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Nutritional Indicators as Predictors of Antiretroviral Therapy Initiation Among HIV-Positive Adults in Kapiri, Zambia 2008-2009

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Master of Public Health

Global Epidemiology

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B.S.
Azusa Pacific University
2012

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ABSTRACT

Nutritional Indicators as Predictors of Antiretroviral Therapy Initiation Among HIV-Positive Adults in Kapiri, Zambia 2008-2009

By Yi No (Enoch) Chen

Background

Co-morbidity of malnutrition and HIV are highly prevalent in sub-Saharan African due to generalized epidemics of HIV/AIDS and famines. Limited research was done to assess the association between nutrition indicators and HIV disease progression in ART-naïve populations in resource scarce settings. It was specifically of our interest to assess the handgrip strength and endurance along with various other nutritional indicators as predictors of time to antiretroviral therapy (ART) initiation (proxy for worsened disease progression).

Methods

From 2008-2009, HIV+ adult males and non-pregnant females that were physically capable for receiving nutritional assessment were followed for 9 months as they made quarterly visits for nutritional evaluation and irregular clinical check-ups at a MSF HIV clinic in Kapiri, Zambia. A sex-stratified multivariate Cox model was used to assess the association between various nutritional indicators and time to ART initiation.

Results

46% of males and 44% of females were initiated on ART during the follow-up period. BMI and MUAC did not independently predict the outcome after controlling for the occurrence of non-severe HIV-associated symptoms and other nutritional indicators in either populations. The mean of the consecutive handgrip strength measures and the extreme food security each independently predicted the time to ART initiation among males, the total number of handgrip produced for the "sphygmomanometer test" independently predicted the outcome for both sexes. An increment on the handgrip mean strength (aHR=0.916, 90% CI 0.841-0.998) and the total number of handgrip (aHR=0.985, 90% CI 0.972-0.997) was protective against ART initiation among males, and having the incident of extreme food insecurity (aHR=0.516, 90% CI 0.314-0.846) were protective against ART initiation for both male and female participants.

Conclusion

"Sphygmomanometer test" may be considered for further clinical use for case identification and management of HIV and malnutrition comorbidity due to its independent association with hastened HIV disease progression, low cost, and technical simplicity. Future research may be needed to understand the mechanism by which total number of grip associate with disease progression

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Chapter I: Background

Acute and Chronic Malnutrition

Malnutrition, or under-nutrition, is a disease state associated with inadequate quantity of nutrient intake, quality of nutrient intake, and/or nutrient absorption/utilization any of which may result in detrimental changes in body weight, composition, and physical function over time (1). Acute and chronic malnutrition are associated with different metabolic adaptations. Compared to chronic malnutrition where metabolic equilibrium is approximately maintained despite being sub-optimal, acute malnutrition indicates negative nutrition balance, which leads to metabolic distress (2). Such metabolic distress is associated with short-termed increase in risk of mortality. However, the health consequences of acute malnutrition in HIV-infected populations have yet to be fully understood by the existing literature.

Vicious cycle of HIV/AIDS and malnutrition

In developing countries, people living with HIV/AIDS (PLHIV) are often at increased risk of malnutrition. The relatively high risk of malnutrition among PLHIV has been attributed to several socioeconomic and physiological mechanisms. HIV/AIDS jeopardizes household economic productivity, which in turn compromises the food security and diet quality (3). Physiologically, HIV/AIDS not only causes PLHIV to have an increased resting metabolic rate and energy expenditure, but the disease also reduces nutrient absorption and utilization capacity (4). In addition, antiretroviral treatment (ART) often causes appetite loss, vomiting and diarrhoea which may reduce nutrient intake quantity (5). Moreover, studies have also suggested that nutrition impairment may aggravate the progression of HIV disease, often measured by outcomes such as all cause death (6-9), the

onset of opportunistic infection (OI) (10), and increased immunodeficiency (decreasing CD4 count) (8) in both ART-naïve and ART-treated populations.

Nutrition indicators and their association with HIV/AIDS disease progression

Body Mass Index (BMI)

The BMI-based the grading system of chronic energy deficiency (CED) has been widely used for identifying and quantifying the severity of under-nutrition in the field (11).

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

Among ART-initiated populations, studies have shown that the a 6-fold and 8-fold increased risk of mortality at three and six months after ART initiation, respectively, among patients whose BMI were below 16.0 kg/m2 compared to normal BMI at ART initiation (12, 13). As for the ART-naïve PLHIV, Van der Sande, et al. found that a baseline BMI below 18 kg/mm3 is significantly associated with all-cause mortality among PLHIV who are not on ART, after adjusting for age, sex, CD4 cell count and HIV type (9). Kelly, et al. found that BMI on average was greater in HIV seropositive patients with OI than seropositive patients without OI in Zambia (10). Literature that addresses the association between BMI and other surrogate measures for HIV disease progression is still limited compared to studies conducted in ART-initiated populations.

Mid-upper arm circumference (MUAC)

MUAC has been widely used for assessing nutrition status in resource-scarce settings, where evaluation of BMI may be limited, due to its minimal requirement on technical equipment (14). Studies have shown that a MUAC below 230 mm is strongly associated with a BMI below 18.5 kg/m2 among adults and that the correlation between the two indicators reduce significantly when MUAC or BMI is below 185 mm or 13 kg/m2

respectively (2). However, there has not been global consensus on the optimal MUAC cut-offs for classifying nutrition status (14).

Similar to BMI, studies have assessed MUAC as a predictor of adverse disease outcomes among PLHIV. Low MUAC is significantly associated with elevated risk of mortality among TB-free and TB-infected PLHIV (6, 15). In addition, a cross-sectional study shows that impaired nutrition status marked by decreased MUAC and BMI is associated with the presence of OI among ART-naïve Zambian PLHIV (10).

Handgrip strength

It has been well documented that malnutrition contributes to myopathic alterations, which are associated with lower production and mobilization of adenosine triphosphate (ATP). This leads to lower force of maximum contraction, reduced relaxation rate after stimulation, and higher fatigability (16). Studies have shown that changes in muscular performances, measured by functional tests such as handgrip strength, become observable before changes in weight and muscle mass when responding to both nutritional deprivation and nutritional repletion (17). Therefore, muscle functional tests may be used as an early indicator for malnutrition. However, further research needs to be conducted to validate its clinical potential as early indicator of malnutrition.

A study of malnutrition among adults during food a crisis in Burundi and Congo-Brazzaville found that a compounded evaluation of muscular strength and weight loss, rather than assessment of BMI only, best predicted the severity of malnutrition among thin patients (18). Another study conducted in India also demonstrated that handgrip strength tests may be used as malnutrition indicator among underweight adults (19). In addition to its predicting capacity, the simplicity and non-invasive nature of voluntary handgrip strength tests make it a widely used functionality index in clinical setting (17). A study conducted on Malawian men and women reveals an independent correlation between

handgrip strength and other anthropometric indicators for nutrition status (e.g. BMI, MUAC, arm-muscle area) (20). A separate study further found that low BMI is associated with reduced hand strength in aging populations (21).

In previous literature, the evaluation of handgrip strength or maximum grip force has been used for describing physical weakness, or low functional status, as part of the frailty phenotypes in HIV-infected adult populations. Those studies have found that advanced HIV disease described by immunological outcomes (e.g. viral loads, CD4 cell) were associated with frailty manifestations in both ART-naïve (22, 23) and ART-initiated populations (24). However, direct measures on handgrip strength and endurance as independent predictor of HIV disease progression among ART-naïve PLHIV has yet to be extensively explored in the existing literature.

Dietary intake and physical capacity

Lack of food security may compromise the quantity and quality of the diet, which is associated with malnutrition and mortality among PLHIV (25). According to Venter et al., CD4 cell count is positively correlated to weight, BMI, MUAC, and level of independence, measured by physical capacity for activities of daily living, among PLHIV (26). However, dietary intake was not found significantly correlated with the CD4 cell count, except when the degree of immunosuppression become extreme.

Chapter II

Introduction

In sub-Saharan Africa, the co-morbidity of HIV/AIDS and malnutrition (under-nutrition) are highly prevalent due to generalized epidemics of HIV/AIDS in combination with famines caused by drought and food insecurity (27). The mutual aggravation between malnutrition and HIV infection has been well documented; HIV/AIDS jeopardizes household economic productivity, which in turn compromises the food security and diet quality, indicators of one's nutrition status (4). On the flip side, HIV/AIDS not only causes PLHIV to have an increased resting metabolic rate and energy expenditure, but the disease also reduces nutrient absorption and utilization capacity because of cytokine activities and diarrhoea (5).

Previous research has attempted to assess the association between nutritional status, using various indicators (e.g. Body Mass Index (BMI), Mid-Upper Arm Circumference (MUAC), diet quality), and worsened disease progression among PLHIV. Past studies have found that BMI and MUAC have been predictive of proxy measures for worsened disease progression (e.g. mortality, low CD4 count) in populations that have already initiated ARV (6-8, 28-30). Fewer studies have been done on ART-naïve PLHIV; these studies have also found significant predictive ability of BMI, MUAC, and diet quality on mortality and occurrence of opportunistic infections (OI), also a proxy measure for worsened HIV disease progression (9, 10, 25). Because they were done among ART-naïve populations, these studies may be more generalization to people living in resource-scarce areas since access to ART may be limited in such settings.

Similar research looking at the predictive ability of other nutritional indicators such as handgrip strength and endurance on worsened HIV disease progression has been limited,

although a past study has shown that a compounded evaluation of muscular strength and weight loss, rather than BMI measurement, best predicted the severity of malnutrition (18). This suggests that muscular strength may be a better indicator of malnutrition than BMI and should further be considered as a predictor for worsened disease progression among PLHIV.

This study explores the predictive ability of various nutritional indicators on worsened HIV disease progression while addressing two limitations of past research. Firstly, this study considers multiple nutritional indicators that few studies have considered in the past, such as handgrip strength and endurance. Unlike previous research, this study uses ART initiation itself as a proxy measure for worsened HIV disease progression. Because this study only considers an ART-naïve population, results from this study may be used to inform malnutrition assessment among PLHIV in resource-scarce settings.

Methods

Study Participants and Study Design

From 2008-2009, HIV-positive adults (i.e. age ≥ 18 years) who attend the HIV clinics sponsored by *Médecins Sans Frontières*'- Operational Centre Barcelona and Athens (MSF-OCBA) at the city of Kapiri, Zambia, were enrolled in a 9-month prospective study. Patients who were enrolled in the study 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 anti-retroviral treatment (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 ARV prior to or upon 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 were exempted from this analysis. The secondary analysis was approved by the Office for Human Research Protections-registered Institutional Review Boards at Emory University.

Nutritional Covariates

Nutritional indicators was 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. The level of appetite was also assessed by quantifying the proportion of ready-to-use therapeutic food (i.e. BP100 biscuits) (%) participants consumed as part of the nutritional assessment. The BP100 consumption was not included in the analysis for the male cohort due to the lack of sensitivity in describing the level appetite (up to 95% of the intervals where male subjects consumed 100% of BP100). Functional capacity of daily living was evaluated by asking participants if they were able to independently execute the following ten daily activities (listed in order of increasing difficulty of physical function): (1) stand, (2) walk, (3) wash and groom, (4) transfer from bed to chair, (5) maintain continence and use a toilet, (6) feed him/herself, (7) go shopping or to market, (8) do basic work at home, (9) do his/her usual work, (10) work in the fields or other heavy work. However, the variable was not included as an exposure in the analysis due to lack of sensitivity (100% of intervals where subjects of both sexes claimed they were capable of *working in the field*).

Food security at household level was assessed by inquiring 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 a 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 failure due to muscle fatigue. The "sphygmomanometer" device was designed such that the cumulative pressure readings (mmHg) resulting from the repeated squeezing could be recorded (31). In addition to the cumulative pressure reading at the end of each trial, the number of handgrip 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. All nutritional indicators except height are time-varying.

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 derived grading system for adult chronic energy deficiency (11). Similarly, MUAC was categorized into the three sex-specific categories used in conditions of food scarcity (32):

	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 (%).

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

$$\textbf{\textit{Slope of measures}}^{*}\textbf{\textit{=}} \frac{(final\ reading - maximum\ reading)}{\#\ of\ trials\ b/w\ the\ maximum\ reading\ and\ the\ final\ reading}$$

$$\textbf{\textit{Deviation of mean strength from the baseline}}^{*}\textbf{\textit{ (\%) =}}$$

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

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

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

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. Age was considered time-independent in this 9-month study. During each visit, participants received diagnoses of HIV-associated symptoms, which are described in the World Health Organization (WHO) disease staging system for HIV infection and disease in adults and adolescents (33). 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

* 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.

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 considers ART initiation as the primary outcome of interest. The MSF-sponsored HIV/AIDS clinic in Kapiri determined a clinical threshold for initiating ART for adult patients based on pre-2010 WHO guidelines of ART eligibility for HIV infected adults and adolescents. CD4 cell count and clinical assessment were regularly monitored from patients at each clinical visit. Participants were immediately admitted to the MSF ART program for regular treatment of ARV regimens if the clinic medical staff observed one of three scenarios.

Participants having CD4+ T-lymphocyte (CD4+) count ≤ 200 cells /mm^3 were initiated on ART irrespective of their WHO's clinical staging. Participants diagnosed with *severe* HIV-associated symptoms, as described in WHO literature (33), were initiated on ART irrespective of their CD4+ count. Participants who had CD4+ count < 350 cells /mm^3 and had *pulmonary tuberculosis, severe bacterial pneumonia, or other severe bacterial infections* were initiated on ART.

Data management and analysis

Data cleaning and analyses were conducted using SAS v9.4 (Cary, NC). Nutrition indicators collected in quarterly consultation visits and hospitalization (i.e. *MUAC, handgrip strength test, sphygmomanometer test, loss of appetite, loss of weight, BP100 consumption, and household food security*) were populated through the interval between each visits.

Missing values for the number of days between visits were reassigned new values by adding or subtracting the number of days based on the last non-missing follow up visit or irregular clinical consultation (90 or 180 days for quarterly follow-up, 30 days for irregular clinical consultation).

Differences in hazard ratios between males and females were assessed by comparing stratified estimates from univariate analyses using Cox models. Statistically significant differences by sex in crude hazard ratios describing the association between covariates (BMI, MUAC and going to sleep with empty stomach) and time to ART initiation suggests that each covariate's effect on the outcome may vary by sex. Because of this, all subsequent analyses were accordingly stratified by sex.

The baseline distribution of age, status of HIV disease progression, and nutrition indicators were described by sex and ART outcome using frequencies and percentages for categorical covariates or using means and standard deviation for continuous covariates. Fisher Exact Chi-square tests (for categorical data) and two-sample equal variance t-tests (for continuous data) were used to compare the distribution of covariates by ART outcome for each sex. The equal variance of continuous data across strata was confirmed.

Cox models (SAS v9.4 PHREG procedure) were used to assess bivariate and multivariate associations between covariates (e.g. age, status of HIV disease progression, nutrition indicators) and time to ART initiation. Confidence intervals of 90% were used due to the explorative nature of this study. Only the covariates that had significant crude hazard ratio ($p=0.10$) in the bivariate analyses were included in the sex-specific multivariate Cox model. All the significant nutrition indicators were treated as exposure variables. All the significant non-nutritional covariates were treated as potential confounders to be controlled for.

Multi-collinearity among exposures and potential confounders was evaluated using condition indices of 20 and variance decomposition proportions of 0.50 as cutoff standards. The proportional hazards assumption was verified for time-independent age and sex variables by examining log [-log(survival probability)] *versus* log(time) plots and Schoenfeld residuals. All exposure variables and covariates were evaluated as potential effect-modifiers for each other and none were found to be significant. Adjusted HRs (aHRs) and 90% CIs were obtained for each nutritional exposure in the final multivariate models.

Results

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

There were 238 males (42%) and 334 females (58%) in the study cohort. 46% (n=110) of the male subjects and 44% (n=148) of the female subjects initiated ART.

For the male cohort, non-ART initiators on average were older (32.55 year vs. 37.00 years, $p < 0.0001$), were less likely to be have non-severe HIV-associated symptoms (38% vs. 55%, p=0.0040), had higher BMI (19.87 vs. 19.19, p=0.024), and had higher MUAC (241.29 mm vs. 233.93 mm, p=0.0361), as compared to the ART initiators at baseline visit.

For the female cohort, non-ART initiators on average were marginally younger (31.0 years vs. 32.56 years, p=0.0514), were likely to be have non-severe HIV-associated symptoms (28% vs. 44%, p=0.0040), had higher BMI (21.12 vs. 20.23, p=0.0327), had marginally higher MUAC (245.74 mm vs. 237.95 mm, p=0.0544), were less likely to experience weight loss (69% vs. 84%, p=0.002) and appetite loss (46% vs. 66%, p=0.0004), consumed marginally larger proportion of BP100 biscuit (98% vs. 95%, p=0.0669), had marginally greater handgrip strength mean (8.91 psi vs. 8.44 psi, p=0.0741) and median (8.88 vs. 8.42, p=0.0822), produced greater number of handgrip in sphygmomanometer test (69.34 vs. 64.24, p=0.0045), and were more marginally likely to

have insufficient meals a household level (50% vs. 40%, p=0.0961), as compared to the ART initiators at baseline visit.

No difference in baseline distribution of BMI classes (i.e. Normal, Mild Thin, Moderate/Severe Thin) between non-ART initiators and ART initiators was observed in both males and females. Difference in baseline distribution of MUAC classes (i.e. Normal, Undernourished, Severe/Extreme Wasting) between non-ART initiators and ART initiators may be observed in males (77% vs. 53%, 24% vs. 40%, 6% vs. 7%), but not in females.

Univariate analysis (Table 2)

A one unit increase in *BMI* and *total number of handgrip* in *"sphygmomanometer test"* reduced the risk of ART initiation by almost 10% and 1.5% respectively for both males and females. Male participants who became *undernourished* and female participants who experienced *severe/extreme wasting* (based on MUAC classification) were almost 1.5 times and 3 times respectively more likely to be initiated on ART than their *well-nourished* counterparts. Males who did not *go to sleep with an empty stomach* were approximately 1.5 times more likely to be initiated on ART than those who *went to sleep with an empty stomach*.

Continuous BMI and continuous MUAC were selected for female-specific multivariate analysis over their categorical counterpart to minimize data loss. In addition, the female multivariate model also included the *total number of handgrip.* Because they are the most predictive handgrip strength measures, *mean* in the male cohort (crude HR= 0.920, 90% CI: 0.862-0.982) and *percent strength loss* in the female cohort (crude HR=1.020, 90% CI: 1.005 - 1.034) were selected for gender-specific multivariate models. Other strong univariate nutritional predictors included in the male multivariate model were *continuous BMI, categorical MUAC, total number of handgrip,* and *sleeping with empty stomach*.

The occurrence of non-severe HIV-associated symptoms was selected as the potential confounder in the multivariate models due to the observed strong association with the ART initiation in both males (Crude HR= 2.534, 90% CI: 1.477-4.350) and females (Crude HR=2.261, 90% CI: 1.322 – 3.869).

Multivariate analyses (Table 3)

No effect-measure modification or collinear variables were found for both male- and female-specific multivariate model. In males, *the mean of hand strength measures*, *total number of handgrips*, and *sleeping with an empty stomach* remained independent predictors of ART initiation after adjusting for the occurrence of non-severe HIV-associated symptoms and other nutritional predictors. In females, only *the total number of handgrip* remained as an independent predictor of ART initiation after adjustment.

Among males, participants who had experiences of *sleeping with an empty stomach* was half as likely to be initiated on ART compared to those who did not (aHR = 0.518, 90% CI 0.316 - 0.849, p=0.0276), after controlling for the occurrence of non-severe HIV-associated symptoms, BMI, MUAC and their performances on the two types of handgrip assessments. A 1 unit increase in total number of handgrip was independently associated with approximately 1.5% and 1.2 % decrease in the risk for ART initiation among males and females respectively. Comparatively, the total number of handgrip was more strongly associated with the time to ART initiation among males (aHR=0.985, 90% CI: 0.972 – 0.997, p=0.0392) than females (aHR=0.988, 90% CI: 0.978 - 0.998, p=0.0584). A 1-psi increase in the mean of handgrip strength measures was marginally but independently associated with 8.4% decrease in the risk for ART initiation (aHR=0.916, 90% C:I 0.841 - 0.998, p=0.0928).

Discussion

In the ART-naïve Zambian adults infected with HIV, the association between nutrition indicators and the time to ART initiation appeared to be different by sexes at large.

While *the mean of the consecutive handgrip strength measures* and the occurrence of *sleeping with the empty stomach* each independently predicted the time to ART initiation among males, *the total number of handgrip* produced for the "sphygmomanometer test" independently predicted the outcome for both sexes. An increment on *the handgrip mean strength* (aHR=0.916, 90% CI 0.841- 0.998) and *the total number of handgrip* (aHR=0.985, 90% CI 0.972-0.997) was protective against ART initiation among males, and having the incident of *sleeping with empty stomach* (aHR=0.516, 90% CI 0.314-0.846) due to food scarcity were protective against ART initiation for both males and females. However, BMI and MUAC, both of which were found to be univariate predictors of the time to ART initiation for both sexes, did not independently predict the outcome after controlling for other covariates in either populations.

In previous literature, the evaluation of handgrip strength or maximum grip force has been used for describing physical weakness, or low functional status, as part of the frailty phenotypes in HIV-infected adult populations. Those studies have found that advanced HIV disease described by immunological outcomes (e.g. viral loads, CD4 cell) were associated with frailty manifestations in both ART-naïve(23, 34) and ART-initiated populations (24).

Despites the known association between HIV disease progression and physical function, there has been limited literature evaluating handgrip strength and endurance measures as an independent predictor of HIV disease progression rather than as an outcome. Our findings suggest that measuring the number of grips on a sphygmomanometer may be more powerful in predicting adverse progression of HIV than measuring average maximum contractile force generated by handgrip (mean hand strength measure) or the temporary decrease of muscle contractile force (percent strength loss), BMI, and MUAC.

It is surprising to find the mean of handgrip measures and the percent strength loss were not strong independent predictors in their respective cohort, while the total number of handgrip in the sphygmomanometer test were in both cohorts. Compared to mean of handgrip measures and percent strength loss, the number of handgrip in the "sphygmomanometer test" seems to weigh in the ability to repeatedly complete the contraction than the magnitude of force exerted. Therefore, it is probable that the total number of handgrips exerted in a pre-specified time may quantify the dynamic muscular endurance more so than other two measurements. However, the association between the number of grips over a pre-specified time period, dynamic muscular endurance and HIV disease progression still need to be investigated. Also, the level of sensitivity of the total number of handgrip over a pre-specific time period in reflecting malnutrition is currently unclear.

It is interesting that the association between BMI and MUAC (the two widely-used indicators for malnutrition), and time to ART initiation was significantly attenuated after controlling for the occurrence of non-severe HIV symptoms and other nutritional indicators for both sexes. This conflicts with previous studies that have found BMI and MUAC to be independently associated with mortality and advanced HIV progression (e.g. opportunistic infection) among ART-naïve PLHIV(9, 10, 26). Our findings that BMI and MUAC do not independently predict short-term disease progression among PLHIV may be due to the short length of our study; previous studies followed participants for longer than our study length of nine months. Our results may not be generalizable for longer lengths of follow-up timeframe. Since the current standard shows that MUAC and BMI highly correlated above BMI of 13 and MUAC of 185 mm (2), it is understandable that if one indicator does not predict disease progression, the other indicator will not either.

Our preliminary data from the assessment of *functional capacity of daily living* found that 100% of participants claimed to be able to complete heavy labors or regular physical tasks required in their work fields without difficulties. Assuming the accuracy of the data, this may imply that our sampled population may not be physically weak in general. The baseline distribution of BMI (32.77% of males & 26.94% of females ≤ 18.4 kg/mm^2) and MUAC (37.55% of males & 24.62% of females < 230 mm /220 mm) also similarly suggest that majority of the participants were not under-nourished by conventional standard (Chronic Energy Deficiency grading system). As a result, our findings could also mean that BMI and MUAC are not strong independent predictors for hastened disease progression among well-nourished or physically well functional PLHIV.

Extreme food insecurity at the household level, described by the occurrence of the subjects going to sleep with an empty stomach, was found to be protective against ART initiation for the male HIV + cohort. However, food insecurity was not found as a significant predictor in the female cohort. We found it interesting that mild to severe food insecurity may not predict the time to ART initiation for both sexes as well as extreme food insecurity does. This result may shed light on how nutrition practitioners in the field can determine a measurement cutoff for food insecurity in assessing one's probability for needing ART in resource-scarce setting.

Because extreme food insecurity has been found associated with worsened HIV disease outcomes (which sets the necessary precondition for the event of ART initiation) in previous studies (35, 36), it is interesting to find that male participants seriously lacking in food on average had longer time to ART initiation, based on the multivariate analysis (aHR= 0.581, 90% CI: 0.357 – 0.947). However, few qualitative studies have described some potential reasons behind this phenomenon: the subject's imminent need for food may compromise their ability to prioritize ARV treatment (37); the subject's knowledge of the

supplementary food requirement for ARV may reduce their desire to start ARV given their ongoing struggle with securing stable food source (38).

There are several limitations to this study that may affect our estimated time to ART initiation. Due to concerns for confidentiality, socioeconomic variables were not included in this analysis. The lack of controlling for socioeconomic variables as potential confounders affecting both nutrition and event of ART initiation may result in inaccurate estimate. People who attend the clinic may share certain characteristics that are not necessarily representative of the general population, resulting in potential selection bias. The loss of data describing number of days between visits may also result in potential over-estimation or under-estimation of survival time.

Moreover, another major limitation for our analysis method was the longitudinal populating of nutrition data between quarterly follow-ups. Due to the limited number of visits where original nutrition values were allowed to vary, the study may not fully capture the evolution of nutrition status, which may bias our estimate in an unknown direction.

In addition, it is worth noting that since 2008, when the data was collected, there have been two modifications in the recommended WHO ART initiation criteria with regard to the CD4 count threshold [2010-2012: CD4 ≤ 350 cells /mm^3(39), 2013 and on: CD4 ≤ 500 cells/mm^3(40)]. This suggests that by recent guidelines, time to ART initiation may in fact be shorter than estimated in this study, thereby affecting the observed association between nutrition indicators and time to ART initiation. However, we felt that using pre-2010 guidelines (e.g. CD4 $\underline{\leq}$ 200 cells/mm^3 or presence of severe HIV-associated symptoms) was a better proxy measure for advanced HIV disease progression than newer guidelines.

This study found that BMI and MUAC, two indicators traditionally used in field assessment of malnutrition, were associated with time to ART initiation (a proxy measure for HIV disease progression) in univariate models but were attenuated after controlling for

other covariates in multivariate models. In males, extreme food security was found to be a strong predictor of disease progression. Finally, the total number of handgrip in the "Sphygmomanometer Test" was also left as a strong predictor of time to ART initiation over BMI and MUAC.

Our finding about the number of handgrip in "the sphygmomanometer test" as a strong independent predictor of time to ART initiation in both sexes may set a novel direction for performance-based anthropometrical assessment of PLHIVs' nutritional statuses in resource-scarce or emergency settings, where the scope of nutritional assessment and access to ART are often limited. In addition to the capacity to independently predict hastened HIV disease progression, the minimum requirement on mechanical equipment and the technical simplicity for conducting "sphygmomanometer test" may offer a greater clinical utility for facilitating the case management of HIV and malnutrition comorbidity in rural Sub-Saharan Africa, than other conventional nutrition assessments.

However, further research should be conducted to fully ensure that policy and programmatic interventions are evidence-based. It may be of interest to investigate the implication that BMI and MUAC are not predictive for short-term disease progression in light of differences between chronic and acute malnutrition. Acute malnutrition is known to be associated with sudden health degradation, as compared to chronic malnutrition, and might potentially lead to faster HIV disease progression. Future research should also investigate the mechanism by which sex interacts with food insecurity and malnutrition and how that interaction affects disease progression and one's desire to initiate ART. Due to limited data, super-stratification by age and baseline handgrip strength was not possible for our analysis so further research should focus on this possible association.

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Tables

Table 1a. Description of Covariates at Baseline Visit by ART Initiation Status among HIV + Adult Males in Kapiri, Zambia, 2008-2009

	Total (N= 238)		Non-ART initiator (N= 128)		ART initiator (N =110)		
	Mean (SD)/ N (%)	n	Mean (SD)/ N (%)	n	Mean (SD)/ N (%)	n	p-value
Non-nutritional covariates							
Age (years)	34.61 (6.97)	238	32.55 (6.49)	128	37.00 (6.78)	110	<.0001
Occurrence of non-severe HIV-associated symptoms	107 (45%)	238	48 (38%)	128	59 (54%)	110	0.0135
Anthropometry							
Continuous BMI (kg/m^2)	19.55 (2.33)	238	19.87 (2.26)	128	19.19 (2.36)	110	0.024
Categorical BMI				128		110	0.253
Normal	160 (67%)		92 (72%)		68 (61.82%)		
Mild Thin	49 (20.59)		23 (17.97%)		26 (23.64%)		
Moderate/Severe Thin	29 (12%)		13 (19.16%)		16 (14.55%)		
Continuous MUAC (mm)	237.87 (27.02)	237	241.29 (25.50)	127	233.93 (28.29)	110	0.0361
Categorical MUAC				127		110	0.0146
Normal	148 (62.45%)		90 (70.87%)		58 (52.73%)		
Undernourished	74 (31.22%)		30 (23.62%)		44 (40.00%)		
Severe/Extreme Wasting	15 (6.33%)		7 (5.51%)		8 (7.27%)		
Appetite and Weight Loss							
Loss of Weight: Yes	203 (85.29%)	238	108 (84.38%)	128	95 (86.36%)	110	0.7162
Loss of Appetite: Yes	117 (49.16%)	238	63 (49.22%)	128	54 (49.09%)	110	0.9843
Handgrip Strength/Fatigue Test							
Mean of measures (psi)	11.65 (3.04)	230	11.89 (2.91)	122	11.39 (3.18)	108	0.2196
Median of measures (psi)	11.63 (3.05)	230	11.85 (2.92)	122	11.39 (3.19)	108	0.2469
Slope of measures	-0.28 (0.12)	229	-0.28 (0.12)	122	-0.28 (0.13)	107	0.9756
Percent strength loss (%)	20.14 (9.62)	229	19.86 (9.42)	122	20.46 (9.89)	107	0.6424

Sphygmomanometer Test							
Test length (sec)	47.57 (10.02)	226	47.08 (10.45)	120	48.13 (9.53)	106	0.7900
Total number of grip	61.42 (17.91)	226	62.85 (19.08)	120	59.79 (16.43)	106	0.2010
Average grip strength (mmHg/grip)	2.45 (0.94)	226	2.43 (0.84)	120	2.47 (1.05)	106	0.8076
Cumulative handgrip strength (mmHg)	138.98 (26.08)	225	140.02 (24.74)	120	137.8 (27.61)	105	0.5260
Household Food Security							
Unable to eat preferred food: Yes	89 (37.55%)	237	45 (35.43%)	127	44 (40.00%)	110	0.5028
Have smaller/fewer meals: Yes	86 (36.29%)	237	43 (33.86%)	127	43 (39.09%)	110	0.4193
No food storage in household: Yes	63 (26.58%)	237	32 (25.20%)	127	31 (28.18%)	110	0.6592
Sleeping empty stomach: Yes	62 (26.16%)	237	32 (25.20%)	127	30 (27.27%)	110	0.7678

Table 1b. Description of Covariates at Baseline Visit by ART Initiation Status among HIV + Adult Females in Kapiri, Zambia, 2008-2009	Total (N= 334)		Non-ART initiator (N= 186)		ART initiator (N =148)		
	Mean (SD)/ N (%)	n	Mean (SD)/ N (%)	n	Mean (SD)/ N (%)	n	p-value
Non-nutritional covariates							
Age (year)	31.69 (7.28)	334	31 (7.10)	186	32.56 (7.43)	148	0.0514
Occurrence of non-severe HIV-associated symptoms	118 (35%)	334	53 (28%)	186	65 (43%)	148	0.0040
Anthropometry							
Continuous BMI (kg/m^2)	20.72 (3.80)	334	21.12 (4.03)	186	20.23 (3.43)	148	0.0327
Categorical BMI		334				148	0.6743
Normal	244 (73%)		139 (75%)		105 (71%)		
Mild Thin	44 (13%)		24 (13%)		20 (14%)		
Moderate/Severe Thin	46 (14%)		23 (12%)		23 (16%)		
Continuous MUAC (mm)	242.28 (36.55)	329	245.74 (38.85)	183	237.95 (33.07)	146	0.0544
Categorical MUAC		329		183		146	0.7336
Normal	248 (75%)		141 (77%)		107 (73%)		
Undernourished	56 (17%)		29 (16%)		27 (18%)		
Severe/Extreme Wasting	25 (8%)		13 (7%)		12 (8%)		
Appetite and Weight Loss							
Loss of Weight: Yes	252 (75%)	334	128 (69%)	186	124 (84%)	148	0.0020
Loss of Appetite: Yes	182 (54%)	334	85 (46%)	186	97 (66%)	148	0.0004
Percent of BP100 consumed (%)	96.56 (13.54)	254	97.99 (10.53)	137	94.87 (16.26)	117	0.0669
Handgrip Strength/Fatigue Test							
Mean of measures (psi)	8.7 (2.32)	314	8.91 (2.23)	176	8.44 (2.41)	138	0.0741
Median of measures (psi)	8.68 (2.36)	314	8.88 (2.26)	176	8.42 (2.46)	138	0.0822
Slope of measures	-0.29 (0.11)	313	-0.29 (0.11)	175	-0.28 (0.11)	138	0.4778
Percent strength loss (%)	26.73 (11.08)	313	26.39 (10.52)	175	27.16 (11.79)	138	0.5457

Sphygmomanometer Test							
Test length (sec)	53.65 (7.87)	311	53.83 (7.89)	175	53.42 (7.86)	136	0.6498
Total number of grip	67.11 (15.78)	311	69.34 (14.91)	175	64.24 (16.44)	136	0.0045
Average grip strength (mmHg/ grip)	1.96 (0.77)	311	1.95 (0.74)	175	1.99 (0.81)	136	0.6354
Cumulative handgrip strength (mmHg)	124.49 (34.70)	310	126.55 (32.73)	175	121.81 (37.06)	135	0.2338
Household Food Security							
Unable able to eat preferred food: Yes	149 (45%)	332	89 (48%)	185	60 (41%)	147	0.2217
Have smaller/fewer meals: Yes	151 (45%)	332	92 (50%)	185	59 (40%)	147	0.0961
No food storage in household: Yes	123 (37%)	332	74 (40%)	185	49 (33%)	147	0.2526
Sleeping with empty stomach: Yes	122 (37%)	332	74 (39%)	185	49 (33%)	147	0.2548

Table 2. Univariate Analysis of Covariates Stratified by Sex, among HIV + Adults in Kapiri, Zambia, 2008-2009

	Male		Female	
	HR	**90% CI**	**HR**	**90% CI**
Non-nutritional covariates				
Age (years)	1.074	(0.519, 2.224)	0.692	(0.331,1.445)
Occurrence of non-severe HIV-associated symptoms	2.479**	(1.415, 4.343)	2.261**	(1.322, 3.869)
Anthropometry				
Continuous BMI (kg/m^2)	0.905*	(0.829, 0.988)	0.91**	(0.864, 0.958)
Categorical BMI				
Normal	ref	ref	ref	ref
Mild Thin	1.342	(0.853, 2.112)	2.312**	(1.53, 3.495)
Moderate/Severe Thin	1.874	(0.998, 3.519)	1.44	(0.893, 2.320)
Continuous MUAC (mm)	0.993	(0.987, 1.000)	0.991**	(0.985, 0.996)
Categorical MUAC				
Normal	ref	ref	ref	ref
Undernourished	1.528*	(1.019, 2.289)	1.482	(0.973, 2.258)
Severe/Extreme Wasting	1.798	(0.798, 4.052)	2.824**	(1.468, 5.433)
Appetite and Weight Loss				
Loss of Weight: Yes	1.193	(0.790, 1.803)	0.945	(0.68, 1.312)
Loss of Appetite: Yes	0.793	(0.543, 1.157)	0.977	(0.722, 1.323)
Percent of BP100 consumed (%)*	N/A	N/A	1.007	(0.994, 1.02)
Handgrip Strength/Fatigue Test				
Mean of measures (psi)	0.92**	(0.862, 0.982)	0.924*	(0.864, 0.988)
Median of measures (psi)	0.924**	(0.865, 0.986)	0.923**	(0.864, 0.987)
Slope of measures	0.225	(0.041, 1.225)	0.377	(0.088, 1.614)
Percent strength loss (%)	1.025*	(1.003, 1.046)	1.02**	(1.005, 1.034)
Deviation of mean measures from the baseline (%)	1.005	(0.990, 1.020)	1.007	(0.998, 1.016)
Sphygmomanometer Test				
Test length (sec)	0.984	(0.964, 1.005)	0.992	(0.974, 1.011)
Total number of grip	0.984**	(0.972, 0.995)	0.985**	(0.975, 0.995)
Average grip strength (mmHg/grip)	1.000	(0.993, 1.007)	1.001	(0.997, 1.006)
Cumulative handgrip strength (mmHg)	1.142	(0.963, 1.356)	1.14	(0.955, 1.361)
Household Food Security				
Unable to eat preferred food: Yes	1.035	(0.700, 1.531)	0.868	(0.638, 1.180)
Have smaller/fewer meals: Yes	1.02	(0.691, 1.506)	0.923	(0.681, 1.252)
No food storage in household: Yes	0.723	(0.469, 1.116)	0.989	(0.717, 1.364)
Sleeping with empty stomach: Yes	0.627*	(0.397, 0.989)	0.947	(0.684, 1.311)

*0.05< p-value ≤ 0.10
**p-value ≤ 0.05

Table 3. Multivariate analysis of time to ART initiation among HIV + adults stratified by gender in Kapiri, Zambia, 2008-2009

Sex-specific Models	aHR	90 % CI	p-value
Male (Event = 109, Censored=604)			
Continuous BMI (kg/m^2)	0.957	(0.846, 1.083)	0.5567
Categorical MUAC			
Normal	ref		
Undernourished	1.022	(0.619, 1.687)	0.9427
Severe/Extreme Wasting	0.611	(0.227, 1.645)	0.4137
Mean of handgrip strength measures (psi)**	0.916	(0.841, 0.998)	0.0921
Total number of handgrip***	0.985	(0.973, 0.997)	0.0378
Sleeping with empty stomach: Yes	0.518	(0.316, 0.849)	0.0284
Female (Event= 144, Censored= 973)			
Continuous BMI (kg/m^2)	0.967	(0.887, 1.054)	0.5186
Continuous MUAC (mm)	0.997	(0.988, 1.006)	0.5324
Percent strength loss (%)**	1.009	(0.994, 1.025)	0.3135
Total number of handgrip***	0.988	(0.978, 0.998)	0.0584

* the occurrence of HIV-associated symptoms was controlled as potential confounder
** measures selected from the hand strength/fatigue test
*** measure selected from the sphygmomanometer test

Chapter III

Summary

In sub-Saharan Africa, the co-morbidity of HIV/AIDS and malnutrition (under-nutrition) are highly prevalent due to generalized epidemics of HIV/AIDS in combination with famines caused by drought and food insecurity (27). The mutual aggravation between malnutrition and HIV infection has been well documented. Few studies have been done to address the association between nutritional indicators and HIV disease progression among ART-naïve HIV-infected populations, which may be more representative to in resource-scarce areas where access to ART may be limited. Therefore, our study aimed to assess the handgrip strength and endurance along with various other nutritional indicators as predictors of time to antiretroviral therapy (ART) initiation (proxy for worsened disease progression).

From 2008-2009, HIV+ adult males and non-pregnant females that were physically capable for receiving nutritional assessment were followed for 9 months as they made quarterly visits for nutritional evaluation and irregular clinical check-ups at a MSF HIV clinic in Kapiri, Zambia. A sex-stratified multivariate Cox model was used to assess the association between various nutritional indicators and time to ART initiation.

In the ART-naïve Zambian adults infected with HIV, 46% of males and 44% of females were initiated on ART during the 9 month follow-up period. The association between nutrition indicators and the time to ART initiation appeared to be different by sexes at large. While *the mean of the consecutive handgrip strength measures* and the occurrence of *sleeping with the empty stomach* each independently predicted the time to ART initiation among males, the *total number of handgrip* produced for the "sphygmomanometer test" independently predicted the outcome for both sexes. An increment on the *handgrip mean strength* (aHR=0.916, 90% CI 0.841-0.998) and the *total*

number of handgrip (aHR=0.985, 90% CI 0.972-0.997) was protective against ART initiation among males, and having the incident of *sleeping with empty stomach* (aHR=0.516, 90% CI 0.314-0.846) due to food scarcity were protective against ART initiation for both males and females. However, BMI and MUAC, both of which were found to be univariate predictors of the time to ART initiation for both sexes, did not independently predict the outcome after controlling for other covariates in either populations.

It is interesting to find the mean of handgrip measures and the percent strength loss were not significant independent predictors in their respective cohort, while the total number of handgrip in the sphygmomanometer test were in both cohorts. However, the level of sensitivity and mechanism by which the total number of handgrip over a pre-specific time period in reflecting malnutrition is currently unknown. Our findings that BMI and MUAC do not independently predict short-term disease progression among PLHIV may be due to the short length of our study; previous studies followed participants for longer than our study length of nine months. Our results may also imply that BMI and MUAC may be poor predictor for hastened disease progression in well-nourished populations, since our preliminary data from the functional capacity assessment suggests that all participants were capable of doing heavy works. Few qualitative studies may have addressed the reasons behind the protective effect of extreme food insecurity: the participant's emergent need for food may compete their desire to prioritize ARV treatment (37, 38); the participant's knowledge of the supplementary food requirement for ARV may compromise their desire to start ARV given their ongoing struggle with securing stable food source.

There are several limitations to this study that may affect our estimated time to ART initiation. Due to concerns for confidentiality, socioeconomic variables were not included in this analysis. The lack of controlling for socioeconomic variables as potential confounders affecting both nutrition and event of ART initiation may result in inaccurate estimate.

Another major limitation for our analysis method was the longitudinal populating of nutrition data between quarterly follow-ups. Due to the limited number of visits where original nutrition values were allowed to vary, the study may not fully capture the evolution of nutrition status, which may bias our estimate in an unknown direction.

Public Health Implications

Our finding about the number of handgrip in "the sphygmomanometer test" as a strong independent predictor of time to ART initiation in both sexes may shed light on the anthropometrical assessment of PLHIVs' nutritional statuses in resource-scarce or emergency settings, where the scope of nutritional assessment and access to ART are often restricted. In addition to the capacity to independently predict hastened HIV disease progression, the minimum requirement on mechanical equipment and the technical simplicity for conducting "sphygmomanometer test" may be of great clinical potential for facilitating the case management of HIV and malnutrition comorbidity in rural Sub-Saharan Africa, than other conventional nutrition assessments (e.g. BMI, MUAC).

Possible Future Directions

The association between the number of grips over a pre-specified time period, dynamic muscular endurance and HIV disease progression still need to be investigated. Moreover, it may be of interest to investigate the implication that BMI and MUAC are not predictive for short-term disease progression in light of differences between chronic and acute malnutrition. Acute malnutrition is known to be associated with short termed mortality, as compared to chronic malnutrition, and might potentially lead to faster HIV disease progression. Future research should also investigate the mechanism by which sex interacts with food insecurity and malnutrition and how that interaction affects disease progression and one's desire to initiate ART. Due to limited data, super-stratification by age

and baseline handgrip strength was not plausible for our analysis, so further research should focus on this possible association.