sub-Saharan Africa and the common patient belief that antiretroviral medications produce distressing levels of hunger is a barrier to treatment adherence. We assessed relationships between appetite, dietary intake and treatment outcome 12 weeks after ART initiation among HIV-infected adults with advanced malnutrition and immunosuppression.
Design: A prospective, observational cohort study. Dietary intake was assessed using a 24 h recall survey. The relationships of appetite, intake and treatment outcome were analysed using time-varying Cox models.
Setting: A public-sector HIV clinic in Lusaka, Zambia.
Subjects: One hundred and forty-two HIV-infected adults starting ART with BMI $<16\,kg/m^2$ and/or $CD4^+$ lymphocyte count <50 cells/μl.
Results: Median age, BMI and $CD4^+$ lymphocyte count were 32 years, $16\,kg/m^2$ and 34 cells/μl, respectively. Twenty-five participants (18 %) died before 12 weeks and another thirty-three (23 %) were lost to care. A 500 kJ/d higher energy intake at any time after ART initiation was associated with an approximate 16 % reduction in the hazard of death (adjusted hazard ratio = 0·84; $P = 0{\cdot}01$), but the relative contribution of carbohydrate, protein or fat to total energy was not a significant predictor of outcome. Appetite normalized gradually among survivors and hunger was rarely reported.
Conclusions: Poor early ART outcomes were strikingly high in a cohort of HIV-infected adults with advanced malnutrition and mortality was predicted by lower dietary intake. Intervention trials to promote post-ART intake in this population may benefit survival and are warranted.

Keywords
HIV
Malnutrition
Antiretroviral therapy
Africa

Access to antiretroviral therapy (ART) treatment for HIV infection in sub-Saharan Africa has expanded rapidly since 2003, but many individuals are not diagnosed until a state of advanced disease and mortality in the early months after initiating therapy remains high[1–4]. Rapid weight loss, particularly loss of lean body mass, was recognized as a negative prognostic indicator early in the HIV epidemic and a primary characteristic of HIV-associated wasting[5–9]. Individuals with a low BMI represent a significant proportion of those presenting for HIV care in the region; in a survey from Lusaka, Zambia, 33 % of patients starting ART had a BMI $<18{\cdot}5\,kg/m^2$ and 9 % had a BMI $<16{\cdot}0\,kg/m^2$[10]. A low BMI is an independent predictor of early (e.g. ≤6 months) mortality after ART initiation in several analyses from sub-Saharan Africa and improving treatment outcomes for this population is a critical challenge for global health efforts[1,11–14].

Anorexia, primarily due to a persistent and heightened inflammatory response, was recognized as a feature of advanced HIV disease and a negative prognostic indicator

*Corresponding author: Email john.r.koethe@vanderbilt.edu

in the pre-ART era in developed countries, but there are limited data on the relationship between dietary intake and health status among HIV-infected adults in resource-limited settings[15–18]. Additionally, patient interviews have demonstrated a widely held belief that ART causes dramatic increases in appetite, which may serve as a barrier to medication adherence and lead to a higher incidence of treatment failure[19–22]. Given the high prevalence of late-stage HIV in sub-Saharan Africa, we hypothesized that poor self-reported dietary intake and/or a rapid increase in appetite among individuals with very low BMI starting ART would predict mortality or loss to care in the early treatment period. To investigate our hypothesis, we enrolled a prospective cohort of adults with advanced malnutrition and immunosuppression initiating ART in Lusaka, Zambia and assessed the relationships between self-reported appetite, dietary intake (total energy, carbohydrate, protein and fat) and 12-week treatment outcome. The overall goal of the research is the development of strategies to identify the subset of low-BMI ART recipients who might benefit from additional diagnostic or therapeutic interventions to improve survival and programme retention.

Experimental methods

In preparation for our prospective cohort study, we conducted focus group discussions with seventy-seven HIV patients and caregivers from the Community Based TB/HIV/AIDS Organization in Lusaka, Zambia to better understand the range of local or indigenous food names, preparation methods and typical portion sizes. The 24 h dietary recall survey used in the present study had an open response format rather than specific response options, and interviewers were trained to probe for details of the foods participants ate or drank, starting from the first to the last food consumed in the day; cooking methods and the amounts consumed; additional ingredients added to staple foods; any sauces or gravies; beverages consumed at home and away from home (e.g. tea, coffee, porridge, soft drinks, other alcoholic and non-alcoholic drinks); any between-meal snacks; and the addition of sugar or fat/margarine to foods or beverages. We utilized artificial food models and serving utensils to assist participants in estimating portion sizes.

The nutrient composition of local staple foods was determined using food composition tables published by the Zambian National Food and Nutrition Commission (available from http://www.nfnc.org.zm). Total carbohydrate, protein and fat intakes were computed using the Nutrition Data System for Research software version 2006, developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, MN, USA (www.ncc.umn.edu). Total energy intake was calculated using the conversion values of 17 kJ/g for carbohydrate and protein, and 37 kJ/g for fat. Foods not available in the database were substituted with foods of similar nutrient composition.

Between 6 November 2006 and 12 November 2007, we enrolled 142 HIV-infected adults initiating ART at a public-sector clinic in Lusaka, Zambia with a BMI $< 16\,kg/m^2$ or a $CD4^+$ lymphocyte count <50 cells/μl in an observational, prospective cohort study to assess nutrition-related predictors of all-cause mortality in the first 12 weeks of treatment. Given the pilot nature of the study we specifically recruited patients with the most advanced malnutrition and immunosuppression, and the final cohort was not representative of the BMI or $CD4^+$ lymphocyte count distribution of all patients presenting for HIV care during the study period. The study setting, eligibility criteria, design and procedures have been previously described[23]. Briefly, individuals were eligible for enrolment if they qualified for ART according to Zambian national guidelines in place at the time (i.e. WHO stage 4 disease and a $CD4^+$ lymphocyte count <200 cells/μl, or WHO stage 3 disease and a $CD4^+$ lymphocyte count <350 cells/μl); were intending to start therapy the same day; met the BMI and/or $CD4^+$ lymphocyte count enrolment criteria; and agreed to adhere to the study visit schedule and laboratory testing requirements. The first-line ART regimen was selected from the national programme formulary by the clinician and included two nucleoside reverse transcriptase inhibitors in combination with one non-nucleoside reverse transcriptase inhibitor.

Participants were evaluated by a research nurse and a clinical officer and/or a supervising physician at the enrolment visit and subsequent study visits at 1, 2, 4, 8 and 12 weeks post-ART initiation. The interviewer-administered 24 h dietary intake survey was performed at ART initiation and at 1, 4 and 12 weeks. Appetite was assessed at every study visit using the question: 'Would you describe your appetite as none, little, normal, hungry, or very hungry?'. Because only one participant on one occasion gave a 'very hungry' response to the appetite scale, this response was reclassified as 'hungry' to avoid singularity in the modelling. While the stated endpoint of the study was 12 weeks (84 d) post-ART initiation and participants were asked to adhere to the visit schedule, the median time to the last study visit among survivors was 88 d. The full follow-up period for all participants is included in the linear mixed models, which incorporate the number of days post-ART rather than the visit number to allow for early or late study visits, but the graphical representations are truncated at 90 d. Linear mixed models were used to assess the relationship between appetite and dietary intake (total energy (kJ/d) and carbohydrate, protein and fat (g/d))[24].

Cox regression models with baseline and time-dependent covariates were used to assess the relationship between appetite categories or dietary intake and time to death or the composite endpoint of time to death or loss to care. We modelled the effect of an incremental increase of 25 g/d for

carbohydrate and 5 g/d for protein; these values were based on the baseline intake ratio. The analysis included appetite values from all visits and dietary intake values from baseline and 1, 4 and 12 weeks. Models were adjusted for sex and a first principal component incorporating previously described risk factors for early mortality on ART (age, BMI, $CD4^+$ lymphocyte count, Hb and serum phosphate level). The first principal component was extracted for age, BMI, square root of $CD4^+$ lymphocyte count, Hb and phosphate using the 'princomp()' function from the covariance matrix in R-software. We adjusted for serum phosphate due to our prior finding that hypophosphataemia is an independent predictor of early mortality in this population[23]. If a participant had no recorded appetite or intake values within a given time interval, he or she was dropped from the risk set for that interval.

To visualize longitudinal data, we plotted appetite score and total energy, carbohydrate, protein and fat intake for the alive, deceased and lost-to-care participants against the number of days on ART. Each participant required a minimum of two recorded values for inclusion and is represented by a single line (participants who had only one recorded value, generally because they had died, were excluded). For each variable we sketched a locally weighted scatterplot smoothing curve by fitting a polynomial surface using local (weighted) least squares regression[25]. R-software 2·11·0 (www.r-project.org) was used for data analyses. Analysis scripts are posted at http://biostat.mc.vanderbilt.edu/wiki/pub/Main/ArchivedAnalyses/analysis-scripts-002.nw.

The study protocol and informed consent documents were approved by the University of Zambia Research Ethics Committee (Lusaka, Zambia) and the Institutional Review Boards at the University of Alabama at Birmingham (Birmingham, AL, USA) and Vanderbilt University (Nashville, TN, USA).

Results

Fifty-nine participants (42 %) had a BMI $<16{\cdot}0\,kg/m^2$, 110 (77 %) had a $CD4^+$ lymphocyte count <50 cells/μl and twenty-seven (19 %) met both eligibility criteria. Eighty-seven participants (61 %) were female, and median age, BMI and $CD4^+$ lymphocyte count were 32 years, $16\,kg/m^2$ and 34 cells/μl, respectively. There were no significant differences according to clinical characteristics, baseline appetite or baseline dietary intake between participants alive, dead or lost to care at 12 weeks, with the exception of age (Table 1). The intra-class correlation coefficient for the 24 h recall survey, which describes the variability in nutritional intake over time for the same participant, was 0·34 for total energy, 0·34 for carbohydrate, 0·24 for protein, 0·21 for fat and 0·17 for appetite.

We assessed the relationship of self-reported appetite and dietary intake using linear mixed models; the estimated dietary intake at ART initiation according to appetite is represented by the intercept value and the daily change in intake is represented by the slope (Table 2). The models incorporate matched appetite and intake values collected at baseline and at 1, 4 and 12 weeks post-ART initiation, and participants were reclassified according to appetite category from visit to visit as warranted. At baseline, appetite was significantly associated with energy, carbohydrate, protein and fat intake ($P<0{\cdot}01$ for all comparisons). Participants reporting a 'normal' appetite had the highest total energy (7398 kJ/d) and carbohydrate (252 g/d), protein (59 g/d) and fat intakes (59 g/d). Conversely, those reporting no appetite had the lowest intakes of total energy (4476 kJ/d), carbohydrate (162 g/d), protein (26 g/d) and fat (31 g/d). Additionally, there were significant differences in the rate of change in energy and carbohydrate intake according to appetite score ($P=0{\cdot}05$ and $P<0{\cdot}01$, respectively). Patients reporting they were 'hungry' at a given study visit had the largest increases per day in energy and carbohydrate intake (23·0 kJ/d and 1·2 g/d, respectively), while those reporting no appetite had the greatest decreases (−43·1 kJ/d and −1·1 g/d, respectively). In contrast, the interaction of appetite score and time was not statistically significant for protein and fat intake. The decline in energy intake during follow-up was greatest for those reporting no appetite (Fig. 1). Finally, we assessed the model's linearity assumption for the relationship between dietary intake variables and time, and found little evidence for non-linearity ($P>0{\cdot}10$ for all comparisons).

Twenty-five participants died during the 12-week follow-up period (mortality rate 87·4 per 100 person-years of follow-up); among those who died, the median time to death was 34 d (interquartile range: 20, 54 d). Thirty-three participants (23 %) were lost to care; the median follow-up time for those lost was 58 d (interquartile range: 45, 71 d). We calculated adjusted hazard ratios (AHR) to represent the estimated ratio of the hazard of death, or the combined endpoint of mortality or loss to care, at any time prior to study completion for a hypothetical pair of participants whose dietary intake values differ by the interval amount (i.e. 500 kJ/d for energy, 25 g/d for carbohydrate, 5 g/d for protein or 5 g/d for fat) at baseline (Table 3a) or after starting ART (Table 3b). Baseline dietary intake was not significantly associated with either mortality or the combined endpoint. At a given time point after ART initiation, however, 500 kJ/d higher energy intake was associated with an approximate 16 % reduction in the hazard of death (AHR = 0·84, $P=0{\cdot}01$). Similar relationships were observed for a 25 g/d carbohydrate increase (AHR = 0·85, $P=0{\cdot}09$), a 5 g/d protein increase (AHR = 0·81, $P=0{\cdot}01$) and a 5 g/d fat increase (AHR = 0·80, $P<0{\cdot}01$). Higher intake was also associated with a reduction in the combined endpoint of mortality or loss to care, which did not reach statistical significance (with the exception of fat intake).

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Table 1 Demographics and clinical characteristics of study participants; HIV-infected adults, Lusaka, Zambia

	All participants (*n* 142)		Outcome at 12 weeks of ART: Alive (*n* 84)		Dead (*n* 25)		Lost to follow-up (*n* 33)	
	n or median	% or IQR	*n* or median	% or IQR	*n* or median	% or IQR	*n* or median	% or IQR
Female sex (%)	87	61·0	53	63·1	12	48·0	22	66·7
Age (years)	32	28, 38	34	29, 38	33·5	29, 41	30§	25, 32
Weight (kg)	46	41, 51	46	41, 52	42	40, 48	46	40, 51
BMI (kg/m^2)	16·4	15·4, 18·5	16·4	15·4, 18·6	15·9	15·2, 17·0	16·7	15·6, 19·2
CD4$^+$ count (cells/μl)	34	21, 47	36	22, 48	31	23, 45	30	20, 47
Hb (g/dl)	9·8	8·8, 11·6	10	8·9, 11·7	9·3	8·6, 11·1	9·7	8·2, 11·0
Baseline energy intake and appetite score								
Total energy (kJ/d)	6125	4082, 7712	6276	4304, 7758	5241	3592, 7218	6485	4057, 7750
Carbohydrate (g/d)	201	140, 273	203	153, 283	181	123, 237	204	145, 257
Percentage of total energy*	59		57		62		60	
Protein (g/d)	49	28, 63	52	32, 65	37	15, 61	40	27, 59
Percentage of total energy*	13		14		12		12	
Fat (g/d)	47	30, 67	48	32, 67	37	20, 59	55	30, 67
Percentage of total energy	30		27		29		29	
Appetite score†	2	2, 3	2	2, 3	2	2, 2	2	2, 3
Appetite distribution (*n*, %)								
None	20	14	11	13	4	16	5	15
Little	78	55	45	54	15	60	18	55
Normal	33	23	20	24	5	20	8	24
Hungry or very hungry	11	8	8	10	1	4	2	6
ART regimen (*n*, %)‡								
ZDV/3TC/EFV	8	6	6	7	1	4	1	3
ZDV/3TC/NVP	34	24	22	26	8	32	4	12
d4T/3TC/EFV	15	11	11	13	3	12	1	3
d4T/3TC/NVP	62	44	39	46	13	52	10	30
TDF/FTC/EFV	4	3	1	1	0		3	9
TDF/FTC/NVP	19	13	5	6	0		14	42

ART, antiretroviral therapy; IQR, interquartile range; ZDV, zidovudine; 3TC, lamivudine; EFV, efavirenz; NVP, nevirapine; d4T, stavudine; TDF; tenofovir; FTC, emtricitabine.
Among the 142 cases included in table, values were missing for the following measurements: twenty-nine (20 %) for baseline Hb (missing from the HIV care programme record), two for age (birth dates unknown) and one for BMI (participant could not stand for height measurement).
*Percentage of total energy intake was calculated from mean intake values, rather than the median absolute values shown in the table, using a conversion factor of 17 kJ/g (4 kcal/g) for carbohydrate and protein, and 37 kJ/g (9 kcal/g) for fat. Percentages may not sum to 100 due to variations in data distribution.
†Appetite scale: 1 = none; 2 = little; 3 = normal; 4 = hungry or very hungry.
‡Test of significance not performed due to sparse cell counts.
§$P < 0{\cdot}05$ for comparison of participants alive, dead and lost to follow-up at 12 weeks.

Table 2 Effect of self-reported appetite on dietary intake; HIV-infected adults, Lusaka, Zambia

Dietary intake variable	Self-reported appetite score	Baseline estimate of dietary intake (intercept)	95 % CI	*P* value	Estimate of change in dietary intake (slope/d)	95 % CI	*P* value
Total energy (kJ/d)	None	4476	3546, 5401	<0·01	−43·1	−108·0, 21·8	0·05
	Little	5606	5142, 6071		−1·3	−25·1, 22·6	
	Normal	7398	6875, 7926		−5·0	−20·1, 10·0	
	Hungry	6435	5422, 7444		23·0	−0·8, 46·9	
Carbohydrate (g/d)	None	162	130, 194	<0·01	−1·1	−3·3, 1·1	<0·01
	Little	192	176, 208		−0·2	−1·0, 0·6	
	Normal	252	234, 271		−0·1	−0·6, 0·4	
	Hungry	211	177, 246		1·2	0·4, 2·0	
Protein (g/d)	None	26	17, 35	<0·01	*		
	Little	45	40, 49				
	Normal	59	54, 65				
	Hungry	56	47, 65				
Fat (g/d)	None	31	21, 41	<0·01	*		
	Little	46	41, 51				
	Normal	59	53, 65				
	Hungry	57	46, 67				

Results of linear mixed-effects model including time, appetite and time×appetite interaction terms and random intercept for patients (*n* 142).
While the final scheduled study visit was at week 12 (84 d post-ART initiation), the median time to the last study visit among survivors was 88 d and linear mixed models incorporate the full follow-up period for all participants.
*A non-significant interaction term was dropped from the protein model ($P = 0{\cdot}44$) and the fat model ($P = 0{\cdot}41$); the overall time effect, or slope, is −0·04 (95 % CI −0·13, 0·04) for protein and −0·04 (95 % CI −0·13, 0·06) for fat. There is little evidence that the relationship between dietary intake variables and time is non-linear ($P > 0{\cdot}10$ for all comparisons).

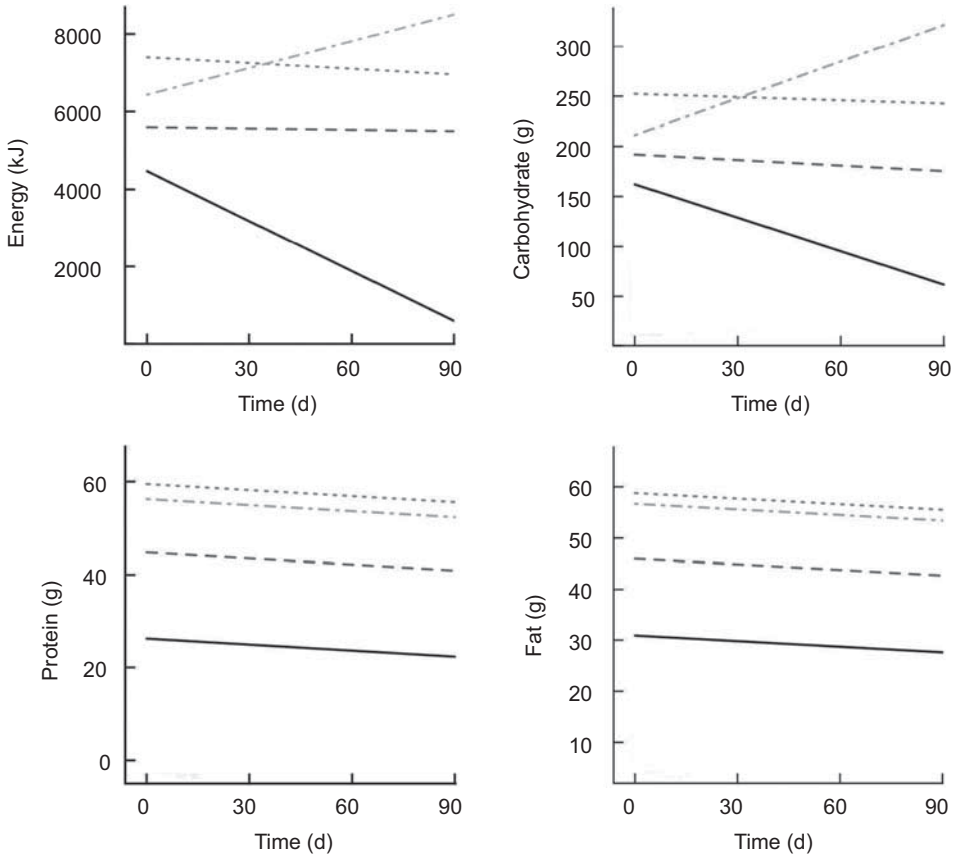

Fig. 1 Effect of appetite (——, none; – – –, little; - - -, normal; —·—, hungry) on dietary intake from initiation of antiretroviral therapy to 90 d; HIV-infected adults (*n* 142), Lusaka, Zambia. Results of linear mixed-effects model including time and appetite. Only one participant reported no appetite at visit five, and zero participants reported no appetite at visit six (12 weeks). The line for 'none' is an extrapolation at these later time points

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Table 3a Baseline (pre-treatment) predictors of mortality and loss to follow-up at 12 weeks of ART*; HIV-infected adults, Lusaka, Zambia

Marker	AHR for mortality	95 % CI	*P* value	AHR for mortality or loss to care	95 % CI	*P* value
Energy (per 500 kJ/d increase)	0·95	0·88, 1·03	0·22	0·96	0·91, 1·01	0·13
Carbohydrate (per 25 g/d increase)	0·95	0·85, 1·06	0·34	0·95	0·88, 1·02	0·19
Protein (per 5 g/d increase)	0·94	0·87, 1·02	0·17	0·95	0·90, 1·00	0·07
Fat (per 5 g/d increase)	0·96	0·89, 1·04	0·29	0·98	0·93, 1·02	0·30
Appetite			0·82			0·78
None *v.* normal	1·53	0·41, 5·76		1·21	0·51, 2·84	
Little *v.* normal	1·22	0·44, 3·38		1·12	0·59, 2·14	
Hungry *v.* normal	0·58	0·07, 5·00		0·63	0·18, 2·23	

ART, antiretroviral therapy; AHR, adjusted hazard ratio.
*While the final scheduled study visit was at week 12 (84 d post-ART initiation), the median time to the last study visit among survivors was 88 d and linear mixed models incorporate the full follow-up period for all participants.

Table 3b Time-dependent predictors of mortality and loss to follow-up at 12 weeks of ART*; HIV-infected adults, Lusaka, Zambia

Marker	AHR for mortality	95 % CI	*P* value	AHR for mortality or loss to care	95 % CI	*P* value
Energy (per 500 kJ/d increase)	0·84	0·73, 0·96	0·01	0·93	0·87, 1·00	0·07
Carbohydrate (per 25 g/d increase)†	0·85	0·71, 1·02	0·09	0·92	0·83, 1·02	0·14
Protein (per 5 g/d increase)†	0·81	0·68, 0·95	0·01	0·97	0·91, 1·04	0·39
Fat (per 5 g/d increase)†	0·80	0·68, 0·94	<0·01	0·92	0·85, 0·99	0·03
Appetite‡			0·76			0·98
None *v.* normal	0·82	0·10, 6·34		0·85	0·20, 3·61	
Little *v.* normal	0·95	0·38, 2·36		1·07	0·60, 1·93	
Hungry *v.* normal	1·89	0·53, 6·80		1·17	0·45, 3·03	

ART, antiretroviral therapy; AHR, adjusted hazard ratio.
Models adjusted for sex, and a first principal component (incorporating age and baseline BMI, $CD4^+$ lymphocyte count, Hb and serum phosphate level; *n* 142).
*While the final scheduled study visit was at week 12 (84 d post-ART initiation), the median time to the last study visit among survivors was 88 d and linear mixed models incorporate the full follow-up period for all participants.
†When the time-dependent models of carbohydrate, protein and fat intake were adjusted for total energy the association with mortality was not significant ($P = 0{\cdot}10$, 0·25 and 0·12, respectively), suggesting the relative proportion of each macronutrient in the diet was not a predictor of outcome.
‡The effect of time-varying appetite on mortality also remained non-significant when we further adjusted the model for total energy intake ($P = 0{\cdot}30$).

When the time-dependent Cox models incorporating total carbohydrate, protein and fat intake were also adjusted for total energy intake, there was no longer a significant association between any of the macronutrient categories and mortality ($P = 0{\cdot}10$, 0·25 and 0·12, respectively). This finding suggests that while total energy intake was a significant predictor of survival in our cohort, either the relative contribution of each macronutrient to total energy was not a predictor of outcome or our study lacked sufficient power to detect a significant effect.

For appetite, the AHR represents the relative hazard of death for a participant reporting a 'normal' appetite *v.* one reporting appetite as 'none', 'little' or 'hungry'. There did not appear to be a significant association between either baseline appetite (Table 3a) or time-varying appetite (Table 3b) and study outcome. The effect of time-varying appetite on mortality remained non-significant when we further adjusted the model for total energy intake ($P = 0{\cdot}30$). Dietary intake and appetite scores normalized gradually over the study period, and we did not observe an abrupt increase in the composite appetite score immediately after starting treatment (Fig. 2). Among the twenty-four deaths with a recorded appetite value at the visit immediately preceding death, one patient (4 %) reported no appetite, three (13 %) reported 'hungry', eight (33 %) reported 'little appetite' and twelve (50 %) reported 'normal appetite'. One deceased participant had a missing value.

Discussion

In a cohort of undernourished adults with advanced immunosuppression starting ART in Zambia, over 40 % of participants were either deceased or lost to care within the initial 12 weeks of treatment, highlighting a need for additional resources and innovative approaches to improve treatment outcomes in this particularly vulnerable population. We found that a failure to increase energy intake while on ART predicted poor treatment outcome after adjusting for several known risk factors, suggesting that persistent anorexia is a marker of increased disease severity independent of $CD4^+$ lymphocyte depletion. Total energy intake, rather than the relative contribution of carbohydrate, protein and fat to energy intake, appeared to be the major dietary determinant of survival, but this finding should be interpreted with caution given the heavily carbohydrate-based Zambian diet and the possibility that our study lacked power to detect a true difference between macronutrient categories. Of note, energy intake at treatment initiation

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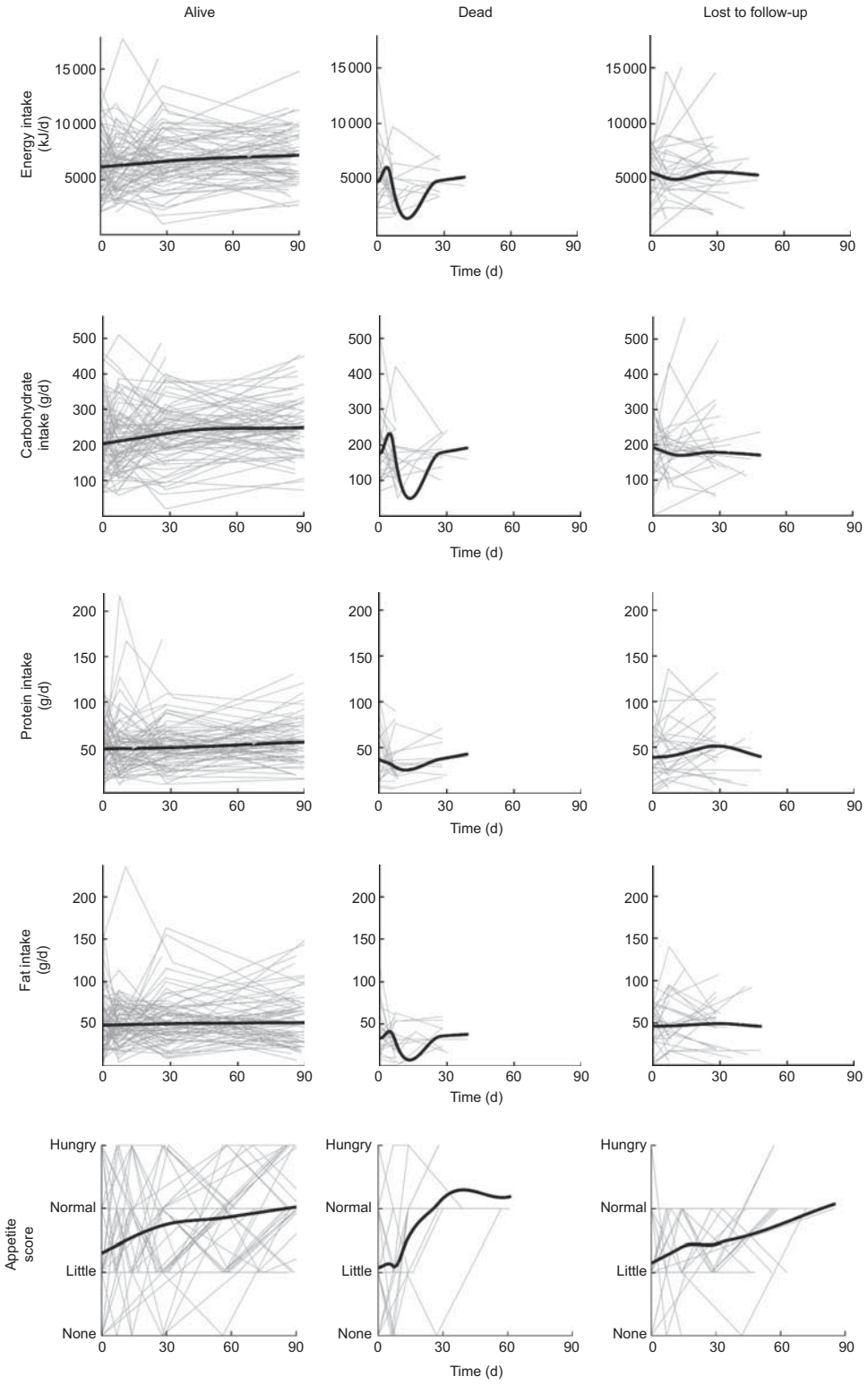

Fig. 2 Dietary intake and appetite scores among participants alive, dead and lost to follow-up at study completion (——, single participants; ▬▬, locally weighted scatterplot smoothing curves); HIV-infected adults (*n* 142), Lusaka, Zambia. Among patients who died or were lost to follow-up, the curves at later time points are driven by the decreasing number of patients still remaining in the study

was not a significant predictor of survival, which may indicate that patients with poor intake prior to beginning ART are not 'consigned' to a poor outcome. To date, the few macronutrient supplementation trials conducted among HIV-infected adults in sub-Saharan Africa have shown minimal benefit, but future studies are warranted

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to identify the subset of patients who will develop poor dietary intake after starting ART (not predicted by baseline intake in our analysis) and whether targeted interventions for those with low dietary intake can improve early survival and retention in care[26–29].

Our observation that appetite normalizes gradually in the first 12 weeks of ART may inform pre-ART patient counselling and community HIV education efforts. Several studies of HIV-infected adults in sub-Saharan Africa not yet on ART found a widely held belief that treatment causes dramatic increases in appetite which, in the absence of sufficient food, will produce distressing levels of hunger[19–22]. While expansion of programmes to alleviate food insecurity among HIV-infected persons is needed, treatment programmes may be justified in addressing concerns regarding hunger as a barrier to medication adherence with evidence that average increases in appetite after ART initiation are likely to be modest and gradual.

A major limitation of our study is the restrictive inclusion criteria, which were based on previous epidemiology studies but reduce the generalizability of our findings[4,10–14]. Our aim was to investigate nutrition-related predictors of treatment outcome among the 'sickest of the sick' presenting to a public HIV clinic in Lusaka, and given the exploratory nature of our study we limited our cohort to those with BMI $< 16\,kg/m^2$ and/or $CD4^+$ lymphocyte count <50 cells/μl to maximize our detectable effect within the constraints of the available resources and sample size. Our observed incidence of mortality and loss to care, and the relationship to dietary intake, should not be extrapolated to patients with higher BMI or $CD4^+$ lymphocyte counts, although additional studies are warranted to determine if low intake remains a predictor of treatment outcome in patients with less severe malnutrition or immunosuppression. While sex and Hb concentration were not significantly different between 12-week outcome categories, the potential effects of unknown confounders (e.g. occult opportunistic infections) could not be assessed in our observational study. Even though we attempted to control for baseline age, BMI, $CD4^+$, Hb and phosphate, there may have been residual confounding as these variables were collapsed into a single principal component to avoid over-fitting given the relatively small sample size[30]. We did not examine differential micronutrient (e.g. Zn or Se) intakes or carbohydrate (e.g. refined flours *v.* whole grains) and protein/fat (e.g. animal *v.* plant) sources. Finally, our sample size at later time points was reduced by a high rate of participant attrition. Our observed loss rate at 12 weeks was higher than the Zambian national ART programme or similar programmes in the region, which we attribute to our selection of patients with advanced disease[31]. While lost participants were slightly younger and may represent a more mobile group, prior studies of intensive ART patient tracking suggest a high proportion of those lost to care represent unrecorded deaths[32,33].

Several assumptions were implicit in our dietary assessment strategy and may have impacted our results. First, we assumed that the dietary recall survey accurately captured portion sizes, and that the calculated intake values derived from Zambian National Food and Nutrition Commission data accurately accounted for items less common in the Western diet (e.g. insects or organ meats). The 24 h dietary recall survey used in the study was developed with participation from focus groups to identify local foods and preparation methods, and it had not been used in prior studies. However, the survey was validated against repeated FFQ in similar individuals in a different suburb of Lusaka prior to utilization in our study; the Spearman correlation coefficients for averaged survey responses and FFQ ranged from 0·44 for protein intake to 0·65 for total energy intake. Second, we assumed the degree of attenuation of true between-person differences due to error in our survey methods was not high enough to prohibit the detection of significant effects. Prior studies observed under-reporting of dietary intake by 24 h recall methods compared with quantified energy expenditure measurements; we could not determine if under-reporting was present in our study and, if present, whether the effect was consistent across the response range[34,35]. Third, many Zambians live in a state of precarious poverty, but we necessarily assumed a degree of homogeneity in food availability and day-to-day meal composition between study visits. Lastly, the staple of the Zambian diet is *nshima*, a firm porridge made from refined maize flour eaten at all meal times, and some participants may have over-reported protein and fat intakes, either from recall bias or a desire to overstate their economic status, which may have raised the aggregate intake estimates.

Conclusion

Delayed HIV testing, coupled with a high prevalence of poverty, food insecurity and chronic undernutrition in many areas of sub-Saharan Africa, complicates the effort to provide effective HIV care and treatment services. In a cohort of individuals with advanced malnutrition and immunosuppression in Zambia, the rates of mortality and loss to care in the first 12 weeks of ART were strikingly high, and a poor treatment outcome was predicted by lower self-reported dietary intake. Our findings suggest that a failure to increase intake likely serves as a marker of increased disease severity independent of immunosuppression, but future trials are needed to determine whether nutritional interventions in the pre-ART or immediate post-ART period may have a role in reducing mortality. Despite tremendous gains in providing access to ART across sub-Saharan Africa, improving health outcomes for the large number of low-BMI individuals remains a major challenge for global health programmes.

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