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Correlation Between Nutritional Indicators and Low CD4 Count (<200 cells>/mm3) among HIV Positive Adults in Kapiri, Zambia 2008-2009

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ABSTRACT

Correlation Between Nutritional Indicators and Low CD4 Count (<200 cells/mm^3) among HIV Positive Adults in Kapiri, Zambia 2008-2009

By Kadija C. Fofana

Background

The co-morbidity of malnutrition and HIV is highly prevalent in sub-Saharan Africa due to the pervasiveness of HIV/AIDS and food insecurity in this region. Limited research has been done to assess the association between nutritional indicators and CD4 count among ART-naïve populations in resource scarce settings. It was specifically of our interest to assess various nutritional indicators as factors correlated with low CD4 cell count (< 200 cells/mm^3).

Methods

From 2008-2009, HIV positive adult males and non-pregnant females completed nutritional assessments at a Medecins Sans Frontiers (MSF) HIV clinic in Kapiri, Zambia. First recorded CD4 cell counts were used in this analysis. In this cross-sectional analysis, sex-stratified multivariate logistic regression models assessed the association between various nutritional indicators and CD4 cell count less than 200 cells/mm^3.

Results

51% of males and 50% of females had a first recorded CD4 count of less than 200 cells/mm^3. Among males, a mid-upper arm circumference (MUAC) categorization as 'undernourished' (aPR= 1.5113, 95% CI = 1.1451-1.9946, p = 0.0035) was associated with CD4 cell count less than 200 cells/mm^3. Among females, an MUAC categorization as 'undernourished' (aPR = 1.4212, 95% CI 1.1027-1.8318, p= 0.0066) was associated with CD4 cell count less than 200 cells/mm^3.

Conclusion

In sex-specific multivariate analyses, MUAC (undernourished) among both males and females was the only nutritional indicator associated with the outcome. It may be of interest to further investigate the impact of MUAC as an insightful anthropometric measure in the evaluation of immunological outcomes among people living with HIV (PLHIV) in light of differences between sex and the overall nutritional status of the studied population.

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Thank you!

Author's Statement Page

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Signature of Author

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Chapter I: Background

Acute and Chronic Malnutrition

Malnutrition is a disease state associated with inadequate nutrient intake, quality of nutrient intake, abnormal nutrient absorption and utilization, any of which may result in detrimental changes in body weight, composition, and physical function over time [1]. Acute malnutrition often results from sudden food shortages and is associated with a high risk of mortality. Chronic malnutrition is associated with persistent poverty, food insecurity and co-morbidity [2].

Acute and chronic malnutrition are associated with different metabolic adaptations. In comparison to chronic malnutrition where metabolic equilibrium is approximately maintained despite being sub-optimal, acute malnutrition is a state of progressive negative energy balance which leads to metabolic distress [3, 4]. Acute and chronic malnutrition become an increased concern among persons living with diseases such as tuberculosis and HIV/AIDS. The co-morbidity of these conditions heightens metabolic demand and can accelerate the advancement of HIV infection to AIDS [5].

Malnutrition and HIV/AIDS

Acquired immune deficiency syndrome (AIDS) is a disease caused by the human immunodeficiency virus (HIV) which impairs the body's immune system and its ability to fight off infection. Malnutrition is described as an imbalance between nutrient intake and the body's demand for growth and maintenance [5]. Despite the suppression of immune defenses, indices of good health can be maintained with medication adherence and sufficient nutrition; however, this is of great concern in developing countries where socioeconomic factors impact one's

ability to acquire and consume nutrient dense food. The interaction of both HIV and malnutrition are important in understanding HIV disease outcomes especially in regions such as sub-Saharan Africa where food insecurity and disease prevalence are excessive and constant. The relatively high risk of malnutrition among people living with HIV (PLHIV) has been attributed to several socioeconomic and biological factors. HIV can jeopardize household economic productivity, which in turn compromises food security and the quality of food consumed. Biologically, HIV not only causes PLHIV to have an increased resting metabolic rate and energy expenditure, but the disease can also diminish appetite and reduce nutrient absorption, attributable in part to side effects of antiretroviral treatment (ART) medications [5].

Purpose of Study

The purpose of this study is to assess whether various nutritional indicators are correlated with CD4 count less than 200 cells/mm^3. Past studies have found that nutritional indicators such as low body mass index (BMI) and food insecurity pose an overall threat to physical health and survival for PLHIV, even among those who are on ART [6, 7] . This thesis will build upon previous research which has examined nutritional indicators as predictors of clinical HIV disease progression among ART naïve PLHIV [8]. The analysis will be conducted using data collected from HIV positive adults in Kapiri, Zambia between 2008 and 2009. An understanding of the relationship between nutrition and poor immunological health status can help clinicians identify individuals who are at higher risk for poor immunological outcomes and target interventions to such persons.

Hypothesis

This study posits that nutritional indicators will have a significant association with CD4 count less than 200 cells/mm^3 in this population of HIV positive adults in Kapiri, Zambia. Null hypothesis: there is no association between nutritional indicators and CD4 count less than 200 cells/mm^3.

Chapter II: Literature Review

Nutritional indicators and their association with low CD4 count

Body Mass Index (BMI)

The chronic energy deficiency (CED) classification system has been commonly used to categorize levels of BMI and identify the severity of malnutrition [9].

Classification of Chronic Energy Deficiency (CED) based on Body Mass Index (BMI)						
CED Level	Extreme wasting	Severe wasting	Severe thinness	Moderate thinness	Mild thinness	Normal
BMI (kg/m^2)	<10.0	10.0 – 12.9	13.0 - 15.9	16.0 – 16.9	17.0 – 18.4	>18.4

Previous studies which have examined the relationship between BMI and CD4 count among populations on ART, have shown that persons with higher BMI levels especially in the normal range (BMI > 18.4 kg/m^2) have reduced progression to AIDS and HIV-related mortality. In a study conducted by Koethe, et al. among ART naïve adults in Nashville, Tennessee, researchers observed that persons with a baseline CD4 count of less than 200 cells/mm^3 and normal BMI had the highest odds of attaining a CD4 count of more than 350 cells/mm^3 at 12 months follow-up [10]. A cross-sectional analytical study conducted by Zachariah, et al. in Malawi to examine the proportion of deaths that occur after initiating ART and associated risk factors, illustrated that persons with a BMI < 16 kg/m^2 had a 6-fold increase in mortality risk within the first 3 months of ART initiation compared to those who had optimal BMI levels [11]. Additionally, studies that have examined the relationship between BMI and CD4 count among ART naïve populations have observed similar relationships. In a study done by van der Sande, et al. in The Gambia, those with a baseline BMI < 18 kg/m^2 had a 3-fold increase in morality risk compared to those who had higher BMI levels [12]. BMI was lower in HIV positive adults who had

opportunistic infections (OI) in comparison to those who were solely seropositive from a longitudinal study conducted in Lusaka, Zambia [13]. Such inferences are suggestive of a notable association between BMI (as a nutritional indicator) and CD4 cell outcomes among PLHIV irrespective of ART treatment.

Mid-upper arm circumference (MUAC)

The use of MUAC in the assessment of nutritional status and adverse health/disease outcomes has been commonly used in resource scarce regions. Despite the differing opinions on MUAC cutoffs and nutritional classifications, past studies have shown that there is an association between MUAC below 230 mm and BMI below 18.5 kg/m^2 among adults. In a study conducted by Liu, et al., among Tanzanian patients on ART, researchers observed that lower MUAC levels were strongly associated with an increased risk of death within 3 months of initiating treatment [14]. Gustafson, et al. observed an increased risk of death among both HIV-positive and HIV- negative patients with tuberculosis who had low MUAC measurements [15]. Additionally, Kelly, et al. found that MUAC measurements were lower in HIV positive adults with OI's in comparison to those who were solely seropositive without OI's [13].

Handgrip strength

The assessment of handgrip strength has been used as a common nutritional evaluation tool, particularly in developing countries, because it is a quick, reliable and inexpensive way to evaluate muscle function and determine nutritional status [16, 17]. It is used to assess the strength of the hand and the forearm muscles using a dynamometer [18]. Diminished muscle strength is often associated with illness and disease such as loss of physical functionality and HIV [19]. The evaluation of muscle mass is of vital importance when exploring the relationship

between malnutrition and CD4 cell count among PLHIV, since disease often impacts muscle function [19]. A study conducted by Vaz et al. among participants in India, suggested that the handgrip strength test is so useful in determining true nutritional status that it could differentiate individuals with chronic malnutrition from those who are just underweight and not undernourished but share similar BMI measures [20].

In addition to its ability to predict muscle function, the handgrip strength test has also been shown to predict bone mineral density [19]. A study conducted among men and women in rural Malawi demonstrated an independent correlation between handgrip strength and other nutritional indicators such as BMI and MUAC, thus supporting the hypothesis that poor nutritional status is correlated with poor handgrip strength [21]. A separate study found that BMI < 18.5 kg/m^2 was associated with reduced handgrip strength in an aging Rwandan refugee population [18].

Previous literature has also evaluated handgrip strength or maximum grip force for describing physical weakness, or low functional status, as part of frailty phenotypes in HIV-infected adult populations. In such studies, HIV infection was associated with an early occurrence of frailty manifestations (e.g. loss of muscle mass and weight, functional impairments, fatigue) [22]. Despite such findings, direct measures of handgrip strength as an independent predictor of CD4 cell count among PLHIV has yet to be extensively explored in the existing literature.

Food Insecurity and Nutritional Intake

Adequate energy intake is a matter of great concern in many developing countries where food insecurity is widespread. In regions of the world such as sub-Saharan Africa,

political climate, corruption, infrastructural instability and economic crises often have direct impacts on food availability and health status of the population [23]. A study conducted by Rotimi et al., found that CED increased among Nigerian adults as economic reforms and political unrest persisted. Another study examining the relationship between nutritional indicators and food insecurity (as a result of economic crises) found that BMI among women and children was in fact sensitive to the economic changes in the Congo [24]. The negative impact of undernutrition is of even greater concern among immunocompromised populations, particularly PLHIV. Previous literature has shown that among PLHIV, food insecurity has been associated with malnutrition, low indices of self-reported health, compromised adherence to ART, retention in care and mortality [25]. A study which examined the relationship between food insecurity and health-related quality of life scores found that food assistance resulted in about a 4- and 3-fold reduction in self- and healthcare care provider- reported HIV-related symptoms respectively, among PLHIV in Uganda [25]. Such results are indicative of the impact that food insecurity has on the physical health status of PLHIV.

In past studies, food security has been shown to be strongly correlated with anthropometric indicators such as BMI and MUAC among PLHIV; however, it has been found to have minimal to no significant association with CD4 cell outcomes [6, 7, 25, 26].

Chapter III:

Introduction

The relationship between nutritional indicators and HIV is especially significant since HIV infection can bring about weight loss and malnutrition. There are several reasons as to why this may occur, which includes increased energy expenditure, decreased energy intake and nutrient absorption failure (as a result from malabsorption and diarrhea). In resource-scarce countries, malnutrition among HIV positive persons is of great concern due to food insecurity and inaccessibility to nutrient dense foods. Socioeconomic climates in such countries can make food accessibility more important than adhering to antiretroviral treatment (ART), which in the long run has a direct impact on one's CD4 count. Side effects of ART treatment may also contribute to issues pertaining to nutrient absorption and weight gain. Medications can even be difficult to take on an empty stomach which may result in people simply not taking them. The purpose of this study is to assess whether various nutritional indicators are correlated with CD4 count less than 200 cells/mm^3. The analysis will be conducted using data collected from HIV positive, ART naïve adults in Kapiri, Zambia between 2008 and 2009. An understanding of the relationship between nutrition and poor immunological health status can help clinicians identify individuals who are at higher risk for poor immunological outcomes and target interventions to such persons.

Methods

Study Participants and Study Design

From 2008-2009, HIV-positive adults (age ≥ 18 years) who attended the HIV clinics sponsored by *Médecins Sans Frontières*'- Operational Centre Barcelona and Athens (MSF-OCBA) in the city of Kapiri, Zambia, were enrolled in a 9-month prospective study. Patients who were enrolled were assessed at study admission and were followed during each of their regular visits (including hospitalizations and clinical consultations) and during quarterly follow-up (months 3 and 6) visits.

During the data collection period, MSF-OCBA HIV clinics used *Follow-Up of Clinical HIV Infection and AIDS* (FUCHIA *v. 1.5.1*) software for the purpose of collecting and storing demographic, clinical (e.g., diagnoses of HIV-associated symptoms and infections), laboratory information (e.g., lymphocytes CD4+ count) and ART monitoring (if patients were initiated on ART) from study subjects at each of their visits. Nutritional information was collected separately using a survey administered at study admission, month 3, month 6, and hospitalization.

The secondary analysis presented here excludes participants who received ART prior to admission, elderly patients who were too weak to stand to be measured anthropometrically and female patients who experienced pregnancy and lactation during the study period. The secondary analysis was approved by the University Research Services and Administration Institutional Review Board at Georgia State University.

Nutritional Covariates

Nutritional indicators were recorded at admission visits, quarterly follow-ups (month 3 and 6), ART initiation and hospitalization visits. Loss of appetite (Yes/No) and loss of weight (Yes/No) were self-reported.

Household food security was assessed by inquiring about the occurrence of the four following scenarios in the last four months prior to the visit: (1) unable to eat the kinds of food the participant preferred due to lack of resources (mild insecurity), (2) having to eat smaller or fewer meals than usual (moderate insecurity), (3) no food stored in the participant's household (severe insecurity), and (4) going to sleep with an empty stomach (extreme insecurity).

The handgrip strength test required participants to squeeze a dynamometer 10 times consecutively with maximum strength, each separated by 30 seconds. A "Sphygmomanometer Test" required participants to repeatedly squeeze on the rubber bulb connected to a sphygmomanometer for 60 seconds or until inability to do so due to muscle fatigue. The sphygmomanometer was designed such that the cumulative pressure readings (mmHg) resulting from the repeated squeezing could be recorded [27]. In addition to the cumulative pressure reading at the end of each trial, the number of handgrips and the trial time span (seconds) were recorded. MUAC was measured to the closest millimeter using non-stretchable measuring tape. Height and weight, which were used for obtaining BMI (kg/m^2), was recorded at every clinical visit. Height was measured to the closest millimeter using an estadiometer, while weight was measured to the closest 100 grams using standing scales. Scales were calibrated daily using a known weight.

BMI and MUAC were considered in both continuous and categorical forms. BMI was categorized into *normal* (BMI ≥ 18.5), *mild thin* (18.5 > BMI ≥ 17.0), and *moderate/severe thin* (BMI < 17.0) using a grading system for categorizing adult chronic energy deficiency [9]. Similarly, MUAC was categorized into the three sex-specific categories [28]:

	Severe/Extreme Wasting	***Undernourished***	***Normal***
Male	< 200 mm	200 mm – 229 mm	≥ 230 mm
Female	< 190 mm	190 mm – 219 mm	≥ 220 mm

The handgrip strength and "sphygmomanometer" tests were used to describe muscular fatigue and strength. The following summary statistics were obtained from the ten handgrip readings: mean (psi), median (psi), slope, percent strength loss (%) and deviation of mean strength from the baseline (%).

Percent strength loss* (%) $= \frac{(maximum\ reading - final\ reading)}{maximum\ reading} \times 100\%$

Slope of measures[1]= $\frac{(final\ reading - maximum\ reading)}{\#\ of\ trials\ b/w\ the\ maximum\ reading\ and\ the\ final\ reading}$

Deviation of mean strength from the baseline* (%) =

$$\frac{(Handgrip\ mean\ of\ the\ current\ visit - Handgrip\ mean\ of\ the\ baseline\ visit)}{Handgrip\ mean\ of\ the\ baseline\ visit} \times 100\%$$

Using readings obtained from the "sphygmomanometer test", average handgrip strength (mmHg per grip) was calculated using the following formula:

$$\boldsymbol{Avg.\ squeeze\ strength} = \frac{cumulative\ pressure\ reading}{\#\ of\ hand\ squeeze}$$

[*] Entries where participants who did not finish at least half of the test (indicated by situations where the number of trials between the maximum reading and final reading was less than 5) were set to missing.

Non-nutritional Covariates

Participants' age (in years) and the occurrence of non-severe HIV-associated symptoms were recorded at every clinical visit regardless of the visit type. During each visit, participants received diagnoses based on HIV-associated symptoms, as described in the World Health Organization (WHO) disease staging system for HIV infection and disease in adults and adolescents [29]. A time-varying binary variable, *occurrence of non-severe HIV-associated symptoms* (excluding pulmonary tuberculosis, severe bacterial pneumonia, or other severe bacterial infections), was created to describe any study intervals where the participants were diagnosed to have at least one of the following clinical conditions: weight loss, minor mucocutaneous manifestations, herpes zoster, recurrent upper respiratory tract infections, bedridden during the last month, oral hairy leukoplakia, unexplained chronic diarrhea > 1 month, unexplained prolonged fever > 1 month, oral candidiasis, vulvovaginal candidiasis > 1 month.

Outcome of Interest

This analysis will consider first recorded CD4 count less than 200 cells /mm^3 as the outcome.

Data management and analysis

Data cleaning and analyses were conducted using SAS v 9.3 and 9.4 (Cary, NC). Nutritional indicators collected in quarterly consultation visits and hospitalizations (i.e. *MUAC, handgrip strength test, sphygmomanometer test, loss of appetite, loss of weight, and household food security*) were populated through the interval between each visits.

The baseline distribution of age, the occurrence of non-severe HIV-associated symptoms and nutritional indicators were described by sex and CD4 outcome using frequencies and percentages for categorical covariates or using means and standard deviations for continuous covariates. Fisher exact chi-square tests (for categorical variables) and two-sample equal variance t-tests for normally distributed data and Mann-Whitney U for non-parametric data (for continuous variables) were used to compare the distribution of covariates by CD4 cell outcome for males and females.

Logistic regression models (SAS v9.3 GENMOD procedure) were used to assess univariate and multivariate associations between covariates and CD4 cell outcome. Only the covariates that had a significant crude prevalence ratio (p=0.05) in the univariate analyses were included in the sex-specific multivariate logistic regression models.

Adjusted prevalence ratios (aPRs) and 95% CIs were obtained for each exposure in the final multivariate models.

Results

Baseline non-nutritional and nutritional covariates (Table 1a & 1b)

Within the study cohort there were 238 males (42%) and 334 females (58%). 51% (n= 122) of the male subjects and about 50% (n= 168) of female subjects had a first recorded CD4 count of less than 200 cells/mm^3.

Among the male cohort, those with a CD4 count of less than 200 cells/mm^3 were more likely to have an occurrence of non-severe HIV-associated symptoms (50% vs. 40%, p = 0.1088), have lower continuous BMI (19.2 kg/m^2 vs. 19.91 kg/m^2, p = 0.0132), have more persons who

categorized as ‘mildly thin’ and ‘moderate/severely thin’ within the BMI classes (*normal, mildly thin and moderate/severely thin*) (61% vs. 74%, 25% vs. 16%, 14% vs. 10%, p = 0.0795), have lower continuous MUAC measures (232.46 mm vs. 243.51 mm, p = 0.0006) and have more persons categorized as ‘undernourished’ within the MUAC classes (*normal, undernourished and severe/extreme wasting*) (40% vs. 23%, p = 0.0034).

Among the female cohort, those with a CD4 count of less than 200 cells/mm^3 were more likely to have an occurrence of non-severe HIV-associated symptoms (42% vs. 29%, p = 0.0148), have lower continuous BMI (20.33 kg/m^2 vs. 21.11 kg/m^2, p = 0.0352), have lower continuous MUAC measures (237.94 vs. 246.81, p = 0.0119), have more persons categorized as ‘undernourished’ and ‘severe/extreme wasting’ within the MUAC classes (*normal, undernourished and severe/extreme wasting)* (with CD4 < 200 - 22% vs. with CD4 > 200 - 12% and with CD4 < 200 - 8% vs. with CD4 > 200 - 7%, p = 0.0335), have more persons experience loss of appetite (61 % vs. 48%, p = 0.0216), have a slightly reduced handgrip strength mean (8.44 vs. 8.94, p = 0.0311) and produced a smaller number of handgrips (65.5 vs. 68.67, p = 0.0429).

Among persons with a first recorded CD4 count greater than 200 cells/mm^3 and those with less than 200 cells/mm^3, there were no significant differences between baseline distributions of age observed in both males and females.

Univariate analysis (Table 2)

Both male and female participants who were 'undernourished' (based on MUAC categorizations) were 1.5 and 1.4 times more likely to have a CD4 count less than 200 cells/mm^3 respectively. Male participants who were categorized as 'mildly thin' based on the BMI categories were approximately 1.4 times more likely to have a CD4 count less than 200 cells/mm^3. The occurrence of non-severe HIV related symptoms was 1.3 times greater among females who had a CD4 count less than 200 cells/mm^3. Among females, those who experienced appetite loss were 1.3 times more likely to have a CD4 count less than cells/mm^3. A 1-psi increase in the mean of handgrip strength measures was slightly protective of CD4 count less than 200 cells/mm^3 among females (aPR = 0.955, 95% CI = 0.912, 1, p = 0.0477).

Multivariate analysis (Table 3)

Collinear variables were not included in both male- and female-specific multivariate models. Among males, MUAC (undernourished) was the only variable associated with CD4 count less than 200 cells/mm^3 (aPR = 1.5113, 95% CI = 1.1451, 1.9946, p = 0.0035).

Among females, the occurrence of non-severe HIV related symptoms was controlled for as a potential confounder. MUAC was also the only variable associated with the outcome. Females categorized as 'undernourished' were 1.4 times more likely to have a CD4 count less than 200 cells/mm^3 compared to females with a higher CD4 count (aPR = 1.4212, 95% CI = 1.1027, 1.8318, p = 0.0066).

Multivariate analysis with household food insecurity covariates

Despite the absence of a statistically significant association found among household food insecurity covariates and CD4 count in the univariate analysis, it was still of interest to consider such observations by adding the household food insecurity variables (unable to eat the kinds of food the participant preferred due to lack of resources, having to eat smaller or fewer meals than usual, no food stored in the participant's household, and going to sleep with an empty stomach) to sex-specific multivariate models. Due to collinearity among household food insecurity variables, each covariate was observed individually in four separate models. In males and females, no statistically significant associations were observed among household food security covariates and the outcome. However, MUAC in both males and females was the only covariate associated with the outcome in each model. The absence of an observed association among household food insecurity covariates supports past literature which deduces that there are little to no associations between food security and low CD4 count but instead stronger associations between food security and nutritional status of PLHIV[25] .

Discussion

Among the HIV positive, ART naive Zambian adults in this study, MUAC was the only variable associated with CD4 count less than 200 cells/mm^3 among both males and females. In previous literature, increases in MUAC as a result of food supplementation have been associated with increases in CD4 count among HIV positive, ART naive persons in Sub-Saharan Africa [25]. Due to MUAC being the sole variable associated with the outcome among all sex specific models, it may of interest to further explore it as an anthropometrical measure that can

lend valuable insight into the impact of nutritional status on HIV disease outcomes and malnutrition comorbidity of PLHIV.

Due to the known strong relationship between CD4 count and non-severe HIV-associated symptoms, the *occurrence of non-severe HIV-associated symptoms* was controlled for as a potential confounder in the female multivariate model. In previous literature, the occurrence of non-severe HIV-associated symptoms has been associated with CD4 count and advanced HIV infection. Such studies have found that conditions such as oral candidiasis, herpes zoster and staphylococcal skin infections are associated with CD4 count and play a substantial role in determining clinical stage of HIV [30-32] . In sub-Saharan Africa, instances of infectious dermatoses are often due to humid environments, overcrowding, poor sanitary conditions and minimal access to treatment and medical supplies [30]. HIV care in resource scarce settings should also include care for such conditions which greatly impact immunological outcomes for PLHIV.

Our finding that BMI was not independently associated with low CD4 count among HIV positive persons may due to the short duration of this study. Studies conducted in the past have followed participants for longer than our study length of nine months. The baseline distribution of categorical BMI among those with CD4 count less than 200 (61% of males & 71% of females > 18.4 kg/mm^2) may also suggest that the majority of our participants were not undernourished by conventional standards (Chronic Energy Deficiency grading system). As a result, our findings could also indicate that BMI is not a strong independent factor associated with low CD4 count in HIV positive persons with optimal BMI measurements.

The presence and/or utilization of food assistance interventions was not examined in this study however, past studies which have examined the association between the integration of food assistance and HIV/AIDS treatment have found that food intervention programs targeting malnourished patients observed a positive effect on weight gain compared to interventions which targeted non-malnourished patients. Given that our population was considerably non-malnourished (with the presence of food assistance unknown), perhaps an association between BMI and low CD4 count was difficult to observe in only 9 months compared to a cohort that may have been distinctly malnourished [7].

Household food security covariates did not have a significant association with low CD4 cell outcome among both males and females. This was initially surprising; however, in support of past literature, this finding sheds light on the stronger associations between food security and anthropometric measures (BMI, MUAC, etc.) as opposed to food security's direct impact on CD4 cell count outcomes among PLHIV [7]. Nevertheless, food security is still of vital importance in the study of nutritional indicators and their relationship with low CD4 cell outcomes since hunger is often a barrier in ART adherence [33]; perhaps, its association with CD4 cell outcomes should be uniquely observed in populations where extreme malnutrition is persistent and thus stronger correlations can be deduced.

There are several limitations to this study that may have ultimately affected the results. Socioeconomic variables were not included in this analysis; therefore, the inability to control for such variables as potential confounders may have resulted in an inaccurate relationship between nutritional indicators and low CD4 cell count. This may have also impacted the overall

response regarding food insecurity among the studied population. In addition, people who attend the clinic may share certain characteristics that are not necessarily representative of the general population, resulting in potential selection bias.

This study found that among sex-specific multivariate models, MUAC (undernourished) was the only covariate significantly associated with the outcome among both males and females.

It may be of interest to further investigate the impact of MUAC as an insightful anthropometric measure in the evaluation of immunological outcomes among PLHIV in light of the differences between sex and the overall nutritional status of the studied population.

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Tables

Table 1a. Description of Covariates at Baseline Visit by First CD4 measurement among HIV + Adult Males in Kapiri, Zambia, 2008-2009							
	Total (N = 238)		CD4>=200 (N=116) (OUTCOME =0)		CD4<200 (N=122) (OUTCOME =1)		
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	p-value (2-tailed)*
Non-nutritional covariates							
Age (years)	34.61	6.97	34.16	6.71	35.04	7.21	0.3283
Occurrence of non-severe HIV-associated symptoms							0.1088
Yes	107	45%	46	40%	61	50%	
No	131	55%	70	60%	61	50%	
Anthropometry							
Continuous BMI (kg/m^2)	19.56	2.32	19.91	2.35	19.2	2.27	0.0132
Categorical BMI							0.0795
Normal	160	67%	86	74%	74	61%	
Mild Thin	49	21%	18	16%	31	25%	
Moderate/Severe Thin	29	12%	12	10%	17	14%	
Continuous MUAC (mm)	237.87	27.02	243.51	26.18	232.46	26.8	0.0006
Categorical MUAC							0.0034
Normal	148	63%	85	73%	63	52%	
Undernourished	74	31%	26	23%	48	40%	
Severe/Extreme Wasting	15	6%	5	4%	10	8%	
Appetite and Weight Loss							
Loss of Weight							0.4772
Yes	203	85%	97	84%	106	87%	
No	35	15%	19	16%	16	13%	
Loss of Appetite							0.5993

Yes	117	49%	55	47%	62	51%	
No	121	51%	61	53%	60	49%	
Handgrip Strength/Fatigue Test							
Mean of measures (psi)	11.65	3.04	11.9	3.08	11.4	3	0.2158
Median of measures (psi)	11.63	3.05	11.9	3.09	11.36	3	0.2089
Slope of measures	-0.278	0.214	-0.266	0.102	-0.29	0.141	0.3365
Percent strength loss (%)	20.14	9.62	19.32	8.95	20.95	10.22	0.242
Sphygmomanometer Test							
Test length (sec)	47.6	10.02	46.67	10.02	48.48	9.99	0.1393
Total number of grip	61.41	17.91	62.96	17.69	59.88	18.08	0.1872
Average grip strength (mmHg/grip)	2.46	0.928	2.38	0.782	2.53	1.05	0.2803
Cumulative handgrip strength (mmHg)	138.99	26.08	139.48	25.93	138.48	26.33	0.6923
Household Food Security							
Unable to eat preferred food							0.6753
Yes	89	38%	42	36%	47	39%	
No	148	62%	74	64%	74	61%	
Have smaller/fewer meals							0.7677
Yes	86	36%	41	35%	45	37%	
No	151	64%	75	65%	76	63%	
No food storage in household							0.9614
Yes	63	27%	31	27%	32	26%	
No	174	73%	85	73%	89	74%	
Sleeping empty stomach							0.9185
Yes	62	26%	30	26%	32	26%	
No	175	74%	86	74%	89	74%	

*For categorical variables, p-values from Chi-square tests (or Fisher's Exact)
*For continuous variables, p-values from t-tests (if normally distributed) or Mann-Whitney U (if non-parametric)

Table 1b. Description of Covariates at Baseline Visit by First CD4 Measurement among HIV + Adult Females in Kapiri, Zambia, 2008-2009							
	Total (N = 334)		CD4>=200 (N = 166) (OUTCOME =0)		CD4<200 (N = 168) (OUTCOME =1)		
	N/Mean	%/SD	N/Mean	%/SD	N/Mean	%/SD	p-value*
Non-nutritional covariates							
Age (years)	31.69	7.27	31.63	7.07	31.75	7.49	0.883
Occurrence of non-severe HIV-associated symptoms							0.0148
Yes	118	35%	48	29%	70	42%	
No	216	65%	118	71%	98	58%	
Anthropometry							
Continuous BMI (kg/m^2)	20.73	3.8	21.11	3.83	20.33	3.72	0.0352
Categorical BMI							0.6583
Normal	244	73%	124	75%	120	71%	
Mild Thin	44	13%	22	13%	22	13%	
Moderate/Severe Thin	46	14%	20	12%	26	16%	
Continuous MUAC (mm)	242.28	36.55	246.81	36.47	237.94	36.21	0.0119
Categorical MUAC							0.0335
Normal	248	75%	131	81%	117	70%	
Undernourished	56	17%	19	12%	37	22%	
Severe/Extreme Wasting	25	8%	11	7%	14	8%	
Appetite and Weight Loss							
Loss of Weight							0.7515
Yes	252	75%	124	75%	128	76%	
No	82	25%	42	25%	40	24%	
Loss of Appetite							0.0216
Yes	182	54%	80	48%	102	61%	
No	152	46%	86	52%	66	39%	
Handgrip Strength/Fatigue Test							
Mean of measures (psi)	8.7	2.32	8.94	2.25	8.44	2.36	0.0311

Median of measures (psi)	8.68	2.36	8.91	2.27	8.42	2.42	0.0361
Slope of measures	-0.29	0.11	-0.29	0.11	-0.28	0.11	0.9608
Percent strength loss (%)	26.73	11.08	26	10.3	27.47	11.81	0.2394
Sphygmomanometer Test							
Test length (sec)	53.64	7.87	53.24	8.03	54.06	7.7	0.344
Total number of grip	67.1	15.77	68.67	16.09	65.5	15.33	0.0429
Average grip strength (mmHg/grip)	1.97	0.77	1.98	0.8	1.96	0.73	0.954
Cumulative handgrip strength (mmHg)	124.5	34.7	127	33.67	121.93	35.64	0.159
Household Food Security							
Unable to eat preferred food							0.1025
Yes	149	45%	81	49%	68	40%	
No	183	55%	83	51%	100	60%	
Have smaller/fewer meals							0.1577
Yes	151	45%	81	49%	70	42%	
No	181	55%	83	51%	98	58%	
No food storage in household							0.3351
Yes	123	37%	65	40%	58	35%	
No	209	63%	99	60%	110	65%	
Sleeping empty stomach							0.3951
Yes	122	37%	64	39%	58	35%	
No	210	63%	100	61%	110	65%	

*For categorical variables, p-values from Chi-square tests (or Fisher's Exact)

*For continuous variables, p-values from t-tests or Mann-Whitney U if non-parametric

Table 2. Univariate Analysis of Covariates Stratified by Sex, among HIV + Adults in Kapiri, Zambia, 2008-2009								
	Male				**Female**			
	PR	**95% CI**		**p-value**	**PR**	**95% CI**		**p-value**
Non-nutritional covariates								
Age (per year increase)	1.01	0.99	1.03	0.3062	1.001	0.986	1.016	0.8791
Occurrence of non-severe HIV-associated symptoms								
Yes	1.22	0.96	1.57	0.1075	1.308	1.061	1.612	0.012
No	ref				ref			
Anthropometry								
Continuous BMI (per kg/m$^{2 \text{ increase}}$)	0.934	0.88	0.99	0.0148	0.972	0.943	1.001	0.0573
Categorical BMI								
Normal	ref				ref			
Mild Thin	1.368	1.043	1.794	0.024	1.017	0.737	1.402	0.9198
Moderate/Severe Thin	1.268	0.895	1.796	0.182	1.149	0.865	1.526	0.3365
Continuous MUAC (mm)	0.992	0.99	1	0.0006	0.997	0.994	1	0.0224
Categorical MUAC								
Normal	ref				ref			
Undernourished	1.523	1.185	1.96	0.001	1.401	1.113	1.761	0.004
Severe/Extreme Wasting	1.566	1.045	2.345	0.0295	1.187	0.819	1.721	0.3659
Appetite and Weight Loss								
Loss of Weight								
Yes	1.14	0.78	1.68	0.4975	1.041	0.809	1.341	0.754
No	ref				ref			
Loss of Appetite								
Yes	1.07	0.834	1.37	0.5994	1.291	1.033	1.612	0.0246
No	ref				ref			
Handgrip Strength/Fatigue Test								
Mean of measures (psi)	0.98	0.936	1.01	0.2172	0.955	0.912	1	0.0477

Median of measures (psi)	0.97	0.935	1.01	0.1813	0.956	0.913	1	0.0508
Slope of measures	0.353	0.113	1.11	0.0738	1.117	0.408	3.064	0.8293
Percent strength loss (%)	1.008	0.996	1.02	0.1582	1.006	0.997	1.016	0.1989
Sphygmomanometer Test								
Test length (sec)	1.001	0.996	1.02	0.1737	1.007	0.992	1.02	0.3655
Total number of grip	0.994	0.987	1.002	0.1886	0.994	0.988	1.001	0.0784
Average grip strength (mmHg/grip)	1.105	0.936	1.305	0.236	0.982	0.854	1.13	0.8038
Cumulative handgrip strength (mmHg)	0.999	0.994	1	0.7724	0.998	0.995	1.001	0.1832
Household Food Security								
Unable to eat preferred food								
Yes	1.056	0.819	1.362	0.6732	0.8352	0.671	1.04	0.1076
No	ref				ref			
Have smaller/fewer meals								
Yes	1.04	0.804	1.343	0.7665	0.856	0.689	1.065	0.1623
No	ref				ref			
No food storage in household								
Yes	0.993	0.748	1.318	0.9615	0.896	0.714	1.124	0.3428
No	ref				ref			
Sleeping with empty stomach								
Yes	1.015	0.766	1.344	0.9182	0.908	0.7235	1.139	0.4018
No	ref				ref			
*0.05< p-value ≤ 0.10; **p-value ≤ 0.05								

Table 3. Multivariate Analysis of CD4<200 among HIV + Adults Stratified by Sex in Kapiri, Zambia, 2008-2009				
Sex-specific Models	**aPR**	**95 % CI**		**p-value**
Male	**(Event = 121)**			
Categorical BMI				
Normal	ref			
Mild Thin	1.1418	0.858	1.5194	0.3631
Moderate/Severe Thin	0.8203	0.466	1.4438	0.4922
Categorical MUAC				
Normal	ref			
Undernourished	1.5113	1.1451	1.9946	0.0035
Severe/Extreme Wasting	1.9408	0.9807	3.8411	0.0569
Female	**(Event = 155)**			
Categorical MUAC				
Normal	ref			
Undernourished	1.4212	1.1027	1.8318	0.0066
Severe/Extreme Wasting	0.8768	0.4895	1.5705	0.6583
Loss of Appetite				
Yes	1.2599	0.9997	1.5878	0.0503
No	ref			
Handgrip Strength Test Mean of Measures (psi)	1.0022	0.9525	1.0545	0.932
* the occurrence of HIV-associated symptoms was controlled for as a potential confounder (female model)				