BODY WASTING AMONG TUBERCULOSIS PATIENTS IN URBAN UGANDA

by

EZEKIEL MUPERE MBChB, M.MED (Paediatrics), M.S

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Dissertation Advisor: Dr. Daniel Tisch PhD, MPH

Department of Epidemiology and Biostatistics

CASE WESTERN RESERVE UNIVERSITY

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CASE WESTERN RESERVE UNIVERSITY

SCHOOL OF GRADUATE STUDIES

We hereby approve the thesis/dissertation of

Ezekiel Mupere

candidate for the PhD degree *.

(signed) Daniel Tisch PhD, MPH
(chair of the committee)

Christopher Whalen, MD, MS

Isabel Parraga, PhD, RD, LD

Mark Schluchter, PhD

Catherine Stein, PhD

(date) March 17th, 2010

*We also certify that written approval has been obtained for any proprietary material contained therein.

DEDICATION

To

My wife Harriet Mupere Babikako for your cheerful love, prayers,

and persuasive encouragement

My children Patience Esther Mupere, Elizabeth Peace Mupere, Ednah Precious Mupere, and those I prayerfully hope to be born, for being a strong encouragement. Desire to embrace this academic path

My elder brother Daniel Bawunha for establishing the foundation of my academic path and for your words of wisdom

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The memory of my late mother Mary Dorothy Wandawa for the exemplary parental love and vision, and for introducing me to the objective of learning a, e, i, ..., and to the objective of learning how to write a love letter; now accomplished. I'm forever indebted.

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Body Wasting among Tuberculosis Patients in Urban Uganda

Abstract

By

EZEKIEL MUPERE

Background Although body wasting is a cardinal feature of tuberculosis, its etiology and management is poorly understood; and its assessment is overlooked in research and in clinical practice.

Objective We established whether body wasting modifies survival and body composition changes during and after tuberculosis treatment; whether HIV modifies dietary intake among tuberculosis patients; whether dietary intake differs by wasting and severity of disease status; and whether dietary intake influences body composition.

Methods Retrospective cohort and cross-sectional designs were employed. Height-normalized body mass (BMI), fat-free mass (FFMI), and fat mass (FMI) indices and 24-hour dietary intake recall were measured.

Results Body wasting was associated with reduced survival and the effect differed by gender. FFMI was found to be a predictor of survival among women whereas BMI was

among men. Wasting was associated with substantial linear increase in FFMI, FMI, and BMI during the first three months but the rate of increase differed by gender and not HIV status. Changes in body composition among men were affected by initial FFMI and BMI, whereas among women by FMI. There were minimal changes in body composition after month 3 and during the one year period after month 12 regardless of the initial body composition, gender, and HIV status. Dietary intake in the study population was monotonous, rich in carbohydrates and deficient in nutrients. Dietary intake at the time of diagnosis was influenced by severity of tuberculosis disease, but not HIV status and in the absence of tuberculosis was influenced by gender. Prediction of body composition by energy and protein intake differed by gender. Energy intake was an important predictor of body composition among women whereas appetite was among men.

Conclusion Results provide theoretical framework to provide targeted nutritional intervention to patients presenting with wasting and patients of female gender. National programs should integrate nutritional health education in the management of tuberculosis. Nutritional assessment should involve establishment of body composition to identify patients that may be at risk of poor survival. Further evaluation is needed to understand changes in dietary intake overtime and its impact on body composition.

Key words: Tuberculosis; body wasting; survival; body composition; dietary intake

Word count: 343

CHAPTER 1

INTRODUCTION

INTRODUCTION

Tuberculosis is the most relevant infectious disease worldwide, and its etiological agent, Mycobacterium tuberculosis, infects one-third of the world population (World Health Organization. Global tuberculosis control. Epidemiology, strategy, financing. WHO 2009). Globally, 9.2 million new cases and 1.7 million tuberculosis-associated deaths occurred in 2006 (Vitoria et al. 2009). In sub-Saharan Africa, where the prevalence and incidence of tuberculosis are among the highest in the world, 79% adults with tuberculosis are also infected with human immunodeficiency virus (HIV) (Lawn and Churchyard 2009; World Health Organization 2009), resulting in elevated mortality. Tuberculosis is frequently found at autopsy of acquired immunodeficiency syndrome (AIDS) patients (Lucas et al. 1994; Lucas et al. 1993), particularly cachectic patients suggesting that tuberculosis exacerbates the wasting process of HIV-infected people in Africa.

Tuberculosis and HIV are both independently associated with body wasting (Scalcini et al. 1991; Suttmann et al. 1995; Harries et al. 1988; Kennedy et al. 1996). In tuberculosis-HIV co-infection, there may be additional metabolic, physical, and nutritional burden, resulting in potential further increase in energy expenditure, malabsorption, and micronutrient deficiency. Thus, the suggested tuberculosis or co-infection malnutrition model (Figure 1:1). In this model because of differences in metabolism, gender differences in body composition at presentation among TB patients have been reported

(Kennedy et al. 1996; Mupere et al. 2010). There may also be increased production of pro-inflammatory cytokines resulting in breakdown of body lipids and proteins (Niyongabo et al. 1999; van Lettow, Fawzi, and Semba 2003) in a patient with already compromised nutrient intake because of reduced appetite. Moreover, wasting itself is a cause of immune-deficiency affecting cellular immunity the key host defense against tuberculosis (Chandra 1991; Fernandes G, Jolly C.A, and Lawrence R.A 2006; Gershwin M.E, Beach R.S, and Hurley L.S 1985). Thus, body wasting may be a risk factor for tuberculosis and tuberculosis might not only worsen the course of HIV-associated immune-depression but also worsen the HIV-associated wasting because recent reports suggest tuberculosis to be the dominant factor in driving the wasting process in co-infection (Mupere et al. 2010; Paton and Ng 2006). These interrelated effects possibly explain the fact that both tuberculosis and wasting are associated with reduced survival during HIV infection (Nunn et al. 1992; Suttmann et al. 1995).

Early detection and timely management of body wasting is important in prevention of morbidity and mortality in tuberculosis. The assessment of body wasting and management is also important during and after tuberculosis treatment to understand the changes in body composition. However up to date, several prior studies particularly in sub-Saharan Africa that assessed body wasting in tuberculosis used body mass index (BMI) (Zachariah et al. 2002; Kennedy et al. 1996; Mugusi et al. 2009). Yet BMI is insensitive to body fatness, particularly at low BMI, as well as with above normal muscle development (Kyle, Genton, and Pichard 2002; Kyle, Piccoli, and Pichard 2003). This implies that previous studies (Zachariah et al. 2002; Mugusi et al. 2009) might have

overestimated mortality due to wasting, and might have failed to reveal precise changes in body composition during and after tuberculosis (Kennedy et al. 1996; Ramakrishnan et al. 1961). Moreover, compared to fat mass or weight in itself, fat-free mass body compartment correlates closely with quality of life, physical functioning, and survival (Wagner, Ferrando, and Rabkin 2000; Mostert et al. 2000). Bioelectrical impedance analysis (BIA) provides a precise and practical method for clinical assessment of fat and fat-free mass (Kyle, Genton, and Pichard 2002; Kyle et al. 2004); however, its application is still limited to research settings that simple and inexpensive methods are needed particularly in sub-Saharan Africa.

Although body wasting and malnutrition play an important role in the clinical course of patients with tuberculosis and HIV and those with dual infection, nutritional status, nutritional intake, and quality of intake are often overlooked in regular clinical practice and in tuberculosis programs. This has led to paucity of information to characterize nutritional intake and quality of intake, and how the intake influence body composition in patients with or without tuberculosis. Characterization of tuberculosis-associated body wasting and nutrient intake not only contributes to the understanding of the pathophysiology but also the management of body wasting.

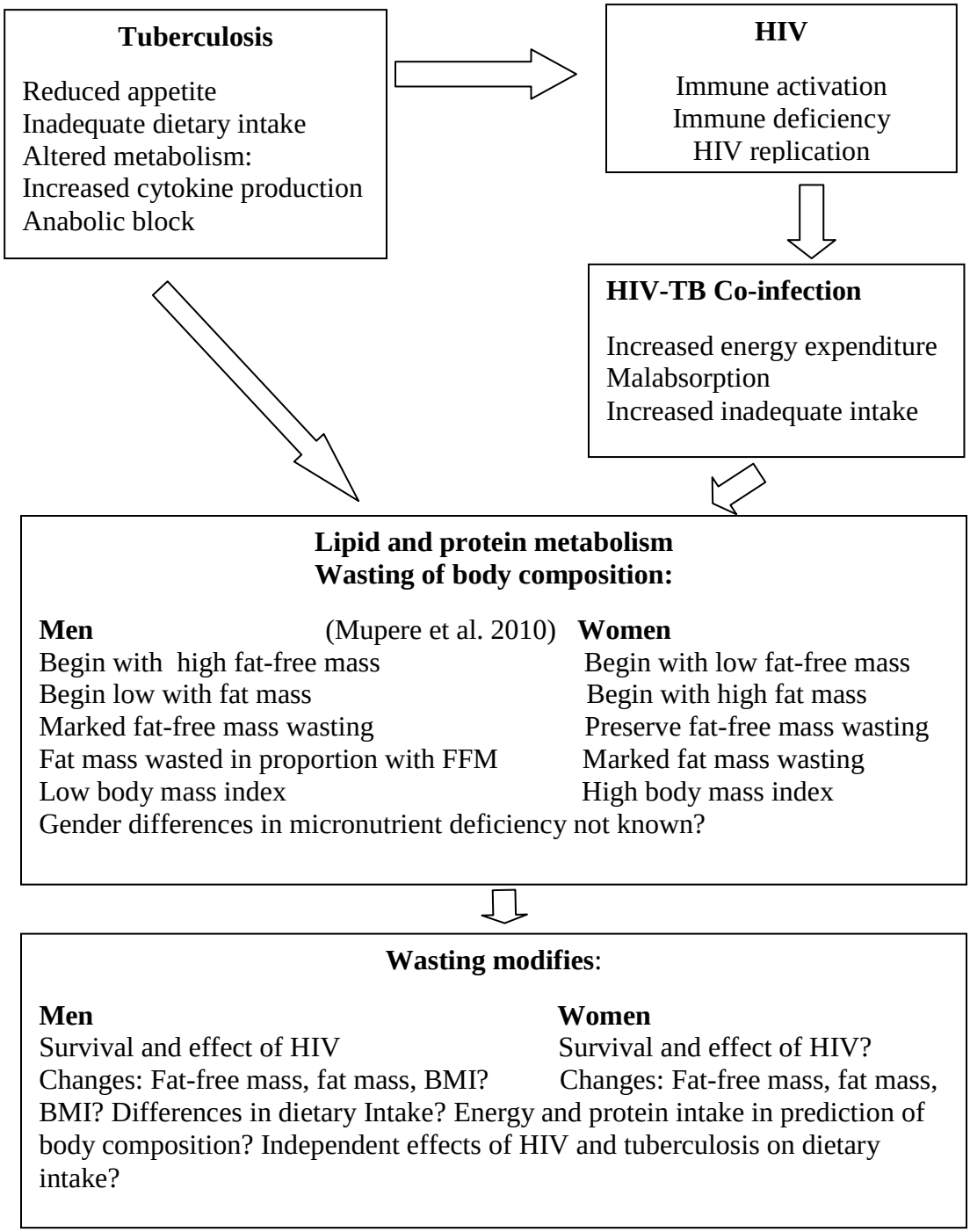
This dissertation was designed to fill gaps in understanding survival and changes in body composition using precise measures of nutritional status; in understanding nutrient intake

and its association with body wasting and body composition measurements; and how body composition can be assessed using simple existing equations in sub-Saharan.

Goal

The goal of this dissertation was to generate information that could be used to improve survival in tuberculosis patients. This dissertation focused first on understanding simple and inexpensive approaches of assessing body wasting. Second, focused on generating information that could aid in understanding of body wasting and its management, that is whether nutritional factors influence body composition in the face of tuberculosis; and whether body wasting as measured by precise measures of body composition modifies the course of tuberculosis.

Figure 1:1 Working tuberculosis – HIV – Malnutrition Model



BMI = body mass index, FFM = fat-free mass

SPECIFIC AIMS

Chapter 4: **Body composition measured with bioelectrical impedance analysis and anthropometry among HIV positive and HIV negative adults with or without tuberculosis in urban Kampala, Uganda.**

Specific Aim:

To establish whether simple anthropometric measurements can be used to provide comparable estimates of body composition to those of bioelectrical impedance analysis.

Hypothesis:

Waist circumference, mid-upper-arm circumference, and body mass index provide similar estimates of body composition to those of bioelectrical impedance analysis.

Chapter 5: **Indicators of dietary adequacy among HIV positive and HIV negative adults with or without tuberculosis in urban Kampala, Uganda.**

Specific Aim:

To evaluate whether simple counting of food items or food groups are indicators of dietary adequacy in a population of HIV positive and HIV negative adults with or without tuberculosis in urban Kampala, Uganda.

Hypothesis:

Simple counting of food items or food groups are predictors of dietary adequacy among HIV positive and HIV negative adults with or without tuberculosis in urban Kampala, Uganda.

Chapter 6: **Predictors of body composition among HIV positive and HIV negative adults with or without tuberculosis in urban Kampala, Uganda.**

Specific Aim:

To establish whether energy and protein intake are predictors of body composition among HIV positive and HIV negative adults with or without tuberculosis in urban Kampala, Uganda.

Chapter 7: **Body wasting and dietary intake among HIV positive and HIV negative adults with or without tuberculosis in urban Kampala, Uganda.**

Specific Aim:

To establish the relationship between body wasting or severity of tuberculosis disease and dietary intake among HIV positive and HIV negative adults with or without tuberculosis in urban Kampala, Uganda.

Hypothesis:

HIV modifies dietary intake among tuberculosis patients.

Dietary intake differs by body wasting.

Chapter 8: **Correlates of dietary intake and adequacy among HIV positive and HIV negative adults with or without tuberculosis in urban Kampala, Uganda.**

Specific Aim:

To establish dietary correlates of energy and protein intake, and correlates of nutrient inadequacy among HIV positive and HIV negative adults with or without tuberculosis in urban Kampala, Uganda.

Hypothesis:

Tuberculosis and HIV do not affect energy and protein intake

Chapter 9: **Impact of body wasting on survival among adult patients with pulmonary tuberculosis in urban Kampala, Uganda.**

Specific Aim:

To establish the effect of body wasting as measured by height-normalized fat mass and lean tissue and body mass indices on survival among adult patients with pulmonary tuberculosis in urban Kampala, Uganda.

Hypothesis:

Body wasting modifies survival among tuberculosis patients in urban Kampala, Uganda.

Chapter 10: **Longitudinal changes in body composition during and after tuberculosis treatment in urban Kampala, Uganda.**

Specific Aim: To establish the rate of change for fat mass, fat-free mass, and BMI among tuberculosis patients in urban Kampala, Uganda.

Hypothesis:

Body wasting modifies longitudinal changes in body composition during and after tuberculosis treatment.

CHAPTER 2

BACKGROUND

BACKGROUND

Nutrition and Tuberculosis

The role of nutrition in tuberculosis leads to consideration of three important questions (Rao K.N and Gopalan C 1966). Does malnutrition predispose to tuberculosis? Does malnutrition influence or modify the course of established infection? Do nutritional factors influence the response to chemotherapy? In the present dissertation, the focus was to understand the influence of body wasting and malnutrition as measured by precise measures of fat and fat-free mass on survival and changes in body composition during and after tuberculosis treatment. Further, to understand the influence of nutritional factors, specifically nutrient intake and its quality on body composition in the presence or absence of tuberculosis.

Effects of nutritional status on tuberculosis

The association between tuberculosis and malnutrition has long been recognized, as malnutrition predisposes people to the development of clinical disease; and tuberculosis often exacerbates malnutrition (Macallan 1999). The host protective immune mechanism of infection with *Mycobacterium tuberculosis* depends critically on the interaction and cooperation between monocyte-macrophages and T-lymphocytes and their cytokines (Rook and Hernandez-Pando 1996). Substantial experimental evidence suggests that malnutrition can lead to secondary immunodeficiency that increase the host's

susceptibility to infection. Severe malnutrition has profound effects on cell-mediated immunity (Chandra 1991), and both macro- and micronutrient deficiency can influence susceptibility to tuberculosis in animal models (Bhuyan and Ramalingaswami 1973; McMurray et al. 1990). Increased risk of tuberculosis can result from alteration in the individual protective function of, or the interaction between T-lymphocytes and macrophages because of nutritional insult (Chan J et al. 1997). Although a causal relationship has yet to be clearly established in humans, malnutrition may impair host responses in patients with tuberculosis, particularly leading to a vicious cycle of malnutrition and infection (Bhaskaram 1992).

An already malnourished individual with compromised cell mediated immunity is more likely to become infected with tuberculosis, and latent infection is more likely to become active tuberculosis. Among individuals with latent tuberculosis, the occurrences of malnutrition may be an important trigger for active tuberculosis development (Cegielski and McMurray 2004). One longitudinal study of participants in a BCG vaccine trial in the United States found the incidence of active tuberculosis was 2.2 times higher in children with low subcutaneous fat stores (skin-fold thicknesses between 0 and 4 mm) compared to with those with 10 mm subcutaneous fat (Comstock and Palmer 1966). In a large study in Norway, the incidence of smear-positive and smear-negative tuberculosis declined significantly with increasing BMI in all age groups. New tuberculosis diagnosis was 5 times higher in the lowest BMI group compared with the highest BMI group (Tverdal 1986). Individuals with immuno-suppression have a greater risk of developing clinical

tuberculosis which explains the increased prevalence of tuberculosis in association with HIV infection.

Effect of tuberculosis on nutritional status

During active tuberculosis, catabolic processes that cause wasting usually begins before the patient is diagnosed; therefore more is known about nutritional status at the time of diagnosis than of the wasting process *per se* (Macallan 1999). Prior studies have examined the effect of tuberculosis on nutritional state and demonstrated extensive nutritional depletion at the time of diagnosis (Onwubalili 1988; Zacharia R et al. 2002; Zachariah et al. 2002). In developing countries, the impact of tuberculosis is even more dramatic. For example, one study in Malawi that evaluated 122 patients revealed a reduction in BMI of 20% from 21.7 to 17.3 with 35% reduction in skinfold thickness and 19% reduction in arm muscle circumference (Harries et al. 1988). Similar degrees of wasting have been reported in other populations (Scalcini et al. 1991). Such losses of both fat and fat-free mass (muscle or lean tissue) represent severe wasting and may pose significant impact on morbidity and mortality of their own in addition to that due to tuberculosis disease itself.

Effect of co-infection with HIV and tuberculosis on nutritional status

Although co-infection with HIV and tuberculosis may be thought to introduce an extra dimension to the pathophysiology of wasting, exacerbating the wasting seen in

tuberculosis or HIV infection alone (Macallan 1999; Lucas et al. 1994), recent studies (Mupere et al. 2010) with a full panel of HIV positive and HIV negative adults with or without tuberculosis suggest gender but HIV as the factor associated with differences in body composition during co-infection. Further, tuberculosis has been suggested as the dominant factor driving the wasting process at the time of diagnosis (Mupere et al. 2010; Paton and Ng 2006). Prior studies that reported conflicting results were limited in terms of sample size, comparison groups, and study populations that were composed of only men (Paton et al. 1999) (Scalcini et al. 1991).

Possible Mechanism of Wasting or effect of tuberculosis on nutrition

In the 21st century, tuberculosis is still the most frequent underlying cause of wasting worldwide. Wasting is regarded as the cardinal features of the disease. However, the pathophysiology of wasting in tuberculosis remains poorly understood (Schwenk A and Macallan D.C 2000). For any infection, there is a complex interaction between the host response and the virulence of the organisms, which modulates the overall metabolic response and the degree and the pattern of tissue loss. In patients with tuberculosis, a reduction in appetite with eventual reduction in energy intake, nutrient malabsorption, micronutrient malabsoption, and altered metabolism leads to wasting (Paton et al. 1999; Macallan et al. 1998). However, factors that make the most dominant contribution in tuberculosis have been difficult to identify because the wasting phase is rarely observed and because of the ethical obligation to commence treatment once a diagnosis of tuberculosis has been made. Observations have been made at the time of diagnosis that

the metabolic rate or resting energy expenditure is increased (Macallan et al. 1998). However, by analogy with HIV infection where wasting phase has been scrutinized (Macallan, Noble et al. 1995), increased energy expenditure is unlikely to be the sole driving force behind wasting in the catabolic phase. It is reduced energy intake which may be more likely to be the primary driving force.

In one study in India, patients with pulmonary tuberculosis were compared with malnourished and normally nourished healthy subjects. Whereas protein synthesis (anabolism) and breakdown (catabolism) in the fasting state were not significantly different between groups, patients with tuberculosis used a larger proportion of proteins (amino acids) from oral feeding for oxidation and hence for energy production than did either control group. The failure to channel food protein into endogenous protein synthesis has been termed “Anabolic block”. This anabolic block represents one of the mechanism for wasting in tuberculosis and other inflammatory status (Macallan et al. 1998; Paton et al. 2003). Tuberculosis may have a greater catabolic effect than HIV infection where similar studies failed to demonstrate anabolic block at the whole body level (Macallan, McNurlan et al. 1995). The difference in metabolic response may be the consequence of differences in the pattern of cytokine activation between tuberculosis and HIV disease states.

Anorexia is also a contributing factor for wasting in tuberculosis. In an unselected U.S. cohort of patients diagnosed with tuberculosis, 45% lost weight and 20% had anorexia

(Miller et al. 2000). Increased production of cytokines with lipolytic and proteolytic activity cause increased energy expenditure in tuberculosis (Verbon et al. 1999). Leptin may also play an important role in wasting (Sarraf et al. 1997). In a study, malnutrition has been associated with atypical presentations of tuberculosis (Madebo, Nysaeter, and Lindtjorn 1997).

Micronutrient malnutrition in tuberculosis

Several micronutrient deficiencies have been described in individuals with tuberculosis (van Lettow, Fawzi, and Semba 2003) and in those with HIV infection (Semba and Tang 1999; Bogden et al. 1990; Beach et al. 1992; Ullrich et al. 1994; Baum et al. 1991; Ehrenpreis et al. 1994; Harriman et al. 1989). Several cross-sectional studies suggest that patients with tuberculosis suffer from deficiencies of vitamin A (Evans and Attock 1971; Smurova and Prokop'ev 1969), thiamin (Arkhipova O.P 1975), vitamin B^6 (Miansikov V.G 1969),folate (Markkanen et al. 1967; Line et al. 1971), and vitamin E (Panasyuk A.V et al. 1991). Deficiencies that have been reported to be more prevalent among HIV-infected adults than in those without HIV infection include vitamin A, vitamin E, thiamin, riboflavin, vitamin B^6, and vitamin C (Beach et al. 1992; Ullrich et al. 1994; Baum et al. 1991; Ehrenpreis et al. 1994; Harriman et al. 1989). Of these deficiencies, vitamin A and D have received the most attention in patients with tuberculosis. The interest in vitamins A and D hinges on the historic use of cod-liver oil as treatment for tuberculosis prior to the era of antibiotics (Whalen C and Semba R.D 2001). Vitamins A, C, E, B^6, and folic acid and minerals zinc, copper, selenium, and iron all have key roles in

metabolic pathways, cellular function, and immune competence (Keusch 1990). The concentration of these may have a role in host defense against tuberculosis (Karyadi et al. 2000). Deficiency of single or multiple nutrients can reduce an individual's resistance to any infection (Chandra 1991; Keusch 1990; Chandra and Kumari 1994).

Changes in Nutritional Status during Tuberculous Chemotherapy

During drug treatment of active tuberculosis without supplementary nutrition, nutritional status usually improves. This can be attributed to a variety of reasons including improved appetite and food intake, reduced energy/nutrient demands, and improved metabolic efficiency. Most improvements, how, are limited to increase in fat mass (Macallan 1999). For example, a study by Schwenk et al. (Schwenk et al. 2004) that investigated the changes in fat mass and protein mass (fat-free mass) in 40 patients receiving standard tuberculosis treatment found after six months of treatment, the patients had gained 9.5 ± 8.95% body weight, mainly due to gain in fat mass with no significant change in protein mass suggesting that clinical recovery from tuberculosis does not guarantee protein mass restoration, even though weight gain is significant. This finding may support the idea that protein metabolism continues to be altered even during treatment, and that clinical and functional recovery from tuberculosis lags behind microbial cure. Alternatively, diet during treatment may have been inadequate in relationship to increased requirements during treatment and recovery, thereby limiting development of lean body mass.

Nutritional treatment of tuberculosis

Nutritional supplementation may help to improve outcome in tuberculosis patients. One study in Singapore (Paton et al. 2004), found that nutritional counseling to increase energy intake combined with provision of supplements, when started during the initial phase of tuberculosis treatment, produced a significant increase in body weight, total lean mass, and physical function after six weeks. A large proportion (46%) of the early weight gain comprised lean tissue, confirming the findings that tuberculosis can mount a protein anabolic response on feeding. In the same study, patients in the nutritional supplementation group continued to show a greater increase in body weight than control subjects during later follow-up. However, the pattern changed toward deposition of predominantly fat mass, whereas in the control group, the weight gain comprised fat lean tissue in approximately equal proportions (Paton et al. 2004). However, the changes in lean tissue described above could be an underestimate of the actual improvement in nutritional status, given that feeding initially leads to a loss of extracellular water that accumulates in malnourished individuals, including those with tuberculosis (Paton et al. 1999). Accelerating the recovery of lean tissue might help to restore physical functions more rapidly. Restoration of physical function might help to shorten the convalescent period and facilitate earlier return to productive work (Paton et al. 2004). Early restoration of nutrition could also lead to immunologic changes that could enhance the clearance of mycobacteria and reduce infectiousness of patient.

Vitamins and minerals can play important role in treatment of tuberculosis. In a trial among 110 new cases of active tuberculosis, subjects received tuberculosis chemotherapy alone, or in addition to injectable thiamin, vitamin B^6, and vitamin C, or oral multivitamin supplement (Volosevich 1982). All groups receiving any vitamin supplementation had significantly better lymphocyte proliferation responses than the group receiving no supplement. Another trial showed that vitamins C and E were effective in improving immune responses to tuberculosis when given as adjuvant to multidrug tuberculosis therapy (Safarian et al. 1990). The supplementation with vitamin A and zinc improved the effectiveness of the antituberculosis drugs in the first two months. The improved outcome was indicated by the higher number of patients with sputum negative for bacilli and significantly lower mean lesion area in the lungs (Karyadi et al. 2002).

CHAPTER 3

STUDY METHODS

Study Design

To address the aims of this dissertation, a hybrid of retrospective cohort and cross-sectional designs were employed. The completed five year Household Contact (HHC) study, the completed phase II prednisolone double blind randomized placebo controlled clinical trial (PD), and the ongoing Kawempe Community Health (KCH) study databases were used for the retrospective design. Datasets with relevant key variables from the HHC, KCH, and PD were created and merged to form one large working database. A total of 753 patients were evaluated for analysis. Of the 753, 314 were enrolled into the HHC, 344 into the KCH, and 95 into the placebo arm of the prednisolone clinical trial (Figure 3:1). The datasets for the three studies were first tested for differences in baseline characteristics before combining for analysis. The datasets were different regarding extent of tuberculosis disease on chest x-ray because the phase II prednisolone trial enrolled only HIV-associated tuberculosis patients with CD4 cell count >200 cells/l compared to HHC and KCH studies (Appendix, Table 13:1). One of our interests was to establish the confounding effect of HIV; therefore, we combined all the three datasets for analysis. The BIA data (specifically, fat-free mass and fat mass) were collected during the KCH study only.

The HHC and KCH studies were observational epidemiologic studies; organized and conducted by the Makerere University and Case Western Reserve University TB research collaboration (Uganda-CWRU) that has been ongoing for the last 20 years in Uganda.

The HHC was the initial household contact study from 1995 to 1999 that described the epidemiology of TB in urban Kampala, Uganda (Guwatudde et al. 2003). The KCH is the second phase of the HHC. The KCH phase started in 2002 and is still ongoing (Stein et al. 2005). The KCH was developed specifically to focus on the determinants of host factors associated with primary infection, re-infection, reactivation, and progression of clinical disease and to identify and track individual strains of mycobacterial TB through Ugandan households and local community. The phase II clinical trial was conducted between 1995 to 2000 to determine whether immunoadjuvant prednisolone therapy in HIV-infected patients with TB who had CD4(+) T cell counts >/=200 cells/ mu L was safe and effective at increasing CD4(+) T cell counts (Mayanja-Kizza et al. 2005). Patients were eligible for analysis if they were 18 or more years of age, had baseline measurements, had an HIV test, and were part of one prospective study conducted by the Uganda-CWRU research collaboration. Adults with a previous history of treated pulmonary TB were excluded in the study.

In a cross-sectional study, 132 participants 18 years or older residing in Kampala district or 20 km from the study site if residence was outside Kampala in Uganda were enrolled. One participant was excluded from the analysis because of prior TB treatment. The study was conducted at the National TB and Leprosy Program (NTLP) Clinic of the national tertiary teaching hospital complex, Mulago between November 2007 and March 2008. Of the 131 participants who were included in the analysis, 31 were HIV positive with TB and 32 were HIV negative with TB and were recruited at the Mulago NTLP Clinic; 38 were HIV positive without TB and recruited at the Infectious Disease Institute Clinic

(IDI) located 500 meters from the Mulago NTLP Clinic; and 30 HIV negative individuals without TB were enrolled from the community where TB patients resided (Figure 3:2).

The retrospective cohort and cross-sectional designs were chosen in view of their advantages. There was a rich existing database on study participants who fit the needed criteria for a retrospective cohort design. A cross-sectional design could easily be implemented in a short period of time for primary data collection to study associations. The retrospective cohort and cross-sectional were thus cost effective and took time constraints into consideration.

In a retrospective cohort, the investigator identifies a cohort of individuals based on their characteristics in the past and then reconstructs their past or up to the present time (or occasionally into the future). The ideal concurrent cohort design in which the investigator identifies the cohort on the basis of current characteristics and is then followed forward in time would be expensive and would require a longer time to complete the study. The potential bias of missingness in data anticipated in a retrospective cohort design was assessed for using standard statistical procedures.

In a cross-sectional design, the investigator evaluates for the exposure and outcome of interest at the same one point in time. The disadvantage with a cross-sectional design is that the presence or absence of both exposure and disease/outcome of interest are

determined at the same time in each individual in the study. It is not possible to establish a temporal relationship between exposure and onset of disease. Therefore, although a cross-sectional study can be very suggestive of a possible risk factor or factors for a disease, with limitations in establishing the temporal relationships, the association cannot reflect a causal relationship.

The institutional review boards at Case Western Reserve University in the United States and Joint Clinical Research Center in Uganda reviewed the protocol and final approval was obtained from the Uganda National Council for Science and Technology. All patients had written informed consent taken to be enrolled in the parent studies. All participants were given appropriate pre- and post-test HIV counseling and AIDS education.

Measurements

In all the four studies, socio-demographic and clinical information was obtained through standardized interviews and physical examination performed by trained medical officers. Venous blood was collected for HIV-1 enzyme immunoassay testing and complete blood and differential counts. HIV infection was documented by enzyme-linked immunosorbent assays. None of the HIV positive patients, neither those who were newly identified with HIV nor those with pre-existing HIV, were on antiretroviral therapy. All participants had posterior-anterior chest X-rays taken at baseline. Expectorated sputum specimens were collected, concentrated, and stained for acid fast bacilli (AFB) with Ziehl-Neelsen stain at

the Wandegeya national reference laboratory in Uganda. AFB smears were reviewed by trained technicians who graded the smears by the number of acid-fast organisms seen on the light microscopy according to criteria established by the WHO (International Union Against Tuberculosis and Lung Disease 1986). Specimens were cultured for mycobacteria tuberculosis on Lowenstein-Jensen medium slants, incubated at 37^0C in air and examined weekly until positive or for 8 weeks. Patients with active tuberculosis were treated with standard four-drug chemotherapy for tuberculosis per guidelines of the Ugandan Ministry of Health.

Nutritional status was assessed using anthropometric measurements such as height and weight and BIA Detroit, MI, RJL Systems. Body weight was determined to the nearest 0.1 kg using a SECA adult balance, and standing height was determined to the nearest 2 mm. Body-mass index (BMI) was computed using the relationship of weight in kilograms divided by height in meters squared (kg/m^2). All BIA measurements were performed by one trained observer (except measurement for the cross-sectional study that had two medical officers) using the same equipment and recommended standard conditions with regard to body position, previous exercise, dietary intake, skin temperature, and voiding of the bladder were taken into consideration in taking BIA measurements (Kyle et al. 2004). All BIA measurements during the KCH study were performed on the day patients were confirmed to have TB disease.

The BIA is a simple, easy, safe, non-invasive technique, that has been recommended for nutritional studies in the clinical setting (Kyle et al. 2004; Kyle, Piccoli, and Pichard 2003) and is a convenient method to determine the lean or fat-free mass and fat body compartments (Kyle, Piccoli, and Pichard 2003; Kyle et al. 2004). Single-frequency BIA was performed at 50 kHz and 800 mA with standard tetrapolar lead placement (Jackson et al. 1988). Before performing measurements on each participant, the BIA instrument was calibrated using the manufacturer's recalibration device. The resistance and reactance were based on measures of a series circuit (Kotler et al. 1996). BIA measurements were performed in triplicate for each subject. Fat-free mass was calculated from BIA measurements using equations that were previously cross-validated in a sample of patients (white, black and Hispanic) with and without HIV infection (Kotler et al. 1996) and have been applied elsewhere in African studies (Villamor et al. 2006; Shah et al. 2001; Van Lettow et al. 2004). Fat mass was calculated as body weight minus fat-free mass.

Operational definition

We used BMI and height-normalized indices (adjusted for height^2) of body composition that partition BMI into fat-free mass index (FFMI) and fat mass index (FMI) (Schutz, Kyle, and Pichard 2002; VanItallie et al. 1990; Kyle, Piccoli, and Pichard 2003) to establish the body wasting status of participants. The FFMI and FMI have the advantages of compensating for differences in height and age (Kyle, Genton, and Pichard 2002). Also, the use of the FFMI and FMI eliminates some of the concerns about differences

between population groups. We defined body wasting as patients having the low fat-free mass index (FFMI) and the low body fat mass index (FMI) corresponding to WHO BMI categories for malnutrition as previously reported (Kyle, Piccoli, and Pichard 2003). The FFMI <16.7 (kg/m^2) for men and <14.6 (kg/m^2) for women and the FMI <1.8 (kg/m^2) for men and <3.9 (kg/m^2) for women corresponds to a BMI of <18.5 kg/m2, the WHO cutoff for malnutrition (World Health Organ Tech Rep 1995) among adults.

Statistical Analyses

Descriptive statistics

This involved distribution of all variables of interest by computing frequencies and proportions for categorical variables, means and medians for continuous variables. In measures analysis, plots of individual participants' and group mean trajectory response profiles were performed to assess how BMI, FFMI, and FMI evolved over time and how measurements made at different time points were related.

Bivariate associations

Chi-square and Fisher's exact tests were used to assess associations and differences in proportions between categorical variables. Fisher's exact test was used where tabular counts were less than five. Student's t-test and analysis of variance (ANOVA) were used to compare continuous variables across categories. Variance ratio testing was performed to determine whether to use equal or unequal variances for the Student's t-test and

Bartlett's test for equal variances was used to assess equality of variance assumption for ANOVA. Non-parametric test (Mann-Whitney test) was used where continuous variables were not normally distributed or when sample size distribution was small.

Stratified analysis

Stratified analysis was performed according to key confounding variables such as gender and HIV to assess for confounding and effect modification.

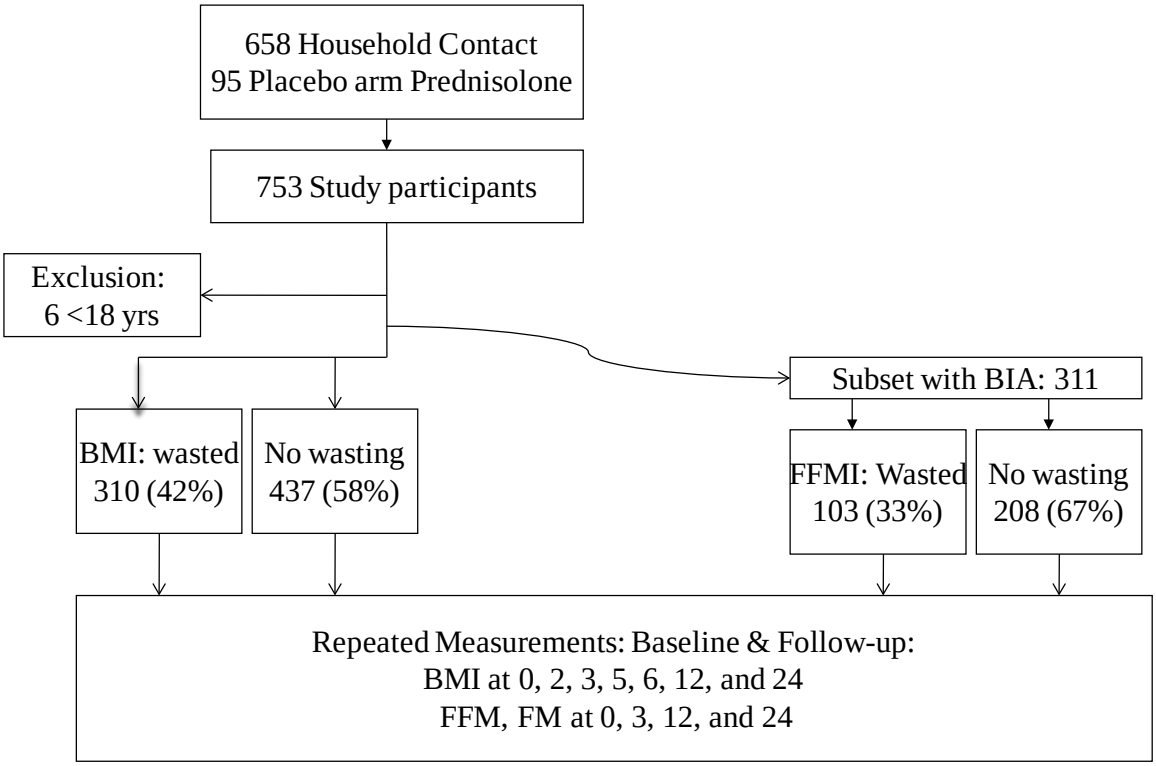
Univariate and multivariable analyses

Univariate analyses were performed to assess unadjusted associations between the outcome variables and the main predictor and the potential confounders.

Multivariable analyses were performed using multivariable modeling to estimate adjusted measures of associations while taking into account multiple confounding variables. Variables for inclusion in the multivariable models were selected based on biological plausibility and statistical significance in univariate analysis.

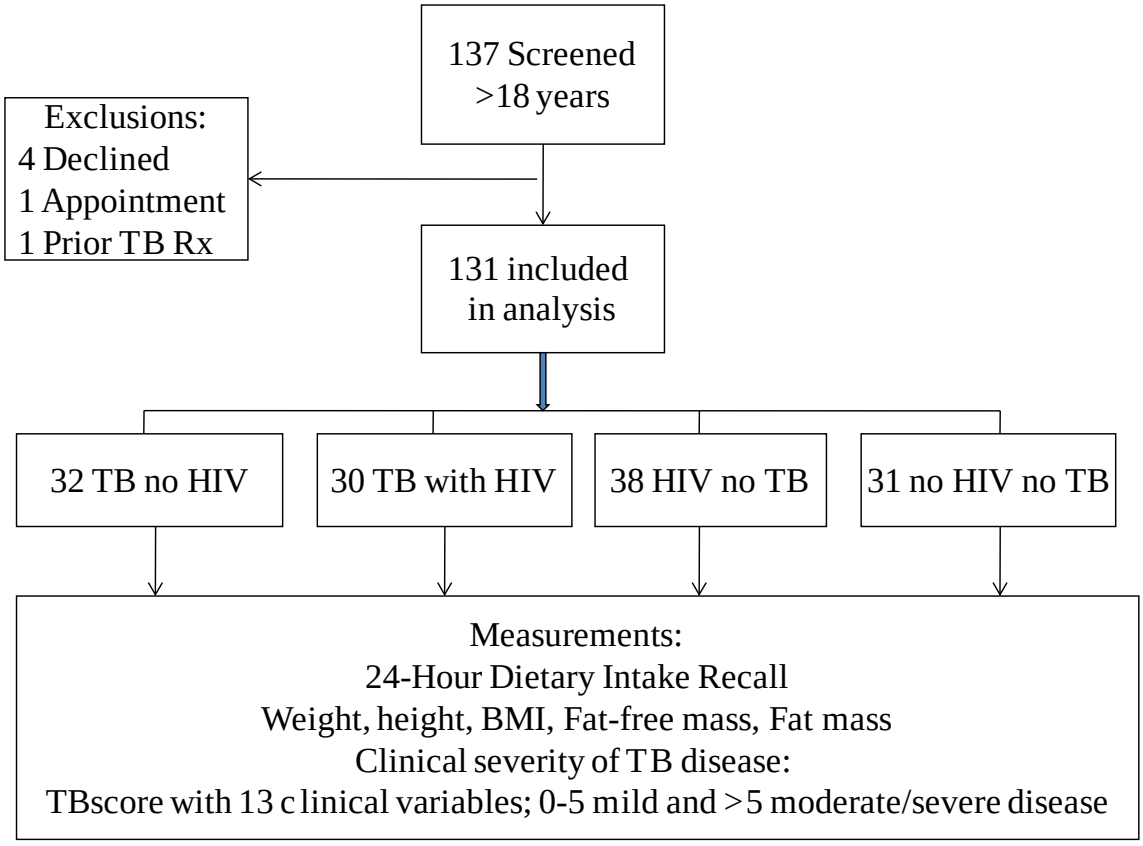
Further analyses were performed according to each specific aim.

Figure 3:1 Retrospective cohort study flow



Household contact includes 344 from the initial household contact study and 314 from the Kawempe Community Healthy study. BMI = body mass index, FFM = fat-free mass, FFMI = fat-free mass index, FM = fat mass, and FMI = fat mass index

Figure 3:2 Cross-sectional study flow diagram



TB = tuberculosis, BMI = body mass index.

CHAPTER 4

BODY COMPOSITION MEASURED WITH BIOELECTRICAL IMPEDANCE ANALYSIS AND ANTHROPOMETRY AMONG HIV POSITIVE AND HIV NEGATIVE ADULTS WITH OR WITHOUT TUBERCULOSIS IN KAMPALA, UGANDA

Abstract

Background Simple and inexpensive method for assessing body composition is lacking in sub-Saharan Africa, a region with high burden of tuberculosis and HIV dual epidemic to ensure early detection and timely management of population groups at risk of fat-free mass (FFM, lean tissue) wasting associated with poor outcome.

Objective We determined to establish whether existing equations that involve simple anthropometric measurements of waist circumference (WC), body mass index (BMI), or mid-upper arm circumference (MUAC) to provide comparable results to those of bioelectrical impedance analysis (BIA).

Method In a cross-sectional study of 131 participants who were screened for active tuberculosis and HIV infection, reactance, resistance, height, weight, MUAC, waist and hip circumferences, and four skinfold thickness (SF): triceps, biceps, subscapular, and suprailiac were measured. We compared fat mass and FFM as measured by BIA and as measured by equations that involved waist circumference, BMI, or MUAC using Bland-Altman plots.

Results On average, the equation that involved WC showed no bias in estimating comparable FFM to that of BIA among men with tuberculosis regardless of HIV status while in women, the equation showed no bias among individuals without tuberculosis regardless of HIV status. The equation showed no bias in estimation of fat mass in comparison to BIA among men and women without tuberculosis regardless of HIV status. The equation that involved four SF underestimated FFM and overestimated fat mass among men and among women regardless of tuberculosis and HIV status. There

was no bias among men and women with tuberculosis regardless of HIV status as regards the equation that involved BMI in estimation of FFM. Concerning fat mass determined by this equation, there was no bias among women without tuberculosis and there was no bias in estimating fat mass among men with tuberculosis regardless of HIV status. There was no bias in fat mass and FFM as determined by the equation that involved MUAC in comparison to BIA among men and women regardless of tuberculosis and HIV status.

Conclusion The existing equations with simple anthropometric measurements that provided comparable results to BIA differed by gender and tuberculosis disease status. During active tuberculosis, equations that involved MUAC and BMI providing comparable results of body composition to those of BIA among men and among women whereas in the absence of active tuberculosis among men, the equation with MUAC provided comparable results and among women, the equation with WC provided comparable results regardless of HIV status. Further studies are needed to validate the BIA and the equation with simple anthropometric measurements in assessing body composition in an African population.

Background

Body wasting and malnutrition are associated with tuberculosis, and co-infection with HIV and tuberculosis may be potentially exacerbate the wasting that occurs in tuberculosis or HIV infection alone (Macallan 1999; Lucas et al. 1994; Schwenk A and Macallan D.C 2000; van Lettow, Fawzi, and Semba 2003). In sub-Saharan Africa with the highest overlapping tuberculosis and HIV infection epidemic, by the time patients present for registration and treatment, a significant proportion have a profound degree of body wasting and malnutrition (Niyongabo et al. 1999; Kennedy et al. 1996; Zachariah et al. 2002). Moreover, progressive loss of body mass in TB and HIV-related wasting are strong risk factors for morbidity, mortality, and impaired physical function (Zachariah et al. 2002; Van Lettow et al. 2004; Tang et al. 2002; Harries et al. 1988). Body weight compartments of fat and fat-free mass differ in their contribution to body wasting and in their contribution to clinical benefit. For example, fat-free mass (the lean tissue) is more closely correlated with morbidity, mortality, quality of life, and physical functioning than fat mass and body weight itself (Wagner, Ferrando, and Rabkin 2000; Mostert et al. 2000; Heitmann et al. 2000).

Assessment of body composition in tuberculosis and HIV patients in sub-Saharan Africa, a region with 79% of the overlapping global HIV-tuberculosis disease burden, (Lawn and Churchyard 2009) is critical to ensure prevention, early detection, and timely management of body wasting. Further, assessment is crucial to understand the

pathophysiology and body compartments involved in body wasting. However, most of the available reference laboratory-based techniques (Norgan 2005), such as air-displacement plethysmography (ADP), underwater weighing and dual X-ray absorptiometry (DXA) that provide accurate data require a high level of technical expertise; they are time-consuming, unportable, and expensive for field settings in sub-Saharan Africa. Bioelectrical impedance analysis (BIA) is an easy, safe, non-invasive, and convenient method recommended to determine to fat and fat-free mass body compartments (Kyle, Piccoli, and Pichard 2003; Kyle, Bosaeus, De Lorenzo, Deurenberg, Elia, Gomez et al. 2004); however, its use in sub-Saharan Africa is still limited to research settings and validation studies are lacking. Skinfold thickness (SF) measurement is a simple and inexpensive recommended method (Norgan 2005); however, it requires multiple measurements and the most widely used Durnin and Womersley equation (Durnin and Womersley 1974) which was established in a Caucasian sample has been found to be unsuitable in African populations (Oosthuizen et al. 1997).

To fill the current gap in assessing body composition in routine clinical and epidemiological settings, and to validate population specific equations for use in sub-Saharan Africa, we present results showing simple existing equations that involve waist circumference, body-mass index (BMI), and mid-upper-arm circumference (MUAC) to provide comparable fat and fat-free mass body composition to that of BIA among HIV positive and HIV negative adults with/or without tuberculosis in urban Kampala, Uganda.

Methods

Subjects

In a cross-sectional study, 132 participants 18 years or older residing in Kampala district or 20 km from the study site if residence was outside Kampala in Uganda were enrolled. One participant was excluded from the analysis because of prior tuberculosis treatment. The study was conducted at the National tuberculosis and Leprosy Program (NTLP) Clinic of the national tertiary teaching hospital complex, Mulago between November 2007 and March 2008. Of the 131 participants who were included in the analysis, 31 were HIV positive with tuberculosis and 32 were HIV negative with tuberculosis and were recruited at the Mulago NTLP Clinic; 38 were HIV positive without tuberculosis and recruited at the Infectious Disease Institute Clinic (IDI) located 500 meters from the Mulago NTLP Clinic; and 30 HIV negative individuals without tuberculosis were enrolled from the community where TB patients resided. The institutional review boards at Case Western Reserve University and Joint Clinical Research Center approved the study, with final approval by the Uganda National Council for Science and Technology. All participants provided written informed consent to the study.

All subjects in the study were given appropriate pre- and post-test HIV counseling and AIDS education. HIV-1 infection was diagnosed on the basis of a positive enzyme-linked immunosorbent assay for HIV-1 antibodies (Recombigen; Cambridge Biotech, Cambridge, MA). At enrollment, basic demographic information and a medical history

were collected, and a standardized physical examination was conducted by a medical officer. Active pulmonary tuberculosis was confirmed by sputum smear microscopy and culture. Patients with active tuberculosis were treated with standard four-drug chemotherapy for tuberculosis per guidelines of the Ugandan Ministry of Health. Similarly, HIV positive patients who were eligible for antiretroviral therapy were started on treatment and cotrimoxazole prophylaxis at the IDI clinic.

Body composition assessment

From anthropometry

Anthropometric measurements included height, weight, MUAC, waist and hip circumferences, and four SF: triceps, biceps, subscapular, and suprailiac. BMI was computed using the relationship of weight in kilograms divided by height in meters squared (kg/m^2). Weight was taken using Hanson digital electronic scales to the nearest 100g. Standing height was measured to the nearest cm using a stadiometer. All circumferences were measured to the nearest 0.1 cm with a non-elastic metric measuring tape. The left MUAC was measured over the biceps at the mid-point between acromion and olecranon with the participant's arm relaxed. The waist circumference was measured on a horizontal plane at the narrowest part of the torso, i.e., the smallest horizontal circumference in the area between the ribs and iliac crest. For measurement of the hip circumference, the measurer squatted beside the participant to judge the level of maximum extension of the buttocks. The circumference was measured at this level on a horizontal plane. The SF measurements were taken on the left side of the body using a

Lange skinfold caliper model 12-1110 to nearest millimeter in each participant. All reported anthropometric measurement values were the mean of duplicates.

The measurements were made using standard procedures (Lohman T.G, Roche A.F, and Martorell R 1988; Frisancho A.R 1990) by two trained medical officers who took the standard history and physical examinations. Technical errors of measurements (TEM) were computed for each trained officer by measuring height, weight, MUAC, waist and hip circumferences, and four SF of a set of 6 individuals. The trained officer and the supervisor made measurements of each individual in succession (reading 1). Serial second measurements of MUAC were then obtained (reading 2). Intra-subject reliability was tested by performing using the duplicates. Intra-subject differences were calculated in absolute values. The TEM = $\sqrt{\sum(\text{reading 1} - \text{reading 2})\text{squared}/2 \text{ X number of duplicates}}$ and the percent reliability (TEM x 100/overall mean of the measurements) for all measurements of each trained medical officer were calculated. Based on six repetitions, the TEM and reliability coefficient were within acceptable limits (Lohman T.G, Roche A.F, and Martorell R 1988; Frisancho A.R 1990) (Appendix, Tables 12:1, 12:2, and 12:3).

The following existing equations validated among Caucasians by Lean et al. (Lean, Han, and Deurenberg 1996) were used to estimate percentage fat mass. The equations were developed from different combination of anthropometric measurements including waist circumference, BMI, and MUAC adjusted for sex and age. We selected these equations

because few simple measurements are needed to estimate fat mass compared to using SF. Furthermore, they were shown to have good prediction of body density with least bias, such as the one involving waist circumference in both men and women. Fat-free mass was computed by subtracting fat mass from weight in kilograms.

Percent fat mass = (0.567 x waist circumference) + (0.101 x age) – 31.8 for men

= (0.439 x waist circumference) + (0.221 x age) – 9.4 for women

= (1.33 x BMI) + (0.236 x age) – 20.2 for men

= (1.21 x BMI) + (0.262 x age) – 6.7 for women

= (1.52 x MUAC) + (0.336 x age) – 38.7 for men

= (1.38 x MUAC) + (0.243 x age) – 16.7 for women.

In addition, the widely used Durnin and Womersely equation (Durnin and Womersley 1974) that transforms the log sum of the four SF was used to show its lack of agreement with the BIA body composition.

Body density = 1.1765 – 0744 x log∑(triceps + biceps + subscapular + suprailiac) for men,

= 1.1567 – 0.0717 x log∑(triceps + biceps + subscapular + suprailiac) for women.

Body density is converted into percent body fat using Siri's equation (Siri W.E 1961).

Percent fat mass = [(4.95/body density) – 4.5] x 100.

From bioelectrical impedance analysis

The single-frequency bioelectrical impedance analyzer (BIA Detroit, MI, RJL Systems) performing at 50 kHz and 800 mA was used for BIA measures with detecting electrodes placed on the wrist and ankle and signal introduction electrodes placed on the first joint of the middle finger and behind the middle toe. Before performing measurements on each subject, the BIA instrument was calibrated using the manufacturer's recalibration device. The resistance and reactance were based on measures of a series circuit (Kotler et al. 1996). BIA measurements were performed in duplicate for each subject. The analyzer was calibrated monthly. Fat-free mass was calculated from BIA measurements using equations that were previously cross-validated in a sample of patients (white, black and Hispanic) with and without HIV infection (Kotler et al. 1996) and have been applied elsewhere in African studies (Shah et al. 2001; Van Lettow et al. 2004; Villamor et al. 2006). Fat mass was calculated as body weight minus fat-free mass.

Analysis

The characteristics of men and women were compared using Wilcoxon-Mann-Whitney test for continuously distributed variables due to lack of normality. Height-normalized indices (adjusted for height^2) of fat mass (FMI) and fat-free mass (FFMI) were computed (Schutz, Kyle, and Pichard 2002; VanItallie et al. 1990; Kyle, Piccoli, and Pichard 2003) and compared between women and men. The FFMI and FMI have the advantages of compensating for differences in height and age (Kyle, Genton, and Pichard 2002). Also,

the use of the FFMI and FMI eliminates some of the differences between population groups.

Fat mass and fat-free mass measured by BIA were compared with the corresponding anthropometric measures using Spearman correlation coefficients (r) and the method of Bland and Altman (Bland and Altman 1986), by plotting the bias (BIA measure – anthropometric measure) against the average of the measure by BIA and anthropometric. The average bias was calculated as the mean difference in the BIA and the anthropometric measures and limits of agreement as mean difference ± 1.96 x S.D. To evaluate whether bias was constant across all levels of the measure, the least-squares regression slope of the bias was estimated. A slope difference from zero indicated that the magnitude of bias depended on the level of the measure. Paired t-tests were used to detect significant differences in body composition obtained using BIA compared to anthropometric method. The main hypothesis tested was that there were no differences in measures of fat mass or fat-free mass by BIA compared to anthropometric method (i.e., zero mean bias) using a two-tailed α of 0.05. Stratified analysis was performed according to gender and HIV status. All analyses were performed using SAS software version 9.2 (SAS Institute, Cary, North Carolina).

Results

Overall men were taller, had more fat-free mass as measured by BIA and equation involving waist circumference, and more fat mass as estimated using equation that

involve a sum of four SF. However, men had lower BMI, SF, hip circumference, and fat mass as measured by BIA and equation involving waist circumference compared to women regardless of tuberculosis and HIV status (Tables 4:1 and 4:2). Men and women had similar waist circumference and MUAC regardless of tuberculosis and HIV status.

There were strong positive correlation coefficients between the measurements made using BIA and the measurements made using equations that involved waist circumference, BMI, or MUAC as presented in Tables 4:3 to 4:7. The high correlation coefficients indicate strong relationships between the measurements made using BIA and the measurements made using equations that involved waist circumference, BMI, or MUAC. However, a comparison of differences between the measurements made using BIA and the measurements made using equations that involve anthropometric measures for individual subjects shows that the high correlation coefficients disguise large inter-method bias and error. For example in table 4:3, whereas BIA and the equation involving sum of four SF correlated well ($r = 0.36$, $p<0.001$) for estimation of fat mass, the equation involving sum of four SF overestimated fat mass by a mean of 19.41 with an error of 6.76.

Fat-free mass determined by the equation using waist circumference showed no bias in the total study population (Table 4:3, Appendix Figure 12:1) and no bias among all men (-0.50 ± 3.53, $p=0.27$) and among all women (0.31 ± 3.94, $p=.52$; Table 4:4) compared to BIA. On average, the equation showed no bias among men with TB regardless of HIV

status while in women, the equation showed no bias among individuals without TB regardless of HIV status. However, fat-free mass was overestimated among HIV negative men with no tuberculosis (-2.42 ± 2.96, p=0.005) and underestimated among HIV positive women with TB (2.45 ± 2.71, p=0.001), but in both the bias did not depend on the level of fat-free mass. The slopes of bias were 0.29 and -0.05, respectively with p-value >0.05 for both (Table 4:4). The equation showed no bias in estimation of fat mass in comparison to BIA among men and women without TB regardless of HIV status although on average there was overestimation of fat mass in the overall population (Table 4:3, Appendix Figure 12:2), in all men and in all women (Table 4:4).

The Durnin and Womersely equation that involved sum of four SF underestimated fat-free mass in the total study population (17.86 ± 7.38, p<0.001) and it overestimates fat mass (-19.41 ± 6.76, p<0.001) compared to BIA (Table 4:3, Appendix Figure 12:3). The bias in fat-free mass and in fat mass measures were depended on the level of fat-free mass and fat mass; the slopes of bias were 0.50 and 0.78, respectively with p<0.001. In general, the Durnin and Womersely equation underestimated fat-free mass and overestimate fat mass among men and among women regardless of TB and HIV status (Table 4:5, Appendix 12:3 and 12:4).

The fat-free mass determined by the equation using BMI showed no bias in the overall population in comparison to BIA (Table 4:3, Appendix Figure 12:5). Specifically in stratified analysis, there was no bias among men and women with TB regardless of HIV

status (Table 5). Regarding fat mass determined by this equation, there was no bias among women without TB regardless of HIV status (Table 5, Appendix 12:6 fat mass for overall population). The slope (0.05, $p>0.05$) of the bias for fat mass among HIV positive men with TB was not significant suggesting that the bias in fat mass measure was not dependent on fat mass (Table 5). Thus, the equation had no bias in estimating fat mass in comparison to BIA among men with TB regardless of HIV status.

For the entire study population on average, the equation using MUAC overestimated fat-free mass in comparison to BIA (-1.40 ± 3.39, $p<0.001$), but the bias in the fat-free measure was not dependent on fat-free mass (Table 2, Appendix Figure 12:7). Similarly in stratified analysis regardless of gender and HIV status, the slopes of the bias for fat-free mass were not significant suggesting lack of dependence for the bias in fat-free mass measure on the fat-free mass (Table 6). One can therefore say that there was no bias in fat-free mass determined by the equation involving MUAC in comparison to BIA among men and women regardless of TB and HIV status. Following the same argument, among men regardless of TB and HIV status, the equation showed no bias in fat mass estimation compared to BIA (Table 6, Appendix Figure 12:8). The equation also showed minimal bias in estimating fat mass among women regardless of TB and HIV status.

Discussion

This is the first cross-sectional study in sub-Saharan Africa to show equations with simple anthropometric measurements that provide comparable results of body

composition among adults to that of BIA. In the present cross-sectional study of 131 participants, we tested existing equations (Lean, Han, and Deurenberg 1996) that use waist circumference, BMI, or MUAC to provide comparable results of body fat and fat-free mass with BIA in a population of HIV positive and HIV negative adults with/or without active TB. The equations that provided comparable results to BIA differed by gender and TB disease status. The equation that involved MUAC or BMI provided comparable results of fat-free mass to that of BIA whereas the equation that involved MUAC provided comparable results of fat mass among men and among women with TB regardless of HIV status. Among men without TB, the equation that involved MUAC provided comparable results of fat and fat-free mass to that of BIA whereas among women without TB, the equation that involved waist circumference provided comparable results of fat and fat-free mass regardless of HIV status. The equations involved a sum of four SF by Durnin and Womersely (Durnin and Womersley 1974), provide biased estimates of fat and fat-free mass that were not comparable to BIA regardless of gender and TB status.

The findings in this study appear to suggest that active TB, not HIV infection, may be the determining factor to consider in selecting equations that will provide comparable results of fat and fat-free mass to that of BIA. In the face of active TB, equations that involved MUAC and BMI were the equations that had no or minimal bias in providing comparable results of body composition to those of BIA among men and among women regardless of HIV status. In the absence of active TB among men, the equation that involved MUAC had no or minimal bias in providing comparable results of body composition to those of

BIA whereas among women, the equation that involved waist circumference had no or minimal bias in providing comparable results regardless of HIV status. To our knowledge, this is the first study in sub-Saharan Africa to provide evidence for selecting appropriate equations that involve simple anthropometric measurements for use in estimating fat and fat-free mass among men and women. Previous studies in Africa (Oosthuizen et al. 1997; Dioum et al. 2005), have evaluated the Durnin and Womersley (Durnin and Womersley 1974) equation that involve a sum of four SF with biased results of body composition similar to what has been revealed in the present study. The major strengths of our study stem from the heterogeneity of the study population that involved a full panel of HIV positive and HIV negative adults with/ or without active TB among men and women.

In the present study, equations that use simple anthropometric measurements to provide comparable results of body composition to those of BIA among men and women differed by TB disease status. The equations that involve MUAC or BMI provided comparable results of body composition to those of BIA among men and women with TB whereas the equation with MUAC and the equation with waist circumference provide comparable results among men and among women without TB, respectively regardless of HIV status. The possible explanation to this gender difference in the face of active TB appears to reflect the effect of TB on the nutritional status of patients with the disease. Further, it reflects the dominant nature of TB disease in inducing the wasting process at the time of diagnosis among patients with HIV associated TB. This finding been has reported previously (Paton and Ng 2006; Mupere et al. 2010), and it is reflected in the results of

the present study. For example in this study, in the presence of active TB both men and women had low comparable BMI and MUAC whereas in the absence of active TB, women had BMI and MUAC of higher magnitude compared to men. Moreover, MUAC has been found to reflect adult nutritional status as defined by BMI (Collins 1996; Powell-Tuck and Hennessy 2003), and MUAC is effective in the determination of malnutrition among adults in developing countries (Bisai and Bose 2009; James et al. 1994). Further, MUAC is a simpler measure than BMI, requiring a minimum of equipment and in practice has been found to predict morbidity and mortality as accurately as deficits in weights (Briend et al. 1989). The equation with waist circumference providing comparable results among women in the absence of active TB is in line with the known fact that women have a higher content of body fat compared to men (Blaak 2001). Moreover, waist circumference has been reported as sensitive indicator of total and central adiposity fat (Taylor et al. 1998; Flegal et al. 2009).

The interpretation of results in the present study is not without limitations. In this study, we used the BIA method in measurement of body composition, yet it is not of reference standard like the dual-energy x-ray absorptiometry. The BIA prediction method used has not yet been validated in the local population. As a result, findings of body composition may be biased because of variations in hydration across ethnic groups (Kyle, Bosaeus, De Lorenzo, Deurenberg, Elia, Manuel Gomez et al. 2004). However, the equations that were used in this study were previously cross validated in individuals of different race (white, black, and Hispanic) among men and women, who were both healthy controls and HIV-infected patients (Kotler et al. 1996). Moreover, the equations have been used

widely in other studies from Africa with meaningful findings (Shah et al. 2001; Van Lettow et al. 2004; Villamor et al. 2006; Mupere et al. 2010). Also care was taken in taking measurements at rest, with proper placement of leads, in participants who had not exercised or taken alcohol, in participants with voided bladder and ambient temperature. However, half of the measurements were in patients with underlying illness that may cause shifts in body water compartments, thereby affecting measurements of fat mass. Our findings are also limited by the cross-sectional nature of the study that as the body composition change while TB patients receive treatment, selection of appropriate of equations may change with time. We cannot evaluate such temporal changes in the present study.

Despite limitations of the present study, findings in this study revealed remarkable gender in the presence or absence of active TB but not HIV that may influence selection of appropriate equations with waist circumference, BMI, or MUAC to provide comparable results of body composition to that of BIA. Further studies are needed to validate the BIA and the equation with simple anthropometric measurements in assessing body composition in an African population.

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Table 4:1 Characteristics of study population with tuberculosis

Characteristics (SD)[1]	HIV positive with TB		HIV negative with TB	
	Men (n=10)	Women (n=21)	Men (n=18)	Women (n=14)
Age, years	30.9 (4.6)	29.2 (5.9)	26.0 (7.3)	26.0 (5.4)
Weigh, kg	54.3 (6.1)	46.9 (7.4)[b]	53.2 (6.5)	49.7 (7.6)
Height, cm	171.8 (9.3)	158.7 (6.8)[a]	171.1 (6.0)	157.7 (12.8)[a]
BMI, kg/m^2	18.4 (1.7)	18.6 (3.0)	18.2 (2.0)	20.3 (4.3)
MUAC, mm	23.0 (2.2)	23.4 (3.0)	23.7 (1.8)	24.5 (2.5)
Triceps ST, mm	6.4 (2.3)	13.2 (6.6)[b]	6.3 (2.0)	16.6 (5.6)[a]
Biceps ST, mm	3.8 (1.0)	6.6 (3.7)	3.6 (0.9)	6.8 (2.7)[a]
Subscapular ST, mm	8.3 (2.7)	11.7 (4.7)[b]	8.5 (1.9)	13.2 (5.9)[b]
Sacral ST, mm	5.6 (1.7)	9.2 (5.1)	5.4 (1.6)	9.8 (5.1)[a]
Waist circumference, cm	72.5 (4.7)	70.1 (6.3)	70.0 (3.7)	68.5 (5.2)
Hip circumference, cm	84.7 (5.1)	86.5 (7.7)	84.4 (4.7)	90.9 (8.1)[b]
BIA FFM, kg	48.7 (6.0)	36.0 (3.8)[a]	48.1 (5.5)	37.6 (6.2)[a]
BIA FFMI, kg/m^2	16.6 (1.3)	15.4 (0.9)[b]	16.6 (1.5)	16.1 (0.9)
WC FFM, kg	47.5 (4.5)	33.6 (4.0)[a]	47.6 (5.0)	36.6 (4.7)[a]
WC FFMI, kg/m^2	16.1 (1.4)	13.3 (1.6)[a]	16.2 (1.5)	15.1 (3.2)[b]
BMI FFM, kg	48.0 (4.9)	35.6 (4.1)[a]	47.7 (4.9)	37.3 (4.8)[a]
BMI FFMI, kg/m^2	16.3 (1.2)	14.1 (1.4)[a]	16.3 (1.3)	15.2 (2.1)[b]
MUAC FFM, kg	50.6 (4.2)	35.9 (3.9)[a]	49.9 (5.2)	38.0 (4.3)[a]
MUAC FFMI, kg/m^2	17.2 (1.5)	14.2 (1.6)[a]	17.0 (1.4)	15.6 (3.0)[b]
BIA Fat mass, kg	5.2 (1.8)	8.3 (5.2)[a]	4.8 (2.3)	10.5 (6.6)[b]
BIA FMI, kg/m^2	1.8 (0.6)	3.3 (2.1)[a]	1.6 (0.8)	4.6 (3.6)[a]
WC Fat mass, kg	6.8 (2.1)	13.2 (3.5)[a]	5.7 (1.8)	13.3 (3.3)[a]

WC FMI, kg/m^2	2.3 (0.6)	5.2 (1.5)[a]	1.9 (0.6)	5.4 (1.5)[a]
BMI Fat mass, kg	6.3 (1.6)	11.2 (3.7)[a]	5.5 (2.3)	12.7 (4.1)[a]
BMI FMI, kg/m^2	2.2 (0.6)	4.5 (1.6)[a]	1.9 (0.8)	5.3 (2.4) [a]
MUAC Fat mass, kg	3.7 (2.2)	10.9 (3.8)[a]	3.4 (2.3)	12.0 (3.7)[a]
MUAC FMI, kg/m^2	1.2 (0.7)	4.3 (1.5)[a]	1.2 (0.8)	4.9 (1.6)[a]
∑4 SF FFM, kg	23.3 (3.5)	21.2 (4.7)[b]	22.8 (3.6)	23.3 (4.9)
∑4 SF FFMI, kg/m^2	7.9 (1.0)	8.4 (1.9)	7.8 (1.1)	9.6 (2.5)[b]
∑4 SF Fat mass, kg	31.0 (2.7)	25.7 (2.7)	30.4 (3.0)	26.7 (3.0)[b]
∑4 SF FMI, kg/m^2	10.5 (0.8)	10.2 (1.1)	10.4 (1.0)	10.9 (2.0)

[a]p-value < 0.001, [b]p-value < 0.05; p-values were obtained with Mann-Whitney test and were comparisons between men and women. [1]Values are means ± standard deviation (SD). TB = Tuberculosis disease, WC = waist circumference, MUAC = mid-upper arm circumference, SF = Skinfold thickness, BMI, body mass index, FFM = Fat-free mass, FFMI = Fat-free mass index, and FMI = Fat mass index.

Table 4:2 Characteristics of study population without tuberculosis

Characteristics (SD)[1]	HIV positive no TB		HIV negative no TB	
	Men (n=17)	Women (n=21)	Men (n=16)	Women (n=14)
Age, years	34.7 (6.5)	29.7 (8.4)[b]	22.4 (3.2)	24.3 (5.4)
Weigh, kg	61.5 (6.3)	57.7 (9.4)	60.5 (6.2)	60.7 (8.7)
Height, cm	170.5 (8.2)	155.0 (5.6)[a]	167.4 (6.6)	159.7 (6.0)[b]
BMI, kg/m^2	21.2 (2.2)	24.2 (4.6)[b]	21.6 (2.3)	23.7 (2.8)[b]
MUAC, mm	27.7 (2.0)	28.5 (3.9)	27.9 (2.1)	29.0 (3.0)
Triceps ST, mm	9.8 (7.2)	20.1 (7.2)[a]	10.5 (4.4)	23.2 (5.7)[a]
Biceps ST, mm	4.5 (2.2)	9.9 (4.4)[a]	5.2 (2.1)	12.1 (3.9)[a]
Subscapular ST, mm	11.0 (3.8)	19.2 (7.1)[a]	12.9 (4.2)	17.8 (4.4)[a]
Sacral ST, mm	8.9 (4.2)	15.1 (6.9)[b]	9.9 (3.9)	16.0 (4.0)[a]
Waist circumference, cm	77.6 (3.5)	77.6 (8.8)	74.6 (5.4)	76.0 (6.1)
Hip circumference, cm	91.1 (5.6)	97.0 (9.9)[b]	90.9 (5.0)	99.3 (6.7)[b]
BIA FFM, kg	51.2 (6.8)	38.2 (3.8)[a]	49.9 (5.2)	41.3 (6.0)[a]
BIA FFMI, kg/m^2	18.3 (1.2)	16.6 (1.2)[a]	18.6 (1.4)	16.6 (1.1)[a]
WC FFM, kg	52.1 (4.6)	39.4 (5.2)[a]	52.3 (3.9)	42.7 (5.0)[a]
WC FFMI, kg/m^2	18.0 (1.6)	16.5 (2.5)	18.7 (1.5)	16.7 (1.6)[b]
BMI FFM, kg	51.8 (4.6)	39.7 (4.0)[a]	51.5 (3.8)	43.2 (4.7)[a]
BMI FFMI, kg/m^2	17.8 (1.4)	16.6 (1.9)[b]	18.5 (1.2)	16.9 (1.2)[b]
MUAC FFM, kg	52.5 (5.3)	40.1 (4.4)[a]	53.1 (3.7)	42.7 (4.6)[a]
MUAC FFMI, kg/m^2	18.1 (1.6)	16.7 (2.1)	19.0 (1.6)	16.7 (1.3)[a]
BIA Fat mass, kg	9.1 (3.2)	17.8 (8.2)[b]	7.9 (2.5)	18.2 (5.4)[a]
BIA FMI, kg/m^2	3.2 (1.2)	7.6 (3.7)[a]	2.9 (1.0)	7.1 (2.1)[a]
WC Fat mass, kg	10.0 (2.4)	18.3 (5.2)[a]	7.5 (2.2)	18.0 (4.1)[a]
WC FMI, kg/m^2	3.5 (0.8)	7.7 (2.4)[a]	2.7 (0.8)	7.0 (1.4)[a]

BMI Fat mass, kg	10.3 (2.7)	18.0 (6.3)[a]	8.2 (2.5)	17.5 (4.3)[a]
BMI FMI, kg/m^2	3.6 (1.0)	7.6 (2.9)[a]	3.0 (1.1)	6.8 (1.6) [a]
MUAC Fat mass, kg	9.6 (2.9)	17.6 (5.7)[a]	6.6 (2.6)	18.0 (4.6)[a]
MUAC FMI, kg/m^2	3.3 (1.1)	7.4 (2.7)[a]	2.4 (0.9)	7.0 (1.7)[a]
∑4 SF FFM, kg	28.2 (3.5)	28.3 (6.1)	27.0 (3.1)	30.4 (5.4)[b]
∑4 SF FFMI, kg/m^2	9.7 (1.3)	11.9 (2.9)[b]	9.7 (1.3)	11.9 (1.8)[a]
∑4 SF Fat mass, kg	33.9 (3.4)	29.4 (3.3)[a]	32.7 (2.6)	30.3 (3.4)
∑4 SF FMI, kg/m^2	11.7 (1.1)	12.3 (1.8)	11.7 (1.0)	11.9 (1.0)

[a]p-value < 0.001, [b]p-value < 0.05; p-values were obtained with Mann-Whitney test and were comparisons between men and women. [1]Values are means ± standard deviation (SD). TB = Tuberculosis disease, WC = waist circumference, MUAC = mid-upper arm circumference, SF = Skinfold thickness, BMI, body mass index, FFM = Fat-free mass, FFMI = Fat-free mass index, and FMI = Fat mass index.

Table 4:3 Comparison fat-free mass and fat mass as measured by BIA and by equations that involved anthropometry measurements for all participants (n=131)

Characteristic	Correlation	Slope, bias (se)	[d]Bias (SD)	95% limits of agreement	*p-value
Waist					
FFm, kg	0.90[a]	-0.04 (0.04)	-0.07 (3.77)	-7.52, 7.38	0.270
Fat mass, kg	0.83[a]	0.21 (0.04)[a]	-1.48 (3.31)	-7.97, 5.01	**0.002**
4 Skinfolds					
FFM, kg	0.43[a]	0.50 (0.10)[a]	17.86 (7.38)	3.40, 32.32	**<0.001**
Fat mass, kg	0.36[a]	0.78 (0.11)[a]	-19.41 (6.76)	-32.66, -6.16	**<0.001**
BMI					
FFM, kg	0.93[a]	0.06 (0.03)	-0.50 (2.87)	-6.13, 5.13	0.356
Fat mass, kg	0.91[a]	0.18 (0.03)[a]	-1.05 (2.32)	-5.60, 3.50	**<0.001**
MUAC					
FFM, kg	0.91[a]	-0.01 (0.04)	-1.40 (3.39)	-8.04, 5.24	**<0.001**
Fat mass, kg	0.87[a]	0.09 (0.04)[b]	-0.15 (2.98)	-5.99, 5.69	**0.002**

[a]p-value < 0.001, [b]p-value < 0.05. Correlations are spearman correlation coefficients. [d]Bias calculated as the mean difference in the BIA and anthropometric measures. 95% limits of agreement calculated as mean difference ± 1.96 x S.D. *P-value for difference obtained by paired t-test. SD = standard deviation, MUAC = mid-upper arm circumference, BMI = body mass index, and FFM = Fat-free mass.

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Table 4:4 Comparison fat-free mass and fat mass measured by BIA and by equation with waist circumference

Characteristic	Correlation	Slope, bias (se)	[d]Bias (SD)	95% limits of agreement	*p-value
All men					
FFM, kg	0.81[a]	0.17 (0.09)	-0.50 (3.53)	-7.42, 6.42	0.270
Fat mass, kg	0.82[a]	0.20 (0.06)[a]	-0.69 (1.66)	-3.94, 2.56	**0.002**
HIV+TB+ men					
FFM, kg	0.81[a]	0.31 (0.14)	1.26 (2.57)	-3.78, 6.30	0.156
Fat mass, kg	0.68[b]	-0.05 (0.22)	-1.60 (1.15)	-3.85, 0.65	**0.002**
HIV-TB+ men					
FFM, kg	0.88[a]	0.08 (0.11)	0.58 (2.35)	-4.03, 5.19	0.307
Fat mass, kg	0.81[a]	0.28 (0.16)	-0.93 (1.50)	-3.87, 2.01	**0.017**
HIV+TB- men					
FFM, kg	0.78[a]	0.43 (0.20)[b]	-0.88 (4.68)	-10.05, 8.29	0.448
Fat mass, kg	0.77[a]	0.34 (0.11)[a]	-0.97 (1.97)	-4.83, 2.89	0.059
HIV-TB- men					
FFM, kg	0.87[a]	0.29 (0.16)	-2.42 (2.96)	-8.22, 3.38	**0.005**
Fat mass, kg	0.87[a]	0.18 (0.10)	0.44 (1.23)	-1.97, 2.85	0.173
All women					
FFM, kg	0.75[a]	-0.13 (0.09)	0.31 (3.94)	-7.41, 8.03	0.518
Fat mass, kg	0.89[a]	0.54 (0.06)a	-2.17 (4.14)	-10.28, 5.94	**<0.001**
HIV+TB+ women					
FFM, kg	0.79[a]	-0.05 (0.17)	2.45 (2.71)	-2.86, 7.76	**0.001**
Fat mass, kg	0.81[a]	0.43 (0.11)[a]	-4.97 (2.62)	-10.11, 0.17	**<0.001**
HIV- TB+ women					

FFM, kg	0.54[b]	0.35 (0.31)	0.98 (5.41)	-9.61, 11.59	0.508
Fat mass, kg	0.66[b]	0.78 (0.20)[a]	-2.85 (4.91)	-12.47, 6.77	0.049
HIV+TB- Women					
FFM, kg	0.73[a]	-0.35 (0.15)[b]	-1.18 (3.20)	-7.45, 5.09	0.108
Fat mass, kg	0.95[a]	0.49 (0.09)[a]	-0.47 (3.84)	-8.00, 7.06	0.579
HIV- TB- women					
FFM, kg	0.71[b]	0.19 (0.18)	-1.36 (3.41)	-8.04, 5.32	0.159
Fat mass, kg	0.72[b]	0.37 (0.20)	0.19 (3.17)	-6.00, 6.38	0.826

[a]p-value < 0.001, [b]p-value < 0.05. Correlations are spearman correlation coefficients. [d]Bias calculated as the mean difference in the BIA and anthropometric measures. 95% limits of agreement calculated as mean difference ± 1.96 x S.D. *P-value for difference obtained by paired t-test. SD = standard deviation, TB- = no TB disease, TB = Tuberculosis disease, HIV- = HIV negative, HIV+ = HIV positive, FFM = Fat-free mass, and FM = Fat mass.

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Table 4:5 Comparison fat-free mass and fat mass measured by BIA and by equation with sum of 4 skinfolds

Characteristic	Correlation	Slope, bias (se)	[d]Bias (SD)	95% limits of agreement	*p-value
All men					
FFM, kg	0.69[a]	0.42 (0.11)[a]	24.03 (4.4)	15.5, 32.6	<**0.001**
Fat mass, kg	0.89[a]	-0.03 (0.10)	-25.23 (2.23)	-29.6, -20.9	<**0.001**
HIV+TB+ men					
FFM, kg	0.67[b]	0.57 (0.17)[a]	25.45 (3.39)	18.8, 32.1	<**0.001**
Fat mass, kg	0.70[b]	-0.42 (0.19)	-25.79 (1.48)	-28.7, -22.9	<**0.001**
HIV-TB+ men					
FFM, kg	0.85[a]	0.44 (0.12)[a]	25.32 (2.86)	19.7, 30.9	<**0.001**
Fat mass, kg	0.81[a]	-0.28 (0.15)	-25.67 (1.65)	-28.9, -22.4	<**0.001**
HIV+TB- men					
FFM, kg	0.52[b]	0.83 (0.27)[a]	22.97 (5.94)	11.3, 34.6	<**0.001**
Fat mass, kg	0.50[b]	-0.07 (0.28)	-24.83 (3.14)	-31.0, -18.7	<**0.001**
HIV-TB- men					
FFM, kg	0.64[b]	0.59 (0.24)[b]	22.82 (4.05)	14.9, 30.8	<**0.001**
Fat mass, kg	0.71[b]	-0.02 (0.23)	-24.81 (2.02)	-28.8, -20.9	<**0.001**
All women					
FFM, kg	0.68[a]	-0.27 (0.10)[a]	12.48 (4.79)	3.1, 21.9	<**0.001**
Fat mass, kg	0.86[a]	0.79 (0.06)[a]	-14.34 (5.08)	-24.3, -4.4	<**0.001**
HIV+TB+ women					
FFM, kg	0.76[a]	-0.25 (0.18)	14.88 (3.26)	8.5, 21.3	<**0.001**
Fat mass, kg	0.71[a]	0.70 (0.12)[a]	-17.40 (3.33)	-23.9, -10.9	<**0.001**
HIV-TB+ women					

FFM, kg	0.44	0.33 (0.36)	14.37 (6.08)	2.5, 26.3	<**0.001**
Fat mass, kg	0.59[b]	0.93 (0.26)[a]	-16.23 (5.61)	-27.2, -5.2	<**0.001**
HIV+TB- Women					
FFM, kg	0.52[b]	-0.56 (0.19)[a]	9.88 (4.53)	1.0, 18.8	<**0.001**
Fat mass, kg	0.92[a]	0.86 (0.09)[a]	-11.53 (5.20)	-21.7, -1.3	<**0.001**
HIV-TB- women					
FFM, kg	0.77[b]	0.12 (0.16)	10.91 (3.6)	4.7, 17.1	<**0.001**
Fat mass, kg	0.77[b]	0.48 (0.16)[a]	-12.08 (3.08)	-18.1, -6.0	<**0.001**

[a]p-value < 0.001, [b]p-value < 0.05. Correlations are spearman correlation coefficients. [d]Bias calculated as the mean difference in the BIA and anthropometric measures. 95% limits of agreement calculated as mean difference ± 1.96 x S.D. *P-value for difference obtained by paired t-test. SD = standard deviation, TB- = no TB disease, TB = Tuberculosis disease, HIV- = HIV negative, HIV+ = HIV positive, FFM = Fat-free mass, and FM = Fat mass.

Table 4:6 Comparison fat-free mass and fat mass measured by BIA and by equation with BMI

Characteristic	Correlation	Slope, bias (se)	[d]Bias (SD)	95% limits of agreement	*p-value
All men					
FFM, kg	0.87[a]	0.20 (0.07)[b]	-0.35 (2.90)	-6.03, 5.33	0.356
Fat mass, kg	0.86[a]	0.04 (0.05)	-0.85 (1.34)	-3.48, 1.78	**<0.001**
HIV+TB+ men					
FFM, kg	0.88[a]	0.20 (0.10)	0.77 (1.84)	-2.84, 4.38	0.218
Fat mass, kg	0.85[b]	0.05 (0.16)	-1.11 (0.08)	-2.67, 0.46	**0.002**
HIV-TB+ men					
FFM, kg	0.89[a]	0.11 (0.11)	0.42 (2.22)	-3.93, 4.77	0.429
Fat mass, kg	0.75[a]	0.00 (0.18)	-0.77 (1.68)	-4.06, 2.52	0.068
HIV+TB- men					
FFM, kg	0.85[a]	0.41 (0.15)[b]	-0.58 (3.89)	-8.20, 7.04	0.547
Fat mass, kg	0.92[a]	0.17 (0.07)[b]	-1.28 (1.27)	-3.77, 1.21	**0.001**
HIV-TB- men					
FFM, kg	0.82[a]	0.31 (0.13)[b]	-1.66 (2.53)	-6.62, 3.30	**0.019**
Fat mass, kg	0.81[a]	0.01 (0.10)	-0.33 (1.16)	-2.60, 1.94	0.279
All women					
FFM, kg	0.83[a]	0.01 (0.07)	-0.63 (2.85)	-6.22, 4.96	**0.067**
Fat mass, kg	0.96[a]	0.37 (0.03)[a]	-1.22 (2.92)	-6.94, 4.50	**0.001**
HIV+TB+ women					
FFM, kg	0.76[a]	-0.08 (0.15)	0.44 (2.49)	-4.44, 5.32	0.432
Fat mass, kg	0.90[a]	0.38 (0.09)[a]	-2.96 (2.37)	-7.61, 1.69	**<0.001**

HIV-TB+ women					
FFM, kg	0.68[b]	0.30 (0.19)	0.30 (3.73)	-7.01, 7.61	0.766
Fat mass, kg	0.96[b]	0.50 (0.09)[a]	-2.16 (3.15)	-8.33, 4.01	**0.023**
HIV+TB- Women					
FFM, kg	0.87[a]	-0.06 (0.11)	-1.51 (1.87)	-5.18, 2.16	**0.001**
Fat mass, kg	0.98[a]	0.28 (0.05)[a]	-0.14 (2.36)	-4.77, 4.49	0.789
HIV-TB- women					
FFM, kg	0.81[a]	0.26 (0.15)	-1.87 (2.96)	-7.67, 3.93	**0.035**
Fat mass, kg	0.78[b]	0.30 (0.15)	0.69 (2.55)	-4.31, 5.69	0.329

[a]p-value < 0.001, [b]p-value < 0.05. Correlations are spearman correlation coefficients. [d]Bias calculated as the mean difference in the BIA and anthropometric measures. 95% limits of agreement calculated as mean difference ± 1.96 x S.D. *P-value for difference obtained by paired t-test. SD = standard deviation, TB- = no TB disease, TB = Tuberculosis disease, HIV- = HIV negative, HIV+ = HIV positive, FFM = Fat-free mass, and FM = Fat mass.

Table 4:7 Comparison fat-free mass and fat mass measured by BIA and by equation with MUAC

Characteristic	Correlation	Slope, bias (se)	[d]Bias (SD)	95% limits of agreement	*p-value
All men					
FFM, kg	0.80[a]	0.21 (0.08)[b]	-2.03 (3.32)	-8.54, 4.48	**<0.001**
Fat mass, kg	0.82[a]	-0.08 (0.07)	0.83 (2.01)	-3.11, 4.77	**0.002**
HIV+TB+ men					
FFM, kg	0.70[b]	0.36 (0.16)	-1.83 (2.86)	-7.44, 3.78	0.073
Fat mass, kg	0.67[b]	-0.07 (0.27)	1.49 (1.37)	-1.20, 4.18	**0.007**
HIV-TB+ men					
FFM, kg	0.82[a]	0.04 (0.12)	-1.74 (2.59)	-6.82, 3.34	**0.011**
Fat mass, kg	0.65[b]	0.01 (0.22)	1.39 (2.06)	-2.65, 5.43	**0.011**
HIV+TB- men					
FFM, kg	0.79[a]	0.26 (0.16)	-1.30 (3.97)	-9.08, 6.48	0.195
Fat mass, kg	0.83[a]	0.12 (0.12)	-0.55 (1.85)	-4.18, 3.08	0.236
HIV-TB- men					
FFM, kg	0.64[b]	0.39 (0.20)	-3.25 (3.53)	-10.17, 3.67	**0.002**
Fat mass, kg	0.70[b]	0.11 (0.17)	1.26 (1.89)	-2.44, 4.96	**0.018**
All women					
FFM, kg	0.77[a]	0.05 (0.09)	-0.85 (3.37)	-7.46, 5.76	**0.038**
Fat mass, kg	0.91[a]	0.38 (0.05)[a]	-1.01 (3.41)	-7.69, 5.67	**0.016**
HIV+TB+ women					
FFM, kg	0.70[a]	-0.02 (0.18)	0.17 (2.74)	-5.20, 5.54	0.781
Fat mass, kg	0.72[a]	0.36 (0.12)[b]	-2.69 (2.69)	-7.96, 2.58	**<0.001**
HIV-TB+ women					

FFM, kg	0.52	0.45 (0.28)	-0.35 (5.04)	-10.23, 9.53	0.797
Fat mass, kg	0.82[b]	0.67 (0.18)[b]	-1.51 (4.50)	-10.33, 7.31	0.232
HIV+TB- Women					
FFM, kg	0.80[a]	-0.16 (0.13)	-1.87 (2.28)	-6.34, 2.60	**0.001**
Fat mass, kg	0.99[a]	0.38 (0.05)[a]	0.22 (2.89)	-5.44, 5.88	0.730
HIV-TB- women					
FFM, kg	0.77[b]	0.29 (0.17)	-1.35 (3.38)	-7.97, 5.27	0.159
Fat mass, kg	0.79[a]	0.22 (0.18)	0.18 (2.95)	-5.60, 5.96	0.824

[a]p-value < 0.001, [b]p-value < 0.05. Correlations are spearman correlation coefficients. [d]Bias calculated as the mean difference in the BIA and anthropometric measures. 95% limits of agreement calculated as mean difference ± 1.96 x S.D. *P-value for difference obtained by paired t-test. SD = standard deviation, TB- = no TB disease, TB+ = Tuberculosis disease, HIV- = HIV negative, HIV+ = HIV positive, FFM = Fat-free mass, and FM = Fat mass.

CHAPTER 5

INDICATORS OF DIETARY ADEQUACY AMONG HIV POSITIVE AND HIV NEGATIVE ADULTS WITH OR WITHOUT TUBERCULOSIS IN URBAN KAMPALA, UGANDA

Abstract

Objective To assess nutritional adequacy of dietary intake and validity of simple low-cost methods to evaluate nutritional adequacy of diets consumed among HIV positive and HIV negative adults with or without tuberculosis in urban Uganda

Methods In a cross-sectional study of 131 HIV positive and HIV negative adults with or without tuberculosis, 24-hour dietary intake recall was assessed. Two different dietary diversity indices were created: food variety score (FVS), a simple count of items, and diet diversity score (DDS), a count of food groups. Mean adequacy ratio (MAR) of intake to recommended intake (each truncated at one) of energy and ten nutrients, was calculated as an indicator of nutrient adequacy.

Results All participants (100%) consumed at least cereals, roots, and tubers, and 90% consumed vegetables not rich in vitamin A such tomatoes and onions while only 45% consumed vitamin-A-rich fruits and vegetables, and only 15% consumed eggs. The mean FVS and DDS for the study population were low 8.1 ± 2.8 and 4.7 ± 1.4, respectively. Both men and women regardless of tuberculosis and HIV status, had carbohydrate and ascorbic acid deficiency in the range of 0 to 30% whereas other nutrient intakes including energy, protein, dietary fiber, calcium, magnesium, zinc, iron, vitamin A, vitamin D, and folate had deficiencies ranging 25% to 100%. When a MAR of 65% was used as a cut-off point for nutrient adequacy, it was found that FVS must be 9 or more and DDS must at least 5. Among women, both FVS and DDS had a high ability to identify participants with an inadequate or adequate diet while among men FVS had a high ability to identify individuals with inadequate diet but low ability to identify those with adequate diet, DDS

had low ability to identify individuals with inadequate diet but had a high ability to identify those with adequate diet.

Conclusion The dietary consumption in this study population was monotonous, rich in carbohydrates and deficient in nutrients regardless of gender, tuberculosis, and HIV status. The ability of FVS and DDS indices to identify individuals with inadequate or adequate diet consumption differed by gender. The FVS was a better predictor of nutritional adequacy among women whereas DDS was among men. Validation in follow-up studies and in different regions is needed.

Background

Micronutrient malnutrition remains one of the largest nutritional problems worldwide, affecting people in both developed and developing countries (WHO 2002). Among individuals with tuberculosis and among individuals with HIV infection, a number of micronutrients deficiencies have been described (van Lettow, Fawzi, and Semba 2003). Moreover, micronutrient deficiencies not only impair host immune functions, but may also affect efficacy of tuberculosis drugs (Thurnham 2004), and impair weight gain which may be important to survival (Paton et al. 2004). The deficiencies may be largely due to a habitually low dietary consumption of micronutrients in relation to requirements or due to anorexia (Hopewell P.C. 1994), impaired absorption of nutrients or increased catabolism.

Dietary diversification is central and sustainable to food based intervention strategies for combating multiple micronutrient deficiencies and total energy intake in developing countries (Tontisirin, Nantel, and Bhattacharjee 2002). Among the foremost steps and important element in planning dietary diversification strategies is dietary assessment. However, validity studies for simple low-cost assessment methods to evaluate the nutritional adequacy of diets across different cultural settings, disease conditions, and age groups are still lacking in sub-Saharan Africa where there is a high burden of multiple micronutrient deficiencies and tuberculosis with HIV co-infection. The present cross-sectional study was conducted to fill this gap by assessing adequacy of dietary intake and

the relationship between food variety or dietary diversity scores and the nutritional adequacy of the diet among HIV positive and HIV negative adults with or without tuberculosis in urban Kampala, Uganda.

Methods

In a cross-sectional study, 132 participants with age 18 or more years residing in Kampala district or 20 km from the study site if residence was outside Kampala in Uganda were enrolled. Data collection was conducted between November 2007 and March 2008, a period that coincides with harvesting and light rains in November and December and dry season in January and February. One participant was excluded from the analysis because of prior tuberculosis treatment. The study was conducted at the National Tuberculosis and Leprosy Program (NTLP) Clinic of the national tertiary teaching hospital, Mulago complex. Of the 131 participants who were included in the analysis, 63 were tuberculosis patients who were recruited at the Mulago NTLP Clinic; 38 were HIV positive patients without TB and recruited at the Infectious Disease Institute Clinic (IDI) located 500 meters from the Mulago NTLP Clinic; and 30 were HIV negative individuals without tuberculosis from the community where enrolled tuberculosis patients resided. The institutional review boards at Case Western Reserve University and Joint Clinical Research Center approved the study, with final approval by the Uganda National Council for Science and Technology. All participants provided written informed consent to the study.

All subjects in the study were given appropriate pre- and post-test HIV counseling and AIDS education. HIV-1 infection was diagnosed on the basis of a positive enzyme-linked immunosorbent assay for HIV-1 antibodies (Recombigen; Cambridge Biotech, Cambridge, MA). At enrollment, basic demographic information and a medical history were collected, and a standardized physical examination was conducted by a medical officer. Active pulmonary TB was confirmed by sputum smear microscopy and culture. Patients with active TB were treated with standard four-drug chemotherapy for tuberculosis per guidelines of the Ugandan Ministry of Health. Similarly, HIV positive patients eligible for antiretroviral therapy were started on treatment and cotrimoxazole prophylaxis at the IDI clinic. Anthropometric measurements included height and weight. Body-mass index (BMI) was computed using the relationship of weight in kilograms divided by height in meters squared (kg/m^2). Weight was taken using Hanson digital electronic bathroom weighing scales to the nearest 100g. Height was measured to the nearest mm by calibrated standing height using a stadiometer. All anthropometric measurement values were the mean of duplicates.

The dietary intake assessment was made using a single 24-hour dietary recall with open ended questions. The reference period for the 24-hour recall was the day prior to the day of the interview. In all instances, the interview was held only with the interviewee, no one else was present except for children. The questionnaire was pre-tested by administering it to 8 individuals selected randomly from the neighboring community to the study site. The assessment was conducted by four trained study nursing staffs and continuously supervised by a nutritionist using local food photographs, portion-size images, and

volumetric vessels to increase the accuracy of the recall. The nutritive value of raw ingredients was computed using the East African food composition table database whose database was imported into the NutriSurvey software (http:www.nutrisurvey.de) to ease the computations. The database used was predominantly for local Ugandan diet. When the East African food composition table was found deficient in certain food items, the United States Department of Agriculture database and the African composition table were used.

We evaluated the dietary adequacy in this study population basing methods that have been described previously (Hatloy, Torheim, and Oshaug 1998). The dietary diversity score (DDS) was defined as the number of food groups consumed over a period of 24 hours. The diet was classified according to nine food groups as recommended by Food and Agricultural Organization (FAO) (Table 5:3). Other remaining food items such as tea, sugar, salt, sweets, spices, commercial energy drinks, and alcohol were not used in the DDS and food variety score (FVS) calculations. The FVS was defined as the number of food items consumed over a 24-hour period, from a possible total of 127 Items. The possible total (n=127) reflects all the difference types of food items eaten by this sample population in a 24-hour period.

To estimate the nutrient adequacy of the diet, we calculated the nutrient adequacy ratio (NAR %) for 10 micronutrients, energy, protein, fat, carbohydrate, and dietary fiber. The NAR for a given nutrient is the ratio of a participant's intake to the daily recommended

allowance for the participant's sex. The Food and Agriculture Organization/World Health Organization 2002 Human Vitamin and Mineral requirements (FAO/WHO 2002) were used for vitamin A, vitamin B_6, vitamin C, thiamin, riboflavin, folate, magnesium, calcium, iron, and zinc whereas energy, fat, protein, carbohydrate, and dietary fiber; the Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Subcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes Food and Nutrition Board (Dietary Reference Intake for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). A report of the Panel on Macronutrients, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 2005) was used (Table 5:4). The recommendation for adequate intake was used for vitamin D (Atkinson and Ward 2001). In the case of iron and zinc, the category for moderate bioavailability was used. The mean adequacy ratio (MAR %) was calculated as a measure of the adequacy of the overall diet, where MAR is the sum of each NAR (truncated at 100%) divided by the number of nutrients (excluding energy, fat, protein, carbohydrates, and dietary fiber) (Madden, Goodman, and Guthrie 1976; Hatloy, Torheim, and Oshaug 1998).

$$\text{MAR (Mean Adequacy Ratio)} = \frac{\sum \text{NAR (each truncated 100\%)}}{\text{Number of nutrients}}$$

NAR was truncated at 100% so that a nutrient with a high NAR could not compensate for a nutrient with a low NAR. For both NAR and MAR a value of 100% is the ideal since it means that the intake is the same as the requirement.

Analytic strategy

All study participants in the analysis were categorized into 4 mutually independent groups: HIV positive patients with and without tuberculosis disease, HIV negative patients with and without tuberculosis disease. Spearman's rank correlation tests were performed between NARs or MAR and FVS or DDS. Measures of central tendency and variability were compared between men and women across 4 mutually exclusive groups using using Wilcoxon-Mann-Whitney test for average age, weight, height, BMI, FVS, DDS, and MAR. A non-parametric test was used because of small size issues in subgroups and nearly all parameters were not normally distributed even after log transformations. We evaluated FVS and DDS for sensitivity and specificity with MAR as the 'gold standard' of nutritionally adequate intake. Sensitivity is the proportion of positives that are correctly identified by the test, while specificity is the proportion of negatives that are correctly identified by the test (Altman D.G 1997). Positive is defined as FVS or DDS below a given cut-off point. Different cut-off points were tested to find the levels of FVS and DDS that would give high sensitivity without losing too much specificity. Those with a nutritionally inadequate diet, defined as MAR below a certain cut-off point, and FVS or DDS below the cut-off point were defined as true positives. Those with a nutritionally adequate diet, or MAR greater than the cut-off point, and FVS

or DDS above the cut-off were defined as true negatives. We used linear regression to estimate MAR scores for different levels of FVS and DDS. All analyses were performed using SAS version 9.2 Cary software, (North Carolina SAS Institute Inc 2004) whereas the receiver operator curves plotted in Microsoft Excel 2007.

Results

Of the 131 participants analyzed, 31 were HIV positive with tuberculosis, 32 were HIV negative with tuberculosis, 38 were HIV positive without tuberculosis, and 30 were HIV negative without tuberculosis. Overall men and women in the study population had similar age except among HIV positive individuals without tuberculosis where men were significantly older than women. The average height was significantly higher among men compared to women regardless of tuberculosis and HIV status (Table 5:1 and 5:2).

A total of 127 different food items were eaten by all adults (n=131) in the study population, corresponding to a theoretical maximum of 127 FVS. The mean FVS was 8.1 ± 2.8 with a minimum score of 1.0 and maximum of 15.0. The mean DDS value for the total sample was 4.7 ± 1.4 with a minimum of 1.0 and maximum of 8.0. There were no significant differences in average FVS, DDS, and MAR between men and women regardless of tuberculosis and HIV status except for FVS among HIV negative individuals without tuberculosis; women had significantly lower average FVS compared to men (Table 5:1 and 5:2). Of note, women had lower magnitudes of FVS, DDS, and MAR compared to men regardless of tuberculosis and HIV status.

All participants in the study sample had consumed some kind of cereal, roots, or tubers, particularly local green plantain, maize meal, sweet potatoes, or rice (Table 5:3). Food items that were consumed by more than 80% of the sample were other vegetables not rich in vitamin A including tomatoes, onions, green pepper, and eggplant. Only 32% of all participants consumed vitamin A rich fruits and vegetables such as green vegetables, carrot, mangoes, and papaya (locally called pawpaws). The least consumed food groups included eggs (15%), dairy/dairy products (25%), and other fruits that are not rich in vitamin A (45%) (Table 5:3). More than 60% of the sample consumed at least legumes and nuts (62%); meat, poultry, and fish (67%); and fats and oils (65%).

The proportion of participants with a nutrient intake below the recommended daily allowance varied between nutrients (Table 5:4). There were no nutrients, for which participants had sufficient nutrient intake, i.e., for which the nutrient adequate ratio (NAR) was 100% for all the participants. Nutrients such as carbohydrate and vitamin C had median NAR above 100%; however, a substantial proportion of participants had intake below the recommended allowance. Nutrients for which nutrient intake for participants were 80% or more below the recommended daily allowance included vitamin D, calcium, iron, and percent protein of energy (Table 5:4).

There were no significant differences in 24-hour dietary nutrient intake deficiencies between men and women for most nutrients except total fat, iron, and folate among HIV

negative individuals without TB; women had a greater proportion of deficiencies compared to men (Tables 5:5 and 5:6). Women had a deficiency of 57% versus 13%, 100% versus 69%, and 71% versus 25% for total fat, iron, and folate, respectively compared to men.

All nutrient adequacy expressed as NAR for the different nutrients correlated positively with Food Variety Score (FVS) and Dietary Density Score (DDS) among both women and men except percent carbohydrate NAR. For example, the correlation between energy intake NAR and FVS was 0.69 and it was 0.56 with DDS among women (Table 5:7). All correlations were significant except percent protein of energy NAR with FVS and DDS regardless of gender, percent fat of energy NAR with FVS among women and men, percent carbohydrate of energy with FVS and DDS among women, calcium and vitamin D NARs with FVS among men. There was also strong positive correlation between FVS or DDS and the Mean Adequacy Ratio (MAR), the overall score for nutritional adequacy of the diet (Table 5:7).

The mean MAR value was 63 ± 23 among women and 71 ± 18 among men (Table 5:7). The ideal cut-off for nutrient adequacy should be 100. This would mean that all nutrients were consumed in adequate amounts. In the present study, none of the participants attained this level. Among women, 59% had MAR greater than or equal to 60; 47% of the women participants had MAR greater than or equal to 65; and 39% had MAR greater than or equal to 75. Whereas among men, 74% had MAR greater than or equal to 60;

59% of the men participants had MAR greater than or equal to 65; and 44% had MAR greater than or equal to 75.

We tested different cut-off points of FVS for sensitivity and specificity against different definitions of a nutritionally adequate diet ranging from MAR = 60 to MAR = 75 as shown in Figures 5:1 and 5:2 receiver operator curves. We performed this in order to find an optimal cut-off point for FVS that can identify the maximum inadequate diets as inadequate (high sensitivity), without losing too much ability to identify those with a nutritionally adequate diet (specificity). The figures show that among women and men the sensitivity and specificity were not much influenced by changing the cut-off points of MAR. We therefore used MAR = 65 as cut-off point for a nutritionally adequate diet. If we were to get a sensitivity of FVS higher than or equal to 75% among women, the cut-off for FVS must be 9 or higher, while to get a specificity of at least 25%, the cut-off for FVS needs to be 11 or lower. Whereas among men, the cut-off for FVS must be 9 or higher to get a sensitivity higher than or equal to 75%, while to get a specificity of at least 25%, the cut-off for FVS needs also to be 11 or lower. With a cut-off for FVS on 9 among women and on 9 among men, the sensitivity will be 76% for women and 76% for men and the specificity 70% for women and 67% for men, respectively. If the cut-off for FVS had been increased by one, the sensitivity would have been increased to 92% among women and compared to 80% among men, but the specificity would decrease to 45% among women and to 50% among men. On the other hand, if the cut-off had decreased by one, the sensitivity would have dropped to 73% among women and 48% among men, and the specificity would have increased to 88% among women and to 83% among men.

We undertook the same exercise to decide the cut-off point for DDS as shown in Figures 5:3 and 5:4. A cut-off point for DDS among women of 5 gave a sensitivity of 70% and a specificity of 85%. Whereas among men, a cut-off point of 5 gave a sensitivity of 64% and a specificity of 83%. If the cut-off point had been increased to 6 among women, the sensitivity would have been 95% and the specificity of 48% whereas among men the sensitivity would have been 96% and specificity 39%. Decreasing the cut-off point to 4 among women, the sensitivity would have decreased to 32% and the specificity increased to 97% whereas among men the sensitivity would have decreased to 16% and specificity increased to 100%. We therefore took a cut-off point for DDS to be 5 in the present study as the only one point that gives both sensitivity higher than 64% and specificity higher than 80% among both women and men.

Our data shows an increasing MAR with increasing DDS and FVS (Table 5:8). The FVS needs to be 7 to 9 to give a MAR above 65 whereas DDS needs to be at least 5 and above to give satisfactory MAR for women and men. The theoretical estimates of linear regression appear to confirm the data (Table 5:9). To achieve a MAR greater than or equal to 65 with a DDS of 5, one will need FVS of at least 9 among women and 5 among men. For a DDS of 7, the FVS would be 7 among women and as few as 3 among men.

The results from the regression model (Table 5:9, foot note) show that it is only FVS that contributes significantly to the fit of the model among women whereas DDS did fit among men even after adjusting for age, HIV status,

Discussion

The present cross-sectional study that analyzed 131 HIV positive and HIV negative adults with or without tuberculosis was conducted to assess nutritional adequacy of dietary intake and validity of simple low-cost methods to evaluate nutritional adequacy of diets consumed among adults in urban Uganda. The dietary consumption in this study population was of low variety and diversity regardless of gender; composed of mostly cereals, roots, tubers, and vegetables not rich in vitamin A. The dietary consumption was deficient in most nutrients except carbohydrates, vitamin C and B_6 that had more than 75% of the study population with 1 nutrient adequate ratio. The deficiency was not affected by gender, tuberculosis, and HIV status except for iron and folate that differed by gender among HIV negative individuals. The FVS and DDS increase were associated with positive increase for nearly all nutrient intake adequacy ratios. The ability of FVS and DDS indices to identify individuals with inadequate or adequate diet consumption differed by gender. Prediction of nutritional adequacy differed by gender. The simple counting of food items (FVS) was a better predictor of nutritional adequacy of the diet among women whereas counting food groups (DDS) was among men. Thus, FVS and DDS can provide a rapid and efficient means to health workers to quickly estimate nutritional adequacy of the diet and also to monitor consumption during management of tuberculosis and HIV.

Although the interpretation of findings in the present study may be limited by the cross-sectional nature of the design, specifically use of a single 24-hour dietary recall that the

nutrition intakes do not reflect health endpoints (Vucic et al. 2009) and overall dietary habits (Biro et al. 2002), we employed local utensils with known size and food photographs to enhance recall and estimation of amount for the intake. Further, the dietary recall overlapped with one of the weekend.

Findings in the present study suggest that dietary consumption in this study population was monotonous, rich in carbohydrates and deficient in nutrients. All participants (100%) consumed at least cereals, roots, and tubers, and 90% consumed vegetables not rich in vitamin A such tomatoes and onions while only 45% consumed vitamin-A-rich fruits and vegetables, and only 15% consumed eggs. The mean FVS and DDS for the study population were only 8.1 ± 2.8 and 4.7 ± 1.4, respectively. Both men and women regardless of tuberculosis and HIV status, had carbohydrate and ascorbic acid deficiency in the range of 0 to 30% whereas other nutrient intakes including energy, protein, dietary fiber, calcium, magnesium, zinc, iron, vitamin A, vitamin D, and folate had deficiencies ranging 25% to 100%. Of note, vitamin D had the worst deficiency range from 90% to 100%. This substantial deficiency in vitamin D may a risk to reactivation of tuberculosis (Sita-Lumbsden A et al. 2007). It is probably difficult to compare results in the present study with other countries on the basis of FVS and DDS because of the different ways in which these indicators have been defined and calculated in different countries (Hatloy, Torheim, and Oshaug 1998). Further, studies are still limited in populations from sub-Saharan Africa. Nevertheless, our findings corroborate with the cross-sectional study among the elderly that was conducted in South Africa (Oldewage-Theron and Kruger 2008). Findings in this study revealed low FVS and DDS, and a dietary consumption that

was rich in carbohydrate and nutrient. The strength of our study; however, was the presence of full panel of control groups that comprised of HIV positive and HIV negative adults with or without tuberculosis.

The monotonous diet in this study population reflects on the subsistence economy in Uganda. Although this study was conducted in urban setting, it appears people purchase mostly agricultural food stuffs similar to the staple food that is grown in their rural home steady. Further, due to lack of public health nutrition education in the general population, people do not know the vital importance of food variety and diversity. People who live at subsistence levels often have no choice but to consume monotonous diets that are poor in nutrients, resulting in poor diet quality (Cannon G 2001). Further, the possible poverty level in this population expose to the monotonous diet. Poor populations suffer most in achieving dietary diversity because of they consume a usual diet based on starchy staple foods containing little or no animal or diary products and few fruit and vegetables, resulting in multiple nutrient deficiencies (Ruel 2003).

Our results show that the FVS and DDS can identify fairly adults with an inadequate nutrient intake. With cut-off points for FVS at 9 and DDS at 5 among women, the indices have high ability to identify those with a nutritionally inadequate and adequate diet whereas among men the indices have lower ability to identify those with inadequate diet, but high ability to identify those with adequate diet. To our knowledge, this is the first study to show gender differences in the ability of FVS and DDS indices to identify

individuals or populations with adequate and inadequate diet. Although the value of FVS and DDS have been established in children (Hatloy, Torheim, and Oshaug 1998; Steyn et al. 2006; Ruel 2003), limited research has been done in other population groups and disease conditions to explore the consequences of low dietary variety on nutritional status and response during treatment, for example in tuberculosis. This study attempted to define dietary variety across a heterogeneous population with or without tuberculosis and HIV.

For nutrition promotion and prevention of malnutrition in the population of HIV positive and HIV negative with or without tuberculosis, a high sensitivity is desirable to identify accurately most subjects at nutritional risk (Habicht, Meyers, and Brownie 1982), as long as false positives do not cause other risks. False positives do not pose any risk in the case of the present because of the high prevalence of nutrient deficiencies. In assessment of how select optimal cut-off points for FVS and DDS for an adequate diet, the choice of cut-off point for MAR did not have a strong influence. In our analysis, changing the cut-off point for MAR from 60 to 75 did not have any vital importance for the conclusions. We used the liberal 65% as the cut-off point for MAR as used in prior studies (Oldewage-Theron and Kruger 2008; Steyn et al. 2006). This is supported by the results of Tables 6 and 7, where it is shown that to reach a MAR of 65, one needs FVS and DDS of at least 9 and 5 or higher, respectively.

The gender differences in the ability of FVS and DDS indices to identify individuals or populations with adequate and inadequate diet could be explained by the cultural factors that may compromise intake among women. For example, unequal distribution of food within households (Carloni 1981; de Hartog A.P 1972), or men may have the opportunity to eat a wider variety or better quality foods outside the home, such as cafes or local restaurants (Holmboe-Ottesen G and Wandel M 1991). The unequal distribution of food within households result from several factors such as women may be trained to show restraint in eating, to give the best foods to men, or to allow others in the family to eat first (Lado 1992; O'Laughlin B 1974; Rosenberg E.M 1980; Dey J 1981).

The present study revealed that diet consumption among HIV positive and HIV negative adults with or without tuberculosis was monotonous, rich in carbohydrates and deficient in nutrients. The ability of FVS and DDS indices to identify individuals with inadequate or adequate diet consumption differs by gender. The simple counting of food items (FVS) was a better predictor of nutritional adequacy of the diet among women whereas counting food groups (DDS) was among men. Thus, FVS and DDS can provide a rapid and efficient means to health workers to quickly estimate nutritional adequacy of the diet, to monitor dietary intake in management of tuberculosis and HIV, and to assess patient's nutritional knowledge and thereafter provide health education. Validation studies are; however, needed in follow-up studies and other regions of the country.

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Table 5:1 Characteristics of adult participants with tuberculosis in Kampala, Uganda

Characteristic [mean, (SD)]	HIV positive with TB (n=31)		HIV negative with TB (n=32)	
	Women (n=21)	Men (n=10)	Women (n=14)	Men (18)
Age in yrs	29.2 (5.9)	30.9 (4.6)	26.0 (5.4)	26.0 (7.3)
Weight in kg	46.8 (7.3)	54.3 (6.1)[b]	50.0 (7.8)	53.2 (6.5)
Height in cm	158.9 (6.7)	171.8 (9.3)[a]	157.4 (13.2)	171.1 (6.0)[a]
BMI in kg/m^2	18.6 (2.9)	18.4 (1.7)	20.5 (4.4)	18.2 (2.0)
FVS	7.1 (2.8)	6.4 (1.7)	8.7 (2.8)	8.7 (2.7)
DDS	4.5 (1.7)	4.7 (1.5)	5.4 (1.6)	4.7 (1.1)
MAR	61.4 (24.3)	68.0 (17.6)	68.7 (17.3)	70.6 (17.4)

[a]p-value <0.004, [b]p-value <0.05. FVS = Food Variety Score: the number of all food items used in the study period (1 – 127). DDS = Dietary Diversity Score: number of food groups eaten (1 – 8): cereals, roots, and tubers; vitamin A-rich fruits and vegetables; other fruits not rich in vitamin A; other vegetables not rich in vitamin A; legumes and nuts; meat, poultry, and fish; fats and oils; diary and products; and eggs. MAR = Mean Adequacy Ratio: ratio of 11 micronutrients: vitamin A, vitamin B_6, vitamin C, vitamin D, thiamin, riboflavin, folate, magnesium, calcium, iron, and zinc.

Table 5:2 Characteristics of adult participants without tuberculosis in Kampala, Uganda

Characteristic [mean, (SD)]	HIV positive with no TB (n=38)		HIV negative with no TB (n=30)	
	Women (n=21)	Men (17)	Women (n=14)	Men (16)
Age in yrs	29.7 (8.4)	34.7 (6.5)[b]	24.3 (5.4)	22.4 (3.2)
Weight in kg	57.7 (9.4)	62.1 (6.6)	60.7 (8.7)	59.8 (5.6)
Height in cm	155.0 (5.6)	170.5 (7.9)[a]	159.7 (6.0)	167.2 (6.8)[b]
BMI in kg/m^2	24.2 (4.6)	21.4 (2.3)[b]	23.7 (2.8)	21.4 (2.3)[b]
FVS	8.2 (3.4)	8.5 (2.4)	7.6 (2.5)	9.6 (2.6)
DDS	4.3 (1.4)	4.8 (1.0)	4.5 (1.5)	5.1 (1.1)[b]
MAR	60.2 (27.3)	68.5 (17.1)	62.6 (19.5)	74.3 (20.0)

[a]p-value <0.004, [b]p-value <0.05. FVS = Food Variety Score: the number of all food items used in the study period (1 – 127). DDS = Dietary Diversity Score: number of food groups eaten (1 – 8): cereals, roots, and tubers; vitamin A-rich fruits and vegetables; other fruits not rich in vitamin A; other vegetables not rich in vitamin A; legumes and nuts; meat, poultry, and fish; fats and oils; diary and products; and eggs. MAR = Mean Adequacy Ratio: ratio of 11 micronutrients: vitamin A, vitamin B_6, vitamin C, vitamin D, thiamin, riboflavin, folate, magnesium, calcium, iron, and zinc.

Table 5:3 Food groups and food items from 24-hour dietary intake recall among HIV positive and HIV negative adults in Kampala, Uganda (n=131)

Food groups	Frequency (%)	%	Food item
Cereals, roots, and tubers	100.0	31.7	Green plantain (Musa acuminata)
		10.3	Maize meal (Zea mays)
		9.9	Sweet potatoes (Ipomoea batatas)
		9.0	Rice (Oryza sativa)
Vitamin-A-rich fruits and vegetables	31.6	34.2	Green vegetables (Amaranthus)
		23.7	Carrot (Daucus carota)
		26.3	Mango fruit (Mangifera)
		13.2	Pawpaw (Papaya, Carica)
Other fruits not rich in vitamin A	44.5	41.7	Passion fruit (Passiflora edulis)
		25.0	Ripe banana (Musa sapientum)
		9.7	Avocado (Persea Americana)
		9.7	Pineaple (Ananas comosus)
Other vegetables not rich in vitamin A	89.8	43.9	Tomato (Solanum lycopersicum)
		24.4	Onion (Allium cepa)

		14.6	Green pepper (Capsicum annum)
		2.4	Eggplant (solanum melongena)
Legumes and nuts	62.1	45.4	Groundnuts (Arachis hypogaes)
		44.4	Beans (Vigna Angularis)
		5.6	Soyabeans (Glycine max)
		4.6	Cowpeas (Vigna unguiculata)
Meat, poultry, and fish	67.1	53.3	Beef
		35.8	Fish
		7.5	Chicken
Fats and oils	64.9	53.9	Ghee
		23.1	Cooking oil
		23.1	Margarine (Blue-band)
Dairy	24.5	76.9	Milk with tea
		23.1	Whole milk
Eggs	15.1	84.2	Boiled eggs

These food groups were the basis of Dietary Diversity Score. In Food Variety Score all food items were included.

Table 5:4 The 24-hour dietary intake recall, recommended daily allowance, frequency of inadequate intake of nutrients among HIV positive and HIV negative adults in Kampala, Uganda (n=131)

Nutrient	24-Hour Intake			RDA		Median (NAR)	Deficit intake (%)
	Median	Q25	Q75	Women	Men		
Energy, kcal	1732	1093	2345	2700	2000	75.5	73
Protein, g	40.5	29.0	62.1	56	46	83.8	60
Total fat, g	36.8	22.2	59.0	30	30	122.7	39
Carbohydrate, g	287	188	414	130	130	144.2	9
Dietary fiber, g	30.8	18.2	49.7	38	25	97.2	53
Protein, % energy	10.0	8.0	12.0	12.5	12.5	80.0	80
Fat, % energy	19.0	14.0	26.0	22.5	22.5	84.4	39
CHO, % energy	70.0	62.0	75.0	60	60	116.7	9
Calcium, mg	196	101	499	1000	1000	19.6	95
Magnesium, mg	177	104	315	260	220	68.9	64
Zinc, mg	5.2	3.1	7.6	7.0	4.9	92.9	56
Iron, mg	7.9	4.9	13.0	14	29	38.6	86

Vitamin A, μg	208	70	551	600	500	35.7	74
Thiamin, mg	0.8	0.5	1.2	1.2	1.1	66.7	70
Riboflavin, mg	0.9	0.5	1.3	1.3	1.1	72.7	66
Vitamin B_6	2.2	1.3	3.1	1.3	1.3	169.2	22
Vitamin C, mg	91	49	178	45	45	202.8	22
Vitamin D, μg	0	0	1.0	5	5	0	98
Folate, μg	341	172	473	400	400	85.3	63

RDA = Recommended Daily Allowance, CHO = carbohydrate. NAR (Nutrient Adequacy Ratio) = actual intake/recommended intake. FAO = Food and Agriculture Organization, WHO = World Health Organization 2002. All NAR for micronutrients estimated using FAO/WHO requirements 2002 except vitamin D which was based on adequate intake (Atkinson and Ward 2001). DRFI = Dietary Reference Intake. NAR for energy, protein, carbohydrates, fat, and dietary fiber were estimated using DRFI.

Table 5:5 Percent of inadequate 24-hour dietary recall intake among HIV positive and HIV negative adults with tuberculosis in Kampala, Uganda

Characteristic	HIV+ with TB (n=31)		HIV- with TB (n=32)	
	Men (n=10)	Women (n=21)	Men (n=18)	Women (n=14)
Energy (kcal) n (%)	8 (80)	16 (76)	12 (67)	10 (71)
Protein (g) n (%)	6 (60)	14 (67)	10 (56)	10 (71)
Total fat (g) n (%)	3 (30)	14 (67)	5 (28)	6 (43)
Carbohydrate (g) n (%)	1 (10)	6 (29)	0 (0)	1 (7)
Dietary fiber (g) n (%)	6 (60)	11 (52)	9 (50)	6 (43)
Protein, % energy n (%)	8 (80)	13 (62)	16 (89)	10 (71)
Fat, % energy n (%)	4 (40)	16 (76)	10 (56)	9 (64)
Carbohydrate, % energy n (%)	4 (40)	4 (19)	5 (28)	3 (21)
Calcium (mg) n (%)	8 (80)	20 (95)	17 (94)	14 (100)
Magnesium (mg) n (%)	9 (90)	13 (62)	8 (44)	10 (71)
Zinc (mg) n (%)	6 (60)	11 (52)	10 (56)	9 (64)
Iron (mg) n (%)	8 (80)	19 (90)	14 (78)	14 (100)

Vitamin A (RE) n (%)	7 (70)	15 (71)	14 (82)	6 (43)
Vitamin D (μg) n (%)	9 (90)	20 (95)	18 (100)	14 (100)
Ascorbic acid (mg) n (%)	2 (20)	6 (30)	5 (28)	2 (14)
Folate (μg) n (%)	8 (80)	15 (71)	13 (72)	7 (50)

[a]p-value <0.001, [b]p-value <0.05. HIV+ = HIV positive, HIV- = HIV negative, TB = tuberculosis.

Table 5:6 Percent of inadequate 24-hour dietary recall intake among HIV positive and HIV negative adults without tuberculosis in Kampala, Uganda

Characteristic	HIV+ with no TB (n=38)		HIV- with no TB (n=30)	
	Men (n=17)	Women (21)	Men (n=16)	Women (n=14)
Energy (kcal) n (%)	15 (88)	14 (67)	11 (69)	10 (71)
Protein (g) n (%)	8 (47)	14 (67)	6 (38)	10 (71)
Total fat (g) n (%)	5 (29)	8 (38)	2 (13)	8 (57)[b]
Carbohydrate (g) n (%)	0 (0)	4 (19)	0 (0)	0 (0)
Dietary fiber (g) n (%)	8 (47)	13 (62)	7 (44)	9 (64)
Protein (% of energy) n (%)	13 (76)	17 (81)	15 (94)	13 (93)
Fat (% of energy) n (%)	10 (59)	14 (67)	9 (56)	8 (57)
Carbohydrate (% of energy) n (%)	3 (18)	2 (10)	0 (0)	4 (29)[b]
Calcium (mg) n (%)	16 (94)	20 (95)	16 (100)	13 (93)
Magnesium (mg) n (%)	13 (76)	14 (67)	8 (50)	9 (64)
Zinc (mg) n (%)	10 (59)	11 (52)	7 (44)	10 (71)

Iron (mg) n (%)	14 (82)	19 (90)	11 (69)	14 (100)[b]
Vitamin A (RE) n (%)	15 (88)	12 (60)	14 (88)	12 (86)
Vitamin D (μg) n (%)	17 (100)	21 (100)	14 (100)	16 (100)
Ascorbic acid (mg) n (%)	4 (23)	3 (15)	3 (19)	2 (14)
Folate (μg) n (%)	11 (65)	14 (67)	4 (25)	10 (71)[b]

[a]p-value <0.001, [b]p-value <0.05. HIV+ = HIV positive, HIV- = HIV negative, TB = tuberculosis.

Table 5:7 Spearman's correlations between Nutrient Adequacy Ratio (NAR) of nutrients and Food Variety Score or Dietary Diversity Score among HIV positive and HIV negative adults with or without tuberculosis in Kampala, Uganda (n=131)

NAR Nutrient	Women (n=70)		Men (n=61)	
	Food Variety Score[1]	Dietary Diversity Score[2]	Food Variety Score[1]	Dietary Diversity Score[2]
NAR Energy (kcal)	0.69	0.56	0.53	0.54
NAR Protein (g)	0.66	0.53	0.50	0.54
NAR Total fat (g)	0.59	0.53	0.54	0.57
NAR Carbohydrate (g)	0.59	0.49	0.46	0.38[b]
NAR Dietary fiber (g)	0.50	0.52	0.26[b]	0.37[b]
NAR Protein (% of energy)	0.18*	0.18*	0.11*	0.10*
NAR Fat (% of energy)	0.18*	0.21[b]	0.23*	0.26[b]
NAR Carbohydrate (% of energy)	-0.22*	-0.20*	-0.28[b]	-0.29[b]
NAR Calcium (mg)	0.70	0.69	0.22*	0.39
NAR Magnesium (mg)	0.63	0.51	0.43	0.31[b]

NAR Zinc (mg)	0.59	0.44	0.39[b]	0.34[b]
NAR Iron (mg)	0.59	0.49	0.29[b]	0.38[b]
NAR Vitamin A (RE)	0.50	0.59	0.30[b]	0.61
NAR Thiamin (mg)	0.59	0.51	0.27[b]	0.39[b]
NAR Riboflavin (mg)	0.61	0.55	0.35[b]	0.60
NAR Vitamin B_6	0.48	0.46	0.40[b]	0.49
NAR Ascorbic acid (mg)	0.38[b]	0.42	0.36[b]	0.45
NAR Vitamin D (μg)	0.29[b]	0.44	0.08*	0.35[b]
NAR Folate (μg)	0.43	0.43	0.62	0.52
Mean Adequacy Ratio (MAR)	0.70	0.64	0.45	0.60

All correlation p-values <0.001 except [b]p-value < 0.05, *p-value >0.05. [1]Number of all food items used in the study period. [2]Number of all food groups consumed (1 – 9): 1) Cereal, roots, and tubers, 2) vitamin-A-rich fruits and vegetables, 3) 0ther fruits not rich in vitamin A, 4) other vegetables not rich in vitamin A, 5) legumes and nuts, 6) meat, poultry, and fish, 7) fats and oils, 8) diary, and 9) eggs and eggs products.

Table 5:8 Mean MAR scores for different levels of Food Variety Score (FVS) and Dietary Diversity Score (DDS) among HIV positive and HIV negative adults in Kampala, Uganda (n=131)

Dietary Diversity Score	**Food Variety Score**				
	1-3	4-6	7-9	10-12	13-15
Women (n=70)					
1	24 (2)	-	-	-	-
2	26 (n=2)	46 (n=5)	-	-	-
3	-	59 (n=4)	-	-	-
4	-	39 (n=8)	**65 (n=9)**	63 (n=1)	-
5	-	44 (n=3)	**65 (n=12)**	**71 (n=5)**	**97 (n=1)**
6	-	-	**73 (n=4)**	**87 (n=4)**	**90 (n=2)**
7	-	-	**77 (n=3)**	**93 (n=2)**	**79 (n=1)**
8	-	-	-	**85 (n=1)**	**90 (n=1)**
9	-	-	-	-	-
Men (n=61)					
1	37 (n=2)	-	-	-	-

2	-	57 (n=1)	-	-	-
3	-	65 (n=1)	-	-	-
4	-	58 (n=7)	58 (n=9)	**68 (n=2)**	-
5	-	**73 (n=4)**	**73 (n=7)**	**75 (n=12)**	**90 (n=1)**
6	-	-	**73 (n=5)**	**89 (n=7)**	-
7	-	-	**91 (n=1)**	**80 (n=1)**	-
8	-	-	-	**92 (n=1)**	-
9	-	-	-	-	-

Table 5:9 Estimated Mean Adequacy Ratio scores for different levels of Food Variety Score (FVS) and Dietary Diversity Score (DDS) from Linear Regression Model among HIV positive and HIV negative adults in Kampala, Uganda (n=131)

Dietary Diversity Score (DDS)	**Food Variety Score**								
	3	5	6	7	8	9	10	12	15
Women (n=70)									
1	32	40	44	49	53	57	61	**70**	**82**
2	35	43	47	51	56	60	64	**73**	**85**
3	38	46	50	54	59	63	**67**	**75**	**88**
4	41	49	53	57	62	**66**	**70**	**78**	**91**
5	43	52	56	60	64	**69**	**73**	**81**	**94**
6	46	55	59	63	**67**	**72**	**76**	**84**	**98**
7	49	58	62	**66**	**70**	**74**	**79**	**87**	**100**
8	52	61	**65**	**69**	**73**	**77**	**82**	**90**	**103**
9	55	63	**68**	**72**	**76**	**80**	**84**	**93**	**105**
Men (n=61)									

1	33	36	37	39	40	41	43	46	50
2	41	43	45	46	48	49	51	54	58
3	48	51	53	54	56	57	58	61	**66**
4	56	59	60	62	63	**65**	**66**	**69**	**74**
5	64	**67**	**68**	**70**	**71**	**73**	**74**	**77**	**81**
6	**72**	**75**	**76**	**77**	**79**	**80**	**82**	**85**	**89**
7	**82**	**82**	**84**	**85**	**87**	**88**	**90**	**93**	**97**
8	**87**	**90**	**92**	**93**	**94**	**96**	**97**	**100**	**105**
9	**95**	**98**	**99**	**101**	**102**	**104**	**105**	**108**	**112**

Regression model for women: MAR = 16.349 + 2.906*DDS + 4.196*FVS.

For men: MAR = 20.593 + 7.785*DDS + 1.453*FVS

Linear Regression Model to Estimate MAR Scores for Women

Dependent variable: MAR; Predictors: DDS and FVS

R^2	Adjusted R^2	Coefficient of variation	p-value
0.502	0.487	26.138	<0.001

	Unstandardized coefficients			
	β	SE	T	p-value
Constant	16.349	6.211	2.63	0.011
DDS	2.906	2.071	1.40	0.165
FVS	4.196	1.106	3.80	0.0003

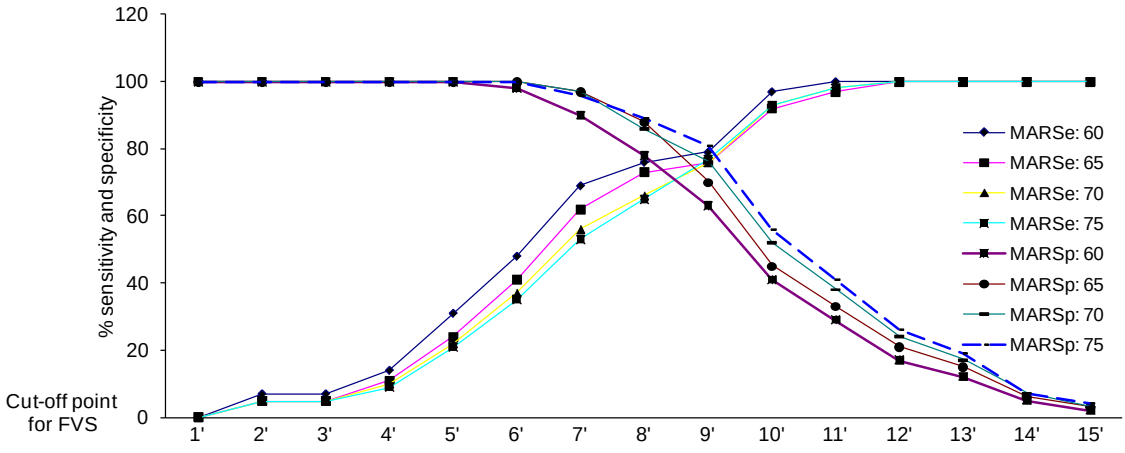
Linear Regression Model to Estimate MAR Scores for Men

Dependent variable: MAR; Predictors: DDS and FVS

R^2	Adjusted R^2	Coefficient of variation	p-value
0.408	0.387	19.752	<0.001

	Unstandardized coefficients			
	β	SE	T	p-value
Constant	20.593	8.118	2.54	0.014
DDS	7.785	1.932	4.03	0.0002
FVS	1.453	0.834	1.74	0.870

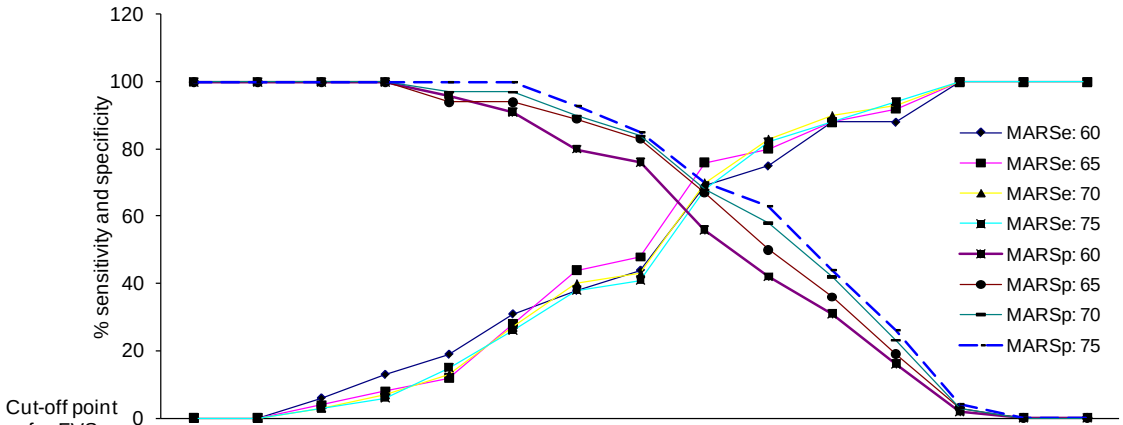
Figure 5:1 Sensitivity (sens) and specificity (spec) for different cut-off points of Food Variety Score (FVS) among women: Mean Adequacy Ratio (MAR) changing from 60 to 75



Cut-off point for FVS	1'	2'	3'	4'	5'	6'	7'	8'	9'	10'	11'	12'	13'	14'	15'
MARSe: 60	0	7	7	14	31	48	69	76	79	97	100	100	100	100	100
MARSe: 65	0	5	5	11	24	41	62	73	76	92	97	100	100	100	100
MARSe: 70	0	5	5	10	22	37	56	66	76	93	98	100	100	100	100
MARSe: 75	0	5	5	9	21	35	53	65	77	93	98	100	100	100	100
MARSp: 60	100	100	100	100	100	98	90	78	63	41	29	17	12	5	2
MARSp: 65	100	100	100	100	100	100	97	88	70	45	33	21	15	6	3
MARSp: 70	100	100	100	100	100	100	97	86	76	52	38	24	17	7	3
MARSp: 75	100	100	100	100	100	100	96	89	81	56	41	26	19	7	4

Sensitivity MAR 60 – 75 = Sensitivity for a given cut-off point of FVS with a cut-off point for MAR varying from 60 to 75. Specificity MAR 60 – 75 = Sensitivity for a given cut-off point of FVS with a cut-off for MAR varying from 60 to 75. Sensitivity = identify nutritionally inadequate diets as inadequate; specificity = identify nutritionally adequate diets as adequate.

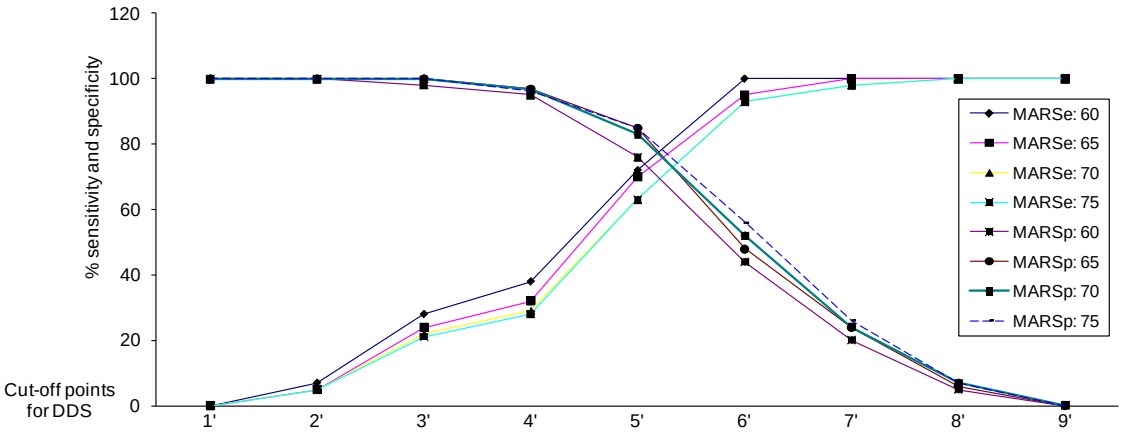
Figure 5:2 Sensitivity (sens) and specificity (spec) for different cut-off points of Food Variety Score (FVS) among men: Mean Adequacy Ratio (MAR) changing from 60 to 75



Cut-off point for FVS	1'	2'	3'	4'	5'	6'	7'	8'	9'	10'	11'	12'	13'	14'	15'
MARSe: 60	0	0	6	13	19	31	38	44	69	75	88	88	100	100	100
MARSe: 65	0	0	4	8	12	28	44	48	76	80	88	92	100	100	100
MARSe: 70	0	0	3	7	13	27	40	43	70	83	90	93	100	100	100
MARSe: 75	0	0	3	6	15	26	38	41	68	82	88	94	100	100	100
MARSp: 60	100	100	100	100	96	91	80	76	56	42	31	16	2	0	0
MARSp: 65	100	100	100	100	94	94	89	83	67	50	36	19	3	0	0
MARSp: 70	100	100	100	100	97	97	90	84	68	58	42	23	3	0	0
MARSp: 75	100	100	100	100	100	100	93	85	70	63	44	26	4	0	0

Sensitivity MAR 60 – 75 = Sensitivity for a given cut-off point of FVS with a cut-off point for MAR varying from 60 to 75. Specificity MAR 60 – 75 = Sensitivity for a given cut-off point of FVS with a cut-off for MAR varying from 60 to 75. Sensitivity = identify nutritionally inadequate diets as inadequate; specificity = identify nutritionally adequate diets as adequate.

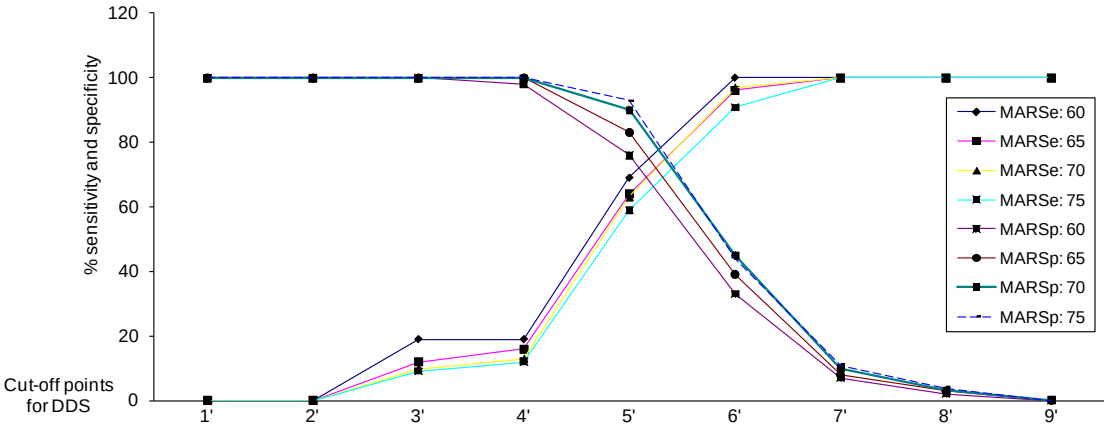
Figure 5:3 Sensitivity (sens) and specificity (spec) % for different cut-off points of Diet Diversity Score (DDS) among women: Mean Adequacy Ratio (MAR) changing from 60 to 75



Cut-off points for DDS	1'	2'	3'	4'	5'	6'	7'	8'	9'
MARSe: 60	0	7	28	38	72	100	100	100	100
MARSe: 65	0	5	24	32	70	95	100	100	100
MARSe: 70	0	5	22	29	63	93	98	100	100
MARSe: 75	0	5	21	28	63	93	98	100	100
MARSp: 60	100	100	98	95	76	44	20	5	0
MARSp: 65	100	100	100	97	85	48	24	6	0
MARSp: 70	100	100	100	97	83	52	24	7	0
MARSp: 75	100	100	100	96	85	56	26	7	0

Sensitivity MAR 60 – 75 = Sensitivity for a given cut-off point of DDS with a cut-off point for MAR varying from 60 to 75. Specificity MAR 60 – 75 = Sensitivity for a given cut-off point of DDS with a cut-off for MAR varying from 60 to 75. Sensitivity = identify nutritionally inadequate diets as inadequate; specificity = identify nutritionally adequate diets as adequate.

Figure 5:4 Sensitivity (sens) and specificity (spec) % for different cut-off points of Diet Diversity Score (DDS) among men: Mean Adequacy Ratio (MAR) changing from 60 to 75



Cut-off points for DDS	1'	2'	3'	4'	5'	6'	7'	8'	9'
MARSe: 60	0	0	19	19	69	100	100	100	100
MARSe: 65	0	0	12	16	64	96	100	100	100
MARSe: 70	0	0	10	13	63	97	100	100	100
MARSe: 75	0	0	9	12	59	91	100	100	100
MARSp: 60	100	100	100	98	76	33	7	2	0
MARSp: 65	100	100	100	100	83	39	8	3	0
MARSp: 70	100	100	100	100	90	45	10	3	0
MARSp: 75	100	100	100	100	93	44	11	4	0

Sensitivity MAR 60 – 75 = Sensitivity for a given cut-off point of DDS with a cut-off point for MAR varying from 60 to 75. Specificity MAR 60 – 75 = Sensitivity for a given cut-off point of DDS with a cut-off for MAR varying from 60 to 75. Sensitivity = identify nutritionally inadequate diets as inadequate; specificity = identify nutritionally adequate diets as adequate.

CHAPTER 6

PREDICTORS OF FAT MASS AND LEAN TISSUE AMONG HIV POSITIVE AND HIV NEGATIVE ADULTS WITH OR WITHOUT TUBERCULOSIS IN URBAN KAMPALA, UGANDA

Abstract

Background Fat and fat-free mass body composition measurements have been reported to permit a more precise evaluation of body wasting and malnutrition than use of body mass index; however, factors that may influence fat and fat-free mass and body mass index (BMI) have not been well characterized.

Objective We evaluated whether energy and protein intake are predictors of fat and fat-free mass and BMI in a population of HIV positive and HIV negative adults with or without tuberculosis in urban Kampala, Uganda.

Methods In a cross-sectional study with 131 adults who were screened for active tuberculosis and HIV infection, energy and protein intakes using a 24-hour dietary recall, weight, height, fat and fat-free mass using bioelectrical impedance analysis were assessed.

Results Energy intake was associated with an increase in BMI among women although intake in the presence of tuberculosis was associated with a decrease in BMI. Protein intake among women with no income and among women with unemployment was associated with a decrease in fat-free mass and fat mass, respectively whereas protein intake among women with tuberculosis was associated with an increase in BMI. Being single among women was associated with an increase in fat-free mass whereas having reduced appetite was associated with a decrease in fat-free mass and fat mass. Among men, tuberculosis was associated with a decrease in fat-free mass. Similarly, having reduced appetite was associated with decrease in fat mass and BMI. HIV did not influence body composition regardless of gender.

Conclusion The present study has revealed that there are remarkable gender differences in how energy and protein intakes influence body composition, and there are important interactions with presence of tuberculosis, lack of income, and unemployment. HIV does not appear to influence nutrient intake on body composition. Further evaluation is needed to understand how these differences would influence body composition over time and survival.

Background

Tuberculosis and human immunodeficiency virus (HIV) are diseases of major public health concern worldwide, with the highest burden in sub-Saharan Africa (WHO 2009; Lawn and Churchyard 2009). Among people with tuberculosis and HIV co-infection, tuberculosis is the leading cause of death in sub-Saharan Africa (Lawn and Churchyard 2009; Corbett et al. 2003).

Both tuberculosis and HIV are independently associated with body wasting, and the wasting in tuberculosis patients is thought to be further exacerbated by the concomitant effects of HIV (Kotler 2000; Macallan 1999; Lucas et al. 1994). In contrast, findings from several cross-sectional studies (Niyongabo et al. 1999; Mupere et al. 2010; Paton and Ng 2006) appear to show no significant differences in body composition between HIV positive adults with tuberculosis and HIV negative adults with tuberculosis suggesting that tuberculosis is the primary factor in driving the process wasting during co-infection. However, gender differences in body composition at presentation among tuberculosis patients have been reported (Kennedy et al. 1996; Mupere et al. 2010). Although poorly understood, the wasting process in tuberculosis and HIV is probably due to a number of factors, including reduced nutrient intake, malabsorption, altered metabolism, and interactions between drugs and nutrients (Paton et al. 1999; Paton et al. 2003; Macallan et al. 1998; Fields-Gardner 1995; Kotler and Grunfeld 1995).

Fat and fat-free mass body composition measurements have been reported to permit a more precise evaluation of body wasting than use of body mass index (BMI) (Kyle, Piccoli, and Pichard 2003; VanItallie et al. 1990; Kyle et al. 2003). Evaluation of fat and fat-free mass allows specific understanding of the body compartment and the extent to which the compartment is involved in the wasting. Moreover, disproportionate loss of fat-free mass referred to as lean tissue may be associated with adverse effects on survival and physical function.

BMI is insensitive to body fatness, particularly at low BMI, as well as with above-normal muscle development (Kyle, Genton, and Pichard 2002; Kyle, Piccoli, and Pichard 2003). The use of height-normalized fat and fat-free mass indexes (fat mass index (FMI) and fat-free mass index (FFMI), respectively) allows partitioning of BMI into fat mass index (FMI) and fat-free mass index (FFMI), i.e., BMI = FFMI + FMI (VanItallie et al. 1990; Kyle et al. 2003). The height-normalized FMI and FFMI eliminate differences in fat and fat-free mass associated with height (Baumgartner et al. 1998). Bioelectrical impedance analysis (BIA) has been recommended as the preferred and precise method for clinical assessment of FFM and fat mass (Kyle, Genton, and Pichard 2002; Kyle et al. 2004). Prior studies conducted in African patients (Niyongabo et al. 1999; Villamor et al. 2006) using BIA have reported reduced fat and fat-free mass at the time when patients present with tuberculosis. However, the factors that may influence fat and fat-free mass indexes and BMI have not been well characterized.

In this cross-sectional study, we evaluated whether energy and protein intake are predictors of fat and fat-free mass indexes and BMI in a population of HIV positive and HIV negative with or without tuberculosis in urban Kampala, Uganda.

Methods

We enrolled 132 participants in a cross-sectional study with age 18 or more years residing in Kampala district or 20 km from the study site if residence was outside Kampala in Uganda. Data collection was conducted between November 2007 and March 2008, a period that coincides with harvesting and light rains in November and December and dry season in January and February. One participant was excluded from the analysis because of prior tuberculosis treatment. The study was conducted at the National Tuberculosis and Leprosy Program (NTLP) Clinic of the national tertiary teaching hospital, Mulago complex. Of the 131 participants who were included in the analysis, 31 were HIV positive and 32 HIV negative tuberculosis patients who were recruited at the Mulago NTLP Clinic; 38 were HIV positive without tuberculosis and recruited at the Infectious Disease Institute Clinic (IDI) located 500 meters from the Mulago NTLP Clinic; and 30 were HIV negative adults without tuberculosis from the community where enrolled tuberculosis patients resided. The institutional review boards at Case Western Reserve University and Joint Clinical Research Center approved the study, with final approval by the Uganda National Council for Science and Technology. All participants provided written informed consent to the study.

All subjects in the study were given appropriate pre- and post-test HIV counseling and AIDS education. HIV-1 infection was diagnosed on the basis of a positive enzyme-linked immunosorbent assay for HIV-1 antibodies (Recombigen; Cambridge Biotech, Cambridge, MA). At enrollment, basic demographic information and a medical history were collected, and a standardized physical examination was conducted by a medical officer. Active pulmonary TB was confirmed by sputum smear microscopy and culture. Patients with active tuberculosis were treated with standard four-drug chemotherapy for tuberculosis per guidelines of the Ugandan Ministry of Health. Similarly, HIV positive patients eligible for antiretroviral therapy were started on treatment and cotrimoxazole prophylaxis at the IDI clinic.

Anthropometric measurements included height and weight. Body-mass index (BMI) was computed using the relationship of weight in kilograms divided by height in meters squared (kg/m^2). Weight was taken using Hanson digital electronic bathroom weighing scales to the nearest 100g. Height was measured to the nearest mm by calibrated standing height using a stadiometer. All anthropometric measurement values were the mean of duplicates. The single-frequency bioelectrical impedance analyzer (BIA Detroit, MI, RJL Systems) performing at 50 kHz and 800 mA was used for BIA measures with detecting electrodes placed on the wrist and ankle and signal introduction electrodes placed on the first joint of the middle finger and behind the middle toe. Before performing measurements on each subject, the BIA instrument was calibrated using the manufacturer's recalibration device. The resistance and reactance were based on measures of a series circuit (Kotler et al. 1996). BIA measurements were performed in

duplicate for each subject. The analyzer was calibrated monthly. Fat-free mass was calculated from BIA measurements using equations that were previously cross-validated in a sample of patients (white, black and Hispanic) with and without HIV infection (Kotler et al. 1996) and have been applied elsewhere in African studies (Shah et al. 2001; Van Lettow et al. 2004; Villamor et al. 2006). Fat mass was calculated as body weight minus fat-free mass.

The dietary intake assessment was made using a single 24-hour dietary recall with open ended questions. The reference period for the 24-hour recall was the day prior to the day of the interview. In all instances, the interview was held only with the interviewee, no one else was present except for children. The questionnaire was pre-tested by administering it to 8 individuals selected randomly from the neighboring community to the study site. The assessment was conducted by four trained study nursing staffs and continuously supervised by a nutritionist using local food photographs, portion-size images, and volumetric vessels to increase the accuracy of the recall from the previous 24 hours. The nutritive value of raw ingredients was computed using the East African food composition table database whose database was imported into the NutriSurvey software (http://www.nutrisurvey.de) to easy the computations. The database used was predominantly for local Ugandan diet. When the East African food composition table was found deficient in certain food items, the United States Department of Agriculture database and the African composition table were used.

Analytic strategy

Spearman correlations were performed between fat-free mass, fat mass, or BMI and energy or protein intake to establish the strengths of association. To establish whether energy and protein intakes are predictors of fat-free mass, fat mass, and BMI, we performed multivariable linear regression analyses with energy and protein intakes as main independent variables including all variables that were associated with a $p < 0.50$ in the unadjusted analyses (Dales and Ury 1978). Height-normalized indexes of fat-free mass, fat mass, and body mass were used in the models. The following variables were adjusted for in multivariable analyses: older age group >30 years, having tuberculosis and HIV infection, no or low level (primary) of education, being single, being separated or divorced, having a household number of more than 2 people, unemployment, having no personal income, current history of alcohol intake, and reduced appetite.

Both univariate and multivariable analyses have been presented in this article. Previous findings (Mupere et al. 2010) revealed gender differences in body composition among individuals with or without tuberculosis regardless of HIV status. Further, there was significant interaction between gender and energy intake. Thus, we stratified our analysis according to gender. Two-way interactions were tested between energy or between protein intakes for all variables involved in each multivariable model. The R-square was used to evaluate the importance variables in the model. Influence diagnostics of the final results was conducted to ensure that the results were not unduly influenced by a few outlying measurements (Vittinghoff E. et al. 2005). The final regression coefficients were

obtained after eliminating participants with influential observations (Neter J., Wasserman W., and Kutner M.H. 1990). Removal of influential points yielded more conservative standard errors of the estimates. All analyses were performed using SAS version 9.2 (Cary software, North Carolina SAS Institute Inc 2004.)

Results

The characteristics of the study population are shown in Table 6:1 and 6:2. Of the 131 participants who were included in the analysis, 53% were females, 47% were males, 53% were HIV positive, and 48% had tuberculosis.

The strengths of association between energy or protein intake and fat-free mass, fat mass, or BMI are shown by spearman's correlation coefficients (Table 6:3). Energy and protein intakes had positive correlations with fat-free mass, fat mass and BMI regardless of gender. Among women, there were significant correlations between energy or protein intake and fat-free mass, fat mass, BMI, or with height-normalized indexes of fat and fat-free mass.

Predictors of fat-free mass

In univariate analysis for the total study population, energy and protein intakes and being single were associated with an increase in fat-free mass whereas tuberculosis, lack of any income, and having reduced appetite were associated with a decrease in fat-free mass

(Tables 6:4 and 6:5). Of note, energy intake among women was associated with a double 0.0004 ± 0.0002 standard error (SE) (p=0.028) increase in fat-free mass compared to men that had 0.0002 ± 0.0003 SE, p=0.418 (Table 6:5). Having tuberculosis and reduced appetite were associated with a decrease in fat-free mass regardless of gender.

In multivariable analysis for the total study population, there was significant interaction between energy intake and gender when the model had gender, HIV status, tuberculosis status, being single, being more two people per household, unemployment status, lack of any income, and reduced appetite as adjusters. Energy intake among women was associated with a significant decrease in fat-free mass, -0.001 ± 0.0003 SE, p=0.004). We thus performed stratified models according to gender adjusting for the same variables but without gender (Table 6:6 and 6:7). In the overall multivariable model, energy intake was associated with an increase in fat-free mass; however, this effect was not noticeable after stratification by gender (Table 6:6 and 6:7). Having tuberculosis was associated with a significant decrease in fat-free mass for the overall population; however, this decrease was double among men compared to women. Having reduced appetite was associated with a significant decrease in fat-free mass. There was a significant interaction between protein intake and income. Protein intake among women with no income was associated with a significant decrease in fat-free mass (Table 6:7). Of note, HIV was not associated with prediction of fat-free mass regardless of gender.

Predictors of fat mass

Energy intake in univariate analysis was associated with a decrease in fat mass of -0.00002 ± 0.0003 SE, p=0.945 for the total population; however, this decrease was noted among men. Energy intake among women was associated with a significant increase in fat mass of 0.001 ± 0.0005 SE, p=0.020 (Table 6:8 and 6:9). Having tuberculosis and reduced appetite were associated with a decrease in fat mass regardless of gender. Of note, HIV was not associated with prediction of fat mass.

There was significant interaction between energy intake and gender in multivariable analysis for the overall study population when energy and protein intakes, gender, tuberculosis, being more two people per household, unemployment, lack of any income, and reduced appetite were independent variables in the model (Table 6:10 and 6:11). Energy intake among women was associated with a significant increase in fat mass, 0.002 ± 0.001, SE, p=0.001. Thus, in stratified analysis according to gender adjusting for the same variables, having reduced appetite was associated with a decrease in fat mass regardless of gender. Of note, women had a fourfold decrease (-4.17 ± 1.94, SE) in fat mass compared to men (-1.90 ± 0.90, SE) (Table 6:11). There was a significant interaction between protein intake and unemployment. Lack of employment among women was associated with a decrease in fat mass.

Predictors of BMI

In univariate analysis, energy intake was associated with an increase in BMI of 0.002 ± 0.001 SE, p=0.014 among women (Table 6:12 and 6:13). Energy intake among men was not significant. Having tuberculosis and reduced appetite were associated with a decrease in fat mass regardless of gender. Of note, HIV was not associated with prediction of fat mass (Table 6:12 and 6:13).

In multivariate analysis, after adjusting for protein intake, tuberculosis, lack of income, and reduced appetite, energy intake was associated an increase of 0.003 ± 0.001 ± SE among women (Table 6:14 and 6:15). Energy intake among men was not significant; however, having reduced appetite was associated with a four unit decrease in BMI among men. There were significant interactions between energy intake and tuberculosis, between energy intake and appetite, and between protein intake and tuberculosis (Table 6:14 and 6:15). Energy intake in the presence of tuberculosis among women was associated with a significant decrease in BMI whereas protein intake in the presence of tuberculosis was associated with a significant increase in BMI among women. None of these were significant among men. Energy intake with reduced appetite was associated with an increase in BMI in the overall population; however, this interaction not significant among women and among men (Table 6:14 and 6:15).

Discussion

In the present cross-sectional study of 131 participants, we evaluated whether energy and protein intakes were important predictors of fat-free mass, fat mass, and BMI in a population of HIV positive and HIV negative adults with or without tuberculosis in urban Uganda. Predictors of fat and fat-free mass and BMI differed by gender. Energy intake was associated with an increase in BMI among women although intake in the presence of tuberculosis was associated with a decrease in BMI. Protein intake among women with no income and among women with unemployment was associated with a decrease in fat-free mass and fat mass, respectively whereas protein intake among women with tuberculosis was associated with an increase in BMI. Being single among women was associated with an increase in fat-free mass whereas having reduced appetite was associated with a decrease in fat-free mass and fat mass. Among men, tuberculosis was associated with a decrease in fat-free mass. Similarly, having reduced appetite was associated with decrease in fat mass and BMI. HIV did not influence body composition regardless of gender.

The cross-sectional design employed in the present study limits the interpretation of finding in the present study to associations rather than causation. The findings suggest that energy and protein intakes, appetite, income, employment, and marital status are important predictors of body composition among women whereas tuberculosis and appetite are important among men. Energy intake in the presence of tuberculosis; reduced appetite among women and among men; tuberculosis among men; protein intake when

there is no income and when there is no employment were associated with negative prediction of body composition. Whereas protein intake when there is tuberculosis among women and being a single woman were associated with positive prediction of body composition. To our knowledge, this study is the first to show how energy and protein intakes influence body composition among women and among men and the interactions with tuberculosis, income, and employment. Of note, HIV infection did not provide any prediction of body composition regardless of gender. This corroborates with the claim in previous reports (Paton and Ng 2006; Mupere et al. 2010) that tuberculosis is the dominant factor in the wasting process even in the presence of HIV and that the disease in itself is associated with wasting (Rubin 1995). The major strengths in the present study is the composition of the study population with HIV positive and HIV negative adults with or without tuberculosis, allowing prediction of body composition in the presence or absence of tuberculosis and HIV infection.

This study found that the influence of energy and protein intakes on body composition differed by gender. A unit increase in energy intake was associated with a unit increase in BMI among women; however, in the face of tuberculosis a unit increase in energy intake was associated with a unit decrease in BMI. Whereas protein intake among women with no income or unemployment were associated with a decrease in fat-free mass and fat mass, and protein intake in the presence of tuberculosis was associated with increase in BMI. Energy and protein intakes among men did not influence body composition. A possible explanation to this gender difference in use of the dietary intake nutrient substrates rests on the differences in lipid and carbohydrate metabolism between men and

women (Tarnopolsky and Ruby 2001; Tarnopolsky 2000, 2008). Women use energy intake to build or maintain their fat content. Thus, an increase in BMI since BMI is a measure of fat content (Garrow and Webster 1985). However, during sub-maximal stress like lack of income or unemployment to purchase adequate nutrient substrates, they do oxidize away the lipid content sparing the lean tissue, and hence the decrease in BMI. It has reported in several reports that women oxidize more lipid and less of carbohydrate as metabolic substrates than men (Tarnopolsky 2000, 2008; Tarnopolsky and Ruby 2001). However, in extreme stress such having tuberculosis disease, women may use protein substrates to maintain the BMI. For men, it appears they are in position to balance the use of nutrient substrates in building and maintaining both fat and fat-free mass content. Thus, no effect is noticed in prediction models. Moreover, it has also been reported that at the time of tuberculosis diagnosis, the average weight group difference in men consisted of lean tissue and fat in equal proportions whereas in women, the average weight group difference consisted predominantly of fat mass (Mupere et al. 2010).

Findings in the present also show gender differences in the effect of reduced on body composition. Reduced appetite among women was associated with decrease in both fat and fat-free mass whereas among men, reduced appetite was associated with decrease in BMI. This suggests that reduced appetite could be a predictor of both fat and fat-free mass among women whereas reduced appetite could be a predictor of BMI among men. This probably reflects on the wasting process and the gender differences in body composition when anorexia sets in. Men waste away their high fat-free mass content to be in proportion with fat content whereas women, waste away their high fat content

sparing the low fat-free mass content. Although, BMI is monotonically related to adiposity (Garrow and Webster 1985), it also correlates positively with the amount of fat-free an individual has. Hence, the level of appetite may reflect on the body composition for an individual. Women have little fat-free mass content, thus requiring daily energy intake to preserve physical function. Men in general display a higher absolute resting metabolic rate with associated energy expenditure than women because of their lager quantity of fat-free mass (Arciero, Goran, and Poehlman 1993). Thus, men require a good appetite to maintain nutrient intake that can meet their metabolic demands.

Another possible explanation is the differences in sex hormones between men and women that the sex hormones may play a role in regulation of symptoms associated anorexia in tuberculosis. Sex hormones are physiologically associated with feeding behavior (Geary 2001). Higher anorectic signals and earlier satiety have been reported in men suffering from chronic illnesses, perhaps contributing to a different response pattern to anorexigenic diseases such as cancer among men and women (Geary 2001). In animal models, inflammation-induced anorexia has been reported to be more severe among male rats (Lennie 2004) and previous reports suggest that estradiol and progesterone have inhibitory effects on anorexia (Eckel 2004). Further, sex hormones or derivatives have been used in treatment of eating disorders with positive results in improving appetite, caloric intake, and nutritional and inflammatory status (Rammohan et al. 2005).

Findings in the present revealed that tuberculosis was a universal predictor of body composition. Having tuberculosis was associated a decrease in fat and fat-free mass and BMI regardless of gender. Wasting is a recognized cardinal feature of tuberculosis. It is likely caused by a combination of reduction in appetite, leading to a decrease in energy intake, interacting with increased losses and altered metabolism as part of the inflammatory and immune responses (Paton et al. 2003; Macallan et al. 1998). Utilization of amino acids and protein synthesis may be inhibited due to the presence of pro-inflammatory cytokines (Macallan et al. 1998).

In conclusion, the present study has revealed that there are remarkable gender differences in how energy and protein intakes influence body composition, and there are important interactions with presence of tuberculosis, lack of income, and unemployment. HIV does not appear to influence nutrient intake on body composition. Further evaluation is needed to understand how these differences would influence body composition over time and survival.

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Table 6:1 Characteristics of the study population (n=131)

Characteristics	All subjects (n=131)
Sex	
Female n (%)	70 (53)
Male n (%)	61 (47)
Age in years	
≤30 n (%)	94 (72)
>30 n (%)	37 (28)
HIV status	
Negative n (%)	62 (47)
Positive n (%)	69 (53)
Tuberculosis	
No n (%)	68 (52)
Yes n (%)	63 (48)
Education	
None/primary level n (%)	69 (53)
Secondary level n (%)	62 (47)

Tribe	
Muganda n (%)	57 (44)
Others n (%)	74 (56)
Marital status	
Married n (%)	56 (43)
Single n (%)	37 (28)
Separated/divorced n (%)	38 (29)
Household number	
One to two n (%)	40 (31)
>2 n (%)	91 (69)
Employed	
No n (%)	54 (41)
Yes n (%)	77 (59)
Income	
Not at all n (%)	47 (36)
Yes n (%)	84 (64)
Takes alcohol	

No n (%)	98 (75)
Yes n (%)	33 (25)
Reduced appetite	
No n (%)	89 (68)
Yes n (%)	42 (32)

Table 6:2 Nutrient intake characteristics of the study population (n=131)

Characteristics	All subjects (n=131)
Energy intake in kcal [mean, SD)]	1820 (874)
Protein intake in g [mean, (SD)]	49.5 (32.1)
Body mass index in kg/m^2 [mean, (SD)]	20.9 (3.8)
Fat-free mass in kg [mean, (SD)]	45.0 (7.0)
Fat-free mass index in kg/m^2 [mean, (SD)]	16.8 (1.6)
Fat mass in kg [mean, (SD)]	10.4 (7.0)
Fat mass index in kg/m^2 [mean, (SD)]	4.1 (3.1)

SD = standard deviation

Table 6:3 Spearman's correlations between energy or protein intake and body mass index, fat or fat-free mass (n=131)

Characteristics	Women (n=70)		Men (n=61)	
	Energy (kcal)	Protein (g)	Energy (kcal)	Protein (g)
Body mass index (kg/m^2)	0.28[b]	0.08	0.10	0.12
Fat-free mass (kg)	0.36[b]	0.13	0.20	0.18
Fat-free mass index (kg/m^2)	0.28[b]	0.06	0.11	0.11
Fat mass (kg)	0.29[b]	0.10	0.04	0.11
Fat mass index (kg/m^2)	0.25[b]	0.08	0.02	0.09

[a]p-value <0.001, [b]p-value <0.05.

Table 6:4 Predictors of fat-free mass in univariate models among HIV positive and HIV negative adults with or without tuberculosis in Kampala, Uganda (n=131)

Characteristics	All (n=131)	
	Unadjusted Estimate (SE)	p-value
Energy intake, kcal	0.001 (0.0002)	**<0.001**
Protein intake, g	0.002 (0.001)	**0.049**
Older age >30 years	-0.23 (0.30)	0.449
HIV positive	-0.34 (0.27)	0.210
Tuberculosis	-1.41 (0.24)	**<0.001**
No/low education	-0.41 (0.43)	0.339
Not Muganda by tribe	-0.34 (0.27)	0.148
Single	0.84 (0.29)	**0.005**
Household >2 people	-0.32 (0.30)	0.279
Unemployed	-0.46 (0.28)	0.095
No income at all	-0.57 (0.28)	**0.045**
Takes alcohol	-0.03 (0.32)	0.928

Reduced appetite	-1.55 (0.26)	**<0.001**

Table 6:5 Predictors of fat-free mass in univariate models among HIV positive and HIV negative adults with or without tuberculosis in Kampala, Uganda stratified by sex (n=131)

Characteristics	Women (n=70)		Men (n=61)	
	Unadjusted Estimate (SE)	p-value	Unadjusted Estimate (SE)	p-value
Energy intake, kcal	0.0004 (0.0002)	**0.028**	0.0002 (0.0003)	0.418
Protein intake, g	0.001 (0.001)	0.275	0.0002 (0.002)	0.910
Older age >30 years	-0.02 (0.32)	0.937	-0.65 (0.45)	0.157
HIV positive	-0.35 (0.28)	0.212	0.14 (0.42)	0.743
Tuberculosis	-0.960 (0.25)	**0.0003**	-1.81 (0.35)	**<0.001**
No/low education	0.12 (0.38)	0.754	-0.60 (0.84)	0.481
Not Muganda by tribe	-0.41 (0.27)	0.144	-0.44 (0.42)	0.301
Single	0.16 (0.28)	0.573	0.98 (0.58)	0.096
Household >2 people	0.10 (0.32)	0.746	-0.28 (0.43)	0.525
Unemployed	0.11 (0.28)	0.692	-0.49 (0.46)	0.283
No income at all	0.18 (0.27)	0.508	-0.62 (0.52)	0.236
Takes alcohol	0.25 (0.31)	0.416	-0.21 (0.50)	0.682

Reduced appetite	-1.15 (0.25)	**<0.001**	-1.64 (0.44)	**0.0004**

Table 6:6 Predictors of fat-free mass in multivariable models among HIV positive and HIV negative adults with or without tuberculosis in urban Kampala, Uganda (n=131)

Characteristic	Overall (n=131)	
	Estimate (SE)	p-value
Energy intake, kcal	0.0004 (0.0002)	**0.025**
Protein intake, kcal	0.0004 (0.001)	0.756
HIV positive	-0.40 (0.24)	0.096
Tuberculosis	-0.86 (0.29)	**0.004**
Single	0.68 (0.24)	**0.005**
Household >2 people	-0.39 (0.26)	0.138
No income	0.36 (0.43)	0.408
Reduced appetite	-0.88 (0.31)	**0.006**
Protein*income	-0.02 (0.01)	**0.036**
R Square	0.41	

[a]p-value <0.001, [b]p-value <0.05. Variables for which p-value was < 0.50 in the unadjusted analyses were included in the multivariable model. Unemployment and other than Muganda tribe were dropped because they did not contribute much to the R-square.

Table 6:7 Predictors of fat-free mass in multivariable models among HIV positive and HIV negative adults with or without tuberculosis in Kampala, Uganda stratified according sex (n=131)

Characteristic	Stratified models			
	Women (n=70)		**Men (n=61)**	
	Estimate (SE)	p-value	Estimate (SE)	p-value
Energy intake, kcal	0.0003 (0.0002)	0.094	0.0004 (0.0004)	0.313
Protein intake, kcal	0.002 (0.001)	0.289	-0.002 (0.003)	0.383
HIV positive	-0.35 (0.25)	0.168	-0.26 (0.42)	0.546
Tuberculosis	-0.59 (0.33)	0.078	-1.42 (0.45)	**0.003**
Single	0.58 (0.25)	**0.022**	0.47 (0.44)	0.295
Household >2 people	-0.36 (0.29)	0.227	0.14 (0.45)	0.755
No income	0.80 (0.41)	0.056	-0.16 (0.89)	0.861
Reduced appetite	-0.79 (0.33)	**0.020**	-0.77 (0.52)	0.144
Protein*income	-0.02 (0.01)	**0.027**	-0.007 (0.01)	0.591
R Square	0.42		0.40	

[a]p-value <0.001, [b]p-value <0.05. Variables for which p-value was < 0.50 in the unadjusted analyses were included in the multivariable model. Unemployment and other than Muganda tribe were dropped because they did not contribute much to the R-square.

Table 6:8 Predictors of fat mass in univariate models among HIV positive and HIV negative adults with or without tuberculosis in Kampala, Uganda (n=131)

Characteristics	All (n=131)	
	Unadjusted Estimate (SE)	**p-value**
Energy intake, kcal	-0.00002 (0.0003)	0.945
Protein intake, g	-0.001 (0.002)	0.536
Older age >30 years	0.09 (0.060)	0.885
HIV positive	0.49 (0.54)	0.367
Tuberculosis	-2.40 (0.50)	**<0.001**
No/low education	0.11 (0.85)	0.90
Not Muganda by tribe	-0.30 (0.55)	0.590
Single	-1.10 (0.59)	0.064
Household >2 people	0.82 (0.59)	0.162
Unemployed	0.88 (0.55)	0.112
No income at all	1.46 (0.55)	0.009
Takes alcohol	0.75 (0.62)	0.23
Reduced appetite	-2.02 (0.55)	**<0.001**

Table 6:9 Predictors of fat mass in univariate models among HIV positive and HIV negative adults with or without tuberculosis in Kampala, Uganda stratified according to sex (n=131)

Characteristics	Women (n=70)		Men (n=61)	
	Unadjusted Estimate (SE)	p-value	Unadjusted Estimate (SE)	p-value
Energy intake, kcal	0.001 (0.0005)	**0.020**	-0.000004 (0.0002)	0.981
Protein intake, g	0.004 (0.003)	0.304	0.0003 (0.001)	0.821
Older age >30 years	0.53 (0.95)	0.581	0.07 (0.32)	0.829
HIV positive	-0.43 (0.85)	0.619	0.45 (0.29)	0.132
Tuberculosis	-3.57 (0.72)	**<0.001**	-1.35 (0.24)	**<0.001**
No/low education	-0.76 (1.15)	0.508	-0.29 (0.60)	0.632
Not Muganda by tribe	-0.29 (0.84)	0.728	-0.20 (0.30)	0.508
Single	-0.11 (0.85)	0.900	-0.006 (0.42)	0.988
Household >2 people	0.62 (0.97)	0.524	0.06 (0.31)	0.849
Unemployed	0.48 (0.83)	0.563	-0.28 (0.33)	0.390
No income at all	0.75 (0.83)	0.374	-0.06 (0.38)	0.869
Takes alcohol	1.19 (0.93)	0.203	-0.23 (0.35)	0.519

Reduced appetite	-3.47 (0.75)	**<0.001**	-1.30 (0.30)	**<0.001**

Table 6:10 Predictors of fat mass in multivariable models among HIV positive and HIV negative adults with or without tuberculosis in Kampala, Uganda (n=131)

Characteristic	Overall model (n=131)	
	Estimate (SE)	**p-value**
Energy intake, kcal	-0.0005 (0.0008)	0.534
Protein intake, g	-0.009 (0.005)	0.077
Tuberculosis	-0.33 (1.31)	0.799
Household >2 people	-2.06 (1.11)	0.066
Unemployed	1.66 (1.17)	0.158
No income	-0.80 (1.50)	0.596
Reduced appetite	-3.99 (1.29)	**0.003**
Energy*household >2 people	0.002 (0.001)	**0.010**
Energy*tuberculosis	-0.003 (0.001)	**<0.001**
Energy*reduced appetite	0.002 (0.001)	**0.005**
Energy*no income	0.002 (0.001)	**0.021**
Protein*tuberculosis	-0.09 (0.02)	**<0.001**
Protein*unemployement	-0.05 (0.02)	**0.003**

R Square	0.41

[a]p-value <0.001, [b]p-value <0.05. Variables for which p-vale was < 0.50 in the unadjusted analyses were included in the multivariable model. Alcohol intake and being single were dropped because they did not contribute much to the R-square.

Table 6:11 Predictors of fat mass in multivariable models among HIV positive and HIV negative adults with or without tuberculosis in Kampala, Uganda (n=131)

Characteristic	Stratified models			
	Women (n=70)		**Men (n=61)**	
	Estimate (SE)	p-value	Estimate (SE)	p-value
Energy intake, kcal	-0.0002 (0.002)	0.880	-0.001 (0.0003)	0.150
Protein intake, g	-0.01 (0.01)	0.539	0.001 (0.003)	0.710
Tuberculosis	-0.37 (2.15)	0.866	-1.49 (0.89)	0.100
Household >2 people	-2.86 (1.72)	0.102	0.33 (0.90)	0.715
Unemployed	2.67 (1.85)	0.155	-0.57 (0.78)	0.468
No income	-1.95 (2.40)	0.420	-0.84 (1.00)	0.407
Reduced appetite	-4.17 (1.94)	**0.036**	-1.90 (0.90)	**0.040**
Energy*household >2 people	0.002 (0.001)	0.080	0.0001 (0.0004)	0.885
Energy*tuberculosis	-0.003 (0.001)	0.070	0.0002 (0.001)	0.751
Energy*reduced appetite	0.001 (0.001)	0.207	0.001 (0.0004)	0.134
Energy*no income	0.002 (0.001)	0.097	0.001 (0.005)	0.264

Protein*tuberculosis	0.07 (0.04)	0.100	-0.003 (0.02)	0.859
Protein*unemployement	-0.08 (0.03)	**0.010**	-0.001 (0.01)	0.938
R Square	0.53		0.51	

[a]p-value <0.001, [b]p-value <0.05. Variables for which p-vale was < 0.50 in the unadjusted analyses were included in the multivariable model. Alcohol intake and being single were dropped because they did not contribute much to the R-square.

Table 6:12 Predictors of body mass index in univariate models among HIV positive and HIV negative adults with or without tuberculosis in Uganda (n=131)

Characteristics	**All (n=131)**	
	Unadjusted Estimate (SE)	**p-value**
Energy intake, kcal	0.001 (0.0004)	0.161
Protein intake, g	0.001 (0.003)	0.786
Older age >30 years	-0.10 (0.74)	0.894
HIV positive	0.15 (0.66)	0.823
Tuberculosis	-3.88 (0.57)	**<0.001**
No/low education	-0.27 (1.04)	0.797
Not Muganda by tribe	-0.71 (0.67)	0.292
Single	-0.22 (0.73)	0.762
Household >2 people	0.53 (0.72)	0.460
Unemployed	0.36 (0.67)	0.594
No income at all	0.89 (0.69)	0.198
Takes alcohol	-0.76 (0.76))	0.319

Reduced appetite	-3.67 (0.63)	**<0.001**

Table 6:13 Predictors of body mass index in univariate models among HIV positive and HIV negative adults with or without tuberculosis in Kampala, Uganda stratified according sex (n=131)

Characteristics	Women (n=70)		Men (n=61)	
	Unadjusted Estimate (SE)	p-value	Unadjusted Estimate (SE)	p-value
Energy intake, kcal	0.002 (0.001)	**0.014**	0.0002 (0.0004)	0.622
Protein intake, g	0.005 (0.004)	0.306	0.0005 (0.003)	0.864
Older age >30 years	0.59 (1.22)	0.633	-0.57 (0.72)	0.434
HIV positive	-0.76 (1.09)	0.490	0.59 (0.67)	0.385
Tuberculosis	-4.66 (0.91)	<**0.001**	-3.15 (0.54)	<**0.001**
No/low education	-0.57 (1.47)	0.698	-0.89 (1.35)	0.514
Not Muganda by tribe	-0.72 (1.08)	0.505	-0.64 (0.67)	0.347
Single	0.08 (1.09)	0.945	0.97 (0.94)	0.306
Household >2 people	0.82 (1.24)	0.514	-0.22 (0.69)	0.755
Unemployed	0.52 (1.07)	0.625	-78 (0.73)	0.293
No income at all	0.96 (1.06)	0.372	-0.69 (0.84)	0.418
Takes alcohol	1.53 (1.19)	0.202	-0.44 (0.80)	0.587

Reduced appetite	-4.78 (0.934)	**<0.001**	-2.95 (0.68)	**<0.001**

Table 6:14 Predictors of body mass index in multivariable models among HIV positive and HIV negative adults with or without tuberculosis in urban Uganda (n=131)

Characteristic	**Overall model (n=131)**	
	Estimate (SE)	**p-value**
Energy intake, kcal	0.001 (0.001)	0.193
Protein intake, g	-0.01 (0.01)	0.105
Tuberculosis	-1.07 (1.52)	0.482
No income	1.01 (0.57)	0.079
Reduced appetite	-4.93 (1.54)	**0.002**
Energy*tuberculosis	-0.002 (0.001)	**0.013**
Energy*appetite	0.002 (0.001)	**0.026**
Protein*tuberculosis	0.06 (0.03)	**0.033**
R Square	0.39	

[a]p-value <0.001, [b]p-value <0.05. Variables for which p-vale was < 0.50 in the unadjusted analyses were included in the multivariable model. Being other than Muganda tribe was dropped because it did not contribute much to the R-square.

Table 6:15 Predictors of body mass index in multivariable models among HIV positive and HIV negative adults with or without tuberculosis in Kampala, Uganda (n=131)

Characteristic	Stratified models			
	Women (n=70)		Men (n=61)	
	Estimate (SE)	p-value	Estimate (SE)	p-value
Energy intake, kcal	0.003 (0.001)	**0.028**	-0.001 (0.001)	0.311
Protein intake, g	-0.02 (0.01)	0.119	0.003 (0.01)	0.622
Tuberculosis	-0.48 (2.27)	0.834	-3.34 (1.76)	0.063
No income	1.01 (0.87)	0.250	-0.69 (0.67)	0.306
Reduced appetite	-4.21 (2.25)	0.066	-4.3 (1.94)	**0.030**
Energy*tuberculosis	-0.004 (0.001)	**0.008**	0.001 (0.001)	0.238
Energy*appetite	0.001 (0.001)	0.580	0.001 (0.001)	0.105
Protein*tuberculosis	0.10 (0.05)	**0.039**	-0.03 (0.03)	0.236
R Square	0.48		0.47	

[a]p-value <0.001, [b]p-value <0.05. Variables for which p-vale was < 0.50 in the unadjusted analyses were included in the multivariable model. Being other than Muganda tribe was dropped because it did not contribute much to the R-square.

CHAPTER 7

BODY WASTING AND DIETARY INTAKE AMONG HIV POSITIVE AND HIV NEGATIVE ADULTS WITH OR WITHOUT TUBERCULOSIS IN URBAN UGANDA, KAMPALA

Abstract

Background The effects of tuberculosis and effect of HIV on dietary intake have not been well described. We aimed to establish the 1) independent effects of tuberculosis and HIV infection on dietary intake, 2) relationship between dietary intake and body wasting as measured by height-normalized fat-free mass (FFMI) and body mass (BMI) indices, and 3) relationship between dietary intake and tuberculosis disease severity among HIV positive and HIV negative adults with/or without tuberculosis in urban Uganda.

Methods In a cross-sectional study of 131 adults who were screened for active tuberculosis and HIV infection, FFMI, BMI, and 24-hour dietary intake recall were assessed.

Results Tuberculosis patients that had moderate/or severe clinical disease had lower dietary intakes for energy, protein, total fat, carbohydrate, calcium, vitamin A, and folate compared to patients with mild disease. Both men and women had comparable dietary intake among patients with tuberculosis regardless of HIV status whereas HIV negative women had reduced energy, protein, and folate intake among individuals without tuberculosis compared to men. Tuberculosis patients with fat-free mass wasting or those with reduced BMI had comparable nutrient intakes with counterparts that had normal fat-free mass or normal BMI.

Conclusion The study revealed that dietary intake at the time of diagnosis was influenced by tuberculosis disease severity, but not tuberculosis disease or HIV status and in the absence of tuberculosis was influenced by gender. Nutritional counseling and

supplementation, early treatment and prevention of tuberculosis are needed to improve dietary intake in populations of sub-Saharan Africa.

Background

Body wasting and malnutrition is endemic in sub-Saharan Africa (Muller and Krawinkel 2005), which also bears the highest burden of tuberculosis patients with human immunodeficiency virus (HIV) co-infection (Lawn and Churchyard 2009). An estimated 1.37 million new cases of tuberculosis with HIV co-infection occurred in 2007; 79% of which were from sub-Saharan Africa. Co-infection with tuberculosis and HIV poses an extra burden to the pathophysiology of body wasting, exacerbating the wasting process seen in tuberculosis or HIV infection alone (Lucas et al. 1994; Macallan 1999). Moreover, co-infection and malnutrition have deleterious interactions. Co-infected patients with malnutrition have high risk of morbidity and mortality (Zachariah et al. 2002; Lucas et al. 1994; Duarte et al. 2009) and tuberculosis is the leading cause of death in co-infected patients in tuberculosis endemic countries, including those with free access to antiretroviral therapy (Saraceni et al. 2008).

Co-infection may lead to poor appetite with decreased nutrient intake, which may interact with altered metabolism associated with both infections as part of the immune and inflammatory responses (Paton et al. 2003) leading to exacerbation of the existing body wasting. Yet poor nutritional status is associated with risk of tuberculosis relapse (Khan et al. 2006) in addition to morbidity and mortality. The goal of nutritional assessment and nutritional support is to intervene early and to preserve lean tissue or fat-free mass body compartment from further wasting because disproportionate loss of fat-free mass is associated with morbidity and mortality (Heitmann et al. 2000). Fat-free mass is a marker

of body wasting and malnutrition, because it is a consequence of negative imbalance between energy (and protein) needs and dietary intake that occurs for more than a few days.

Assessment of dietary intake is essential in nutritional management and in understanding of body wasting and malnutrition. Despite the high burden of malnutrition and the high burden of co-infection with associated body wasting, assessment of dietary intake is often neglected in clinical practice and national tuberculosis programs. Thus, the effects of tuberculosis and effect of HIV among co-infected patients on dietary intake have not been well described. The present cross-sectional study was conducted to establish the 1) independent effects of tuberculosis and HIV infection on dietary intake, 2) relationship between dietary intake and body wasting, and 3) relationship between dietary intake and TB disease severity. The study was conducted among HIV positive and HIV negative adults with/or without active tuberculosis in urban Kampala, Uganda.

Subjects and methods

In a cross-sectional study, 132 participants 18 years or older residing in Kampala district or 20 km from the study site if residence was outside Kampala in Uganda were enrolled. One participant was excluded from the analysis because of prior TB treatment. The study was conducted at the National tuberculosis and Leprosy Program (NTLP) Clinic of the national tertiary teaching hospital, Mulago complex between November 2007 and March 2008. Of the 131 participants who were included in the analysis, 63 were tuberculosis

patients who were recruited at the Mulago NTLP Clinic; 38 were HIV positive without tuberculosis and recruited at the Infectious Disease Institute Clinic (IDI) located 500 meters from the Mulago NTLP Clinic; and 30 were HIV negative without tuberculosis from the community where enrolled tuberculosis patients resided. The institutional review boards at Case Western Reserve University and Joint Clinical Research Center approved the study, with final approval by the Uganda National Council for Science and Technology. All participants provided written informed consent to the study.

All subjects in the study were given appropriate pre- and post-test HIV counseling and AIDS education. HIV-1 infection was diagnosed on the basis of a positive enzyme-linked immunosorbent assay for HIV-1 antibodies (Recombigen; Cambridge Biotech, Cambridge, MA). At enrollment, basic demographic information and a medical history were collected, and a standardized physical examination was conducted by a medical officer. Active pulmonary tuberculosis was confirmed by sputum smear microscopy and culture. Patients with active tuberculosis were treated with standard four-drug chemotherapy for tuberculosis per guidelines of the Ugandan Ministry of Health. Similarly, HIV positive patients eligible for antiretroviral therapy were started on treatment and cotrimoxazole prophylaxis at the IDI clinic.

We defined body wasting of participants using body mass index (BMI) and height-normalized indices (adjusted for height^2) of body composition that partition BMI into fat-free mass index (FFMI) and fat mass index (FMI) (Kyle, Piccoli, and Pichard 2003;

VanItallie et al. 1990; Schutz, Kyle, and Pichard 2002) to establish the body wasting status of participants. The FFMI and FMI have the advantages of compensating for differences in height and age (Kyle, Genton, and Pichard 2002). Also, the use of the FFMI and FMI eliminates some of the differences between population groups. We defined body wasting as patients having the low fat-free mass index (FFMI) and the low body fat mass index (FMI) as previously recommended (Kyle, Piccoli, and Pichard 2003; VanItallie et al. 1990). The low FFMI of 16.7 (kg/m^2) for men and 14.6 (kg/m^2) for women and the low FMI of 1.8 (kg/m^2) for men and 3.9 (kg/m^2) for women corresponds to a BMI of <18.5 kg/m2, the WHO cutoff for malnutrition (World Health Organ Tech Rep 1995) among adults.

Anthropometric measurements included height and weight. Body-mass index (BMI) was computed using the relationship of weight in kilograms divided by height in meters squared (kg/m^2). Weight was taken using Hanson digital electronic scales to the nearest 100g. Height was measured to the nearest cm by calibrated standing height using a stadiometer. All anthropometric measurement values were the mean of duplicates. The single-frequency bioelectrical impedance analyzer (BIA Detroit, MI, RJL Systems) performing at 50 kHz and 800 mA was used for BIA measures with detecting electrodes placed on the wrist and ankle and signal introduction electrodes placed on the first joint of the middle finger and behind the middle toe.

Before performing measurements on each subject, the BIA instrument was calibrated using the manufacturer's recalibration device. The resistance and reactance were based on measures of a series circuit (Kotler et al. 1996). BIA measurements were performed in duplicate for each subject. The analyzer was calibrated monthly. Fat-free mass was calculated from BIA measurements using equations that were previously cross-validated in a sample of patients (white, black and Hispanic) with and without HIV infection (Kotler et al. 1996) and have been applied elsewhere in African studies (Shah et al. 2001; Van Lettow et al. 2004; Villamor et al. 2006). Fat mass was calculated as body weight minus fat-free mass.

We classified tuberculosis patients into two categories of clinical disease severity as follows: mild and moderate/or severe tuberculosis using the TBscore. HIV negative participants without tuberculosis were classified as no disease category. The clinical tuberculosis score is a low-cost tool that has been developed recently and validated to assess severity of clinical TB disease in resource limited settings (Wejse et al. 2008). The score has a maximum of 13 clinical variables each scoring 1 point as follows: self-reported symptoms of cough, hemoptysis, dyspnea, chest pain, and night sweating; anemic conjunctivae, tachycardia, positive finding at lung auscultation, axillary temperature $>37.0^{0}$C, body mass index (BMI) <18, BMI <16, middle upper arm circumference (MUAC) <220 mm, MUAC <200. Clinical severity categories were generated using the following cutoffs: mild 0 – 5 and moderate/severe > 5. Higher scores are associated with severe disease.

The dietary intake assessment was made using a single 24-hour dietary recall with open ended questions. The questionnaire was pre-tested by administering it to 8 individuals selected randomly from the neighboring community to the study site. The assessment was conducted by four trained study nursing staffs and supervised a nutritionist using local food photographs, portion-size images, and volumetric vessels to increase the accuracy of the recall from the previous 24 hours. The nutritive value of raw ingredients was computed using the East African food composition table database whose database was imported into the NutriSurvey software (http://www.nutrisurvey.de) to easy the computations. When the East African food composition table was found deficient in certain food items, the United States Department of Agriculture database and the African composition table were used.

Analysis

All study participants in the analysis were categorized into 4 mutually independents groups: HIV positive patients with and without tuberculosis disease, HIV negative patients with and without tuberculosis. Measures of central tendency and variability were compared between women and men across 4 mutually exclusive groups, between patients with and patients without reduced FFMI, between patients with and without reduced BMI, and between patients with mild and with moderate/severe disease using Wilcoxon-Mann Whitney test for average weight, height, BMI, fat and fat-free mass, FFMI, FMI, and nutrient intake parameters due to lack of normality.

We made comparisons using analysis of variance between HIV positive patients with tuberculosis and HIV positive patients without tuberculosis, between HIV negative patients with tuberculosis and HIV negative individuals without tuberculosis, between HIV positive patients with tuberculosis and HIV negative patients with tuberculosis, and between HIV positive individuals without tuberculosis and HIV negative individuals without tuberculosis to understand the independent effects of tuberculosis and HIV infection on dietary intake and nutritional status. We used Bonferroni to adjust for multiple comparisons. We compared proportions of nutrient inadequacy between women and men across the 4 mutually exclusive groups, between patients with and without reduced FFMI, between patients with and without reduced BMI, and between patients with mild and patients with moderate/severe clinical tuberculosis using chi-square and Fischer's exact tests. Fischer's exact test was used where expected counts were less than 5. A p-value of <0.05 was considered significant in all analyses except for multiple comparisons which was set at <0.01. All analyses were performed using SAS version 9.2 (Cary software, North Carolina SAS Institute Inc 2004).

Results

Of the 131 participants analyzed, 31 were HIV positive with tuberculosis, 32 were HIV negative with tuberculosis, 38 were HIV positive without tuberculosis, and 30 were HIV negative without tuberculosis. Overall men and women in the study population had similar age regardless of HIV status except among HIV positive individuals without

tuberculosis; men were significantly older than women 34.7 ± 6.5 (SD) versus 29.7 ± 8.4 (SD), respectively.

Among HIV positive and HIV negative patients with tuberculosis, men and women had comparable BMI whereas among HIV positive and HIV negative individuals without tuberculosis, women had significantly higher BMI compared to men (Table 7:1 and 7:2). Men had significantly higher fat-free mass and significantly lower fat mass compared to women regardless of tuberculosis and HIV status. Similarly, men had a higher magnitude of height-normalized FFMI and a lower height-normalized FMI compared to women regardless of tuberculosis and HIV status. Height-normalized FFMI and FMI eliminate differences in fat and fat-free mass associated with height (Baumgartner et al. 1998). Men with tuberculosis had significantly higher proportion of individuals with reduced FFMI compared to women regardless of HIV status (Table 7:1 and 7:2). For example among HIV positive patients with tuberculosis, 7 out of 10 (70%) for men had reduced FFMI compared to 2 out of 21 (10%) for women ($p<0.001$). The clinical TB severity score was comparable between men and women regardless of HIV status. Regardless of gender on multiple comparisons, we found no differences in average BMI, fat and fat-free mass, and tuberculosis clinical severity score between HIV positive patients with tuberculosis and HIV positive patients without tuberculosis, between HIV negative patients with tuberculosis and HIV negative individuals without TB, between HIV positive patients with tuberculosis and HIV negative patients with tuberculosis, and between HIV positive individuals without tuberculosis and HIV negative individuals without tuberculosis.

In general, there were no significant differences in average 24-hour dietary intake recall between men and women for most nutrients except average energy, protein, total fat, and folate among HIV negative individuals without tuberculosis; dietary fiber among HIV positive individuals without tuberculosis; magnesium and zinc intake among HIV negative patients with tuberculosis (Tables 7:3 and 7:4). Of note, however, men had a high magnitude of average dietary intake for most nutrients, for example energy intake was 2380 ± 703 for men versus 1598 ± 567 for women among HIV negative individuals without tuberculosis, 2027 ± 1111 for men versus 1437 ± 920 for women among HIV positive patients with tuberculosis (Table 7:3 and 7:4).

On average, BMI, fat mass, and height-normalized FMI were significantly lower among tuberculosis patients with reduced fat-free mass, reduced BMI, and moderate/severe TBscore compared to patients with normal fat-free mass, normal BMI, and mild TBscore. However, the average severity TBscore was significantly higher among patients with reduced fat-free mass, reduced BMI, and moderate/severe TBscore (Table 7:5 and 7:6). The average fat-free mass and height-normalized FFMI were similar between TB patients with mild and patients with moderate/severe TBscore. However, patients with mild TBscore had significantly higher proportion of individuals with reduced fat-free mass (16 out of 39 (41%)) compared to patients with moderate/severe TBscore (4 out of 24 (17%), $p < 0.05$) (Table 7:5 and 7:6).

Tuberculosis patients with moderate/severe TBscore had significantly lower average 24-hour dietary intake recall for average energy, protein, total fat, dietary fiber, calcium, vitamin A, and folate compared to patients with mild TBscore (Table 7:7 and 7:8). For example, energy intake among patients with moderate/severe TBscore was 1460 ± 722 compared to 2215 ± 940 among patients with mild TBscore. However, there were no significant differences in average 24-hour dietary intake recall between tuberculosis patients with reduced fat-free mass or reduced BMI and patients with normal fat-free mass or normal BMI (Table 7:7 and 7:8).

Discussion

In this cross-sectional study, we aimed to establish the relationship between dietary intake and body wasting; the independent effects of tuberculosis and HIV infection, and tuberculosis disease severity on dietary intake. In a study population of 131 HIV positive and HIV negative adults with/or without active tuberculosis from urban Uganda, we found that the 24-hour dietary intake recall varied by severity of tuberculosis disease, but not tuberculosis disease or HIV status. In the absence of tuberculosis, dietary intake varied by gender. The dietary intake differed by severity of clinical tuberculosis disease categories of mild and moderate/or severe disease. Men and women with tuberculosis had similar dietary intake regardless of HIV status. HIV negative women without tuberculosis had lower levels of dietary intake for energy, protein, and folate compared to HIV negative men without tuberculosis. Dietary intake did not differ by severity of nutritional status.

Findings of the present study suggest that in the face of tuberculosis disease, dietary intake is affected by severity of disease but not HIV infection; and there is no association with body wasting. While in the absence of tuberculosis, dietary intake is affected by gender, and not HIV infection. Tuberculosis patients that had moderate/or severe clinical disease had lower dietary intakes for energy, protein, total fat, carbohydrate, calcium, vitamin A, and folate compared to patients with mild disease. Both men and women had comparable dietary intake among patients with tuberculosis regardless of HIV status whereas HIV negative women had reduced energy, protein, and folate intake among individuals without tuberculosis compared to men. Tuberculosis patients with fat-free mass wasting or those with reduced BMI had comparable nutrient intakes with counterparts that had normal fat-free mass or normal BMI. To our knowledge, this is the first study to have evaluated the effect of tuberculosis disease severity on dietary intake and whether there are differences in dietary intake between HIV positive and HIV negative adults with tuberculosis. Our results are consistent with recent findings from India in which the study (Swaminathan et al. 2008) found comparable nutrient dietary intakes between HIV positive patients with tuberculosis and HIV positive individuals without tuberculosis. This study however, had no comparable group of HIV negative patients with tuberculosis to establish the synergist effect of tuberculosis and HIV infection. The strengths of our study hinges on the full panel of HIV positive and HIV negative adults with/or without tuberculosis. However, the study limited findings are limited by the cross-sectional nature of the design that the associations are not causal between differences between groups.

The present study demonstrated that dietary intake at the time of tuberculosis diagnosis was influenced by disease severity and in populations without tuberculosis was influenced by gender. Dietary intake differed by tuberculosis disease severity and not by tuberculosis disease or HIV status. While in populations without tuberculosis, nutrient intakes differed by gender particularly among HIV negative individuals. Women had reduced intakes for energy, protein, and folate. Despite high proportions of patients with body wasting as assessed by reduced fat-free mass (32% (20/63) with reduced fat-free mass) or BMI (56% (35/63) with reduced BMI), nutrient intakes were not associated with body wasting. Nutrient intakes were similar between individuals with wasting and those without. Two potential reasons can explain the findings in the present study. First, the disparity in reduced appetite between patients with mild clinical disease and those with moderate/or severe disease. Patients with moderate/or severe clinical disease present with marked low appetite that impends the nutrient intake other than barriers to food access. Further, the comparability of appetite level among men and women with tuberculosis, and among patients with/or without body wasting explains the gender and the wasting status similarity in nutrient intake. One can postulate that tuberculosis disease affects the appetite level equally in men and in women regardless of body wasting status, thus, compromising nutrient intake at nearly the same rate regardless of food access barriers. Thus, the gender differences in body composition during tuberculosis as revealed in the present and in previous reports (Mupere et al. 2010) could be explained by the differences in altered metabolism. Men generally, experience higher metabolic rate because of the larger quantities of fat-free mass compared to women (Arciero, Goran, and

Poehlman 1993) and during tuberculosis, this process is probably pronounced with associated wasting.

The gender differences in dietary intake among HIV negative individuals without tuberculosis could be explained by the cultural factors that may compromise intake among women. For example, unequal distribution of food within households (Carloni 1981; de Hartog A.P 1972), or men may have the opportunity to eat a wider variety or better quality foods outside the home, such as cafes or local restaurants (Holmboe-Ottesen G and Wandel M 1991). The unequal distribution of food within households result from several factors such as women may be trained to show restraint in eating, to give the best foods to men, or to allow others in the family to eat first (Lado 1992; O'Laughlin B 1974; Rosenberg E.M 1980; Dey J 1981).

To conclude, the study revealed that dietary intake at the time of diagnosis was influenced by tuberculosis disease severity, but not tuberculosis disease or HIV status and in the absence of tuberculosis was influenced by gender. Nutritional counseling and supplementation, early treatment and prevention of tuberculosis are needed to improve dietary intake in population of sub-Saharan Africa.

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Table 7:1 Select characteristics among HIV positive and HIV negative adults with tuberculosis

Characteristic [mean, (SD)]	**HIV positive with TB (n=31)**		**HIV negative with TB (n=32)**	
	Men (n=10)	Women (n=21)	Men (n=18)	Women (14)
Age in yr	30.9 (4.6)	29.2 (5.9)	26.0 (7.3)	26.3 (4.6)
BMI kg/m^2	18.4 (1.7)	18.6 (3.0)	18.2 (2.0)	20.3 (4.3)
BMI				
<18.5 kg/m^2 (%)	7 (70)	12 (57)	11 (61)	5 (36)
≥18.5 kg/m^2 (%)	3 (30)	9 (43)	7 (39)	9 (64)
Fat-free mass in kg	49.1 (4.5)	38.8 (3.2)[a]	49.1 (4.7)	39.9 (5.6)[a]
FFMI in kg/m^2	16.6 (1.3)	15.4 (0.9)[b]	16.6 (1.5)	16.1 (0.9)
FFMI				
<16.7 for M, <14.6 for W (%)	7 (70)	2 (10)[a]	11 (61)	0 (0)[a]
≥16.7 for M, ≥14.6 for W (%)	3 (30)	19 (90)	7 (39)	14 (100)
Fat mass in kg	5.2 (1.8)	8.3 (5.2)	4.8 (2.3)	10.5 (6.6)[b]

FMI in kg/m2	1.8 (0.6)	3.3 (2.1)	1.6 (0.8)	4.6 (3.6)[a]
FMI				
<1.8 for M, <3.9 for W (%)	5 (50)	14 (67)	11 (61)	8 (57)
≥1.8 for M, ≥3.9 for W (%)	5 (50)	7 (33)	7 (39)	6 (43)
Severity TBscore	6.5 (1.5)	5.6 (2.6)	6.8 (2.3)	5.9 (2.4)
Severity TBscore category				
Mild ≤5 (%)	2 (20)	10 (48)	6 (33)	6 (43)
Moderate/severe >5 (%)	8 (80)	11 (52)	12 (67)	8 (57)

[a]p-value <0.001, [b]p-value <0.05. BMI = body mass index, FFMI = fat-free mass index, FMI = fat mass index, SD = standard deviation, W = women, M = men.

Table 7:2 Select characteristics among HIV positive and HIV negative adults without tuberculosis

Characteristic [mean, (SD)]	**HIV positive, no TB (n=38)**		**HIV negative, no TB (n=30)**	
	Men (n=17)	Women (21)	Men (n=16)	Women (14)
Age in yr	34.7 (6.5)	29.7 (8.4)[b]	22.4 (3.2)	24.3 (5.4)
BMI kg/m^2	21.2 (2.2)	24.2 (4.6)[b]	21.6 (2.3)	23.7 (2.8)[b]
BMI				
<18.5 kg/m^2 (%)	2 (12)	5 (24)	1 (6)	1 (7)
≥18.5 kg/m^2 (%)	15 (88)	16 (76)	15 (94)	13 (93)
Fat-free mass in kg	53.0 (4.8)	39.8 (3.0)[a]	51.9 (3.9)	42.5 (4.9)[a]
FFMI in kg/m^2	18.3 (1.2)	16.6 (1.2)[a]	18.6 (1.4)	16.6 (1.1)[a]
FFMI				
<16.7 for M, <14.6 for W (%)	2 (12)	0 (0)	1 (6)	1 (7)
≥16.7 for M, ≥14.6 for W (%)	15 (88)	21 (100)	15 (94)	13 (93)
Fat mass in kg	9.1 (3.2)	17.8 (8.2)[b]	7.9 (2.5)	18.2 (5.4)[a]

FMI in kg/m2	3.2 (1.2)	7.6 (3.7)[a]	2.9 (1.0)	7.1 (2.1)[a]
FMI				
<1.8 for M, <3.9 for W (%)	3 (18)	5 (24)	1 (6)	1 (7)
≥1.8 for M, ≥3.9 for W (%)	14 (82)	16 (76)	15 (94)	13 (93)

[a]p-value <0.001, [b]p-value <0.05. BMI = body mass index, FFMI = fat-free mass index, FMI = fat mass index, SD = standard deviation, W = women, M = men.

Table 7:3 Dietary intake of 24-hour recall among HIV positive and HIV negative adults with tuberculosis

Characteristic [mean, (SD)][1]	**HIV positive with TB (n=31)**		**HIV negative with TB (n=32)**	
	Men (n=10)	Women (n=21)	Men (n=18)	Women (n=14)
Energy (kcal)	2027 (1111)	1437 (920)	2094 (831)	1567 (511)
Protein (g)	60.6 (48.6)	49.5 (44.2)	56.0 (29.5)	42.8 (22.3)
Total fat (g)	59.5 (60.2)	32.4 (38.4)	56.5 (38.9)	39.8 (24.9)
Carbohydrate (g)	303 (158)	245 (141)	348 (139)	269 (82)
Dietary fiber (g)	42.7 (32.9)	30.2 (22.5)	41.4 (23.2)	39.8 (25.0)
Protein, % energy	11.9 (6.5)	13.2 (8.5)	10.7 (2.1)	10.7 (3.7)
Fat, % energy	23.4 (13.8)	15.9 (9.4)	22.5 (10.4)	21.1 (8.5)
CHO, % energy	64.7 (16.5)	70.7 (13.8)	66.9 (10.2)	68.3 (9.9)
Calcium (mg)	978 (1532)	558 (1029)	297 (319)	264 (200)
Magnesium (mg)	267 (267)	261 (250)	302 (160)	176 (134)[b]
Zinc (mg)	7.7 (5.9)	5.6 (4.5)	6.9 (3.2)	4.4 (2.1)[b]
Iron (mg)	11.9 (12.5)	11.5 (12.6)	11.8 (8.2)	9.0 (5.4)

Vitamin A (RE)	469 (568)	493 (108)	545 (835)	779 (745)
Ascorbic acid (mg)	105 (64)	108 (140)	142 (159)	130 (80)
Vitamin D (μg)	1.1 (2.3)	1.0 (1.5)	0.6 (1.1)	0.6 (0.9)
Folate (μg)	300 (221)	315 (278)	346 (257)	375 (183)

[a]p-value <0.001, [b]p-value <0.05. CHO = carbohydrate, [1]Characteristic values are means ± standard deviation (SD). TB = tuberculosis

Table 7:4 Dietary intake of 24-hour recall among HIV positive and HIV negative adults without tuberculosis

Characteristic [mean, (SD)][1]	**HIV positive, no TB (n=38)**		**HIV negative, no TB (n=30)**	
	Men (n=17)	Women (21)	Men (n=16)	Women (14)
Energy (kcal)	1954 (699)	1651 (1105)	2380 (703)	1598 (567)[a]
Protein (g)	56.9 (34.5)	38.3 (24.8)	60.4 (21)	35.9 (16.3)[a]
Total fat (g)	47.2 (28.5)	34.0 (20.0)	60.7 (25.1)	38.2 (23.3)[b]
Carbohydrate (g)	333 (125)	301 (242)	416 (119)	274 (124)
Dietary fiber (g)	45.4 (27.8)	26.3 (16.8)[b]	40.1 (18.6)	23.3 (14.6)
Protein, % energy	11.2 (3.3)	9.7 (3.3)	9.8 (1.9)	8.9 (2.5)
Fat, % energy	20.8 (8.9)	19.9 (9.4)	21.4 (4.4)	20.5 (9.2)
CHO, % energy	68.0 (10.4)	70.6 (11.0)	68.7 (5.3)	67.7 (14.3)
Calcium (mg)	415 (414)	263 (404)	417 (454)	346 (406)
Magnesium (mg)	238 (204)	251 (336)	278 (181)	190 (150)
Zinc (mg)	7.1 (4.3)	5.7 (4.8)	7.2 (3.3)	3.8 (1.8)
Iron (mg)	11.1 (7.7)	11.5 (14.2)	12.4 (7.0)	7.0 (5.3)

Vitamin A (RE)	188 (238)	959 (1794)	936 (2716)	285 (314)
Ascorbic acid (mg)	129 (103)	142 (142)	144 (87)	86 (51)
Vitamin D (μg)	0.6 (1.2)	0.1 (0.4)	0.5 (0.8)	0.6 (0.8)
Folate (μg)	362 (174)	312 (190)	513 (218)	293 (148)[b]

[a]p-value <0.001, CHO = carbohydrate, [b]p-value <0.05. [1]Characteristic values are means ± standard deviation (SD). TB = tuberculosis

Table 7:5 Select characteristics among patients with/without wasting (n=63)

Characteristic [mean, (SD)]	Fat-free mass		BMI	
	Not wasted (n=43)	Wasted (n=20)	Not wasted (n=28)	Wasted (n=35)
Age in yr	28.1 (5.4)	27.4 (8.0)	28.0 (5.7)	27.8 (6.7)
BMI kg/m^2	19.8 (3.2)	16.9 (1.2)[a]	21.3 (2.8)	16.9 (1.3)[a]
BMI				
<18.5 kg/m^2 (%)	16 (37)	19 (95)[a]	-	-
≥18.5 kg/m^2 (%)	27 (63)	1 (5)	-	-
Fat-free mass in kg	42.2 (6.5)	46.2 (5.5)[b]	43.8 (7.3)	43.1 (5.7)
FFMI in kg/m^2	16.3 (1.4)	15.6 (0.8)[b]	16.8 (1.4)	15.5 (0.8)[a]
FFMI				
<16.7 for M, <14.6 for W (%)	-	-	1 (4)	19 (54)[a]
≥16.7 for M, ≥14.6 for W (%)	-	-	27 (96)	16 (46)
Fat mass in kg	8.8 (5.3)	4.1 (2.0)[a]	10.9 (5.3)	4.4 (2.2)[a]
FMI in kg/m2	3.6 (2.6)	1.4 (0.6)[a]	4.4 (2.8)	1.6 (0.9)[a]
FMI				

<1.8 for M, <3.9 for W (%)	20 (47)	5 (25)	7 (25)	31 (89)[a]
≥1.8 for M, ≥3.9 for W (%)	23 (53)	15 (75)	21 (75)	4 (11)
Severity TBscore	5.6 (2.2)	8.0 (7.5)[b]	5.0 (2.1)	7.1 (2.1)[a]

[a]p-value <0.001, [b]p-value <0.05. FFMI = fat-free mass index, FMI = fat mass index, BMI = body mass index, W = women, M = men, and SD = standard deviation. Fat-free mass wasting = FFMI <16.7 kg/m^2 for men and <14.6 kg/m^2 for women, BMI wasting = <18.5 kg/m^2 for men and women.

Table 7:6 Select characteristics among patients with/without severity of clinical tuberculosis

Characteristic [mean, (SD)]	Severity TBscore	
	Mild ≤5 (n=39)	Moderate/severe >5 (n=24)
Age in yr	28.0 (6.8)	27.7 (6.0)
BMI kg/m^2	20.2 (3.8)	18.0 (2.1)[b]
BMI		
<18.5 kg/m^2 (%)	24 (62)	11 (46)
≥18.5 kg/m^2 (%)	15 (38)	13 (54)
Fat-free mass in kg	43.2 (7.0)	43.6 (6.1)
FFMI in kg/m^2	16.3 (1.2)	15.9 (1.3)
FFMI		
<16.7 for M, <14.6 for W (%)	16 (41)	4 (17)[b]
≥16.7 for M, ≥14.6 for W (%)	23 (59)	20 (83)
Fat mass in kg	9.6 (6.2)	5.9 (3.5)[b]
FMI in kg/m2	4.0 (3.2)	2.2 (1.4)[b]

FMI		
<1.8 for M, <3.9 for W (%)	26 (67)	12 (50)
≥1.8 for M, ≥3.9 for W (%)	13 (33)	12 (50)
Severity TBscore	3.9 (1.3)	7.6 (1.6)[a]

[a]p-value <0.001, [b]p-value <0.05. FFMI = fat-free mass index, FMI = fat mass index, BMI = body mass index, W = women, M = men, and SD = standard deviation. Fat-free mass wasting = FFMI <16.7 kg/m^2 for men and <14.6 kg/m^2 for women, BMI wasting = <18.5 kg/m^2 for men and women.

Table 7:7 Dietary intake of 24-hour recall among tuberculosis patients with/without body wasting (n=63)

Characteristic [mean, (SD)][1]	Fat-free mass		BMI	
	Not wasted (n=43)	Wasted (n=20)	Not wasted (n=28)	Wasted (n=35)
Energy (kcal)	1680 (790)	1893 (1070)	1727 (702)	1763 (1018)
Protein (g)	50.3 (33)	54.5 (44.3)	52.4 (36.8)	51.0 (37.3)
Total fat (g)	39.4 (32.3)	57.8 (54.2)	39.1 (22.8)	50.2 (50.9)
Carbohydrate (g)	288 (138)	290 (137)	296 (140)	283 (135)
Dietary fiber (g)	37.6 (24.4)	37.4 (27.0)	37.7 (25.1)	37.3 (25.4)
Protein, % energy	12.0 (6.5)	11.1 (4.5)	12.1 (6.6)	11.5 (5.4)
Fat, % energy	18.8 (9.6)	23.1 (12.0)	19.8 (9.0)	20.5 (11.7)
CHO, % energy	69.2 (12.2)	65.9 (12.8)	68.3 (11.6)	68.1 (13.3)
Calcium (mg)	448 (759)	565 (1125)	529 (895)	450 (885)
Magnesium (mg)	244 (193)	279 (242)	254 (161)	255 (242)
Zinc (mg)	5.7 (3.4)	6.8 (5.3)	5.5 (2.5)	6.5 (5.0)
Iron (mg)	11.2 (9.4)	10.9 (11.4)	10.3 (7.2)	11.7 (11.8)

Vitamin A (RE)	559 (608)	519 (807)	588 (708)	514 (650)
Vitamin D (μg)	0.9 (1.6)	0.7 (1.2)	0.8 (1.7)	0.8 (1.2)
Ascorbic acid (mg)	121 (112)	125 (150)	123 (126)	121 (125)
Folate (μg)	351 (227)	298 (270)	330 (225)	338 (256)

[a]p-value <0.001, [b]p-value <0.05. [1]Characteristic values are means ± standard deviation (SD). FFMI = fat-free mass index, FMI = fat mass index, BMI = body mass index, W = women, and M = men. CHO = carbohydrate, Fat-free mass wasting = FFMI <16.7 kg/m^2 for men and <14.6 kg/m^2 for women, BMI wasting = <18.5 kg/m^2 for men and women.

Table 7:8 Dietary intake of 24-hour recall among tuberculosis patients with/without severe clinical TBscore (>5)

Characteristic [mean, (SD)][1]	Severe TBscore	
	Mild ≤5 (n=39)	Moderate/severe >5 (n=24)
Energy (kcal)	2215 (940)	1460 (722)[b]
Protein (g)	70.5 (46.4)	40 (20.6)[b]
Total fat (g)	61.6 (50.3)	35.2 (30.6)[b]
Carbohydrate (g)	348 (130)	252 (128)[b]
Dietary fiber (g)	42.4 (27.4)	34.5 (23.4)
Protein, % energy	12.5 (7.6)	11.3 (4.6)
Fat, % energy	21.8 (10.8)	19.1 (10.3)
CHO, % energy	65.7 (13.4)	69.7 (11.8)
Calcium (mg)	772 (1330)	308 (344)[b]
Magnesium (mg)	312 (245)	220 (177)
Zinc (mg)	7.2 (5.0)	5.3 (3.3)
Iron (mg)	12.5 (10.9)	10.2 (9.5)

Vitamin A (RE)	751 (798)	421 (555)[b]
Vitamin D (μg)	0.7 (1.2)	0.9 (1.6)
Ascorbic acid (mg)	151 (131)	105 (119)
Folate (μg)	452 (283)	262 (179)[b]

[a]p-value <0.001, [b]p-value <0.05. [1]Characteristic values are means ± standard deviation (SD). FFMI = fat-free mass index, FMI = fat mass index, CHO = carbohydrate, BMI = body mass index, W = women, and M = men. Fat-free mass wasting = FFMI <16.7 kg/m^2 for men and <14.6 kg/m^2 for women, BMI wasting = <18.5 kg/m^2 for men and women.

CHAPTER 8

CORRELATES OF DIETARY INTAKE AMONG HIV POSITIVE AND HIV NEGATIVE ADULTS WITH OR WITHOUT TUBERCULOSIS IN URBAN KAMPALA, UGANDA

Abstract

Background Although understanding nutritional intake is important in the management of tuberculosis, its assessment in clinical and in research practice is often overlooked.

Objective We sought to determine correlates of energy and protein intake, and correlates of inadequate dietary intake.

Methods In a cross-sectional study of 131 HIV positive and HIV negative adults with or without tuberculosis who were enrolled from urban Uganda; 24-hour dietary intake recall was assessed.

Results There was female gender interaction between having tuberculosis and reduced appetite, and between having tuberculosis and being a current alcohol taker in the model for energy intake. Women that had tuberculosis with reduced appetite or tuberculosis with history of taking alcohol had decreased energy intake. Also women who had history of alcohol intake had decreased protein intake. There was no compromise with energy and protein intake among men. Women were associated with inadequate iron intake. Further, women with tuberculosis were associated with inadequate folate intake. Individuals with tuberculosis residing in households of more than two people or those with no or low education were associated with inadequate vitamin A intake.

Conclusions The present study revealed that correlates of energy and protein intake differ by gender. Women and individuals having tuberculosis who reside in overcrowded households or who have no or low education are at vulnerable state of inadequate nutrient intake. Further studies are needed to evaluate changes in nutrient intake and the impact on survival.

Background

In sub-Saharan Africa, tuberculosis is the most common cause of death from a curable infectious disease (Frieden et al. 2003). The incidence of clinical tuberculosis has increased in sub-Saharan Africa due to the human immunodeficiency virus (HIV/acquired immune-deficiency syndrome (AIDS) pandemic (Harries et al. 2001; Lawn and Churchyard 2009), and despite adequate chemotherapy for tuberculosis, mortality is still high among those co-infected with HIV (Haller et al. 1999).

Tuberculosis and HIV infections are both independently associated with body wasting and malnutrition. The wasting may be caused by a combination of decreased appetite, leading to a decrease in energy intake, interacting with increased losses and altered metabolism as part of the inflammatory and immune responses (Paton et al. 1999; Paton et al. 2003; Macallan et al. 1998). Moreover, wasting leads to impaired physical function (Harries et al. 1988) and increased mortality in patients with tuberculosis (Mehta J.B et al. 1996; Rao et al. 1998; Zachariah et al. 2002; Mitnick et al. 2003). Although body wasting and malnutrition appear to separately play an important role in the clinical course of patients with tuberculosis and HIV and among those with co-infection, nutritional status and nutritional intake are often overlooked in clinical practice and in tuberculosis programs. Dietary intake studies are limited to characterize the nutritional intake, nutritional status and outcomes among patients with tuberculosis and HIV infection.

In the present cross-sectional study, we sought to determine correlates of energy and protein intake, and correlates of inadequate dietary intake in a population of HIV positive and HIV negative patients with or without tuberculosis enrolled from urban Kampala, Uganda.

Methods

In a cross-sectional study, we enrolled 132 participants age 18 years or older residing in Kampala district or 20 km from the study site if residence was outside Kampala in Uganda. Data collection was conducted between November 2007 and March 2008, a period that coincides with harvesting and light rains in November and December and dry season in January and February. One participant was excluded from the analysis because of prior tuberculosis treatment. The study was conducted at the National Tuberculosis and Leprosy Program (NTLP) Clinic of the national tertiary teaching hospital, Mulago complex. Of the 131 participants who were included in the analysis, 31 were HIV positive and 32 were HIV negative with tuberculosis and were recruited at the Mulago NTLP Clinic; 38 were HIV positive patients without tuberculosis and were recruited at the Infectious Disease Institute Clinic (IDI) located 500 meters from the Mulago NTLP Clinic; and 30 were HIV negative individuals without tuberculosis and were recruited from the community where enrolled tuberculosis patients resided. The institutional review boards at Case Western Reserve University and Joint Clinical Research Center approved the study, with final approval by the Uganda National Council for Science and Technology. All participants provided written informed consent to the study.

All subjects in the study were given appropriate pre- and post-test HIV counseling and AIDS education. HIV-1 infection was diagnosed on the basis of a positive enzyme-linked immunosorbent assay for HIV-1 antibodies (Recombigen; Cambridge Biotech, Cambridge, MA). At enrollment, basic demographic information and a medical history were collected, and a standardized physical examination was conducted by a medical officer. Active pulmonary TB was confirmed by sputum smear microscopy and culture. Patients with active TB were treated with standard four-drug chemotherapy for tuberculosis per guidelines of the Ugandan Ministry of Health. Similarly, HIV positive patients eligible for antiretroviral therapy were started on treatment and cotrimoxazole prophylaxis at the IDI clinic.

The dietary intake assessment was made using a single 24-hour dietary recall with open ended questions. The reference period for the 24-hour recall was the day prior to the day of the interview. In all instances, the interview was held only with the interviewee, no one else was present except for children. The questionnaire was pre-tested by administering it to 8 individuals selected randomly from the neighboring community to the study site. The assessment was conducted by four trained study nursing staffs and continuously supervised by a nutritionist using local food photographs, portion-size images, and volumetric vessels to increase the accuracy of the recall from the previous 24 hours. The nutritive value of raw ingredients was computed using the East African food composition table database whose database was imported into the NutriSurvey software (http:www.nutrisurvey.de) to easy the computations. The database used was predominantly for local Ugandan diet. When the East African food composition table was

found deficient in certain food items, the United States Department of Agriculture database and the African composition table were used.

To estimate the nutrient adequacy of the diet, we calculated the nutrient adequacy ratio (NAR) (%) for 11 micronutrients, energy, protein, fat, carbohydrate, and dietary fiber. The NAR for a given nutrient is the ratio of a participant's intake to the daily recommended allowance for the participant's sex. The Food and Agriculture Organization/World Health Organization 2002 Human Vitamin and Mineral requirements (FAO/WHO 2002) were used for vitamin A, vitamin B_6, vitamin C, vitamin D, thiamin, riboflavin, folate, magnesium, calcium, iron, and zinc whereas energy, fat, protein, carbohydrate, and dietary fiber; the Panel on Macronutrients, Panel on the Definition of Dietary Fiber, Submcommittee on Upper Reference Levels of Nutrients, Subcommittee on Interpretation and Uses of Dietary Reference Intakes Food and Nutrition Board (Dietary Reference Intake for Energy, Carbohydrate, Fiber, Fat, Fatty Acids, Cholesterol, Protein, and Amino Acids (Macronutrients). A report of the Panel on Macronutrients, Subcommittees on Upper Reference Levels of Nutrients and Interpretation and Uses of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes 2005) was used. The recommendation for adequate intake was used for vitamin D (Atkinson and Ward 2001). In the case of iron and zinc, the category for moderate bioavailability was used.

Analytic strategy

We performed bivariate, univariate, and multivariable analyses. Chi-square and Fisher's Exact tests were used to compare proportions. Fisher's Exact test was used when tabular counts were less than 5. Mann-Whitney test was used to compare dietary intake variables due to lack of normality. To determine the independent correlates of absolute energy and protein intakes, multivariable linear regression analyses including all variables that were associated with a $p < 0.50$ in the unadjusted analyses (Dales and Ury 1978). The following variables were evaluated in unadjusted analyses: older age group >30 years, having tuberculosis and HIV infection, no or low level (primary) of education, being separated or divorced, being single, having a household number of more than 2 people, unemployment, having no personal income, current history of alcohol intake, and reduced appetite were evaluated.

We controlled for body size by including height in the regression model for energy intake because half of the participants had tuberculosis which could in itself lead to changes in intake. Furthermore, height was correlated with energy intake. The results of the multi-regression analyses are presented along with the mean unadjusted intakes for each subgroup variable considered. We adjusted for energy intake in all regression analyses of protein intake to address the composition of the participant's diets, independent of absolute intake. The R square was used to establish variables that were important for the reduced models. The residuals of the final models were found to be normally distributed for energy and protein intake. We evaluated for two-way interactions between

tuberculosis or between HIV and all the important variables for both the energy and protein intake models. Significant interactions were found between tuberculosis and alcohol intake and between tuberculosis and reduce appetite in the energy intake model for women.

Correlates of dietary inadequacy, i.e., intakes less than the recommended daily allowance were identified with preliminary unadjusted analyses by using linear models with a log link function and binomial distribution for prevalence response variable (Wacholder 1986). All variables that showed a p-value <0.50 in the unadjusted analyses for energy, protein, vitamins A and D, folate, and zinc intakes were included in a multivariable full model (Mickey and Greenland 1989). The Quasi-likelihood Information Criteria (QIC) and Quasi-likelihood under the independence Criteria (QICu) goodness fit tests were used in choosing the best models that fit the data. The analysis was performed using SAS GENMOD procedure (SAS Institute 2003). We evaluated for two-way interactions between tuberculosis, between HIV, or between gender and all the important variables for models with energy, protein, vitamins A and D, folate, and zinc deficiency as main outcome. Significant interactions were found between female gender and reduced appetite for the model with protein deficiency, between tuberculosis and being more than people per household for the model with vitamin A deficiency, and between tuberculosis and gender for the model with folate deficiency as main outcomes. The prevalence ratios and 95% confidence intervals (CIs) for each of the independent correlates of dietary inadequacy on the basis of binomial regression models with log link function have been

reported in this paper (Mickey and Greenland 1989). All analyses were performed using SAS version 9.2 (Cary software, North Carolina SAS Institute Inc 2004).

Results

The characteristics of the study population are shown in Table 8:1. Of the 131 participants who were included in the analysis, 53% were females, 47% were males, 53% were HIV positive, and 48% had tuberculosis. Women and men differed significantly by employment and income. Women had a higher proportion of individuals who were unemployed and without income compared to men. However, men had higher a proportion of individuals who were single compared to women.

The variables that were correlated with energy and protein intakes at a significance level of $p < 0.50$ in the unadjusted analysis are shown in Tables 8:2 and 8:3. For each of these variables, the mean energy and protein intakes are shown. None of the bivariate energy means was significantly different among both women and men. Also the bivariate protein means were comparable among women. There were significant interactions between having tuberculosis and reduced appetite ($p=0.018$), and between having tuberculosis and being a current alcohol taker in the model for energy intake among women ($p=0.020$) (Table 8:2). Women that had tuberculosis and had reduced appetite or were current alcohol takers had decreased energy intake. Further, women who were current alcohol takers had decreased protein intake (Table 8:3). Energy and protein intakes were not

affected by any factor among men (Table 8:2 and 8:3). Of note, having HIV infection did influence energy and protein intakes regardless of gender.

The correlates of inadequate intakes of energy, protein, vitamin A and D, zinc, iron, and calcium are shown in Tables 8:4, 8:5, and 8:6. Intakes were considered inadequate if they were below the recommended daily allowance. Energy intake was inadequate in 73% (96/131) of the participants. Inadequate intakes of protein, vitamin A and D, zinc, iron, folate, and calcium were found in 60%, 74%, 98%, 56%, 86%, 63%, and 95% of participants, respectively. Women were strongly associated with inadequate protein and iron intakes whereas men were associated vitamin A inadequate intake (Table 8:4 and 8:5). Participants with no or low level of education and participants that were not married (singles), had inadequate vitamin A and iron intake, respectively. Furthermore, participants with reduced appetite were associated with inadequate vitamin A and folate intakes.

The multivariable analyses of the correlates of inadequate energy, protein, vitamins A and D, folate, and zinc intakes are shown in Table 8:6. The variables that correlated with inadequate intake for energy, protein, vitamins A and D, folate, and zinc at $p < 0.50$ in the unadjusted models were evaluated for their importance in the full model are presented in Table 8:6 together with results of the reduced models. No factor was found to influence inadequate energy intake. Being a female was significantly associated with inadequate vitamin A and iron intake, and being a female with reduced appetite was associated with

inadequate protein intake. Having no or low level of education and being more than two people per household in the face of tuberculosis were significantly associated with inadequate vitamin A intake. Further, being a female with tuberculosis and having reduced appetite were associated with inadequate folate intake. No factor influenced inadequate vitamin D and zinc intakes.

Discussion

We sought to determine correlates of energy and protein intake, and correlates of inadequate dietary intake in this cross-sectional study of 131 HIV positive and HIV negative adults with or without tuberculosis who were enrolled from urban Uganda. Correlates of energy and protein dietary intakes differed by gender. Protein intake among women was influenced by alcohol intake whereas energy intake among women with tuberculosis was influenced by reduced appetite or alcohol intake. Energy intake was not affected by any study variables. Gender, reduced appetite, level of education, and tuberculosis were important factors that were associated with inadequate intakes for vitamin A, iron, protein, and folate.

The caveats to the interpretation of results in the present study are not limited to the cross-sectional nature of the study but also use of a single 24-hour dietary recall in nutritional assessment that we cannot comment on the seasonal effects or habitual consumption. Findings in this study suggest the vulnerability of the female gender with compromised nutrient intake and are at worse state of inadequacy in nutrient intake

compared to male gender. Also individuals in overcrowded households and with no or low level of education in the face of tuberculosis are at worse state of nutrient inadequacy. There was female gender interaction between having tuberculosis and reduced appetite, and between having tuberculosis and being a current alcohol taker in the model for energy intake. Women that had tuberculosis with reduced appetite or tuberculosis with history of taking alcohol had decreased energy intake. Also women who had history of alcohol intake had decreased protein intake. There was no compromise with energy and protein intake among men. Women were associated with inadequate iron intake. Further, women with tuberculosis were associated with inadequate folate intake. Individuals with tuberculosis residing in households of more than two people or those with no or low education were associated with inadequate vitamin A intake.

The gender differences in correlates of energy and protein dietary intake in this study population suggests the cultural factors that may compromise intake among women. The vulnerability of individuals with tuberculosis residing in households of more than two people or those with no or low education to inadequate vitamin A intake reflects on the poverty level of the community. For example, unequal distribution of food within households (Carloni 1981; de Hartog A.P 1972), or men may have the opportunity to eat a wider variety or better quality foods outside the home, such as cafes or local restaurants (Holmboe-Ottesen G and Wandel M 1991). The unequal distribution of food within households result from several factors such as women may be trained to show restraint in

eating, to give the best foods to men, or to allow others in the family to eat first (Lado 1992; O'Laughlin B 1974; Rosenberg E.M 1980; Dey J 1981).

The present study revealed that correlates of energy and protein intake differ by gender. Women and individuals having tuberculosis who reside in overcrowded households or who have no or low education are at vulnerable state of inadequate nutrient intake. Further studies are needed to evaluate changes in nutritient intake and the impact on survival.

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Table 8:1 Characteristics of the study population (n=131)

Characteristics	All subjects (n=131)	Women (n=70)	Men (n=61)	p-value
	n (%)	n (%)	n (%)	
Age in years				
≤30	94 (72)	52 (74)	42 (69)	0.491
>30	37 (28)	18 (26)	19 (31)	
HIV status				
Negative	62 (47)	28 (40)	34 (56)	0.072
Positive	69 (53)	42 (60)	27 (44)	
Tuberculosis				
No	68 (52)	35 (50)	33 (54)	0.640
Yes	63 (48)	35 (50)	28 (46)	
Education				
None/primary level	69 (53)	29 (41)	33 (54)	0.147
Secondary level	62 (47)	41 (59)	28 (46)	
Tribe				

Muganda	57 (44)	30 (43)	27 (44)	0.872
Others	74 (56)	40 (57)	34 (56)	
Marital status				
Married	56 (43)	29 (41)	27 (44)	0.744
Single	75 (57)	41 (59)	34 (56)	
Household number				
One to two	40 (31)	17 (24)	23 (38)	0.100
>2 people	91 (69)	53 (76)	38 (62)	
Employed				
No	54 (41)	36 (51)	18 (30)	**0.011**
Yes	77 (59)	34 (49)	43 (70)	
Income				
Not at all	47 (36)	35 (50)	12 (80)	**<0.001**
Yes	84 (64)	35 (50)	49 (20)	
Takes alcohol				
No	98 (75)	51 (73)	47 (77)	0.581
Yes	33 (25)	19 (27)	14 (23)	

Appetite				
No	42 (32)	27 (61)	15 (75)	0.087
Yes	89 (68)	43 (39)	46 (25)	

Table 8:2 Correlates of dietary energy intake among women and men

Characteristics	**Women (n=70)**	**Multivariate model**	**Men (n=61)**	**Multivariate model**
	Mean (SD)	**Estimate (SE)**	**Mean (SD)**	**Estimate (SE)**
Age in years				
≤30	1437 (683)		2184 (849)	
>30	1815 (1153)	425.0 (235.0)	1976 (729)	-
HIV status				
Negative	1583 (530)		2229 (775)	
Positive	1544 (1010)	-	1981 (854)	-297.4 (234.8)
Tuberculosis				
No	1630 (917)		2161 (723)	
Yes	1489 (776)	698.3 (341.5)[b]	2070 (920)	-
Education				
Secondary level	1546 (950)		2121 (841)	
None/primary level	1579 (689)	-46.4 (209.9)	2117 (803)	110.7 (224.5)

Marital status				
Married	1731 (783)	-	2133 (863)	
Single	1439 (878)		2108 (786)	126.1 (231.6)
Household number				
One to two	13228 (974)		2080 (682)	
>2	1634 (797)	355.1 (239.3)	2143 (892)	-
Income				
Yes	1637 (796)		2087 (912)	
Not at all	1482 (899)	118.0 (204.5)	2127 (798)	-
Takes alcohol				
No	1491 (776)		2060 (813)	
Yes	1744 (1013)	682.9 (298.1)[b]	2319 (813)	238.7 (250.5)
Appetite				
Normal	1463 (989)		1862 (770)	
Reduced	1621 (749)	830.3 (498.8)	2203 (818)	-370.1 (250.0)
TB*reduced appetite	-	-425.2 (584.0)[b]	-	-

TB*alcohol intake	-	-1161.0 (484.5)[b]	-	-
R^2		0.28		0.10

[a]p-value <0.001, [b]p-value <0.05; bivariate p-values. Energy intakes were adjusted for height. Multivariate models show only those variables for which p < 0.50 in the unadjusted analyses.

Table 8:3 Correlates of dietary protein intake among women and men

Characteristics	**Women (n=70)**	**Multivaiate model**	**Men (n=61)**	**Multivariate model**
	Mean (SD)	Estimate (SE)	Mean (SD)	Estimate (SE)
Age in years				
≤30	36.6 (23.9)		59.0 (27.3)	
>30	52.1 (43.2)	3.0 (6.5)	56.1 (41.9)	-
Tuberculosis				
No	37.3 (21.6)		58.6 (28.4)	
Yes	46.8 (36.7)	10.5 (5.4)	57.6 (36.6)	-
Education				
No or primary level	45.5 (25.6)		60.0 (37.4)	
Secondary level	39.6 (33.3	-	56.0 (25.3)	-5.2 (5.0)
Tribe				
Muganda	37.8 (22.7)		60.9 (35.5)	
Others	45.3 (34.8)	-8.2 (5.5)	56.0 (29.7)	-

Marital status				
Married	45.2 (25.8)		61.0 (39.8)	
Single	39.9 (33.2)	-	55.9 (25.0)	3.4 (5.3)
Household number				
One to two	42.7 (47.1)		54.3 (18.7)	
>2	41.9 (23.1)	-	60.4 (38.2)	4.6 (5.6)
Takes alcohol				
No	44.7 (34.0)		58.3 (35.2)	
Yes	35.1 (15.0)	-13.9 (6.2)[b]	57.5 (20.0)	-
Appetite				
No	43.7 (34.1)		61.5 (31.2)[b]	
Yes	39.4 (23.4)	-	47.7 (33.9)	-4.1 (6.0)
R^2		0.50		0.67

[a]p-value <0.001, appetite (p=0.036) [b]p-value <0.05; bivariate p-values. Protein intakes were adjusted for energy intakes. Multivariate models show only those variables for which $p < 0.50$ in the unadjusted analyses.

Table 8:4 Proportions of adult individuals with inadequate dietary intakes of energy, protein, and micronutrients in relation to socio-demographic, HIV, and tuberculosis variables in Kampala, Uganda

Characteristics	Energy	Protein	Vitamins	
			A	D
Gender				
Female	50/70 (71)	48/70 (69)[b]	46/70 (66)[b]	69/70 (99)
Male	46/61 (75)	30/61 (49)	51/61 (84)	60/61 (98)
Age in years				
≤30	69/94 (73)	55/94 (59)	69/94 (73)	93/94 (99)
>30	27/37 (73)	23/37 (62)	28/37 (76)	36/37 (97)
HIV status				
Negative	43/62 (62)	36/62 (58)	47/62 (76)	62/62 (100)
Positive	53/69 (77)	42/69 (61)	50/69 (72)	67/69 (97)
Tuberculosis				
No	50/68 (74)	38/68 (56)	54/68 (79)	68/68 (100)
Yes	46/63 (73)	40/63 (63)	43/63 (68)	61/63 (97)

Education				
Secondary level	43/62 (69)	35/62 (56)	41/62 (66)[b]	61/62 (98)
None/primary level	53/69 (77)	43/69 (62)	56/69 (81)	68/69 (99)
Tribe				
Muganda	41/57 (72)	35/57 (61)	45/57 (79)	56/57 (98)
Others	55/74 (74)	43/74 (58)	52/74 (70)	73/74 (99)
Marital status				
Married	39/56 (70)	33/56 (59)	36/56 (64)[b]	55/56 (98)
Single	57/75 (76)	45/75 (60)	61/75 (81)	74/75 (99)
Household number				
One to two	32/40 (80)	55/91 (60)	60/91 (66)	90/91 (99)
>2	64/91 (70)	23/40 (58)	37/40 (93)	39/40 (98)
Employed				
Yes	59/77 (77)	47/77 (61)	58/77 (75)	75/77 (97)
No	37/54 (69)	31/54 (77)	39/54 (72)	54/54 (100)
Income				

Yes	64/84 (76)	51/84 (61)	63/84 (75)	82/84 (98)
Not at all	32/47 (68)	27/47 (57)	34/47 (72)	47/47 (100)
Takes alcohol				
No	73/98 (74)	57/98 (58)	71/98 (72)	96/98 (98)
Yes	23/33 (70)	21/33 (64)	26/33 (79)	33/33 (100)
Appetite				
Normal	62/89 (70)	48/89 (54)	71/89 (80)[b]	87/89 (98)
Reduced	34/42 (81)	30/42 (71)	26/42 (62)	42/42 (1000

[a]p-value <0.001, [b]p-value <0.05; bivariate p-values.

Table 8:5 Proportions of adult individuals with inadequate dietary intakes of energy, protein, and micronutrients in relation to socio-demographic, HIV, and tuberculosis variables in Kampala, Uganda

Characteristics	Minerals			
	Zinc	**Iron**	**Folate**	**Calcium**
Gender				
Female	41/70 (59)	66/70 (94)[b]	46/70 (66)	67/70 (96)
Male	33/61 (54)	47/61 (77)	36/61 (59)	57/61 (93)
Age in years				
≤30	51/94 (54)	81/94 (86)	56/94 (60)	90/94 (96)
>30	23/37 (62)	32/37 (86)	26/37 (70)	34/37 (92)
HIV status				
Negative	36/62 (58)	53/62 (85)	34/62 (55)	60/62 (97)
Positive	38/69 (55)	60/69 (87)	48/69 (70)	64/69 (93)
Tuberculosis				
No	38/68 (56)	58/68 (85)	39/68 (57)	65/68 (97)
Yes	36/63 (57)	55/63 (87)	43/63 (68)	59/63 (59)

Education				
Secondary level	37/62 (60)	51/62 (82)	40/62 (65)	59/62 (95)
None/primary level	37/69 (54)	62/69 (90)	42/69 (61)	65/69 (94)
Tribe				
Muganda	32/57 (56)	48/57 (84)	38/57 (67)	53/57 (93)
Others	42/74 (57)	65/74 (88)	44/74 (59)	71/74 (96)
Marital status				
Married	29/56 (52)	50/56 (89)	35/56 (63)	53/56 (95)
Single	45/75 (60)	63/75 (84)	47/75 (63)	71/75 (95)
Household number				
One to two	52/91 (57)	81/91 (89)	58/91 (64)	85/91 (93)
>2	22/40 (55)	32/40 (80)	24/40 (60)	39/40 (98)
Employed				
Yes	44/77 (57)	65/77 (84)	49/77 (49)	73/77 (95)
No	30/54 (56)	48/54 (88)	33/54 (61)	51/54 (94)
Income				
Yes	45/84 (54)	69/84 (82)	56/84 (67)	78/84 (93)

Not at all	29/47 (62)	44/47 (94)	26/47 (55)	46/47 (98)
Takes alcohol				
No	56/98 (57)	87/98 (89)	63/98 (64)	94/98 (96)
Yes	18/33 (55)	26/33 (79)	19/33 (58)	30/33 (91)
Appetite				
Normal	49/89 (55)	76/89 (85)	48/89 (54)[b]	85/89 (96)
Reduced	25/42 (60)	37/42 (88)	34/42 (81)	39/42 (93)

[a]p-value <0.001, [b]p-value <0.05; bivariate p-values.

Table 8:6 Correlates of inadequate dietary intakes of key nutrients from multivariate models among adult individuals in Kampala, Uganda

Characteristics	Full model[1]		Reduced model[2]	
	Prevalence ratio (95% CI)	**p-value**	**Prevalence ratio (95% CI)**	**p-value**
Inadequate energy intake				
HIV positive	1.07 (0.85, 1.34)	0.58	1.07 (0.85, 1.34)	0.58
No education/primary level	1.08 (0.87, 1.34)	0.62	1.08 (0.87, 1.34)	0.62
Single	0.91 (0.73, 1.14)	0.42	0.91 (0.73, 1.14)	0.42
>2 per household	0.91 (0.73, 1.14)	0.43	0.91 (0.73, 1.14)	0.43
No income	0.93 (0.73, 1.17)	0.52	0.93 (0.73, 1.17)	0.52
Reduced appetite	1.16 (0.94, 1.43)	0.16	1.16 (0.94, 1.43)	0.16
QIC	900.8		900.8	
Inadequate protein intake				
Female	1.34 (0.99, 1.81)	0.06	1.62 (1.08, 2.43)	**0.020**
Tuberculosis	0.97 (0.68, 1.40)	0.88	0.97 (0.68, 1.40)	0.88
No education/primary level	1.05 (0.79, 1.40)	0.73	1.06 (0.80, 1.40)	0.69

Single	1.29 (0.90, 1.85)	0.17	0.98 (0.74, 1.30)	0.87
Reduced appetite	0.96 (0.72, 1.28)	0.79	1.81 (1.81, 3.02)	**0.023**
Female*reduced appetite	-	-	0.59 (0.34, 1.03)	**0.063**
QIC	564.1		554.6	
Inadequate Vitamin A				
Female	0.80 (0.66, 0.98)	**0.029**	0.75 (0.61, 0.92)	**0.01**
Tuberculosis	0.95 (0.76, 1.18)	0.62	1.35 (1.04, 1.74)	**0.02**
No education/primary level	1.28 (1.05, 1.57)	**0.015**	1.28 (1.05, 1.56)	**0.01**
Other than Muganda	1.19 (0.98, 1.44)	0.08	1.16 (0.96, 1.40)	0.14
Single	0.84 (0.68, 1.04)	0.11	0.83 (0.68, 1.02)	0.08
>2 per household	0.77 (0.65, 0.92)	**0.004**	1.03 (0.79, 1.34)	0.84
Takes alcohol	1.00 (0.82, 1.24)	0.96	1.06 (0.87, 1.29)	0.57
Reduced appetite	0.83 (0.64, 1.09)	0.17	0.85 (0.66, 1.10)	0.23
TB*>2 per household	-	-	0.56 (0.39, 0.82)	**0.003**
QIC	929.8		919.0	
Inadequate folate				
Female	1.12 (0.85, 1.48)	0.42	1.57 (1.02, 2.42)	**0.04**

Age >30 years	1.13 (0.87, 1.47)	0.35	1.21 (0.91, 1.62)	0.19
HIV positive	1.17 (0.87, 1.58)	0.30	1.09 (0.83, 1.43)	0.52
Tuberculosis	0.99 (0.70, 1.39)	0.94	0.82 (0.64, 1.06)	0.13
No education/primary level	0.84 (0.65, 1.09)	0.19	0.99 (0.77, 1.27)	0.94
Other than Muganda	1.02 (0.79, 1.34)	0.83	0.73 (0.50, 1.09)	0.12
Single	0.94 (0.72, 1.22)	0.65	0.97 (0.75, 1.26)	0.81
No income	0.82 (0.60, 1.12)	0.21	0.83 (0.61, 1.13)	0.23
Reduced appetite	1.45 (1.03, 2.03)	**0.03**	1.48 (1.07, 2.04)	**0.02**
TB*female	-	-	1.92 (1.13, 3.28)	**0.02**
QIC	603.1		600.8	
Iron				
Female	1.20 (1.03, 1.40)	**0.02**	1.20 (1.03, 1.40)	**0.02**
Single	1.05 (0.91, 1.22)	0.49	1.05 (0.91, 1.22)	0.49
>2 people per household	1.03 (0.85, 1.25)	0.74	1.03 (0.85, 1.25)	0.74
Unemployment	0.91 (0.73, 1.13)	0.40	0.91 (0.73, 1.13)	0.40
No income	1.16 (0.93, 1.44)	0.20	1.16 (0.93, 1.44)	0.20
Takes alcohol	0.89 (0.75, 1.06)	0.19	0.89 (0.75, 1.06)	0.19

QIC	1800.4		1800.4	
Vitamin D				
HIV positive	0.95 (0.90, 1.01)	0.13	0.95 (0.90, 1.01)	0.13
Tuberculosis	0.92 (0.83, 1.03)	0.13	0.92 (0.83, 1.03)	0.13
No education/primary level	1.01 (0.97, 1.06)	0.57	1.01 (0.97, 1.06)	0.57
Unemployment	1.00 (0.98, 1.03)	0.81	1.00 (0.98, 1.03)	0.81
No income	1.03 (0.99, 1.08)	0.65	1.03 (0.99, 1.08)	0.65
Takes alcohol	1.02 (0.99, 1.04)	0.22	1.02 (0.99, 1.04)	0.22
Reduced appetite	1.09 (0.98, 1.22)	0.13	1.09 (0.98, 1.22)	0.13
QIC	16188.0		16188.0	
Inadequate zinc intake				
Age >30 years	1.24 (0.89, 1.72)	0.21	1.24 (0.89, 1.72)	0.21
No education/primary level	0.88 (0.65, 1.20)	0.43	0.88 (0.65, 1.20)	0.43
Single	0.86 (0.63, 1.17)	0.33	0.86 (0.63, 1.17)	0.33
No income	1.16 (0.86, 1.58)	0.33	1.16 (0.86, 1.58)	0.33
QIC	520.7	-	520.7	-

[1]The adjusted analyses first controlled for all variables that showed an association with inadequate intake of the outcome variable at $p < 0.50$ in unadjusted models. [2]Shows best model.

CHAPTER 9

IMPACT OF BODY WASTING ON SURVIVAL AMONG ADULT PATIENTS WITH PULMONARY TUBERCULOSIS IN URBAN KAMPALA, UGANDA

Abstract

Background Body mass index (BMI) may over estimate body wasting and mortality due to wasting because it is insensitive to body fatness at low BMI and above normal muscle development. We assessed the impact of HIV and body wasting on survival in tuberculosis patients using precise measures of nutritional status, the height-normalized fat-free mass (FFMI) and fat mass (FMI) indices.

Methods In a retrospective cohort study of adult patients, 310 patients with baseline wasting and 437 without wasting as measured by BMI (kg/m^2); 103 with baseline wasting and 208 without wasting as measured by fat-free mass index (kg/m^2); and 401 HIV positive and 346 HIV negative patients were followed for survival.

Results During the follow-up period, 19% of 310 patients with baseline wasting by BMI died compared to 11% of 437 without wasting, a crude risk ratio of 1.74 (95% confidence interval (CI): 1.22, 2.48). Of 103 with baseline wasting by fat-free mass index, 16% died, compared to 7% without wasting, crude risk ratio of 2.31 (95% CI: 1.10, 3.92). In stratified survival analysis, survival proportion was significantly lower among men with reduced BMI compared to men with normal BMI; and lower among women with reduced fat-free mass index compared to women with normal fat-free mass index. In multivariable Cox regression model using anthropometric data, the relative hazard of death when patient had reduced BMI was 1.85 (95% CI: 1.25, 2.73). In a nested model, the relative hazard for death was 1.70 (95% CI: 1.03, 2.81) for men with reduced BMI and 1.83 (95% CI: 0.96, 3.50) for women with reduced BMI. In a model using fat-free

mass index data, the relative hazard of death when patients had reduced fat-free mass index was 1.88 (0.96, 3.65). In a nested model, the relative hazard of death was 6.83 (95% CI: 2.14, 21.74) for women with reduced fat-free mass index compared to women with normal fat-free mass and 0.80 (95% CI: 0.35, 1.84) for men with reduced fat-free mass index. In Kaplan-Meier analysis, men had significantly lower survival compared to women (p=0.016) Cox regression analysis HIV positive men had 1.62 (95% confidence interval (CI): 1.05, 2.52) hazard of death compared to HIV positive women. HIV negative men had 0.57 (95% CI: 0.10, 3.31) hazard of death compared to HIV negative women.

Conclusion Findings show that body wasting is associated with reduced survival that differed by gender. BMI is a better predictor of death among men whereas fat-free mass index among women. There was gender differences in survival with poor outcomes among HIV positive men.

Background

Tuberculosis is among the foremost infectious cause of mortality worldwide. Globally, recent reports showed 9.2 million new cases and 1.7 million tuberculosis-associated deaths to have occurred in 2006 (Vitoria et al. 2009). In HIV-infected individuals, tuberculosis is the leading cause of death accounting for up to 11% of AIDS-related mortality worldwide (Corbett et al. 2003; Holmes et al. 2003). In sub-Saharan Africa where there is a high burden of both TB and human immunodeficiency virus (HIV) infection, case fatality rates for tuberculosis in HIV-infected patients are extremely high (up to 40%) (Corbett et al. 2003; Mugusi et al. 2009). Tuberculosis is frequently found at autopsy of acquired immunodeficiency syndrome (AIDS) patients (Lucas et al. 1993), particularly cachectic patients suggesting that tuberculosis exacerbates the wasting process of HIV-infected people in Africa.

Body wasting is regarded as a cardinal feature of tuberculosis. A significant proportion of African tuberculosis patients have a marked degree of wasting by the time they present for registration and treatment (Kennedy et al. 1996; Harries et al. 1988; Zachariah et al. 2002). Wasting associated with tuberculosis is likely caused by a combination of decreased appetite, leading to a decrease in energy intake, interacting with increased losses and altered metabolism resulting from the inflammatory and immune responses (Paton et al. 1999; Paton et al. 2003; Macallan 1999). Wasting is associated with impaired physical function (Harries et al. 1988), longer hospitalization days and

increased mortality in patients with tuberculosis (Rao et al. 1998; Zachariah et al. 2002; Mitnick et al. 2003). It has been reported that in patients with both TB and HIV co-infection, the wasting process is exacerbated (Macallan 1999; Lucas et al. 1994). In contrast, findings from several cross-sectional studies appear to show no large differences in body composition between HIV-infected adults with tuberculosis and HIV-negative adults with tuberculosis at presentation (Shah et al. 2001; Niyongabo et al. 1999; Niyongabo et al. 1994; Mupere et al. 2010) suggesting that TB is the dominant factor inducing wasting. This has been shown in several reports (Mupere et al. 2010; Paton and Ng 2006). However, gender differences in body composition at presentation among TB patients have been reported (Kennedy et al. 1996; Mupere et al. 2010).

Although the association of malnutrition with tuberculosis, and its impact on co-infection with tuberculosis and HIV has been described (Macallan 1999; van Lettow, Fawzi, and Semba 2003) in clinical settings and in several studies that have evaluated mortality in tuberculosis (Zachariah et al. 2002; Mugusi et al. 2009), the extent of wasting has been assessed using body mass index (BMI). However, BMI is insensitive to body fatness, particularly at low BMI, as well as with above-normal muscle development (Kyle, Genton, and Pichard 2002; Kyle, Piccoli, and Pichard 2003). Thus, previous estimates of mortality between malnourished and individuals with normal nutrition might have been overestimated. Furthermore, the confounding effects of gender and HIV infection on survival among tuberculosis patients using precise estimates of body composition have not yet been described. Fat and fat-free mass body composition measurements have been shown to permit a more precise evaluation of nutritional status (VanItallie et al. 1990;

Kyle, Piccoli, and Pichard 2003). Bioelectrical impedance analysis (BIA) has been recommended as the practical and precise method for clinical assessment of fat and fat-free mass (Kyle et al. 2004; Kyle, Genton, and Pichard 2002). In this study, we evaluated the impact of body wasting using fat and fat-free mass and BMI as measures of body wasting; and the impact of HIV infection on survival among patients with pulmonary tuberculosis. Our results show for the first time gender differences of observed survival using fat-free mass.

Methodology

Study Design

We conducted a retrospective cohort study that consisted of 753 adult pulmonary tuberculosis patients having confirmed HIV status and defined baseline body wasting or not using the completed five year Household Contact (HHC) study, the completed phase II prednisolone double blind randomized placebo controlled clinical trial, and the ongoing Kawempe Community Health (KCH) study. Of the 753 patients, 314 were enrolled into the HHC, 344 into the KCH, and 95 into the placebo arm of the prednisolone clinical trial. The HHC and KCH studies were observational epidemiologic studies; organized and conducted by the Makerere University and Case Western Reserve University tuberculosis research collaboration (Uganda-CWRU) that has been ongoing for the last 20 years in Uganda. The HHC was the initial household contact study from 1995 to 1999 that described the epidemiology of tuberculosis in urban Kampala, Uganda (Guwatudde et al. 2003). The subsequent KCH started in 2002 and is still ongoing (Stein et al. 2005).

The KCH was developed specifically to focus on the determinants of host factors associated with primary infection, re-infection, reactivation, and progression of clinical disease and to identify and track individual strains of mycobacterial tuberculosis through Ugandan households and local community. The phase II clinical trial was conducted between 1995 to 2000 to determine whether immunoadjuvant prednisolone therapy in HIV-infected patients with tuberculosis who have CD4(+) T cell counts >/=200 cells/ mu L is safe and effective at increasing CD4(+) T cell counts.

The institutional review boards at Case Western Reserve University in the United States and Joint Clinical Research Center in Uganda reviewed the protocol and final approval was obtained from the Uganda National Council for Science and Technology. All patients in the HHC and KCH had written informed consent to be enrolled in the study. All participants in both HHC and KCH were given appropriate pre- and post-test HIV counseling and AIDS education. HIV-1 infection was diagnosed on the basis of a positive enzyme-linked immunosorbent assay for HIV-1 antibodies (Recombigen; Cambridge Biotech, Cambridge, MA). HIV-seropositive participants who were newly identified with HIV were not on antiretroviral therapy at the time of measurement; no patients with pre-existing HIV infection at the time of household evaluation were on antiretroviral therapy because patients were enrolled before the advent of antiretroviral therapy in Uganda. During follow-up, patients who became eligible were started on antiretroviral therapy.

At enrollment, basic demographic information and a medical history were collected, and a standardized physical examination was conducted by a medical officer. Active tuberculosis was confirmed by sputum smear microscopy and culture. Patients with active tuberculosis were treated with standard four-drug chemotherapy for tuberculosis per guidelines of the Ugandan Ministry of Health. Adults with a previous history of treated pulmonary tuberculosis were excluded in the study. Of the 753 participants who were enrolled in the three studies, 6 were excluded because of being below 18 years of age, leaving 747 participants in total available for anthropometric analysis.

The datasets for the three studies were first tested for differences in baseline characteristics before combining for analysis. The datasets were different regarding extent of tuberculosis disease on chest x-ray because the phase II prednisolone trial enrolled only HIV-associated tuberculosis patients with CD4 cell count >200 cells/l compared to HHC and KCH studies (Appendix, Table 13:1). One of our interests was to establish the confounding effect of HIV; therefore, we combined all the three datasets for analysis. The BIA data (specifically, fat-free mass and fat mass) were collected during the KCH study only. Of the 344 participants who were enrolled in KCH, 33 were excluded due to lack of BIA measurements (n=29) data and being below 18 years of age (n=4), leaving 311 participants in total available for BIA analysis. However, there were no differences in baseline age, gender, weight, height, BMI, smoking status, hemoglobin, chest x-ray disease extent, and history of weight loss between participants who were included and those who were excluded.

Measurements

In all the three studies, socio-demographic and clinical information was obtained through standardized interviews and physical examination performed by trained medical officers. Venous blood was collected for HIV-1 enzyme immunoassay testing and complete blood and differential counts. HIV infection was documented by enzyme-linked immunosorbent assays. All participants had posterior-anterior chest X-rays taken at baseline. Expectorated sputum specimens were collected, concentrated, and stained for acid fast bacilli (AFB) with Ziehl-Neelsen stain at the Wandegeya national reference laboratory in Uganda. AFB smears were reviewed by trained technicians who graded the smears by the number of acid-fast organisms seen on the light microscopy according to criteria established by the WHO (International Union Against Tuberculosis and Lung Disease 1986). Specimens were cultured for mycobacteria tuberculosis on Lowenstein-Jensen medium slants, incubated at 37^0C in air and examined weekly until positive or for 8 weeks.

Nutritional status was assessed using anthropometric measurements such as height and weight and BIA Detroit, MI, RJL Systems. Body weight was determined to the nearest 0.1 kg using a SECA adult balance, and standing height was determined to the nearest 2 mm. Body-mass index (BMI) was computed using the relationship of weight in kilograms divided by height in meters squared (kg/m^2). All BIA measurements were performed by one trained observer using the same equipment and recommended standard conditions with regard to body position, previous exercise, dietary intake, skin

temperature, and voiding of the bladder were taken into consideration in taking BIA measurements (Kyle et al. 2004). All BIA measurements during the KCH study were performed on the day patients were confirmed to have tuberculosis disease.

The BIA is a simple, easy, safe, non-invasive technique, that has been recommended for nutritional studies in the clinical setting (Kyle et al. 2004; Kyle, Piccoli, and Pichard 2003) and is a convenient method to determine the lean or fat-free mass and fat body compartments (Kyle, Piccoli, and Pichard 2003; Kyle et al. 2004). Single-frequency BIA was performed at 50 kHz and 800 mA with standard tetrapolar lead placement (Jackson et al. 1988). Before performing measurements on each participant, the BIA instrument was calibrated using the manufacturer's recalibration device. The resistance and reactance were based on measures of a series circuit (Kotler et al. 1996). BIA measurements were performed in triplicate for each subject. Fat-free mass was calculated from BIA measurements using equations that were previously cross-validated in a sample of patients (white, black and Hispanic) with and without HIV infection (Kotler et al. 1996) and have been applied elsewhere in African studies (Villamor et al. 2006; Shah et al. 2001; Van Lettow et al. 2004). Fat mass was calculated as body weight minus fat-free mass.

Exposure variable

Baseline body wasting was the main exposure. We used BMI and height-normalized indices (adjusted for height^2) of body composition that partition BMI into fat-free mass

index (FFMI) and fat mass index (FMI) (Schutz, Kyle, and Pichard 2002; VanItallie et al. 1990; Kyle, Piccoli, and Pichard 2003) to establish the body wasting status of participants. The FFMI and FMI have the advantages of compensating for differences in height and age (Kyle, Genton, and Pichard 2002). Also, the use of the FFMI and FMI eliminates some of the differences between population groups. We defined body wasting as patients having the low fat-free mass index (FFMI) and the low body fat mass index (FMI) corresponding to WHO BMI categories for malnutrition as previously reported (Table 9:1) (Kyle, Piccoli, and Pichard 2003). The FFMI <16.7 (kg/m^2) for men and <14.6 (kg/m^2) for women and the FMI <1.8 (kg/m^2) for men and <3.9 (kg/m^2) for women corresponds to a BMI of <18.5 kg/m2, the WHO cutoff for malnutrition (WHO Tech Rep 1995) among adults.

Table 9:1 Definitions of low and normal fat and fat-free mass index values for corresponding body mass index in adults

Characteristic	Low	Normal
Body mass index (BMI)[a]		
Women and men in kg/m^2	< 18.5	≥ 18.5
Fat-free mass index (FFMI)[b]		
Women in kg/m^2	< 16.7	≥ 16.7
Men in kg/m^2	< 14.6	≥ 14.6

Fat mass index (FMI)[b]		
Women in kg/m^2	< 1.8	≥ 1.8
Men in kg/m^2	< 3.9	≥ 3.9

[a]World Health Organization categories, sex independent (WHO Tech Rep 1995). [b]Kyle et al (Kyle, Piccoli, and Pichard 2003; Kyle et al. 2003).

Study outcome variable

Observed survival was the main study outcome. We defined observed survival as the period between enrollment in the study and death or censoring. Participants for the three studies were censored at the last clinic visit when they were known to be alive or at the end of the study observation. During the conduct of the three studies at the Makerere University-Case Western Reserve University research collaboration, mortality was assessed through a standard interview of family members or review of hospital records. When a participant failed to keep a scheduled visit, the health visitor made a visit to the participant's home to determine the vital status of the study participant. The family members also provided the date of death and prominent symptoms at the time of death.

Statistical analysis

Baseline characteristics for both participants with and participants without baseline wasting were compared using the χ^2 test or Fisher's exact test (where tabular counts were less than 5) for binary data and student's t-test for continuous variables or Wilcoxon-

Mann Whitney test for variables not normally distributed. Concordance in estimating wasting between the BMI cut-off of <18.5 kg/m2 and the FFMI cut-off of <16.7 (kg/m^2) for men and <14.6 (kg/m^2) for women, and the concordance in estimating wasting between BMI cut-off level and the FMI cut-off of <1.8 (kg/m^2) for men and <3.9 (kg/m^2) for women was assessed using kappa, κ. Where κ = 0 represents no agreement, 0.- 0.2 represents slight agreement, 0.2 – 0.4 represents fair agreement, 0.4 – 0.6 represents moderate agreement, 0.6 – 0.8 represents substantial agreement, and 0.8 – 1.0 represents almost perfect agreement, beyond chance (McGinn et al. 2004).

Mortality rates were estimated and stratified according to sex, young and old age group, HIV status, anemia, smoking status, alcohol intake status, history of weight loss, and presence or absence of moderate/ or far advanced disease extent on chest X-ray. The incident rate of death was estimated using person-years method for the study population. The overall distributions of survival for participants presenting with or without body wasting were estimated using the Kaplan-Meier method and compared using the log-rank test (Kaplan E.I and Meier P 1958). Overall the observed range of the data, the probabilities of death did not reach 50% so the median time from diagnosis of tuberculosis with body wasting as assessed by reduced BMI and FFMI to death could not be estimated.

A series of Cox proportional hazards models (Hosmer D.W.Jr and Lemeshow S 1999) were fit after testing for the proportional hazards assumptions for each variable. The

proportional hazards assumption was tested by graphical methods and goodness of fit Schoenfeld residuals (Appendix, Table 13:2). Observed survival was the depended variable in each model. The independent variables tested included age, sex, HIV status, presence or absence of anemia, smoking and alcohol intake status, presence or absence of history of weight loss, and presence or absence of moderate/or far advanced tuberculosis disease extent on chest X-ray. Variables that were associated with survival in a univariate analysis with $p < 0.30$ or with biological plausibility were evaluated in a series of multivariable models.

All two-way interactions between baseline body wasting status as measured by reduced BMI or FFMI and the main effects were compared; the only significant interaction was with sex in the models involving FFMI variable for body wasting status. Furthermore, in our previous study (Mupere et al. 2010) we found that there are gender differences in body composition among patients with pulmonary tuberculosis. Thus, we developed separate stratified Cox models for participants according to sex status. Using a chunk wise test, interactions with sex, HIV, and age were found to be important in the model for reduced BMI whereas sex, age, and hemoglobin were important in the model for reduced FFMI. Hence separate stratified Cox regression models were performed according to HIV status and according to young (≤30 years) or older (>30 years) age groups to understand the independent effect of HIV and age on hazard of death. All variables fulfilled the proportional hazard assumption within the gender, HIV status, and age group strata. Models were compared using -2 log likelihood tests. All analyses were performed using SAS version 9.1.3 (Cary software, North Carolina SAS Institute Inc. 2000 – 2004).

Results

Descriptive statistics

Of the 747 patients who were included in the anthropometric data analysis, 395 (53%) were men and 352 (47%) were women; 401 (54%) were HIV positive, 345 (46%) were HIV negative, and 1 had unknown HIV status; and the mean age was 30.8 ± 8.9 SD years. Women had significantly higher BMI (20.3 ± 3.3 versus 18.6 ± 2.1) compared to men (Table 9:2). Of the 311 patients included in the BIA analysis, 164 (53%) were men and 147 (47%) were women; 138 (45%) were HIV positive, 172 (55%) were HIV negative, and 1 had unknown HIV status; and the mean age was 29.9 ± 9.2 SD years. Women had significantly lower FFMI (15.8 ± 1.1 versus 16.6 ± 1.4) and significantly higher FMI (4.4 ± 2.8 versus 2.0 ± 0.8) compared to men (Table 9:2). Among men, FFMI had a strong positive correlation with BMI whereas among women, FMI had a strong positive correlation with BMI. These gender differences in body composition and correlation with BMI reflect on the high fat body content among women and the high fat-free mass among men as previously reported (Mupere et al. 2010). Furthermore, the strengths of correlation between BMI and FMI suggest that BMI is a measure of body fatness.

Among women, there was fair concordance [$\kappa = 0.34$, (95% CI: 0.18, 0.50)] between FFMI (women <14.6 kg/m^2) and BMI (<18.5 kg/m^2) cut-off for assessing body wasting with 34% of the women having both reduced FFMI and BMI whereas among men there was moderate concordance [$\kappa = 0.57$, (95% CI: 0.45, 0.69)] with 80% of participants

having both reduced FFMI (for men <16.7 kg/m^2)) and BMI (<18.5 kg/m^2) (Table 9:3). Fat mass index (FMI <3.9 kg/m^2) and BMI cut-off for body wasting among women had substantial concordance [$\kappa = 0.61$, (95% CI: 0.49, 0.73)] with 100% of participants having both reduced FFMI and BMI whereas among men, the concordance was moderate [$\kappa = 0.52$, (95% CI: 0.39, 0.65)] with 64% of participants having both reduced FMI (<1.8 kg/m^2) and BMI (Table 9:3). Of the 747 patients who were included in the anthropometric data analysis, 310 (42%) had body wasting at presentation and 437 (58%) no wasting based on BMI cut-off of < 18.5 kg/m^2 for both men and women. In the study population of 311 participants that had BIA measurements, 103 (33%) had body wasting at presentation and 208 (67%) no wasting using FFMI cut-off of <16.7 kg/m2 for men and <14.6 kg/m2 for women. Whereas using FMI cut-off of <3.9 kg/m^2 for women and for <1.8 kg/m^2 for men, 135 (43%) had baseline wasting and 176 (57%) had no wasting.

Baseline characteristics

Men had a higher frequency of reduced BMI and FFMI compared to women at presentation (Table 9:4). For example men had a proportion of 63% (194/310) for reduced BMI compared to 37% (116/310) among women. Men had a proportion of 80% (82/103) of reduced FFMI compared to 20% (21/103) in women. Patients who presented with anemia (hemoglobin ≤10 mg/dl), history of prior smoking and current alcohol intake had a lower frequency of reduced BMI and FFMI. Patients who presented with moderate/far advanced disease on chest x-ray and history of weight loss had a higher frequency of reduced BMI and FFMI (Table 9:4). Of note, there were no differences in

body wasting at presentation between HIV positive and HIV negative tuberculosis patients regardless of whether BMI, FFMI, and FMI cut-off was used in assessing wasting (Appendix, Table 13:3). This suggests the lack of HIV impact on tuberculosis body wasting as previously reported (Mupere et al. 2010). HIV positive patients had a significantly higher frequency of older individuals (64% (200/312) versus 46% (201/434)), anemic individuals (74% (89/121) versus 51% (173/342)), current alcohol intake (62% (174/279) versus 49% (226/466), and lower frequency of history of weight loss (51% (295/578) versus 64% (105/165)) than HIV negative patients at presentation.

Survival analysis

During the mean follow-up period of 31 ± 23 (SD) months for the anthropometric data, there were a total of 105 deaths. Of these 105 deaths, 76 occurred within the first 6 months during tuberculosis treatment, 18 occurred in the first year after completion of tuberculosis treatment at 6 months, and only 11 occurred more than one year after treatment. The overall annual mortality rate was 55.1 per 100 years of observation. The mortality rates were 393.6 per 100 person months of observation in the first 6 months, 326.9 per 100 person years of observation in the first year following treatment, and 6.0 per 100 person years of observation more than one year following treatment. Most deaths (n=99) occurred among tuberculosis patients with HIV infection. In addition to HIV status, wasting as measured by BMI was also common (n=58). Of the 310 patients who presented with reduced BMI ≤ 18.5 kg/m^2 19% died compared to 11% of the 437 patients

with normal BMI >18.5 kg/m^2, leading to a crude risk ratio of 1.74 (95%: CI, 1.22 – 2.48) (Table 9:5).

Among patients with reduced BMI, 32% of the 167 that had HIV infection died compared to 20% who died of the 234 that had HIV infection with normal BMI at presentation, leading to a relative risk of 1.61 (95% CI: 1.50, 2.27) (Table 9:5). Among HIV negative tuberculosis patients; however, the relative risk of death associated with body wasting at presentation was 7.06 (95% CI: 0.83, 59.81) compared with patients without wasting (Table 9:5). The relative risk of death associated with body mass wasting at presentation among tuberculosis patients increased significantly after stratifying by younger age group ≤30 years, hemoglobin >10 mg/dl, non-current alcohol intake status, and normal/or mild disease extent on chest x-ray (Table 9:5).

During the mean follow-up period of 26 ± 16 (SD) months for the BIA data, there were a total of 30 deaths. Of these 30 deaths, 15 occurred within the first 6 months during tuberculosis treatment, 13 occurred in the first year after completion of tuberculosis treatment at 6 months, and only 2 occurred more than one year after treatment. The overall annual mortality rate was 45.1 per 100 years of observation. The mortality rates were 141.4 per 100 person months of observation in the first 6 months, 283.3 per 100 person years of observation in the first year following treatment, and 3.3 per 100 person years of observation more than one year following treatment. Most deaths (n=29) occurred among tuberculosis patients with HIV infection.

In addition to HIV status, wasting as measured by FFMI was also common (n=16). Of the 103 patients who presented with reduced FFMI 16% died compared to 7% of the 208 patients with normal FFMI, leading to a crude risk ratio of 2.31 (95%: CI, 1.17 – 4.54) (Table 9:6). Among patients with reduced FFMI, 32% of the 47 that had HIV infection died compared to 15% who died of the 91 that had HIV infection with normal FFMI at presentation, leading to a relative risk of 2.07 (95%: CI, 1.10 – 3.92) (Table 6). However, co-infected patients with reduced FFMI had a higher mortality of 32% (15/47) compared to 15% (14/91) among co-infected patients with normal FFMI, leading to a relative risk of 2.07 (95% CI: 1.10, 3.92) (Table 9:6). The relative risk of death associated with body wasting at presentation among tuberculosis patients increased after stratifying by female sex, younger age group <30 years, anemia (hemoglobin ≤10 mg/dl), non-current smoking, and normal/or minimal disease extent on chest X-ray (Table 9:6). The relative risk of death associated with fat-free mass wasting at presentation among tuberculosis patients increased significantly after stratifying by female sex, normal/or mild extent of x-ray disease, anemia (hemoglobin ≤10 mg/dl), history of past smoking, and history of weight loss. The risk of death among women with fat-free mass wasting was dramatic with an estimate of 6.00 (95% CI: 2.14, 16.86) (Table 9:6).

Kaplan-Meier analysis

When we performed a Kaplan-Meier analysis using anthropometric data, the overall unadjusted survival for patients who presented with body wasting (BMI <18.5 kg/m^2) had significantly lower survival compared to patients who presented with normal nutrition

(BMI ≥ 18.5 kg/m^2) (p = 0.001, log-rank test). When the Kaplan-Meier analysis was stratified according to gender, survival proportion was significantly lower among men with reduced BMI <18.5 kg/m^2 at presentation compared to men with normal BMI ≥ 18.5 kg/m^2 at presentation (p = 0.033, log-rank test; Figure 9:1). For women with reduced BMI at presentation, the survival proportion was lower than women with normal BMI, but this difference was not statistically significant (p = 0.119, log-rank test; Appendix Figure 13:1).

When we performed a Kaplan-Meier analysis using the BIA data, the overall unadjusted survival for patients who presented with fat-free mass body wasting (FFMI <16.7 kg/m^2 for men and <14.6 kg/m^2 for women) had significantly lower survival compared to patients who presented with normal nutrition (FFMI ≥16.7 kg/m^2 for men and ≥14.6 kg/m^2 for women) (p = 0.016, log-rank test). When the Kaplan-Meier analysis was stratified according to sex, survival proportion was significantly lower among women with reduced fat-free mass (FFMI <18.5 kg/m^2) at presentation compared to women with normal fat-free mass (FFMI ≥14.6 kg/m^2) at presentation (p = 0.0004, log-rank test; Figure 9:2). For men with reduced FFMI at presentation, the survival proportion was not different from men who had normal FFMI (p = 0.647, log-rank test; Appendix Figure 13:2).

When we performed a Kaplan-Meier analysis according to sex status, men had significantly lower unadjusted survival compared to women (p=0.035, log-rank test;

Appendix Figure 13:3). When the Kaplan-Meier analysis was stratified according to HIV status, survival proportion was significantly lower among HIV positive men compared to HIV positive women (p = 0.016, log-rank test; Figure 9:3). For HIV negative men, the survival proportion was not different from HIV negative women (p = 0.937, log-rank test; Appendix Figure 13:4).

Cox Proportional Hazard Regression

In the univariate Cox proportional hazards model, the unadjusted relative hazard for death in patients with reduced BMI <18.5 kg/m^2 at presentation compared to patients who presented with normal BMI ≥18.5 kg/m^2 was 1.80 (95% CI, 1.23, 2.64). Similarly, the unadjusted relative hazard for death in patients with reduced FFMI (<16.7 kg/m^2 for men and <14.6 kg/m^2 for women) at presentation compared to patients who presented with normal FFMI (≥16.7 kg/m^2 for men and ≥14.6 kg/m^2 for women) was 2.34 (95% CI, 1.14, 4.80; Table 9:7). Furthermore, men, older age group >30 years, HIV positive status, anemia (hemoglobin ≤10 mg/dl), and history of weight loss at presentation were significantly associated with increased relative hazards of death (Table 9:7).

In multivariable Cox proportional hazards model for anthropometric data, after adjusting for age, HIV, current smoking status, history of weight loss, and chest X-ray disease extent, the relative hazard for death when patients had reduced BMI <18.5 kg/m^2 at presentation was 1.85 (95% CI, 1.25, 2.73; Table 9:8 and 9:9). Basing on our prior findings and the descriptive statistics presented in this paper that body composition differ

by gender (Mupere et al. 2010), we fitted separate nested Cox regression models with the same covariates according to gender (Table 9:9). Men with reduced BMI <18.5 kg/m^2 at presentation had a significantly 1.70 (95% CI: 1.03, 2.81) times greater relative hazard of death than men with normal BMI ≥18.5 kg/m^2. A 1.83 (95% CI: 0.96, 3.50) relative hazard of death was found among women presenting with reduced BMI compared to women presenting with normal BMI; however, this was not significant. The differences in the relative hazard of death suggest interaction across the gender stratum. Older patients >30 years of age among men presenting with reduced BMI also had significantly greater relative hazard of death compared to younger men. In addition, HIV positive and patients with history of weight loss presenting with reduced BMI had significantly greater relative hard of death compared to HIV negative and patients without history of weight loss regardless of gender, respectively (Table 9:9).

In a multivariable model with reduced BMI as main predictor and after adjusting for age, sex, prior smoking status, history of weight loss, and extent of disease on chest x-ray, patients with reduced BMI had a 1.75 (95% CI: 1.18, 2.60) times greater hazard of death compared to individuals with normal BMI. Among HIV positive patients in stratified Cox regression, individuals with reduced BMI had a significant 1.63 (95% CI: 1.09, 2.44) times greater hazard of death compared to individuals with normal BMI whereas among HIV negative patients, patients with reduced BMI had a 6.95 (95% CI: 0.78, 61.89) times greater hazard of death compared to patients with normal BMI (Table 9:10 and 9:11). This suggests interaction according to HIV status when patients present with/or without reduced BMI. There were also potential interactions according to gender, age group, and

prior history of smoking. HIV positive men, HIV positive older patients, and HIV positive patients with prior history of smoking had significant hazards of death compared to HIV positive women, HIV positive young patients, and HIV positive patients with no prior history of smoking (Table 9:11). The converse was true that HIV negative men, HIV negative older patients, and HIV negative patients with prior history of smoking had similar hazards of death compared to HIV negative women, HIV negative young patients, and HIV negative patients with no prior history of smoking. There were no significant interactions between the reduced BMI variable for wasting and all the variables adjusted for in the model (Appendix, Table 13:4). However, interactions with male sex, positive HIV status, and older age group were found to be important in the reduced BMI multivariable model (Appendix, Table 13:5).

In a multivariable model with reduced BMI as main predictor and after adjusting for HIV positive status, male sex, prior smoking status, history of weight loss, and extent of disease on chest x-ray, patients with reduced BMI had a 1.78 (95% CI: 1.20, 2.64) times greater hazard of death compared to patients with normal BMI. Among young patients in stratified Cox regression, individuals with reduced BMI had a significant 2.85 (95% CI: 1.41, 5.77) times greater hazard of death compared to individuals with normal BMI whereas among old patients, individuals with reduced BMI had a 1.39 (95% CI: 0.86, 2.24) times greater hazard of death compared to patients with normal BMI (Appendix, Tables 13:6, 13:7, 13:8, and 13:9). This also suggests interaction according to age group stratum of young (≤30 years) and old (>30 years) when patients present with/or without reduced BMI.

In the multivariable Cox proportional hazards model using reduced FFMI as main predictor after adjusting for age, HIV, and anemia (hemoglobin ≤10 mg/dl) the relative hazard for death when patients had reduced FFMI (<16.7 kg/m^2 for men and <14.6 kg/m^2 for women) at presentation was 1.88 (95% CI, 0.96, 3.65; Table 9:12 and 9:13). When sex, HIV, age, and hemoglobin were included in this model, there was a statistically significant interaction between patients presenting with reduced FFMI and gender [hazard ratio (HR), 0.122 (95% CI, 0.030, 0.56)]. Furthermore, basing on our prior findings that body composition differ by gender (Mupere et al. 2010), we fitted separate stratified Cox regression models with the same covariates according to gender (Table 9:13). Women with reduced FFMI <14.6 kg/m^2 at presentation had nearly 7 fold greater relative hazard of death than women with normal FFMI ≥14.6 kg/m^2. While men presenting with reduced FFMI <16.7 kg/m^2 had a protective hazard of death of 0.80 (95% CI, 0.35, 1.84) compared to men presenting with normal FFMI ≥16.7 kg/m^2, although this was not significant. Older patients >30 years of age among women presenting with reduced FFMI also had significantly greater relative hazard of death compared to young women. In addition, HIV positive patients presenting with reduced FFMI had significantly greater relative hazard of death compared to HIV negative patients regardless of gender (Table 9:13).

Interactions of reduced FFMI variable with HIV, age, and hemoglobin in the model were not significant; however, they were found to be important in the model (Appendix, Tables 13:12 and 13:13). In a multivariable model with reduced FFMI as main predictor and after adjusting for age, sex, and hemoglobin, individuals with reduced BMI had a

1.50 (95% CI: 0.73, 3.08) times greater hazard of death compared to individuals with normal FFMI. Among HIV positive patients in stratified Cox regression, individuals with reduced FFMI had a non-significant 1.50 (95% CI: 0.72, 3.12) times greater hazard of death compared to individuals with normal FFMI whereas among HIV negative patients, the hazard of death for presenting with reduced FFMI could not be estimated because of very events (Appendix, Tables 13:14 and 13:15). This suggests that HIV is not a confounder when patients present with/or without reduced BMI.

In a multivariable model with reduced FFMI as main predictor and after adjusting for HIV positive status, male sex, and hemoglobin, patients with reduced BMI had a non-significant 1.55 (95% CI: 0.76, 3.15) times greater hazard of death compared to patients with normal FFMI. Among young patients in stratified Cox regression, individuals with reduced FFMI had a non-significant 1.89 (95% CI: 0.55, 6.52) times greater hazard of death compared to individuals with normal FFMI. Similarly, among old patients, individuals with reduced FFMI had a non-significant 1.52 (95% CI: 0.63, 3.69) times greater hazard of death compared to patients with normal FFMI (Appendix, Tables 13:13 – 13:16). This also suggests that age is not a confounder when patients present with/or without reduced FFMI.

There was no significant relative hazard of death between fat mass body wasting and any of the main effect variables in both univariate, multivariable, and stratified Cox models.

Discussion

To our knowledge, this is the first study to report the effect of body composition on survival among tuberculosis patients and the involved gender differences. In this retrospective cohort study of adult patients with pulmonary tuberculosis in urban Uganda, body wasting as measured by reduced fat-free mass and body mass indexes was associated with reduced survival, but the effect varied according to gender of the patient. Among men with reduced BMI <18.5 kg/m^2 at diagnosis, the effect of body mass wasting was substantial whereas in women with reduced BMI, the effect was minimal. Among women with reduced fat-free mass index (FFMI <14.6 kg/m^2) at diagnosis, the effect of fat-free mass wasting was dramatic with a 7 fold risk of death whereas among men presenting with reduced FFMI, the effect on observed survival was protective. The current results indicate that reduced body mass is a predictor of survival among men whereas reduced fat-free mass is a predictor of survival among women and the effect of wasting is greatest early in the first year following diagnosis of tuberculosis. Fat mass wasting appears not to be predictor of survival regardless of gender.

This study found gender differences in the measures of body wasting and malnutrition and the corresponding effect on observed survival. Compared to FFMI, BMI was found to be a better measure of body wasting associated with the observed survival in men whereas FFMI was better measure in women. This appears to suggest that BMI may underestimate mortality in women whereas FFMI may underestimate mortality in men. A possible explanation stems from the fact that BMI is composed of both fat and fat-free

mass each of which influence BMI in the same direction concerning mortality as previously hypothesized (Allison et al. 1997). However, fat and fat-free mass may influence mortality in opposite directions; that is, fat-free mass may be protective and fat mass deleterious. Though BMI is monotonically related to adiposity (Garrow and Webster 1985), it also correlates positively with the amount of fat-free mass an individual has. In our study, BMI had a significant positive correlation of 0.85 in men and 0.58 in women. Thus, the inverse gender differences in fat and fat-free mass explains the differences in correlation. The high hazard of death reported in this study among men and among women may be an indicator of excessively low amount of fat mass in men and low amount of fat-free mass in women regardless of BMI. However, body fat mass wasting was not associated with risk of death regardless of among women and men.

The findings of the present appear to suggest that the effects of body wasting and malnutrition on tuberculosis are not apparent when there is no comorbidity, yet tuberculosis is associated with malnutrition (Macallan 1999; Schwenk A and Macallan D.C 2000). In the face of comorbidities such as HIV and anemia, the effects of body wasting and malnutrition become detectable because the force of mortality from comorbidity overwhelms the existing malnutrition. Results of the present study and similar to previous studies in sub-Saharan Africa (Shah et al. 2001; Zachariah et al. 2002), show that more than 30% of tuberculosis patients present with body wasting and malnutrition regardless of gender or HIV status, and whether BMI or BIA parameters were used in assessing nutritional status. Furthermore in the present study, there were no differences in body wasting between HIV positive and HIV negative patients at the time

of diagnosis suggesting that tuberculosis may be the driving factor in inducing the wasting process and the role of HIV is minimal. This finding is consistent with previous studies (Mupere et al. 2010; Paton and Ng 2006). However overtime in the present study, results revealed heterogeneity in the effects of HIV on survival in the presence of body wasting as measured by reduced BMI. Patients that presented with reduced BMI (<18.5 kg/m^2) and were HIV positive had a significant 1.63 (95% CI: 1.09, 2.44) hazard of death compared to patients that presented with normal BMI and were HIV positive. Yet there was minimal effect on observed survival among patients that presented with reduced BMI and were HIV negative. Malnutrition in itself is a cause of immunodepression (Hernandez-Pando, Orozco, and Aguilar 2009); thus, tuberculosis might worsen the course of HIV-associated immunodepression. These interrelated effects possibly explain the facts that both tuberculosis and malnutrition are associated with reduced survival among HIV-infected patients (Nunn et al. 1992; Suttmann et al. 1995).

In this study, more than 75% of deaths occurred early in the first year of follow-up. There are several potential reasons for the early deaths of tuberculosis patients in the present study. First, late presentation with severe and extensive tuberculosis; more than 75% of the participants had moderate/or far advanced disease on chest x-ray. Second, most (>90%) deaths were HIV-related; yet HIV-tuberculosis co-infection is associated with extra burden of nutritional alterations that may lead to poor outcomes. The extra burden on nutritional status may include increased energy expenditure, nutrient malabsorption, reduced intake, micronutrient malnutrition, and increased production of inflammatory cytokines with lipolytic and proteolytic activity (van Lettow, Fawzi, and Semba 2003;

Niyongabo et al. 1994; Melchior et al. 1993). Third, about 25% of the study population presented with anemia (hemoglobin ≤10 mg/dl); yet anemia is a life-threatening HIV-related complication that may be associated with poor outcome. Finally, wasting status at diagnosis; we have shown that body wasting regardless of whether assessed by BMI or fat-free mass index was associated with an increased hazard of death which could be early or late.

Findings in the present study show gender differences in survival and the survival was modified by HIV infection. HIV positive men had poor survival compared to HIV positive women; however, HIV negative men and HIV negative women had similar survival. Our findings suggest that in the face of co-infection, survival is poor among HIV positive men while in the absence of HIV, survival is similar by gender. Our findings are similar to previous studies of mortality in HIV-infected patients in Africa in which the rate of mortality was higher in men than in women (Lucas et al. 1993; Sani et al. 2006). Our study however, had a large sample size and a heterogeneous study population that included ambulatory and inpatients compared to previous studies (Sani et al. 2006; Lucas et al. 1993) enrolled only in-patients with probable advanced disease. The poor survival among HIV positive men could be due to delay in presentation for care among men. Prior studies have explained the late presentation among men to be due to a false sense of security concerning relative risk HIV infection (Luginaah, Yiridoe, and Taabazuing 2005). Further studies are needed to evaluate the socioeconomic and biologic factors that predispose HIV positive men to poor survival.

The caveat to the interpretation of findings in this study include 1) the method (BIA) used in measurement of body composition is not of reference standard like the dual-energy x-ray absorptiometry, 2) the BIA prediction method used has not yet been validated in the local population. As a result, findings of body composition may be biased because of variations in hydration across ethnic groups (Kyle et al. 2004). However, the equations that were used in this study were previously cross validated in individuals of different race (white, black, and Hispanic) among men and women, who were both healthy controls and HIV-infected patients (Kotler et al. 1996). Moreover, the equations have been used widely in other studies from Africa with meaningful findings (Shah et al. 2001; Van Lettow et al. 2004; Villamor et al. 2006; Mupere et al. 2010). We also took care to take measurements at rest, with proper placement of leads, in participants who had not exercised or taken alcohol, in participants with voided bladder and ambient temperature. However, measurements were in patients with underlying illness that may cause shifts in body water compartments, thereby affecting measurements of fat mass. Our findings also limited by the lack of dietary intake assessment to give further insight in the interpretation of gender differences in body composition and observed survival.

Despite the limitations of the present study, the strengths of this study are that a large number of patients were studied, long duration of follow-up period to observe survival, and assessing of nutritional status using both BMI and the precise measures of fat and fat-free mass.

The findings in this study indicate that body wasting exerts greatest effect on observed survival among tuberculosis patients with body wasting co-infected with HIV, and that BMI is a better predictor of death among men whereas FFMI is a better predictor of death among women. These observations provide evidence for the need to provide nutritional interventions among HIV co-infected patients with wasting and evaluation of nutritional status should be involve BMI, fat and fat-free mass.

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Table 9:2 Mean body mass, fat and fat-free mass indexes; spearman correlations between body mass index and fat or fat-free mass indexes among adult women and men in urban Uganda

Characteristic	Mean (SD)[a]		Correlations with BMI[b]	
	Women (n=147)	Men (n=164)	Women (n=147)	Men (n=164)
[1]BMI, kg/m^2	20.0 (3.3)	18.6 (2.1)	1	1
FFMI, kg/m^2	15.8 (1.1)	16.6 (1.4)	0.58	0.85
FMI, kg/m^2	4.4 (2.8)	2.0 (0.8)	0.92	0.68

BMI = body mass index, FFMI = fat-free mass index, FMI = fat mass index. [1]Three hundred fifty two women and 401 men were involved in estimation of mean BMI; [a]all p-values were <0.001 for mean differences between women and men; [b]all correlations between FFMI or FMI and BMI among women and men were significant with p-values <0.001.

Table 9:3 Concordance between low body mass index and low fat-free or fat mass indexes corresponding to body mass index in assessing wasting among adults in urban Uganda

Characteristic	Women		
	Normal BMI	[a]Reduced BMI	Kappa, κ (95% CI)
FFMI index kg/m^{2b}			
Reduced, n (%)	5/100 (5)	16/47 (34)	0.34 (0.18, 0.50)
Normal, n (%)	95/100 (95)	31/47 (66)	
FMI index kg/m^{2b}			
Reduced, n (%)	0/47 (0)	47/47 (100)	0.61 (0.49, 0.73)
Normal, n (%)	71/100 (71)	29/100 (29)	
	Men		
FFMI kg/m^{2b}			
Reduced, n (%)	15/76 (20)	61/76 (80)	0.57 (0.45, 0.69)
Normal, n (%)	71/92 (77)	21/92 (23)	
FMI kg/m^{2b}			

Reduced, n (%)	27/76 (36)	49/76 (64)	0.52 (0.39, 65)
Normal, n (%)	80/92 (87)	12/92 (13)	

FFMI = fat-free mass index, FMI = fat mass index, BMI = body mass index. [a]Reduced BMI = <18.5 kg/m^2. [b]Low FFMI for women <14.6 kg/m^2 and for men <16.7 kg/m^2; low FMI for women <3.9 and for men <1.8 kg/m^2.

Table 9:4 Baseline characteristics of pulmonary tuberculosis patients with normal versus malnutrition

Characteristic	Normal BMI (n=437)	Low BMI (n=310)	Normal FFMI (n=208)	Low FFMI (n=103)
	n (%)	n (%)	n (%)	n (%)
Sex				
Females	236 (54)	116 (37)[a]	126 (61)	21 (20) [a]
Males	201 (46)	194 (63)	82 (39)	82 (80)
Age (years)				
≤30	257 (59)	177 (57)	135 (65)	59 (57)
>30	1880 (41)	133 (43)	73 (35)	44 (43)
HIV status				
Negative	202 (46)	143 (46)	116 (56)	56 (54)
Positive	234 (54)	167 (54)	91 (44)	47 (46)
Hemoglobin (g/dl)[1]				
>10	216 (81)	126 (64)[a]	151 (76)	73 (74)

≤10	51 (19)	70 (36)	48 (24)	26 (26)
Fat mass index (kg/m^2)[2]				
Normal	149 (79)	27 (22)[a]	124 (61)	52 (51)
Low	39 (21)	95 (78)	79 (39)	49 (49)
Chest x-ray disease extent[3]				
Normal/mild	75 (17)	36 (12)[b]	39 (19)	10 (10)[b]
Moderate/far advanced	362 (83)	274 (88)	169 (81)	93 (90)
Smoker[4]				
No	374 (86)	219 (71)[a]	176 (85)	62 (60)[a]
Yes	61 (14)	90 (29)	31 (15)	41 (40)
Takes alcohol[5]				
No	266 (61)	201 (65)	151 (73)	64 (62)[b]
Yes	170 (39)	109 (35)	56 (27)	39 (38)
History weight loss[6]				
No	111 (26)	54 (17)[b]	38 (18)	13 (13)
Yes	324 (74)	255 (83)	168 (82)	90 (87)

[a]p-value <0.001, [b]p-value <0.05, FFMI = fat-free mass index, BMI = body mass index. [1]284 missed hemoglobin measurement due to lack of blood; [2]FFMI and FFMI was not measured; [3]eight missed extent variable; [4]three missed history of ever smoked; [5]one

missed history of alcohol intake; [6]four missed history of weight loss; FFMI low <16.7 kg/m^2 for men and <14.6 kg/m^2 for women, normal ≥ 16.7kg/m^2 for men, ≥14.6 kg/m^2 for women; low BMI <18.5 kg/m^2 for men and women.

Table 9:5 Stratified Analysis of mortality among tuberculosis with normal (≥18.5) and low (<18.5) body mass index (BMI kg/m^2) according to key variables [deaths/number at risk (%)]

Category	Normal BMI (n=437)	Low BMI (n=310)	RR of death (95% CI)
	n (%)	n (%)	
Deaths			
No	390 (89)	252 (81)	1.74 (**1.22, 2.48**)
Yes	47 (11)	58 (19)	
Sex			
Female	21/236 (9)	17/116 (15)	1.65 (0.90, 3.00)
Male	26/201 (13)	41/194 (21)	1.63 (**1.04, 2.56**)
Age group			
≤30 years	13/257 (5)	21/177 (12)	2.35 (**1.21, 4.56**)
>30 years	34/180 (19)	37/133 (28)	1.47 (0.98, 2.22)
HIV-serostatus[1]			
Negative	1/202 (0.5)	5/143 (3.5)	7.06 (0.83, 59.81)

Positive	46/234 (20)	53/167 (32)	1.61 (**1.5, 2.27**)
Hemoglobin[2]			
>10 mg/dl	13/216 (6)	17/126 (13)	2.24 (**1.13, 4.46**)
≤10 mg/dl	10/51 (20)	16/70 (23)	1.17 (0.58, 2.35)
Smoker[3]			
No	41/374 (11)	43/219 (20)	1.79 (**1.21, 2.66**)
Yes	6/61 (10)	14/90 (16)	1.58 (0.64, 3.89)
Takes alcohol[4]			
No	25/266 (9)	39/201 (19)	2.06 (**1.29, 3.30)**
Yes	22/170 (13)	19/109 (17)	1.35 (0.77, 2.37)
Weight loss[5]			
No	5/111 (5)	6/54 (11)	2.47 (0.79, 7.72)
Yes	42/324 (13)	52/255 (20)	1.57 (**1.08, 2.28**)
Chest x-ray extent[6]			
Normal/minimal	9/75 (12)	10/36 (28)	2.31 (**1.03, 5.19**)
Moderate/far advanced	38/357 (11)	48/271 (18)	1.66 (**1.12, 2.47**)

[1]One missed HIV status; [2]284 missed hemoglobin measurement due to lack of blood; [6]eight missed extent variable; [3]three missed history of ever smoked; [4]one missed history of alcohol intake; [5]four missed history of weight loss; low BMI <18.5 kg/m^2.

Table 9:6 Stratified Analysis of mortality among tuberculosis with normal and low fat-free mass index (FFMI kg/m^2) according to key variables [deaths/number at risk (%)]

Category	Normal FFMI (n=208)	Low FFMI (n=103)	RR of death (95% CI)
Deaths			
No	194 (93)	87 (84)	2.31 (**1.17, 4.54**)
Yes	14 (7)	16 (16)	
Sex			
Female	6/126 (5)	6/21 (29)	6.00 (**2.14, 16.86**)
Male	8/82 (10)	10/82 (12)	1.25 (0.52, 3.01)
Age group			
≤30 years	5/135 (4)	5/59 (8)	2.29 (0.69, 7.61)
>30 years	9/73 (12)	11/44 (25)	2.03 (0.91, 4.50)
HIV-serostatus[1]			
Negative	0/116 (0)	1/56 (1.8)	-
Positive	14/91 (15)	15/47 (32)	2.07 (**1.10, 3.92**)

Hemoglobin[2]			
>10 mg/dl	8/160 (5)	7/77 (9)	1.82 (0.68, 4.83)
≤10 mg/dl	6/48 (13)	9/26 (35)	2.79 (**1.11, 6.92**)
Smoker[3]			
No	12/176 (7)	11/62 (18)	2.60 (**1.21, 5.59**)
Yes	2/31 (6)	5/41 (12)	1.89 (0.39, 9.10)
Takes alcohol[4]			
No	10/151 (7)	9/64 (14)	2.12 (0.91, 4.98)
Yes	4/56 (7)	7/39 (18)	2.51 (0.79, 8.00)
Weight loss[5]			
No	2/38 (5)	0/13 (0)	-
Yes	12/168 (7)	16/90 (18)	2.49 (**1.23, 5.03**)
Chest x-ray extent[6]			
Normal/minimal	2/39 (5)	5/10 (50)	9.75 (**2.21, 43.06**)
Moderate/far advanced	12/164 (7)	11/93 (12)	1.62 (0.74, 3.52)

[1]One missed HIV status; [2]15 missed hemoglobin measurement due to lack of blood; [6]eight missed extent variable; [3]one missed history of ever smoked; [4]one missed history of alcohol intake; [5]four missed history of weight loss; FFMI low (<16.7 kg/m^2 for men and <14.6 kg/m^2 for women, normal (≥ 16.7kg/m^2 for men, ≥14.6 kg/m^2 for women).

Table 9:7 Univariate Analysis of factors associated with survival

Characteristic	Deaths/N (%)	Relative hazard (95% CI)
Fat-free mass index (kg/m^2)[a]		
Normal	14/208 (7)	1
Low	16/103 (16)	2.34 (**1.14, 4.80**)
Fat mass index (kg/m^2)[a]		
Normal	16/176 (9)	1
Low	14/135 (10)	1.23 (0.60, 2.52)
Body mass index (kg/m^2)		
Normal	47/437 (11)	1
Low	58/310 (19)	1.80 (**1.23, 2.64**)
Sex		
Female	38/352 (11)	1
Male	67/395 (17)	1.66 (**1.12, 2.48**)
Age (years)		
≤30	34/434 (8)	1

>30	71/313 (23)	3.15 (**2.09, 4.74**)
HIV-serostatus[1]		
Negative	6/345 (2)	1
Positive	99/401 (25)	16.24 (**7.13, 37.02**)
Hemoglobin (g/dl)[2]		
>10	30/342 (9)	1
≤10	26/121 (21)	1.63 (**1.00, 2.69**)
Smoker[3]		
No	84/593 (14)	1
Yes	20/151 (13)	0.98 (0.60, 1.60)
Takes alcohol[4]		
No	64/467 (14)	1
Yes	41/279 (15)	1.10 (0.75, 1.63)
Chest x-ray extent[6]		
Normal/minimal	19/111 (17)	1
Moderate/far advanced	86/628 (14)	0.73 (0.44, 1.19)
Weight loss[5]		

No	11/165 (7)	1
Yes	94/579 (16)	2.34 (**1.44, 4.80**)

FFMI = fat-free mass index, BMI = body mass index, 95% CI = confidence interval. [1]One missed HIV status; [2]284 missed hemoglobin measurement due to lack of blood; [2]fat and fat-free mass was not measured; [6]eight missed extent variable; [3]three missed history of ever smoked; [4]one missed history of alcohol intake; [5]four missed history of weight loss; [a]311 had FMI and FFMI, respectively); FFMI low <16.7 kg/m^2 for men and <14.6 kg/m^2 for women, normal ≥ 16.7kg/m^2 for men, ≥14.6 kg/m^2 for women; low BMI <18.5 kg/m^2 for men and women.

Table 9:8 Relative hazards [HR, 95% confidence intervals (CIs)] for death among tuberculosis patients with normal compared with patients having low body mass index (BMI)

Characteristics	Deaths/N (%)	Overall model
		HR (95% CI)
BMI (kg/m^2)		
Normal (≥18.5)	47/437 (11)	1
Low (<18.5)	58/310 (19)	1.85 (**1.25, 2.73**)
Age (years)		
≤30	34/434 (8)	1
>30	71/313 (23)	2.31 (**1.53, 3.49**)
HIV status[1]		
Negative	6/345 (2)	1
Positive	99/401 (25)	15.86 (**6.92, 36.32**)
Smoker[2]		
No	84/593 (14)	1

Yes	20/151 (13)	0.69 (0.42, 1.14)
Weight loss[3]		
No	11/165 (7)	1
Yes	94/579 (16)	3.40 (**1.81, 6.37**)
Chest x-ray extent[4]		
Normal/minimal	19/111 (17)	1
Moderate/far advanced	86/628 (14)	0.80 (0.49, 1.32)

[1]One missed HIV status; [4]eight missed extent variable; [2]three missed history of ever smoked; [3]four missed history of weight loss; low BMI <18.5 kg/m^2.

Table 9:9 Relative hazards [HR, 95% confidence intervals (CIs)] for death among tuberculosis patients with normal compared with patients having low body mass index (BMI) stratified according to sex status

Characteristics	Deaths/N (%)	Stratified models	
		Women (n=352)	Men (n=395)
		HR (95% CI)	HR (95% CI)
BMI (kg/m^2)			
Normal (≥18.5)	47/437 (11)	1	1
Low (<18.5)	58/310 (19)	1.83 (0.96, 3.50)	1.70 (**1.03, 2.81**)
Age (years)			
≤30	34/434 (8)	1	1
>30	71/313 (23)	1.77 (0.93, 3.37)	2.57 (**1.46, 4.54**)
HIV status[1]			
Negative	6/345 (2)	1	1
Positive	99/401 (25)	12.61 (**3.84, 41.37**)	18.48 (**5.76, 59.26**)
Smoker[2]			
No	84/593 (14)	1	1

Yes	20/151 (13)	0.38 (0.05, 2.78)	0.71 (0.37, 1.37)
Weight loss[3]			
No	11/165 (7)	1	1
Yes	94/579 (16)	2.60 (**1.00, 6.76**)	4.27 (**1.84, 9.95**)
Chest x-ray extent[4]			
Normal/minimal	19/111 (17)	1	1
Moderate/far advanced	86/628 (14)	0.91 (0.42, 1.99)	0.61 (0.35, 1.04)

[1]One missed HIV status; [4]eight missed extent variable; [2]three missed history of ever smoked; [3]four missed history of weight loss; low BMI <18.5 kg/m^2.

Table 9:10 Relative hazards [HR, 95% confidence intervals (CIs)] for death among tuberculosis patients with normal compared with patients having low body mass index (BMI)

Characteristics	Deaths/N (%)	Overall model
		HR (95% CI)
BMI (kg/m^2)		
Normal (≥18.5)	47/437 (11)	1
Low (<18.5)	58/310 (19)	1.75 (**1.18, 2.60**)
Age (years)		
≤30	34/434 (8)	1
>30	71/313 (23)	3.10 (**2.05, 4.69**)
Gender		
Female	38/352 (11)	1
Male	67/395 (17)	1.63 (**1.07, 2.50**)
Smoker[2]		
No	84/593 (14)	1

Yes	20/151 (13)	0.56 (0.33, 0.93)
Weight loss[3]		
No	11/165 (7)	1
Yes	94/579 (16)	2.70 (**1.44, 5.07**)
Chest x-ray extent[4]		
Normal/minimal	19/111 (17)	1
Moderate/far advanced	86/628 (14)	0.66 (0.40, 1.09)

[1]One missed HIV status; [4]eight missed extent variable; [2]three missed history of ever smoked; [3]four missed history of weight loss; low BMI <18.5 kg/m^2.

Table 9:11 Relative hazards [HR, 95% confidence intervals (CIs)] for death among tuberculosis patients with normal compared with patients having low body mass index (BMI) stratified according to HIV status

Characteristics	Deaths/N (%)	Stratified models	
		HIV negative (n=402)	**HIV positive (n=345)**
		HR (95% CI)	**HR (95% CI)**
BMI (kg/m^2)			
Normal (≥18.5)	47/437 (11)	1	1
Low (<18.5)	58/310 (19)	6.95 (0.78, 61.89)	1.63 (**1.09, 2.44**)
Age (years)			
≤30	34/434 (8)	1	1
>30	71/313 (23)	4.89 (0.84, 28.39)	2.10 (**1.37, 3.22**)
Gender			
Female	38/352 (11)	1	1
Male	67/395 (17)	0.57 (0.10, 3.31)	1.62 (1**.05, 2.52**)
Smoker[2]			
No	84/593 (14)	1	1

Yes	20/151 (13)	1.20 (0.18, 8.17)	0.56 (**0.33, 0.96**)
Weight loss[3]			
No	11/165 (7)	1	1
Yes	94/579 (16)	-	3.46 (**1.84, 6.49**)
Chest x-ray extent[4]			
Normal/minimal	19/111 (17)	1	1
Moderate/far advanced	86/628 (14)	-	0.73 (0.44, 1.21)

[1]One missed HIV status; [4]eight missed extent variable; [2]three missed history of ever smoked; [3]four missed history of weight loss; low BMI <18.5 kg/m^2.

Table 9:12 Relative hazards [HR, 95% confidence intervals (CIs)] for death among tuberculosis patients with normal compared with low fat-free mass index (FFMI)

Characteristics	Deaths/N (%)	Overall model
		HR (95% CI)
FFMI in kg/m^2		
Normal (≥18.5)	14/208 (7)	1
Low (<18.5)	16/103 (16)	1.88 **(0.96, 3.65**)
Age (years)		
≤30	11/212 (5)	1
>30	24/128 (19)	2.57 (**1.26, 5.28**)
HIV-serostatus[1]		
Negative	1/186 (0.5)	1
Positive	34/153 (22)	34.43 (**4.66, 254.32**)
Hemoglobin (mg/dl)[2]		
>10	18/242 (7)	1

≤10	16/83 (47)	1.68 (0.86, 3.28)

[1]One missed HIV status; [2]15 missed hemoglobin measurement due to lack of blood; FFMI low (<16.7 kg/m^2 for men and <14.6 kg/m^2 for women, normal (≥ 16.7kg/m^2 for men, ≥14.6 kg/m^2 for women).

Table 9:13 Relative hazards [HR, 95% confidence intervals (CIs)] for death among tuberculosis patients with normal compared with low fat-free mass index (FFMI) stratified according to sex status

		Stratified models	
Characteristics	**Deaths/N (%)**	**Women (n=165)**	**Men (n=175)**
		HR (95% CI)	**HR (95% CI)**
FFMI in kg/m^2			
Normal (≥18.5)	14/208 (7)	1	1
Low (<18.5)	16/103 (16)	6.83 (**2.14, 21.74**)	0.80 (0.35, 1.84)
Age (years)			
≤30	11/212 (5)	1	1
>30	24/128 (19)	3.54 (**1.09, 11.47**)	2.22 (0.87, 5.66)
HIV-serostatus[1]			
Negative	1/186 (0.5)	1	1
Positive	34/153 (22)	-	21.44 (**2.84, 161.99**)
Hemoglobin (mg/dl)[2]			
>10	18/242 (7)	1	1

≤10	16/83 (47)	0.73 (0.23, 2.32)	2.88 (**1.26, 6.57**)

[1]One missed HIV status; [2]15 missed hemoglobin measurement due to lack of blood; FFMI low (<16.7 kg/m^2 for men and <14.6 kg/m^2 for women, normal (≥ 16.7kg/m^2 for men, ≥14.6 kg/m^2 for women).

Figure 9:1 Survival distribution among adult men presenting with wasted body mass (BMI <18.5 kg/m^2) compared to men with normal body mass in urban Kampala, Uganda

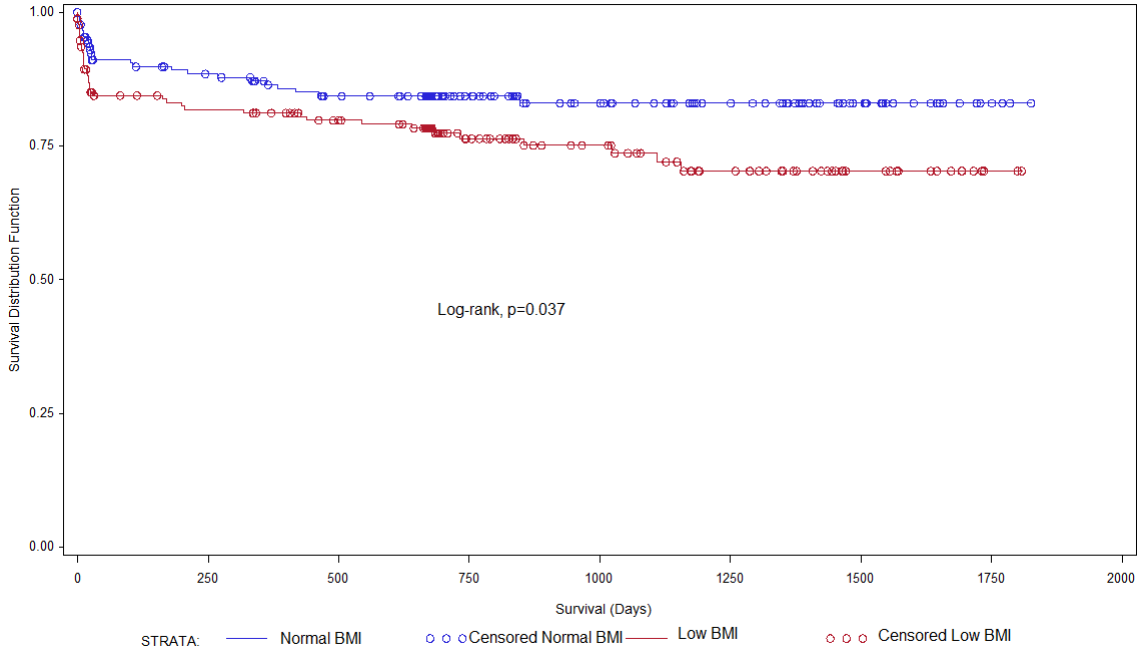


Figure 9:2 Survival distribution among adult women with baseline fat-free mass wasting (FFMI <16.7 kg/m^2 for men, <14.6 kg/m^2 for women) compared to women with normal fat-free mass in urban Uganda

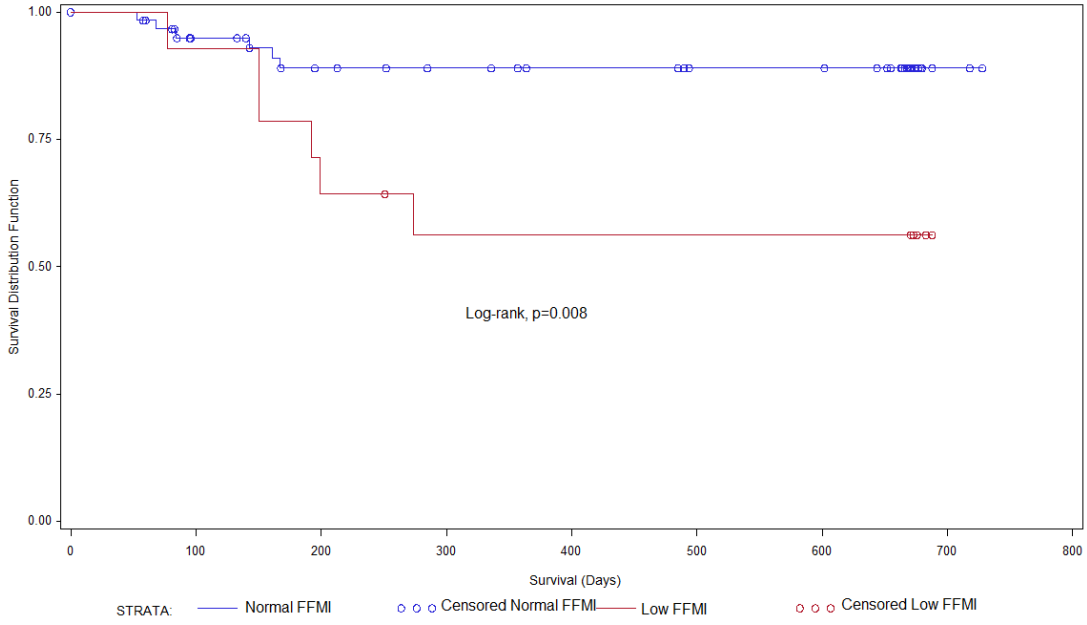
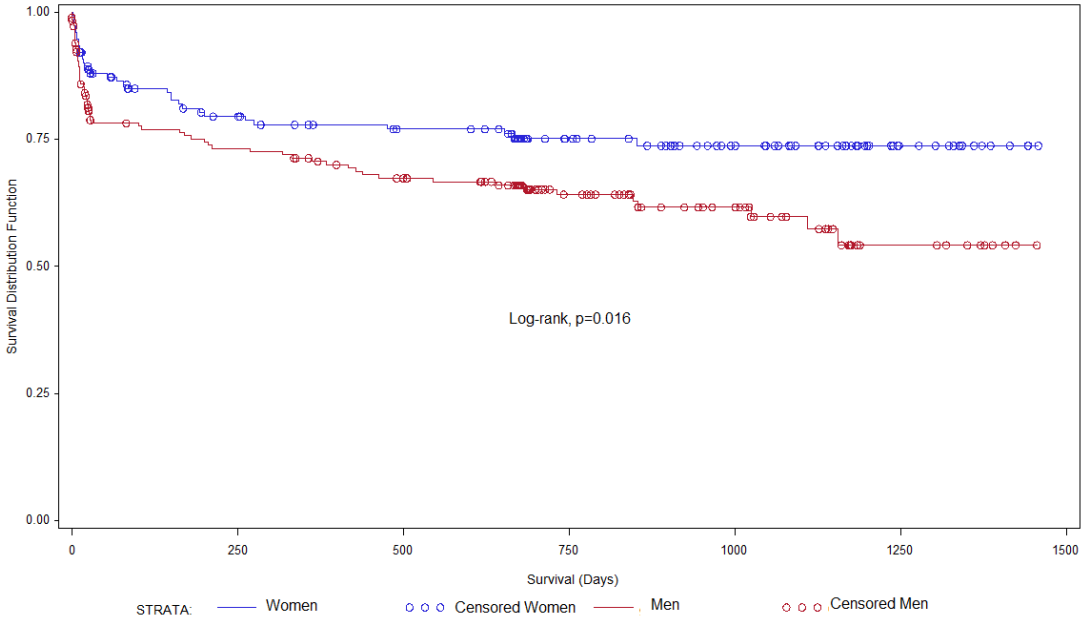


Figure 9:3 Survival distribution Men compared with Women among HIV positive tuberculosis patients in urban Uganda



Data truncated at 1462 days of follow-up

CHAPTER 10

LONGITUDINAL CHANGES IN BODY COMPOSITION AMONG HIV POSITIVE AND HIV NEGATIVE ADULT PATIENTS WITH PULMONARY TUBERCULOSIS IN URBAN KAMPALA, UGANDA

Abstract

Background Follow-up studies are limited to understand nutritional changes during and after tuberculosis treatment. The effect of body wasting at the time of diagnosis and HIV infection on rate of change for fat-free mass, fat mass, and body mass index (BMI) during and after treatment were evaluated among tuberculosis patients in urban Kampala, Uganda.

Methods In a retrospective cohort study of 717 adult patients, BMI was assessed at baseline, 2, 3, 5, 6, 12, and 24 months whereas fat-free mass index (FFMI) and fat mass index (FMI) were evaluated at baseline, 3, 12, and 24 months. Longitudinal mixed effects two piecewise models with knots at month 3 and month 12 were fit to the data.

Results There were no differences in body wasting as assessed by reduced FFMI, FMI, and BMI between HIV positive and HIV negative patients at presentation. In stratified mixed effects two spline models during the first three months of treatment, the gain in FFMI among patients that presented with reduced fat-free mass at diagnosis was dramatic in men with rate of 4.55 kg/m^2 (95% confidence interval (CI): 1.26, 7.83); however, the gain was minimal among women who presented with reduced FFMI with rate of 2.07 kg/m^2 (95% CI: -0.74, 4.88). In stratified models for FMI as dependent variable, women with reduced fat mass at presentation had a substantial gain in FMI at rate of 3.55 kg/m^2 (95% CI: 0.40, 6.70) whereas men had a rate of 3.16 kg/m^2 (0.80, 5.52). In stratified models with BMI as dependent variable, men with reduced BMI at presentation gained BMI at a rate of 6.45 kg/m^2 (95% CI: 3.02, 9.87) whereas women at a rate of 3.30 kg/m^2 (95% CI: -0.11, 6.72). There were minimal changes in FFMI, FMI, and BMI during the

first three months of treatment in stratified models according to HIV status. Furthermore, there were minimal changes in FFMI, FMI, and BMI after month 3 and during the one year follow-up after month 12.

Conclusion Gender but not HIV was associated with longitudinal body composition changes during the initial phase of treatment among tuberculosis patients that presented with body wasting. Further evaluation is needed to under the impact of providing nutritional interventions as adjuvant treatment on body composition among tuberculosis patients in sub-Saharan.

Background

The global burden of tuberculosis remains enormous because there are insufficient tuberculosis control programs and higher rates of tuberculosis and human immunodeficiency virus (HIV) co-infection. The incidence remains high, with 9.2 million new cases reported to have occurred in 2006 only (Vitoria et al. 2009). The majority of these cases occurred in Asia, but the highest population rate has been observed in Africa where the prevalence of HIV infection is at its highest.

Body wasting is regarded as a cardinal feature of tuberculosis; however, the pathophysiology of wasting remains poorly understood (Schwenk A and Macallan D.C 2000). A significant proportion of African tuberculosis patients have a marked degree of wasting by the time they present for registration and treatment (Kennedy et al. 1996; Harries et al. 1988; Zachariah et al. 2002). Wasting is associated with impaired physical function (Harries et al. 1988), longer hospitalization days and increased mortality in patients with tuberculosis (Rao et al. 1998; Zachariah et al. 2002; Mitnick et al. 2003). Thus, early diagnosis of body wasting in tuberculosis is essential if timely interventions are to be instituted.

Wasting associated with tuberculosis is likely caused by a combination of decreased appetite and altered metabolism resulting from the inflammatory and immune responses

(Paton et al. 1999; Paton et al. 2003; Macallan 1999). The decreased appetite may lead to a decrease in energy intake, interacting with increased losses with a resultant body wasting. Although antituberculosis treatment is highly successful (Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. Joint Tuberculosis Committee of the British Thoracic Society 1998), many patients remain underweight after 6 months of treatment (Onwubalili 1988) suggesting that full recovery may take a longer than the treatment itself.

It has been reported that in patients with both tuberculosis and HIV co-infection, the wasting process is exacerbated (Macallan 1999; Lucas et al. 1994). In contrast, findings from several cross-sectional studies appear to show no large differences in body composition between HIV-infected adults with tuberculosis and HIV-negative adults with tuberculosis at presentation (Shah et al. 2001; Niyongabo et al. 1999; Niyongabo et al. 1994; Mupere et al. 2010) suggesting that tuberculosis is the dominant factor inducing wasting. This has been shown in several reports (Mupere et al. 2010; Paton and Ng 2006). However, the wasting process at the time of TB diagnosis according to previous reports appear to differ by gender (Kennedy et al. 1996; Mupere et al. 2010).

Nutritional changes at the time of tuberculosis diagnosis are well documented using both anthropometry and bioelectrical impedance analysis (BIA) in several reports (van Lettow, Fawzi, and Semba 2003; Paton et al. 1999; Shah et al. 2001; Van Lettow et al. 2004; Villamor et al. 2006; Mupere et al. 2010); however, follow-up studies are still limited to

understand nutritional changes during and after tuberculosis treatment. The limited follow-up studies (Kennedy et al. 1996; Ramakrishnan et al. 1961) found weight gain to be a poor indicator of clinical response in tuberculosis. Furthermore, weight or body mass index (BMI) provides limited information about nutritional alterations in patients with tuberculosis. In addition, BMI is insensitive to body fatness, particularly at low BMI, as well as with above-normal muscle development (Kyle, Genton, and Pichard 2002; Kyle, Piccoli, and Pichard 2003). Measurement of body composition is necessary to obtain a true picture of the nutritional status in tuberculosis because body compartments differ in their contribution to weigh gain and its clinical benefit. Fat-free mass (FFM) and fat mass body composition measurements have been shown to permit a more precise evaluation of nutritional status (VanItallie et al. 1990; Kyle, Piccoli, and Pichard 2003). Fat-free mass (FFM) is more closely correlated with quality of life and physical functioning than are fat mass (FM) and body weight (Wagner, Ferrando, and Rabkin 2000; Mostert et al. 2000). BIA has been recommended as the preferred and precise method for clinical assessment of FFM and fat mass (Kyle et al. 2004; Kyle, Genton, and Pichard 2002). One follow-up study that evaluated FFM and FM had a small sample size, enrolled only HIV negative tuberculosis patients, and followed patients for only 6 months (Schwenk et al. 2004). In this large retrospective study, we evaluated the effect of baseline body wasting and HIV infection on the rate of change of FFM, FM, and BMI during and after treatment among tuberculosis patients in urban Uganda, Kampala.

Methodology

Study Design

A retrospective cohort study was conducted with the study population that consisted of 745 adult pulmonary tuberculosis patients having confirmed HIV status and defined baseline body wasting. The study used the completed five year Household Contact (HHC) study, the completed phase II prednisolone double blind randomized placebo controlled clinical trial, and the ongoing Kawempe Community Health (KCH) study. Of the 745 patients, 314 were enrolled into the HHC, 341 into the KCH, and 90 into the placebo arm of the prednisolone clinical trial (Figure 10:1 and 10:2). The HHC and KCH studies were observational epidemiologic studies; organized and conducted by the Makerere University and Case Western Reserve University tuberculosis research collaboration (Uganda-CWRU) that has been ongoing for the last 20 years in Uganda. The HHC was the initial household contact study from 1995 to 1999 that described the epidemiology of tuberculosis in urban Kampala, Uganda (Guwatudde et al. 2003). The KCH is the second phase of the HHC. The KCH phase started in 2002 and is still ongoing (Stein et al. 2005). The KCH was developed specifically to focus on the determinants of host factors associated with primary infection, re-infection, reactivation, and progression of clinical disease and to identify and track individual strains of mycobacterial tuberculosis through Ugandan households and local community. The phase II clinical trial was conducted between 1995 to 2000 to determine whether immunoadjuvant prednisolone therapy in HIV-infected patients with TB who had CD4(+) T cell counts >/=200 cells/ mu L was safe and effective at increasing CD4(+) T cell counts (Mayanja-Kizza et al. 2005). Patients were eligible for this present study if they had baseline and

follow-up body measurements, had an HIV test, and were part of one prospective study conducted by the Uganda-CWRU research collaboration.

The institutional review boards at Case Western Reserve University in the United States and Joint Clinical Research Center in Uganda reviewed the protocol and final approval was obtained from the Uganda National Council for Science and Technology. All patients in the HHC and KCH had written informed consent to be enrolled in the study. All participants in both HHC and KCH were given appropriate pre- and post-test HIV counseling and AIDS education. HIV-1 infection was diagnosed on the basis of a positive enzyme-linked immunosorbent assay for HIV-1 antibodies (Recombigen; Cambridge Biotech, Cambridge, MA). None of the HIV positive patients, neither those who were newly identified with HIV nor those with pre-existing HIV, were on antiretroviral therapy.

At enrollment, basic demographic information and a medical history were collected, and a standardized physical examination was conducted by a medical officer. Active tuberculosis was confirmed by sputum smear microscopy and culture. Patients with active tuberculosis were treated with standard four-drug chemotherapy for tuberculosis per guidelines of the Ugandan Ministry of Health. Adults with a previous history of treated pulmonary tuberculosis were excluded in the study. Of the 745 participants who were enrolled in the three studies, 28 were excluded due to lack of anthropometric follow-up data and being below 18 years of age, leaving 717 participants in total

available for analysis. The BIA data were collected during the KCH study only. Of the 341 participants who were enrolled in KCH, 63 were excluded due to lack of BIA follow-up data and being below 18 years of age, leaving 278 participants in total available for analysis (Figure 10:2). However, there were no differences in baseline age, gender, weight, height, BMI, smoking status, hemoglobin, chest x-ray disease extent, and history of weight loss between participants who were included and those who were excluded.

Measurements

Nutritional status was assessed using anthropometric measurements such as height and weight and BIA Detroit, MI, RJL Systems. Body weight was determined to the nearest 0.1 kg using a SECA adult balance, and standing height was determined to the nearest 2 mm. Anthropometric measurements for the present retrospective study were performed during the HHC and KCH at scheduled visits including baseline, 2, 3, 5, 6, 12, and 24 months on follow-up. Body-mass index (BMI) was computed using the relationship of weight in kilograms divided by height in meters squared (kg/m^2). All BIA measurements were performed by one trained observer using the same equipment and recommended standard conditions with regard to body position, previous exercise, dietary intake, skin temperature, and voiding of the bladder were taken into consideration in taking BIA measurements (Kyle et al. 2004). All BIA measurements during the KCH study were performed on the day patients were confirmed to have tuberculosis disease and on scheduled visits at 3, 12, and 24 months.

The BIA is a simple, easy, safe, non-invasive technique, that has been recommended for nutritional studies in the clinical setting (Kyle et al. 2004; Kyle, Piccoli, and Pichard 2003) and is a convenient method to determine the lean or fat-free mass and fat body compartments (Kyle, Piccoli, and Pichard 2003; Kyle et al. 2004). Single-frequency BIA was performed at 50 kHz and 800 mA with standard tetrapolar lead placement (Jackson et al. 1988). Before performing measurements on each participant, the BIA instrument was calibrated using the manufacturer's recalibration device. The resistance and reactance were based on measures of a series circuit (Kotler et al. 1996). BIA measurements were performed in triplicate for each subject. Fat-free mass (FFM) was calculated from BIA measurements using equations that were previously cross-validated in a sample of patients (white, black and Hispanic) with and without HIV infection (Kotler et al. 1996) and have been applied elsewhere in African studies (Villamor et al. 2006; Shah et al. 2001; Van Lettow et al. 2004). Fat mass (FM) was calculated as body weight minus FFM.

Definitions

We used BMI and height-normalized indices (adjusted for height^2) of body composition that partition BMI into fat-free mass index (FFMI) and fat mass index (FMI) (Schutz, Kyle, and Pichard 2002; VanItallie et al. 1990; Kyle, Piccoli, and Pichard 2003) to establish the body wasting status of participants. The FFMI and FMI have the advantages of compensating for differences in height and age (Kyle, Genton, and Pichard 2002). Also, the use of the FFMI and FMI eliminates some of the differences between

population groups. We defined body wasting as patients having the low fat-free mass index (FFMI) and the low body fat mass index (FMI) corresponding to WHO BMI categories for malnutrition as previously reported (Table 10:1) (Kyle, Piccoli, and Pichard 2003). The FFMI <16.7 (kg/m^2) for men and <14.6 (kg/m^2) for women and the FMI <1.8 (kg/m^2) for men and <3.9 (kg/m^2) for women corresponds to a BMI of <18.5 kg/m2, the WHO cutoff for malnutrition (WHO Tech Rep 1995) among adults.

Table 10:1 Definitions of low and normal fat and fat-free mass index values for corresponding body mass index in adults

Characteristic	Low	Normal
Body mass index (BMI)[a]		
Women and men in kg/m^2	< 18.5	≥ 18.5
Fat-free mass index (FFMI)[b]		
Women in kg/m^2	< 16.7	≥ 16.7
Men in kg/m^2	< 14.6	≥ 14.6
Fat mass index (FMI)[b]		
Women in kg/m^2	< 1.8	≥ 1.8
Men in kg/m^2	< 3.9	≥ 3.9

[a]World Health Organization categories, sex independent (WHO Tech Rep 1995). [b]Kyle et al (Kyle, Piccoli, and Pichard 2003; Kyle et al. 2003).

Statistical analysis

Hypothesis

The hypothesis tested in analysis of this data was: the null hypothesis stated that there would be no difference in the rate of change for FFMI, FMI, and BMI between patients with baseline body wasting and patients with no baseline wasting; and between HIV positive and HIV negative patients during and after the course of tuberculosis treatment in urban Kampala, Uganda. The study hypothesis (alternative) was that patients with baseline wasting and HIV infection were associated with increased rates of FFMI, FMI, and BMI compared to patients with no baseline wasting and with HIV negative during and after treatment among tuberculosis patients in urban Kampala, Uganda.

Descriptive statistics

Baseline characteristics for participants with baseline wasting were compared with participants who had no baseline wasting using the χ^2 test or Fisher's exact test (where expected counts were less than 5) for binary data and student's t-test for continuous variables or Wilcoxon-Mann Whitney test for variables not normally distributed.

Exploration of data

In order to gain insights for the covariate structure and model building, we explored data by conducting correlation structure matrices for FFMI, FMI, and BMI; plots of individual profile trajectories, boxplots, and mean profiles per exposure group of baseline wasting

and no wasting overtime. The raw correlation coefficients along and off the diagonals were clearly unique for BMI suggesting a heterogeneous covariance structure. However, correlation coefficients for both FFMI and FMI were nearly the same along the diagonals and appear to decay with time suggesting stationary structure (Appendix, Table 14:1). Plots of individual FFMI, FMI, and BMI profiles over time have different intercepts and different positive slopes suggesting importance of random intercepts and slopes in the models (Appendix, Figures 14:1 – 14:3). The boxplots and mean profiles for three indexes showed linear increasing trends over time suggesting inclusion of interaction terms between the indexes with time to be important (Appendix, Figures 14:4 – 14:15).

Missing observations

The 278 participants from the KCH study who were included in the BIA analysis contributed 1,112 observations, 205/1,112 (18%) of which were missing observations. However, the 717 participants from all the three studies who were included in the anthropometric data analysis contributed 4,875 observations, 781/4,875 (16%) of which were missing observations (Figure 10:1). In order to understand the nature of missingness and whether the missing observations were nonignorable, we used the logistic regression approach for outcome-dependent missing (Ridout 1991). We performed separate generalizing estimating equations (GEE) models for FFM, FMI, and BMI using Proc GENMOD with a logit link function to assess the effect of having wasting (low FFMI, low FMI, or BMI <18.5 kg/m^2) versus no wasting (normal/high FFMI, normal/high FMI, or BMI ≥18.5 kg/m^2) at baseline on to the probability of missing FFM, FMI, or BMI

overtime adjusting factor for baseline sex, age, HIV status, history of weight loss, chest x-ray disease extent, and hemoglobin level. In both models of FFMI and FMI, for outcome dependent missing, the missing probability was not related to the baseline wasting and the lag measure (Appendix, Tables 14:2 and 14:3). Thus, we assumed the data missing not to be informative on the outcome variable and ignorable for FFMI, FMI and BMI.

Model building

The aim was to specify the appropriate mean and covariance structures of the data. The main outcome vectors of the participant's FFMI, FMI, and BMI were modeled as linear combinations of baseline covariates and baseline body wasting status in separate models. Changes in FFMI, FMI, or BMI over time were estimated using multilevel linear random effect/mixed effects models with random intercept and random slope, accounting for correlation of repeated measurements within each individual (Laird and Ware 1982; Singer J.D and Willet J.B 2003; Bryk A.S and Ruandenbush S.W 2002). Multilevel modeling of change involves two levels: level one that describes how the outcome in each individual changes overtime (within-person change), and level two that describes how the within-person changes differ across persons (between-person differences in change) (Singer J.D and Willet J.B 2003). We used full maximum likelihood estimation method for parameter estimation and type 3 F-test for testing significance. We assumed a spatial exponential covariance structure. The spatial exponential covariance structure was plausible because the intervals between serial data points were different by design. The

exponential covariance structure is among the spatial correlation structures that takes the form: $\boldsymbol{\varepsilon_{ij} = U_i(t_{ij}) + e_{ij}}$. The $U_i(t_{ij})$ are assumed to have a normal distribution, with 0 mean, variance σ2 u, and correlation Corr { $U_i(t_{ij})$, $U_i(t_{ik})$} = $\rho^{(|tij - tik|)}$. This correlation becomes weaker as the separation increases. The e_{ij} are the usual sampling or measurement errors. The LOCAL option was added to the REPEATED statement in SAS to decompose the errors into $U_i(t_{ij})$ and e_{ij}.

The appropriateness of the covariance structure was assessed using Akaike Information Criteria (AIC) and Bayesian Information Criteria (BIC) (Littell, Pendergast, and Natarajan 2000). The quadratic and cubic terms were assessed using –2 log likelihood (-2LL) and found to significantly improve the model (Appendix, Table 14:4). A model with random intercepts and random slopes was assessed using -2LL and found to be better than one without random intercepts or random slopes (Appendix, Table 14:4). We also compared a piecewise model with two knots at month 3 and at month 12 with linear and polynomial models. The knots in the piecewise were chosen a priori basing on the scheduled data point measurements. The piecewise model was found to fit the data better (Appendix, Table 14:5). Furthermore, a piecewise model with random intercepts and random slopes was better than one without. We assessed for normality of the residuals at modeling levels to identify the best function form of each variable included in the model.

We first fitted an unconditional mean model (outcome only, no predictors) to determine whether the differences in average FFMI, FMI, and BMI across visits and persons were

non-zero and whether there was significant within- and between-person variability (Singer J.D and Willet J.B 2003). After confirming non-zero variability in FFMI, FMI, and BMI across visits and persons, and the existence of significant within-person and between person variability, an unconditional growth model (with time as the only predictor) was then fit to estimate the population average rate of FFMI, FMI, BMI increase (slope) and initial status (intercept), and to determine if significant variability existed in both statistics. The unconditional growth model showed significant variability in both the initial status and the rate of change of FFMI, FMI, and BMI, suggesting the need for predictor variables to explain the heterogeneity. The main predictor was baseline body wasting using the following cutoffs alluded to above: low FFMI of 16.7 (kg/m^2) for men and 14.6 (kg/m^2) for women, low FMI of 1.8 (kg/m^2) for men and 3.9 (kg/m^2) for women (Kyle, Piccoli, and Pichard 2003; Schutz, Kyle, and Pichard 2002), and the corresponding BMI cutoff of <18.5 kg/m2 (WHO Tech Rep 1995). The following were other covariates used to assess associations with the dependent variables overtime: number of visits in the study to adjust for missing data points, age categorized as young (≤ 30 years) and old (> 30 years), sex, HIV sero-status, hemoglobin categorized as anemic (≤ 10g/dl) and not anemic (>10), smoking status, history of weight loss, history of taking alcohol now, and chest x-ray disease extent categorized as normal/minimal and moderate/far advanced. All covariates were time-invariant. The interval between study visits was adjusted to an annual scale to facilitate the interpretation of rates of FMI, FMI, and BMI decline per year.

We performed univariate analysis; variables with significant linear rates of FFMI, FMI, and BMI change and those with biological association with the three indexes such as age and extent of chest x-ray disease involvement were included in the initial multivariable model. Conditional mixed-effects model was fitted to the BMI data in view of the informative missing data (non-ignorable). Age was the only variable that was dropped from all the final multivariable models because it did not improve the model fits. The complete set of the covariates at each visit were used in the analysis; neither last-observed-carried-forward (LOCF) nor imputation was applied. Differences in rates of FFMI, FMI, and BMI change were assessed by fitting in separate models with baseline body wasting for FFMI, FMI, and BMI cutoffs*time interaction term variables. To assess for the confounding effects of HIV, we fitted stratified models according to HIV strata. Follow-up data were censored at the last visit. We assessed for the basic assumptions of multivariate normality and linearity, all final models had normally distributed residuals. The analysis will be performed using SAS MIXED procedures (SAS Institute). All analyses were performed using SAS version 9.1.3 Cary software, North Carolina SAS Institute Inc. 2004.

Results

Descriptive statistics

Of the 717 patients who were included in the analysis, 293 had reduced BMI (<18.5 kg/m^2 for women and men) at diagnosis (Figure 10:1). Among the 293 with reduced

BMI, 153 were HIV positive and 115 were women. Two hundred seventy eight patients, a subset of the 717 were involved in the fat and fat-free mass analysis (Figure 10:2). Of the 278 patients, 94 had reduced FFMI (<16.7 kg/m2 for men and <14.6 kg/m^2 for women). Among the 94 with reduced FFMI, 41 were HIV positive and 19 were women. Of the 278 patients, 120 had reduced FMI (<1.8 kg/m2 for men and <3.9 kg/m^2 for women). Among the 120 with reduced FMI, 52 were HIV positive and 69 were women.

Baseline characteristics of the study population are presented in Table 10:2. There were gender differences at the time of diagnosis. Men had significantly higher proportions of reduced FFMI and BMI compared to women whereas women had significantly higher proportions of reduced FMI compared to men. There were no differences in body wasting between HIV positive and HIV negative patients at presentation regardless of nutritional assessment measure suggesting that HIV probably does not affect body wasting in co-infected patients as previously reported (Mupere et al. 2010; Paton and Ng 2006). Patients who presented with history of prior smoking and moderate/or far advanced disease extent on chest x-ray had higher frequency of body wasting as assessed by FFMI and BMI compared to those without history of prior smoking and without moderate/or far advanced disease on chest x-ray (Table 10:2).

Rate of change for fat-free mass, fat mass, and body mass index in univariate spline models

Fat-free mass index

Overall, the population average FFMI linear trajectory had a rate of 2.43 (95% CI, 1.34, 3.52) kg/m^2 increase per month before month 3 on tuberculosis treatment in univariate mixed effects model with FFMI as the dependent variable (Table 10:3). However, after month 3 the FFMI decreased significantly at a rate of -2.57 (95% CI; -3.87, -1.27) kg/m^2 per month. There were minimal changes in FFMI after month 12 over the subsequent one year. On average at baseline, month 3, and month 12, FFMI was -1.40 (95% CI; -1.69, -1.11), -0.76 (95% CI; -1.17, -0.35), and -1.49 (95% CI; -2.12, -0.85) kg/m^2 significantly lower among patients that presented with reduced fat-free mass compared to patients that had normal fat-free mass, respectively. Patients that presented with reduced fat-free mass had a significantly rapid gain in FFMI before 3 months on treatment at rate of 4.02 (95% CI; 3.14, 4.91) kg/m^2 compared to a modest gain of 1.59 (95% CI; 0.96, 2.23) kg/m^2 per month among those that had normal fat-free mass (Table 10:3). The difference in slopes was 2.43 (95% CI; 1.34, 3.52). Before month 3 is the intensive phase of tuberculosis treatment. There were no gains in FFMI after month 3 regardless of the amount of fat-free mass a patient may have presented with at diagnosis. This period coincides with continuous phase of tuberculosis treatment. However after month 12, patients presenting with reduced fat-free mass maintained the significant rapid gain compared to patients that had normal fat-free mass as suggested by the significant difference in slopes of 2.52 (95% CI; 1.17, 3.87) after 12 months (Table 10:3).

Fat mass index

In univariate mixed effects spline model for FMI (Table 10:3), there was a significant gain in the average rate of FMI linear trajectory for the overall population before month 3 at 2.41 (95% CI: 1.33, 3.48) per month. After month 3, the rate of linear trajectory decreased at a rate of -2.46 (95% CI: -3.78, -1.13) per month. The rate of linear trajectory was minimal per year after month 12. On average, FMI was -2.28 (95% CI; -2.76, -1.80), -1.67 (95% CI; -2.18, -1.16), and -2.50 (95% CI; -3.37, -1.62) kg/m^2 significantly lower among patients presenting with reduced fat mass compared to patients presenting with normal fat mass at baseline, month 3, and month 12, respectively. Patients presenting with reduced fat mass had a significantly rapid gain in FMI before month 3 at rate of 2.99 (95% CI; 2.18, 3.80) kg/m^2 compared to a no significant gain of 0.58 (95% CI; -0.12, 1.29) kg/m^2 per month among those presenting with normal fat mass at diagnosis (Table 10:3). There was significant difference in slopes of 2.41 (95% CI; 1.33, 3.48). Both patients with reduced or normal fat mass at presentation gained in FMI at the same rate per month after month 3. However after month 12, only patients presenting with reduced fat mass attained the significant gain per year compared to patients that presented with normal fat mass with a difference of 2.62 (95% CI: 2.22, 4.03) in slopes (Table 10:3).

Body mass index

Unadjusted rate of BMI changes in mixed effects spline model with BMI as the dependent variable are presented in Table 10:3. The overall population average rate of BMI linear trajectory gain was 2.72 (95% CI, 1.74, 3.69) kg/m^2 per month before month

3. However, after month 3 the BMI decreased significantly at a rate of -2.94 (95% CI; -4.07, -1.81) kg/m^2 per month. There was minimal change in the total population rate of BMI change after month 12. On average at baseline and at month 12, population BMI was 2.72 (95% CI; 2.74, 3.69) and 2.23 (95% CI; 1.61, 4.05) kg/m^2 significantly lower among patients that presented with reduced BMI compared to patients that presented with normal BMI, respectively. There was minimal difference in population BMI at month 3 between patients that presented with reduced BMI and normal at diagnosis. Patients that presented with reduced BMI had a significantly higher rate of gain in BMI before 3 months and after month 12 compared to the rate among patients that presented with normal BMI (Table 10:3). The differences in slopes were 2.72 (95% CI; 1.74, 3.69) before month and 2.83 (95% CI; 1.71, 4.05) after month 12, respectively. There was no difference in slope for rate of BMI gain between patients had and patients that did not have reduced BMI at presentation after month 3.

Rate of change for fat-free mass, fat mass, and body mass index in multivariable mixed spline models and stratification models according to gender

Fat-free mass

In multivariable mixed effects two spline model at month 3 and at month 12 with FFMI as the dependent variable and after adjusting for HIV, anemia (hemoglobin $\leq$10 mg/dl), prior smoking status, history of weight loss, and extent of disease on chest x-ray, the population average for FFMI at baseline, month 3, and month 12 was -1.60 (95% CI: -1.90, -1.31), -1.02 (95% CI: -1.40, -0.64), and -1.10 (95% CI: -1.50, -0.70) kg/m^2

significantly lower among patients that presented with reduced fat-free mass compared to patients that had normal fat-free mass, respectively. On average among women at baseline, month 3, and month 12, FFMI was -1.85 (95% CI: -2.29, -1.40), -1.27 (95% CI: -1.79, -0.76), and -1.27 (95% CI: -1.80, -0.73)] significant lower among individuals that presented with reduced fat-free mass compared to those that had normal fat-free mass at presentation, respectively. Similarly, among men at baseline, month 3, and month 12, FFMI was -2.15 (95% CI; -2.45, -1.85), -1.68 (95% CI: -2.11, -1.24), and -1.89 (95% CI: -2.35, -1.43) for individuals that presented with reduced fat-free mass compared to patients that had normal fat-free mass, respectively.

In the overall two spline model during the first three months, patients that presented with reduced fat-free mass had a significantly gain in FFMI at rate of 2.68 (95% CI: 0.68, 4.67) kg/m^2 per month whereas patients that presented with normal fat-free mass had minimal change in FFMI at a rate of 0.35 (95% CI: -1.38, 2.08) kg/m^2 per month (Table 10:4). In stratified mixed effects two spline models, the gain in FFMI among patients that presented with reduced fat-free mass at diagnosis was however dramatic in men at rate of 4.55 (95% CI: 1.26, 7.83) (Table 10:5). The gain was minimal among women that presented with reduced fat-free mass with a rate of 2.07 (95% CI: -0.74, 4.88). The slopes were significantly different during the first three months between patients that presented with reduced fat-free mass and those that had normal fat-free mass at diagnosis for the overall population model and in stratified models for women and men. There were no changes in FFMI after month 3 and during the one year of follow-up after month 12 in the total population and in stratified models for women and men (Tables 10:4 and 10:5).

Fat mass

After adjusting for HIV, anemia (hemoglobin ≤10 mg/dl), prior smoking status, history of weight loss, and extent of disease on chest x-ray in multivariable mixed effects two spline model at month 3 and at month 12 with FMI as the dependent variable, the total population average for FMI at baseline, month 3, and month 12, was -2.15 (95% CI: -2.62, -1.69), -1.57 (95% CI: -2.06, -1.08), and -1.64 (95% CI: -2.24, -1.04)] significant lower among patients that presented with reduced fat mass compared to those that had normal fat mass at diagnosis, respectively. On average among women at baseline, month 3, and month 12, FMI was -4.02 (95% CI: -4.65, -3.39), -3.17 (95% CI: -3.90, -2.58), and -3.46 (95% CI: -4.34, -2.37) significant lower among individuals that presented with reduced fat mass compared to those that had normal fat mass at diagnosis, respectively. Similarly, among men at baseline, month 3, and month 12, FMI was -1.28 (95% CI; -1.47, -1.09), -0.76 (95% CI: -1.09, -0.44), and -0.88 (95% CI: -1.26, -0.50) for individuals that presented with reduced fat mass compared to patients that had normal fat mass, respectively.

During the first three months in the overall two spline model, patients that presented with reduced fat mass had a significantly gain in FMI at rate of 2.23 (95% CI: 0.30, 4.16) kg/m^2 per month whereas patients that presented with normal fat mass had minimal change in FMI at a rate of -0.11 (95% CI: -1.98, 1.73) kg/m^2 per month (Table 10:4). In stratified mixed effects two spline models, the gain in FMI among patients that presented with reduced fat mass at diagnosis was higher in women at rate of 3.55 (95% CI: 0.40,

6.70) compared to men at rate of 3.16 (95% CI: 0.80, 5.52) (Table 10:5). The slopes were significantly different during the first three months between patients that presented with reduced fat mass and those that had normal fat mass at diagnosis for the overall population model and in stratified models for women and men. After month 12 during the one year follow-up, both patients that presented with/ or without reduced fat mass had modest significant gains in fat mass; however, there was no significant difference in slopes (Tables 10:4 and 10:5). There were minimal changes in FMI after month 3 and before month 12 among women and men regardless of initial fat mass.

Body mass index

The population average BMI at baseline, month 3, and month 12 in multivariable mixed effects two spline model at month 3 and at month 12 with BMI as the dependent variable and after adjusting for HIV, anemia (hemoglobin ≤10 mg/dl), prior smoking status, history of weight loss, and extent of disease on chest x-ray was -3.69 (95% CI; -4.09, -3.30), -3.30 (95% CI; -3.71, -2.88), and -3.62 (95% CI; -4.16, -3.07) kg/m^2 significantly lower among patients that presented with reduced BMI compared to patients that had normal BMI, respectively. On average among women at baseline, month 3, and month 12, BMI was -4.23 (95% CI: -4.97, -3.48), -3.89 (95% CI: -4.67, -3.12), and -3.86 (95% CI: -4.88, -2.84)] significant lower among individuals that presented with reduced BMI compared to those that had normal BMI at diagnosis, respectively. Similarly, among men at baseline, month 3, and month 12, BMI was -3.13 (95% CI; -3.49, -2.77), -2.71 (95%

CI: -3.13, -2.29), and -3.19 (95% CI: -3.71, -2.66) for individuals that presented with reduced BMI compared to individuals that had normal BMI, respectively.

In the overall two spline model during the first three months, patients that presented with reduced BMI had a significantly gain in BMI at rate of 3.83 (95% CI: 1.67, 5.99) kg/m^2 per month whereas patients that presented with normal BMI had modest gain in BMI at a rate of 2.25 (95% CI: 0.33, 4.17) kg/m^2 per month (Table 10:4). In stratified mixed effects two spline models, the gain in BMI among patients that presented with reduced BMI at diagnosis was however substantial in men at rate of 6.45 (95% CI: 3.02, 9.87) (Table 10:5). The gain was minimal among women that presented with reduced BMI with a rate of 3.30 (95% CI: -0.11, 6.72). The slopes were significantly different during the first three months between patients that presented with reduced BMI and those that had normal BMI at diagnosis for the overall population model and in stratified models for men. There were minimal changes in BMI after month 3 and during the one year of follow-up after month 12 in the total population and in stratified models for women and men (Tables 10:4 and 10:5).

Rate of change for fat-free mass, fat mass, and body mass index in multivariable mixed spline models and stratification models according to HIV status

Fat-free mass

In multivariable mixed effects two spline model at month 3 and at month 12 with FFMI as the dependent variable when HIV was replaced by gender among the adjusters (Tables 10:6 and 10:7), the population average for FFMI at baseline, month 3, and month 12 was -2.05 (95% CI: -2.31, -1.80), -1.57 (95% CI: -1.90, -1.24), and -1.72 (95% CI: -2.06, -1.37) kg/m^2 significantly lower among patients that presented with reduced fat-free mass compared to patients that had normal fat-free mass, respectively. On average among HIV negative individuals in stratified models at baseline, month 3, and month 12, FFMI was -1.77 (95% CI: -2.04, -1.49), -1.35 (95% CI: -1.78, -0.93), and -1.51 (95% CI: -1.93, -1.10)] significant lower among individuals that presented with reduced fat-free mass compared to those that had normal fat-free mass at presentation, respectively. Similarly, among HIV positive individuals at baseline, month 3, and month 12, FFMI was -2.40 (95% CI; -2.83, -1.98), -1.80 (95% CI: -2.32, -1.28), and -1.98 (95% CI: -2.51, -1.33) significantly lower for individuals that presented with reduced fat-free mass compared to individuals that had normal fat-free mass, respectively.

In the overall model and in stratified models according to HIV status during the three months, after month 3, and during the one year period of follow-up after month 12, there were minimal changes in FFMI regardless of the initial fat-free mass level at diagnosis. However, the slopes were significantly different during the first three months between

patients that presented with reduced fat-free mass and those that had normal fat-free mass at diagnosis for the overall population model and in stratified models according to HIV status (Tables 10:6 and 10:7).

Fat mass

When HIV was replaced by gender among the adjusters in multivariable mixed effects two spline model at month 3 and at month 12 with FMI as the dependent variable, the total population average for FMI at baseline, month 3, and month 12, was -2.69 (95% CI: -3.04, -2.33), -2.03 (95% CI: -2.45, -1.62), and -2.26 (95% CI: -2.74, -1.77) significant lower among patients that presented with reduced fat mass compared to those that had normal fat mass at diagnosis, respectively. On average in stratified models among HIV positive individuals at baseline, month 3, and month 12, FMI was -2.59 (95% CI: -3.06, -2.12), -2.18 (95% CI: -2.73, -1.63), and -2.28 (95% CI: -2.09, -1.60) significant lower among individuals that presented with reduced fat mass compared to those that had normal fat mass at diagnosis, respectively. Similarly, among HIV negative indivdiuals at baseline, month 3, and month 12, FMI was -2.85 (95% CI; -3.40, -2.30), -1.77 (95% CI: -2.36, -1.17), and -2.23 (95% CI: -2.90, -1.56) for individuals that presented with reduced fat mass compared to patients that had normal fat mass, respectively.

During the first three months in the overall two spline model, patients that presented with reduced fat mass had a significantly gain in FMI at rate of 2.10 (95% CI: 0.25, 3.96) kg/m^2 per month whereas patients that presented with normal fat mass had minimal change in FMI at a rate of -0.53 (95% CI: -2.32, 1.27) kg/m^2 per month (Tables 10:6 and

10:7). In stratified mixed effects two spline models according to HIV status, there were minimal changes in FMI regardless of the initial fat mass level. However, the slopes were significantly different during the first three months between patients that presented with reduced fat mass and those that had normal fat mass at diagnosis for the overall population model and in stratified models according to HIV status. After month 3 and before month 12 in the overall population model and in stratified models according to HIV status, patients that presented with normal fat mass at diagnosis, had significant gain in FMI; however, there were no differences in slopes between the rate of increase in patients that presented with reduced fat mass and those that had normal fat mass (Tables 10:6 and 10:7).

Body mass index

The population average BMI at baseline, month 3, and month 12 in multivariable mixed effects two spline model at month 3 and at month 12 with BMI as the dependent variable when HIV was replaced by gender among the adjusters was -3.59 (95% CI; -3.98, -3.20), -3.22 (95% CI; -3.63, -2.80), and -3.47 (95% CI; -4.02, -2.03) kg/m^2 significantly lower among patients that presented with reduced BMI compared to patients that had normal BMI, respectively. On average among HIV negative individuals in stratified models at baseline, month 3, and month 12, BMI was -3.49 (95% CI: -4.08, -2.91), -2.91 (95% CI: -3.56, -2.26), and -3.15 (95% CI: -3.95, -2.34) significant lower among individuals that presented with reduced BMI compared to those that had normal BMI at diagnosis, respectively. Similarly, among HIV positive individuals at baseline, month 3, and month

12, BMI was -3.70 (95% CI; -4.23, -3.17), -3.48 (95% CI: -4.01, -2.95), and -3.70 (95% CI: -4.43, 2.97) for individuals that presented with reduced BMI compared to individuals that had normal BMI, respectively.

In the overall two spline model during the first three months, patients that presented with reduced BMI had a significantly gain in BMI at rate of 2.87 (95% CI: 0.78, 4.96) kg/m^2 per month whereas patients that presented with normal BMI had minimal gain in BMI at a rate of 1.38 (95% CI: -0.42, 3.17) kg/m^2 per month (Tables 10:6 and 10:7). In stratified mixed effects two spline models, the gain in BMI among patients that presented with reduced BMI at diagnosis was however substantial in HIV positive individuals at rate of 3.16 (95% CI: 0.51, 5.82). The gain was minimal among HIV negative individuals that presented with reduced BMI with a rate of 3.39 (95% CI: -0.03, 6.80). The slopes however were not different during the first three months between patients that presented with reduced BMI and those that had normal BMI at diagnosis for HIV positive individuals in the stratified model. There were marginal changes in BMI after month 3 and during the one year of follow-up after month 12 in the total population and in stratified models for HIV negative and HIV negative individuals (Tables 10:6 and 10:7).

Discussion

To our knowledge, this is the first study to report a two year follow-up of changes in body composition and how the changes differ by gender and by HIV status among tuberculosis patients in urban Uganda, Kampala. In this retrospective cohort study of adult patients with pulmonary tuberculosis in urban Uganda, body wasting as measured

by reduced fat-free mass, fat mass, and body mass indexes was associated with a substantial linear increase in fat-free mass, fat mass and body mass index during the first three of months tuberculosis treatment, but the increase varied by gender and not by HIV status of the patient. Changes in body composition among men were affected by the initial fat-free mass and BMI whereas in women, body composition changes were affected by the initial fat mass. The body composition changes among HIV positive and HIV negative patients with tuberculosis appear not to be influenced by the initial fat-free mass, fat mass, and BMI at diagnosis. There were minimal changes in body composition after three months of tuberculosis treatment and during the one year period of follow-up after month 12 among regardless of the initial body composition, gender and HIV status suggesting lack of catch-up to normal nutritional status for patients that present with body wasting.

Our findings appear to suggest that in the face of body wasting and malnutrition during the first three months of tuberculosis treatment, changes in body composition are affected by gender but not HIV. HIV appears to play a marginal role for changes in BMI in co-infected individuals. Men that had reduced fat-free mass and BMI at diagnosis attained dramatic linear increases in fat-free mass and BMI during the first three months of tuberculosis treatment compared to men that had normal fat-free mass and BMI. However, women who presented with reduced fat mass had substantial linear increase in fat mass compared to women that had normal fat mass. There were no changes in FFMI

and FMI during the first three months of tuberculosis treatment regardless of HIV status. There was no difference in slopes between patients that had reduced BMI and those that had normal BMI at diagnosis regardless of HIV status during the first three months of tuberculosis treatment.

This study is the first to report that the initial fat-free mass and BMI influences the subsequent changes in body composition among men with tuberculosis. However, the notion that the initial fat mass in women may influence subsequent changes in body composition has been reported previously in during HIV (Swanson et al. 2000). Results of the present study are consistent with previous studies (Paton et al. 2004) that revealed total lean tissue referred to as fat-free mass increased during the first six weeks of tuberculosis treatment and thereafter the increase was in fat mass. In our present study, there were minimal changes in body composition after month 3 with slight increase in fat mass for men and slight increase in BMI for HIV positive individuals. The prior study (Paton et al. 2004); however, was limited by sample size of only 36 participants, the study population comprised of only patients who were wasted (BMI <18.5 kg/m^2) and had no HIV, and it had a short duration of follow-up for only 6 months. The strengths of the present study include: large number of study participants comprising of women and men, both wasted and not wasted, both HIV positive and HIV negative individuals, and long duration of follow-up.

The present study has shown that patients who presented with reduced fat and fat-free mass gained in body composition at a higher rate than patients who presented with normal levels of fat and fat-free mass, particularly during the first three months of tuberculosis treatment. However, the gain was predominantly fat mass among women whereas men gained predominantly fat-free mass plus substantial levels of fat mass. The potential explanation appears to rest on the gender differences in fat-free mass content. Women tend to have low fat-free mass compared to men, yet fat-free mass has been shown to be a significant determinant of fat oxidation (Nagy et al. 1996; Toth et al. 1996). In several reports after adjusting for difference in fat-free mass, resting fat oxidation is lower in women than men (Nagy et al. 1996; Horton et al. 1998; Toth et al. 1998). Thus, this gender differences in fat metabolism as explained elsewhere (Blaak 2001), is associated with lower basal fat oxidation that may contribute to the increased fat storage or gain in women compared to men. Moreover, longitudinal studies have shown that low rates of fat utilization predict subsequent weight (Zurlo et al. 1990). Besides differences in lipolysis, other factors such as differences in hormone action may contribute to differences in fat oxidation. Higher levels of androgens in men stimulate the formation of the nucleic acids essential for protein biosynthesis (Mooradian, Morley, and Korenman 1987) with eventual increase in lean tissue.

In normal healthy adults, protein catabolism equals protein anabolism; however, protein catabolism exceeds protein anabolism in tuberculosis (Macallan et al. 1998). In general; however, the catch-up linear increase in lean tissue during the first three months among patients that presented with reduced fat-free mass levels suggest that patients with

tuberculosis can mount a protein anabolic response during treatment (Paton et al. 2003; Macallan et al. 1998). It may be possible that the degree of body wasting offsets the stimulus of tuberculosis on protein metabolism till a net state of anabolism (Tomkins et al. 1983) even as the patient become sterile from the causative organism during treatment. In the present study, there minimal changes in fat-free mass regardless of gender and HIV status after month 3 on follow-up. Alternatively, the response could be explained by the effective adaptive response of protein metabolism to chronic inflammatory state (Paton et al. 2001).

Despite the dramatic linear increase in fat-free mass, fat mass, and BMI among patients who presented with body wasting, these patients did not normalize their indices for body composition. That is they did not regain body composition comparable to patients presenting without wasting. There may be several explanations for this. It is possible that patients who present with wasting at the time of tuberculosis diagnosis were of slim body build before disease as compared to the patients that present with normal nutritional status. While on tuberculosis treatment, the patients with apparent regain the original body composition status prior to onset of tuberculosis disease. Following attainment of the original body composition, there are minimal changes in lean tissue and individuals adapt effective energy-sparing mechanism in balance with the usual energy intake (Kurpad, Muthayya, and Vaz 2005; Ferro-Luzzi et al. 1997). It is also possible that households where tuberculosis occurs in Uganda, and in other countries in sub-Saharan region, there is food insecurity compromising energy intake. Thus, persistently low body composition may mark lack of access to sufficient calorie and protein intake. The

persistently low body composition measures even after effective tuberculosis treatment may be a marker for future health risks. Among patients with wasting who do not normalize, there may be consequences regarding survival and physical function in the event of any future disease insult. Further research is needed to understand the health risk among these patients.

In this study, we used the BIA method in measurement of body composition, yet it is not of reference standard like the dual-energy x-ray absorptiometry. The BIA prediction method used has not yet been validated in the local population. As a result, findings of body composition may be biased because of variations in hydration across ethnic groups (Kyle et al. 2004). However, the equations that were used in this study were previously cross validated in individuals of different race (white, black, and Hispanic) among men and women, who were both healthy controls and HIV-infected patients (Kotler et al. 1996). Moreover, the equations have been used widely in other studies from Africa with meaningful findings (Shah et al. 2001; Van Lettow et al. 2004; Villamor et al. 2006; Mupere et al. 2010). We also took care to take measurements at rest, with proper placement of leads, in participants who had not exercised or taken alcohol, in participants with voided bladder and ambient temperature. However, measurements were in patients with underlying illness that may cause shifts in body water compartments, thereby affecting measurements of fat mass. Our findings also limited by the lack of dietary intake assessment to give further insight in the interpretation of gender differences in longitudinal body composition changes.

Despite limitations of the present study, findings in this study revealed remarkable gender but not HIV differences in longitudinal body composition changes during the initial phase of treatment among tuberculosis patients that presented with body wasting and malnutrition. Body composition changes among men were affected by the initial fat-free mass whereas among women by fat mass. Further evaluation is needed to under the impact of providing nutritional interventions as adjuvant treatment on body composition among TB patients in sub-Saharan and evaluation of nutritional status should be involve BMI, fat and fat-free mass.

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Table 10:2 Baseline characteristics of the study population with/without baseline wasting

	FFMI		FMI		BMI	
Characteristic	Normal (n=184)	Wasting (n=94)	Normal (n=158)	Wasting (n=120)	Normal (n=424)	Wasting (n=293)
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Age (years)						
≤30	122 (66)	54 (57)	99 (63)	77 (64)	252 (59)	170 (58)
>30	62 (34)	40 (43)	59 (37)	43 (36)	172 (41)	123 (42)
Sex						
Female	115 (62)	19 (20)[a]	65 (41)	69 (58)[b]	232 (55)	115 (39)[a]
Male	69 (38)	75 (80)	93 (59)	51 (42)	192 (45)	178 (61)
HIV-serostatus						
Negative	105 (57)	53 (56)	90 (57)	68 (57)	198 (47)	140 (48)
Positive	79 (43)	41 (44)	68 (43)	52 (43)	226 (53)	153 (52)
HGB (mg/dl)[1]						
>10	140 (76)	72 (77)	135 (85)	77 (64)[a]	208 (81)	118 (64)[a]

≤10	44 (24)	22 (23)	23 (15)	43 (36)	48 (19)	67 (36)
Smoker[2]						
No	159 (87)	56 (60)[a]	127 (80)	88 (74)	364 (86)	210 (72)[a]
Yes	24 (13)	38 (40)	31 (20)	31 (26)	58 (14)	82 (28)
Takes alcohol[3]						
No	135 (74)	59 (63)	106 (67)	88 (74)	259 (61)	192 (66)
Yes	48 (26)	35 (37)	52 (33)	31 (26)	164 (39)	101 (34)
Extent CXR[4]						
Normal/minimal	38 (21)	8 (9)[b]	26 (17)	20 (17)	74 (18)	33 (11)[b]
Mod/advanced	143 (79)	86 (91)	131 (83)	98 (83)	346 (82)	257 (89)
Weight loss[5]						
No	32 (17)	12 (13)	31 (20)	13 (11)	107 (25)	52 (18)[b]
Yes	151 (83)	82 (87)	126 (80)	107 (89)	315 (75)	240 (82)

[a]p-value <0.001, [b]p-value <0.05. BMI = body mass index, FFMI = fat-free mass index, FMI = fat mass index. [1]276 missed hemoglobin measurement due to lack of blood for BMI data; [4]three missed extent variable in BIA data and 7 in BMI data; [3]one missed history of prior smoking in BIA data and 3 missed in BMI data; [3]one missed history of alcohol intake for BMI and BIA data; [5]one missed history of weight loss for BIA data and 3 missed in BMI data; FFMI wasting (<16.7 kg/m^2 for men and <14.6 kg/m^2 for women, normal (≥ 16.7kg/m^2 for men, ≥14.6 kg/m^2 for women); reduced BMI <18.5 kg/m^2.

Table 10:3 Unadjusted rate of change for fat-free mass (FFMI), fat mass (FMI), and body mass index (BMI) among pulmonary patients with reduced FFMI, FMI, and BMI in Kampala, Uganda

Characteristic	Rate	SE	95% CI
Baseline fat-free mass index			
Not wasted, slope before 3 mo	1.59	0.32	**0.96, 2.23**
Wasted, slope before 3 mo	4.02	0.45	**3.14, 4.91**
Not wasted, slope after 3 mo	0.06	0.11	-0.15, 0.28
Wasted, slope after 3 mo	-0.07	0.16	-0.39, 0.24
Not wasted, slope after 12 mo	0.11	0.09	-0.06, 0.29
Wasted, slope after 12 mo	0.06	0.14	-0.21, 0.33
Difference in slope before 3 mo	2.43	0.56	**1.34, 3.52**
Difference in slope after 3 mo	-0.14	0.19	-0.52, 0.24
Difference in slope after 12 mo	-0.05	0.16	-0.37, 0.27
Baseline fat mass index			
Not wasted, slope before 3 mo	0.58	0.36	-0.12, 1.29
Wasted, slope before 3 mo	2.99	0.41	**2.18, 3.80**

Not wasted, slope after 3 mo	1.07	0.16	**0.77, 1.38**
Wasted, slope after 3 mo	1.02	0.18	**0.67, 1.38**
Not wasted, slope after 12 mo	0.23	0.13	-0.03, 0.49
Wasted, slope after 12 mo	0.39	0.15	**0.10, 0.68**
Difference in slope before 3 mo	2.41	0.55	**1.33, 3.48**
Difference in slope after 3 mo	-0.05	0.24	-0.52, 0.42
Difference in slope after 12 mo	0.17	0.20	**-0.22, 0.55**
Baseline body mass index			
Not wasted, slope before 3 mo	3.94	0.32	**3.32, 4.56**
Wasted, slope before 3 mo	6.66	0.38	**5.91, 7.41**
Not wasted, slope after 3 mo	0.94	0.13	**0.69, 1.18**
Wasted, slope after 3 mo	0.72	0.15	**0.42, 1.02**
Not wasted, slope after 12 mo	0.30	0.10	**0.10, 0.50**
Wasted, slope after 12 mo	0.20	0.12	-0.05, 0.40
Difference in slope before 3 mo	2.72	0.50	**1.74, 3.69**
Difference in slope after 3 mo	-0.22	0.20	-0.61, 0.17
Difference in slope after 12 mo	-0.11	0.16	-0.42, 0.21

Fat-free mass wasting = FFMI <16.7 kg/m^2 for men and <14.6 kg/m^2 for women, fat mass wasting = FMI <1.8 kg/m^2 for men and <3.9 kg/m^2 for women; reduced BMI <18.5 kg/m^2 for women and men.

Table 10:4 Adjusted rate of change for fat-free mass (FFMI), fat mass (FMI), and body mass index (BMI) among tuberculosis patients presenting with reduced FFMI, FMI, and BMI in Kampala, Uganda

Characteristics	Overall model		
	Rate	**SE**	**95% CI**
Baseline fat-free mass index			
Not wasted, slope before 3 mo	0.35	0.88	-1.38, 2.08
Wasted, slope before 3 mo	2.68	1.05	**0.68, 4.67**
Not wasted, slope after 3 mo	0.52	0.31	-0.09, 1.13
Wasted, slope after 3 mo	0.41	0.36	-0.30, 1.12
Not wasted, slope after 12 mo	0.02	0.23	-0.44, 0.48
Wasted, slope after 12 mo	-0.05	0.28	-0.60, 0.50
Difference in slope before 3 mo	2.33	0.57	**1.20, 3.45**
Difference in slope after 3 mo	-0.10	0.20	-0.51, 0.30
Difference in slope after 12 mo	-0.07	0.17	-0.40, 0.26
Baseline fat mass index			

Not wasted, slope before 3 mo	-0.11	0.93	-1.94, 1.73
Wasted, slope before 3 mo	2.23	0.98	**0.30, 4.16**
Not wasted, slope after 3 mo	1.18	0.41	**0.38, 1.98**
Wasted, slope after 3 mo	1.08	0.43	**0.23, 1.93**
Not wasted, slope after 12 mo	0.38	0.31	-0.24, 0.99
Wasted, slope after 12 mo	0.58	0.34	-0.08, 1.24
Difference in slope before 3 mo	2.33	0.55	**1.26, 3.41**
Difference in slope after 3 mo	-0.09	0.24	-0.57, 0.38
Difference in slope after 12 mo	0.20	0.20	-0.19, 0.59
Baseline body mass index			
Not wasted, slope before 3 mo	2.25	0.98	**0.33, 4.17**
Wasted, slope before 3 mo	3.83	1.10	**1.67, 5.99**
Not wasted, slope after 3 mo	1.22	0.44	**0.36, 2.07**
Wasted, slope after 3 mo	0.79	0.49	-0.17, 1.76
Not wasted, slope after 12 mo	0.23	0.35	-0.46, 0.91
Wasted, slope after 12 mo	0.08	0.40	-0.71, 0.87
Difference in slope before 3 mo	1.58	0.60	**0.40, 2.75**

Difference in slope after 3 mo	-0.43	0.28	-0.97, 0.11
Difference in slope after 12 mo	-0.14	0.23	-0.60, 0.32

Fat-free mass and BMI multivariable models were adjusted for HIV, status of anemia, prior smoking status, history of weight loss, and extent of disease on chest x-ray. Fat mass multivariable model was adjusted for HIV, prior smoking status, history of weight loss, and extent of disease on chest x-ray. Fat-free mass wasting = FFMI <16.7 kg/m^2 for men and <14.6 kg/m^2 for women, fat mass wasting = FMI <1.8 kg/m^2 for men and <3.9 kg/m^2 for women; reduced BMI <18.5 kg/m^2 for women and men.

Table 10:5 Adjusted rate of change for fat-free mass (FFMI), fat mass (FMI), and body mass index (BMI) among tuberculosis patients presenting with reduced FFMI, FMI, and BMI stratified according to gender in Kampala, Uganda

Characteristics	Stratified models					
	Women			Men		
	Rate	SE	95% CI	Rate	SE	95% CI
Baseline fat-free mass index						
Not wasted, slope before 3 mo	-0.21	1.03	-2.24, 1.81	2.67	1.62	-0.52, 5.85
Wasted, slope before 3 mo	2.07	1.43	-0.74, 4.88	4.55	1.67	**1.26, 7.83**
Not wasted, slope after 3 mo	0.49	0.38	-0.25, 2.23	0.57	0.54	-0.50, 1.63
Wasted, slope after 3 mo	0.50	0.55	-0.57, 1.58	0.28	0.57	-0.84, 1.40
Not wasted, slope after 12 mo	0.30	0.31	-0.32, 0.92	-0.25	0.37	-0.98, 0.47
Wasted, slope after 12 mo	0.13	0.49	-0.83, 1.09	-0.28	0.39	-1.05, 0.50
Difference, slope before 3 mo	2.29	0.97	**0.38, 4.19**	1.88	0.77	**0.36, 3.39**
Difference, slope after 3 mo	0.01	0.39	-0.75, 0.77	-0.29	0.26	-0.79, 0.22
Difference, slope after 12 mo	-0.17	0.36	-0.87, 0.53	-0.02	0.19	-0.40, 0.35
Baseline fat mass index						

Not wasted, slope before 3 mo	0.13	1.38	-2.58, 2.83	1.10	1.23	-1.31, 3.51
Wasted, slope before 3 mo	3.55	1.60	**0.40, 6.70**	3.16	1.20	**0.80, 5.52**
Not wasted, slope after 3 mo	1.80	0.64	**0.54, 3.07**	-0.09	0.46	-1.00, 0.82
Wasted, slope after 3 mo	1.41	0.75	-0.06, 2.89	-0.24	0.46	-1.14, 0.65
Not wasted, slope after 12 mo	0.11	0.48	-0.83, 1.05	0.92	0.37	**0.20, 1.65**
Wasted, slope after 12 mo	0.21	0.57	-0.91, 1.33	1.03	0.35	**0.35, 1.72**
Difference, slope before 3 mo	3.42	0.96	**1.54, 5.30**	2.06	0.61	**0.86, 3.25**
Difference, slope after 3 mo	-0.39	0.44	-1.26, 0.48	-0.15	0.23	-0.61, 0.30
Difference, slope after 12 mo	0.10	0.35	-0.59, 0.80	0.11	0.19	-0.27, 0.49
Baseline body mass index						
Not wasted, slope before 3 mo	1.97	1.43	-0.83, 4.77	4.75	1.66	**1.49, 8.00**
Wasted, slope before 3 mo	3.30	1.74	-0.11, 6.72	6.45	1.75	**3.02, 9.87**
Not wasted, slope after 3 mo	1.57	0.67	**0.27, 2.88**	0.67	0.56	-0.42, 1.76
Wasted, slope after 3 mo	1.62	0.83	-0.00, 3.24	0.03	0.58	-1.11, 1.17
Not wasted, slope after 12 mo	0.22	0.49	-0.75, 1.18	0.51	0.48	-0.43, 1.46
Wasted, slope after 12 mo	-0.11	0.62	-1.33, 1.11	0.56	0.51	-0.45, 1.57
Difference, slope before 3 mo	1.33	1.08	-0.80, 3.46	1.70	0.77	**0.20, 3.20**

Difference, slope after 3 mo	0.05	0.52	-0.98, 1.07	-0.64	0.27	**-1.16, -0.12**
Difference, slope after 12 mo	-0.32	0.40	-1.11, 0.46	0.04	0.25	-0.44, 0.53

Fat-free mass and BMI multivariable models were adjusted for HIV, status of anemia, prior smoking status, history of weight loss, and extent of disease on chest x-ray. Fat mass multivariable model was adjusted for HIV, prior smoking status, history of weight loss, and extent of disease on chest x-ray. Fat-free mass wasting = FFMI <16.7 kg/m^2 for men and <14.6 kg/m^2 for women, fat mass wasting = FMI <1.8 kg/m^2 for men and <3.9 kg/m^2 for women; reduced BMI <18.5 kg/m^2 for women and men.

Table 10:6 Adjusted rate of change for fat-free mass (FFMI), fat mass (FMI), and body mass index (BMI) among tuberculosis patients presenting with reduced FFMI, FMI, and BMI in Kampala, Uganda

Characteristics	Overall model		
	Rate	**SE**	**95% CI**
Baseline fat-free mass index			
Not wasted, slope before 3 mo	-0.35	0.87	-2.05, 1.36
Wasted, slope before 3 mo	1.59	1.04	-0.46, 3.64
Not wasted, slope after 3 mo	0.34	0.31	-0.27, 0.95
Wasted, slope after 3 mo	0.15	0.38	-0.60, 0.90
Not wasted, slope after 12 mo	0.11	0.23	-0.34, 0.57
Wasted, slope after 12 mo	0.06	0.30	-0.53, 0.65
Difference in slope before 3 mo	1.93	0.60	**0.75, 3.11**
Difference in slope after 3 mo	-0.19	0.22	-0.62, 0.23
Difference in slope after 12 mo	-0.05	0.18	-0.40, 0.30
Baseline fat mass index			

Not wasted, slope before 3 mo	-0.53	0.91	-2.32, 1.27
Wasted, slope before 3 mo	2.10	0.94	**0.25, 3.96**
Not wasted, slope after 3 mo	1.60	0.39	**0.82, 2.37**
Wasted, slope after 3 mo	1.30	0.41	**0.49, 2.10**
Not wasted, slope after 12 mo	0.40	0.31	-0.20, 1.00
Wasted, slope after 12 mo	0.59	0.32	-0.05, 1.23
Difference in slope before 3 mo	2.63	0.56	**1.53, 3.73**
Difference in slope after 3 mo	-0.30	0.24	-0.77, 0.17
Difference in slope after 12 mo	0.19	0.20	-0.20, 0.58
Baseline body mass index			
Not wasted, slope before 3 mo	1.38	0.91	-0.42, 3.17
Wasted, slope before 3 mo	2.87	1.07	**0.78, 4.96**
Not wasted, slope after 3 mo	1.35	0.41	**0.55, 2.16**
Wasted, slope after 3 mo	1.01	0.48	0.07, 1.96
Not wasted, slope after 12 mo	0.14	0.33	-0.51, 0.78
Wasted, slope after 12 mo	0.01	0.40	-0.76, 0.79
Difference in slope before 3 mo	1.49	0.61	**0.31, 2.68**

Difference in slope after 3 mo	-0.34	0.28	-0.88, 0.20
Difference in slope after 12 mo	-0.12	0.24	-0.59, 0.34

Adjusted for HIV,age, status of anemia, smoking status, history of weight loss, and extent of disease on chest x-ray

Table 10:7 Adjusted rate of change for fat-free mass (FFMI), fat mass (FMI), and body mass index (BMI) among tuberculosis patients presenting with reduced FFMI, FMI, and BMI stratified according to HIV in Kampala, Uganda

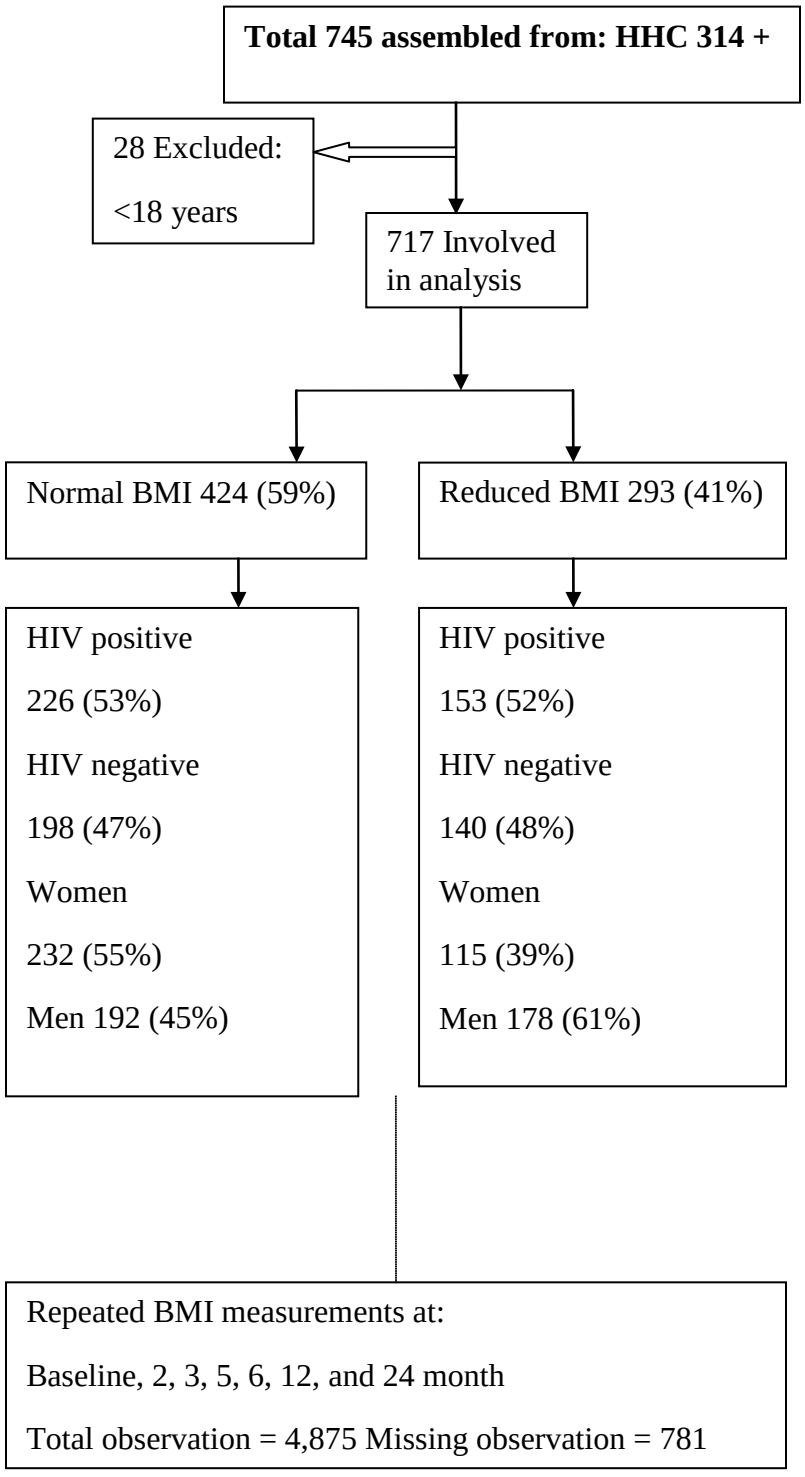
Characteristics	Stratified models					
	HIV negative			HIV positive		
	Rate	SE	95% CI	Rate	SE	95% CI
Baseline fat-free mass index						
Not wasted, slope before 3 mo	-0.26	1.04	-2.31, 1.79	-0.58	1.58	-3.69, 2.53
Wasted, slope before 3 mo	1.40	1.26	-1.08, 3.88	1.84	1.89	-1.88, 5.56
Not wasted, slope after 3 mo	0.02	0.40	-0.77, 0.81	0.71	0.54	-0.35, 1.77
Wasted, slope after 3 mo	-0.20	0.49	-1.16, 0.76	0.55	0.65	-0.73, 1.83
Not wasted, slope after 12 mo	0.26	0.23	-0.18, 0.71	-0.19	0.48	-1.15, 0.76
Wasted, slope after 12 mo	0.19	0.28	-0.37, 0.75	-0.25	0.66	-1.55, 1.04
Difference, slope before 3 mo	1.66	0.72	**0.24, 3.07**	2.42	0.99	**0.46, 4.38**
Difference, slope after 3 mo	-0.22	0.27	-0.76, 0.32	-0.16	0.34	-0.83, 0.51
Difference, slope after 12 mo	-0.07	0.16	-0.39, 0.24	-0.06	0.39	-0.82, 0.71
Baseline fat mass index						

Not wasted, slope before 3 mo	0.33	0.98	-1.60, 2.27	-2.54	1.76	-6.00, 0.93
Wasted, slope before 3 mo	1.97	1.04	-0.07, 4.01	1.79	1.80	-1.76, 5.35
Not wasted, slope after 3 mo	1.26	0.55	**0.18, 2.34**	2.04	0.64	**0.78, 3.30**
Wasted, slope after 3 mo	1.13	0.58	-0.06, 2.27	1.42	0.65	**0.14, 2.70**
Not wasted, slope after 12 mo	0.49	0.41	-0.31, 1.29	-0.15	0.49	-1.11, 0.81
Wasted, slope after 12 mo	0.41	0.42	-0.42, 1.24	0.56	0.51	-0.46, 1.57
Difference, slope before 3 mo	1.63	0.57	**0.51, 2.76**	4.33	1.03	**2.30, 6.36**
Difference, slope after 3 mo	-0.13	0.31	-0.73, 0.48	-0.62	0.38	-1.37, 0.13
Difference, slope after 12 mo	-0.08	0.23	-0.54, 0.37	0.71	0.34	**0.03, 1.38**
Baseline body mass index						
Not wasted, slope before 3 mo	1.06	1.51	-1.90, 4.02	2.26	1.14	**0.02, 4.51**
Wasted, slope before 3 mo	3.39	1.74	-0.03, 6.80	3.16	1.35	**0.51, 5.82**
Not wasted, slope after 3 mo	1.06	0.63	-0.18, 2.90	1.68	0.52	**0.67, 2.70**
Wasted, slope after 3 mo	0.74	0.72	-0.68, 2.16	1.38	0.63	**0.15, 2.62**
Not wasted, slope after 12 mo	0.20	0.46	-0.70, 1.10	0.15	0.43	-0.69, 0.99
Wasted, slope after 12 mo	0.11	0.54	-0.94, 1.17	0.21	0.54	-0.85, 1.28
Difference, slope before 3 mo	2.33	0.96	**0.45, 4.20**	0.90	0.78	-0.63, 2.43

Difference, slope after 3 mo	-0.32	0.40	-1.09, 0.46	-0.30	0.37	-1.03, 0.43
Difference, slope after 12 mo	-0.09	0.30	-0.68, 0.51	0.06	0.34	-0.60, 0.73

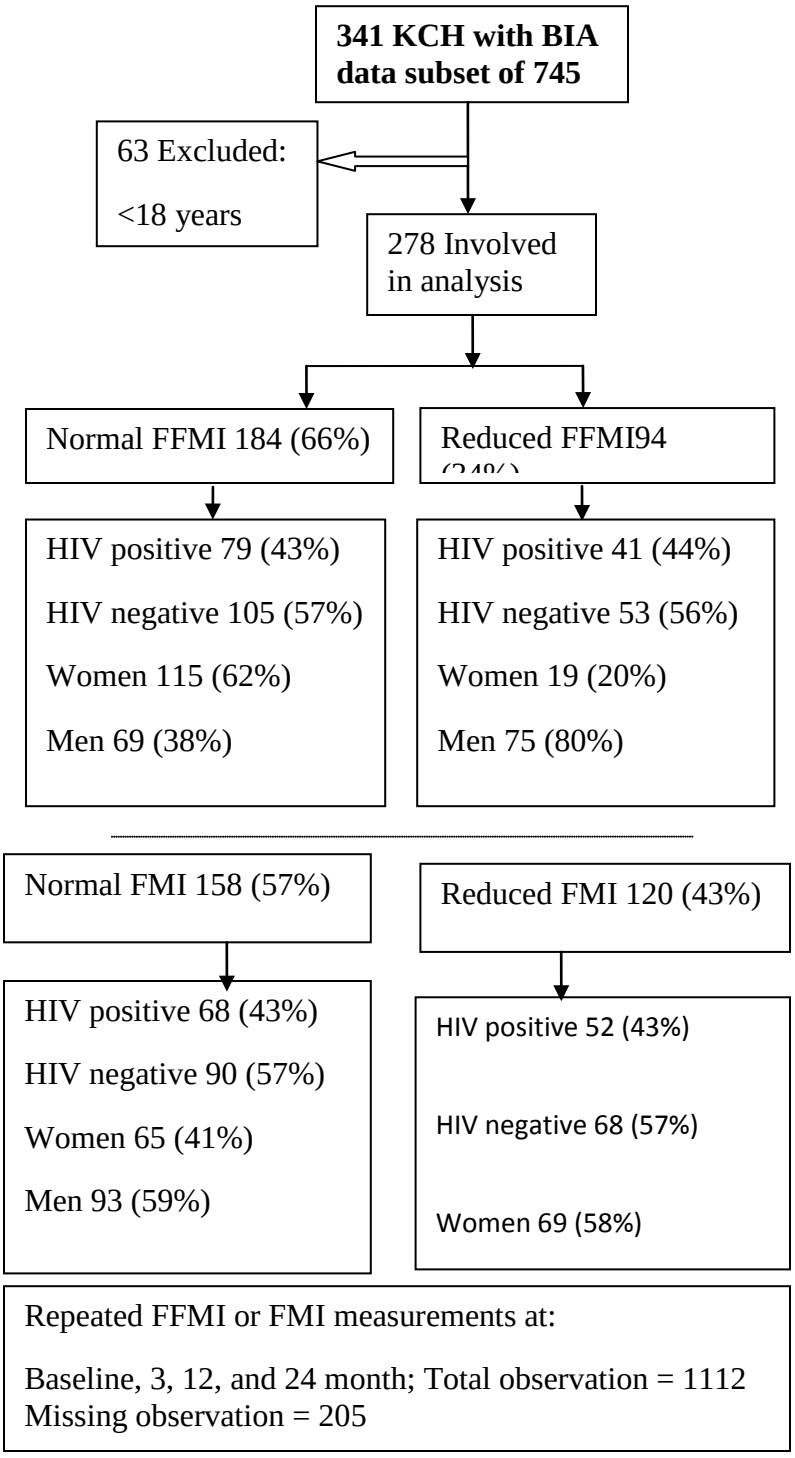
Adjusted for HIV,age, status of anemia, smoking status, history of weight loss, and extent of disease on chest x-ray

Figure 10:1 Overall Study flow diagram



Reduced BMI <18.5 kg/$m^2$for men and women.

Figure 10:2 Study flow diagram for BIA data



FFMI wasting (<16.7 kg/m^2 for men and <14.6 kg/m^2 for women, normal (≥ 16.7kg/m^2 for men, ≥14.6 kg/m^2 for women).

CHAPTER 11

SUMMARY OF RESULTS AND GENERAL CONCLUSIONS

DISCUSSION

Introduction

Body wasting is a cardinal feature of tuberculosis and is probably one of the determinants of disease severity and outcome. However, its etiology and its management are poorly understood, and its assessment is overlooked in research and in clinical practice. Body wasting is loss of body mass, most notably muscle or lean body mass referred to as fat-free mass. The simple and portable bioelectrical impedance analysis (BIA) device provides the precise and practical approach of partitioning body weight into fat and fat-free mass in clinical medicine. However, it may not be easily affordable and accessible in sub-Saharan Africa where it is needed to detect body wasting early enough among tuberculosis and HIV patients. Sub-Saharan Africa has a high burden of tuberculosis and HIV-associated tuberculosis. The widely used body mass index (BMI) in assessing body wasting is popularly a measure of body fat and it gives unreliable results of wasting when it is low. Thus, BMI overestimates body wasting. BMI can be partitioned into body fat mass (FMI) and fat-free mass (FFMI) indices by dividing fat and fat-free mass with height. Body composition in this dissertation refers to fat and fat-free mass compartments of the body weight.

The data that was used to generate results in this dissertation were obtained from cross-sectional and retrospective cohort designs. The cross-sectional design enrolled 131 HIV positive and HIV negative adults with or without tuberculosis in urban Uganda. In this

design, participants were assessed for waist circumference (WC), BMI, mid-upper-arm circumference (MUAC), and the 24-hour dietary intake recall. In a retrospective cohort design, 745 adult tuberculosis patients that were merged from three completed NIH funded prospective studies at the Uganda-Case Western Reserve University research collaboration were analyzed. All patients were screened for HIV infection and had BMI measurements at month 0, 2, 3, 5, 6, 12, and 24 on follow-up. A subset (314) of the 745 had BIA fat and fat-free mass measurements at month 0, 3, 12, and 24 on follow-up. Any case of deaths and date was documented on follow-up.

Purpose

The purpose of this dissertation was to generate information that could be used to improve survival in tuberculosis patients. This dissertation focused first on understanding simple and inexpensive approaches of assessing body wasting. Second, focused on generating information that could aid in understanding of body wasting and its management, that is whether nutritional factors influence body composition in the face of tuberculosis; and whether body wasting as measured by precise measures of body composition modifies the course of tuberculosis.

SUMMARY OF RESULTS

Chapter Four: Body Composition Measured with Bioelectrical Impedance Analysis and Anthropometry among HIV Positive and HV Negative Adults with or without Tuberculosis in Urban Kampala, Uganda

Analysis in this chapter established whether known existing equations that estimated body composition among Caucasians could provide comparable results of body composition to those of BIA device in an African population in Uganda. The equations involved simple measurements such as WC, BMI, and MUAC. Findings among 131 HIV positive and HIV negative adults with or with tuberculosis revealed that existing equations that provided comparable results of body composition to those of BIA differed by gender and tuberculosis status. The equation that involved MUAC or BMI provided comparable results of lean tissue to that of BIA whereas the equation that involved MUAC provided comparable results of fat mass among men and women with tuberculosis regardless of HIV status. Among men without tuberculosis, the equation that involved MUAC provided comparable results of fat and lean tissue to that of BIA whereas among women without tuberculosis, the equation that involved WC provided comparable results of fat and lean tissue regardless of HIV status.

Chapter Five: Indicators of Dietary Adequacy among HIV Positive and HIV Negative Adults in Urban Kampala, Uganda

Analysis in this chapter involved 131 HIV positive and HIV negative adults with or without tuberculosis from urban Uganda to assess nutritional adequacy of dietary intake and the validity of simple low-cost methods to evaluate nutritional adequacy of diets consumed among HIV positive and HIV negative adults with or without tuberculosis in urban Uganda. Findings revealed that all participants (100%) consumed at least cereals, roots, and tubers, and 90% consumed vegetables not rich in vitamin A such tomatoes and onions while only 45% consumed vitamin-A-rich fruits and vegetables, and only 15% consumed eggs.

The mean FVS and DDS for the study population were low 8.1 ± 2.8 and 4.7 ± 1.4, respectively. Both men and women regardless of tuberculosis and HIV status, had carbohydrate and ascorbic acid deficiency in the range of 0 to 30% whereas other nutrient intakes including energy, protein, dietary fiber, calcium, magnesium, zinc, iron, vitamin A, vitamin D, and folate had deficiencies ranging 25% to 100%. When a MAR of 65% was used as a cut-off point for nutrient adequacy, it was found that FVS must be 9 or more and DDS must at least 5. Among women, both FVS and DDS had a high ability to identify participants with an inadequate or adequate diet while among men FVS had a high ability to identify individuals with inadequate diet but low ability to identify those with adequate diet, DDS had low ability to identify individuals with inadequate diet but had a high ability to identify those with adequate diet.

Chapter Six: Predictors of Fat and Lean Tissue among HIV Positive and HIV Negative Adults with or without Tuberculosis in Urban Kampala, Uganda.

Analysis in this chapter aimed to establish factors that may influence fat mass, fat-free mass (lean tissue), and BMI among 131 HIV positive and HIV negative adults with or without tuberculosis in urban Uganda. We found that energy intake was associated with an increase in BMI among women (0.003 ± 0.001 SE, p=0.028) although intake in the presence of tuberculosis was associated with a decrease in BMI (-0.004 ± 0.001 SE, p=0.008). Protein intake among women with no income (-0.02 ± 0.01 SE, p=0.027) and among unemployed women (-0.08 ± 0.03 SE, p=0.010) was associated with a decrease in lean tissue and fat mass, respectively whereas protein intake among women with tuberculosis was associated with an increase in BMI (0.10 ± 0.05 SE, p=0.039). Being a single woman (0.58 ± 0.25 SE, p=0.022) was associated with an increase in lean tissue whereas having reduced appetite (-0.79 ± 0.33 SE, p=0.020) was associated with a decrease in lean tissue and fat mass (-4.17 ± 1.94 SE, p=0.036). Among men, tuberculosis (-1.42 ± 0.45 SE, p=0.003) was associated with a decrease in lean tissue. Similarly, having reduced appetite was associated with decrease in fat mass (-1.90 ± 0.90 SE, p=0.040) and BMI (-2.95 ± 0.68 SE, p<0.001). HIV did not influence body composition regardless of gender.

Chapter Seven: Body Wasting and Dietary Intake among HIV Positive and HIV Negative Adults with or without Tuberculosis in Urban Kampala, Uganda

The analysis in this chapter involved 131 HIV positive and HIV negative adults with or with tuberculosis to evaluate the independent effects of tuberculosis and HIV, to evaluate whether dietary intake differs by body wasting and severity of tuberculosis disease. We found that tuberculosis patients that had moderate/or severe clinical disease had lower dietary intake for energy, protein, total fat, carbohydrate, calcium, vitamin A, and folate compared to patients with mild disease. Both men and women had comparable dietary intake among patients with TB regardless of HIV status whereas HIV negative women had reduced energy, protein, and folate intake among individuals without TB compared to men. Tuberculosis patients with wasting of lean tissue or those with reduced BMI had comparable nutrient intake with counterparts that had normal lean tissue or normal BMI.

Chapter Eight: Correlates of Dietary Adequacy among HIV Positive and HIV Negative Adults with or without Tuberculosis in Urban Kampala, Uganda

In this chapter, we evaluated dietary correlates of energy and protein intake and correlates of inadequate nutrient intake. There was female gender interaction between having tuberculosis and reduced appetite, and between having tuberculosis and being a current alcohol taker in the model for energy intake. Women that had tuberculosis with reduced appetite or tuberculosis with history of taking alcohol had decreased energy intake. Also women who had history of alcohol intake had decreased protein intake. There was no compromise with energy and protein intake among men. Women were associated with

inadequate iron intake. Further, women with tuberculosis were associated with inadequate folate intake. Individuals with tuberculosis residing in households of more than two people or those with no or low education were associated with inadequate vitamin A intake.

Chapter Nine: Impact of Body Wasting on Survival among Adult Patients with Pulmonary Tuberculosis in Urban Kampala, Uganda

In this chapter, we evaluated the impact of HIV and body wasting on survival in tuberculosis patients using precise measures of nutritional status, the height-normalized fat-free mass (FFMI) and fat mass (FMI) indices. During the follow-up period, 19% of 310 patients with baseline wasting by BMI died compared to 11% of 437 without wasting, a crude risk ratio of 1.74 (95% confidence interval (CI): 1.22, 2.48). Of 103 with baseline wasting by fat-free mass index, 16% died, compared to 7% without wasting, crude risk ratio of 2.31 (95% CI: 1.10, 3.92).

In stratified survival analysis, survival proportion was significantly lower among men with reduced BMI compared to men with normal BMI; and lower among women with reduced fat-free mass index compared to women with normal fat-free mass index. In multivariable Cox regression model using anthropometric data, the relative hazard of death when patient had reduced BMI was 1.85 (95% CI: 1.25, 2.73). In a nested model, the relative hazard for death was 1.70 (95% CI: 1.03, 2.81) for men with reduced BMI and 1.83 (95% CI: 0.96, 3.50) for women with reduced BMI. In a model using fat-free

mass index data, the relative hazard of death when patients had reduced fat-free mass index was 1.88 (0.96, 3.65). In a nested model, the relative hazard of death was 6.83 (95% CI: 2.14, 21.74) for women with reduced fat-free mass index compared to women with normal fat-free mass and 0.80 (95% CI: 0.35, 1.84) for men with reduced fat-free mass index. In Kaplan-Meier analysis, men had significantly lower survival compared to women (p=0.016) Cox regression analysis HIV positive men had 1.62 (95% confidence interval (CI): 1.05, 2.52) hazard of death compared to HIV positive women. HIV negative men had 0.57 (95% CI: 0.10, 3.31) hazard of death compared to HIV negative women.

Chapter Ten: Longitudinal Changes in Body Composition among Tuberculosis Patients with or without Body Wasting in Urban Kampala, Uganda

In this chapter, longitudinal data analysis was conducted to assess whether body wasting as measured by height-normalized measures of nutritional status at diagnosis of tuberculosis, and whether HIV infection modifies longitudinal changes in body composition during and after tuberculosis treatment. Results in this chapter revealed that there were no differences in body wasting as assessed by reduced lean tissue, fat mass, and BMI between HIV positive and HIV negative patients at diagnosis of tuberculosis. In stratified mixed effects two spline models during the first three months of treatment, the gain in lean tissue among patients that presented with wasted lean tissue at diagnosis was dramatic in men with rate of 4.55 kg/m^2 (95% confidence interval (CI): 1.26, 7.83) per

month; however, the gain was minimal among women who presented with reduced lean tissue with rate of 2.07 kg/m^2 (95% CI: -0.74, 4.88).

In stratified models for fat mass as dependent variable, women with reduced fat mass at presentation had a substantial gain in fat mass at rate of 3.55 kg/m^2 (95% CI: 0.40, 6.70) whereas men had a rate of 3.16 kg/m^2 (0.80, 5.52). In stratified models with BMI as dependent variable, men with reduced BMI at presentation gained BMI at a rate of 6.45 kg/m^2 (95% CI: 3.02, 9.87) whereas women at a rate of 3.30 kg/m^2 (95% CI: -0.11, 6.72). There were minimal changes in lean tissue, fat mass, and BMI during the first three months of treatment in stratified models according to HIV status. Further, there were minimal changes in lean tissue, fat mass, and BMI after month 3 and during the one year follow-up after month 12.

Conclusion

In this dissertation, we have shown that body composition can reliably be assessed using inexpensive and easy to measure anthropometric assessments such as waist circumference, MUAC, and BMI. Precise estimation of fat-free mass is essential to identify patients with body wasting so that appropriate and early interventions are instituted. The cross-sectional nature of the study limits making conclusions beyond the time of diagnosis among tuberculosis. However, since the study population included participants with and without tuberculosis, one can infer that the equations evaluated in

this dissertation can reliably be used to monitor changes in body composition during and after tuberculosis treatment.

Several conclusions were generated following our working model in this dissertation (Figure 1). This dissertation has shown that the dietary consumption in the study population of HIV positive and HIV negative adults with or without tuberculosis from urban Uganda was monotonous, rich in carbohydrates and deficient in nutrients regardless of gender, tuberculosis, and HIV status. The ability of FVS and DDS indices to identify individuals with inadequate or adequate diet consumption differed by gender. The FVS was a better predictor of nutritional adequacy among women whereas DDS was a better predictor among men.

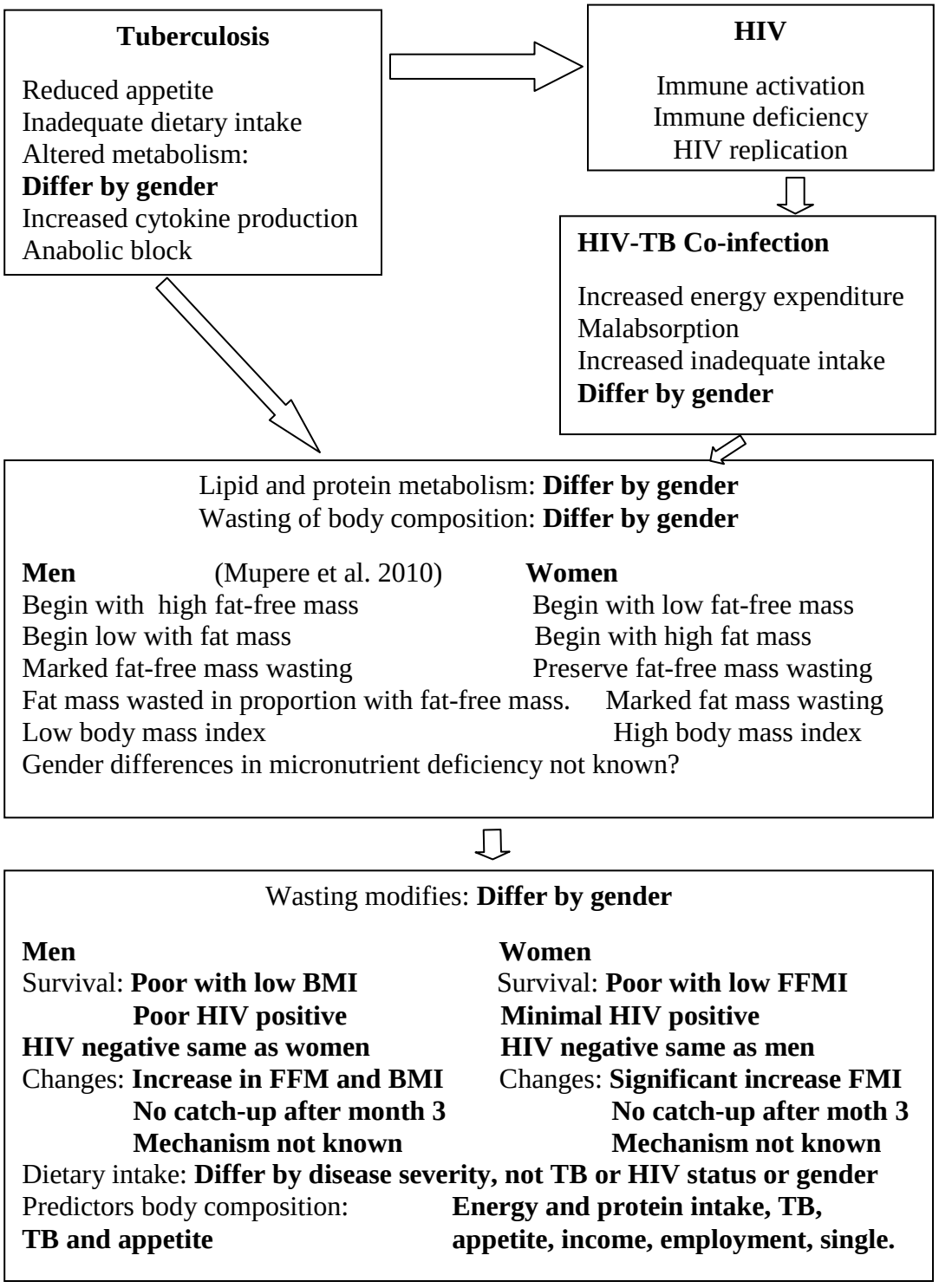
Findings in this dissertation suggest that there are remarkable gender differences in how energy and protein intake influence body composition, and we found important interactions in the face of tuberculosis, and when there is no income. HIV does not appear to influence nutrient intake on body composition. At the time of tuberculosis diagnosis, the 24-hour dietary intake recall varied by severity of tuberculosis disease, but not tuberculosis disease or HIV status. However, in the absence of tuberculosis, dietary intake varied by gender. Both men and women had comparable dietary intake among patients with tuberculosis regardless of HIV status whereas HIV negative women had reduced energy, protein, and folate intake among individuals without tuberculosis compared to men. As regards dietary correlates, findings suggest that correlates of energy

and protein intake differ by gender. Women and individuals having tuberculosis who reside in households with two or more people or who have no or low education are at vulnerable state of inadequate nutrient intake.

We have shown in this dissertation that body wasting is associated with poor survival and this effect differed by gender. Men with reduced BMI at the time of tuberculosis had poor survival whereas women with reduced lean tissue had poor survival suggesting that BMI is a better predictor of death among men whereas wasting of lean tissue is a better predictor of death among women. Further, survival differed by gender; men had poor survival compared to women. However, this gender difference in survival was modified by HIV. It is HIV positive men that had poor survival compared to HIV positive women.

Our results suggest that body wasting at the time of tuberculosis diagnosis modifies longitudinal changes in body composition during tuberculosis treatment. The effect however, differed by gender. Men with wasted lean tissue and reduced BMI had dramatic increase in lean tissue and BMI whereas women with reduced fat mass had significant increase in fat mass during the first three months of tuberculosis treatment. HIV infection did not influence changes in body composition. Of note, there were minimal changes in body composition after month 3 and during the one year follow-up after month 12 regardless of gender, HIV status, and the initial level of body composition.

Figure 11:1 Overall conclusions: Tuberculosis – HIV – malnutrition model



FFMI = fat-free mass index, FMI = fat mass index, BMI = body mass index.

Limitations and Future Studies

Findings in this dissertation, demonstrated poor survival among patients that presented with body wasting. The survival differed by gender. Men had poor survival when BMI was low, whereas women had poor survival when lean tissue was wasted. This provides compelling evidence to evaluate nutritional interventions that can improve survival among patients with body wasting. In evaluating nutritional interventions however, gender differences will need to be considered.

Our results revealed that there were minimal changes in body composition after month 3 and during the one year follow-up after month 12 regardless of gender, HIV status, or the initial level of body composition. Yet, patients that presented with wasting had dramatic increase in lean tissue and BMI for men and fat mass for women; however, there was no catch-up to normal nutritional status. Studies are needed to evaluate the mechanisms for the lack of catch-up among patients that presented with wasting and the lack of changes in body composition after month 3.

To address the limitations in this dissertation, validation studies with reference methods such as air-displacement plethysmography, underwater weighing and dual X-ray absorptiometry (DXA) are needed to validate the BIA regression equations and the existing equations that involve simple anthropometric measurements used in estimation of body composition. Validation in follow-up studies and in different populations because of variations in hydration is needed.

In this dissertation, a single 24-hour recall was used to assess dietary intake. However, four multiple-pass 24-hour recalls have been shown to be the most appropriate method for a study of diet and nutrition in low-income households (Vucic et al. 2009). A whole year-round study is recommended to understand the habitual consumption in Uganda. Further, evaluation is needed to understand changes in dietary intake over time and how these changes would affect body composition and survival.

We found simple counting of food items or food groups can give fairly good assessment of nutritional adequacy. The study however, was cross-sectional and was conducted in an urban setting. The conclusions might therefore be valid for similar urban settings, but the methods and approaches are equally valid for rural areas. To attain generalizability of conclusions and to understand whether dietary adequacy would change with habitual consumption, additional studies are recommended in rural settings, in different socioeconomic, and in different ethnic groups. Also follow-up studies are needed to understand how dietary adequacy changes during different seasons of the year.

Strengths

Findings in the present dissertation were generated using a large database that provided adequate power to detect differences in survival and changes in body composition by gender and body wasting. The data provided adequate power to interactions with survival between gender and HIV infection. To our knowledge, this is the first study to show the effect of wasting on survival using height-normalized fat-free mass rather than BMI that

may overestimate wasting among women and thus, overestimate survival due to wasting. Height-normalized fat-free mass provide a precise measure of nutritional status than BMI (Kyle, Piccoli, and Pichard 2003; Kyle, Genton, and Pichard 2002; VanItallie et al. 1990). The median follow-up period for participants in the data used for analysis in this dissertation was more than two years; suggesting a longer period of follow-up than the previous studies (Sani et al. 2006; Lucas et al. 1993). Thus, our findings are embedded with a temporal relationship between enrolment to time of death or censoring and between enrolments to different time points when changes in body composition were assessed on follow-up.

We had a full panel of control groups that enabled to this dissertation to show the independent effects of tuberculosis and HIV on dietary intake. Further, the dissertation has shown the biologic and socioeconomic plausibility.

Public Health Implications

Findings in this dissertation suggest the need for national tuberculosis programs to address the nutritional needs of tuberculosis patients at the time of diagnosis, during and after treatment. The nutritional needs may range from health education to provision of nutritional supplements. Results revealed that patients with body wasting had poor survival and those that survived after month 3, did not catch-up to normal nutritional status. The findings provide theoretical framework for targeted nutritional intervention to tuberculosis patients that present with body wasting, particularly women with reduced

lean tissue, men with reduced BMI or HIV positive men. There is potential that if nutritional needs are addressed, this may improve survival and adherence to treatment.

Our findings contribute to an increased understanding of the potential methods of assessing body wasting using simple and inexpensive anthropometric measurements. This implies that during regular clinical practice and in public field surveys, body composition can easily be assessed to identify individuals and population groups at risk of poor outcome. Early identification of body wasting enables timely institution of management to prevent poor outcome.

The monotonous diet with substantial nutrient deficiencies in this dissertation, suggests the need for fortification of common food items in Uganda. Fortification of staple foods has been shown to improve micronutrient intake among adults in South Africa (Steyn et al. 2008). In this dissertation, we have shown that simple indices of food variety score and dietary diversity score can be used to identify individuals or families with inadequate nutrient intake. Thus, these simple scores can be used in management of tuberculosis and in public health settings as tools to provide health education so that individuals or families understand when to have an adequate diet.

To address the nutritional needs of tuberculosis patients and the nutritional needs of the community where tuberculosis patients reside, will require a collaborative effort of

several stakeholders including clinicians, healthcare professionals, policy makers at the Ministry of Health in Uganda, program managers for the poverty eradication scheme and for various existing non-government organizations and the will of the political organs in the country. The clinicians, the healthcare professionals and the public health practitioners should strive to understand the reasons for poor survival, failure to attain normal nutritional status after therapy, and poor diet consumption among tuberculosis patients in order to develop and implement targeted interventions.

CHAPTER 12

EXTRA TABLES AND FIGURES FOR CHAPTER FOUR

Table 12:12:1 Mean intra-supervisor, mean intra-observer, and mean inter-observer technical error of measurement prior to data collection

Measurement (n=6)	Difference between trainee and supervisor	Technical Error of Measurement		
		Intra-Supervisor Mean	Intra-Observer Mean	Inter-Observer Mean
Weight (kg)	0.79	0.000	0.068	0.620
Height (cm)	0.19	0.037	0.059	0.037
MUAC (cm)	0.65	0.022	0.017	0.042
Triceps ST (mm)	1.11	0.036	0.054	1.242
Biceps ST (mm)	0.39	0.029	0.049	0.155
Subscapular ST (mm)	0.30	0.034	0.057	0.088
Sacral iliac ST (mm)	0.58	0.034	0.041	0.335
Waist circumference (cm)	0.07	0.067	0.035	0.005
Hip circumference (cm)	0.43	0.043	0.026	0.184
Resistance (ohms)	0.84	0.146	0.165	0.712
Reactance (ohms)	0.23	0.044	0.046	0.051

ST = skinfold thickness, MUAC=mid-upper arm circumference.

Table 12:12:2 Coefficient of reliability prior to data collection

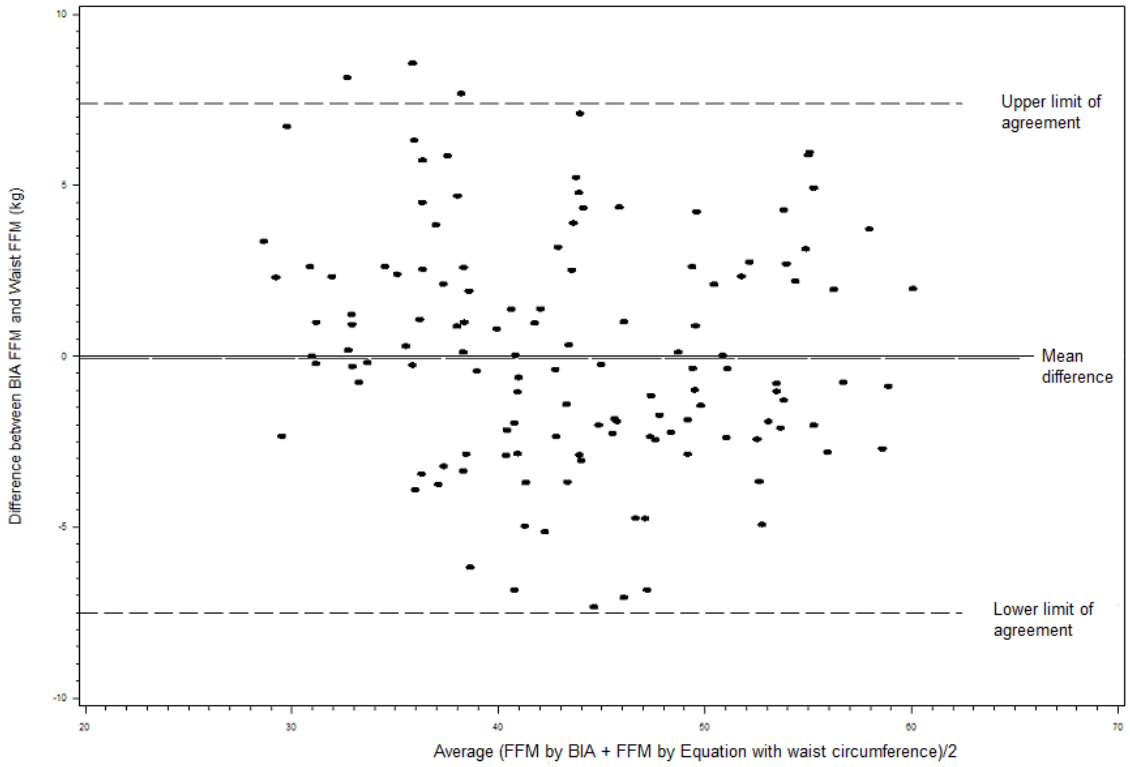
Measurement (n=6)	Reference(Frisancho A.R 1990; Lohman T.G, Roche A.F, and Martorell R 1988)		Coefficient of Reliability
	Intra-observer	Inter-observer	
Weight (kg)	1.200	1.500	0.99
Height (cm)	0.692	0.953	0.90
MUAC (cm)	0.347	0.425	1.00
Triceps ST (mm)	0.800	1.890	1.00
Biceps ST (mm)	0.600	0.600	0.98
Subscapular ST (mm)	1.830	1.530	0.96
Sacral iliac ST (mm)	1.000	1.700	1.00
Waist circumference (cm)	1.000	1.000	0.74
Hip circumference (cm)	1.230	1.380	1.00
Resistance (ohms)	-	-	0.96
Reactance (ohms)	-	-	0.96

ST = skinfold thickness, MUAC=mid-upper arm circumference.

Table 12:12:3 Guide for comparison of inter-observer error (Frisancho A.R 1990)

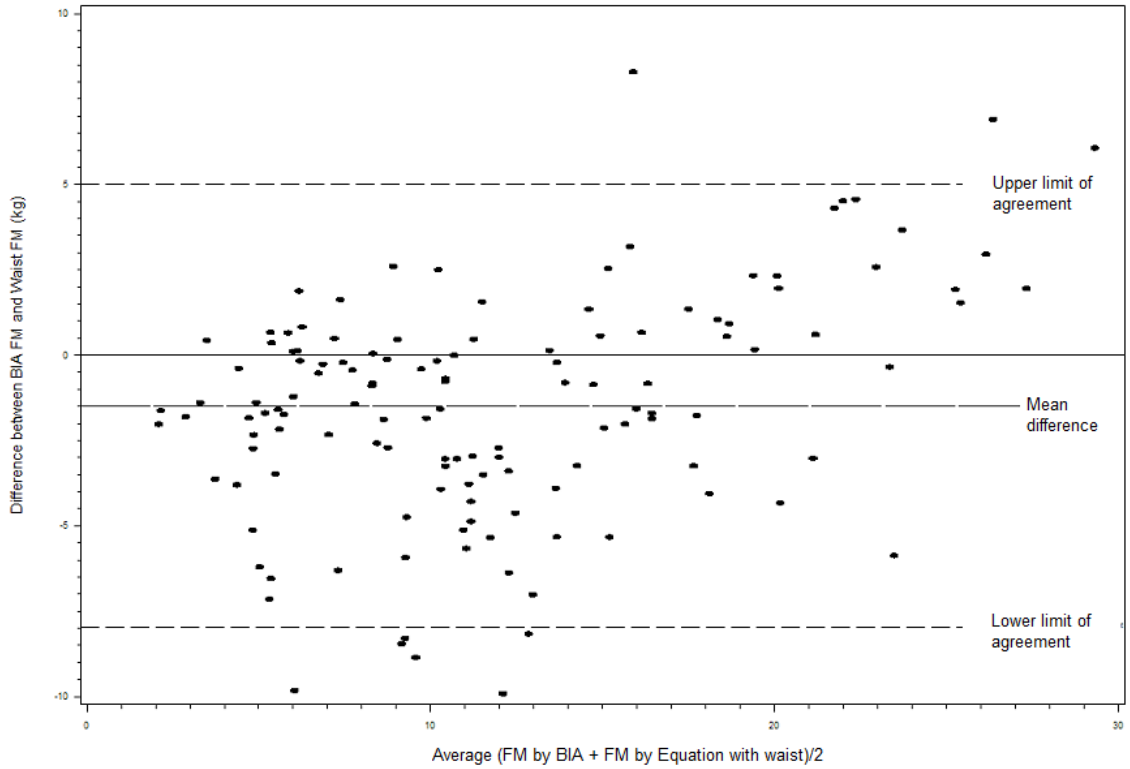
Measurement	**Difference between trainee and supervisor**			
	Good	**Fair**	**Poor**	**Gross Error**
Weight (kg)	0 to 0.1	> 0.2	0.3 to 0.4	≥ 0.5
Height (cm)	0 to 0.5	0.6 to 0.9	1.0 to 1.9	≥ 2.0
Mid upper arm circumference (mm)	0 to 5	6 to 9	10 to 19	≥ 20

Figure 12:1 Fat-free mass measured by BIA compared with fat-free mass measured by equation involving waist circumference



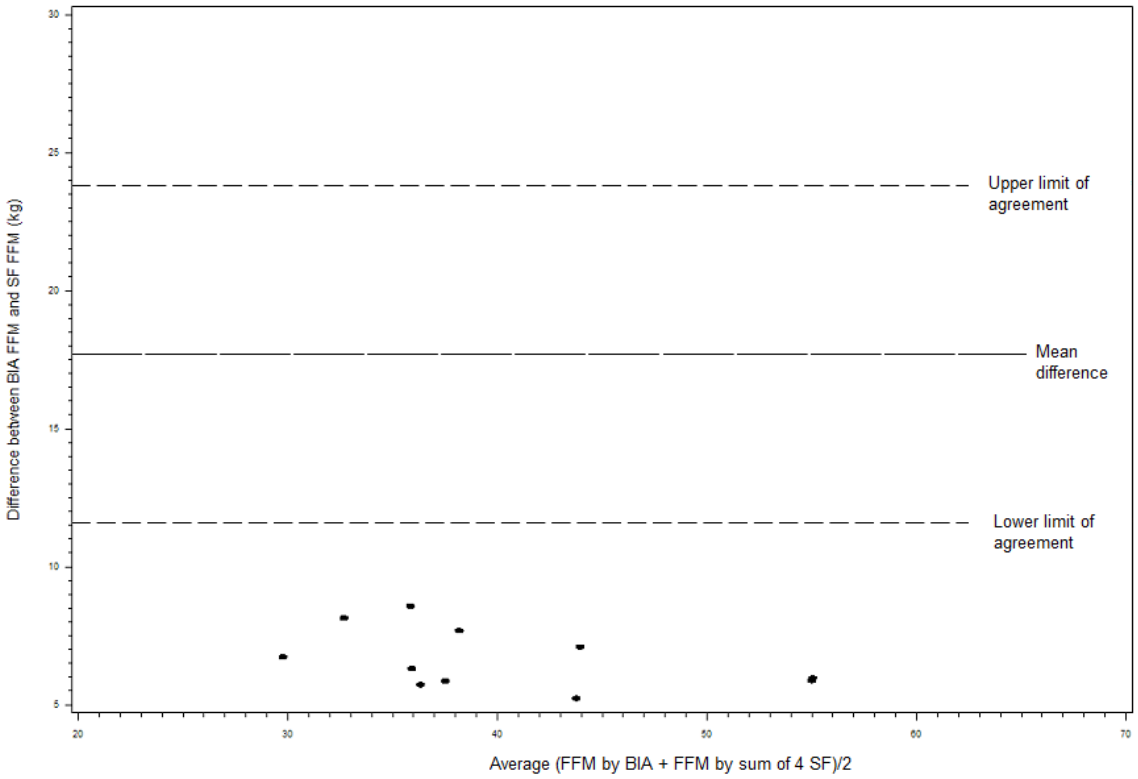
BIA = bioelectrical impedance analysis, FFM = fat-free mass

Figure 12:2 Fat mass measured by BIA compared with fat mass measured by equation involving waist circumference



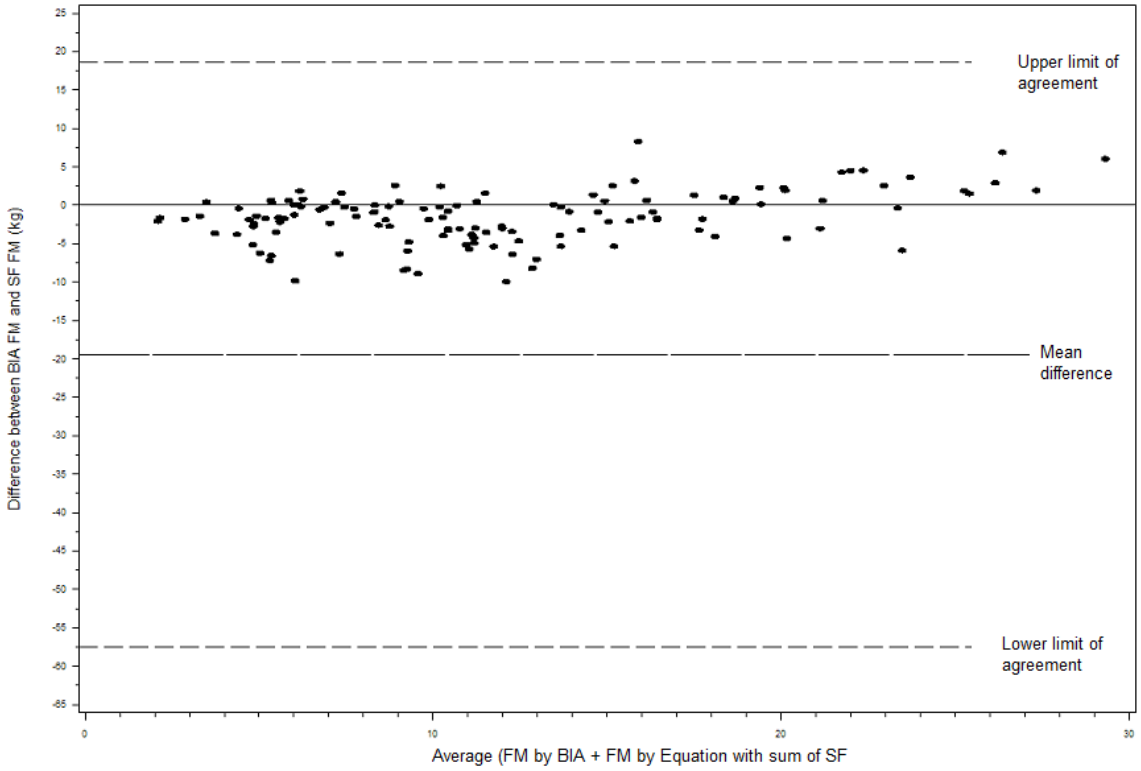
BIA = bioelectrical impedance analysis, FM = fat mass, Waist = waist circumference

Figure 12:3 Fat-free mass measured by BIA compared with fat-free mass measured by Durnin & Womersely equations involving sum of 4 skinfold thickness



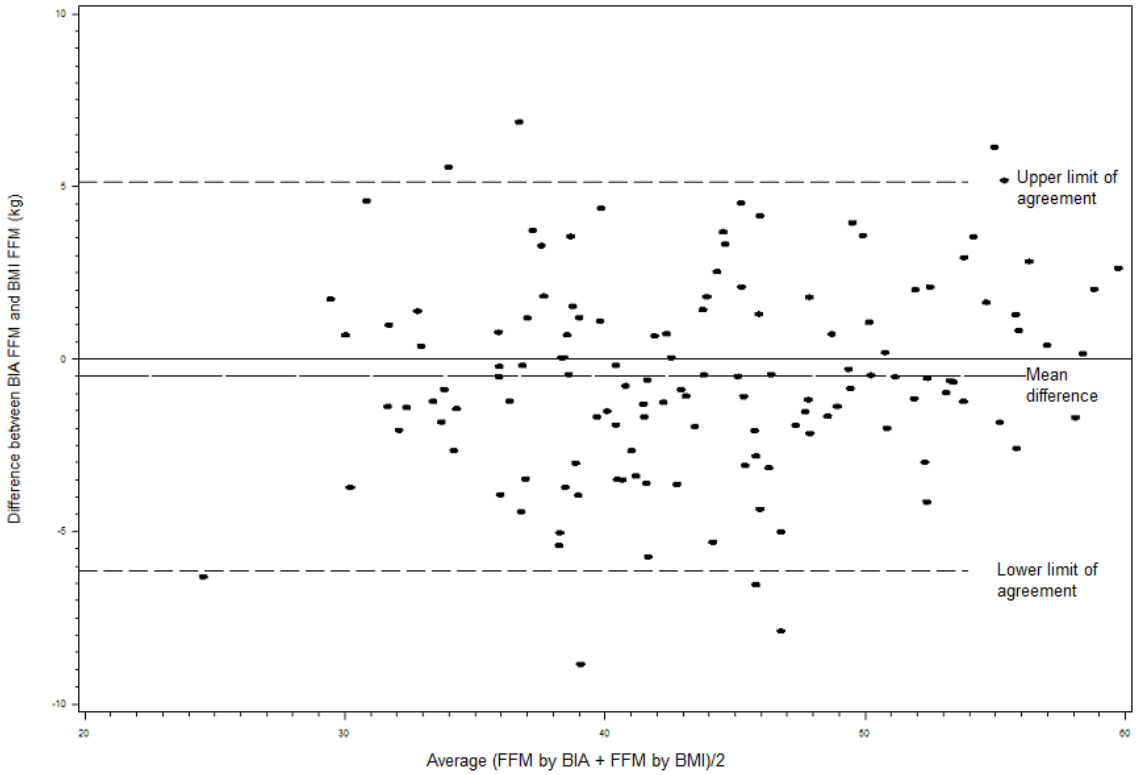
BIA = bioelectrical impedance analysis, FFM = fat-free mass, ST = skinfold thickness.

Figure 12:4 Fat mass measured by BIA compared with fat mass measured by Durnin & Womersely equations that involves sum of 4 skinfold thickness



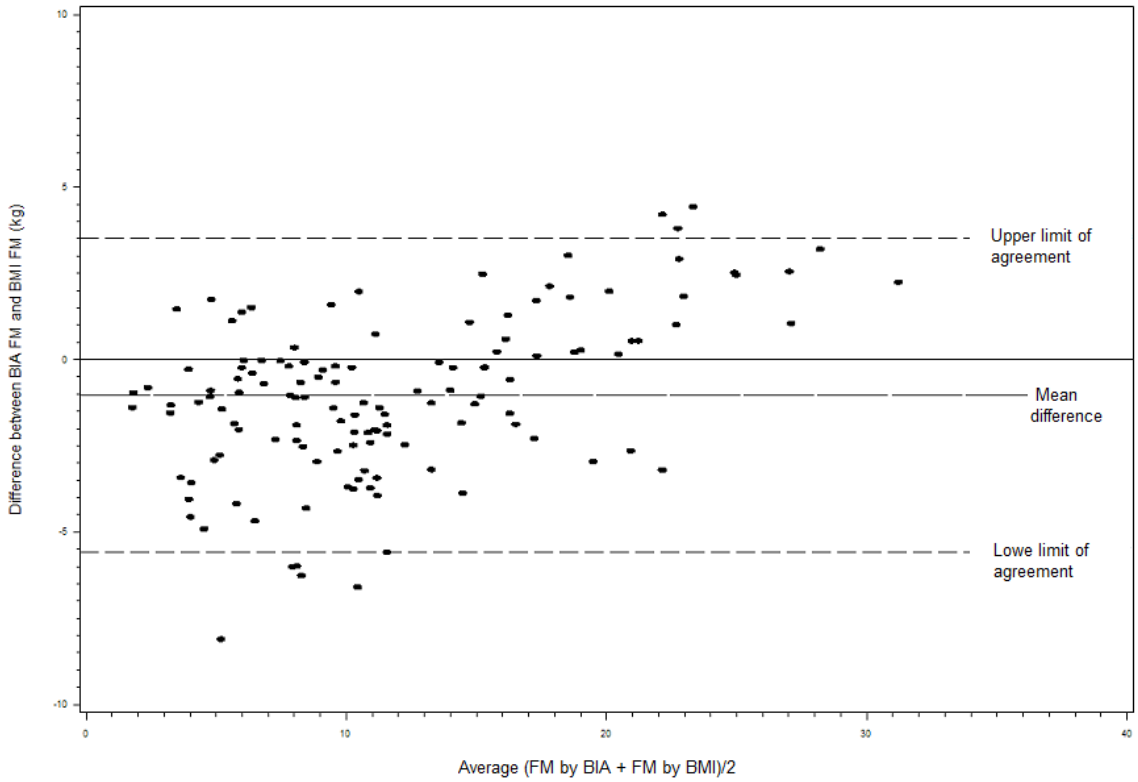
BIA = bioelectrical impedance analysis, FM = fat mass, ST = skinfold thickness.

Figure 12:5 Fat-free mass measured by BIA compared with fat-free mass measured by equation involving BMI



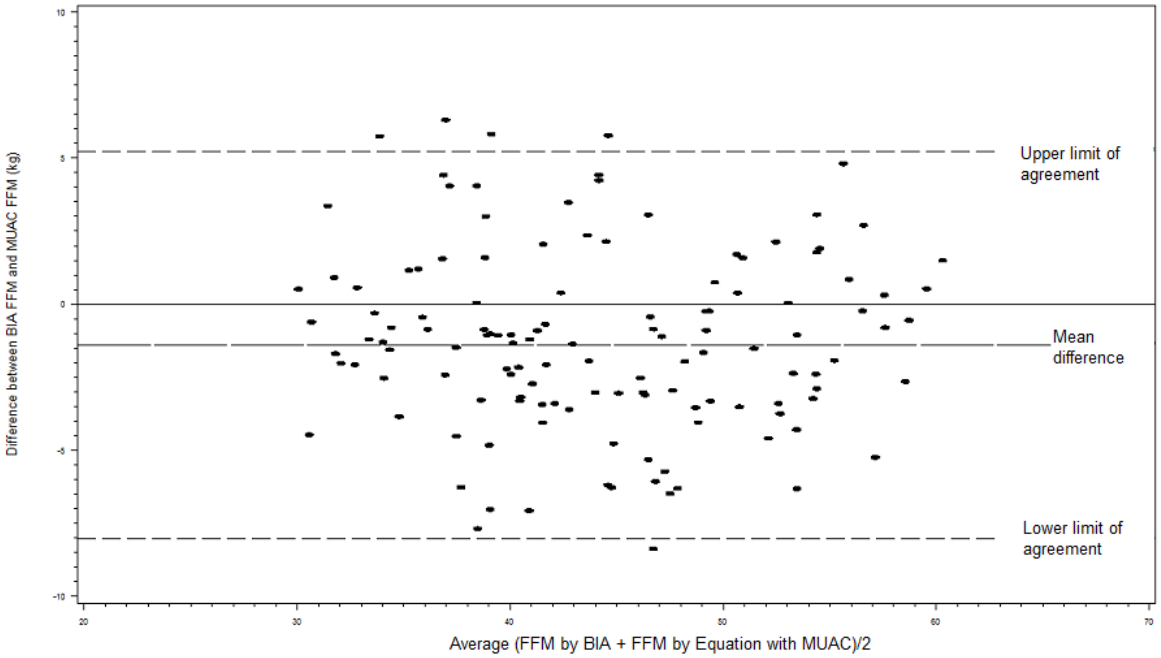
BIA = bioelectrical impedance analysis, FFM = fat-free mass, BMI = body mass index.

Figure 12:6 Fat mass measured by BIA compared with fat mass measured by equation involving BMI



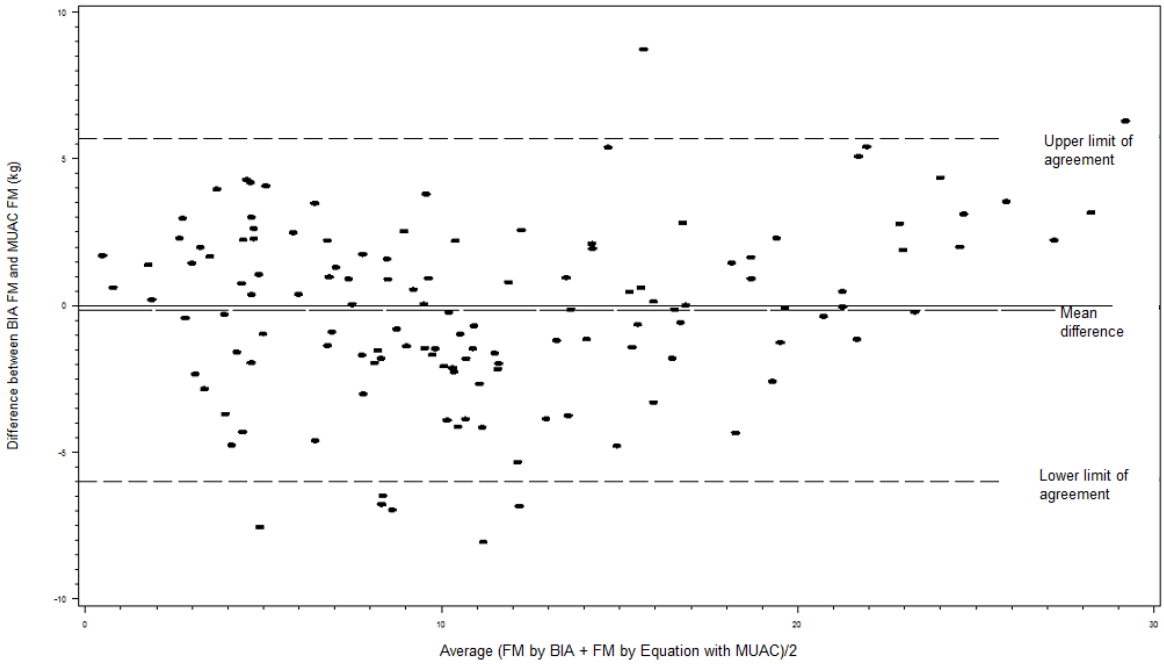
BIA = bioelectrical impedance analysis, FM = fat mass, BMI = body mass index

Figure 12:7 Fat-free mass measured by BIA compared with fat-free mass measured by equation involving MUAC



BIA = bioelectrical impedance analysis, FFM = fat-free mass, MUAC = mid-upper-arm circumference

Figure 12:8 Fat mass measured by BIA compared with fat mass measured by equation involving MUAC



BIA = bioelectrical impedance analysis, FM = fat mass, MUAC=mid-upper arm circumference.

CHAPTER 13

EXTRA TABLES AND FIGURES FOR CHAPTER NINE

Table 13:1 Comparison of key baseline variables across phase II prednisolone study, household contact study, and Kawempe community health study

[1]Characteristics [mean, (SD)]	Phase II Prednisolone (n=95)	Household Contact (n=312)	Kawempe study (n=340)	p-value
Sex				
Male (%)	59 (62)	163 (52)	178 (51)	0.172
Female (%)	36 (38)	151 (48)	166 (49)	
HIV status				
Negative (%)	0 (0)	159 (51)	186 (55)	**<0.001**
Positive (%)	95 (100)	153 (49)	153 (45)	
Age in years	30.7 (7.2)	31.8 (9.0)	29.6 (9.2)	**0.003**
Weight in kg	52.0 (6.8)	52.3 (8.7)	51.6 (8.4)	0.297
Height in cm	165.7 (8.8)	164.2 (9.3)	163.8 (8.7)	0.077
BMI in (kg/m^2)	19.0 (2.6)	19.4 (2.9)	19.2 (2.8)	0.383
Hemoglobin in g/dl	11.0 (1.8)	11.6 (2.4)	11.4 (2.2)	0.070
Chest x-ray disease				

Normal/mild (%)	4 (4)	54 (17)	53 (16)	**0.007**
Moderate/far advanced (%)	89 (96)	257 (83)	282 (84)	

[1]Continuous variables are means ± standard deviation (SD).

Table 13:2 Assessing the proportional hazards assumption with a statistical test: Correlations between ranked failure time and Schoenfeld residuals

Characteristic	Mean Residuals	Ranked failure time	p-value
Sex	-1.02×10^{-8}	0.30	0.120
Age (years)	8.47×10^{-8}	-0.21	0.284
HIV status	4.84×10^{-7}	0.29	0.129
Hemoglobin (g/dl)	1.07×10^{-7}	0.06	0.760
Fat mass index (kg/m^2)	-1.96×10^{-8}	-0.05	0.788
Fat-free mass index (kg/m^2)	-2.16×10^{-8}	-0.09	0.646
Body mass index (kg/m^2)	2.06×10^{-8}	-0.03	0.864
Chest x-ray disease extent	-7.89×10^{-8}	0.15	0.440
Smoker	1.75×10^{-8}	0.06	0.766
Takes alcohol	6.80×10^{-8}	0.24	0.215
History weight loss	5.50×10^{-8}	-0.21	0.285

Table 13:3 Baseline characteristics of pulmonary tuberculosis patients between HIV negative and HIV positive

Characteristic	HIV negative (n=345)	HIV positive (n=401)
Sex		
Females [n (%)]	165/351 (47)	186/351 (53)
Males [n (%)]	180/395 (46)	215/395 (54)
Age (years)		
≤30 [n (%)]	233/434 (54)	201/434 (46)[a]
>30 [n (%)]	112/312 (36)	200/312 (64)
Hemoglobin (g/dl)[1]		
>10 [n (%)]	169/342 (49)	173/342 (51)[a]
≤10 [n (%)]	32/121 (26)	89/121 (74)
Body mass index (kg/m^2)		
Normal [n (%)]	202/436 (46)	234/436 (54)
Low [n (%)]	143/310 (46)	167/310 (54)
Fat-free mass index (kg/m^2)		

Normal [n (%)]	116/207 (56)	91/207 (44)
Low [n (%)]	56/103 (54)	47/103 (46)
Fat mass index (kg/m^2)		
Normal [n (%)]	98/176 (56)	78/176 (44)
Low [n (%)]	71/127 (56)	56/127 (44)
Chest x-ray disease extent		
Normal/mild [n (%)]	46/111 (41)	65/111 (59)
Moderate/far advanced [n (%)]	296/627 (47)	331/627 (53)
Smoker		
No [n (%)]	272/592 (46)	320/592 (54)
Yes [n (%)]	73/151 (48)	78/151 (52)
Currently takes alcohol		
No [n (%)]	240/466 (51)	226/466 (49)[a]
Yes [n (%)]	105/279 (38)	174/279 (62)
History weight loss		
No [n (%)]	60/165 (36)	105/165 (64)[b]
Yes [n (%)]	283/578 (49)	295/578 (51)

[a]p-value <0.001, [b]p-value <0.05.

Table 13:4 Multivariable Relative hazards [HR, 95% confidence intervals (CIs)] for death among tuberculosis patients with normal compared with patients having low body mass index (BMI)

Characteristic	Deaths/N (%)	Relative hazard	95% Confidence Interval
Body mass index (kg/m^2)			
Normal	47/437 (11)	1	-
Low	58/310 (19)	13.39	**1.23, 146.19**
Sex			
Female	38/352 (11)	1	-
Male	67/395 (17)	1.52	**0.83, 2.76**
Age (years)			
≤30	34/434 (8)	1	-
>30	71/313 (23)	3.06	**1.61, 5.83**
HIV-serostatus[1]			
Negative	6/345 (2)	1	-
Positive	99/401 (25)	42.68	**5.88, 309.73**
Smoker[3]			

No	84/593 (14)	1	-
Yes	20/151 (13)	0.57	0.23, 1.40
Chest x-ray extent[6]			
Normal/minimal	19/111 (17)	1	-
Moderate/far advanced	86/628 (14)	0.96	0.46, 1.99
Weight loss[5]			
No	11/165 (7)	1	-
Yes	94/579 (16)	3.54	**1.88, 6.66**
Reduced BMI*sex		1.06	0.45, 2.48
Reduced BMI*HIV		0.25	0.03, 2.23
Reduced BMI*age		0.55	0.24, 1.29
Reduced BMI*smoker		1.05	0.35, 3.11
Reduced BMI*extent		0.64	0.24, 1.75

-2LL reduced model - -2LL full model: 1202.115 – 1193.495 = 8.62; df = 5, p=0.125.
[1]One missed HIV status; [6]eight missed extent variable; [3]three missed history of ever smoked; [5]four missed history of weight loss; low BMI <18.5 kg/m^2.

Table 13:5 Multivariable Relative hazards [HR, 95% confidence intervals (CIs)] for death among tuberculosis patients with normal compared with patients having low body mass index (BMI)

Characteristic	Deaths/N (%)	Relative hazard	95% Confidence Interval
Body mass index (kg/m^2)			
Normal	47/437 (11)	1	-
Low	58/310 (19)	9.21	**0.99, 85.90**
Sex			
Female	38/352 (11)	1	-
Male	67/395 (17)	1.52	**0.85, 2.73**
Age (years)			
≤30	34/434 (8)	1	-
>30	71/313 (23)	3.04	**1.60, 5.78**
HIV-serostatus[1]			
Negative	6/345 (2)	1	-
Positive	99/401 (25)	41.95	**5.78, 304.28**
Smoker[3]			

No	84/593 (14)	1	-
Yes	20/151 (13)	0.60	0.36, 1.00
Chest x-ray extent[6]			
Normal/minimal	19/111 (17)	1	-
Moderate/far advanced	86/628 (14)	0.77	0.47, 1.27
Weight loss[5]			
No	11/165 (7)	1	-
Yes	94/579 (16)	3.53	**1.88, 6.65**
Reduced BMI*sex		1.03	0.45, 2.34
Reduced BMI*HIV		0.26	0.03, 2.29
Reduced BMI*age		0.56	0.24, 1.32

-2LL reduced model - -2LL full model: 1202.115 – 1194.245 = 7.87; df = 3, p=0.0488.
[1]One missed HIV status; [6]eight missed extent variable; [3]three missed history of ever smoked; [5]four missed history of weight loss; low BMI <18.5 kg/m^2.

Table 13:6 Relative hazards [HR, 95% confidence intervals (CIs)] for death among tuberculosis patients with normal compared with patients having low body mass index (BMI)

Characteristics	Deaths/N (%)	Overall model
		HR (95% CI)
BMI (kg/m^2)		
Normal (≥18.5)	47/437 (11)	1
Low (<18.5)	58/310 (19)	1.78 (**1.20, 2.64**)
HIV status		
Negative	6/345 (2)	1
Positive	99/401 (25)	18.18 (7**.96, 41.52**)
Gender		
Female	38/352 (11)	1
Male	67/395 (17)	1.70 (**1.12, 2.59**)
Smoker[2]		

No	84/593 (14)	1
Yes	20/151 (13)	0.62 (0.37, 1.04)
Weight loss[3]		
No	11/165 (7)	1
Yes	94/579 (16)	3.70 (**1.97, 6.94**)
Chest x-ray extent[4]		
Normal/minimal	19/111 (17)	1
Moderate/far advanced	86/628 (14)	0.73 (0.44, 1.21)

[1]One missed HIV status; [4]eight missed extent variable; [2]three missed history of ever smoked; [3]four missed history of weight loss; low BMI <18.5 kg/m^2.

Table 13:7 Relative hazards [HR, 95% confidence intervals (CIs)] for death among tuberculosis patients with normal compared with patients having low body mass index (BMI) stratified according to Age group

Characteristics	Deaths/N (%)	Stratified models	
		Young ≤30 yr (n=434)	Old >30 yr (n=313)
		HR (95% CI)	HR (95% CI)
BMI (kg/m^2)			
Normal (≥18.5)	47/437 (11)	1	1
Low (<18.5)	58/310 (19)	2.85 (1.41, 5.77)	1.39 (0.86, 2.24)
HIV status			
Negative	6/345 (2)	1	1
Positive	99/401 (25)	23.94 (5.70, 100.60)	11.75 (**4.27, 32.36**)
Gender			
Female	38/352 (11)	1	1
Male	67/395 (17)	1.15 (0**.57, 2.31**)	1.88 (**1.08, 3.25**)
Smoker[2]			

No	84/593 (14)	1	1
Yes	20/151 (13)	0.49 (0.17, 1.43)	0.61 (0.34, 1.11)
Weight loss[3]			
No	11/165 (7)	1	1
Yes	94/579 (16)	1.96 (0.84, 4.56)	6.24 (2**.27, 17.18**)
Chest x-ray extent[4]			
Normal/minimal	19/111 (17)	1	1
Moderate/far advanced	86/628 (14)	0.65 (0.26, 1.61)	0.78 (0.42, 1.43)

[1]One missed HIV status; [4]eight missed extent variable; [2]three missed history of ever smoked; [3]four missed history of weight loss; low BMI <18.5 kg/m^2.

Table 13:8 Relative hazards [HR, 95% confidence intervals (CIs)] for death among HIV positive tuberculosis patients compared with HIV negative patients

Characteristics	Deaths/N (%)	Overall model
		HR (95% CI)
HIV status		
Negative	6/345 (2)	1
Positive	99/401 (25)	15.66 (**6.84, 35.86**)
Age group		
≤30 years	34/434 (8)	1
>30 years	71/313 (23)	2.23 (**1.47, 3.38**)
Gender		
Female	38/352 (11)	1
Male	67/395 (17)	1.64 (**1.08, 2.50**)
Smoker[2]		
No	84/593 (14)	1
Yes	20/151 (13)	0.64 (0.39, 1.07)

Weight loss[3]		
No	11/165 (7)	1
Yes	94/579 (16)	3.51 (**1.87, 6.59**)
Chest x-ray extent[4]		
Normal/minimal	19/111 (17)	1
Moderate/far advanced	86/628 (14)	0.81 (0.49, 1.34)

[1]One missed HIV status; [4]eight missed extent variable; [2]three missed history of ever smoked; [3]four missed history of weight loss; low BMI <18.5 kg/m^2.

Table 13:9 Relative hazards [HR, 95% confidence intervals (CIs)] for death among HIV positive tuberculosis patients compared with HIV negative patients stratified according to BMI categories

Characteristics	Deaths/N (%)	Stratified models	
		Normal BMI (n=437)	Low BMI (n=310)
		HR (95% CI)	HR (95% CI)
HIV status			
Negative	6/345 (2)	1	1
Positive	99/401 (25)	42.86 (**5.90, 311.47**)	10.65 (**4.20, 27.02**)
Age group			
≤30 years	34/434 (8)	1	1
>30 years	71/313 (23)	3.10 (**1.63, 5.91**)	1.68 (0.97, 2.92)
Gender			
Female	38/352 (11)	1	1
Male	67/395 (17)	1.51 (0.83, 2.75)	1.59 (0.87, 2.92)
Smoker[2]			

No	84/593 (14)	1	1
Yes	20/151 (13)	0.57 (0.23, 1.40)	0.60 (0.32, 1.12)
Weight loss[3]			
No	11/165 (7)	1	1
Yes	94/579 (16)	3.75 (**1.48, 9.54**)	3.37 (**1.43, 7.97**)
Chest x-ray extent[4]			
Normal/minimal	19/111 (17)	1	1
Moderate/far advanced	86/628 (14)	0.98 (0.47, 2.03)	0.63 (0.32, 1.25)

[1]One missed HIV status; [4]eight missed extent variable; [2]three missed history of ever smoked; [3]four missed history of weight loss; low BMI <18.5 kg/m^2.

Table 13:10 Multivariable Relative hazards [HR, 95% confidence intervals (CIs)] for death among tuberculosis patients with normal compared with patients having low fat-free mass index (FFMI)

Characteristic	Deaths/N (%)	Relative hazard	95% Confidence Interval
Fat-free mass index (kg/m^2)			
Normal	14/208 (7)	1	-
Low	16/103 (16)	-	-
Sex			
Female	12/147 (8)	1	-
Male	18/164 (11)	3.34	**1.23, 9.08**
Age (years)			
≤30	10/194 (5)	1	-
>30	20/117 (17)	2.24	0.84, 5.95
HIV-serostatus[1]			
Negative	1/172 (0.6)	1	-
Positive	29/138 (21)	-	-
Hemoglobin			

>10 mg/dl	14/224 (6)	1	-
≤10 mg/dl	15/74 (20)	1.34	0.52, 3.49
Reduced FFMI*sex		0.13	**0.03, 0.56**
Reduced FFMI*age		1.61	0.35, 7.34
Reduced FFMI*HIV		-	-
Reduced FFMI*hemoglobin		2.00	0.49, 8.12

-2LL reduced model - -2LL full model: 332.269 – 321.399 = 10.870; df = 4, p=0.028.
[1]One missed HIV status; [2]15 missed hemoglobin measurement due to lack of blood; FFMI low (<16.7 kg/m^2 for men and <14.6 kg/m^2 for women, normal (≥ 16.7kg/m^2 for men, ≥14.6 kg/m^2 for women).

Table 13:11 Relative hazards [HR, 95% confidence intervals (CIs)] for death among tuberculosis patients with normal compared with low fat-free mass index (FFMI)

Characteristics	Deaths/N (%)	Overall model
		HR (95% CI)
FFMI in kg/m^2		
Normal (≥18.5)	14/208 (7)	1
Low (<18.5)	16/103 (16)	1.50 **(**0.73, 3.08)
Gender		
Female	12/147 (8)	1
Male	18/164 (11)	1.55 (**0.72, 3.37**)
Age (years)		
≤30	10/194 (5)	1
>30	20/117 (17)	3.57 (**1.73, 7.35**)
Hemoglobin (mg/dl)^2		
>10	14/224 (6)	1

≤10	15/74 (20)	2.85 (1.45, 5.61)

[1]One missed HIV status; [2]15 missed hemoglobin measurement due to lack of blood; FFMI low (<16.7 kg/m^2 for men and <14.6 kg/m^2 for women, normal (≥ 16.7kg/m^2 for men, ≥14.6 kg/m^2 for women).

Table 13:12 Relative hazards [HR, 95% confidence intervals (CIs)] for death among tuberculosis patients with normal compared with low fat-free mass index (FFMI) stratified according to HIV status

Characteristics	Deaths/N (%)	Stratified models	
		HIV negative (n=186)	**HIV positive (n=153)**
		HR (95% CI)	**HR (95% CI)**
FFMI in kg/m^2			
Normal (≥18.5)	14/208 (7)	1	1
Low (<18.5)	16/103 (16)	-	1.50 (0.72, 3.12)
Gender			
Female	12/147 (8)	1	1
Male	18/164 (11)	-	1.53 (0.69, 3.39)
Age (years)			
≤30	10/194 (5)	1	1
>30	20/117 (17)	-	2.21 (**1.06, 4.60**)
Hemoglobin $(mg/dl)^2$			

>10	14/224 (6)	1	1
≤10	15/74 (20)	-	1.65 (0.82, 3.30)

[1]One missed HIV status; [2]15 missed hemoglobin measurement due to lack of blood; FFMI low (<16.7 kg/m^2 for men and <14.6 kg/m^2 for women, normal (≥ 16.7kg/m^2 for men, ≥14.6 kg/m^2 for women).

Table 13:13 Relative hazards [HR, 95% confidence intervals (CIs)] for death among tuberculosis patients with normal compared with low fat-free mass index (FFMI)

Characteristics	Deaths/N (%)	Overall model
		HR (95% CI)
FFMI in kg/m^2		
Normal (≥18.5)	14/208 (7)	1
Low (<18.5)	16/103 (16)	1.55 **(0.76, 3.15**)
Gender		
Female	12/147 (8)	1
Male	18/164 (11)	1.92 (**0.90, 4.11**)
HIV-serostatus[1]		
Negative	1/172 (0.6)	1
Positive	29/138 (21)	41.68 (5**.67, 306.41**)
Hemoglobin (mg/dl)[2]		
>10	14/224 (6)	1

≤10	15/74 (20)	1.79 (0.90, 3.55)

[1]One missed HIV status; [2]15 missed hemoglobin measurement due to lack of blood; FFMI low (<16.7 kg/m^2 for men and <14.6 kg/m^2 for women, normal (≥ 16.7kg/m^2 for men, ≥14.6 kg/m^2 for women).

Table 13:14 Relative hazards [HR, 95% confidence intervals (CIs)] for death among tuberculosis patients with normal compared with low fat-free mass index (FFMI) stratified according to age group

Characteristics	Deaths/N (%)	Stratified models	
		Young ≤30 years (n=212)	**Old >30 years (n=128)**
		HR (95% CI)	**HR (95% CI)**
FFMI in kg/m^2			
Normal (≥18.5)	14/208 (7)	1	1
Low (<18.5)	16/103 (16)	1.89 (0.55, 6.52)	1.52 (0.63, 3.69)
Gender			
Female	12/147 (8)	1	1
Male	18/164 (11)	1.62 (0.45, 5.80)	1.56 (0.58, 4.19)
HIV-serostatus[1]			
Negative	1/172 (0.6)	1	1
Positive	29/138 (21)	-	16.03 (**2.14, 119.84**)
Hemoglobin (mg/dl)[2]			

>10	14/224 (6)	1	1
≤10	15/74 (20)	1.43 (0.42, 4.91)	2.02 (0.89, 4.58)

[1]One missed HIV status; [2]15 missed hemoglobin measurement due to lack of blood; FFMI low (<16.7 kg/m^2 for men and <14.6 kg/m^2 for women, normal (≥ 16.7kg/m^2 for men, ≥14.6 kg/m^2 for women).

Table 13:15 Relative hazards [HR, 95% confidence intervals (CIs)] for death among HIV positive tuberculosis patients compared with HIV negative patients

Characteristics	Deaths/N (%)	Overall model
		HR (95% CI)
HIV status		
Negative	1/172 (0.6)	1
Positive	29/138 (21)	34.37 **(4.65, 254.20**)
Age (years)		
≤30	10/194 (5)	1
>30	20/117 (17)	2.33 (**1.12, 4.83**)
Gender		
Female	12/147 (8)	1
Male	18/164 (11)	1.89 (0**.91, 3.91**)
Hemoglobin $(mg/dl)^2$		
>10	14/224 (6)	1

≤10	15/74 (20)	1.86 (0.94, 3.67)

[1]One missed HIV status; [2]15 missed hemoglobin measurement due to lack of blood; FFMI low (<16.7 kg/m^2 for men and <14.6 kg/m^2 for women, normal (≥ 16.7kg/m^2 for men, ≥14.6 kg/m^2 for women).

Table 13:16 Relative hazards [HR, 95% confidence intervals (CIs)] for death among HIV positive tuberculosis patients compared with HIV negative patients stratified according to fat-free mass index (FFMI) categories

Characteristics	Deaths/N (%)	Stratified models	
		Normal FFMI (n=208)	Low FFMI (n=103)
		HR (95% CI)	HR (95% CI)
HIV status			
Negative	1/172 (0.6)	1	1
Positive	29/138 (21)	-	14.80 (**1.93, 113.58**)
Age (years)			
≤30	10/194 (5)	1	1
>30	20/117 (17)	2.04 (0.68, 6.10)	3.50 (**1.10, 11.11**)
Gender			
Female	12/147 (8)	1	1
Male	18/164 (11)	2.28 (0.77, 6.75)	0.43 (0.14, 1.31)
Hemoglobin $(mg/dl)^2$			

>10	14/224 (6)	1	1
≤10	15/74 (20)	1.50 (0.51, 4.42)	2.64 (0.95, 7.39)

[1]One missed HIV status; [2]15 missed hemoglobin measurement due to lack of blood; FFMI low (<16.7 kg/m^2 for men and <14.6 kg/m^2 for women, normal (≥ 16.7kg/m^2 for men, ≥14.6 kg/m^2 for women).

Figure 13:1 Survival distribution among women with low baseline body mass index (BMI) (<18.5 kg/m^2) compared to women with normal BMI in Uganda

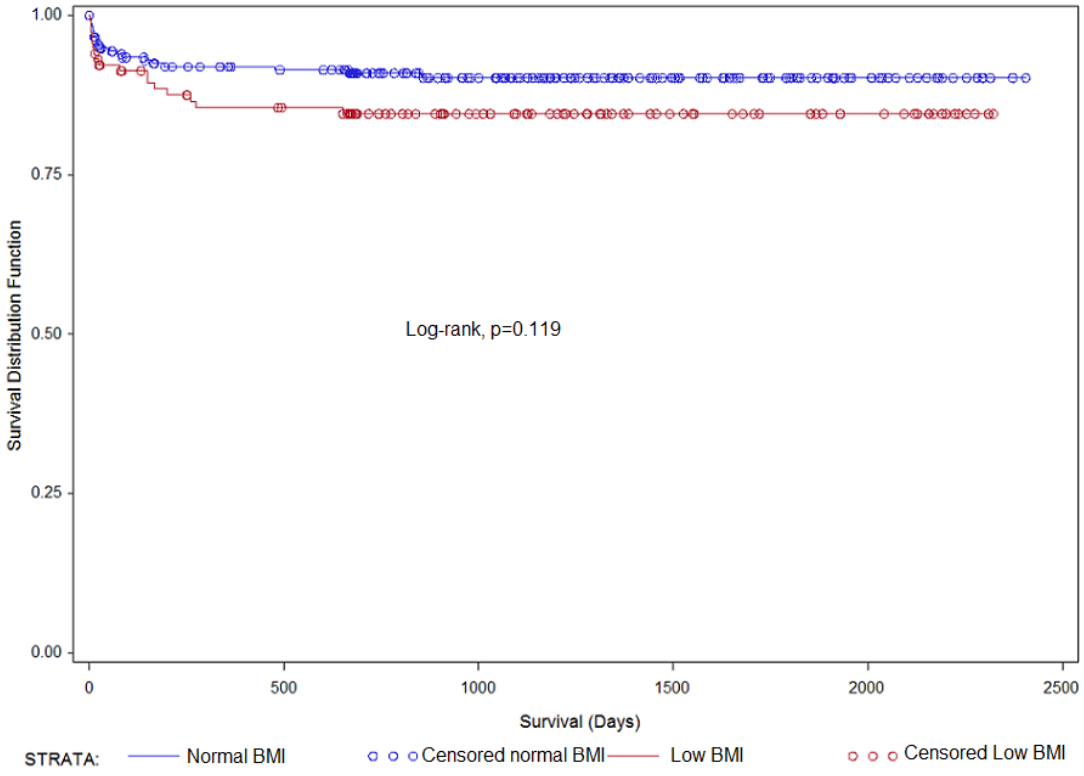


Figure 13:2 Survival distribution among men with low (<16.7 kg/m^2 for men, <14.6 kg/m^2 for women) baseline fat-free mass index (FFMI) compared to men with normal FFMI in Uganda

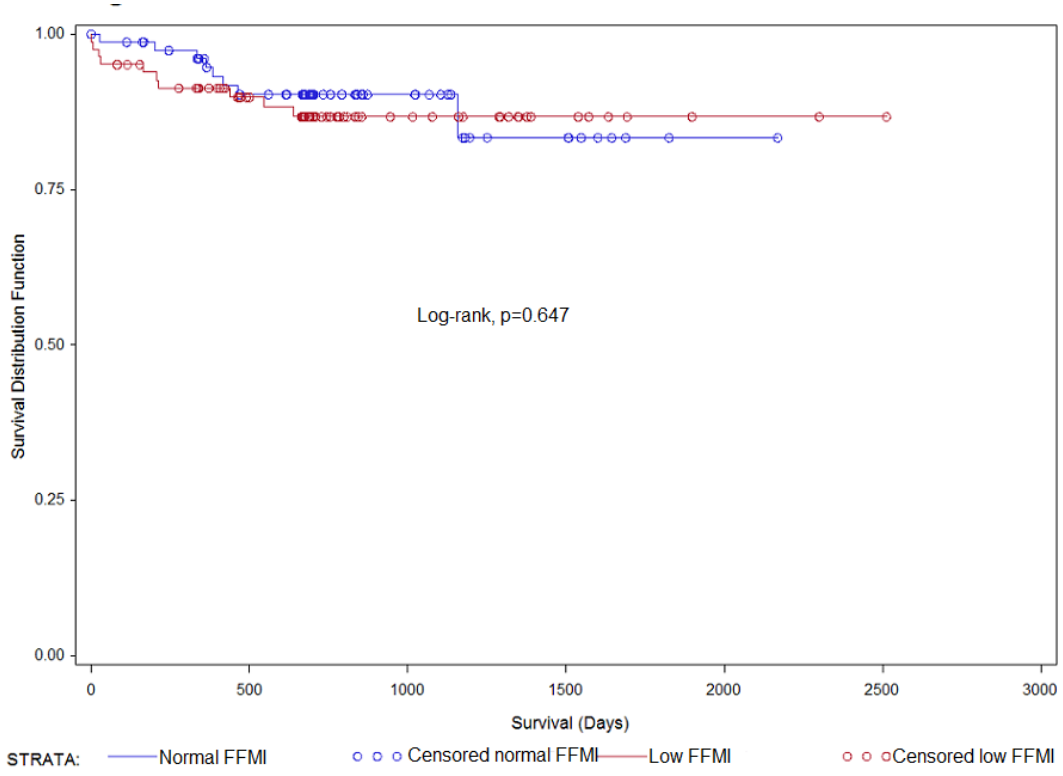
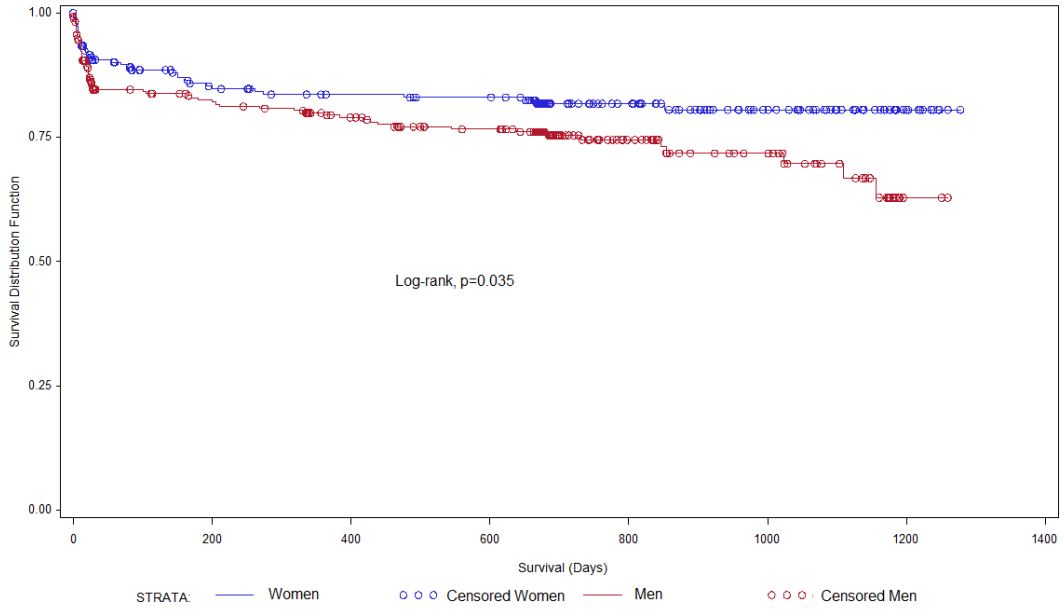
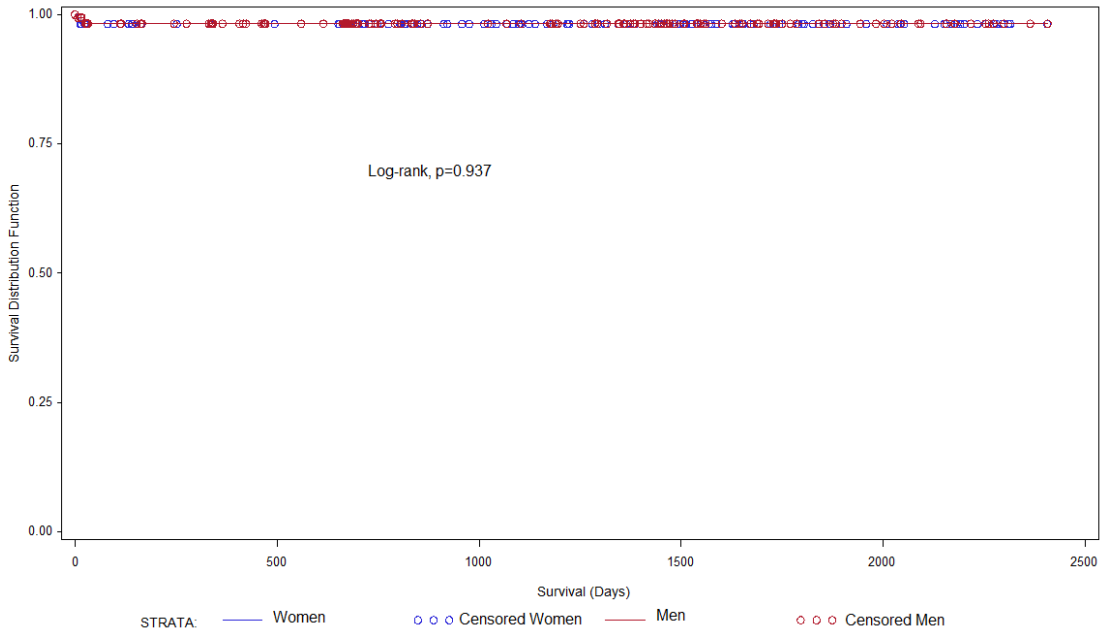


Figure 13:3 Survival distribution among Men compared to Women tuberculosis patients in urban Uganda



Data truncated at 1280 days of follow-up

Figure 13:4 Survival distribution among Men compared with Women among HIV negative tuberculosis patients in Uganda



CHAPTER 14

EXTRA TABLES AND FIGURES FOR CHAPTER TEN

Table 14:1 Spearman raw correlation matrix for fat-free mass, fat mass, and body mass index over different visit time points

Visit (Month)					
Fat-free mass					
0	Fat-free mass	1			
3	Fat-free mass	0.73	1		
12	Fat-free mass	0.69	0.78	1	
24	Fat-free mass	0.68	0.72	0.78	
Fat mass					
0	Fat mass	1			
3	Fat mass	0.88	1		
12	Fat mass	0.85	0.87	1	
24	Fat mass	0.81	0.85	0.90	
Body mass index					
0	Body mass index	1			
2	Body mass index	0.83	1		
3	Body mass index	0.88	0.91	1	
5	Body mass index	0.82	0.87	0.90	1

6	Body mass index	0.68	0.77	077	0.77	1	
12	Body mass index	0.82	0.83	0.86	0.85	0.74	1
24	Body mass index	0.75	0.80	0.80	0.83	0.71	0.89

Table 14:2 Regression estimates for effects of baseline wasting, lag FFMI measure, and baseline characteristics on probability of missing

Covariate	Estimate	Standard error	95% CI
Proc GENMOD	**FFMI**		
Intercept	-1.04	1.79	-4.56, 2.48
Baseline wasting	-0.34	0.41	-1.25, 0.47
Baseline FFMI	-0.03	0.12	-0.26, 0.20
Lag FFMI	-0.11	0.10	-1.07, 0.29
Sex	0.28	0.28	-0.27, 0.82
Age	0.15	0.20	-0.25, 0.54
HIV	0.42	0.20	**2.10, 0.04**
Smoker	0.29	0.26	-0.23, 0.81
Hemoglobin	-0.42	0.23	-0.87, 0.02
History of weight loss	0.09	0.25	-0.40, 0.58
Chest x-ray extent	-0.11	0.27	-0.63, 0.41
Time*baseline wasting	0.02	0.02	-0.02, 0.06
Proc MIXED	**FFMI**		
Intercept	15.65	0.50	**14.67, 16.63**
Probability missing	-0.06	0.12	-0.30, 0.18

Baseline wasting	-1.68	0.14	**-1.95, -1.41**
Lag FFMI	0.04	0.03	-0.02, 0.09
Sex	1.74	0.13	**1.48, 2.00**
Age	0.10	0.12	-0.13, 0.34
HIV	0.06	0.12	-0.18, 0.29
Smoker	-0.14	0.15	-0.44, 0.17
Hemoglobin	-0.34	0.14	**-0.60, -0.07**
History of weight loss	-0.03	0.15	-0.33, 0.28
Chest x-ray extent	-0.10	0.16	-0.40, 0.21
Time*missing	-0.01	0.01	-0.02, 0.01
Random intercept (b_{0i}) variance	0.458	0.098	**<0.001***
Random slope (b_{1i}) variance	0.007	0.004	0.133*
Covariance slopes (b_{0i}, b_{1i})	0.0004	0.0003	0.097*
Autocorrelation; exponential	0.8610	0	-
Residual (measurement error)	0.567	0.053	**<0.001***

Table 14:3 Regression estimates for effects of baseline wasting, lag FMI measure, and baseline characteristics on probability of missing

Covariate	Estimate	Standard error	95% CI
Proc GENMOD	**FMI**		
Intercept	-3.84	0.63	**-5.08, -2.59**
Baseline wasting	0.45	0.40	-0.34, 1.24
Baseline FMI	-0.10	0.07	-0.03, 0.24
Lag FMI	-0.04	0.05	-0.14, 0.06
Sex	0.25	0.31	-0.35, 0.84
Age	0.16	0.20	-0.23, 0.55
HIV	0.44	0.20	**0.05, 0.83**
Smoker	0.32	0.27	-0.20, 0.84
Hemoglobin	-0.29	0.24	-0.76, 0.17
History of weight loss	0.17	0.26	-0.34, 0.67
Chest x-ray extent	-0.01	0.27	-0.53, 0.51
Time*baseline wasting	-0.02	0.02	-0.06, 0.03
Proc MIXED	**FMI**		
Intercept	6.37	0.36	**5.66, 7.08**
Probability missing	0.31	0.20	-0.08, 0.70

Baseline wasting	-2.18	0.20	**-2.57, -1.79**
Lag FMI	0.03	0.02	-0.01, 0.07
Sex	-2.91	0.21	**-3.32, -2.49**
Age	-0.02	0.20	-0.42, 0.38
HIV	-0.14	0.20	-0.54, 0.25
Smoker	0.24	0.26	-0.26, 0.75
Hemoglobin	-0.44	0.24	-0.90, 0.03
History of weight loss	-0.52	0.26	-1.03, -0.02
Chest x-ray extent	-0.45	0.26	-0.96, 0.06
Time*missing	0.005	0.01	-0.02, 0.03
Random intercept (b_{0i}) variance	1.721	0.207	**<0.001***
Random slope (b_{1i}) variance	0.004	0.009	0.642*
Covariance slopes (b_{0i}, b_{1i})	0.003	0.0006	**<0.001***
Autocorrelation; exponential	0.9997	3.383E8	0.500*
Residual (measurement	0.684	0.061	**<0.001***

error)

*p-values

Table 14:4 Assessing contributions of polynomials, random intercepts, and random slopes in mixed models

Fat-free mass						
Model	AIC	-2RLL	Parms (df+1)	Dif-2RLL	df	p-value
Linear model	2768.2	2762.2	3	-	-	-
Quadratic model	2751.4	2745.4	3	16.8		
Cubic model	2730.3	2724.3	3	37.9		
Fixed intercepts	2691.6	2673.6	3	-	-	-
Random intercepts	2691.6	2673.6	3	0	0	NA
Random Intercepts and slopes	2668.6	2646.6	5	27	2	**<0.001**
Fat mass						
Linear model	3197.6	3191.6	3	-	-	-
Quadratic model	3182.0	3176.0	3	15.6	0	NA
Cubic model	3190.5	3184.5	3	7.1	0	NA

Fixed intercepts	3155.6	3137.6	3	-	-	-
Random intercepts	3155.6	3137.6	3	0		
Random intercepts and slopes	3107.4	3085.4	5	52.2	2	**<0.001**
Body mass index						
Linear model	15923.8	15917.8	3	-	-	-
Quadratic model	15768.2	15762.2	3	155.6	0	NA
Cubic model	15688.8	15682.8	3	235.0	0	NA
Fixed intercepts	15650.0	15632.0	3	-	-	-
Random intercepts	15646.4	15626.4	4	5.6	1	
Random intercepts and slopes	15539.5	15515.5	6	116.5	3	**<0.001**

AIC = Akaike Information Criteria, -2LL = -2 log likelihood, df = degrees of freedom, NA = not applicable.

Table 14:5 Assessing Piecewise and polynomial models; random intercepts, and random slopes in mixed models

Model	AIC	-2RLL	Parms (df+1)	Dif -2RLL	df	p-value
Fat-free mass						
Linear model	2779.4	2767.4	6	-	-	-
Quadratic model	2755.6	2737.6	9	29.8	3	**<0.001**
2 Spline model	2714.8	2686.8	15	NA	NA	NA
Random intercepts	2734.7	2722.7	6	-	-	-
Random early slope	2715.8	2699.8	8	22.9	2	**<0.001**
Random early & 3 months slopes	2709.5	2687.5	11	35.2	5	**<0.001**
Random early, 3, & 12 months slopes	2714.8	2686.8	15	35.9	9	**<0.001**
Fat mass						
Linear model	3210.4	3202.4	6	-	-	-
Quadratic model	3276.4	3262.4	9	60	3	**<0.001**

2 Spline model	3274.8	3252.8	15	NA	NA	NA
Random intercepts	3357.2	3361.2	6	-	-	-
Random early slope	3273.2	3265.2	8	96	2	**<0.001**
Random early & 3 months slopes	3276.4	3264.4	11	96.8	4	**<0.001**
Random early, 3, & 12 months slopes	3274.8	3252.8	15	108.4	9	**<0.001**
Body mass index						
Linear model	16307.3	16295.3	6	-	-	-
Quadratic model	16003.5	15983.5	9	311.8	3	**<0.001**
2 Spline model	15887.2	15859.2	15	NA	NA	NA
Random intercepts	16079.2	16067.2	6	-	-	-
Random early slope	15911.8	15895.8	8	171.4	2	**<0.001**
Random early & 3 months slopes	15894.2	15872.2	11	195.0	5	**<0.001**
Random early, 3, & 12 months slopes	15887.2	15859.2	15	208.0	8	**<0.001**

AIC = Akaike Information Criteria, -2LL = -2 log likelihood, df = degrees of freedom, NA = not applicable.

Figure 14:1 Individual profiles for fat-free mass over time

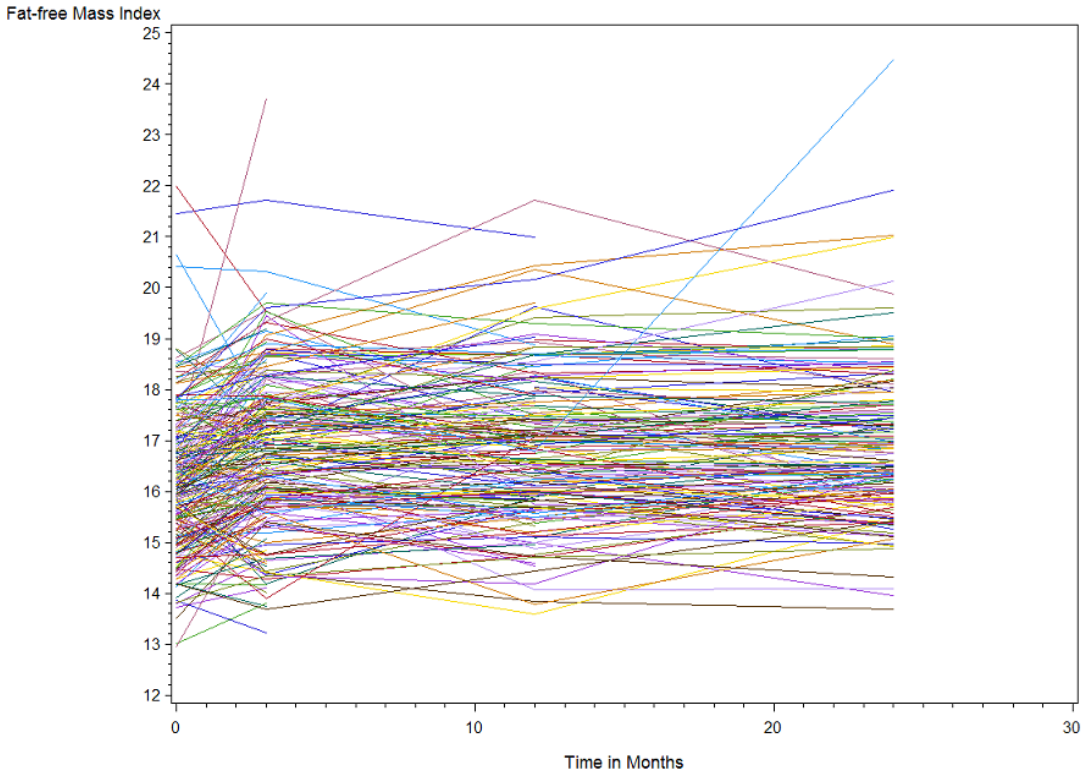


Figure 14:2 Individual profiles for fat mass index over time

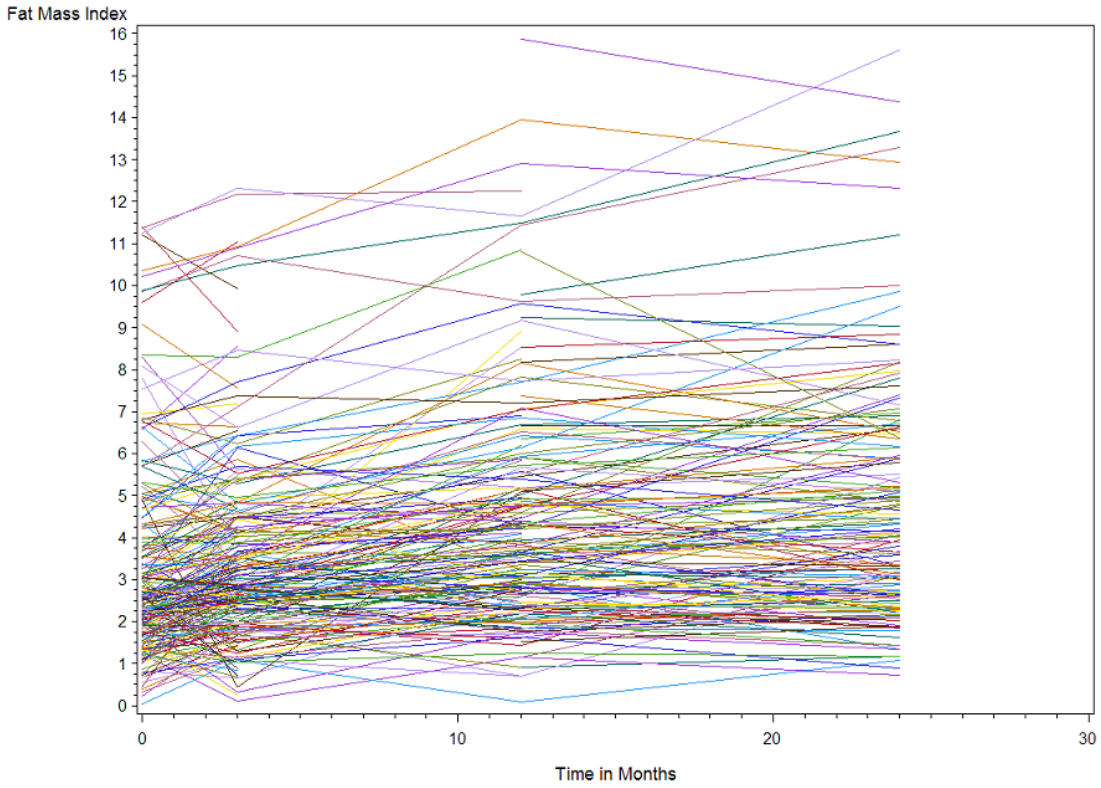


Figure 14:3 Individual profiles for BMI over time

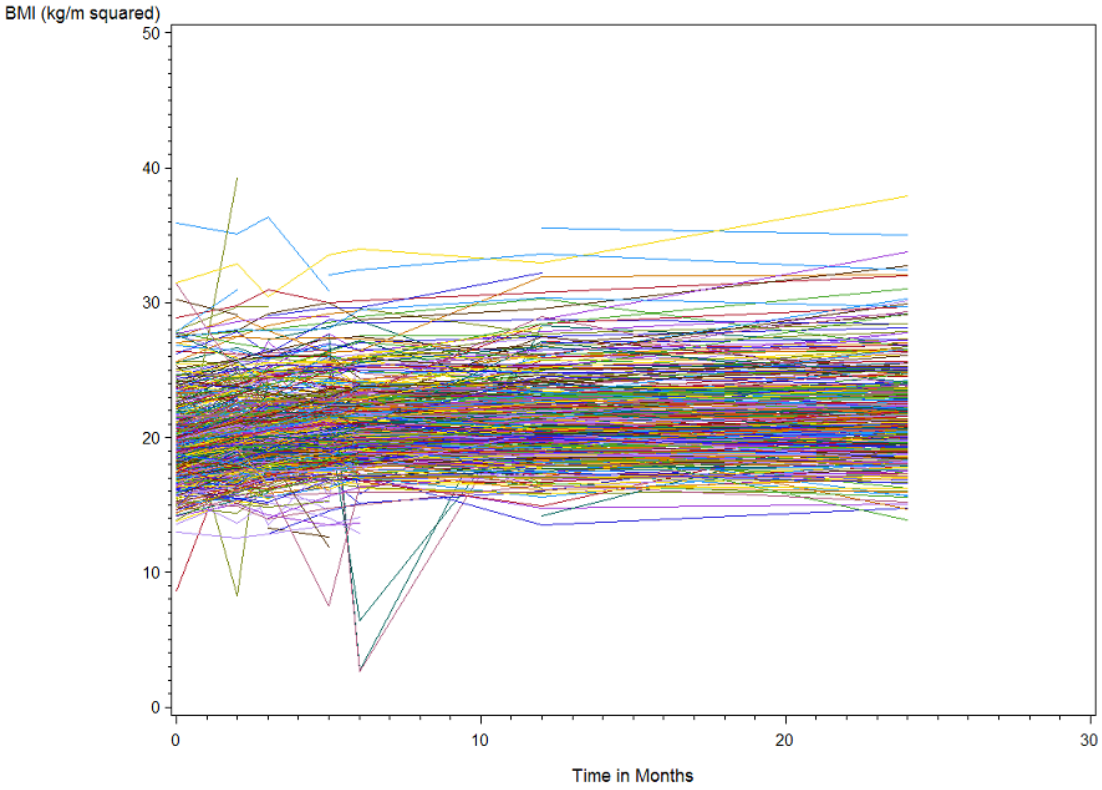


Figure 14:4 Box plots for fat-free mass index over time

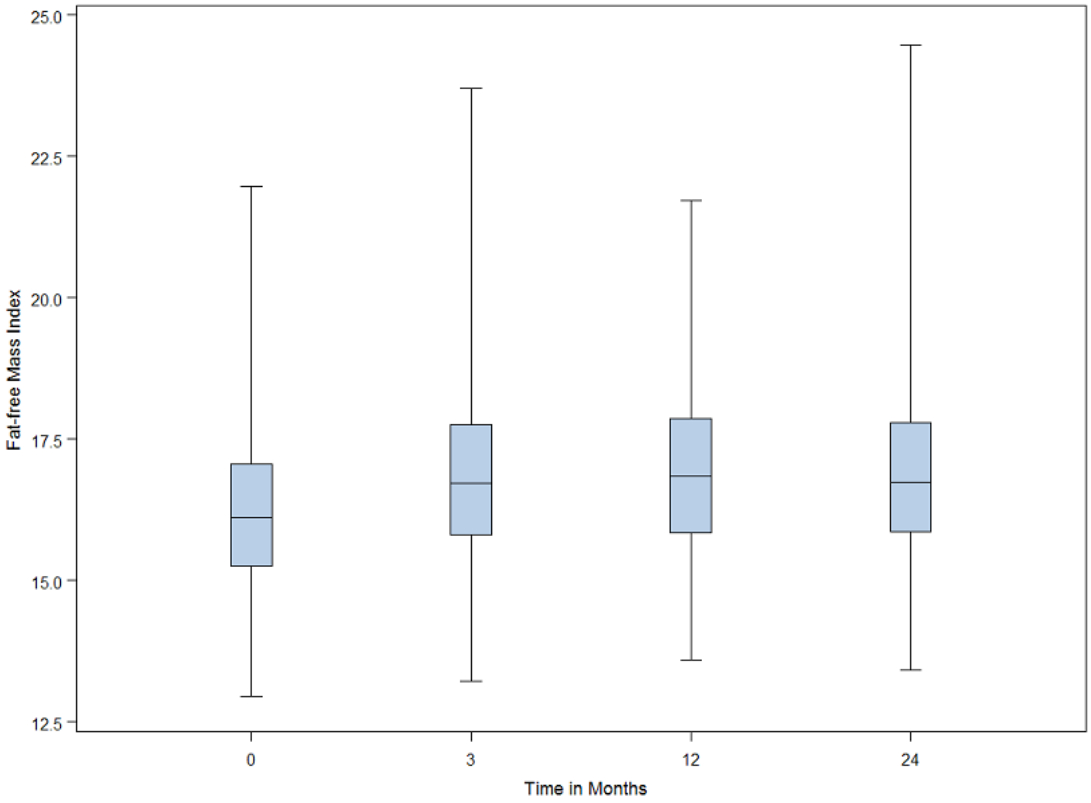


Figure 14:5 Box plots for fat mass index over time

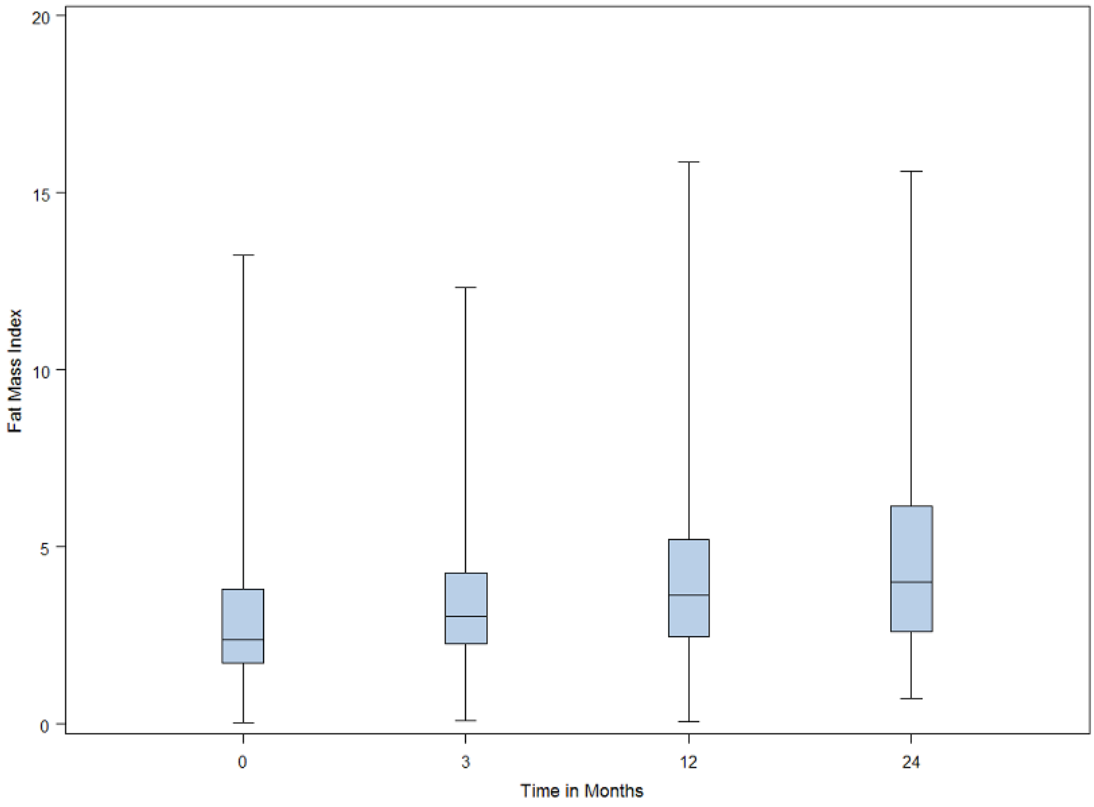


Figure 14:6 Box plots for BMI over time

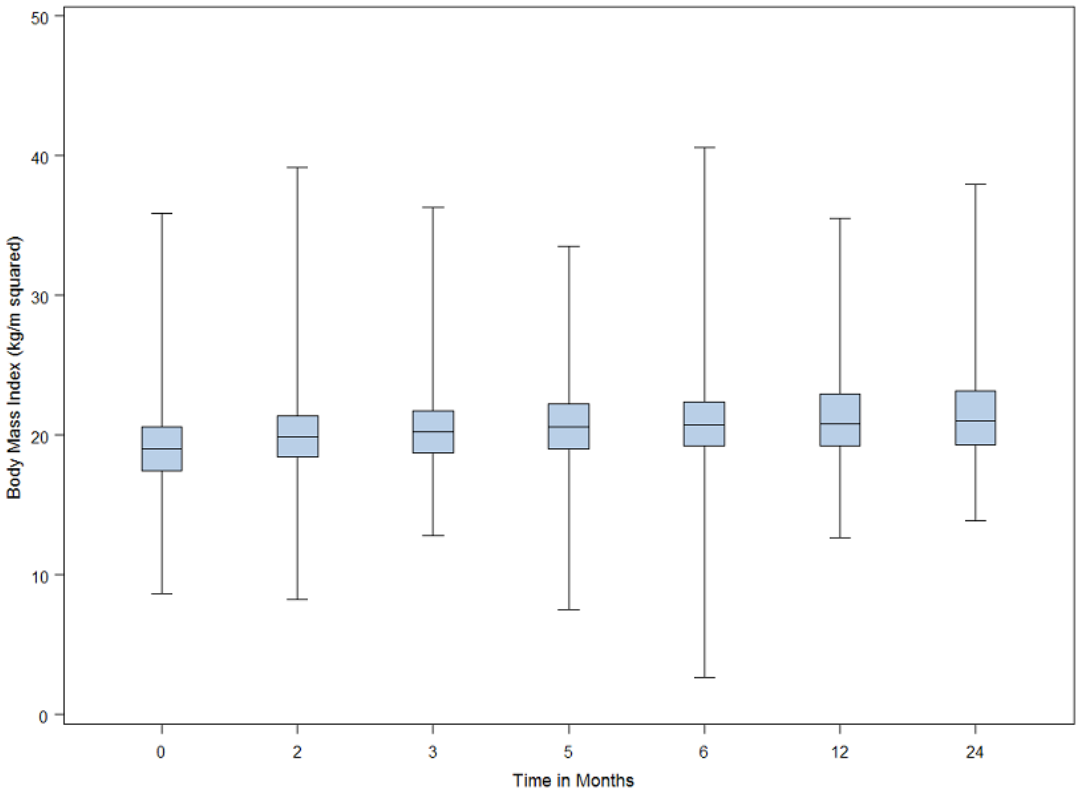


Figure 14:7 Mean profile for FFMI among patients with compared to patients without baseline wasting

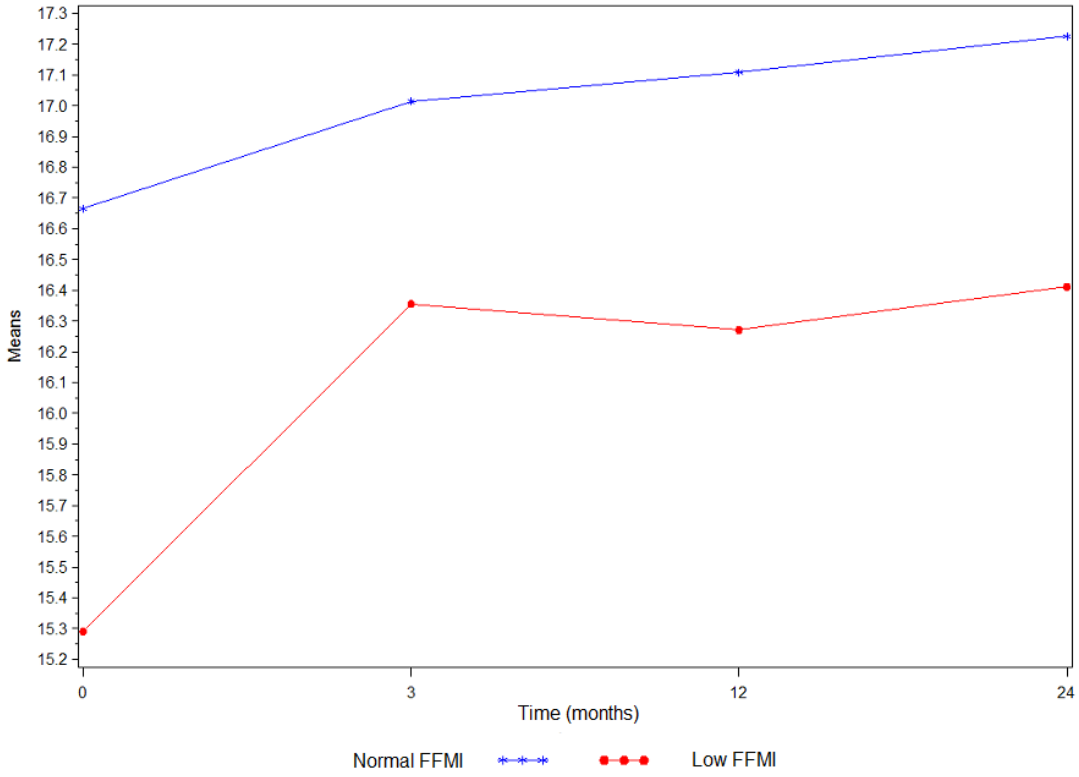


Figure 14:8 Mean profile for FFMI among men compared to mean profile among women

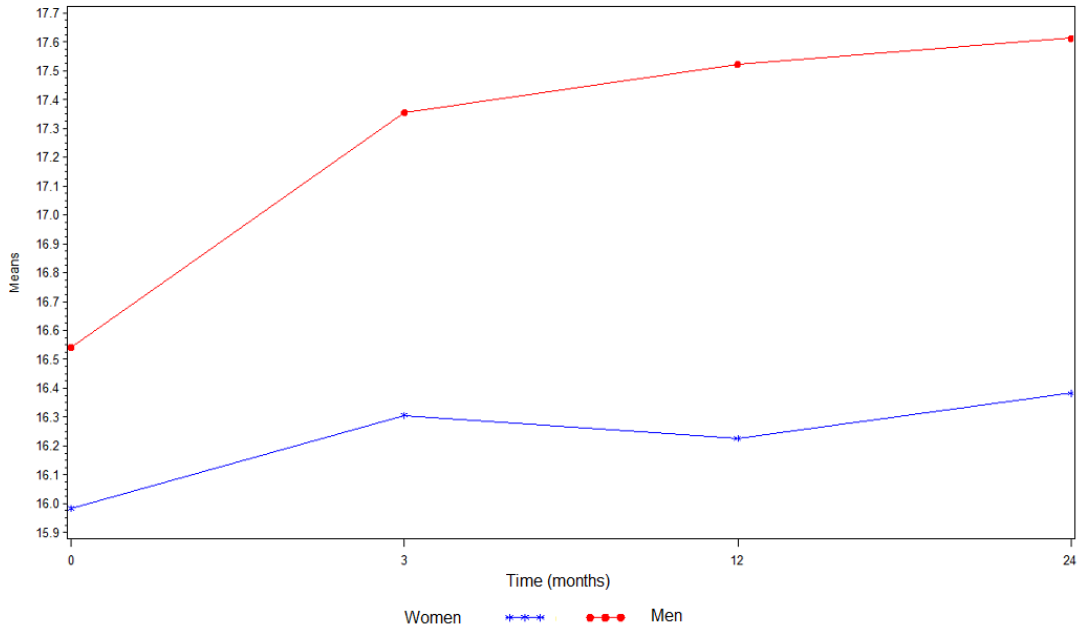


Figure 14:9 Mean profile for FFMI among HIV negative compared to mean profile among HIV positive patients

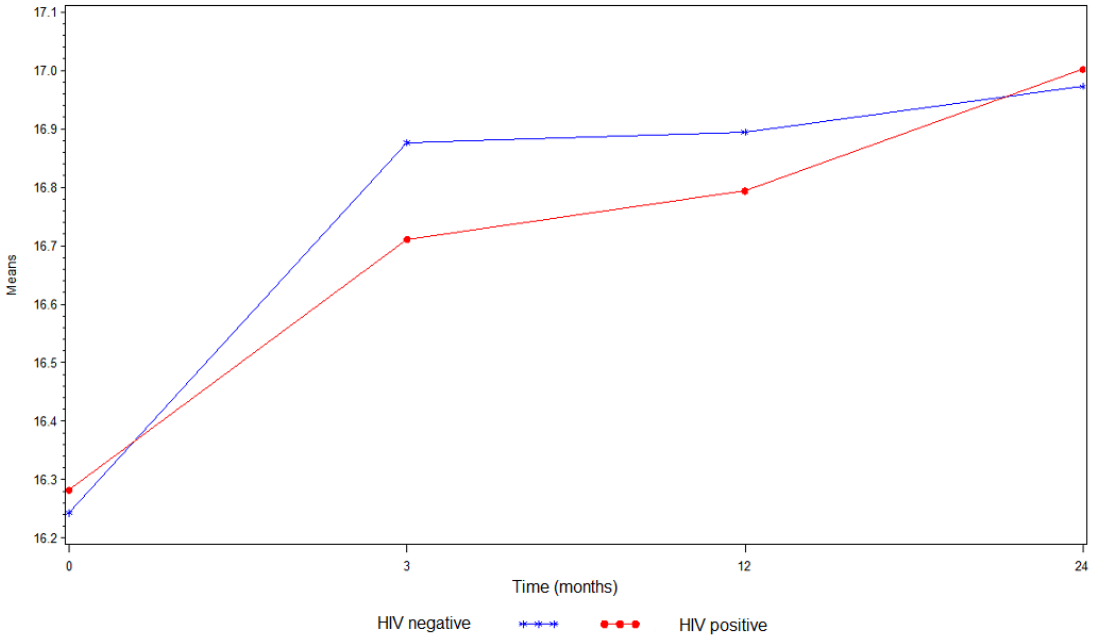


Figure 14:10 Mean profile for FMI among patients with compared to patients without wasting

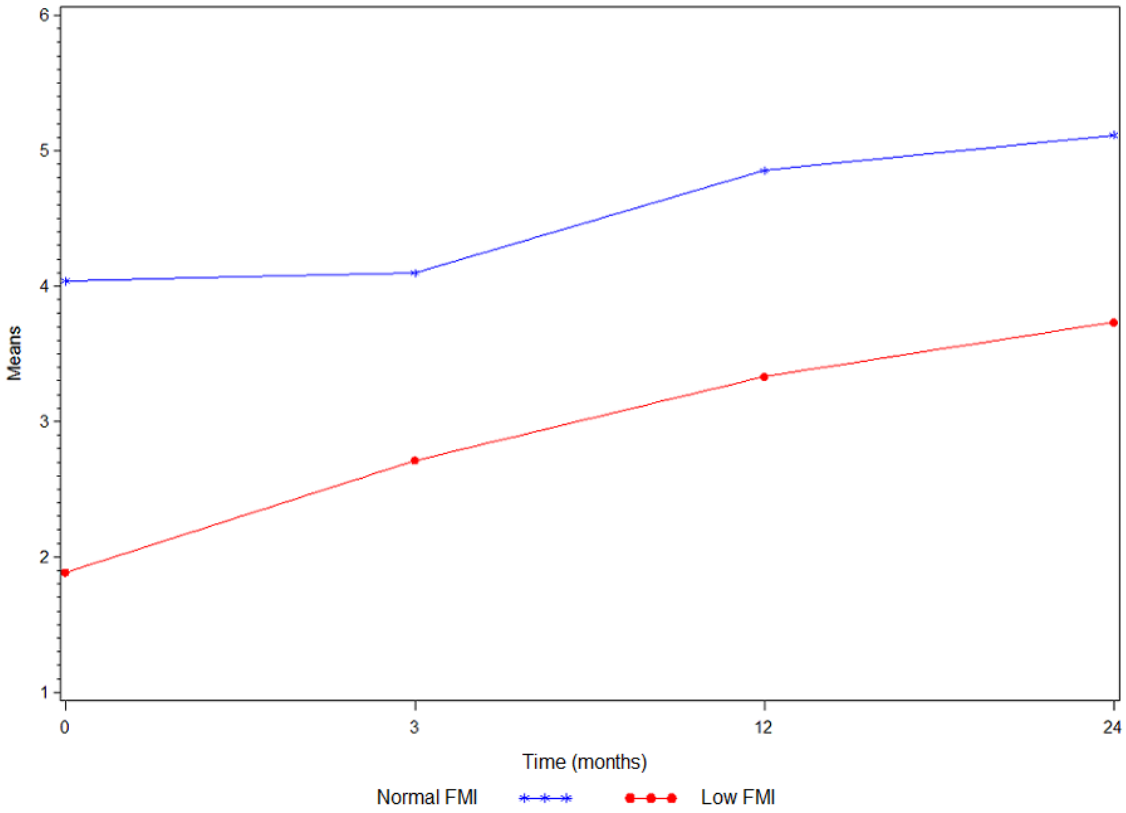


Figure 14:11 Mean profile for FMI among men compared to mean profile among women

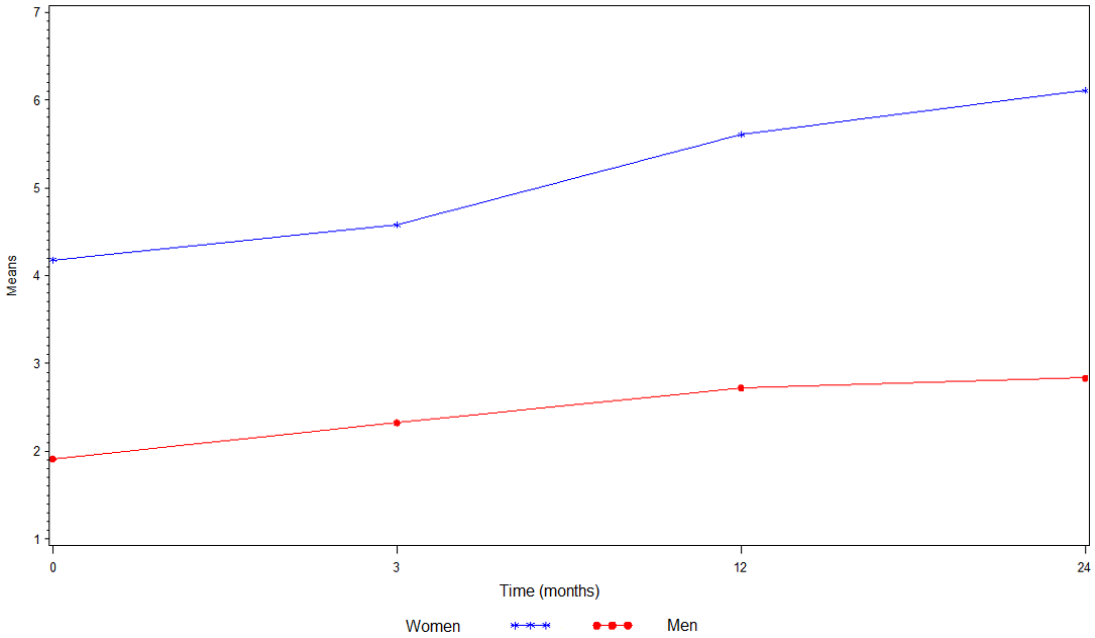


Figure 14:12 Mean profile for FMI among HIV negative compared to mean profile among HIV positive patients

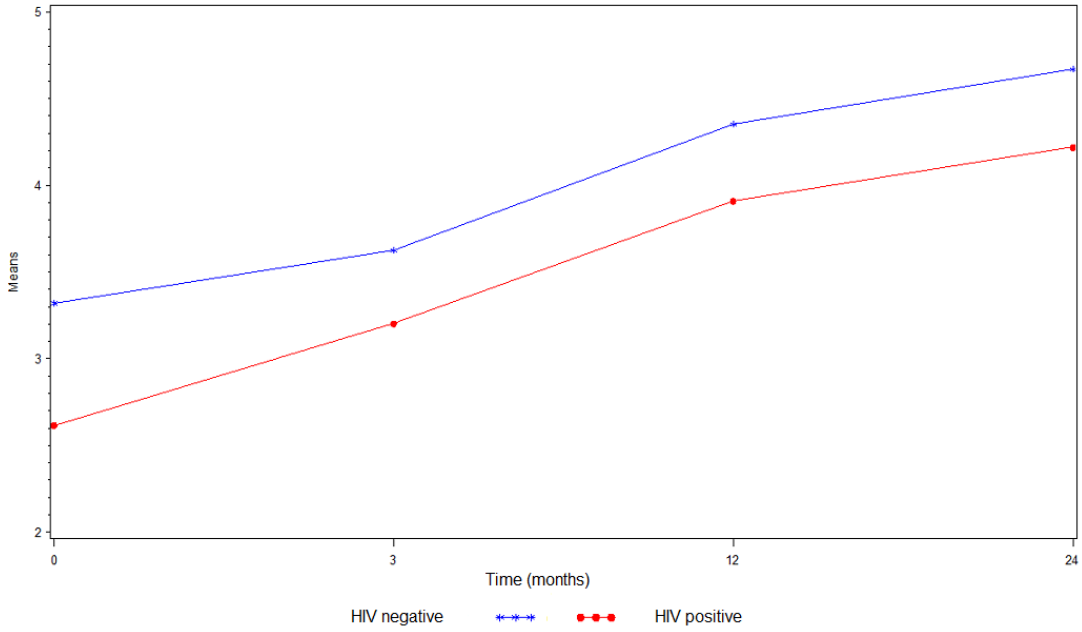


Figure 14:13 Mean profile for BMI among patients with compared to patients without wasting

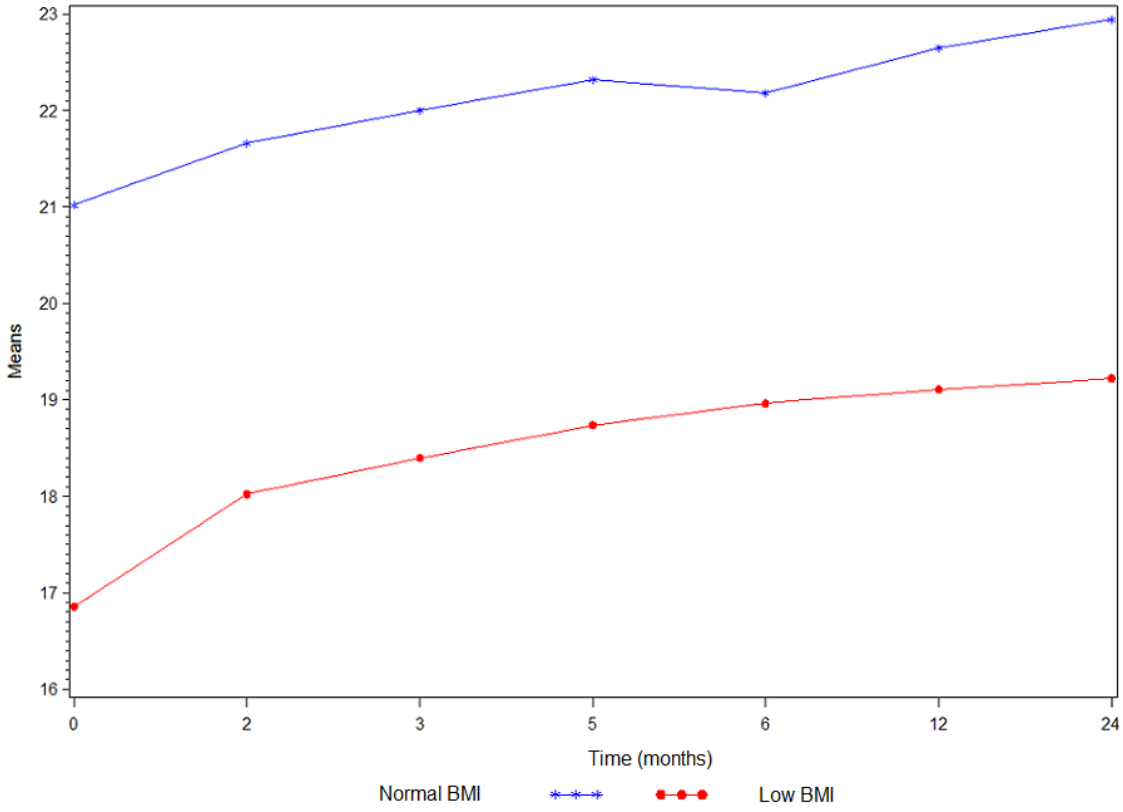


Figure 14:14 Mean profiles for BMI among men compared to mean profile among women

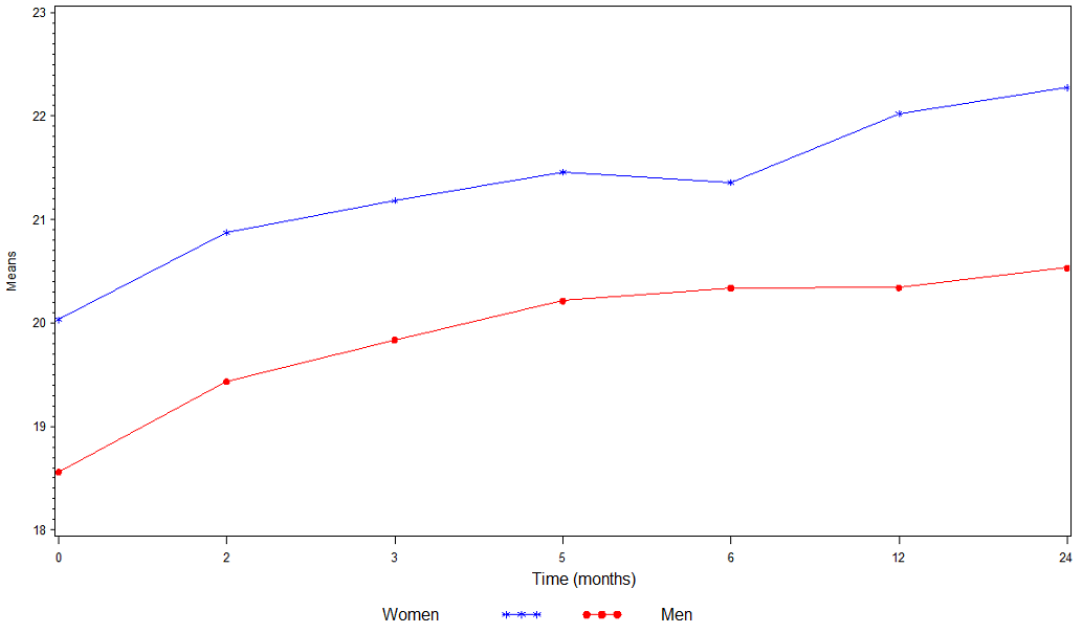
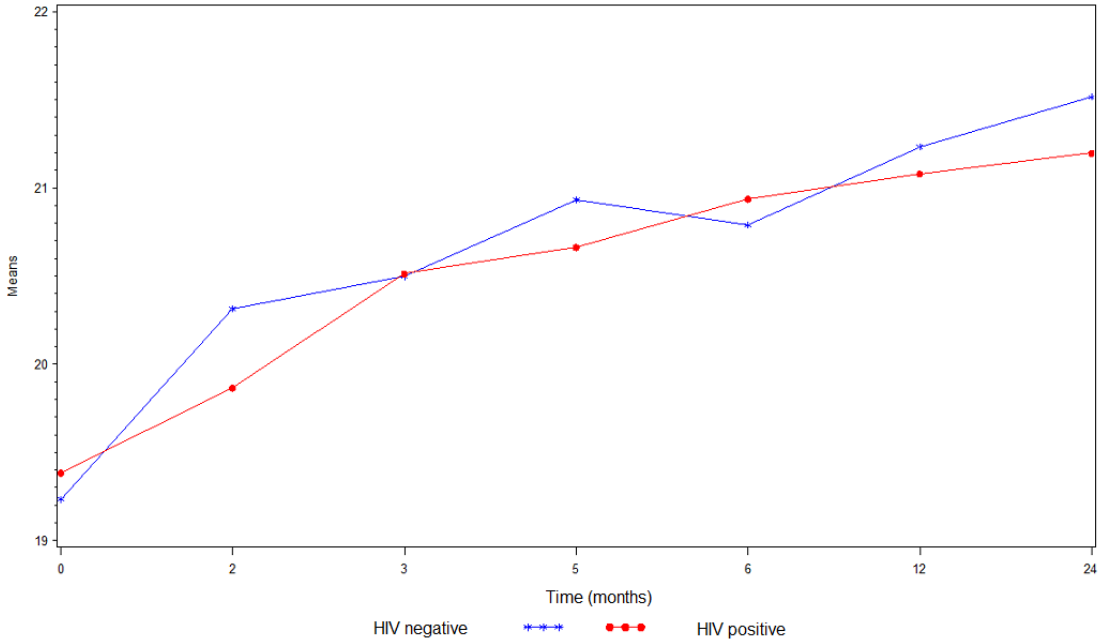


Figure 14:15 Mean profile for BMI among HIV negative compared to mean profile among HIV positive patients



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