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Randomised controlled trial comparing the impact of supplementary feeding with either ready-to-use therapeutic food or corn-soy blend among malnourished anti-retroviral therapy clients in Malawi

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MacDonald Joseph Ndekha

A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, in fulfilment of the requirement for the degree of Doctor of Philosophy (Medicine)

Johannesburg, 2013

ACADEMIC DISSERTATION

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DECLARATION

I declare that this thesis is my own work. It is being submitted for the degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



10 April 2013

_____ _____

Signature **Date**

ETHICS APPROVAL

The clinical trial was approved by the College of Medicine Research Ethics Committee of the University of Malawi College of Medicine (P. 04/05/350R), Committee for Research on Human Subjects (Medical) at the University of the Witwatersrand, Johannesburg (Ethics No. MO50950) and the Human Studies Committee of the Washington University School of Medicine in St. Louis.

The Clinical Trial was registered with the Current Controlled Trials - #ISRCTN67515515.

PUBLICATIONS ARISING FROM THE STUDY

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van Oosterhout JPG, Ndekha MJ, Moore E, Kumwenda JJ, Zijlstra EE and Manary MJ. The benefit of supplementary feeding for wasted Malawian adults initiating ART. *AIDS Care* 2010; **22:** 737-42.

Manary MJ, Ndekha MJ and van Oosterhout JPG. Supplementary feeding in the care of the wasted HIV infected patient. *M Med J* 2010; **22**: 46-9.

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PREFACE

Sub-Saharan Africa is the epicentre of global human immunodeficiency virus (HIV) infection,[1] and Malawi, a small South East African country with a population estimate of 13 million has one of the highest HIV prevalence rates in the world.[1] In keeping with the World Health Organization (WHO) '3 by 5' initiative aimed at providing antiretroviral therapy (ART) to 3 million individuals by 2005,[2] tremendous efforts have been made to increase access to ART in resource-limited countries,[3,4] and ART delivery programmes in such settings have proven their efficiency.[5-9]

However, after the remarkable advances achieved through the introduction of ART in the management of HIV infection, wasting, a clinical condition associated with a poor prognosis in AIDS remain a significant problem in the majority of ART Programmes in the sub Saharan Africa.[16,17] HIV-associated wasting reflects a complex interplay of nutritional factors, such as sub-optimal dietary intake, and a consequence of the chronic HIV infection, which brings about increased metabolic demand for energy and nutrients without concomitant increase in dietary intake, diarrhoea and other opportunistic infections, malignancy and mal-absorption.[18-21] Identification of the dietary factor for the HIV associated wasting is important, especially in the developing world where food insecurity is common.

With the advent of Global Fund support for ART, integration of supplementary feeding in ART programmes has received increasing public health and political emphasis in recent years, such

that it is advocated by both the governmental and non-governmental ART delivery programmes as one of the important strategies to improve outcomes of wasted HIV infected patients initiated on ART. However, evidence is lacking of the effectiveness of supplementary feeding in wasted adult AIDS patients in a typically resource-poor health system, from which programmatic decisions can be made. For instance, in Malawi there have been national discussions about this question, and currently the national AIDS feeding recommendations made on the basis of "expert" advice rather than scientific evidence. There is a clear need to understand whether or not "specialised" food supplements incorporated in ART programmes hasten recovery.

This clinical trial answers an important operational question faced by many ART delivery programmes all over the sub-Saharan Africa in the care of wasted HIV infected adults: "Will supplementary feeding of wasted AIDS patients with "specialised" food supplement in conjunction with ART enhance recovery?"

ABSTRACT

Objectives: To investigate the effect of two different food supplements on body mass index (BMI) and fat-free body mass in wasted HIV-infected Malawian adults commencing highly active antiretroviral therapy (ART).

Design: Randomised controlled, investigator blinded, clinical trial.

Setting: Large, public ART clinic in a referral hospital in Blantyre, Malawi.

Participants: 491 adults (>18 years) initiating ART with a body mass index (BMI) <18.5.

Interventions: After screening for study-eligibility, consenting new ART registrants were randomised to receive either ready-to-use therapeutic food (RUTF) (n=245), or corn-soy blend (CSB) (n=246) supplements.

Main outcome measures: The primary outcomes were changes in BMI and fat-free body mass following completion of an initial 3.5-month of both ART and supplementary feeding, and subsequently after 9.5 months of ART alone once supplementary feeding had stopped. Secondary outcomes were survival, hospitalisations, changes in health-related quality of life (HRQoL) assessment scores at 3.5, 6.5, 9.5 and 12.5 months, improvements from baseline in CD4 count, serum albumin, haemoglobin and HIV RNA viral load at 3.5 months, and adherence to ART.

Results: A total of 1,343 new ART registrants during the study period were screened for study eligibility, from which some 511 individuals were study-eligible. Of these, 491 individuals (96%) were enrolled, 245 and 246 in the RUTF and CSB cohorts, respectively, with a mean BMI of 16.5 kg/m^2. Following the 3.5-month supplementary feeding, study participants in the RUTF

group had a significantly greater increase in BMI (2.1 [SD 1.8]) v 1.6 [SD 1.6] kg/m^2, mean difference 0.50, 95% CI 0.10 to 0.80; p<0.01), and fat-free body mass (2.9 [SD 3.2] v 2.2 [SD 3.0] kg, mean difference 0.70, 95% CI 0.20 to 1.20; p< 0.01) compared to participants in the CSB cohort. No significant differences in CD4 count, HIV viral load, HRQoL measurements or ART adherence were noted between the two cohorts. Mortality was high and similar in both cohorts (27% v 26% in the RUTF and CSB cohorts, respectively). Multivariate Cox hazard modelling identified male gender (HR 1.75, 95% CI 1.32 to 2.31), lack of access to cotrimoxazole prophylaxis (CTX) (HR 2.4, 95% CI 1.3 to 4.7), severe wasting (BMI <16.0) at baseline (hazard ratio [HR] 10.3, 95% confidence interval [CI] 1.3 to 79.7), lower lean body mass (% body composition) (HR 10.3, 95% CI 1.2 to 86.8) at baseline and weight gain ≥ 10% of the initial body weight at 1.5-month study follow-up (HR 3.9, 95% CI 1.8 to 8.4), as factors significantly associated with high "early" (3.5-month) mortality. Trial retention rate on completion of the 3.5-month feeding intervention was 162/245 (66.1%) and 174/246 (70.7%) in the RUTF and CSB cohorts, respectively. Both groups continued with ART only thereafter. Nine and half months after the feeding intervention stopped, both cohorts had a similar BMI and fat-free body mass. Additionally, health-related quality of life, ART adherence, hospitalisations and mortality were similar between the two cohorts. Cox hazard modelling identified a lower lean body mass (% body composition) (HR 130, 95% CI 6.3 to 2699), a CD4 count of 50-199 (HR 3.7, 95% CI 1.2 to 11.1) and a CD4 count <50 (HR 11.9, 95% CI 2.1 to 65.2) at 3.5-month follow-up as factors significantly associated with post-supplementary feeding ART mortality.

Conclusions: Supplementary feeding with RUTF resulted in a greater increase in BMI and fat-free body mass compared to feeding with CSB while study participants were receiving the food supplements. Although feeding with RUTF can ameliorate an established risk factor for

mortality in HIV infection- BMI - the benefit is maintained only during the supplementary feeding period, and there was no evidence that this conferred any other benefits to study participants as they continued with ART. Targeted feeding of wasted ART patients for a period longer than 3 months, or pre-ART supplementary feeding of wasted patients to improve their BMI, merits future research.

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ABBREVIATIONS

AIDS	Acquired Immune Deficiency Syndrome
BMI	Body Mass Index
CDC	Centers for Disease Control
CSB	Corn-soy blend
CTX	Cotrimoxazole
ART	Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HRQoL	Health-related Quality of Life
IRIS	Immune Reconstitution Inflammatory Syndrome
MUAC	Middle-Upper-Arm Circumference
QECH	Queen Elizabeth Central Hospital
RDA	Recommended Dietary Allowance
RUTF	Ready-to-use-therapeutic food
TB	Tuberculosis
UNICEF	United Nations Children's Economic Fund
WFP	World Food Programme
WHO	World Health Organization

CHAPTER 1 LITERATURE REVIEW

1.1 Introduction

The benefits of antiretroviral therapy (ART) in the management of human immunodeficiency virus (HIV) disease are well established[22-26] by suppressing plasma HIV-1 RNA to undetectable levels, and enhancing immune function to optimally protect against opportunistic infections and HIV-related malignancies, ART improves survival of patients living with HIV/AIDS. Since use of ART became widespread, the prognosis of patients infected with HIV has dramatically improved; HIV-related morbidity and mortality has declined, improving life expectancy and turning HIV from being a terminal infection into a chronic disease.[25,26] However, the care of AIDS patients in the developing world is made more difficult by the additional clinical problem of under-nutrition; In sub-Saharan Africa, particularly in resource-constrained settings, AIDS often manifests as wasting.[16] Wasting is associated with a poor prognosis in AIDS and is a strong independent predictor of survival in HIV-infection.[10-15]

It is not an easy task to review the huge literature on the subject of HIV treatment. However, the literature review below provides an overall view of the various methodological issues related to the treatment of AIDS, and factors that need to be taken into account when designing and implementing nutritional intervention programmes for wasted AIDS patients living in resource-limited operational settings. The literature review is in two phases. The first phase focuses on the HIV disease process, covering more general issues such as the pathophysiology of HIV

infection, i.e., the immune response to HIV infection and to ART medication, adherence to ART medication and patient-based self-reported outcome measures of ART medication such as the Health-related quality of life assessments. The second phase literature review focuses on the role of nutrition in the management of HIV disease, with special attention for the resource-limited settings where the majority of individuals are food insecure.[16] This includes a review of the human body composition, the synergistic relationship between nutrition and HIV infection, i.e., how HIV infection affects nutrition and how nutrition affects HIV, the severity of under-nutrition to affect prognosis in HIV infection, and supplementary feeding strategies most commonly used in the management of childhood malnutrition and the chronically-ill under-nourished adults living in the resource-limited settings.

1.2 The Immune response to HIV infection and to ART

1.2.1 The immune response to HIV infection

The immunopathogenic mechanisms of HIV infection have been investigated.[27-30] Dendritic cells are a population of potent antigen-presenting cells derived from the bone marrow and present in body tissues. These cells are vital in the initiation of T-cell responses, particularly to new antigens.[31] They migrate through the body, bind and process antigens and activate T cells, and are the first to appear at sites of inflammation in mucous membranes.[31,32] The cells function by taking up antigens and processing them into peptides that are associated with surface major histocompatibility complex proteins, the complex that interacts with the lymphocyte antigen receptor. The cells then migrate to lymphoid organs and activate T cells in the paracortical regions by presenting the major histocompatibility complex-bound antigen to the T cells.[31] Given this, a model of the

initiation of HIV infection is that HIV enters through a defect or site of inflammation in a mucous membrane, and is bound by dendritic or Langerhans cells.[33-35] Dendritic cells then carry HIV to a lymphoid organ and migrate to the paracortical region rich in $CD4^+$ T cells.[33-35] These $CD4^+$ T cells are activated by the dendritic cells and are exposed to bound HIV, leading to their productive infection and to subsequent wide dissemination of virus.[33-35] The dendritic cells also interact with $CD8^+$ T cells in lymphoid organs and initiate an immune response that partially controls HIV replication.[33,34]

The lymphoid tissue is the major reservoir for and site of persistent viral replication early in the course of HIV infection.[33] Soon after HIV enters the body, it is widely disseminated, predominantly to lymphoid tissues.[3033,36,37] In the early stages of HIV infection, the lymph nodes of persons with progressing HIV disease are activated and hyper-plastic, and many virions trapped in the germinal centres of lymph nodes in an extracellular manner on follicular dendritic cells.[33,37] This occurs when production of virus by individual cells within lymphoid tissue is low.[33,35] The virus continues to be trapped by follicular dendritic cells in the germinal centres of the lymph nodes, initiating continuous immune stimulation and constant exposure to infection of $CD4^+$ T cells that reside in or are migrating through the lymph nodes.[27,30] The HIV trapped on the follicular dendritic cells is infectious for $CD4^+$ T cells, even though the virions are coated with neutralizing antibodies.[38] Thus, the mechanisms operable in an appropriate immune response to HIV, particularly activation of the immune system, are paradoxically the same mechanisms that propagate HIV infection and lead to the ultimate destruction of lymphoid tissue and to profound immune-suppression.[30] The HIV trapped on the follicular dendritic cells is infectious not only on the $CD4^+$ T cells, but also bone marrow progenitor cells, developing thymocytes and thymic stromal cells associated with marked disruption of the thymic micro-

environment. In this regard, HIV-infected persons have a high incidence of cytopaenias and other hematologic abnormalities, and haematopoiesis has been shown to be depressed.[39] Several factors, such as abnormal cytokine production in the bone marrow, and infection of stromal or other bone marrow cells contribute to the overall hematologic defects in HIV infection.[39] The infection of progenitor cells in bone marrow and the thymus contribute to the lack of regeneration of immunocompetent cells.[38] In advanced-stage disease the virus is present at high levels in the plasma and rapidly turns over.[40,41]

The burst of virus replication early in the course of HIV disease is partially contained by cytokine secretions,[42,43] cell-mediated[28,44] and humoral[28,45] immune responses. As part of the normal immune-regulatory homeostatic mechanism, body cells communicate with each other through the secretion of cytokines.[42,43] In early, intermediate or advanced stages of the infection, cytokines in the lymph nodes of HIV-infected individuals are hyper-expressed and (in some cases) dysregulated, compared with the lymph nodes of individuals with other infections.[46] Cytokines such as interleukin-l β, interleukin-6, granulocyte-macrophage colony-stimulating factor and tumour necrosis factor-a up-regulate HIV expression.[47-49] Such observations assume potential physiologic relevance in light of the fact that several pro-inflammatory cytokines capable of inducing HIV expression are chronically over-expressed in the lymphoid tissue of HIV-infected persons.[46] Nevertheless a tightly controlled autocrine loop of endogenous cytokine control of HIV expression exists,[50] and down-regulate the expression of HIV.[50] Thus the expression of HIV is partly modulated by the endogenous cytokine network, generally responsible for maintaining the homeostasis of the immune system.[50]

Cell-mediated and humoral immune responses specific to HIV infection have also been investigated.[34,44,51-53] The cell-mediated immunity consists predominantly of HIV-specific cyto-toxic T lymphocytes critical in the elimination of virus-expressing cells, resulting in decreased virus production.[28,44] The humoral immune response, composed of antibodies against different HIV proteins contribute to the down-regulation of viraemia through the formation of immune complexes composed of virus particles, immunoglobulin and complement (C') that may be trapped in the reticulo-endothelial system.[28,45] The appearance of trapped virus in the follicular dendritic cell network of germinal centres in lymph nodes coincides with an increase in the levels of C' binding antibodies.[28,48] In contrast, neutralizing antibodies are detected only several months after sero-conversion. Hence the down-regulation of viraemia during the transition from the acute to the chronic phase of the HIV infection is likely to result from the combined action of both cellular and humoral immune responses.[28,45] Thus throughout the early years of HIV infection, the body's CD4 cell levels appear normal, because of the dynamic compensatory process of the virus versus the CD4 cell depletion and replication that is in balance, keeping pace with the effects of HIV.

However, despite the robust immune responses leading to the down-regulation of viral replication, the virus is not completely eliminated from the body, and a state of chronic persistent viral replication and chronic activation of the immune system result in a progressive deterioration of the immune function and clinically apparent disease or AIDS.[30,33,51,52,54,55] The profound immunosuppression that occurs during this phase of HIV infection is the end stage of the immuno-pathogenic events that began at the time of the primary infection when the virus disseminated and seeded the lymphoid organs, and continued for years through the clinically-

latent but microbiologically active stages of infection. Although numerous factors undoubtedly contribute to this, lack of the ability to completely regenerate or repopulate the $CD4^+$ T lymphocyte cells may be due to failure of the bone marrow, the thymic progenitor cells or the thymic and lymphoid tissue stromal environment that is critical in the generation of immuno-competent cells.[30,31,40,48,49] HIV infection impairs the thymic function, leading to continuous depletion of the CD4 T cells and progressive immunodeficiency.[29] Therapeutic strategies that regenerate the normal immune system, maintain or restore an intact thymic and lymphoid stromal microenvironment are vital to the reconstitution of the immune system in HIV-infected individuals.[30,31,40,48,49]

1.2.2 The immune response to ART

The ability of ART to improve prognosis in HIV-infected individuals is contingent on ART reducing HIV RNA to undetectable levels, and improving the immune system to a level that optimally protects against opportunistic infections and HIV-related malignancies.[22-24] Treatment with ART blocks viral replication, leading to enlargement of the thymus and augmented thymic production of naive T-lymphocytes, thereby tipping the balance toward CD4+ cell repopulation,[24,56,57] allowing at least a partial immune reconstitution to occur. Hence patients on ART have a significantly greater increase in CD4 cell count (cell x 10^6) than their counterparts not on ART.[58,59]

The dynamics of immune response to ART have been investigated[59-63] and the immune restoration in HIV infected individuals following ART initiation occurs in two phases, acutely

and during prolonged therapy. One to two weeks after ART initiation, a 90% decrease in the circulating HIV RNA levels occur.[60] Coincident with the fall in HIV concentrations is an early rapid increase in the circulating CD4+ T-lymphocyte counts, largely representing a redistribution of activated CD45Ro memory cells previously sequestered in lymphoid tissue, and a generalized reduction in apoptotic cell death.[59] With continued ART for 4 - 6 weeks, naïve CD4+ cells begin to increase, the source of the sustained increase likely being the thymus,[61] and patients have evidence of amplified delayed hypersensitivity reactions and in vitro lymphocyte proliferation assays to common antigens such as candida species.[62] With continued therapy, responses improve towards both common antigens, as well as antigens from microbes that cause opportunistic infections.[62] Following the initial rapid increase in CD4 T lymphocyte counts during the first 3 – 6 months of ART, a second phase of slower increase persists over subsequent months and years. This represents expansion of naive CD45RA cells as thymic function is restored, resulting in the long-term sustained rise in CD4 cell count. This correlates with the magnitude of viral load suppression, and its stability over time.[63]

Predictive factors for the rate of immune-reconstitution in ART-naïve patients reaching sustained viral load suppression have also been investigated.[64-66] Severity of pre-treatment CD4 cell depletion determines the CD4 cell number normalisation (defined as CD4 cell count values comparable to those measured in the HIV-negative individuals) after ART initiation; The lower the pre-treatment CD4 T cell count, the longer the immune-normalisation takes,[67] and to compensate for the significantly lower baseline CD4 cell count, the net increase over baseline is much larger in patients with lower, compared to higher values at baseline. A history of opportunistic infections, probably a reflection of the lower pre-treatment CD4 count status in

those who had experienced opportunistic infections, is another factor that influences rate of immune response to ART, such that individuals with previous episodes of opportunistic infections, have a significantly greater CD4 count increase following ART initiation.[65] Another determinant of immunological response to ART is age; evidence[66] suggests that immune normalisation in ART patients over 50 years of age is significantly slower than in younger patients, despite their better virological response, which partly explains their higher risk of clinical progression.[65,67,68]

The level of expression of several inflammatory cytokine mRNA species in lymph node biopsies, another parameter of immune activation after induction of ART has been investigated,[60] where cytokine mRNAs for IFN-γ, IL-1β, IL-6, and MIP-1α decreased significantly in lymph node tissue after ART.[60] Whether the resolution of active viral replication by ART alter the expression of adhesion molecules, a key determinant of the re-circulation of lymphocytes between blood and tissue sites[60] was investigated by staining frozen sections of lymph nodes with mAb's specific for adhesion molecules ICAM-1 and VCAM-1,[60] the adhesive molecules being integrins that mediate lymphocyte-endothelial cell interactions and promote sequestration of circulating lymphocytes in tissue,[60] levels of which are known to increase in tissue after stimulation with inflammatory cytokines.[69-75] The ICAM-1 and VCAM-1 were expressed in high concentrations in tissues obtained before therapy and substantially declined after ART,[60] suggesting the viral antigen stimulated the immune activation in lymphoid tissue during periods of high viral replication, and suppression of viral replication by ART may have resulted in a substantially decreased antigenic stimulus, reduced inflammatory cytokine expression, reduced adhesion

molecule expression and a net redistribution of lymphocytes from the previously inflamed tissues into peripheral blood.[60]

1.3 Adherence to the ART medication

Full adherence to medication implies taking all doses as prescribed for optimal treatment effect. However, both research and practice have shown that strict adherence with regard to ART is difficult to achieve for the majority of AIDS patients, such that even highly motivated patients miss doses.[76,77] As such a lower adherence cut-off level of 95% have been suggested,[77-82] adherence level below which has been associated with poor response to treatment.[81,82] ART adherence is a dynamic process, such that patients with suboptimal adherence to the therapy have diverse reasons for their non-adherence.[82] The World Health Organization (WHO) groups factors influencing ART adherence as socioeconomic, health-care system, condition, therapy and patient-related.[82] Barriers to ART adherence typically reported in developed countries include the frequency and the severity of therapy side effects, stigma associated with being HIV positive, inconvenience to daily routine and pharmacy refills.[82] Additionally schedule for dietary intake such as before, during and after an ART dose is reportedly an enormous challenge to therapy adherence in people living with HIV/AIDS.[82] In sharp contrast, disruptions in drug supplies are reported major barriers to adherence in the resource-limited settings.[82] Additionally as opposed to the issue of the dietary adherence schedule as an obstacle to ART adherence reported in the developed world, the major obstacle to ART initiation and its adherence in Rwanda, was the fear of developing too great an appetite in the face of food insecurity.[83] Thus, addressing issues of ART adherence in resource-limited settings in the sub-Saharan Africa may require somewhat

different approaches to those in developed countries. However, despite the complexity of ART adherence, a high level of adherence is the most important determinant of successful treatment outcomes in the management of HIV and AIDS.[79,84-88] The risk of virological failure, viral mutations, development of drug resistance, medication failure and transmission of resistant HIV viruses make ART adherence a public health concern.[86,87] This is the case particularly in resource-limited settings due to poor access to care and monitoring, limited availability of alternative ART regimens, and the fact that future ART treatment options become limited due to cross-resistance.[88]

The utility of different measures of ART adherence have been evaluated,[76,82] and all cited measures of adherence have different strengths and limitations with regard to practical application and identifying deficient adherence.[76] Estimates of ART adherence from patients' self-reports are less complex to obtain than other methods.[76,82] However due to social desirability bias where patients wish to impress their health care provider(s) as complying to the medication protocol, all forms of self-reports inevitably over-estimate medication adherence compared with other adherence measures.[76,82] To increase validity of self-reported adherence, a preamble is suggested before asking adherence questions, to reassure patients the information will not be held against them, and that problems with adherence are nearly universal.[76,82] An attractive alternative in assessing ART adherence is "pill counting" the pills remaining in the patients' drug bottle, such that refill adherence is a surrogate for ART adherence. However ART patients could be less than optimally adherent to treatment protocol despite maintaining a high level of refill adherence, due to pill dumping. Other measures of ART adherence include pharmacy-based approaches, electronic monitoring, biochemical assays, or a combination of some of methods.[76]

Despite limitations of the cited ART adherence measures, efforts to evaluate adherence in the course of routine HIV care are encouraged as it offers an opportunity to remind patients of the critical role of strict ART adherence.[76,82]

1.4 Health-related Quality of Life assessment in patients with HIV infection

Until recently HIV clinical trials and intervention studies have used as their primary outcome measures, traditional clinical measures of mortality, occurrence of opportunistic infections, progression to a clinical definition of AIDS, occurrence of adverse events etc, and biological markers such as HIV viral suppression and changes in CD4 cell count measures.[89] However, the public health community perceives the concept of health as a multidimensional construct, such that although the biochemical and morbidity information may indicate need for treatment, these do not always correlate with the way people feel, and often correlate poorly with functional capacity and well-being of patients.[89]

Patient's self-perceptions and perceived-efficacy of a treatment have important implications as they motivate health-seeking behaviour and therapy adherence.[89,90] A clinical trial involving two cohorts of severely malnourished HIV-negative Malawian children reported superior outcomes with RUTF than with fortified CSB feeding, and a higher loss to follow-up rate in the CSB than in the RUTF feeding cohort.[90] The higher loss to follow-up in the CSB feeding cohort was assumed to be due to the presumed lack of benefit; the caretakers of the children may have thought continued follow up visits to the treatment facility would not be beneficial, after a slow progress in the first weeks of therapy. It has also been shown that patient's self-reported "health

days" report works as both an outcome measure and as a powerful predictor of mortality and morbidity that is better than many objective measures of health.[89]

The health-related quality of life (HRQoL) is a patient-based outcome measure defined by the Centre for Disease Control (CDC) as an individual's or group's perceived physical and mental health over time.[89] With increased longevity achievable with ART medication, making HIV infection more of a chronic disease,[25,26] HRQoL has emerged as a significant medical outcome measure in HIV-infected individuals, and supplements the traditional clinical measures of morbidity and assess effectiveness of new therapies. Interest in the HRQoL assessments has led to the development of a number of structured questionnaires designed specifically for HIV patients, some of which are the general health days, the physically unhealthy days, the mentally unhealthy days and the physical-mental health "activity limitation" days per time period, i.e., during the previous month.[89]

1.5 The link between nutrition and HIV/AIDS

1.5.1 Human body composition

Human body weight is a total of adipose tissue, skeletal muscle, bone, blood and visceral organs.[91] The body consists of cellular and tissue-system levels, the cellular level consisting of cells, extra cellular fluid and extra cellular solids.[91] The widely used body composition model considers total cellular mass as composed of two compartments, adipose fat tissue and fat-free tissue.[91] The energy-dense adipose fat tissue, located mainly in the subcutaneous and internal or

visceral compartments is a primary site of lipid storage, and includes adipocytes, blood vessels and structural elements. The fat-free body cell mass, largely consisting of muscles and visceral organs plus supporting tissues, is the body's main functional compartments where most metabolic processes take place.[91] Stable quantitative relationships exist between the various body composition levels over a specified time, permitting body composition at various levels of body composition to be derived from whole-body level measurements using equations.[92]

Suboptimal dietary intake, or illnesses that induce anorexia, elevated metabolic (catabolic) rates or preferential catabolic loss of lean tissue result in weight loss which may reflect changes in the lean body mass and/ or the fat mass.[93,94] In HIV-negative individuals, dietary energy restriction brings about metabolic adaptations (a decrease in resting energy expenditure) that blunt weight loss, preserving lean body mass, helping maintaining body weight.[98,99] Similarly in HIV infection, despite metabolic disturbances and increased resting energy expenditure, most HIV-infected individuals maintain their weight,[98,99] and rapid weight loss, either due to suboptimal caloric intake and/or accompanied by anorexia is usually caused by secondary infections[95] and predict impending complications,[95] hence early diagnosis is critical. Nevertheless, sustained caloric restriction alone may also result in wasting, as both adipose and lean tissue are used for fuel, although the proportion of lean tissue loss depends on the amount of fat stored; the greater the adipose tissue mass, the smaller the lean body mass loss and vice versa.

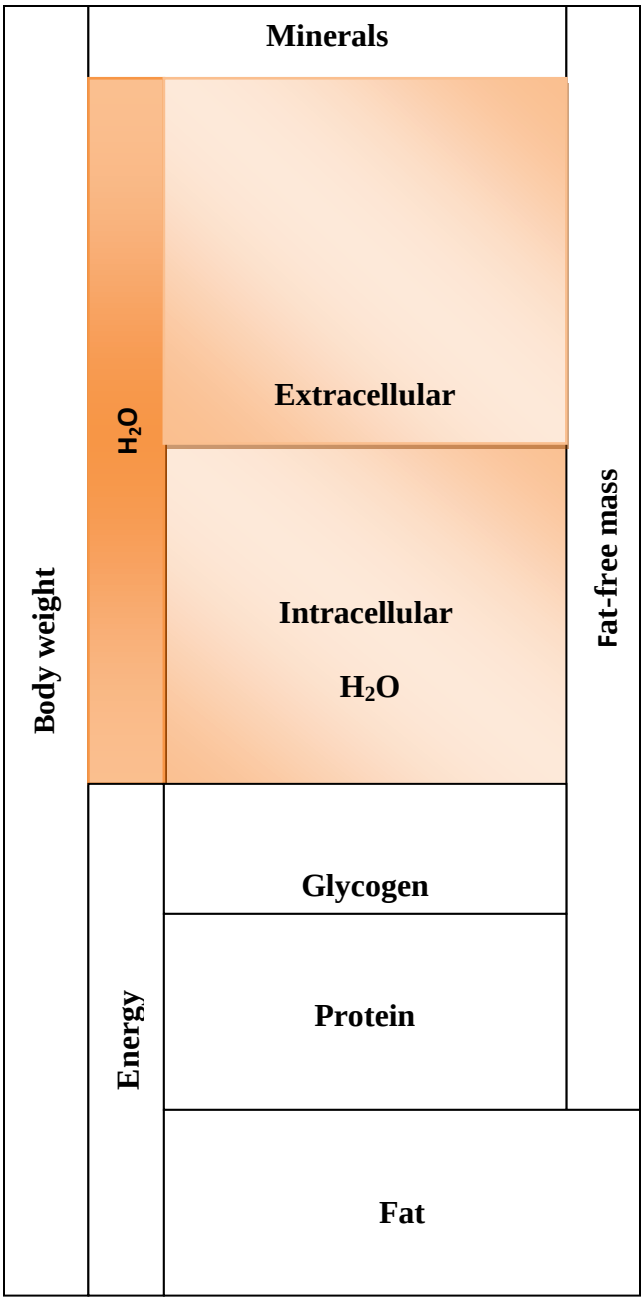


Figure 1.1 Major components of body weight
Source: Adapted from the American Society for Clinical Nutrition.[91]

1.5.2 Anthropometric measurements and indices

Anthropometry is defined as measurements of physical dimensions and gross composition of human body at different age levels and degrees of nutritional status.[96] However, some anthropometric measurements have no meaning alone unless they related to age or other anthropometric measurements of the individual. For example the value for body weight alone has no meaning unless related to age, or height of the individual where weight and height measurements are combined to calculate body mass index (BMI), ponderal index or weight related to height through the use of reference data.[96] Anthropometric indices are combinations of measurements derived from single or a combination of raw measurements,[96] and are essential for the interpretation of some anthropometric measurements.[96]

The BMI determined by dividing weight in kilograms by the square of the height in metres (weight / height^2) measure body weight corrected for height,[96] and is considered a good index of body fat and protein stores.[91,95,96] The body stores are of interest as they reflect stores needed to cope with physiological stress from reduced intake, or increased demand due to increased physical activity level, pregnancy or infection.[93,95,96] A single BMI cut-off point of 18.5 is classified as wasting in both sexes,[95,97,98] and BMI 17.0 – 18.49, BMI 16.0 – 16.99 and BMI <16.0 has been adopted as mild, moderate and severe wasting, respectively.[95,97,98] BMI correlates with many health-related indices such as mortality risk,[10,93,97,99-101] the risk increasing with increasing grades of under-nutrition.[11-13,102] A BMI cut-off<17 has been associated with increased illness in adults, hence it is considered a reasonable cut-off value for moderate risk.[97,98,103] A BMI cut-off <16 has been associated with a markedly increased risk of ill-health,

poor physical performance, lethargy and death, hence this cut-off point has validity as an extreme limit.[97,98,103]

A waist circumference measure provides an index of both subcutaneous and intra-abdominal adipose tissue.[96] Studies that have analysed the association of anthropometric measures and abdominal visceral fat have found waist circumference to be the best anthropometric correlate of the amount of visceral adipose tissue,[104] and a better predictor of central obesity as it is a better predictor of abnormal visceral fat obtained with computed tomography than is the waist-hip ratio. Thus while the BMI (kg/m2) is a measure of general obesity, the waist circumference provide information about health risk in addition to the BMI; a measure of central obesity where the visceral adipose tissue is stored.[104] Several other studies have shown waist circumference as a predictor of health risk than the other anthropometric parameters; the waist circumference has been shown to be a better predictor of the metabolic syndrome, diabetes mellitus type 2 than is the BMI,[105-109] a better predictor for cardiovascular risk than the waist-hip ratio, hip circumference and BMI,[106,110,111] stroke and coronary heart disease,[109] and all-cause mortality.[108] Waist circumference is conceptually easily measured and interpreted.[112-114] However, waist circumference cannot distinguish abdominal fat and total body fat, and does not differentiate between subcutaneous fat and visceral fat.[106,112,114] Additionally it has not been shown that the consistent association exists between waist circumference with visceral fat after adjustment for age and BMI; and body fat distribution is different across racial, sex and age.[106,112,114,115] Mid-upper-arm-circumference (MUAC) measurement reflects the mass of three tissues; bone, muscle and fat, the latter two being particularly sensitive to body weight changes.[95,96] MUAC changes thus reflect more accurately an increase or decrease of tissue reserves of energy and protein, than

body weight per se.[91,95,96] Thus the arm muscle area, calculated from triceps skin-fold (TSF) cm and mid-arm circumference (cm) using a formulae [(MAC – π x TFS) 2/4π] – 10 and [(MAC – π x TFS) 2/4π] – 6.5 for males and females, respectively, a more specific measure of the more labile fraction of lean tissue can be obtained.[95]

Selection of anthropometric indices for nutritional assessment systems depend on their sensitivity and specificity.[96] Sensitive indices exhibit large changes during and after nutritional deprivation and intervention, respectively, and correctly diagnose malnourished individuals. Such indices are selected for nutritional assessment systems involving nutritional screening and surveillance.[96] Similarly anthropometric indices with high specificity are desirable to identify healthy well-nourished individuals correctly, thereby avoiding unnecessary interventions.[96]

Previously, the focus of anthropometry has been on infants and young children, owing to their vulnerability, and the benefits of anthropometry in characterising growth and wellbeing.[96] However, recent scientific advances have demonstrated the utility of anthropometry throughout life.[96-99,101,103] Anthropometric measurements are useful in nutritional assessments, particularly when chronic imbalance between intakes and expenditures of protein and energy occur, and a disease state, as such disturbances modify patterns of physical growth and relative proportions of body tissues.[93,95,97] Additionally since body dimensions at all ages reflect the overall health and welfare of individuals and populations,[96] anthropometry may be used to predict performance and health status of population groups,[96] including survival in HIV infection. Anthropometry remains the single most universally applicable, inexpensive, and non-invasive method available to assess the size, proportion and composition of the human body.

1.5.3 The synergistic relationship between nutrition and HIV infection

In aetiological terms malnutrition (under-nutrition) is considered "primary" when it is due to sub-optimal dietary quantity and quality, or "secondary" when it is a consequence of chronic infections.[19-21] In the sub-Saharan Africa this difference is often not easy to make, especially in the context of HIV-infection, due to the complex interaction between severe food deficits, on one hand, and where malnutrition itself may be the underlying cause of acute infectious diseases, or promote expression of latent infections, such as tuberculosis, on the other hand.[19-21]

Nutritional status is one of the most important determinants of resistance to infections;[19,20,116] generalized malnutrition can cause significant impairment of several important mechanisms of immune protection including cell-mediated immunity, phagocytic function, antibody concentration, and cytokine production. Malnutrition and infection negatively affect each other; [19,20,116] while malnutrition limits cell mediated immunity and increases susceptibility to infection, infection leads to nutritional stress and weight loss, thereby weakening immune function and nutritional status.[19,20,116] HIV infection occurs at a higher level of immune function than most other infections, hence under-nutrition and HIV infection negatively affect each other.[19,20,116] Under-nutrition impairs immune function, contributing to increased incidence, severity and duration of infections,[19,20,116] impairs immune response to ART,[19,20,116] prolonging the period during which individuals are at risk of the HIV-related opportunistic infections thereby directly or indirectly increasing the risk of mortality.[19,20,116]

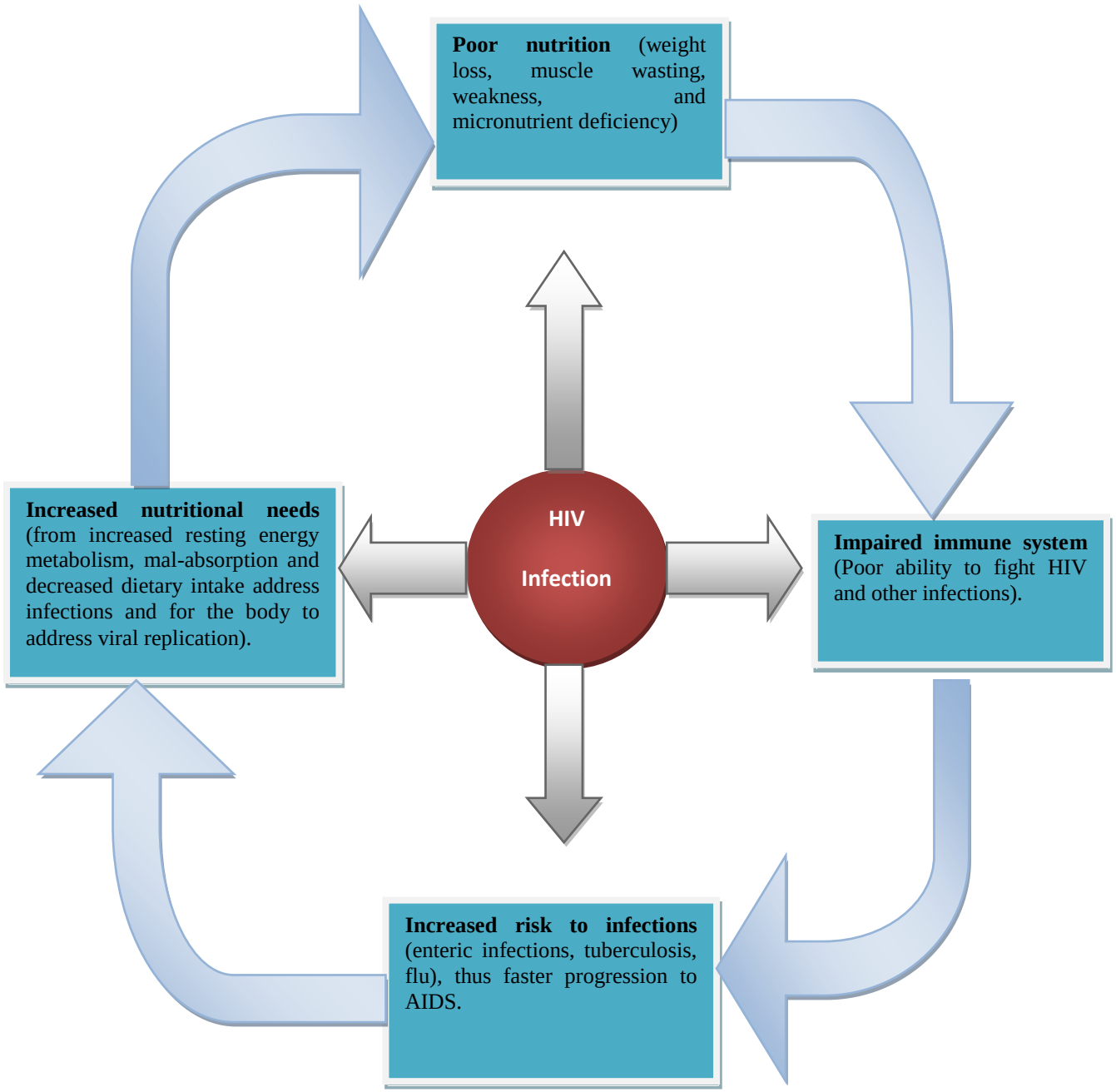


Figure 1.2 The cycle of malnutrition and infection in HIV
Source: Adapted from RCQHC Training Manual 2003.[19]

On the other hand HIV is associated with loss of appetite, diarrhoea, fever, etc, which lead to reduced dietary intake, mal-absorption, increased nutrient losses and altered metabolism, with consequent weight loss and further immune compromise.[19,20,116]

1.5.4 Under-nutrition and prognosis in HIV infection

1.5.4.1 Anthropometric changes in HIV infection

Weight loss is a frequent symptom in HIV infection,[16] and severe weight loss of >10% of the initial body mass in HIV infection is a common manifestation of HIV infection, and a diagnostic criterion in the classification of HIV disease.[117] The underlying factors of weight loss in HIV-infection are quite diverse, although most of them result in a significant mismatch between dietary energy intake, which is often reduced, and increased energy expenditure through HIV-associated opportunistic infections.[19,20,116] Chronic HIV-infection brings about metabolic alterations that result in excessive cytokine production, on one hand, and a chronic catabolic state fuelled by increased energy requirement, on the other hand, to mount a continuous immunological response that persists despite decreased caloric intake.[18,19,127,94] Thus failure to compensate for the decrease in the resting energy expenditure during decreased caloric intake accelerates negative energy balance.

Tuberculosis (TB) is an important HIV co-infection in the sub-Saharan Africa,[118,119] and adds to and / or accelerates the worsening of malnutrition in HIV/TB co-infection through multiple mechanisms: As with HIV infection, in active TB the metabolic rate or resting energy expenditure is increased, resulting in increased energy needs to meet the basic demands for body function.[120,121] At the same time energy intakes are likely to decline as a result of illness-

associated anorexia[120,121] and utilization of amino acids and protein synthesis inhibited due to the presence of pro-inflammatory cytokines.[120,121] This combination of conditions result in weight loss with eventual wasting, if energy intakes are not increased or energy expenditures decreased.[120,121] With the anti-TB chemotherapy of active TB however, nutritional status usually improves, even without supplementary nutrition,[120] although most improvements are limited to increases in fat mass with little effect on muscle tissue.[120] The improvements may be due to a variety of reasons, including improved appetite and food intake, reduced energy/nutrient demands and improved metabolic efficiency.[120,122] Since the two infections, HIV and active TB, are independently associated with malnutrition, individuals with TB/HIV co-infection are at greatest risk of malnutrition;[122-124] the TB/HIV co-infection poses an additional metabolic, physical, and nutritional burden, resulting in potential further increase in energy expenditure, mal-absorption, micronutrient deficiency and increased production of pro-inflammatory cytokines resulting in the breakdown of body lipids and proteins.[123,124] Additionally the co-infection may lead to poor appetite with decreased nutrient intake, which may interact with the altered metabolism associated with both infections, as part of the immune and inflammatory responses.[123,125]

HIV-associated wasting may be more likely to occur in the context of virological and immunological failure, secondary infection,[94] clinically significant diarrhoea or anorexia that compromises dietary intake, mal-absorptive disorders that impair nutrient absorption,[19,20,116] and in Africa, the additional food insecurity secondary to poverty,[18,126] than in a clinical setting where optimal management of opportunistic infections take place, and where the HIV infected individuals have optimal dietary intake. Weight loss in HIV infection involves depletion of both

lean and fat tissue.[127,128] The loss of fat and lean mass may partly be dictated by the severity of illness and the initial body composition before weight loss, with fat loss more prominent among persons with a greater percentage of body fat at baseline.[138] Because women have a proportionally greater fat mass and smaller muscle mass than men of equivalent weights, loss of lean tissue is lesser in women, although the loss also gradually increases as body weight and BMI continue to fall.[91]

HIV infection and treatment with antiretroviral therapy have been associated with unique fat distribution abnormalities collectively referred to as lipodystrophy syndrome.[129,130] Wasting involving changes in whole body lean and fat mass is distinguished from changes in fat distribution in lipodystrophy,[140] and, although HIV-associated lipodystrophy often involves increased fat in the trunk area, considerable loss of fat in the face and extremities is often seen. [127,128] One of the fat mal-distribution is lipoatrophy, commonly associated with NRTIs, most notably stavudine, characterized by loss of subcutaneous tissue from facial pads, extremities and buttocks, with a differential diagnosis that includes weight loss and wasting.[129,130] In patients with peripheral lipoatrophy in the presence of retention or increases of fat in the central region, malnutrition per se is unlikely to be the primary factor.[139] In fact, it has been shown some fat-distribution abnormalities are more likely to occur in patients who have experienced the most robust responses to ART medication.[94] Additionally, lactic acidosis, a rare but potentially fatal condition is often accompanied by rapid weight loss (including abdominal pain and fatigue) and thus might be misclassified as classic wasting.[139]

HIV infected individuals with a high fat content may lose substantial amounts of lean tissue resulting from tissue catabolism and gluconeogenesis during illness, the muscle being lost preferentially, as amino acids are transferred to visceral organs to produce acute-phase proteins and to support other functions, such as the immune activity. The preferential loss of lean tissue is of particular significance, as it is loss of this protein-rich tissue responsible for control and maintenance of organ metabolism, which is the determining factor in the individual's survival at low body weight. Hypoalbuminaemia in association with immune incompetence is a sign of body's response to the HIV infection; hence measurement of serum albumin is a valuable simple tool for assessing the immune competence and overall health of individual patients.

Most organs contribute in variable proportions to weight loss, the brain and the spinal cord being exceptions.[95] Weight loss of most organs is accompanied by cytological changes ranging from cloudy swelling and degenerative changes to mitochondrial brown atrophy.[95] The heart is compromised, becoming susceptible to arrhythmias, anaemia develops due to reduced erythropoiesis, the capacity of the liver to handle drugs, metabolites, hormones, or dietary toxins is impaired and the immune system itself is depressed. With a defective immunological response, the stress of even a mild infection is magnified, followed by a progressive development of life-threatening conditions, such as septicaemia, parasitaemia, or miliary tuberculosis.[95] Wasting, particularly loss of metabolically active lean tissue is an independent predictor of survival in adult HIV infected patients; Kotler et al. demonstrated that loss of body cell mass as determined by potassium – 40 isotope analysis is an important determinant of increased mortality in patients with advanced HIV disease,[131] while Suttmann et al., demonstrated improved survival in AIDS patients with a body cell mass >30% weight or albumin >30 g / l.[94] Weight gain resulting from

increased caloric intake usually occurs during recovery from infection. However, the weight gain is often incomplete as lean body mass may not be regained as efficiently as fat[94] and the decrease in physical activity due to lethargy and fatigue from illness contributes to failure to rebuild the lean body mass.[94]

1.5.4.2 Severity of under-nutrition and survival in HIV infection

The prognostic value of wasting in HIV infection has been extensively investigated, and a number of studies in the sub-Saharan African have shown a correlation between wasting at HIV diagnosis and clinical disease progression, including the short-term risk of low BMI at HIV diagnosis on mortality.[10-15] In the Gambian clinical cohort, 51% of patients with HIV infection died, those with a low baseline BMI within three months of HIV diagnosis being at greatest risk.[10] Additional analysis of the same study showed that median survival time of patients presenting with a baseline BMI <16 v BMI >22 was 0.8 years and 8.9 years, respectively, and a BMI <18.4 cut-off reflected the optimal combination of specificity and sensitivity to predict mortality within the six months following diagnosis, and when the effect on mortality was estimated per unit decrease in BMI, a one-unit decrease in BMI resulted in a 21% increase in mortality rate. Further analysis with the inclusion of baseline CD4+ cell count in the multivariate analysis only slightly reduced the effect of baseline BMI on survival which remained highly significant. The relatively modest, albeit highly significant correlation between BMI and CD4+ cell count, as well as the observation that BMI remained an independent predictor of survival after controlling for CD4+ cell count in this study suggests that BMI captures a different physiological risk for death than the risk reflected by CD4+ cell count. A study from Ivory Coast that involved 510 HIV-1 or HIV-1 and 2 dual infected patients reported a correlation between low BMI at diagnosis and subsequent higher mortality.[14] A clinical cohort from rural

Uganda in which prevalence, incidence and mortality associated with tuberculosis in HIV-infected patients initiating ART were assessed, TB prevalence, incidence, and mortality were all associated with a BMI <18.[13] A tuberculosis clinical cohort from rural Malawi with a 80% co-infection with HIV found a low BMI (BMI<17) at diagnosis as an independent risk factor for early mortality, defined as death within the first 4 weeks of commencing tuberculosis treatment.[15]

Outcomes of patients initiated on ART in Malawi and other developing countries suggest that despite ART, about 10 – 15% of individuals die within a median follow-up period of 15 months, a substantial proportion (about 70%) of these deaths occurring very early after ART commencement.[132-134] Considerable evidence suggests that among the highly significant risk factors associated with such "early" deaths include increasing grades of wasting.[11,12] In a clinical cohort of adult ART patients from a rural district of Malawi, the majority of deaths (61%) in the first 3 months of ART initiation occurred in wasted patients (BMI <16.0 to 18.5), the mortality rate increasing with increasing grades of wasting.[11] In a related clinical cohort of children on adult fixed-dose ART treatment in a central hospital in Malawi, significant risk factors for the high early mortality observed within 3 or 6 months of ART initiation included severe wasting.[12] Body Mass Index is a strong and independent predictor of survival in HIV infection; reduced survival in those with wasting, and improved survival in those not wasted at baseline.

1.6 Food security

Food security exists "when all people at all times have both physical and economic access sufficient to meet their dietary needs in order to lead a healthy and productive life".[135] Dietary

diversity, defined as the number of different foods or food groups, measured by summing the number of foods or food groups consumed over a reference period,[136,137] is considered a key determinant of a high quality diet, as it ensures adequate intake of essential nutrients that enhance good health.[136] Several indicators are used to define a healthy diet:[138] Dietary quality is the nutrient adequacy that meet requirements for energy and essential nutrients.[138] Nutrient adequacy ratio is the ratio of a particular nutrient to its recommended dietary allowance.[138] Mean adequacy ratio of a nutrient is the average of the nutrient adequacy ratio computed by summing the nutrient adequacy ratio, and dividing by the number of nutrients.[138] Energy intake tends to increase with greater dietary diversity, while nutrient density either remain constant (nutrient intake increases proportionally) or increases in diets of enhanced quality.[135] However, the dietary diversity score based on food groups, where food groups are selected on their specific nutrient content or their unique contribution to nutrient adequacy is considered a stronger determinant of nutrient adequacy, than food variety score based on individual foods.[139] As such[135,139] most dietary guidelines advocate a more diversified diet both across and within food groups.

A number of food security surveys among people living with HIV/AIDS in the sub-Saharan Africa, notably two surveys[140,141] suggest that the majority of people living with HIV/AIDS subsist on low quality diets. A baseline survey in Mozambique to establish food security status of households in HIV/AIDS affected areas reported a mean dietary diversity score of 4.3, about 97% of households consuming predominantly plant-base diets and only less than 10% of the households consuming meat or meat products.[140] A cross-sectional study in urban Uganda to establish how HIV affected households were coping in terms of response to food shortages reported a mean dietary diversity score of 6, with 59% of households consuming less than 6 food

groups the day prior to the dietary interview.[141] While food insecurity and hunger are common among populations in the sub-Saharan Africa, with its effects on morbidity, mortality and poverty, the epidemic of HIV infection and AIDS has worsened food insecurity in the sub-Saharan Africa.[142] With up to 25% of the labour force infected with HIV in some countries,[143] long-term strategies for food security and poverty reduction are challenged;[142,126,144] the human capital is depleted, agricultural resources diverted, and farm and non-farm income lost, affecting overall agricultural production, exacerbating the food insecurity situation among the high HIV-prevalent communities.

1.7 Selective feeding programmes

1.7.1 Therapeutic feeding programme

The most severely malnourished individuals have complications ranging from infections, impaired lever and intestinal functions and problems related to electrolyte imbalance[145,146] hence a combination of high quality clinical care and a specialized feeding protocol is crucial to avoid death. A therapeutic feeding programme is a supervised feeding of special foods and intensive clinical care to rehabilitate the most severely malnourished.[145,146] This include feeding regimens that include small, frequent meals with the quantity determined according to bodyweight, correction of electrolyte imbalances and infectious disease complications and the use of Resomal, a low sodium, high potassium rehydration solution.[145,146].

Treatment protocols for severely malnourished adults have also been developed, and these are similar to those for children.[147,148] However, the design of adult therapeutic feeding programmes

is often more complicated than those for children.[147,148] Additionally the potential for adult centres to become quasi-hospices for those with chronic illnesses, to undermine survival strategies, and to contribute to adverse outcomes for the children of the inpatients, are some factors that should be taken into account in the programme design. The acceptability in adults of a milk-based diet might also be poorer.[147,148]

1.7.2 Supplementary feeding programme

Even if the overall population food needs are adequately met, inequities with regard to the distribution system, disease and other social factors resulting in high degrees of malnutrition in certain vulnerable groups. The vulnerable groups may be targeted to receive food supplements as an "addition", to upgrade their defective family diet to a level that responds to their increased needs. Supplementary feeding is a "preventive" intervention, with the general objective of maintaining and/or improving the nutrition status of vulnerable groups, thereby preventing the "moderately" becoming severely malnourished.[146,149] However, as infections may often be an underlying cause of malnutrition, beneficiaries of the supplementary feeding programme can only recover effectively from malnutrition if proper care is taken of the additional medical complications. Hence a standard supplementary feeding programme includes basic clinical investigations on all new admissions, and routine clinical surveillance to identify and manage sick beneficiaries.[146,149]

Traditionally, targeted feeding programmes have prioritised undernourished children under 5 because of their greater vulnerability and increased risk of dying. HIV/AIDS and HIV-TB co-

infection in the sub-Saharan Africa alters this picture to include adults.[138,118,119] Other nutritionally vulnerable groups are pregnant women in their third trimester and lactating women up to six months after delivery (the period when the infant is entirely dependent on breast feeding), admission of which is usually coordinated by the antenatal services. malnourished adults needing treatment become an issue of public health significance, the following MUAC cut-offs has been recommended for admissions to feeding centres; MUAC (cm) cut-offs < 18.5 and < 16.0 for moderate and severe under-nutrition, respectively.[21,99,101]

A typical supplementary ration composition consists of a cereal or blended food as a base providing the main source of energy and protein, with protein providing about 15% of the total energy,[146,149] to allow for compensation of a protein deficient family diet. The energy density of the supplement(s) is enhanced by adding a high energy source, usually oil.[146,149] Additionally the supplement may be made to provide a balanced mix of essential micronutrients (vitamins and minerals) lacking in the cereal base.[146,149] Strategies of supplementary feeding commonly used in the resource-limited developing countries include "Wet" and "Dry" rations.[146,149]

1.7.2.1 Wet ration strategy

Wet "on-the-spot" ration is an intervention strategy involving distribution of cooked food(s) at a feeding centre.[146,149,150] Among the strengths of the strategy include the fact that it ensures a high level of adherence to the intervention as the food supplement is consumed by the intended recipient under supervision.[146,149,150] Additionally assistance is given to beneficiaries who are too ill, and/or unable to eat.[146,149,150] The major limitation of the strategy is that it is expensive to administer requiring an organised, "functioning" facility.[146,149,150] Additionally, programme

beneficiaries and their caretakers have to travel to the feeding centre for scheduled feedings, a situation which may result in higher default rates.[146,149,150]

1.7.2.2 Dry ration strategy

Dry "take-home ration" strategy is a home-based intervention strategy involving distribution of food supplement(s) to be prepared for consumption by the beneficiaries or their care-takers at home.[146,149,150] Major advantages of the strategy include the fact that caretakers and/or beneficiaries are able to provide or undergo nutritional rehabilitation at home, respectively, while taking care of their families and home duties,[146,149,150] and that the programme is less expensive to administer requiring modest personnel, infrastructure and materials.[146,149,150] A major limitation with the strategy is lack of a guarantee that the food supplement(s) will be consumed by the intended recipient. A number of factors are important:[161,151,152] The household food security situation determine how much of the food supplement is actually available to the intended beneficiary; if the household is food insecure with no coping means, the food supplement may be the only food source for the whole family than just for the intended beneficiary alone. For instance a review of feeding programmes in refugee reception centres in Eastern Sudan showed that food supplements were shared by all children in the family. Additionally, contrary to the essence of supplementary feeding, which is meant to complement the defective habitual diet to meet the increased needs of the vulnerable groups, children in the feeding programme were not getting their share of habitual family foods.[163] Beneficiaries with limited means may have many other needs than dietary requirements alone. Thus if the other needs are not met by other means, part of the food supplement (s) may sensibly be bartered or sold to meet the other social needs.

Other determinants of compliance with regard to home-base supplementary feeding include familiarity (including the preparation before consumption) and acceptability of the food supplement; For example in an evaluation of the discharge outcomes of three supplementary feeding programmes during a food crisis involving 40,233 children, where supportive family rations were distributed, rice given out in Liberia was highly welcomed by families, whereas in Burundi this was less so.[163] A food supplement that is not palatable nor culturally acceptable, for example a food taboo, may result in non-adherence, or the food supplement sensibly bartered or sold to buy preferred, culturally acceptable foods.[146,149,150] A food supplement that require lengthy, complicated preparation process before consumption, i.e., grinding whole grain cereals, prolonged cooking, etc., may result in a compromised adherence to the dietary regimen.[161] Thus issues regarding adherence to supplementary feeding are likely to differ between the wet "on-the-spot" and the home-based dry "take-home" intervention strategies. Currently in Malawi, ready-to-use therapeutic food (RUTF) and corn-soy blend (CSB) flour are food supplements most extensively used by both the government and by non-governmental organizations in the management of childhood malnutrition and chronically-ill under-nourished adults.

1.7.2.2.1 The value of ready-to-use therapeutic food and corn-soy blend

The traditional CSB formulation is 80:20 maize-soy flour mixture,[153,154] and the energy density of porridges prepared from such mixes is approximately 2 to 4 kJ/g.[153,154] To improve the energy density of such mixes, oil is often added, and the nutrient content enhanced by micronutrient fortification.[153,154] CSB porridges require prolonged cooking before consumption. For example cooking before consumption of the traditional Malawian CSB porridge (Phala) takes about 1 hour. When the food supplement is administered as a wet "on-the-spot" ration,[146,149,150]

beneficiaries have to travel to the feeding centre for scheduled feedings, while as when it is administered as a Dry "take-home" ration,[146,149,150] beneficiaries or their care-takers usually save portions of the cooked CSB meal for a number of feedings between family meals during the day. CSB formulation is similar to many cereal-legume combinations often advocated as healthy foods and is a typical supplementary feeding strategy for both undernourished children and the chronically ill adults in the developing world. The daily CSB ration sizes for beneficiaries are normally not consistent with the beneficiary's nutritional requirements, which vary with age, sex, physical activity level [155]and disease state of an individual,[156] and differ between different food aid agencies in sub-Saharan Africa, such that it largely depends on the programme's capacities and modalities. RUTF is a relatively newly developed lipid-based formulation consisting of peanut butter, milk powder, oil, sugar, and selected micronutrients with equivalence to the WHO F-100 therapeutic milk formulation used during in-patient care of severely malnourished children.[157] Because of its low water content RUTF resists bacterial contamination, can be kept at ambient conditions for several weeks without significant degradation, thereby providing suitable alternative to the supervised, inpatient, high-energy density feedings in a form that can safely and easily be given at home as a dry ration.[90,157] Additionally, in a striking contrast to CSB, RUTF is ready to use and does not require cooking or any form of special preparation before consumption.

Preliminary investigations leading to the current study have consistently shown that use of RUTF allows rehabilitation of severe acutely malnourished children in Malawi to occur at home, resulting in greater compliance and successful treatment outcomes, to a greater extent than by the use of CSB.[90,158-160] In 2001, in a clinical effectiveness trial, the imported RUTF made by

Nutriset in France resulted in anthropometric recovery in 95% of HIV-negative children, and was superior to the standard supplementary fortified CSB.[90] In 2002, in a therapeutic equivalence clinical trial, the locally produced RUTF in Malawi using local ingredients was shown to produce equally successful outcomes to the imported RUTF product in the treatment of paediatric malnutrition.[158] In 2003, in a clinical effectiveness trial involving 1200 children, in which home-based therapy with locally produced RUTF was compared to the "improved" standard nutritional rehabilitation which used a milk-based formula (F-100, Nutriset, France) recommended by the World Health Organization (WHO), weight recovery rates were significantly higher (79% v 46% $p<0.0001$) for those receiving RUTF compared to those receiving standard F-100 therapy.[159] In 2001 and 2002, before the advent of ART treatment, 60% of malnourished HIV-positive children who were treated with RUTF but not ART achieved normal weight-for-height, a recovery rate which was superior to CSB.[160]

A study from urban Malawi in HIV-infected adults not receiving ART showed no effect of CSB on mortality or clinical complications.[161] In rural Malawi an ART programme administered by Medicines Sans Frontier provided CSB and RUTF as a supplementary food in 2003 and 2004 and compared the growth rates among clients. Adults in both years had similar anthropometric characteristics upon admission, but those who received RUTF in 2004 had weight gain rates that were double those achieved by study participants receiving CSB (1.5 v 0.8 kg/month; $p = 0.04$).[162]

RUTF has a higher energy density[157] more than 5 times that of CSB - thereby allowing adequate dietary energy intake in the malnourished anorexic patients. The milk powder in the RUTF

formulation is animal-based, a dietary component required for optimal growth[157] diets that are entirely plant based lack. Beneficiaries of the RUTF food supplement and their care-takers regard RUTF as a special "medicinal" food supplement rather than a primary food source for the whole family,[90] hence it is less likely to be diverted into intra-household sharing, sold or diverted for other purposes. More importantly RUTF is ready-to-eat needing no fuel or other resources for its preparation,[157] thereby reducing inconvenience to daily routine. Use of the locally produced RUTF in home-based therapy for the mild to moderate and severe malnutrition is currently standard in many treatment facilities in Malawi.

The limited effect of supplementary feeding with CSB has previously been evaluated.[163-166] A randomised controlled trial in the South of Niger compared the effectiveness of supplementary feeding with either RUTF or CSB pre-mix in the rehabilitation of the moderately malnourished children.[163] An overall recovery rate in this study was 79.1% and 64.4% in the RUTF and CSB, respectively, (p<0.001). There were more transfers to the inpatient therapeutic feeding centre in the CSB pre-mix group (19.1%) compared to the RUTF group (9.3%) (p 0.003). Additionally, average weight gain was higher (95% CI: 0.46 –1.70) and length of stay 2 weeks shorter (p <0.001) in the RUTF group. A study from rural Malawi that compared the effect of CSB with that of RTUF in the home treatment of moderately malnourished children, reported that although both food supplements resulted in modest weight gain, the effect lasted longer after RTUF than the CSB intervention.[164] A randomized, controlled, single-blind trial in the same area compared growth and incidence of malnutrition in infants receiving long-term dietary supplementation with ready-to-use fortified spread or micronutrient-fortified CSB;[165] the one-year-long complementary feeding with the fortified spread was likely to boost linear growth, hence a decrease in the

incidence of severe stunting in the most disadvantaged individuals, than feeding with maize–soy flour. Another Malawian randomized, clinical effectiveness trial compared recovery rates among children with moderate wasting who received either milk/peanut fortified spread, soy / peanut fortified spread, or CSB,[166] where children in either of the fortified spread cohorts were more likely to recover than those receiving CSB (80% in both fortified spread groups versus 72% in the CSB group; p <0.01). Additionally, rate of weight gain in the first 2 weeks was greater among children receiving milk / peanut fortified spread (2.6 $g.kg^{-1}.d^{-1}$ n = 465) or children receiving soy / peanut fortified spread (2.4 $g.kg^{-1}.d^{-1}$ n = 450) than among children receiving CSB (2.0 $g.kg^{-1}.d^{-1}$ n = 447; p <0.05).

A number of factors associated with such poor outcomes with the CSB supplementary feeding have been suggested; CSB dietary regimen is similar to components of the Malawian traditional staple and is prepared as porridge or soft dough by the same method used with the traditional staple. With such physical resemblance (including the processing method) to the local staple, supplementary feeding with CSB is normally viewed as a family food source, and likely to be diverted into intra-household sharing, than for the intended beneficiary alone. Additionally, normally the whole family (children and adults) eat from a common plate at mealtimes, a cultural practice that encourages greater sharing of the food supplement, and food preparation for the under-nourished children or the chronically ill adults will often be done by others, a situation promoting sharing of the food supplement. The energy-density of porridges prepared from the CSB is low, approximately 4 kJ/g. Thus large volumes of the food supplement must be consumed, to help one achieve RDA for energy and nutrients, which may not be feasible for the sick anorexic individuals, on one hand, or may compromise achievement of one's RDA for

energy and nutrients by displacing other energy and nutrient dense traditional foods in one's habitual diet. More importantly in contrast with RUTF which does not require cooking or any special preparation before consumption, CSB requires prolonged cooking before consumption. Various logistic considerations, such as poor access to fuel wood, labour and time involved in the food preparation imply additional time and resources, to manage separate and recommended number of feedings per / day for the patient in a rural subsistence agrarian economy, a situation that may compromise adherence to the dietary regimen. Thus considering the on-going rapid ART scale-up occurring in Malawi and other developing countries, and the problem of concomitant malnutrition in patients initiating ART, when considering large-scale nutritional interventions for ART scale-up programmes, the dry ration RUTF appears to be more practical, than the CSB food supplement.

1.8 Statement of the problem and rationale for the clinical trial

Malawi has one of the highest HIV/AIDS prevalence rates in the world,[1] with 14% of those aged 15 – 49 years infected.[1,167] In keeping with the goal to "Universal Access" to ART by 2010 adopted by the G8 countries in July 2005 and by the WHO,[1] the Malawi government's inspirational goal is to have 170,000 HIV infected patients on treatment by year 2010, increasing this number each year by the number of patients becoming eligible for ART (approximately 85,000 new patients per year).[167] However, the care of AIDS patients in the developing world is made difficult by the additional problem of under-nutrition, with the prevalence of wasting in the clinically symptomatic (WHO Stage III of HIV disease) AIDS patients in sub-Saharan Africa estimated at 50%.[16] Thus with the on-going rapid ART scale-up program in Malawi and other

developing countries, the problem of concomitant malnutrition in HIV infected patients initiating ART is likely to increase. Additionally even with the remarkable advances ART has made in the management of HIV infection, weight loss and muscle wasting remain a significant clinical problem in the majority of ART patients in the sub Saharan Africa. Wasting is associated with poor prognosis in AIDS.[10-15]

Evidence of the benefits of nutritional intervention in AIDS patients has been sparse and inconsistent; Two studies in Europe and North America among very ill HIV infected patients receiving total parenteral nutrition indicate that this form of nutritional supplementation had a beneficial effect on anthropometry, immune function and quality of life indicators.[168,169] However, two other small studies of less than 100 closely-monitored individuals receiving oral food supplements did not show any improvement in anthropometry, body composition or immune function for those patients receiving either standard or immune-enhancing food supplementation when compared to nutritional counselling.[170,171] A multicenter study in North America of 536 AIDS patients on ART comparing a specially formulated dietary supplement with a standard dietary supplement and a control group of no food supplement found that there were no differences in weight gain, body composition or disease progression among the three groups.[172] While not ameliorating wasting, provision of food supplements to patients receiving ART did improve compliance with medication treatment regimens.[173] Professional associations of nutritionists and highly regarded international experts have taken the position that food supplementation, while unlikely to be harmful, is of unproven efficacy.[142,174]

Food insecurity in the sub-Saharan Africa is common.[126,140,141,144] As such, although recommendations concerning nutrition in HIV treatment needs appropriate evidence, integration

of supplementary feeding in ART programmes has become an increasing public health and political priority in the recent years, and has often been advocated by both governmental and non-governmental organisations as one important strategy to improve outcomes of wasted HIV infected patients on ART. Individual treatment programmes and clinicians have been justified in routinely prescribing nutritional support, as this may provide a benefit and do no harm. Evidence of the effectiveness of supplementary feeding in wasted adult AIDS patients in a typically resource-poor health system is lacking; there is no body of scientific evidence, nor are there any series of published controlled trials on the benefits of nutritional intervention in improving outcomes of wasted AIDS patients on ART is available, from which evidence-based intervention guidelines can be developed. Because of which current HIV/AIDS feeding guidelines, i.e., types and amounts of food supplements, and the optimum duration of nutritional intervention are largely based on expert opinion rather than evidence. For instance with the advent of the programmatic, community-based ART scale-up programme, the Government of Malawi implemented a supplementary feeding programme for all severely (BMI <16.0) and moderately (BMI 16.0 – 16.99) wasted AIDS patients on ART with a specialized lipid-based RUTF food supplement. The dietary regimen was chosen on the basis of its efficacy and effectiveness in home-based treatment of paediatric malnutrition. UNICEF-Malawi facilitated this initiative by purchasing 200 tons of imported RUTF for the national ART scale-up programme.

In 2005 when the study was planned, RUTF and CSB, foods most extensively used for supplementary feeding in Malawi were costing $0.78 and $0.19, respectively, per patient per day. Wasted HIV infected individuals will regain weight and have fewer clinical complications if ART suppresses plasma HIV-1 RNA viral replication[23,24] and the patients have optimal dietary

intake.[20,175] Therefore a strict study design to determine whether individuals will have better clinical and nutritional outcomes if they consume CSB or RUTF food supplement is inappropriate, as nutritional recovery and the benefits it imparts to those on ART, can be achieved using either food. One might then ask why not consider only the most inexpensive food supplement, which would be CSB? However, evidence of the effectiveness of supplementary feeding is lacking in wasted AIDS patients in the typically poor-resourced health system in sub-Saharan Africa, raising uncertainties about the benefits of such interventions in the management of such patients. It is important to investigate the potential for better compliance with ART as well as improved health status, decreased morbidity, and increased longevity with food supplements given concurrently with antiretrovirals (ARVs). A therapeutic effectiveness as opposed to an efficacy trial with adult HIV-patients on whether the RUTF supplement given with ART in Malawi improves nutritional and clinical outcome over a CSB supplementation is warranted. Without such a study, adequate evidence is unlikely to become available, to provide scientifically-based recommendations concerning supplementary feeding in ART programs in the sub-Saharan Africa including Malawi. In addition to effectiveness, cost considerations of food supplementation deserve careful consideration; while the supplementary food could add productivity and longevity to those suffering from HIV, on the other hand, it could simply divert resources from ART programs, limiting coverage of this vital treatment. This study will offer an evidence-based answer to the important clinical question, "Does a specialized nutrient-dense food supplement given with ART in sub-Saharan Africa improve outcome over a cereal/legume supplement?"

CHAPTER 2 METHODOLOGY

2.1 Study design

2.1.1 Study objectives

To compare the performance of two different supplementary feeding strategies in wasted adult AIDS patients initiating ART in a typically resource-limited setting where there was a high (50%) prevalence of wasting in individuals living with HIV/AIDS.

2.1.2 Hypothesis

The study tested the hypothesis that among wasted HIV infected Malawian adults initiating ART concurrently with a short-term 3.5-month supplementary feeding programme, those receiving short-term nutrient-dense RUTF were more likely to show an increase in BMI and fat-free body mass, experience fewer significant clinical events and attain higher CD4 counts, than their counterparts receiving CSB food supplement, at the end of the supplementation and over the following 9.5-months of ART treatment. The 3.5-month duration of the nutritional intervention was chosen based on earlier "treatment success" nutritional intervention studies (both oral and parenteral), among HIV infected adults, that utilized intervention periods ranging from 2 to 4 months.[168,169,170,171,172]

2.1.3 Study outcome measures

2.1.3.1 Primary outcome measures

Changes in BMI and fat-free body mass following 3.5 months of ART and supplementary feeding with either RUTF or CSB, and after 9.5 months of ART following the initial 3.5 months of supplementary feeding and ART.

2.1.3.2 Secondary outcome measures

- The number of significant clinical events in study participants, defined as hospitalisations and deaths, at 3.5, 6.5, 9.5 and 12.5 month study follow-up,
- The monthly change in HRQoL assessment at 3.5, 6.5, 9.5 and 12.5 month study follow-up,
- The change from baseline in serum albumin and haemoglobin at 3.5 month study follow-up,
- The change from baseline in CD4 count (cells x 10^6/l) and HIV RNA viral load suppression at 3.5 month study follow-up.
- Compliance with ART regimen.

2.1.4 Sample size calculation

A sample size of 450 (225 individuals in each treatment group) was determined based on detecting a mean difference in the primary outcome measures, BMI and fat-free body mass of 0.5 (standard deviation [sd] ± 1.74) between the two intervention groups on completion of initial phase 1 intervention (3.5m ART and nutritional intervention), with 95% specificity ($\alpha = 0.05$, two-tailed) and 80% power ($ß = 0.20$, two-tailed). Thus half of the alpha was allotted to testing the statistical significance in the RUTF intervention and the other to the CSB intervention, 0.025

in each tail of the distribution of the test statistic. The difference in BMI of 0.5 was chosen because it has been associated with a significant difference in mortality rate in earlier studies.[95]

This sample size also allowed detection of the difference in severe clinical events (such as mortality or hospitalisation) of 25% with a 95% specificity and 80%power at 3.5-month study follow-up period, 3.5 months, 6.5 months, 9.5 months and 12.5 months study follow-ups, given that such events (except mortality) occur several times a year for most HIV infected individuals. The sample size calculation allowed for a15% attrition (loss of 68 individuals) owing to factors such as losses to follow-up and death. This proportion was based on reports of previous studies on early mortality[11,12] and loss to follow-up rates reported in ART programmes in low income countries, including Malawi.[176-178]

2.1.5 Eligibility criteria for study participation

All individuals presenting at Queen Elizabeth Central Hospital's (QECH) ART clinic aged ≥18 years, and meeting eligibility criteria for ART initiation according to the Malawi national HIV treatment guidelines (WHO stage III or IV or any WHO stage with a CD4 count <200/mm^3)[179] were screened for study eligibility (Appendix A). Participants aged ≥18 years old with a BMI <18.5 and initiating ART (ART-naïve) were invited to participate in the study. The trial BMI cut-off of is based on the WHO guideline for chronic energy deficiency (adult malnutrition),[95] BMI ≤18.5, shown to increase mortality risk for individuals with a wasting disease such as HIV infection, especially when accompanied by under-nutrition. This has been shown to be relevant in Abidjan, Cote d'Ivoire,[14] Malawi[11,15] and Uganda.[13] Additionally, consultation with the

Ministry of Health and Population in Malawi indicates that a BMI <18.5 cut-off is a local guideline for adult malnutrition. Therefore this clinical trial adopted the BMI <18.5 cut-off as an inclusion criteria, to ensures that all of the study participants are meeting the WHO criteria. HIV-related malignancies such as Kaposi sarcoma and lymphoma were not an obstacle to ART initiation or study exclusion criteria, as treatment of such complications included provision of ART and use of cytotoxic drugs, i.e., bleomycin, vincristine, etoposide, cyclophosphamide, methotrexate which can be combined with ART without any contraindications.[179]

2.1.6 Exclusion criteria from study participation

Study participation exclusion criteria included HIV-infected individuals aged <18 years, pregnant or lactating women, enrolment in another supplementary feeding programme or ART patients transferred-in from other ART facilities. Additionally tuberculosis (TB), an important HIV co-infection in the sub-Saharan Africa[118,119] including Malawi was a study exclusion criteria. Bacteriology and radiology remain recommended methods for diagnosing active TB. Thus every potential ART registrant was clinically screened for cough, fever, night sweats, TB contact, etc, and positive response to any of these symptoms qualified them for sputum analysis and chest Xray,[179] according to the National tuberculosis control programme guidelines.[180] A pulmonary TB (PTB) suspect is a patient presenting with persistent cough for three weeks or more, usually accompanied by fever, chest pain, shortness of breath, loss of weight and haemoptysis.[180] Symptoms or signs due to extra-pulmonary tuberculosis (EPTB) depended on the sight involved, i.e., lymphadenopathy, pleural effusion, pericardial effusion, ascites, spinal disease and meningitis.[180,119] Tests on pleural and ascetic fluid included protein, white blood cells

and differential white cell count, gram stain and Ziehl-Neelsen stain.[180,119] Tests on needle aspiration/lymph node biopsy for macroscopic caseation, acid-fast bacillus and caseating granulomas on histology were made, as well as tests on CSF for protein, glucose, white blood cells and differential white cell count, gram stain, Ziehl-Neelsen stain and Indian Ink to rule out cryptococcal meningitis.[180,119]

Bacteriology was first through direct sputum smear examinations on all TB-suspect ART registrants, with a maximum of three sputum smears, and, while waiting for laboratory findings, management of the symptomatic TB suspects included treatment with non-anti-TB antibiotics. TB suspect ART registrants with smear-negative microscopy under-went a further chest X-ray diagnosis, and findings suggestive of PTB in patients with smear-negative microscopy had to be supported by clinical findings by a study Clinical Officer who decided on the actual diagnosis. Thus a TB patient case was a patient who had been reliably diagnosed with TB. Culture testing was an expensive TB bacteriology and not available at the treatment facility during the study period, except for special cases such as the TB 'relapses', a category of patients having been treated and completed TB treatment but developed active TB with smear-positive sputum,[180] or treatment 'failures', a category of TB patients who were sputum-smear positive five months or more after commencement of anti-TB treatment.[180] As such cases were suggestive of being drug resistant to the standard anti-TB treatment, their sputum were being sent to another referral hospital with the diagnostic capacity, results of which were not immediately available to guide the ART initiation and study enrolment decision. Drug combination for the initial phase of TB treatment include rifampicin which interacts with nevirapine, because of which those with newly-diagnosed TB co-infection were not eligible for ART initiation until the initial phase of

the anti-TB treatment was completed and patients initiated on the anti-TB treatment continuation, whose drug combination does not include rifampicin.

Additionally, although not a routine ART-eligibility screening criteria, liver functioning tests were done on patient cases with clinical signs of liver failure, i.e., patients presenting with hepatomegaly, tender liver, jaundice, etc.[179] Tests included alanine aminotransferase (ALT) and aspartate aminotransferase (AST) status, and graded according to the Division of AIDS Table for Grading the Severity of Adult and Paediatric Adverse Events (DAIDS), December, 2004. Patient cases with ALT and AST levels more than 5 times normal were considered having liver failure. Since the First-line ART regimen includes nevirapine which is hepatotoxic, ART patient cases presenting with such conditions were having their ART medication stopped, to avoid putting them on a therapy containing a drug that is hepatotoxic. ART patient cases with moderate grade abnormal liver functioning tests, i.e., ALT and AST levels 2.6 – 5.0 times upper limit of normal, were switched from Triomune® (NVP, 3TC, d4T) to ART regimen containing efavirenz (EFV, d4T, 3TC) by senior clinical consultants.[179]

2.2 Study setting

The clinical trial was implemented at the ART clinic of the QECH, Blantyre, and the major referral hospital in Malawi. The clinic offers services such as HIV voluntary counselling and testing, staging of HIV disease progression for established HIV infected individuals, management of HIV-related opportunistic diseases and ART. The ART clinic is run by the Department of Internal Medicine of the University of Malawi College of Medicine. In 2005,

when the study was planned, the study clinic was enrolling 150 new ART registrants monthly, about 32% of whom were wasted (BMI <18.5).

2.3 Identification of the study population

Most of the study participants were identified from the QECH medical words, from in-patients admitted for HIV-related illnesses. Thus, physicians from the University of Malawi's College of Medicine Department of Internal Medicine working in the hospital medical wards referred such in-patients (patients admitted for HIV-related illnesses) to ART clinic on discharge, for the WHO clinical staging (a complete clinical assessment for HIV-related illnesses). Additionally, voluntary counselling and rapid on-site HIV-testing services were available within the QECH, and HIV testing conducted using rapid whole blood test kits following the WHO strategy for HIV antibody testing.[181,182] Following this, all HIV sero-positive positive patients were referred to the same ART clinic staging of the HIV infection, and categorised using the WHO clinical and/or immunological staging system.[179] Following this, ART non-eligible individuals were scheduled for HIV clinic appointments for the management of their HIV-related opportunistic illnesses, while ART -eligible individuals were invited to commence ART medication, and if willing scheduled for ART initiation in the company of a supporter to ensure treatment support. The two (patient and his/her supporter) underwent pre- ART group counselling sessions during which they were educated on HIV infection and AIDS. The content included:

- HIV infection lowering natural immunity making individuals vulnerable to opportunistic infections,
- ART therapy, its value and that life-long adherence was key to treatment success,

- The various combinations of ART medicines,
- Potential side-effects of ART medication,
- Risks of HIV re-infection,
- The importance of a healthy diet in HIV infection.

This extensive counselling ensured a select group of patients well prepared for ART adherence.

2.4 The Antiretroviral treatment regimens

Currently available antiretroviral drugs belong to two major classes: reverse transcriptase inhibitors (RTIs) and protease inhibitors (PIs).[179] The reverse transcriptase inhibitors are further divided into 3 groups: nucleoside reverse transcriptase inhibitors (NsRTIs), nucleotide reverse transcriptase inhibitors (NtRTIs) and non-nucleoside reverse transcriptase inhibitors.[179] The different classes of antiretroviral drugs are shown in table 2.1.

Table 2.1 Different classes of antiretroviral drugs

NsRTI	NtRTI	NNRTI	PI
Zidovudine (ZDV)	Tenofovir (TDF)	Nevirapine (NVP)	Nelfinavir (NFV)
Didanosine (ddI)		Efavirenz (EFV)	Saquinavir (SQV)
Lamivudine (3TC)			Ritonavir (RTV)
Stavudine (d4T)			Lopinavir (LPV)
Zalcitabine (ddC)			Indinavir (IDV)
Abacavir (ABC)			Amprenavir (APV)

The antiretroviral treatment regimens fall into three categories; The First-line, the Alternative First-Line and the Second-Line Regimens: Components of the First-Line regimen include stavudine (d4T), a nucleoside reverse transcriptase inhibitor, lamivudine (3TC), a nucleoside reverse transcriptase inhibitor, and nevirapine (NVP), a non-nucleoside reverse transcriptase inhibitor co-formulation tablets as a triple therapy. For adults, formulation depends on body weight cut point, d4T/3TC/NVP-30 for body weight ≤60 kg or d4T/3TC/NVP-40 for body weight > 60 kg. Initiation of the triple therapy (d4T/3TC/NVP) is such that patients are given drugs for two weeks as follows: d4T/3TC/NVP 1 tablet morning plus d4T/3TC 1 tablet evening, after which they are reviewed at the treatment unit and provided there are no side effects they are given drugs for 30 days d4T/3TC/NVP 1 tablet morning plus 1 tablet evening. Stavudine is combined with lamivudine as a dual therapy.

Several Alternative First-Line regimen substitutions are available in case of adverse drug reactions to the First-Line regimen: For instance in case of several peripheral neuropathy: which will likely be due to the stavudine component, the alternative is a combination of zidovudine (AZT), lamivudine (3TC) and nevirapine (NVP). For liver disease such as hepatitis, which will likely be due to the nevirapine, the alternative combination is stavudine (d4T), lamivudine (3TC) and efavirenz (EFV). In case of severe skin reactions, which will likely be due to the nevirapine component the alternative is a combination of stavudine (d4T), lamivudine (3TC) and efavirenz (EFV). The second-line regimen is used when patients have failed the first-line regimen. Treatment failure is defined as either the development of a new WHO Clinical Stage 4 feature or a CD4 count of <30% of peak value or of <200/mm^3, confirmed one month later in a patient who has been on ART for 6 months or more and has been adhering to therapy. A reasonable dual

nucleoside component alternative to d4T/3TC is zidovudine and didanosine. Because of cross-resistance with other members of the NNTTs class, nevirapine is replaced with a protease inhibitor nelfinavir as the first choice, and if unavailable then is replaced with indinavir. The following drug regimen is therefore the chosen Second-Line option: zidovudine (ZDV) + didanosine (ddI) + nelfinavir (NFV).

2.5 The study foods

Table 2.2 Nutrients provided by the two study food supplements, expressed as amount per/day and compared with estimated average requirement (EAR) for adult men and women

Nutrient	RUTF 250g/day	CSB 375g/day	EAR Women	EAR Men
Energy ($kJ \cdot d^{-1}$)	5694	5694	12644	13252
Energy (kcal $d^{-1)}$	1360	1360	3022	3222
Protein ($g \cdot d^{-1}$)	35.5	50	46	56
Calcium ($mg \cdot d^{-1}$)	830	258	1000	1000
Phosphorus ($mg \cdot d^{-1}$)	700	1050	580	580
Magnesium ($mg \cdot d^{-1}$)	240	500	255	330
Potassium ($mg \cdot d^{-1}$)	2880	1700	4700	4700
Selenium ($\mu g \cdot d^{-1}$)	78	22	45	45
Zinc ($mg \cdot d^{-1}$)	8	8	8	11
Copper ($mg \cdot d^{-1}$)	0.9	2.9	0.9	0.9
Iron ($mg \cdot d^{-1}$)	8	16	18	8
Vitamin A ($\mu g \cdot d^{-1}$)	710	1040	500	625
Vitamin C ($mg \cdot d^{-1}$)	90	26	60	75
Vitamin D($\mu g \cdot d^{-1}$)	5	6	5	5
Vitamin E ($mg \cdot d^{-1}$)	52	32.5	12	12
Niacin ($mg \cdot d^{-1}$)	14	13	11	12
Folic Acid ($\mu g \cdot d^{-1}$)	400	153	320	320
Thiamine ($mg \cdot d^{-1}$)	1.1	1.3	0.9	1.0
Riboflavin ($mg \cdot d^{-1}$)	1.3	0.8	0.9	1.1
Vitamin B_6 ($mg \cdot d^{-1}$)	1.3	1	1.1	1.1
Vitamin B_{12} ($\mu g \cdot d^{-1}$)	1.4	0.5	2.0	2.0

Source: Institute of Medicine.[155] Dietary Reference Intakes For Energy, Carbohydrate, Fiber, Fat, Protein and Amino Acids (Macronutrients). *National Academy of Sciences.* 2002 Washington DC.

Nutritional composition of the two study dietary regimens is compared in table 2.2. Energy density (energy per unit)[155] was higher in RUTF. In this clinical trial the quantity of food

supplements provided were designed to have the same level of energy when appropriate amounts were used; for instance 245g/day RUTF and 374 g/day CSB provided the same dietary caloric intake. Neither of the food supplements provided amounts of micronutrients significantly exceeding estimated average requirements[155] for non-pregnant and non-lactating adults. RUTF provided the estimated average requirement for many micronutrients such as vitamins A, E, C, B_1, selenium, folic acid and copper, while micronutrient content of the daily CSB was lower (about 55% daily estimated average requirement) for selenium, vitamin C, folic acid and vitamin $B_{12.}$ The two food supplements were produced locally in accordance with international food safety specifications. The RUTF was formulated by the investigative team as an optimal form of dry ration food supplement. The CSB adopted the World Food Programme (WFP) formulation.

The amounts of each food supplement given were designed to provide 50% of the daily estimated average requirement for energy, in keeping with the WHO nutritional guidelines that took into account, that clinically symptomatic adults living with HIV/AIDS needs 30% more energy than non-HIV infected healthy individuals.[156] Thus it was estimated what the daily estimated average requirement for an ordinary HIV-negative Malawian was, 13 252 kilojoules[155] and 30% was added to this requirement as an estimated need of the wasted, clinically-symptomatic HIV-infected individuals.[156] The size of the food supplement was determined by estimating this shortfall in an average clinically symptomatic HIV infected adult (2.7196 $kJ \cdot d^{-1}$), then distributing twice as much food, in keeping with the standard recommended by the World Bank.[183]

During the study period, commercial food container sizes in Malawi included 200g, 250g, 400g, 500g, 1kg, 2.5kg, 5kg, 10kg and 20kg containers. A 250g plastic container was chosen for packaging the daily RUTF rations, and the exact size of the RUTF food supplement modified to be compatible with the container size. Thus study participants in the RUTF feeding cohort received one bottle per day containing 45% energy estimated average requirement, closest to the 50% daily estimated average requirement energy supplement goal. This translated into a 7.5kg monthly RUTF ration, given in conjunction with ART during the monthly ART follow-up visit for a period of 3.5 months. The CSB on the other hand was packed in 11.5kg bags (CSB ration for 1 month translated into a daily ration of 375g/day), and as with the RUTF supplement, given in conjunction with the monthly ART follow-up visit for a period of 3.5 months. Study participants were advised to use portions of the daily rations of the study foods in a number of feedings per day between the general family meals. Traditionally families eat from a common plate at mealtimes. However, for the feeding trial, the common dietary adherence advice to study participants of both intervention groups and their supporters was to consider the food supplements as a part of the HIV treatment and that the supplements should not be shared. The importance of giving the full ration to the intended beneficiary was emphasized at enrolment, and the advice repeated at each study visit.

In Africa, ART regimens, particularly those including stavudine, are associated with metabolic side effects such as lipodystrophy, dyslipidaemias, and insulin resistance in individuals with BMI $\geq$25,[184] RUTF dietary regimen has a high fat content, hence it was decided the period of supplementary feeding that includes RUTF intervention be a short, fixed duration of 3.5 months,

to avoid putting patients in the RUTF intervention who would have recovered from wasting at an increased risk of metabolic complications.

2.6 Randomization

2.6.1 Sequence generation

A computer random number generator (Microsoft Excel) was used to prospectively generate a randomization list of 1 – 500 assignments utilising random permuted block lengths of 50 at a time in assigning the two dietary regimens, such that 25 study participants were assigned to each of the nutritional interventions.

2.6.2 Allocation concealment

Using the randomization codes, the study food supplements were matched with study numbers. The list of randomization codes was kept in a room separate from the study clinic, out of sight from the principal investigator and study staff collecting outcome data. Upon completing informed consent, study participants were enrolled and assigned study numbers. After all study procedures and measurements were completed, study participants were referred to a separate room, where a designated independent hospital staff member not affiliated to the study, dispensed the appropriate food supplement based on the study participant's study number.

The study food supplements were started simultaneously with ART initiation. The first ART dosage was a two-week starter-pack of a two-drug combination of stavudine and lamivudine. New ART registrants were required to return for review two weeks after ART initiation, and attend monthly follow-ups thereafter. Consistent with this, the first food supplement ration was for 2 weeks at study onset, then monthly thereafter for the first 3.5 months of ART initiation.

2.6.3 Implementation

Randomization sequence and codes for the study dietary regimens were prepared by an independent medical intern with good background in biostatistics. The principal investigator and co-investigators enrolled study participants and performed study follow-up measurements. During follow-up visits each study participant remained in the dietary allocation throughout the intervention period and collected his/her assigned study food supplement directly from the separate room. Thus, neither study participants in either feeding cohort, nor those dispensing the study food supplements were blinded to the dietary assignments. However to ensure unbiased clinical and laboratory study measurements, the principal investigator and co-investigators remained blinded to the dietary assignments study participants were allocated to until study completion.

2.7 Study implementation

2.7.1 Enrolments

Signed informed consent or, for those not able to write, a finger print, was obtained from all consenting new ART registrants. The consent form consisted of two sections, a participant information sheet and the consent form itself (Appendix B). The information sheet introduced the investigators and summarised the negative relationship between malnutrition and HIV infection. Additionally it summarised the study measurements involved, routine and additional clinical procedures study participants would have to undergo, and questionnaires they would have to answer. The information sheet also informed the study participants, that no direct personal benefits were to be expected, although their participation was important for a better understanding of the effective supplementary feeding programmes in AIDS care. The consent form promised confidentiality for study participants, emphasizing responsibility of the research team in this regard. It was emphasised study participation was completely voluntary and participants had the right to withdraw at any point during study follow-ups. Contact details of the investigators were offered should more information was needed. Patients declining study participation were not in any way affected in their ability to access the ART care available at the study clinic.

Several clinical examination and measurement tools and questionnaires were designed to facilitate data collection. The questionnaires included study participant demographic characteristics (Appendix C), clinical status details (Appendix D), HRQoL measures (Appendix

E I, Appendix E II and Appendix E III) and the qualitative food frequency questionnaire (Appendix F). In formulating the questionnaires, the following requirements were taken into account:[185] questions had to be clear and unambiguous, user-friendly, not offensive or embarrassing, and fair. Some questions were open-ended, aiming at obtaining detailed description of issues such as hospitalisations that had occurred and treatments administered and, study participant's home directions, for the purposes of defaulter follow-ups. Others were closed questions with specific response categories for situations in which the answer could be expressed either as "yes/no", as was the case for the ART adherence interview, or the HRQoL questionnaire. Study measurements included standardised anthropometric measurements and clinical examinations.

Study staff consisted of the principal investigator, two clinical officers and two nurses who had undergone a three-week government sponsored ART delivery training workshop, and an aide. Additionally the study staff underwent training on the study measurements and procedures before study enrolment commenced. The principal investigator, together with the dedicated study staff were part of the day-to-day study clinic work. This study team conducted study follow-up measurements in conjunction with the monthly ART clinic visits, under the supervision of physicians in the Department of Medicine, University of Malawi's College of Medicine.

2.7.2 Data collection

Study enrolments commenced in January 2006, after ethical approval from all ethical review committees involved was secured. Study procedures were conducted after the general ART

services, i.e., voluntary counselling and testing, management of opportunistic infections and ART were completed. Upon enrolment, basic socio-demographic data, such as birth date, age, sex, occupation, measures of economic status (for example, radio, bicycle, dwelling house roofing material), contact address was recorded, and habitual dietary intake assessed using a qualitative food frequency questionnaire. The food frequency questionnaire was modelled on a series of focus group discussions on the habitual dietary intakes of out-patients attending general ART clinic prior to study commencement. However, individuals are more likely to accurately recall dietary intake of their recent, rather than that of their remote past, hence dietary assessments commenced with a 24-hour dietary recall interview on foods consumed the day prior to the dietary interview. A qualitative food frequency questionnaire followed the 24-hour dietary intake recall interview, whereby the frequency of consumption of the foods reported in the 24-hour dietary recall interview were assessed using the following frequency categories: daily, weekly or monthly. Habitual dietary assessments were done using three different methods: total number of different food items consumed, whether or not animal-based foods were consumed and a 12-point dietary diversity score that has previously been correlated with household food security.[186]

HRQoL information was collected using a locally adapted version of the 14-item CDC HRQoL assessment tool,[89] to compare baseline and changes with duration of intervention, in morbidity and quality of life between the intervention groups. Assessment of the "General" Health utilised a response scale of 1 to 5, where 1 was considered "Excellent" or "Normal" General Health, 5 the worst score representing "Ill" General Health and 3 "Fair" General Health, halfway between the Excellent and Ill General Health. "Physical" and "Mental" health was assessed by the

number of days during the past 30 days the study participants' "Physical" or "Mental" Health was not good. Activity-Limitation or Disability days were considered as the number of days in the past 30 days the patient was not able to do usual activities, i.e., self-care, work or recreation due to poor physical and/or mental health.

Body weight, height, MUAC, Waist and Hip circumference were measured by trained staff, and body fat and fat-free body mass calculated. The body weight in kilograms was measured by having study participants stand on a digital scale (CAS, model no. BW-150 accurate to 0.01kg) with light clothing, the reading taken and recorded. Height in millimetres (measurements taken once at enrolment) was done by having the participant stand upright on a height board (Code: SECALE, Hamburg, Germany) with the head positioned such that the Frankfurt plane was horizontal, feet together, knees straight, and heels, buttocks, shoulder blades and head in contact with the vertical surface of the height board. The movable headboard was then lowered gently until it touched the crown of the head, the measurement taken to the nearest millimetre and recorded. The measurements were done in triplicate by a single observer, and values averaged. The BMI was then calculated as weight / height^2.

MUAC was measured by having the study participant stand erect and side-on to the measurer, with arms relaxed and hanging loosely by the side. Those in sleeved garments were asked to roll up the sleeves. The measurements were done by determining the mid-point of the left upper arm from the tip of the acromion process to the tip of the olecranon. The tape measure was then rapped gently but firmly around the arm at the midpoint, and the measurement taken and recorded. The waist circumference measurement was done with the aid of a tape measure (Quick

Medical, Seattle, Washington, USA); the study participant was asked to stand erect with abdomen relaxed. The lowest rib margin was first located, the iliac crest then palpated and located. The tape measure was then rolled horizontally midway between the lowest rib margin and the iliac crest, and positioned firmly around the abdomen, at about the level of the umbilicus, and a reading was taken to the nearest millimetre and recorded. Fat-free body mass was measured using a body composition analyser bioelectrical impedance Quaatum 2000 device (RJL Systems, Clinton Township, Michigan). Electrodes were attached on study participants' finger, wrist, foot and toe with the use of painless sticky patches, the device was then switched on, and reactance and resistance readings recorded. Calculations of fat-free (lean) body mass were then made using Kotler's sex-specific predictive equation for fat-free body mass for wasted HIV infected adults, using height (cm), resistance (ohms), reactance (ohms) and weight (kg).[92] All tools had a less than 1% measurement error. All tools had a less than 1% measurement error.

Note: Bioelectrical impedance measures body composition accurately in any state of hydration, there are no distortions added to the resistance measurement because of changes in body water content. That being said, if a typical subject is 1% dehydrated, the lean body mass estimate will be 0.2% lower than it would be if a subject was fully hydrated. While subjects are likely to have small variations in hydration status (2%), they are unlikely to 5% dehydration and escape clinical detection. The expected changes in fat free body mass related to recovery from malnutrition are expected to be 5-10% of total weight, much larger than the variations introduced by hydration status, and this will not prevent them from being detected by bioelectrical impedance.

Blood samples were collected in three test tubes, two purple-top EDTA and one red-top non-EDTA, clotted samples. Sample collection, preparation and storage protocols for the blood samples are detailed in appendix G. Samples for the CD4 count (FACS Count, Becton-Dickinson, Franklin Lakes, New Jersey, USA) and full blood counts were processed by the Malawi-Liverpool Wellcome Trust Clinical Research Laboratory staff, almost immediately after collection and laboratory results were made available the same day. Samples for serum albumin and the HIV RNA viral load were processed by the same laboratory and stored at temperature -80^0 C, pending shipment to Washington University's St. Louis School of Medicine Research Laboratory, where they were assayed in a batch. Second blood samples were drawn from participants completing 3.5 months of study follow-up and processed in the same manner as baseline samples. HIV viral load (Roche Amplicor®; Roche, Basel. Switzerland; detection level 48 copies /ml) was also included at 3.5 months follow-up, and target Not Detected were assay samples that did not yield a result. ART adherence was measured with a locally designed, previously validated, questionnaire (Appendix I) that consisted of four questions: did you miss a tablet that day, week, month or ever before.[187] Pill counts during study follow-up visits were also made once study participants' commenced ART.

Second dietary intake assessments were administered to study participants completing the first 3.5 months of follow-ups. The contribution made by the study food supplements was excluded from analysis when the habitual dietary intakes of the two cohorts were compared. Thus dietary assessments and laboratory tests were done twice during the study, upon admission and after 3.5 months study follow-up. Additionally study participants were each invited to an open-ended focus group discussion about their experiences with the study food supplements at the end of the

supplementation period at 3.5 month study follow-up. Each group session involved an average of eight study participants, identified by the staff member responsible for the dispensation of the study food supplements, and composed of study participants from both intervention groups who were completing their supplementary feeding. Prior to each session of the focus group, formal consent was obtained by the facilitator moderating the session, and study participants willing to participate in the focus group discussion were invited. In an effort to obtain more objective information, an independent experienced social scientist from the University of Malawi who was not involved in any aspect of the study developed the focus group discussion guide and facilitated the sessions. The discussion guide (Appendix H) was designed with a series of questions to facilitate the group discussion from general to specific experiences with the study food supplements, i.e., acceptability, usage, sharing with family members, and barriers to usage of the study food supplements, all issues related to compliance to the nutritional intervention. All the 12 group sessions utilized the same discussion guide (Appendix H), confidentiality, anonymity, group size, diversity of study participants from cohorts, facilitator and tape recorder. After each group session, participants were offered snacks.

Following completion of the 3.5-month of ART and supplementary feeding, an additional 9-month post-supplementary feeding ART study follow-up visits were conducted. The post-supplementary feeding study follow-ups were conducted in the same manner as with follow-up visits at 6.5, 9.5 and 12 months, using the same study procedures described earlier, with the exception of laboratory tests and dietary assessments. Data collection was done by the Principal Investigator and trained study staff using standardised procedures. To enhance the quality of data collection, study staff involved in data collection were re-trained and supervised on study

measurements and procedures during the entire course of the study. Additionally, to validate the quality of anthropometric measurements such as weight, height, MUAC and waist circumference, each study clinic commenced by re-calibrating the measuring instruments to ascertain their accuracy with regard to their calibration specifications. The digital scale for body weight was re-calibrated using at least two standard masses of different weights, one at a time, then a third measurement combining the two masses. In circumstances where the readings were not consistent with the known weights of the masses, re-setting of the scale done, or another accurate scale used. The height board and the tape measure for MUAC and waist circumference were re-calibrated using a ruler of known length. There was no validation of research assistants' measurements. Treatment outcomes were recorded on standardised master follow-up form (Appendix D) during the monthly study follow-up visits.

In summary the clinical trial consisted of two intervention phases: Phase I intervention consisted of ART medication provided concurrently with supplementary feeding during follow-up visits 0.5, 1.5, 2.5, 3.5 months, and Phase II intervention consisted of ART alone without supplementary feeding during follow-up visits 6.5, 9.5 and 12.5 months. Thus, study participation involved a total of 7 follow-up visits in a study timeline of 12.5 months. Table 2.3 below summarizes the data collected at the monthly visits for the study participants.

Table 2.3 Summary of data collection during monthly study follow-up visits for study participants

Study activities	Follow-up months:												
	0	1	2	3	4	5	6	7	8	9	10	11	12
ART													
Supplementary feeding													
Socio-demographic questions													
Height													
Albumin, CD4 count, haemoglobin													
Dietary survey (food frequency)													
HIV viral load													
Focus groups on use of RUTF/CSB													
Weight, bioelectrical impedance													
Clinical symptoms													
Health-related Quality of Life assessment													
ART compliance													

For study participants who failed to return for a scheduled study follow-up visit, home visits were made to ascertain survival status of the defaulting study participants, and where possible study measurements and procedures completed. If a study participant had died, date and circumstances of death were ascertained by interviewing the closest relatives. For study participants transferred out to other traceable ART clinics, efforts were made to contact them and study measurements performed. If a study participant had died, date and circumstances of death were ascertained by interviewing the closest relatives. For study participants transferred out to other traceable ART clinics, efforts were made to contact them and study measurements performed. If a study participant had died, date and circumstances of death were ascertained by interviewing the closest relatives. For study participants transferred out to other traceable ART clinics, efforts were made to contact them and study measurements performed. Study participants not known to have died but who had not been seen at a scheduled study follow-up visit, could

not be located during active tracing for a period exceeding two months[177] or refused further contact with the study were considered to be lost to follow-up.

2.8 Data cleaning

To enhance the quality of the data, several measures were taken, both during data collection and processing. Firstly questionnaire check was performed as soon as the measurements were taken and recorded. The exercise involved physical checking of the completed questionnaires by the Principal Investigator for accuracy and completeness of the measurements. In cases where some values were questionable, the Principal Investigator checked the recorded values with the responsible study staff. Following this the data were doubly entered into two Excel 2007 databases (Microsoft, Seattle, USA) by two different individuals, and the datasets matched, to check for any irregularities in the data entry, and where any mismatch between the two databases was detected, the Principal Investigator physically checked the questionnaires to verify the correct value. Finally "exploratory" data analysis was performed, where frequency tables of each variable were produced, to check if the number of observations entered were correct, and if there were any missing or incorrect values in the database. Where such problems were detected, corrections were done by verifying with the completed questionnaires.

2.9 Statistical procedures

All numerical variables were entered as such, and new variables, for example the fat-free body mass calculated using Kotler's sex-specific predictive equation for fat-free body mass for wasted HIV infected adults,[92] $LBM = [(50/121) \times (Ht)^{1.48} \times (R^2 + Xc^2)^{-0.275}] + [0.42 \times (Wt)] + [0.49]$ and

LBM = [(4/101) x $(Ht)^{1.97}$ x ($R^2 + Xc^2)^{-0.245}$] + [0.081 x (Wt)] + [0.07] for males and females, respectively, and FBM = (Wt) – (LBM) , % LBM = (LBM) ÷ (Wt) and % FBM = (FBM) ÷ (Wt). In the equations R and Xc stand for resistance (ohms) and reactance (ohms), respectively. Body weight changes, BMI changes, albumin changes, haemoglobin changes, etc, were derived from existing variables. To facilitate data entry, variables measured on a categorical scale, for example gender, food type, WHO stage at ART initiation and cotrimoxazole prophylaxis (CTX) access were pre-coded. An intention-to-treat analysis[188] was utilized to examine the potentially informative drop-out events, deaths, loss-to-follow-ups and voluntary withdrawals from study participation during study follow-ups.

Continuous variables were summarised using means (standard deviations) if normally distributed or medians (inter-quartile range) if not. The Student *t*-test and rank-sum test were applied in the comparisons of the normally distributed and the skewed continuous data, respectively. Categorical variables were summarised by number (percentage). Comparison of categorical variables was performed using the Pearson's $\chi 2$ test. Additionally the Fisher's exact test was applied if observations within cells were less than 5. A *p*-value <0.05 was considered significant for all comparisons between the two intervention groups.BMI during the initial phase I intervention period was measured at four subsequent points (2, 6, 10, and 14 weeks after ART commencement) so the anthropometric recovery for each study participant was assessed during each of these distinct time intervals. The rate of change in BMI during each of these intervals for each participant was calculated. To determine whether rates of change in BMI during the phase I intervention period differed between the two cohorts, mean changes in BMI during each interval for each cohort was compared using Student's *t*-test. Weight gain during recovery from wasting

follows an exponential decay pattern; faster when individuals are more wasted, and gradually decreases as they recover from wasting and approach a normal BMI.[189] Given this, mean values for change in BMI for each intervention group were used to determine the shape of the BMI recovery curve, using an exponential modelling programme (Graph Pad Prism 3.03 Graph Pad Software Inc., San Diego CA). Median weight gains at different time points were stratified by nutritional status at baseline, severe wasting (BMI<16) and mild to moderate wasting (BMI≥16 to BMI ≤18.5). Weight changes were stratified as weight gain ≥10%, weight gain <10% or weight loss from the baseline body mass. A log-rank test was used to compare weight changes between each nutritional status strata.

Study participants were stratified into thirds for the three different measures of habitual dietary intake, and the change in BMI for those receiving RUTF and CSB between each third compared, to determine whether supplementary feeding was more beneficial among participants with greater food insecurity.

Factors associated with mortality were investigated using univariate and multivariate Cox proportional hazard models. However survival for HIV- infected patients improve following ART medication and the duration of therapy. Because of which the prognostic models on the factors associated with mortality were categorised into "overall", considered as the cumulative incidence of death during the 1-year study period,[11] "early" considered as deaths occurring during the first 3.5 months of ART commencement[11] and "post-supplementary feeding" mortality, considered as the mortality occurring during 9.5 months after the nutritional intervention had stopped. In the univariate analysis, factors investigated for the "overall"

mortality, included the study food assignment, study participants' socio-demographic characteristics, criteria for ART initiation, CTX access, anthropometric status and laboratory markers at baseline, anthropometric status at 1.5-month, 2.5-month and 3.5-month, and laboratory markers at 3.5-month study follow-ups. The same factors (with the exception of anthropometric status at 2.5 and 3.5 months study follow-ups, and laboratory markers at 3.5 months study follow-up) were included as possible factors for "early" mortality. Additionally, for short term mortality the early response was measured by anthropometric measurements at 2-weeks study follow-up. Factors investigated for influencing post-supplementary feeding mortality during the 9.5 months phase II study follow-ups included study participants' anthropometric status and laboratory markers (including the HIV RNA viral load) at 3.5 months study follow-up, as baseline factors at commencement of phase II, in addition to patient characteristics at ART initiation. As mortality occurring after phase I intervention was being assessed, anthropometric status at 6.5 and 9.5 months study follow-ups were additional factors investigate. All factors associated with death with a Wald statistic *p*-value <0.05 were considered significant.

In a multivariate regression analysis covariates investigated for the overall 1-year mortality included study participant gender, CTX access, severe wasting (BMI <16.0), lower lean body mass (percentage of body composition), lower haemoglobin status, lower albumin status at baseline, severe wasting (BMI <16.0) and changes in body weight at 1.5 months and at 2.5 months study follow-ups, body weight changes, lower lean body mass (percentage of body composition) and lower CD4 cell count (<200 cells x 10^6/l) at 3.5 month study follow-up. Covariates included in the prognostic model for the assessment of the short-term "early"

mortality during phase I intervention were limited to patient characteristics between baseline and 1.5 months study follow-ups, and included study participant gender, CTX access, severe wasting (BMI <16.0), lower lean body mass (percentage of body composition), lower CD4 cell count (<50 cells x 10^6/l), lower haemoglobin status (<8.0 g/dl) and lower albumin status (<3.5 g/dl) at baseline and severe wasting (BMI <16.0) and body weight changes at 1.5 month study follow-up). Covariates included in the prognostic model for the assessment of mortality during phase II intervention included severe wasting (BMI <16.0), lower lean body mass (percentage of body composition) and lower CD4 cell count (<200 cells x 10^6/l) at 3.5 month study follow-up, and severe wasting at 6.5 months study follow-up.

For all the 3 prognostic models, the multivariate regression analysis utilized a backward stepwise model selection procedure, chosen on the basis that for each of the models the first step includes all the regression terms significant at the univariate analysis. Using a Wald statistic *p*-value that was not significant, factors were sequentially removed from the prognostic model one at a time, beginning with the least significant factor. A likelihood ratio test was used to compare the two models, the original model having all the variables that the second model had except one variable, to assess the contribution of the single differentiating variable to the model. A variable was dropped from the model if a comparison between the two models resulted in a *p*-value >0.05, and retained if the *p*-value was <0.05, before the next variable with largest Wald statistic was removed. The final multivariate prognostic model was achieved when the likelihood ratio test between the last two models was not significant.

After assessing for all possible interactions of factors in the model, Schoenfeld residuals were created, to test for possible violations of the assumption of proportional hazard, which is the fundamental assumption upon which Cox proportional hazards model is built, followed by a global test. The assumption was considered not violated if the *p*-value of the global test was >0.05 and violated if the global test *p*-value was <0.05. In the latter case the model was rejected. Co-variates in the model were investigated to assess variation of these variables against the natural log of time, and any variable with a *p*-value <0.05 was considered a time varying covariate, and thus violated the assumption of proportional hazards.

Due to its irregular availability in Blantyre during the study period, routine access to CTX before and during ART had not been fully implemented at the time of the study. As such, adherence to CTX was not part of the study, and given the uncertainty of CTX adherence by study participants, reference to CTX in the regression analysis was CTX access, as opposed to CTX adherence. Additionally, as most of the ART registrants at the study clinic were referrals from peripheral health centres, with varying pre-ART CTX access backgrounds, it was not possible to know study participants who have had access to CTX prior to ART, and for how long. Therefore, study participants who were given (had access to) CTX at any time during the study period were considered as having had access to CTX in the regression analysis. Time to death in study participants who died during study follow-ups was described using Kaplan–Meier estimates. First I described time to death by the feeding cohort, then by factors significantly associated with mortality, and a log-rank test was used to compare the survival functions of each strata. All analyses were performed using Stata software (version 10; Stata Corp., College Station, Texas, USA).

Interim data analysis, requested by the main funding agency of the clinical trial, the USAID Academy of Educational Development (AED), and the Malawi National AIDS Commission to guide ART supplementary feeding policy was performed 15 months after the clinical trial commencement, at a time point after all study participants had been enrolled and completed the initial Phase 1 intervention. The impact of the two study food supplements on the BMI, lean body mass, and serum albumin was compared at this time. Detailed results of the interim data analysis are presented elsewhere.[102] In summary 491 (96% of all eligible individuals during the study period) were enrolled from January to December 2006. No adverse reactions to either food were reported. There were no significant differences in the demographic, anthropometric or clinical characteristics between the two study groups at baseline. 17 (3.4%) participants were lost to follow-up and 21 (4.3%) were known to be alive, but missed their 3.5 months clinic visit and no anthropometric measurements were made. The mean BMI was 16.5 kg/m^2on enrolment. After 3.5 months patients receiving RUTF had a greater increase in BMI (2.2 ±1.9 vs. 1.7 ± 1.6 kg/m^2, p=0.001) and fat-free body mass (2.9 ± 3.2 vs. 2.2 ±3.0 kg, p=0.04) than those receiving CSB. The mortality rate in the first 3.5 months was high and similar for those receiving RUTF and CSB (27% vs. 26%). No significant differences in the CD4 count, HIV viral load, quality of life assessment or ART adherence were noted between the two groups during the supplementary feeding period. 17 (3.5%) subjects were lost to follow-up. 3 months after the supplementary feeding was completed; surviving subjects had very similar BMIs and fat-free body mass, and no differences in quality of life or ART adherence.

Both the alpha and the sample size were not adjusted for the interim analysis. The ART patient care protocol was the standard used by all ART delivery programmes in Malawi and the region,

and study foods, the food supplements already in use by the various organizations in Malawi, as opposed to a drug trial. As such no stopping rules were necessary for the analysis as is normally the case with drug trials. The clinical trial protocol was approved by three Ethical review boards, including the Committee for Research on Human Subjects (Medical) of the University of the Witwatersrand.

CHAPTER 3.0 RESULTS

3.1 Participants flow

The trial profile, shown in Figure 3.1, outlines the number of study participants who were enrolled, and randomly assigned to and received the intended dietary assignments, completed the study protocol and who were analysed for primary outcomes. Study enrolment commenced in January 2006 and was completed by December 2006, during which time 1,343 new ART registrants were screened for study eligibility. A total of 832 individuals (61.9% of new ART registrants during study period) were excluded because of a BMI $\geq$18.5kg/m^2 exceeding study participation inclusion criteria which was BMI <18.5 kg/m^2, while 511 individuals (38% of new ART registrants during the study period) fulfilled criteria for study participation with BMI <18.5 kg/m^2. Of the 511 study eligible ART registrants, 20 individuals (3.9%) were not enrolled for the following reasons: 11 individuals (2.2%) declined study participation, 4 individuals (0.8%) were pregnant and 5 individuals (0.9%) missed study eligibility screening. Thus, 491 (491/511 [96%]) study-eligible ART registrants during the study period were enrolled. The study participants were subjected to block randomization of 50 at a time, so that 25 of the enrolled study participants were assigned to each of the study dietary regimens, ensuring fairly equal numbers of study participants in both intervention groups; 245 and 246 in RUTF and CSB cohorts, respectively. The enrolled study participants were subsequently followed monthly for the period of one year.

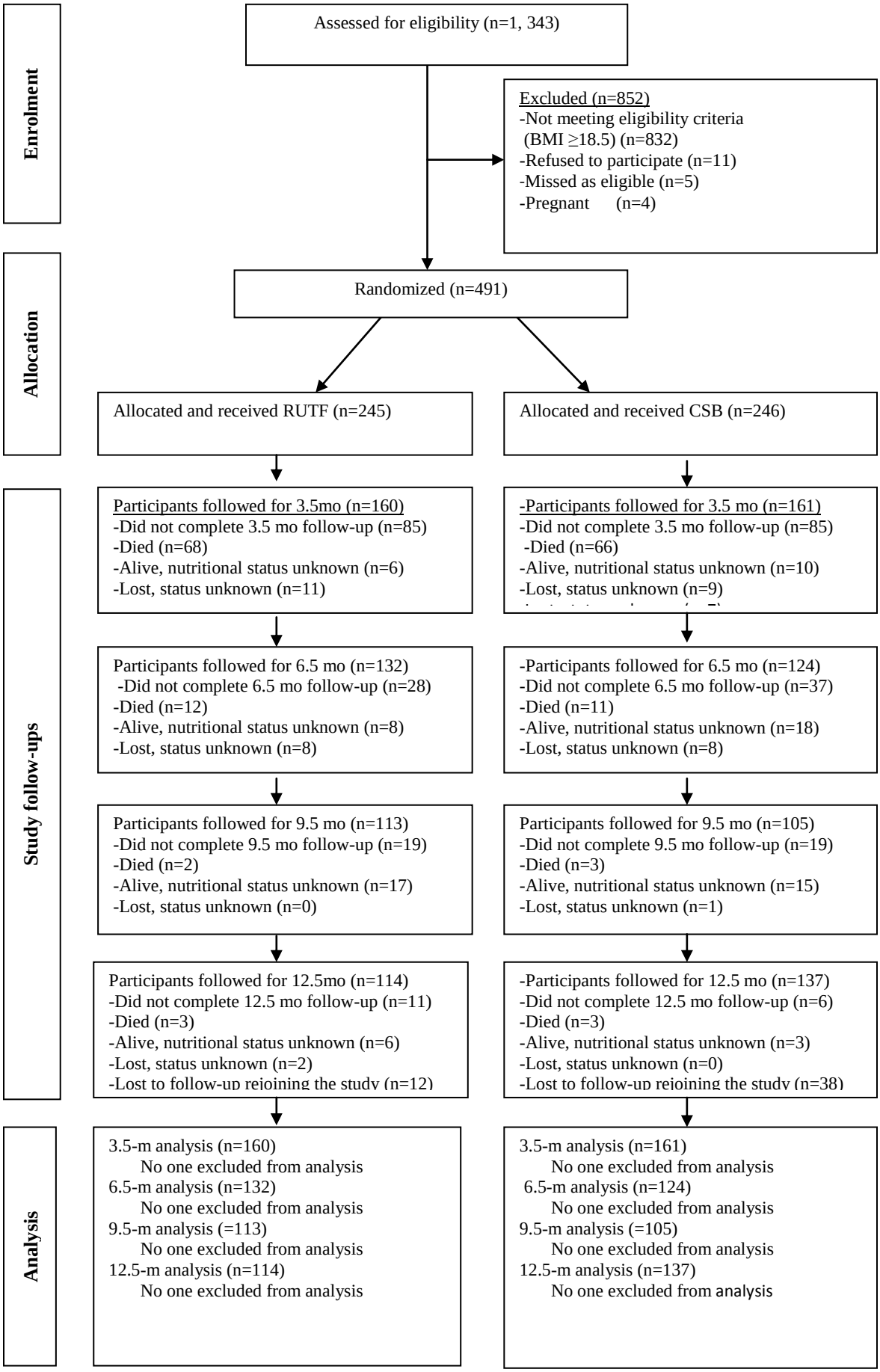


Figure 3.1 Trial profile

Due to attrition over the follow-up period, the trial retention rate on completion of the initial 3.5-month phase I intervention (ART and 3.5 month supplementary feeding) was 321 participants, 160 and 161 participants in the RUTF and CSB cohorts, respectively. Much of the early attrition was due to the high "early" mortality that occurred during phase I intervention, 68 / 245(27.7%) and 66 / 246 (26.8%) of the RUTF and CSB enrolments, respectively. The "true" losses to follow-up over the entire study follow-up period are shown in Figure 3.1; of the survivors of the initial phase I intervention, 4.5% and 3.5% in the RUTF and CSB cohorts, respectively, were true losses to follow-up, while a total of 16 individuals, 6 and 10 in the RUTF and the CSB cohorts were known to be alive but their nutritional status unknown.

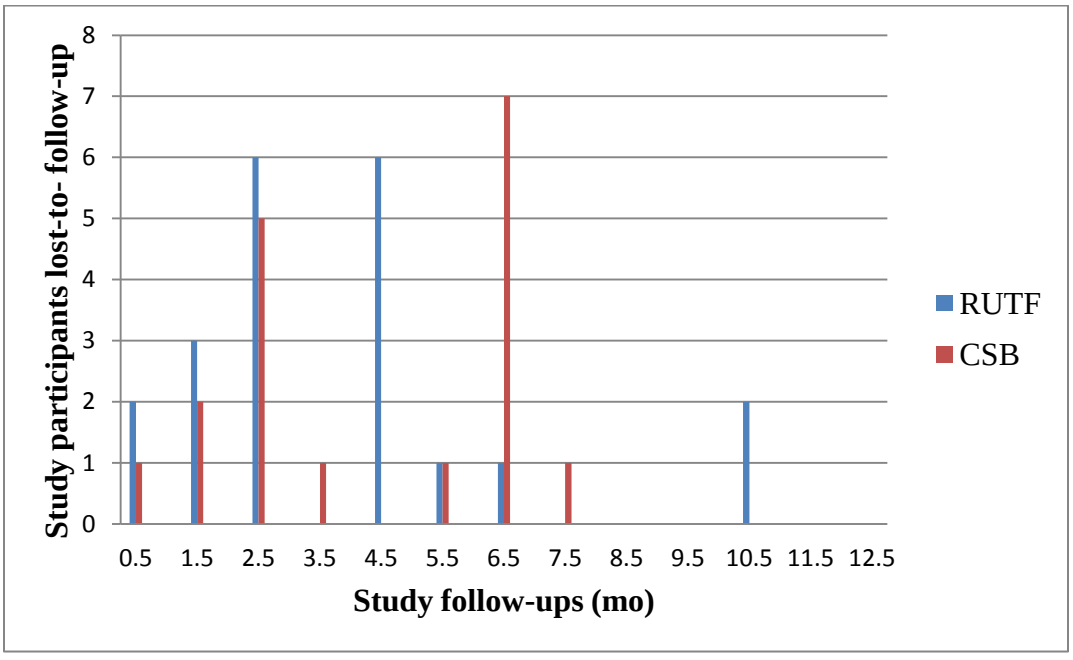


Figure 3.2 True losses to follow-up over the follow-up period

All 321 study participants who survived the initial 3.5-month phase I intervention continued with subsequent phase II post-supplementary feeding ART follow-up. The number of study participants in both cohorts increased towards the end of the study period, with more study participants at 12.5 month than at 6.5-month and 9.5-month study follow-up periods, when some true losses to follow-up during the earlier study follow-ups re-joined the study follow-ups. The trial retention rate at completion of the 12.5-month study period was 133, (133 / 245 [54.3%]) and143, (143 / 246 [58.1%]) in the RUTF and the CSB cohorts, respectively. Participants in the two treatment arms contributed a total of 4,309 person-months of follow-up.

3.2 Patient characteristics at ART initiation stratified by a feeding cohort

Baseline characteristics of study participants in the two intervention groups were balanced at ART initiation (Table 3.1). No significant differences in demographic characteristics, eligibility for ART initiation, anthropometric, immunological or HRQoL indicators, or in dietary practices were evident between the participants of the two intervention groups.

Table 3.1 Status of study participants at study initiation. Values are means (SD) unless stated otherwise

Patient characteristics:		RUTF (N = 245)	CSB (N=246)
Demographics			
Age (years)		36.1 (10.7)	36.0 (10.1)
Women, no. (%)		152 (62.0)	142 (57.7)
WHO stage at ART initiation:			
Stage I/II, no. (%)		19.0 (7.8)	21 (8.5)
Stage III, no. (%)		160 (65.6)	160 (65.3)
Stage IV, no. (%)		65 (26.6)	64 (26.1)
TB status, no. (%)		60 (28.2)	47 (21.8)
Anthropometric:			
Weight (kg)		42.5 (6.0)	43.0 (5.5)
Height (cm)		160.2 (8.3)	161.2 (7.7)
BMI (wt/ht^2)		16.5 (1.5)	16.5 (1.4)
FFBM (% body composition)		96.3 (10.0)	95.5 (7.0)
FFBM (kg)		40.1 (6.8)	40.8 (5.7)
MUAC (cm)		20.4 (2.2)	20.8 (4.1)
Waist circumference (cm)		65.4 (6.1)	65.8 (5.6)
No (%) by nutritional status:			
Severe (BMI<16.0)		81 (33.1)	81 (32.9)
Moderate (BMI≥16.0-≤18.5)		164 (66.9)	165 (67.1)
Laboratory results:			
CD4 count (cells x 10^6/l)		131 (140)	141 (162)
Albumin (g/l)		23.7 (7.6)	24.0 (7.8)
Haemoglobin (g/l)		95 (19)	98 (22)
HRQoL indicators:			
General Health	Good	25/222 (11.2)	29/230 (12.6)
	Fair	64/222 (28.8)	54/230 (23.4)
	Ill	133/222 (59.9)	147/230 (63.9)
Physically unhealthy days/month		17.6 (11.8)	16.2 (11.3)
Mentally unhealthy days/month		6.1 (9.4)	6.4 (10.0)
Mental/physical limitation days/month		17.6 (11.8)	13.2 (13.1)
Habitual diet			
Dietary diversity score (range 0-12)		2.9 (1.4)	2.8 (1.4)
No (%) who consumed animal products		66 (26)	62 (257)
Number of different foods consumed within 24 hrs		8.6 (4.0)	7.8 (3.7)

BMI = body mass index, CSB = corn soy blend, FFBM = fat free body mass, HRQoL = Health-related Quality of Life, MUAC = mid-upper-arm circumference, RUTF = ready-to-use therapeutic food.

3.3 Primary outcome measures

Trial primary outcome measures (increases in BMI and fat-free body mass) in the two intervention groups are compared in table 3.2

Table 3.2Anthropometric outcomes of wasted HIV infected adults at end of phase I (initial 3.5 month nutritional intervention). Numbers are means (SD) unless stated otherwise

Variable	RUTF N = 245)	CSB N = 246	Difference (95% CI)	*p*-value
3.5-month follow-up				
Gain in Body Mass Index (kg/m^2)(n=156, 165)	2.1 (1.8)	1.6 (1.6)	0.4 (0.1, 0.8)	0.01*
Gain in fat-free body mass (kg)(n=154, 160)	2.9 (3.2)	2.2 (3.0)	0.7 (0.2, 1.2)	<0.01*
Gain in mid-upper-arm circumference(cm) (n=154, 150)	2.0 (2.1)	1.4 (2.0)	0.5 (0.1, 0.9)	0.02*
Weight gain (kg) (n=156, 166)	5.5 (4.8)	4.4 (4.4)	1.1 (0.1, 2.1	0.03*
No(%) gained ≥10% with reference to weight at baseline	31 (19.8)	16 (9.6)	-	
No (%) gained <10% with reference to weight at baseline	111 (71.1)	124 (74.7)	-	
No (%) lost weight with reference to weight at baseline	14 (8.9)	26 (15.5)	-	0.03* γ
Missing data (Did not complete 3.5-mo follow-up)	89 (36.2)	80 (32.5)	-	
No (%) by nutritional status				
Severely malnourished(BMI<16.0)	10 (6.4)	12 (7.2)	-	
Moderately malnourished (BMI≥16.0-≤18.5)	53 (33.9)	68 (41.2)	-	0.35γ
Well nourished (BMI >18.5)	93 (59.6)	85 (51.5)	-	
Body Mass Index (kg/m^2) (n=156, 165)	19.0 (2.1)	18.4 (1.7)	0.5 (0.1, 0.9)	0.01*
Fat-free body mass (% of body composition) (n=156, 161)	90.2 (10.4)	91.2 (9.3)	-0.0 (-0.0, 0.0)	0.36

CSB = corn soy blend, RUTF = ready-to-use therapeutic food, * = statistically significant, value for trend, γ = *p* value for trend

Following completion of phase 1 intervention, study participants in RUTF cohort had a significantly greater increase in BMI than their counterparts in the CSB cohort, 2.1(kg/m^2) in the RUTF versus 1.6 (kg/m^2) in the CSB intervention groups (difference 0.40, 95% CI 0.10 to 0.80; p<0.01), and fat-free body mass, 2.9kg versus 2.2 kg in the RUTF and CSB, respectively, (difference 0.70, 95% CI 0.20 to 1.20; p<0.01). Additionally study participants in RUTF cohort had significantly greater increase in weight gain, 5.5kg in the RUTF versus 4.4kg in the CSB

intervention groups (difference 1.10, 95% CI 0.10 to 2.10; p= 0.03) and MUAC gain, 2.0cm versus 1.4cm (difference 0.50, 95% CI 0.10 to 0.90; p= 0.03). A sub-analysis of BMI changes revealed that the gain in BMI in both groups declined with time (Figure 3.3). Mathematical modelling of BMI changes between each measurement interval indicated a similar coefficient in the exponential term in the two models; the exponential decay models fitted both curves well (r^2 = 0.98) although the curves consisted of only four data points, the primary difference in the two curves being a vertical shift due to RUTF usage, resulting in a consistently higher BMI gain. Thus while a declining trend in the rate of BMI changes with duration of intervention was evident in both cohorts, the BMI changes were greater by a constant amount in RUTF (0.045 kg/m^2/week) compared to CSB cohort throughout the intervention period (p = 0.04).

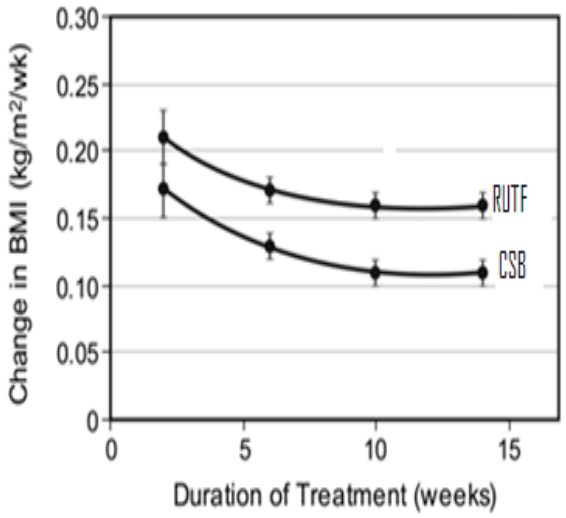


Figure 3.3 Rate of BMI change: Data points represent mean (95% CI)

Outcomes of study participant subgroups stratified by the quality of their habitual pre-enrolment diet and type of supplementary feeding are presented in Table 3.3. Neither RUTF nor CSB

nutritional interventions affected any dietary subgroup differently; diet on enrolment had no effect on outcome or on the benefit of either food supplement.

Table 3.3 Changes in BMI at completion of phase I intervention stratified by initial habitual dietary intake. Values are means (sd) unless stated otherwise

		Body Mass Index Changes					
Variable		RUTF (N = 245)			CSB (N = 246)		
		N	Mean (SD)	*p* value	N	Mean (SD)	*p* value
Animal products	None consumed yesterday	124	1.6 (1.6)	0.37	113	2.1 (1.8)	0.17
	Consumed yesterday	42	1.9 (1.6)		43	2.5 (2.0)	
Different foods consumed yesterday	0 – 6 foods	55	1.7 (1.6)	0.83	41	2.2 (1.6)	0.97
	7 – 9 foods	59	1.6 (1.7)		53	2.1 (2.2)	
	10 – 20 foods	52	1.5 (1.6)		62	2.2 (1.7)	
Dietary diversity Score	1 (lowest) -2	56	1.8 (0.4)	0.49	56	2.0 (1.9)	0.85
	3	56	1.4 (1.6)		54	2.3 (1.8)	
	4 - 12	58	1.7 (1.6)		46	2.2 (2.0)	

Diet categorized by 3 methods: presence of animal products, number of different foods consumed and a 12 point dietary diversity score,[186] subjects divided into tertiles and changes in BMI compared. The significance indicated the difference between the different consumption patterns in each group

Primary outcomes stratified by study participant's pre-treatment anthropometric compromise (pre-treatment BMI) are presented in table 3.4. Following completion of phase 1 intervention, study participants with severe wasting at baseline had a significantly greater increase in BMI, bodyweight and MUAC, BMI gain 2.6(kg/m^2) versus 1.6 (kg/m^2) (difference 0.9, 95% CI 0.5 to 1.3; p <0.01), body weight 6.7kg versus 4.3kg (difference 2.4, 95% CI 1.3 to 3.5; p<0.01) and MUAC gain 2.4cm versus 1.5cm (difference 0.8, 95% CI 0.3 to 1.4; p 0.001). Additionally when rates of weight gain was compared by degrees of wasting at baseline, a significantly greater proportion of individuals gaining ≥10% of their baseline weight had a baseline BMI <16.0 compared to those with a baseline BMI ≥16.0 at completion of phase I intervention and

throughout the entire study period (Kaplan-Meir log-rank test $p<0.01$) (Fig. 3.4.0), indicating that the nutrition intervention worked better if the pre-intervention nutrition status was lower, than when it was higher.

Table 3.4 Anthropometric outcomes of wasted HIV infected adults at end of phase I (initial 3.5 month nutritional stratified by the severity of wasting at baseline. Numbers are means (SD) unless stated otherwise

Variable	BMI <16.0 N = 86	BMI ≥16.0 N = 236	Difference (95% CI)	*p*-value
3.5-month follow-up				
Gain in Body Mass Index (kg/m^2) (n=86, 235)	2.6 (1.8)	1.6 (1.6)	0.9 (0.5, 1.3)	<0.01*
Gain in fat-free body mass (kg) (n=83, 231)	2.3 (4.4)	2.2 (3.8)	0.1 (-0.8, 1.1)	0.7
Gain in MUAC (cm) (n=83, 231)	2.4 (2.3)	1.5 (1.9)	0.8 (0.3, 1.4)	0.001*
Weight gain (kg) (n=86, 236)	6.7 (4.8)	4.3 (4.4)	2.4 (1.3, 3.5)	<0.01*
No(%) gained ≥10% with reference to baseline weight	22 (25.5)	25 (10.5)	-	
No (%) gained <10% with reference to baseline weight	59 (68.6)	176 (74.5)	-	
No (%) lost weight with reference to baseline weight	5 (5.8)	35 (14.8)	-	0.001 γ
Missing data (Did not complete 3.5-mo follow-up)			-	
No (%) by nutritional status				
Severely malnourished (BMI<16.0)	15 (17.4)	7 (2.9)	-	
Moderately malnourished (BMI≥16.0-≤18.5)	41 (47.6)	80 (34.0)	-	<0.01 γ
Well nourished (BMI >18.5)	30 (34.8)	148 (62.9)	-	
Body Mass Index (kg/m^2) (n=86, 235)	17.7 (2.1)	19.0 (1.7)	-1.3 (-1.7, -0.8)	<0.01*
Fat-free body mass (% body composition) (n=83, 234)	92.1 (11.3)	90.3 (9.2)	0.0 (-0.0, 0.0)	0.15

CSB = corn soy blend, RUTF = ready-to-use therapeutic food, * = statistically significant, value for trend, γ = *p* value for trend

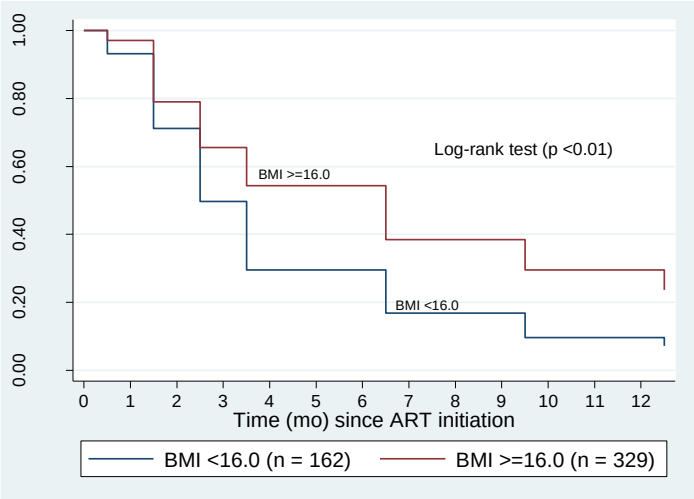


Figure 3.4 Study participants gaining weight ≥10% by baseline BMI

The focus group discussion sessions suggested that both RUTF and CSB food supplements were universally highly appreciated. Additionally, nearly all participants said sharing of study food supplements by dependents and family members was common, although CSB was more likely to be shared than RUTF. However the analysis was not adjusted for the reportedly greater CSB sharing; quantitative food intake assessment by study participants was not part of the study. As such, given that sharing of the study foods was common in both intervention groups, it is not certain which intervention was affected most by the sharing, CSB or RUTF.

Anthropometric outcomes of study participants during phase II (post-supplementary feeding study follow-ups are compared in table 3.5. The difference in BMI increase that was apparent between the two cohorts on completion of the phase I intervention was no longer apparent during subsequent follow-up visits, such that the two cohorts had similar BMIs 3.5, 6.5 and 9.5 months after supplementary feeding was stopped.

Table 3.5 Anthropometric outcomes of study participants during phase II (post-supplementary feeding) study follow-ups. Numbers are means (SD) unless stated otherwise

Variable	RUTF N = 144	CSB N = 162	Difference (95% CI)	*p*-value
6.5-month follow-up				
Gain in Body Mass Index (kg/m^2)	2.7 (2.0)	2.6 (2.1)	0.1 (-0.4, 0.5)	0.73
Gain in fat-free body mass (kg)	4.1 (9.3)	3.5 (5.8)	0.5 (-1.2, 2.3)	0.57
Gain in mid-upper-arm circumference (cm)	2.7 (2.6)	2.8 (2.3)	-0.1 (-0.7, 0.4)	0.65
Weight gain (kg) with reference to weight at baseline	6.9 (5.2)	6.8 (5.6)	0.1 (-1.1, 1.3)	0.87
No. (%) gained ≥10% with reference to weight at baseline	84 (34.0)	25 (25.2)	-	
No. (%) gained <10% with reference to weight at baseline	58 (23.6)	46 (56.7)	-	0.73*
No. (%) lost weight with reference to weight at baseline	14 (5.7)	12 (14.8)	-	
Missing data (did not complete 3.5-mo follow-up)	85	85		
No. (%) by nutritional status:				
Severely malnourished (BMI <16.0)	7 (4.8)	4 (2.8)	-	
Moderately malnourished (BMI ≥16.0 - <18.5)	32 (22.2)	41 (29.3)	-	0.39*
Well nourished (BMI >18.5)	105 (72.9)	117 (83.5)	-	
BMI (kg/m^2)	19.5 (2.2)	19.4 (2.8)	0.1 (-0.4, 0.5)	0.78
Fat-free body mass (% of body composition)	90.4 (18.9)	89.6 (13.9)	0.0 (-0.0, 0.0)	0.66
9.5-month follow-up	**N = 138**	**N = 144**		
Gain in Body Mass Index (kg/m^2)	3.1 (2.3)	3.2 (2.3	-0.1 (-0.7, 0.3)	0.55
Gain in fat-free body mass (kg)	5.2 (9.6)	3.8 (4.8)	1.3 (-0.5, 3.3)	0.17
Gain in mid-upper-arm circumference (cm)	3.7 (3.6)	3.6 (2.4)	0.0 (-0.7, 0.7)	0.97
Weight gain (kg) with reference to weight at baseline	7.9 (5.8)	8.5 (6.0)	-0.6 (-2.0, 07)	0.37
No. (%) gained ≥10% with reference to weight at baseline	9 (7.0)	12 (9.0)	-	0.09*
No. (%) gained <10% with reference to weight at baseline	16 (12.5)	24 (18.0)	-	
No. (%) lost weight with reference to weight at baseline	11 (8.6)	4 (3.0)	-	
Missing data (did not complete 9.5-mo follow-up	19	19		
No. (%) by nutritional status				
Severely malnourished (BMI <16.0)	3 (2.1)	1 (0.7)	-	
Moderately malnourished (BMI ≥16.0 to ≤ 18.5)	28 (20.2)	27 (18.7)	-	
Well nourished (BMI >18.5)	107 (77.5)	116 (80.5)	-	
Body Mass Index (kg/m^2)	19.9 (2.3)	20.1 (2.1	-0.1 (-0.6, 03)	0.57
Fat-free body mass (% body composition)	88.3 (18.2)	86.8 (8.9)	0.0 (-0.0, 0.0)	0.37
12.5-month follow-up	**N = 138**	**N = 144**		
Gain in Body Mass Index (kg/m^2)	3.4 (2.3)	3.5 (2.5)	-0.1 (-0.7, 0.4)	0.58
Gain in fat-free body mass (kg)	4.4 (3.8)	5.1 (4.3)	-0.7 (-1.6, 02)	0.15
Gain in mid-upper-arm circumference (cm)	3.8 (2.5)	3.9 (2.4)	-0.1 (-0.7, 0.4)	0.58
Weight gain (kg) with reference to weight at baseline	8.7 (5.9)	9.3 (6.3)	-0.5 (-2.0, 0.8)	0.43
No. (%) gained ≥10% with reference to weight at baseline	5 (3.7)	7 (4.9)	-	
No. (%) gained <10% with reference to weight at baseline	20 (15.0)	21 (14.6)	-	0.92*
No. (%) lost weight with reference to weight at baseline	3 (2.2)	3 (2.1)	-	
Missing data (did not complete 12.5-mo follow-up)	11	6		
No. (%) by nutritional status				
Severely malnourished (BMI <16.0)	3 (2.1)	1 (0.7)	-	
Moderately malnourished (BMI ≥16.0 to ≤ 18.5)	28 (20.2)	27 (18.7)	-	
Well nourished (BMI >18.5) (BMI >18.5)	107 (77.5)	116 (80.5)	-	
Body Mass Index (kg/m^2)	3.4 (2.3)	3.5 (2.5)	-0.1 (-0.7, 0.4)	0.58
Fat-free body mass (% body composition)	86.0 (11.2)	87.8 (10.9)	-0.0 (-0.0, 0.0)	0.17

CSB = corn soy blend, RUTF = ready-to-use therapeutic food, * = *p* value for trend

3.4 Secondary outcome measures

3.4.1 Response of laboratory markers

Immunological, haematological and virological responses to ART therapy in study participants in the two intervention groups are compared in Table 3.6. Following completion of phase I intervention no significant differences between the two cohorts with respect to changes in CD4 cell count, albumin and haemoglobin status from baseline to the end of the supplementary feeding period were noted between the two intervention groups. Viral replication was effectively suppressed in both cohorts, with similar proportions of study participants achieving plasma viraemia levels <50, 50–1000 and >1000 copies/ml in both intervention groups.

Table 3.6 Response in laboratory markers from baseline to completion of phase I (initial 3.5 month nutritional intervention. Numbers are means (sd) unless stated otherwise

Variables	**RUTF N = 160**	**CSB N = 161**	**Difference (95% CI)**	***p*-value**
Increase in CD4 count (cells x 10^6/L (n=152, 155)	164 (141)	144 (127)	19 (-10, 49)	0.20
CD4 count (cell x 10^6/L at 3.5 months (n=155, 160)	290 (185)	297 (199)	-6.3 (-49, 36)	0.77
CD4 cell count ≥200 no, (%)	104/155 (67.1)	102/160 (63.7)	-	
CD4 cell count 50 – 199 no, (%)	47/155 (30.3)	53/160 (33.1)	-	0.79*
CD4 cell count <50 no, (%)	4/155 (2.5)	5/160 (3.1)	-	
Increases in haemoglobin (g/dl) (n=153, 160)	1.3 (1.7)	1.2 (2.2)	0.1 (-0.3, 0.5)	0.53
Haemoglobin g/dl at 3.5 months (n=156, 161)	11.2 (1.7)	11.3 (1.8)	-0.0 (-0.3, 0.3)	0.95
Haemoglobin ≥10.0 g/dl, no. (%)	131/156 (83.9)	133/161 (82.6)	-	
Haemoglobin 8.0 – 9.9 (g/dl) no, (%)	25/156 (16.0)	28/161 (17.3)	-	0.76
Increase in albumin (g/dl) (n = 154, 153)	0.56 (0.71)	0.59 (0.75)	-0.0 (-0.1, 0.1)	0.72
Albumin status (g/dl) at 3.5 months (n=154, 156)	3.1 (0.7)	3.1 (0.7)	0.0 (-0.1, 0.1)	0.76
Albumin ≥3.5 (g/dl)	58/154 (37.6)	61/156 (39.1)	-	
Albumin <3.5 (g/dl)	96/154 (62.3)	95/156 (60.9)	-	0.82
No (%) by HIV viral load at 3.5 months:				
<50 copies/ml no, (%)	60/161 (37.2)	60/162 (37.0)	-	
50–1000 copies/ml no, (%)	57/161 (35.4)	61/162 (37.6)	-	0.96*
>1000 copies/ml no, (%)	5/161 (3.1)	4/162 (2.5)	-	
TND no, (%)	39/161 (24.2)	37/162 (22.8)	-	

CSB = corn-soy blend, RUTF = ready-to-use therapeutic food, TND = Target Not Detected, * = *p* value for trend

3.4.2 Adherence to ART regimen

Table 3.7 ART adherence in study participants during the whole study period: values are numbers (percentages) of participants experiencing the event.

Follow-up	Adherence question	RUTF N = 36	CSB N = 29	*p*-value
1.5-mo	Missed tablet yesterday?	4 (2.2)	1 (0.5)	0.20
	Missed tablet last week?	8 (4.5)	6 (3.2)	0.59
	Missed tablet last month?	9 (5.0)	6 (3.2)	0.43
	Ever missed Triomune® tablet?	12 (6.7)	11 (6.0)	0.83
	Had to stop ART at any time?	3 (1.6)	5 (2.7)	0.72
3.5-mo		**N = 50**	**N = 68**	
	Missed tablet yesterday?	1 (0.6)	4 (2.4)	0.37
	Missed tablet last week?	10 (6.2)	12 (7.3)	0.82
	Missed tablet last month?	9 (5.6)	14 (8.5)	0.38
	Ever missed Triomune® tablet?	26 (16.3)	34 (20.8)	0.39
	Had to stop ART at any time?	4 (2.5)	4 (2.4)	1.00
6.5-mo		**N = 60**	**N = 77**	
	Missed tablet yesterday?	2 (1.4)	4 (2.7)	0.68
	Missed tablet last week?	7 (5.1)	9 (6.2)	0.80
	Missed tablet last month?	8 (5.8)	9 (6.3)	0.81
	Ever missed Triomune® tablet?	42 (30.6)	50 (34.9)	0.38
	Had to stop ART at any time?	1 (0.7)	5 (3.5)	0.21
9.5-mo		**N = 67**	**N = 79**	
	Missed tablet yesterday?	1 (0.7)	2 (1.4)	1.00
	Missed tablet last week?	6 (4.6)	7 (5.2)	1.00
	Missed tablet last month?	7 (5.4)	10 (7.4)	0.62
	Ever missed Triomune® tablet?	51 (39.8)	57 (42.5)	0.70
	Had to stop ART at any time?	2 (1.5)	3 (2.2)	1.00
12.5-mo		**N = 84**	**N = 106**	
	Missed tablet yesterday?	1 (0.7)	6 (4.3)	0.06
	Missed tablet last week?	11 (8.2)	12 (8.6)	0.83
	Missed tablet last month?	8 (6.0)	16 (11.5)	0.09
	Ever missed Triomune® tablet?	60 (45.1)	66 (47.8)	0.71
	Had to stop ART at any time?	4 (3.0)	6 (4.3)	0.75

CSB = corn-soy blend, RUTF = ready-to-use therapeutic food

Self- reported adherence to ART in the two intervention groups are compared in Table 3.7. Adherence to ART regimen was good and similar in both intervention groups at each study

follow-up visit, with few study participants reporting missing a Triomune® dose the previous day, or at least one Triomune® dose the previous week.

3.4.3 Health-related Quality of Life outcomes

Health-related quality of life outcomes in the two intervention groups are reported in Figures 3.5, 3.6, 3.7 and 3.8 and tables 3.8, 3.9, 3.10 and 3.11.There were significant reductions in the proportions of individuals reporting bad health days per month for the four HRQoL indicators in both intervention groups with increased duration of therapy (Figures 3.5, 3.6, 3.7 and 3.8). There were rapid improvements in the four HRQoL during the first 6 weeks, followed by plateauing of the responses, although the response in the "activity limitation" indicator were more gradual. A paired *t*-test (Table 3.8) indicated no significant differences between the cohorts for all the four comparisons during each of the study follow-up periods.

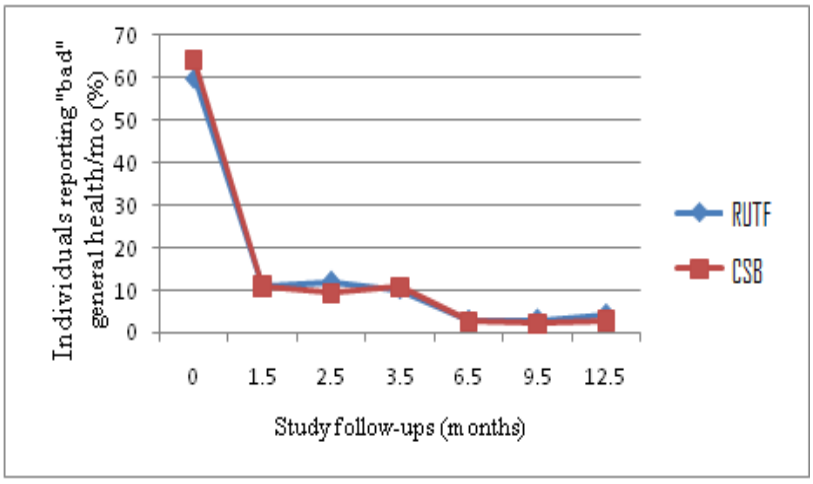


Figure 3.5 Proportions of study participants (%) reporting "bad" general Health per month with duration of therapy

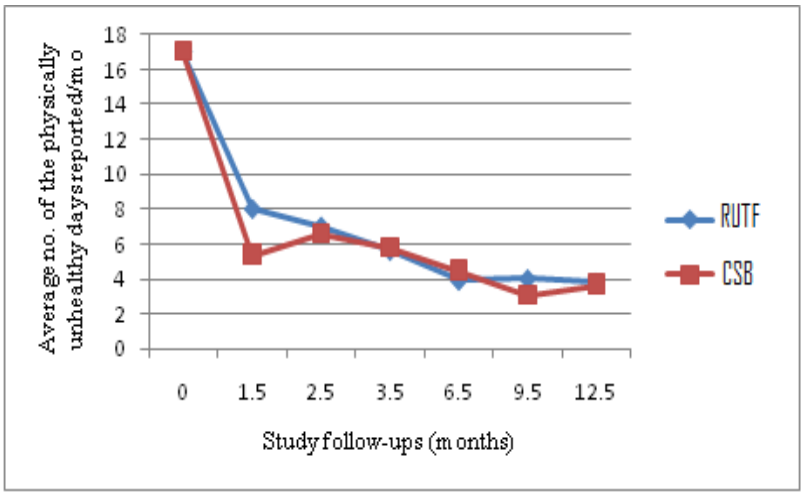


Figure 3.6 Improvements in physical health with duration of therapy

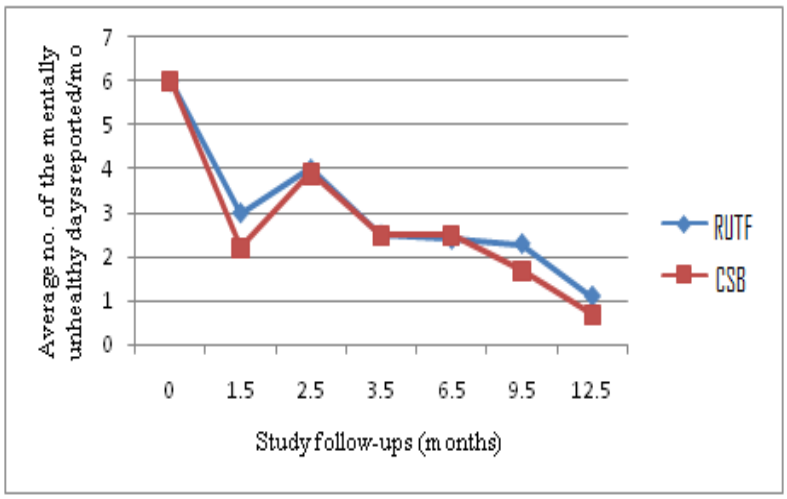


Figure 3.7 Improvements in mental health with duration of therapy

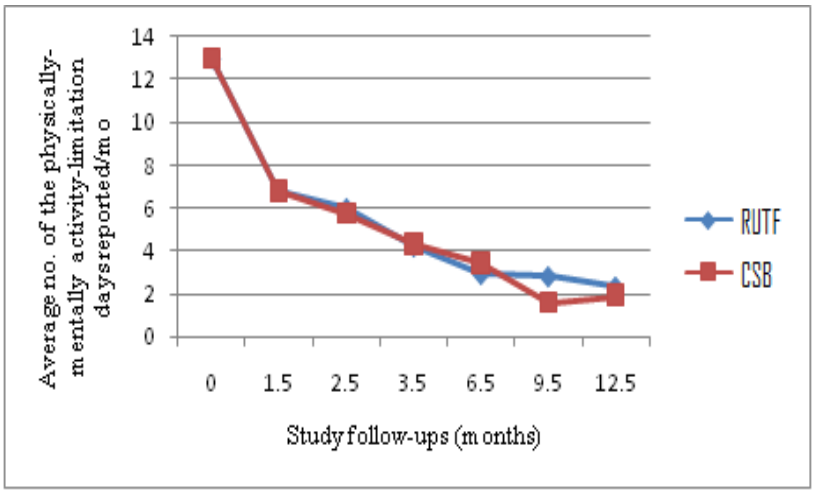


Figure 3.8 Improvements in "Activity-Limitation" days with duration of therapy

Table 3.8 Health-related Quality of Life outcomes in wasted HIV-infected adults. Numbers are means (SD) unless stated otherwise.

Follow-up	HRQoL indicator	RUTF N = 149	CSB N = 158	Difference (95% CI)	*p*-value
3.5-mo					
	General Health no, (%) (n=149, 158)				
	Good	110 (73.8)	119 (75.3)	-	
	Fair	24 (16.1)	22 (13.9)	-	0.89*
	Ill	15 (10.0)	17 (10.7)	-	
	Physically unhealthy days/mo (n=147, 158)	5.5 (7.9)	5.8 (8.5)	-0.2 (-2.1, 1.6	0.79
	Mentally unhealthy days/mo (n=148, 157)	2.4 (5.1)	2.5 (5.7)	-0.0 (-1.2, 1.2)	0.96
	Physical/Mental limitation days/mo (n=149, 157)	4.2 (8.3)	4.3 (8.9)	-0.1 (-2.0, 1.8)	0.90
6.5-mo		N = 137	N = 144		
	General Health no, (%) (n=137, 144)				
	Good	113 (82.4)	116 (80.5)	-	
	Fair	20 (14.6)	24 (16.6)	-	0.93*
	Ill	4 (2.9)	4 (2.7)	-	
	Physically unhealthy days/mo (n=137, 142)	3.8 (7.0)	4.5 (8.4)	-0.6 (-2.5, 1.1)	0.47
	Mentally unhealthy days/mo (n=136, 143)	2.3 (6.0)	2.5 (7.1)	-0.1 (-1.7, 1.4)	0.85
	Physical/Mental limitation days/mo (n=137, 143)	2.9 (7.2)	3.4 (8.6)	-0.5 (-2.3, 1.3)	0.59
9.5-mo		N = 127	N = 134		
	General Health no, (%) (n=127, 134)				
	Good	111 (87.4)	118 (88.0)	-	
	Fair	12 (9.4)	13 (9.7)	-	0.95*
	Ill	4 (3.1)	3 (2.2)	-	
	Physically unhealthy days/mo (n=127, 132)	3.9 (7.2)	3.1 (6.1)	0.8 (-0.7, 2.4)	0.30
	Mentally unhealthy days/mo (n=127, 134)	2.2 (5.9)	1.7 (5.3)	0.5 (-0.8, 1.9)	0.42
	Physical/Mental limitation days/mo (n=127, 134)	2.8 (7.6)	1.5 (5.0)	1.2 (-0.3, 2.7)	0.13
12.5-mo		N = 137	N = 143		
	General Health no, (%) (n=137, 142)				
	Good	111 (81.0)	124 (87.3)	-	
	Fair	20 (14.6)	14 (9.8)	-	0.33*
	Ill	6 (4.3)	4 (2.8)	-	
	Physically unhealthy days/mo (n=133, 142)	3.7 (7.4)	3.6 (7.7)	0.1 (-1.6, 1.9)	0.88
	Mentally unhealthy days/mo (n=136, 139)	1.0 (3.9)	0.7 (3.0)	0.3 (-0.4, 1.1)	0.41
	Physical/Mental limitation days/mo (n=137, 142)	2.3 (6.6)	1.9 (5.6)	0.4 (-1.0, 1.8)	0.58

For the General Health scale of 1 Excellent – 5 Very Ill general health, 1 - 3 = Good general health, 4 = Fair general health, 5 = Ill general health, * = p value for trend

Table 3.9 Improvement in HRQoL outcomes in wasted HIV-infected adults comparing data at commencement, the end of phase I and at study completion (12.5- months).

Cohort	HRQoL indicator	Interval		Mean reduction (95% CI)	*p-value*
		Baseline	3.5 mo		
RUTF	Physically unhealthy d/mo (n=142)	16.6 (11.9)	5.7 (8.0)	10.9 (8.6, 13.2)	<0.01*
	Mentally unhealthy d/mo (n=145)	5.6 (8.7)	2.4 (5.1)	3.1 (1.5, 4.8)	< 0.01*
	Physical/Mental limitation d/mo (n=148)	11.3 (12.2)	4.2 (8.4)	7.1 (4.9, 9.3)	<0.01*
CSB	Physically unhealthy d/mo (n=150)	15.3 (11.2)	5.8 (8.4)	9.4 (7.2, 11.5)	<0.01*
	Mentally unhealthy d/mo (n=153)	6.3 (9.7)	2.3 (5.6)	3.9 (2.2, 5.7)	<0.01*
	Physical/Mental limitation d/mo (n=153)	12.5 (12.4)	4.4 (9.0)	8.1 (5.7, 10.4)	<0.01*
RUTF		Baseline	12.5 mo		
	Physically unhealthy d/mo (n=128)	16.1 (11.8)	3.8 (7.5)	12.2 (9.6, 14.8)	<0.01*
	Mentally unhealthy d/mo (n=133)	5.7 (8.5)	1.0 (3.9)	4.7 (3.2, 6.1)	<0.01*
	Physical/Mental limitation d/mo (n=136)	10.8 (12.2)	2.3 (6.6)	8.4 (6.3, 10.6)	<0.01*
CSB	Physically unhealthy d/mo (n=133)	15.1 (11.2)	3.7 (7.8)	11.3 (9.1, 13.6)	<0.01*
	Mentally unhealthy d/mo (n=136)	6.3 (9.5)	0.5 (1.7)	5.8 (4.2, 7.4)	<0.01*
	Physical/Mental limitation d/mo (n=138)	12.0 (12.2)	1.9 (5.6)	10.0 (7.8, 12.2)	<0.01*
		3.5 mo	12.5 mo		
RUTF	Physically unhealthy d/mo (n=125)	5.1 (7.4)	3.5 (6.8)	1.6 (-0.1, 3.4)	0.06
	Mentally unhealthy d/mo (n= 129)	2.3 (4.7)	1.0 (4.0)	1.2 (0.2, 2.3)	0.01*
	Physical/Mental limitation d/mo (n=131)	2.8 (6.0)	2.3 (6.7)	0.5 (-0.9, 2.0)	0.47
CSB	Physically unhealthy d/mo (n=137)	4.9 (7.6)	3.7 (7.8)	1.2 (-0.5, 2.9)	0.17
	Mentally unhealthy d/mo (n=133)	2.2 (5.0)	0.7 (3.1)	1.4 (0.6, 2.3)	0.00*
	Physical/Mental limitation d/mo (n=136)	3.2 (7.3)	1.9 (5.7)	1.3 (-0.1, 2.8)	0.07

CSB = corn-soy blend, RUTF = ready-to-use therapeutic food, HRQoL = Health-related Quality of Life, * = statistically significant.

Table 3.10 Comparison of Health-related Quality of Life outcomes in wasted HIV-infected adults with "bad" HRQoL indicators at ART commencement, phase II (Post-supplementary feeding ART) and at study completion (12.5 months).

Cohort	HRQoL indicator	Interval		Mean reduction (95% CI)	*p*-value
		Baseline	3.5 mo		
RUTF	Physically unhealthy d/mo (n=130)	18.1 (11.3)	6.0 (8.2)	12.1 (9.7, 14.5)	<0.01*
	Mentally unhealthy d/mo (n=73)	11.2 (9.4)	3.0 (5.1)	8.1 (5.6, 10.6)	<0.01*
	Physical/Mental limitation d/mo (n=96)	17.5 (11.1)	5.1 (9.2)	12.3 (9.5, 15.1)	<0.01*
CSB	Physically unhealthy d/mo (n=138)	16.6 (10.7)	5.7 (8.3)	10.9 (8.7, 13.0)	<0.01*
	Mentally unhealthy d/mo (n=78)	12.4 (10.5)	2.2 (5.0)	10.2 (7.8, 12.5)	<0.01*
	Physical/Mental limitation d/mo (n=105)	18.3 (10.9)	5.2 (9.7)	13.0 (10.2, 15.9)	<0.01*
		Baseline	12.5 mo		
RUTF	Physically unhealthy d/mo (n=118)	17.5 (11.2)	3.8 (7.7)	13.6 (11.0, 16.2)	<0.01*
	Mentally unhealthy d/mo (n=71)	10.7 (9.1)	1.4 (5.1)	9.3 (7.1, 11.5)	<0.01*
	Physical/Mental limitation d/mo (n=85)	17.2 (11.2)	2.9 (7.3)	14.3 (11.7, 17.0)	<0.01*
CSB	Physically unhealthy d/mo (n=122)	16.4 (10.7)	3.6 (7.7)	12.8 (10.6, 14.9)	<0.01*
	Mentally unhealthy d/mo (n=73)	11.8 (10.2)	0.6 (1.8)	11.2 (8.8, 13.5)	<0.01*
	Physical/Mental limitation d/mo (n = 122)	17.6 (10.9)	2.1 (5.9)	15.5 (13.0, 17.9)	<0.01*
		3.5 mo	12.5 mo		
RUTF	Physically unhealthy d/mo (n=111)	5.4 (7.6)	3.5 (7.0)	1.9 (0.0, 3.9)	0.04*
	Mentally unhealthy d/mo (n=66)	3.0 (5.1)	1.5 (5.3)	1.5 (-0.2, 3.4)	0.08
	Physical/Mental limitation d/mo (n=82)	3.8 (7.1)	2.9 (7.4)	0.8 (-1.3, 3.0)	0.44
CSB	Physically unhealthy d/mo (n=119)	4.7 (7.2)	3.7 (7.8)	1.0 (-0.9, 2.9)	0.29
	Mentally unhealthy d/mo (n=72)	1.8 (3.9)	0.6 (1.8)	1.2 (0.3, 2.2)	0.01*
	Physical/Mental limitation d/mo (n =119)	3.5 (7.5)	2.1 (6.0)	1.4 (-0.4, 3.2)	0.13

CSB = corn-soy blend, RUTF=ready-to-use therapeutic food, HRQoL=Health-related Quality of Life, * = statistically significant.
Bad General Health = For the General Health scale of 1 – 5, 1 Excellent – 5 Very Ill/bad general health
Bad physical health = Physically unhealthy days reported /month
Bad mental health = Mentally unhealthy days reported / month
Bad physical – mental activity limitation days = Disability days due to physical-mental activity limitation

Table 3.11 Comparison of Health-related Quality of Life outcomes in wasted HIV-infected adults with better HRQoL indicators at ART commencement, Phase II (ART only) and at study completion (12.5 months)

Cohort	HRQoL indicator	Interval		Mean reduction (95% CI)	*p*-value
		Baseline	3.5 mo		
RUTF	Physically unhealthy days absent (n =12)	0.0 (0.0)	2.3 (5.4)	-2.3 (-5.7, 1.1)	0.16
	Mentally unhealthy days absent(n =72)	0.0 (0.0)	1.8 (5.0)	-1.8 (-3.0, -0.6)	<0.01*
	Activity limitation days absent(n =52)	0.0 (0.0)	2.4 (6.3)	-2.4 (-4.1, -0.6)	0.01*
CSB	Physically unhealthy days absent(n=12)	0.0 (0.0)	7.7 (9.5)	-7.7 (-13, -1.6)	0.01*
	Mentally unhealthy days absent(n=75)	0.0 (0.0)	2.5 (6.3)	-2.5 (-3.9, -1.0)	0.001*
	Activity limitation days absent(n=60)	0.0 (0.0)	2.6 (6.9)	-2.6 (-4.7, -0.6)	0.01*
		Baseline	12.5 mo		
RUTF	Physically unhealthy days absent (n=12)	0.0 (0.0)	4.2 (5.9)	-4.2 (-8.4, 0.0)	0.05*
	Mentally unhealthy days absent (n=62)	0.0 (0.0)	0.5 (1.7)	-0.5 (-1.0, -0.1)	0.01*
	Activity limitation days absent (n=12)	0.0 (0.0)	1.3 (5.2)	-1.3 (-2.8, 0.0)	0.06
CSB	Physically unhealthy days absent (n=15)	0.0 (0.0)	4.3 (9.5)	-4.3 (-10.7, 2.0)	0.15
	Mentally unhealthy days absent (n=67)	0.0 (0.0)	0.4 (1.6)	-0.4 (-0.8, 0.0)	0.05*
	Activity limitation days absent (n=15)	0.0 (0.0)	1.5 (5.1)	-1.5 (-3.1, -0.0)	0.04*
		3.5 mo	12.5 mo		
RUTF	Physically unhealthy d/mo (n=22)	2.5 (5.1)	3.5 (5.3)	-0.9 (-4.0, 2.5)	0.57
	Mentally unhealthy d/mo (n=67)	1.6 (4.0)	0.6 (1.8)	0.9 (-0.0, 2.0)	0.06
	Activity limitation d/mo (n=51)	1.3 (2.9)	1.3 (5.2)	0.0 (-1.5, 1.5)	1.00
CSB	Physically unhealthy d/mo (n=24)	6.5 (10.0)	4.1 (8.6)	2.4 (-2.1, 7.0)	0.27
	Mentally unhealthy d/mo (n=71)	2.6 (6.0)	0.9 (4.1)	1.7 (0.1, 3.3)	0.03*
	Activity limitation d/mo (n=)	2.7 (7.1)	1.6 (5.0)	1.1 (-1.4, 3.8)	0.37

CSB = corn-soy blend, RUTF = ready-to-use therapeutic food, HRQoL = Health-related Quality of Life, * = statistically significant.
Good General Health = For the General Health scale of 1 – 5, 1 Excellent – 5 Very Ill/bad general health
Good Physical health = No physically unhealthy days reported /month
Good mental health = No mentally unhealthy days reported / month
Good physical – mental activity limitation days = No disability days due to physical-mental activity limitation reported.

Improvements in physical health, mental health and the physical-mental "activity" limitation in each of the treatment groups related to duration of intervention are compared in Table 3.9. In the RUTF cohort, a paired *t*-test indicated significant reductions in the number of physically unhealthy days per month compared to baseline values at 3.5 months (treatment effect size 10.9 days, 95% CI 8.6 to 13.2; p <0.01) and at 12.5 months study completion compared to baseline values (treatment effect size 12.2 days, 95% CI 9.6 to 14.8; p<0.01), Significant reductions in the number of mentally unhealthy days per month were evident at 3.5 months compared to baseline values (treatment effect size 3.1 days, 95% CI 1.5 to 4.8; p<0.01),at study completion compared

to baseline values (treatment effect size 4.7 days, 95% CI 3.2 to 6.1; $p<0.01$) and between onset of phase II intervention, 3.5 months and study completion (treatment effect size 1.2 days, 95% CI 0.2 to 2.3; p = 0.01). Significant reductions in the number of physical-mental "activity-limitation" days per month was evident at 3.5 month compared to baseline values (treatment effect size 7.1 days, 95% CI 4.9 to 9.3; p = 0.01) and at study completion compared to baseline values (treatment effect size 8.4 days, 95% CI 6.3 to 10.6; $p<0.01$), but not between onset of phase II intervention, 3.5 months and study completion.

In the CSB cohort, a paired *t*-test indicated a significant reduction in the number of physically unhealthy days per month at 3.5 months compared to baseline values (treatment effect size 9.4 days, 95% CI 7.2 to 11.5; $p<0.01$), at 12.5 month study completion compared to baseline values (treatment effect size 11.3 days, 95% CI 9.1 to 13.6; $p<0.01$), but not between onset of phase II intervention and study completion. Significant reductions compared to baseline values in the number of mentally unhealthy days experienced per month were evident at 3.5 months (treatment effect size 3.9 days, 95% CI 2.2 to 5.7; $p<0.01$), at 12.5 month study completion compared to baseline values (treatment effect size 5.8 days, 95% CI 4.2 to 7.4; $p<0.01$) and between 3.5 months and 12.5 months study completion (treatment effect size 1.4 days, 95% CI 0.6 to 2.3; $p<0.01$). Significant reduction from baseline in the number of physical-mental health activity limitation days per month were evident at completion of phase I intervention, 3.5 months, (treatment effect size 8.1 days, 95% CI 5.7 to 10.4; $p<0.01$), from baseline and study completion (treatment effect size 10.0 days, 95% CI 7.8 to 12.2; $p<0.01$), but not between the onset of phase II intervention and study completion.

A sub-analysis on the improvements on the HRQoL in study participants initiating ART with "Ill" health are compared in table 3.10. In the analysis "Ill" health meant at least the presence of physically ill, mentally ill, and physical-mental "activity-limitation" (disability) days that study participants experienced the month before study enrolment. In the RUTF cohort, a significant reduction in the number of physically unhealthy days experienced per month was evident at 3.5 months compared to baseline values (treatment effect size 12.1 days, 95% CI 9.7 to 14.5; $p<0.01$), at 12.5 month study completion compared to baseline values (treatment effect size 13.6 days, 95% CI 11.0, 16.2; $p<0.01$) and between onset of phase II intervention and study completion (treatment effect size 1.9 days, 95% CI 0.0 to 3.9; p 0.04. A significant reduction in the number of mentally unhealthy days experienced per month were evident at 3.5 month compared to baseline values (treatment effect size 8.1 days, 95% CI 5.6 to 10.6; $p<0.01$) and at 12.5 month study completion. Significant reductions in the number of disability days experienced per month due to physical or mental ill health was evident at 3.5 month compared to baseline (treatment effect size 12.3 days, 95% CI 9.5 to 15.1; $p<0.01$) and at 12.5 month study completion (treatment effect size 14.3 days, 95% CI 11.7 to 17.0; $p<0.01$). In the CSB cohort significant improvements in physical health was evident at 3.5 month compared to baseline (treatment effect size 10.9 days, 95% CI 8.7 to 13.0; $p<0.01$) and at 12.5 month study completion compared to baseline values (treatment effect size 12.8 days, 95% CI 10.6 to 14.9; $p<0.01$).Significant improvements in mental health were evident at 3.5 month compared to baseline values (treatment effect size 10.2 days, 95% CI 7.8 to 12.5; $p<0.01$), at 12.5 month study completion compared to baseline values (treatment effect size 11.2 days, 95% CI 8.8 to 13.5; $p<0.01$) and between on-set of post-supplementary feeding follow-up at 3.5 month and study completion at 12.5 month (treatment effect size 1.2 days, 95% CI 0.3 to 2.2; p 0.01).

Significant improvements in the disability days were evident at 3.5 month compared to baseline (treatment effect size 13.0 days, 95% CI 10.2 to 15.9; $p<0.01$) and at 12.5 month study completion compared to baseline (treatment effect size 15.5 days, 95% CI 13.0 to 17.9; $p<0.01$).

A further sub-analysis on the HRQoL changes in study participants initiating ART with "good" health are reported in table 3.11.This strata of study participants consisted of individuals who reported 1 from a general health scale of 1 to 5, absence of physically ill days, absence of mentally ill days and absence of disability days due to physical and mental ill health the previous month before study enrolment. In the RUTF cohort, significant deterioration in study participants' physical health was evident at 12.5 month study follow-up, with physically unhealthy days per month absent at ART initiation reported (treatment effect size - 4.2 days, 95% CI -8.4 to 0.0; p 0.05). Significant deterioration in study participants' mental health was evident at 3.5 month study follow-up, with mentally-ill health days per month absent at ART initiation reported (treatment effect size - 1.8 days, 95% CI -3.0 to -0.6; $p<0.01$), and at 12.5 month study completion, with mentally-ill health days per month absent at ART initiation reported (treatment effect size -0.5 days, 95% CI -1.0 to -0.1; p 0.01). Significant deterioration in study participants' ability status was evident at 3.5 months study follow-up, with disability days per month absent at ART initiation reported (treatment effect size -2.4 days, 95% CI -4.1 to -0.6; p 0.01). In the CSB cohort significant deterioration in study participants' physical health was evident at 3.5 month study follow-up, with physically ill health days per month absent at ART initiation reported (treatment effect size -7.7, 95% CI -13.0 to -1.6; p 0.01).Significant deterioration in study participants' mental health was evident at 3.5 month study follow-up, with mentally ill health days per month absent at ART initiation reported (treatment effect size -2.5

days, 95% CI -3.9 to -1.0; *p* 0.001), at 12.5 months study completion with mentally ill health days per month absent at ART initiation reported (treatment effect size -0.4 days, 95% CI -0.8 to 0.0; *p* 0.05) and between 3.5 month and study completion at 12.5 months with disability days reported at 3.5 months study follow-up significantly deteriorating further (treatment effect size 1.7 days, 95% CI 0.1 to 3.3; *p* 0.03).

3.4.4 Significant clinical events

3.4.4.1 Hospitalisations

Hospitalisations (severe clinical events) in the two intervention groups are compared in Table 3.12. No significant difference in the numbers of hospitalisations was evident in the two cohorts at each of the follow-up visits, but were much commoner in the first months of phase I intervention, and then only a few thereafter.

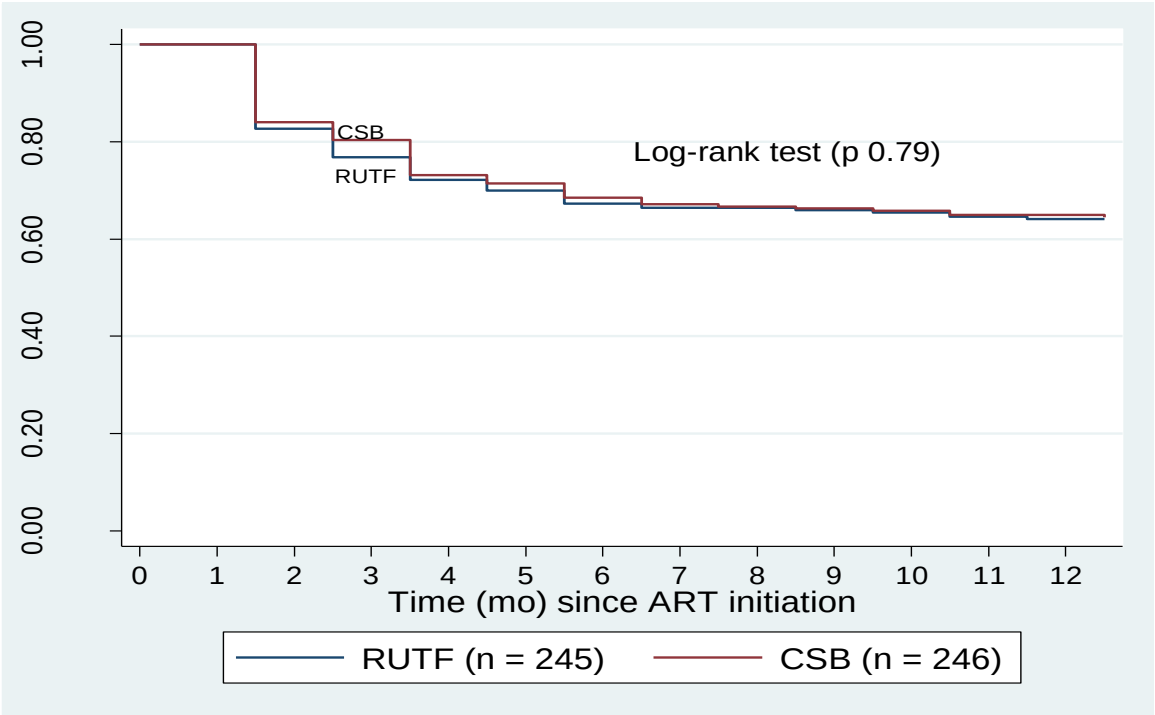
Table 3.12 Number of study participants (percentage) hospitalised during each study follow-up period.

Follow-up period	RUTF	CSB	*p*-value
0- 3.5-mo no, (%)	50/245 (20.4)	49/242 (20.2)	1.00
3.6 – 6.5-mo no, (%)	7/135 (5.2)	5/143 (3.5)	0.56
6.6 – 9.5 mo no, (%)	3/130 (2.3)	3/136 (2.2)	1.00
9.6 - 12.5 mo no, (%)	3/130 (2.3)	3/136 (2.2)	1.00

CSB = corn-soy blend, RUTF = ready-to-use therapeutic food. *Hospitalisations as severe clinical events during each follow-up period were counted as one regardless of the number of times an individual was hospitalized during a particular follow-up period.

3.4.4.2 Mortality

The trial registered a very high mortality rate, with just over a third (171/491 [34.8%]) of study participants demising. The majority of deaths (134/171 [78.4%]) occurred early during the initial phase I intervention, and this was similar in both cohorts (RR: 1.04, 95% CI 0.93 to 1.17; p = 0.49. No significant differences in the mortality rates (RR 0.96, 95% CI 0.75 to 1.22; p = 0.72, and in the timing to death were noted between the two cohorts during each of the study follow-up periods (Kaplan-Meir log rank test p = 0.79) (Fig. 3.9).



Person-time	0	1.5	2.5	3.5	4.5	5.5	6.5	7.5	8.5	9.5	10.5	11.5	12.5
At risk	491	409	372	357	349	336	331	330	328	326	322	321	320
Deaths	0	82	37	15	8	13	5	1	2	2	4	1	1

Figure 3.9 Survival probability of study participants of the two after ART initiation.

Baseline patient characteristics of survivors compared to those who died during study follow-ups are compared in Table 3.13. At baseline the two sub-groups had significantly different nutritional status with those dying having:

- lower BMIs (16.8 [1.2] v 15.8 [1.6]) (difference 0.9, 95% CI 0.7 to 1.2; $p<0.01$),
- lower fat-free body mass percentage of body composition (95.0 [7.3] v 91.0 [11.9]) (difference -0.1, 95% CI -0.1 to -0.0; $p = 0.01$),
- lower MUAC (21.0 [1.9] v 19.5 [2.5]) (difference 1.5, 95% CI 1.1 to 2.0; $p <0.01$),
- smaller waist circumference (66.3 [4.8] v 64.5 [5.3]) (difference 1.8, 95% CI 0.8 to 2.8; $p<0.01$),
- poorer albumin concentrations (2.6 [0.7] v 2.0 [0.6]) (difference 0.5, 95% CI 0.4 to 0.7; $p<0.01$) and,
- lower haemoglobin values (1.0 [1.9] v 9.1 [2.2]) (difference 0.8, 95% CI 0.4 to 1.2; $p <0.01$) in the survivors and the mortality groups, respectively.

The mortality group had significantly fewer females ($p<0.01$), significantly fewer individuals initiating ART with WHO stage III but significantly more with WHO IV criteria ($p<0.01$). The mortality groups had significantly higher proportion of participants who were severely malnourished (BMI <16.0). In contrast it had a significantly lower proportion of participants who were mildly to moderately malnourished (BMI ≥16.0 - <18.5) ($p<0.01$). Additionally the mortality group had significantly less access to the preventive CTX prophylaxis at ART initiation ($p<0.01$).

Table 3.13 Initial patient characteristics of surviving study participants compared to those who died during study follow-ups. Values are means (SD) unless stated otherwise

Patient characteristics	Survivors	Deaths	Difference (95% CI)	*p*-value
Demographics				
Age (years) (n=281, 165)	35.8 (10.0)	36.4 (11.2)	-0.6 (-2.6, 1.4)	0.55
Women, no. (%)	184/287 (64.1)	87/168 (51.7)	-	<0.01*
WHO stage at ART initiation:				
Stage I/II, no. (%)	21/287 (7.3)	14/167 (8.3)	-	
Stage III, no. (%)	207/287 (72.1)	94/167 (56.2)	-	<0.01*
Stage IV, no. (%)	59/287 (20.5)	59/167 (35.3)	-	
Anthropometric:				
BMI (wt/ht^2) (n=287, 168)	16.8 (1.2)	15.8 (1.6)	0.9 (0.7, 1.2)	<0.01*
FFBM (% body composition) (n=283, 168)	95.0 (7.3)	91.0 (11.9)	4.0 (-4.0, -5.0)	<0.01*
FFBM (kg) (n=283, 168)	41.4 (5.6)	41.6 (6.2)	-0.1 (-1.3, 0.9)	0.75
MUAC (cm) (n=283, 168)	21.0 (1.9)	19.5 (2.5)	1.5 (1.1, 2.0)	<0.01*
Waist circumference (cm) (n=282, 168)	66.3 (4.8)	64.5 (5.3)	1.8 (0.8, 2.8)	<0.01*
No (%) by nutritional status:				
Severe (BMI<16.0)	213/287 (74.2)	88/168 (52.3)	-	
Moderate (BMI≥16.0-≤18.5)	74/287 (25.7)	80/168 (47.6)	-	<0.01*
Laboratory results:				
CD4 count (cells x 10^6/l) (n=279, 165)	141.5 (151.1)	126 (157)	14.8 (-14.7, 44.4)	0.32
Albumin (g/l) (n=283, 167)	2.6 (0.7)	2.0 (0.6)	0.5 (0.4, 0.7)	<0.01*
Haemoglobin (g/l) (n=279, 165)	10.0 (1.9)	9.1 (2.2)	0.8 (0.4, 1.2)	<0.01*
HRQoL indicators:				
General Health				
Good	36/300 (12)	18/152 (11.8)	-	
Fair	76/300 (25.3)	42/152 (27.6)	-	0.88
Ill	188/300 (62.6)	92/152 (60.5)	-	
Physically unhealthy days/mo (n=288, 147)	16.5 (11.3)	17.8 (11.8)	-1.2 (-3.5, 1.0)	0.27
Mentally unhealthy days/mo (n=295, 150)	6.0 (9.4)	6.0 (10.3)	-0.9 (-2.8, 0.9)	0.33
Mental/Physical limitation days/mo (n=296, 153)	13.1 (12.6)	12.6 (13.1)	0.4 (-2.0, 2.9)	0.72
CTX				
Access	216/287 (75.2)	96/166 (57.8)	-	<0.01*
No access	71/287 (24.7)	70/166 (42.1)	-	

BMI = body mass index, CSB = corn soy blend, FFBM = fat free body mass, HRQoL = Health-related Quality of Life, MUAC = mid-upper-arm circumference, RUTF = ready-to-use therapeutic food, *= Statistically significant

3.4.4.3 Risk factors associated with mortality

3.4.4.3.1 Risk factors associated with "Overall" mortality

Risk factors associated with the "overall" study mortality are reported in Table 3.14. Cox univariate analysis attributed the following as independent risk factors of the "overall" study mortality: male sex, no access to the preventive CTX, severe wasting (BMI <16.0) at baseline,

severe immune depletion (CD4 count <50), lower haemoglobin values (<10.0 g/dl) poorer albumin concentrations (<3.5g/dl) at baseline, weight gain ≥10% of the baseline at 1.5 months follow-up, severe wasting (BMI <16.0) at 1.5 months follow-up, severe wasting at 2.5 months follow-up, weight gain ≥10% of the baseline at 3.5 months follow-up, lower lean body mass at 3.5 months follow-up and a CD4 cell count <199 at 3.5 months follow-up. When all variables (both protocol-specified and new variables derived from existing variables by calculations) were included in a multivariate prognostic model, the "backward-elimination likelihood ratio test" retained the following factors as covariates significantly associated with "overall" study mortality; severe wasting (BMI <16.0) at baseline, severe anaemia (haemoglobin level <8.0g/dl) at baseline and weight gain ≥10% of the baseline at 1.5 months and 2.5 months study follow-ups. No significant interactions by intervention group among the protocol specified and the new variables derived from calculations by intervention groupwere important in predicting overall mortality during the 12.5-month study period.

3.4.4.3.2 Risk factors associated with the high "Early" mortality

Patient characteristics significantly associated with the high "early" mortality using Cox univariate analysis included: male sex, "no access" to the preventive CTX, severe wasting (BMI <16.0), lower lean body mass percentage of body composition, severe immune depletion (CD4 count <50), severe anaemia (haemoglobin level <8.0g/dl), poor albumin concentration (<3.5g/dl) at baseline, severe wasting (BMI <16.0) and weight gain ≥10% at 1.5 months study follow-up (Table 3.15). When all variables (both protocol-specified and new variables derived from existing variables by calculations) were included in a multivariate prognostic model, the likelihood ratio test backward elimination retained male sex, "no access" to the preventive CTX,

severe wasting (BMI <16.0), lower lean body mass percentage of body composition at baseline and weight gain ≥10% at 1.5 month study follow-up as co-variates significantly associated with "early" mortality. No significant interactions by intervention group among the protocol specified variables and the new variables derived from calculations were important in predicting the "early" mortality.

3.4.4.3.2 Risk factors associated with the "post-supplementary feeding" mortality

On univariate analysis, post-supplementary feeding mortality was significantly associated with severe wasting (BMI <16.0), lower lean body mass percentage of body composition and severe immune depletion (CD4 count <199) at 3.5-month study follow-up (Table 3.16). When all variables (both protocol-specified and new variables derived from existing variables by calculations) were included in a multivariate prognostic model, the likelihood ratio test backward elimination retained lower lean body mass percentage of body composition and severe immune depletion (CD4 count [(cells x 10^6/l) <199]) at 3.5 month as co-variates significantly associated with mortality during the post-supplementary feeding study follow-up period. No significant interactions by intervention group among the protocol specified variables and the new variables derived from calculations by intervention groupwere important in predicting the post-supplementary feeding mortality.

Table 3.14 Cox model analysis showing hazard ratio of factors associated with "Overall" mortality after ART initiation

		Univariate analysis (N = 168)		*Multivariate analysis (N = 168)*	
Factor		HR‡ (95% CI)	*P* value	HR‡ (95% CI)	*P* value
Food	CSB				
	RUTF no, (%)	1.0 (0.7, 1.4)	0.67		
Sex	Female				
	Male no, (%)	1.4 (1.0, 1.9)	0.02*		
Age (yrs)	<35				
	≥35 no, (%)	1.0 (0.7, 1.3)	0.91	3.4 (0.6, 17.9)	0.15
ART initiation criteria	WHO Stage I/II				
	WHO Stage III no, (%)	0.8 (0.4, 1.4)	0.45	1.1 (0.1, 11.1)	0.89
	WHO Stage IV no, (%)	1.3 (0.7, 2.4)	0.29	0.1 (0.0, 4.9)	0.23
CTX	Access				
	No access no, (%)	1.7 (1.3, 2.4)	<0.01*		
Baseline BMI	≥16.0				
	<16.0 no, (%)	2.0 (1.5, 2.8)	<0.01*	2.37 (1.81, 3.10)	<0.01*
Baseline FFBM (%)		39.3 (15.3, 100.8)	<0.01		
Baseline FFBM (kg)		1.0 (0.7, 1.0)	0.81		
Baseline CD4 cell count	≥200				
	50 – 199 no, (%)	0.7 (0.4, 1.1)	0.18		
	<50 no, (%)	1.5 (1.0, 2.3)	0.03*		
Baseline Haemoglobin (g/l)	≥10.0				
	8.0 – 9.9 no, (%)	1.5 (1.0, 2.2)	0.03*	1.4 (0.3, 5.8)	0.63
	<8.0 no, (%)	2.4 (1.6, 3.6)	<0.01*	0.0 (1.4, 0.9)	0.05*
Baseline Albumin (g/l)	≥3.5				
	<3.5 no, (%)	3.3 (1.3, 8.2)	0.02*		
Bodyweight changes at 1.5-mo	≥10% gain	5.1 (3.4, 7.7)	<0.01*	89.8 (5.7, 1410.9)	<0.01*
	<10% gain				
	Weight loss				
BMI at 1.5-mo	≥16.0				
	<16.0 no, (%)	3.6 (2.2, 6.1)	<0.01*	0.1 (0.0, 5.9)	0.25
Body weight changes at 2.5-mo	≥10% gain	4.0 (2.5, 6.6)	<0.01*	0.0 (0.0, 0.4)	0.02*
	<10% gain				
	Weight loss				
BMI at 2.5-mo	≥16.0				
	<16.0 no, (%)	5.1 (2.8, 9.3)	<0.01*	0.6 (0.0, 21.3)	0.81
Bodyweight changes at 3.5-mo	≥10% gain	5.3 (2.9, 9.6)	<0.01*		
	<10% gain				
	Weight loss				
FFBM (%) at 3.5-mo		275.8(25.2, 3013.6)	<0.01*		
FFBM(kg) at 3.5-mo		1.0 (0.9, 1.0)	0.45		
CD4 count at 3.5 mo	≥200				
	50 – 199 no, (%)	3.5 (1.5, 8.1)	<0.01*		
	<50 no, (%)	15 (5.0, 45.0)	<0.01*		
Haemoglobin (g/l) at 3.5-mo	≥10.0				
	8.0 – 9.9				
	<8.0 no, (%)	1.4 (0.6, 3.3)	0.39		
Albumin (g/l) at 3.5-mo	≥3.5				
	<3.5 no, (%)	1.9 (0.8, 4.6)	1.12		

BMI = Body Mass Index, CTX = cotrimoxazole, FFBM = fat-free body mass, FFBM (%) = fat-free body mass percentage of body composition, MUAC = mid-upper-arm circumference, * = Statistically significant

Table 3.15 Cox model analysis showing hazard ratio of factors associated with "Early" mortality after ART initiation

Factor		*Univariate analysis (N = 134)*		*Multivariate analysis (N = 134)*	
	CSB	HR‡ (95% CI)	*P* value	HR‡ (95% CI)	*P* value
Food	RUTF no, (%)	0.8 (0.6, 1.2)	0.42		
	Female				
Sex	Male no, (%)	1.62 (1.32, 1.86)	<0.01*	1.75 (1.32, 2.31)	<0.01*
	<35				
Age (yrs)	≥35 no, (%)	1.0 (0.7, 1.4)	0.92		
	Stage /II				
ART initiation criteria	Stage III no, (%)	0.8 (0.4, 1.5)	0.51	0.7 (0.2, 2.6)	0.69
	Stage IV no, (%)	1.4 (0.7, 2.7)	0.26	1.4 (0.4, 5.2)	0.55
	Access				
CTX	No access no, (%)	2.2 (1.5, 3.1)	<0.01*	2.4 (1.3, 4.7)	0.01*
	≥16.0				
Baseline BMI	<16.0	2.1 (1.5, 2.9)	<0.01*	10.3 (1.3, 79.7)	0.02*
Baseline FFBM (%)		35.1(13.0, 94.7)	<0.01*	10.3 (1.2, 86.8)	0.03*
Baseline FFBM (kg)		0.9 (0.9, 1.0)	0.74		
	≥200				
Baseline CD4 cell count	50 – 199	0.6 (0.4, 1.1)	0.13	0.4 (0.1, 1.1)	0.08
(cells x 10^6/l)	<50	1.5 (1.0, 2.4)	0.04*	1.0 (0.4, 2.3)	0.83
	≥10.0				
Baseline haemoglobin	8.0 – 9.9 no, (%)	1.3 (0.9, 2.1)	0.13		
(g/l)	<8.0 no, (%)	2.9 (1.9, 4.4)	<0.01*		
Baseline albumin (g/l)	≥3.5				
	<3.5 no, (%)	4.3 (1.3, 13.7)	0.01*		
	≥16.0				
BMI at 1.5 mo	<16.0	3.3 (2.2, 5.0)	<0.01*		
	≥10%	7.0 (4.2, 11.8)	<0.01*	3.9 (1.8, 8.4)	<0.01*
Bodyweight changes at	<10%				
1.5-mo	Weight loss				

BMI = body mass index, CTX = cotrimoxazole, FFBM = fat-free body mass, FFBM (%) fat-free body mass percentage of body composition, MUAC = mid-upper-arm circumference, * = Statistically significant

Table 3.16 Cox model analysis showing hazard ratio of factors associated with "post-supplementary feeding" mortality after ART initiation

Factor		*Univariate analysis (N = 34)*		*Multivariate analysis (N = 34)*	
		HR‡ (95% CI)	*P* value	HR‡ (95% CI)	*P* value
Food	CSB				
	RUTF no, (%)	1.3 (0.6, 2.7)	0.40		
Sex	Female				
	Male no, (%)	1.9 (0.9, 3.8)	0.07		
Age (yrs)	<35				
	≥35 no, (%)	1.0 (0.5, 2.1)	0.79		
ART initiation criteria	Stage /II				
	Stage III no, (%)	0.7 (0.2, 2.6)	0.69		
	Stage IV no, (%)	1.1 (0.3, 4.2)	0.83		
CTX	Access				
	No access no, (%)	0.4 (0.1, 1.2)	0.13		
Weight changes at 3.5-mo	≥10%	0.5 (0.2, 1.3)	0.19	0.6 (0.2, 1.8)	0.39
	<10%				
	Weight loss				
BMI at 3.5 mo	≥16.0				
	<16.0	5.6 (2.5, 12.8)	<0.01*		
FFBM (%) at 3.5-mo		275.8 (25.2, 3013.6)	<0.01*	130.4 (6.3, 2699.9)	<0.01*
FFBM (kg) at 3.5-mo		1.0 (0.9, 1.0)	0.45		
CD4 cell count (cells x 10^6/l) at 3.5-mo	≥200				
	50 – 199 no, (%)	3.5 (1.5, 8.1)	<0.01*	3.7 (1.2, 11.1)	0.03*
	<50 no, (%)	15.0 (5.0, 45.0)	<0.01*	11.9 (2.1, 65.2)	<0.01*
Haemoglobin (g/l) at 3.5-mo	≥10.0				
	8.0 – 9.9 no, (%)	1.5 (0.6, 3.6)	0.29		
Albumin (g/l) at 3.5-mo	≥3.5				
	<3.5 no, (%)	1.5 (0.6, 3.6)	0.29	1.4 (0.4, 4.4)	0.55
HIV viral load	<50				
	50 – 1,000	1.3 (0.5, 3.1)	0.53		
	>1,000	1.3 (0.0, -)	1.00		
	TND	1.6 (0.6, 4.0)	0.30		
Weight changes at 6.5-mo	≥10%	2.5 (0.7, 8.3)	0.13	3.6 (0.4, 29.9)	0.22
	<10%				
	Weight loss				

BMI = body mass index, CTX = cotrimoxazole, FFBM = fat-free body mass, FFBM (%) = fat-free body mass percentage of body composition, MUAC = mid-upper-arm circumference, *= Statistically significant

Considering survival probability as an outcome, study participants' sex (Kaplan-Meir log rank test p =<0.01) (Fig. 3.10), access to CTX (Kaplan-Meir log rank test p<0.01 (Fig. 3.11), severe wasting (BMI <16.0) at ART initiation (Kaplan-Meir log rank test p = 0.02) (Fig. 3.12, haemoglobin status at ART initiation (Kaplan-Meir log rank test p<0.01) (Fig. 3.13), BMI at 1.5

months follow-up (Kaplan-Meir log rank test $p<0.01$) (Fig. 3.14), body weight changes at 1.5 month follow-up (Kaplan-Meir log rank test $p<0.01$) (Fig. 3.15), body weight changes at 2.5 month follow-up (Kaplan-Meir log rank test $p = 0.02$) (Fig. 3.16) and CD4 cell count (cells x 10^6/l)at 3.5 month study follow-up (Kaplan-Meir log rank test $p<0.01$) (Fig. 3.17) were important factors.

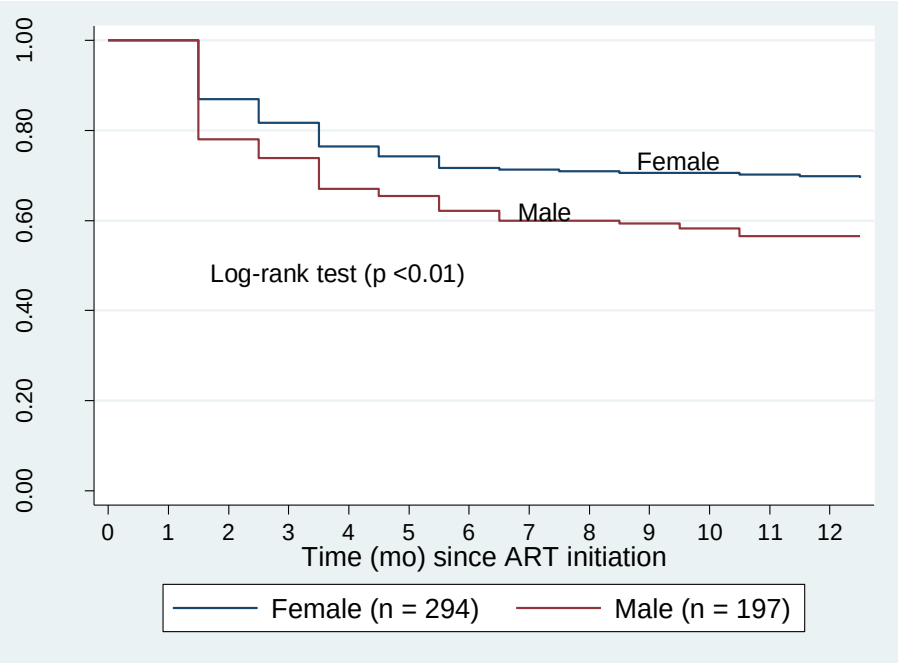


Figure 3.10 Kaplan-Meier Survival Curve of study participants stratified by sex.

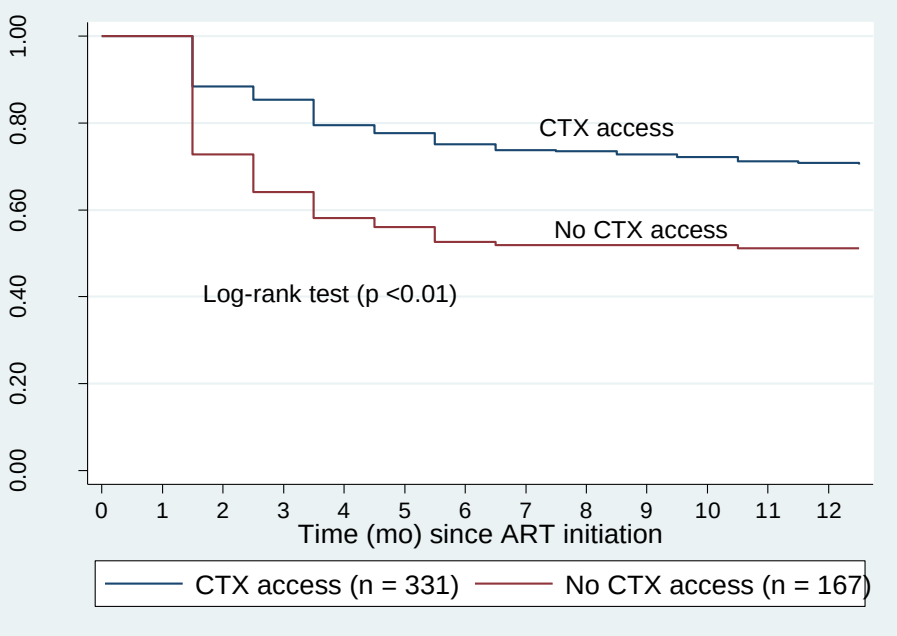


Figure 3.11 kaplan-Meier Survival Curve of study participants stratified by access to CTX

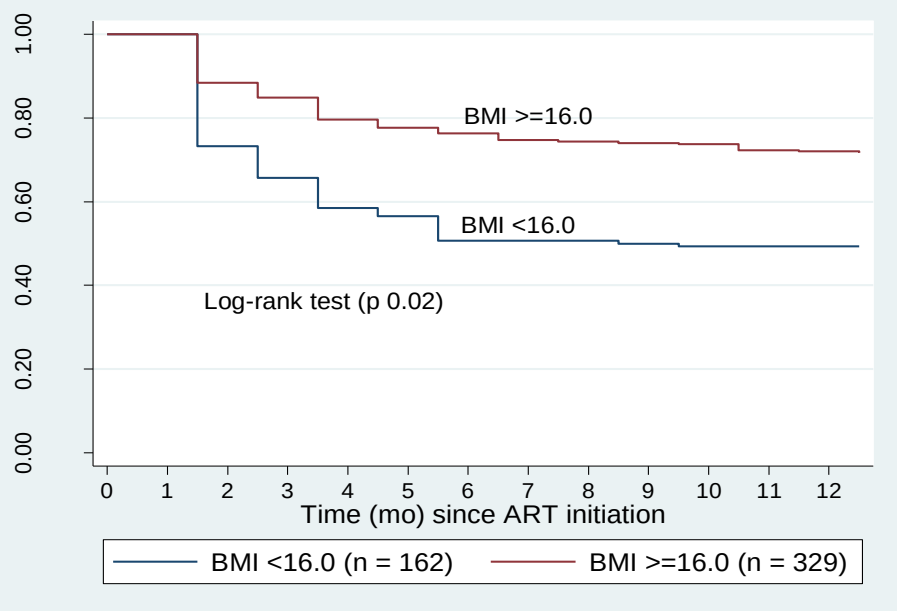


Figure 3.12 Kaplan-Meier Survival Curve of study participants stratified by BMI at ART initiation

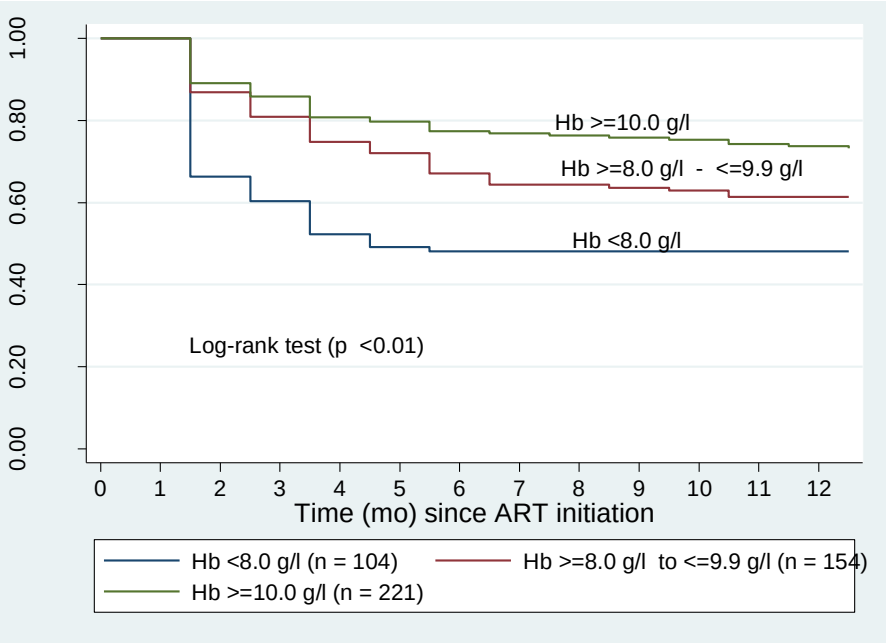


Figure 3.13 Kaplan-Meier Survival Curve of study participants stratified by Haemoglobin status at baseline

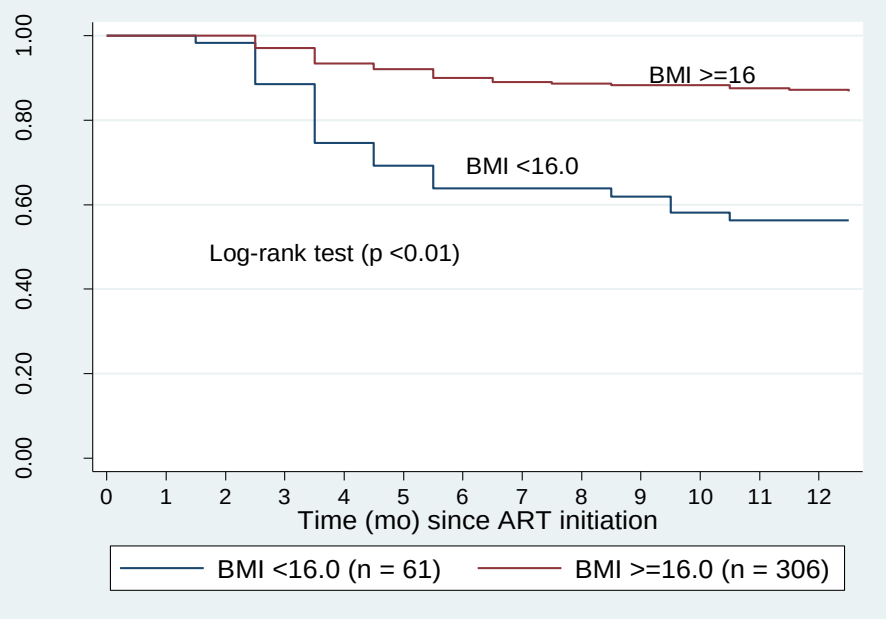


Figure 3.14 Kaplan-Meier Survival Curve of study participants stratified by BMI at 1.5-month study follow-up

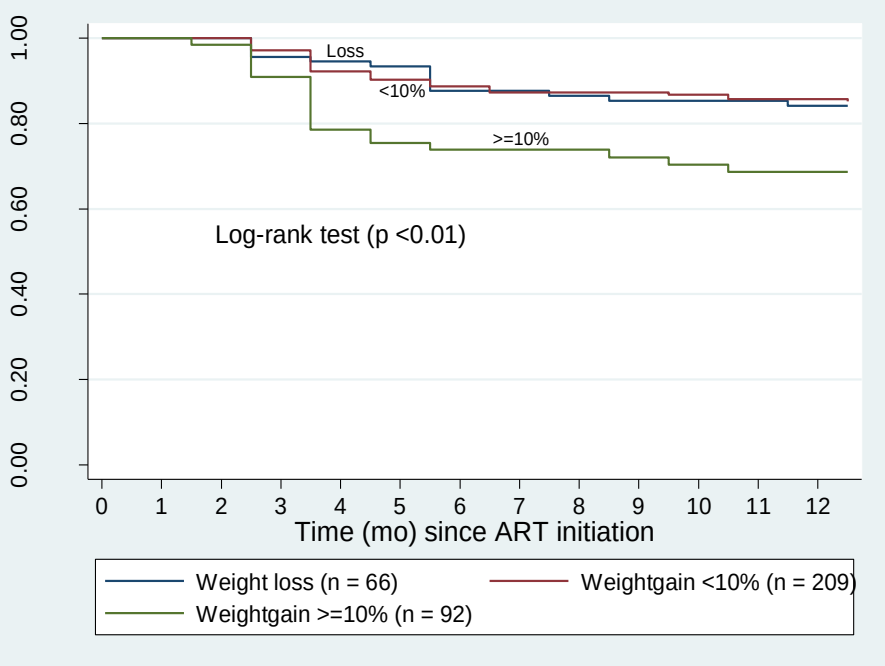


Figure 3.15 Kaplan-Meier Survival Curve of study participants stratified by body weight changes at 1.5-month follow-up

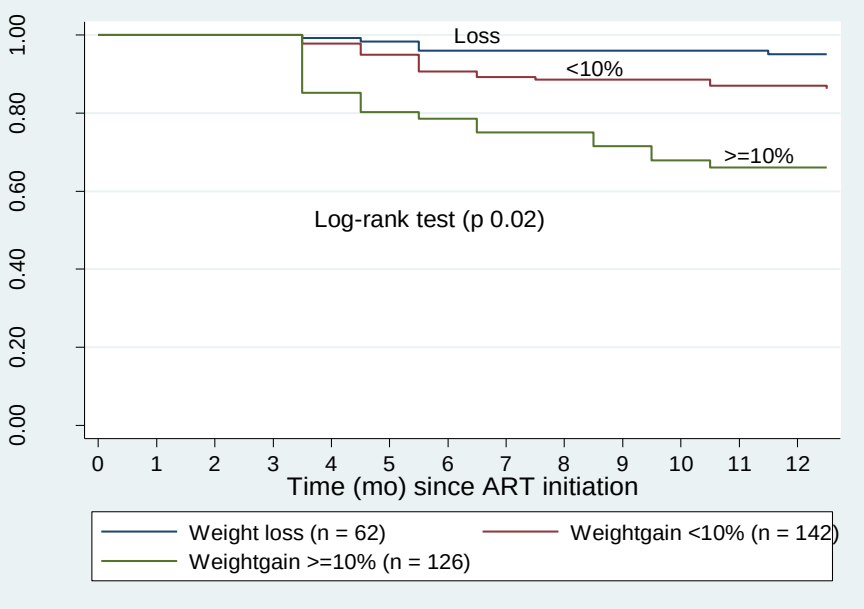


Figure 3.16 Kaplan-Meier Survival Curve of study participants stratified by bodyweight changes at 2.5 month-study follow-up

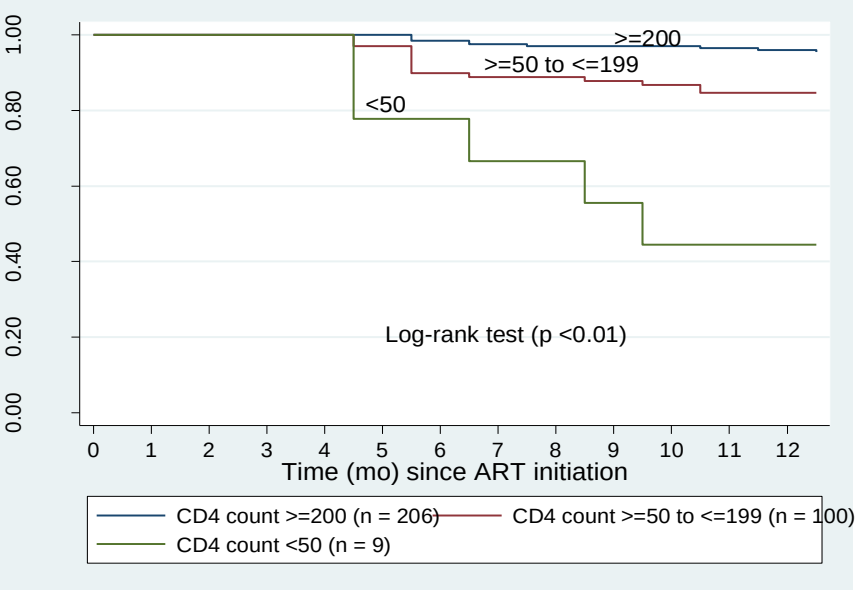


Figure 3.17 Kaplan-Meier Survival Curve of study participants stratified by CD4 cell count at 3.5-month study follow-up

CHAPTER 4 .0 DISCUSSION

4.1 Principal findings

In wasted adult AIDS patients commencing ART, short-term supplementary feeding with energy-dense RUTF resulted in a greater increase in BMI, fat-free body mass, weight and MUAC, than feeding with CSB during the first 3.5 months phase I intervention. No significant differences in CD4 cell count, haemoglobin or albumin increases, HIV RNA viral load suppression, adherence to ART regimen, HRQoL, habitual dietary practices, hospitalisations or survival were evident between the two intervention groups.

Considering weight gain as an outcome measure, the proportions of study participants that gained weight ≥10% of the baseline body mass was considerable and similar in both treatment arms; large proportions of participants in both cohorts gained weight ≥10% of their original body mass from baseline to 3.5 months after ART commencement. However, patients who entered post-supplementary feeding study follow-ups with a higher BMI and fat-free body mass resulting from RUTF feeding did not maintain a higher BMI and fat-free body mass compared to their counterparts in the CSB feeding cohort. Neither were there improved clinical outcomes, including ART adherence or HRQoL between the two cohorts during the subsequent 9-months post-supplementary feeding study follow-ups.

The clinical trial observed a high mortality rate in the study participants, with most deaths occurring during the initial 3.5 months of ART. Severe wasting (BMI <16.0) at baseline, lower lean body mass at baseline, lack of failure to receive CTX and weight gain ≥10% of initial body mass at 1.5 month study follow-up were co-variates statistically most strongly associated with high "early" mortality. There was improved survival following completion of phase I intervention, with only 7% of the overall study mortality occurring during the 9-month post-supplementary feeding study follow-up. Lower lean body mass and lower CD4 count <200 (cells x 10^6/l) at commencement of phase II intervention (3.5 months) were variables statistically most strongly associated with post-supplementary feeding mortality.

4.2. Anthropometric outcomes

4.2.1 Weight gain

Weight gain during phase I intervention was considerable, resulting in mean gains of 13% and 10% on initial body mass, in RUTF and CSB study participants, respectively, with 39% and 40% of study participants in the RUTF and CSB arms, respectively, achieving weight gain ≥10% of initial body mass. The magnitude of weight gain, BMI gain and fat-free body mass gain described in this study is greater than that reported in other studies.[190-192] A prospective cohort study to investigate whether protease inhibitor (nelfinavir)-containing ART regimen affects body composition differently in HIV-infected and AIDS patients without wasting syndrome reported weight, BMI, and fat-free body mass increases of 3.7 kg, 1.3 kg/m^2 and 1.0 kg, respectively, after 24-weeks of therapy.[190] An HIV cohort study in Boston and Rhode Island area of the US reported weight and BMI gains of 1.54 kg and 0.50 kg/m^2, respectively after a 12-month PI

treatment, while lean body mass did not change.[191] A prospective 48-week multisite observational study reported median increases in body weight and lean body mass of 2.6 kg and 1.0 kg, respectively, after 16-weeks of therapy.[192] In contrast a study involving HIV infected patients on standard antiretroviral and oxandrolone management reported higher increases in body cell mass and lean soft tissue of 3.6 kg and 3.0 kg, respectively, over the course of 18.6 weeks of treatment[193] than the fat-free body mass increase reported in the present study. Oxandrolone is a synthetic anabolic steroid prescribed to promote muscle re-growth in disorders which cause involuntary weight loss, thus the weight gain with oxandrolone therapy is really comparable to that achieved with food supplements.

4.2.2 The superiority of RUTF over CSB in anthropometric recovery

During every interval of the four intervals during phase I intervention (at 0.5-month, 1.5-month, 2.5-month and 3.5-month study follow-ups) study participants receiving RUTF gained more BMI than those receiving CSB, suggesting RUTF supplement conferred a differential benefit compared to CSB throughout the entire phase I intervention period rather than simply in the first few weeks of therapy. While the CSB ration per person per month was bigger in quantity than the RUTF ration, the fat-free mass contributed about the same fraction of weight gain in each intervention group suggesting a greater proportion of the RUTF ration provided was consumed than the CSB ration. RUTF might have promoted greater weight gain because of its higher energy density, thereby allowing adequate energy intake in patients with some degree of anorexia. In addition, the focus group discussions indicated RUTF supplement was shared less often than CSB food supplement. RUTF is ready to eat, while CSB needs cooking before

consumption. Cooking or any form of food preparation for ill adults will often be done by relatives or dependents, a practice that may be more conducive to sharing of the food supplement. Additionally CSB is similar to components of the staple food in Malawi; this might have encouraged greater sharing of the food supplement with family members, while RUTF was regarded as a special "medicinal" food supplement for patients, arguably because of its ready-to-use form and the small rations provided. Although there were differences in the micronutrient content between the two study food supplements, it is estimated there were adequate amounts of all micronutrients in both dietary regimens to promote weight gain, if the supplements were consumed in addition to the habitual diet.

Given that CSB was more likely to be shared compared to RUTF, if the analysis was adjusted to take into account the greater CSB sharing, it could be speculated CSB intervention would have been as good as or better than RUTF on the study primary outcomes. However the analysis was not adjusted for the reportedly greater CSB sharing; quantitative assessment of study food intake by study participants and household food security survey of the study participants, one of the important determinants of the availability of food supplements to the intended beneficiary, were not part of the study. Thus given that food sharing was common in both intervention groups, it is not certain which intervention was affected most by the sharing, CSB or RUTF.

The observation that supplementary feeding with higher energy-dense food supplement in wasted HIV-infected persons resulted in greater anthropometric recovery than feeding with CSB is similar to findings from earlier feeding studies in Malawi. An ART programme in rural Malawi that provided CSB food supplement in 2003 and energy-dense fortified spread in 2004

indicated that patients receiving the fortified spread had greater weight gain compared to their counterparts who received CSB (1.5 v 0.8 kg/month; $p = 0.04$).[162] In a therapeutic trial at Queen Elizabeth Central Hospital, a major referral hospital in Malawi, severely malnourished HIV-infected Malawian children who received energy-dense RUTF had greater weight-for-height improvement than their counterparts who received CSB.[160] In another feeding study involving adults with AIDS in urban Malawi, those receiving energy-dense vegetable oil and CSB food supplement had greater improvement in BMI than those receiving CSB food supplement alone.[161]

4.2.3 Supplementary feeding with either RUTF or CSB and the Community-based ART programme

The Malawian government through the Global Fund obtained its first-line ART regimen for $15 per patient per month.[167] The CSB cost the study $5.40 per patient per month, while RUTF was three times as expensive at $16 per patient per month. In almost all ART treatment facilities in Malawi, supplementary feeding programmes are normally conducted in conjunction with the scheduled ART clinic visits. Thus, such programmes do not have any additional expense on the part of the ART clients.

However, it must be borne in mind that utilization of individual supplementary foods by programme beneficiaries depends on several factors. For instance while the current market price for the CSB dietary regimen is two thirds cheaper for the HIV feeding programme compared to that of the RUTF, the CSB dietary regimen requires prolonged cooking before consumption, as

opposed to the RUTF regimen which is ready to use requiring no special preparation before consumption. Thus for a home-based nutritional intervention, if the various logistical issues such as fuel wood, other resources etc. involved in the CSB preparation, with the additional time required to manage separate and recommended number of feedings per/day were to be factored into the comprehensive cost benefit analysis of the study foods, it is possible the CSB-based intervention would be more costly compared to the RUTF-based intervention; with the additional hidden costs having to be met by the programme beneficiaries. Although considered in the original study plan, a cost-effective analysis of the two study foods was not conducted during this study.

4.2.4 The habitual dietary intakes

Habitual diets of study participants in both intervention groups were poor. Using a 12-point dietary diversity score,[186] a means of assessment, only 30% of individuals in both intervention groups achieved a dietary diversity score of 4/12, an indication that the habitual diets of study participants in both intervention groups were poor.[186] The diets were predominantly plant-based, and only a quarter of individuals reported having consumed flesh foods (meat, fish or poultry) the previous day. Fairly similar dietary practices have been reported in other food consumption surveys among people living with HIV/AIDS in Mozambique and Uganda.[140,141] A baseline survey in Mozambique to establish food security status of households in HIV/AIDS affected areas reported a mean dietary diversity score of 4.3, about 97% of households consuming predominantly plant-base diets and only less than 10% of the households consuming meat or meat products.[140] A cross-sectional study in an urban Uganda to establish how HIV affected households in terms of response to food shortages reported a mean dietary diversity score of 6,

with 59% of households consuming less than 6 food groups the day prior to the dietary interview.[141]

While the habitual dietary practices reported in this study are in some respects similar to those reported among people living with HIV/AIDS in the region, care must be taken in interpreting findings of the dietary survey. The present findings were reported in the context of a supplementary feeding trial, where study participants (including their supporters) were informed on the dietary survey as part of the questionnaires they would have to be interviewed on. Food security surveys in the context of food aid are always faced with respondent bias, as respondents strive to justify their need for food aid. It is possible our study participants may not have readily understood the purpose of the dietary assessment, thereby under-reporting their actual habitual dietary practices, concerned that their habitual dietary practices may not justify the need for supplementary feeding. The "flat-slope effect" or "talking a good diet"[96] is another possibility; having met the inclusion criterion for a supplementary feeding clinical trial, wasting, some individuals may have decided to over-report their habitual dietary practices in the dietary survey that was investigating their problem, under-nutrition. This might have been the case, especially with the finding that 26% of the study participants reported having consumed flesh foods (meat, fish or poultry) the day prior to the dietary interview, an indication of a reasonably high quality diet among this population, when only 30% of individuals managed to achieve a dietary diversity score of 4 food items per day out of a standard 12-point dietary diversity score[186] indicating a poor quality diet, and arguably, food insecurity among study participants.

Additionally, the effect of the study food supplements on the participants' habitual dietary practices is a potential confounder. Study participants were instructed or counselled on supplementary feeding as an important component of AIDS therapy that enhances recovery of wasted AIDS patients, and that the purpose of the study was to determine the best form of nutritional support for wasted patients on ART programme in a typically resource-limited operational setting. It can be speculated that such information may have motivated the "food-secure" study participants to displace the intake of their habitual family foods in favour of the study food supplements. For "food-insecure" households, the study food supplements might have compromised the main food source to the study participants, so that the habitual family foods are more available to the other family members, with study participants not getting their share of the habitual family foods during their study participation, an observation reported in earlier supplementary feeding surveys.[152] In either case, the reported dietary intakes may not reflect the actual habitual dietary practices of the study participants. A comprehensive household food security survey, in addition to the 24-hour dietary interview used in the study, would provide more insight into the actual dietary practices of our study participants. However, I retain confidence in the reported habitual dietary intakes. The focus group discussions by an independent social science researcher revealed that sharing of the study food supplements with family was common in both intervention groups, an observation reported in the earlier supplementary feeding studies,[152,164] implying that the study food supplements were a major food source for the study participants and their families. This finding makes the presence of under-reporting of the habitual dietary intake rather unlikely; after "group counselling" sessions at ART initiation", which also involved study participants' supporters to promote adherence to the ART regimen and supplementary feeding by study participants, it can be speculated a study

food supplement would not “quickly” be diverted into a “common” family pot if the family was food-secure.

Supplementary feeding with either RUTF or CSB did not affect participants’ habitual dietary practices differently, and the quality of habitual diet on enrolment had no effect on outcome or on the benefit of RUTF over CSB. Additionally when the change in BMI in subgroups of those deemed to have a better or worse diet was examined, there was no difference in the response to the supplementary food observed. Thus, there was no evidence that those with a worse diet benefited more from an energy dense food than those with a better diet.

4.3 Immune response to ART

4.3.1 HIV RNA viral suppression

Viral replication was effectively suppressed in both cohorts with similar proportions of study participants, 37% of study participants in both groups achieving plasma viraemia levels <50 copies/ml, and 35.4% v 37.6% in the RUTF and CSB cohorts respectively, achieving plasma viraemia 50-1000 copies/ml. Immune response following successful ART treatment has been evaluated in a number of studies[134,194-196] and is comparable to findings of the present study. A 12-month ART study in Maputo, Mozambique in patients with average baseline BMI of 20 kg/m^2 reported undetectable viral load (<500 copies/ml) in 72% of the study participants.[194] A workplace ART programme in South Africa in patients with baseline weight of 63 kg reported viral load <400 copies/ml in 71% of ART-naïve individuals after 12 months of ART.[195] Another

community-based ART programme in a South African township reported undetectable HIV RNA level (<400 copies/ml) in 88% of patients after 3 months of therapy[134] while a South African private-sector HIV and AIDS disease management programme reported a sustained viral load suppression (<400 copies/mL) in 73% of patients whose compliance was 100% of antiretroviral drugs.[196] Together these findings suggest that in the sub-Saharan region, the level of detectable viraemia following successful ART medication is reassuringly low.

4.3.2 CD4 cell count, haemoglobin and albumin increases following phase I intervention

The study found no evidence that one form of supplementary feeding was superior to the other in ensuring increases in CD4 count, haemoglobin or albumin status following completion of phase I intervention. The mean increase (combined) in CD4 count of 157 cells × 10^6/l in participants of both cohorts on completion of phase I intervention at 3.5-month study follow-up is higher than data reported in some studies in sub-Saharan Africa.[3,4,190, 197] Similar increases in the CD4 cell count were reported in Malawi[3] and Zambia[4] but only after one year as opposed to 3.5 months of antiretroviral therapy. From other areas of the world, a study in New York City to measure the impact of ART treatments on a wide range of clinical outcomes reported a CD4 cell count increase of 66 cells x 10^6after 3 months of ART,[197] while in Vienna researchers reported an increase of 94 cells x 10^6 after 6 months of ART.[190]

The rate of immune reconstitution following successful viral suppression is influenced by a wide range of factors including a history of opportunistic infections[62] and severity of pre-ART CD4 cell depletion.[63] Individuals with previous episodes of opportunistic infections at ART initiation

have a potential for a significantly greater CD4 count increase, than those who did not.[62] In this study, as in most resource-poor settings in sub-Saharan Africa, the majority of study participants, 65% and 26%, respectively, initiated ART with WHO stages III and IV criterion of the HIV disease, respectively, stages of the disease characterised by various opportunistic infections.[179] Additionally use of the preventive CTX as a standard of care was not routine when the study commenced. Thus it can be speculated that the majority of study participants in this study have had a history of "untreated" HIV-related opportunistic infections associated with stages III and IV of HIV disease prior to ART commencement. The majority of participants of the present study commenced ART with severe CD4 cell depletion at baseline. Consistent with the concept of the severity of pre-ART immune-depletion influencing immune-re-constitution during ART,[63] the net CD4 cell count increase over baseline was much larger in patients with lower, compared to those with higher baseline values. Additionally this was a randomised comparison of the effectiveness of two different dietary regimes in wasted AIDS patients initiating ART, which was not the case in the earlier studies. Together all these conditions, i.e., the "untreated" pre-ART opportunistic infections coupled with the irregularities in the availability of the preventive CTX during the study period, the severe pre-ART CD4 cell depletion and the nutritional intervention might explain the higher CD4 cell count increases from baseline reported in the present study compared to data reported in earlier studies.

Increases in haemoglobin and albumin concentrations following phase I intervention also compare favourably with findings of two earlier investigations.[197,198] A New York City study reported increases in haemoglobin and albumin concentrations of 0.9 g/dl and 0.22 g/dl, respectively, after 3 months of ART,[209] while a study in Cameroon to assess the effect of ART in

the management of HIV/AIDS reported a negligible increase in albumin of 0.08 g/dl within 3 months of therapy.[214]

4.4 Adherence to the antiretroviral therapy and the supplementary feeding programme

4.4.1 Outcomes on adherence to ART regime

Adherence to the ART regimen was excellent in both supplementary feeding cohorts, with no suggestion one form of supplementary feeding was superior to the other. The mean adherence rates of 98% for "missed tablet yesterday" and 94% for "missed tablet last week" in both intervention groups compare favourably with earlier ART adherence studies from Baltimore (USA),[199] Cameroon [200] and South Africa.[201] In Baltimore, a 6-month observational study reported a mean 1-day and 1-week self-report adherence of 79% and 78%, respectively, and a mean 1-day and 1-week electronically-monitored adherence of 57% and 53%, respectively a far poorer medication adherence level than reported in the present study. A strong relationship existed between both measures and the concurrent HIV viral load.[199] A similar study in Cameroon reported a self-report adherence of 98% and a nevirapine drug level monitored adherence of 89%,[200] while a prospective cohort study of HIV-infected children on ART in Cape Town reported a "medication return" adherence of 94% during the first year of treatment. In this study, compliance/adherence was an important covariate associated with viral suppression.[201]

However, all forms of patient self-report adherence assessment methods inevitably over-estimate medication adherence compared with other methods of assessing adherence.[76] Nevertheless, I

remain confident in the reported level of ART adherence, as the study participants received various forms of intensified ART adherence support and close monitoring. Firstly, the trial took place in the context of the first public ART programme in a referral hospital in Blantyre, Malawi, where physicians involved in this pilot-phase public ART delivery programme were sensitive to barriers to ART adherence and played a more proactive role in supporting ART adherence. Secondly the ART adherence interview with study participants during monthly study follow up visits, and attempts to trace patients who miss scheduled study follow-up visits to ascertain their survival status, were means of reinforcing ART adherence in the study participants. Additionally the rates of ART adherence in this study compare favourably with reports from some validation studies on ART adherence which showed self-reported adherence was as good as other more sophisticated methods in predicting viral response.[199-201] Together these findings highlight the fact that a reasonable level of ART adherence is possible in sub-Saharan Africa.

4.4.2 Outcomes on adherence to supplementary feeding

Feedback from focus group discussions indicated that both RUTF and CSB food supplements were universally highly appreciated. However, nearly all participants said sharing of the study food supplements (both the RUTF and the CSB) with dependents and family members was common, although CSB was more likely to be shared than RUTF. The observation of food sharing is consistent with reports from supplementary feeding programmes that have evaluated adherence with regard to supplementary feeding. A review of feeding programmes in refugee reception centres in Eastern Sudan reported that supplementary foods were shared by all children in the family. A study from rural Malawi that compared the effect of maize- soy flour with that of

RTUF in the home treatment of moderately malnourished children reported that neither supplement was consumed in the quantities required by the intended beneficiaries; only 30% and 43% of the supplementary RTUF and maize-soy flour, respectively, provided was consumed by the intended beneficiaries.[164] The findings of the present study are additional evidence to findings of the earlier reports, that food sharing is unavoidable in any scenario of supplementary feeding in a population with largely food insecure background.

4.5 Changes in Health-related Quality of Life

There was no evidence that one form of supplementary feeding was superior to the other in improving the four health-related quality of life (HRQoL) indicators throughout the entire study period. In both intervention groups there were significant improvements in physical health and physical-mental "activity-limitation" days only during the phase I intervention, while mental health days continued to improve significantly until study completion.

The reported improvements in the health-related quality of life indicators in this study are comparable with data reported in earlier studies that have evaluated HRQoL responses following ART medication. A multicentre, randomised trial to compare the impact on quality of life of treatment with ritonavir (RTV)/saquinavir (SQV) versus RTV/SQV/stavudine reported significant improvements in quality of life regarding health distress, energy/fatigue, mental health, health perceptions, physical function and overall quality of life in both intervention groups.[202] Another open label, prospective observational study reported a significant decrease in prevalence of neuro-cognitive impairment from 81% (baseline) to 50% following six months of

ART.[203] In a study that aimed to measure changes in body cell mass and quality of life in HIV-infected individuals undergoing oxandrolone therapy, weight gain was significantly associated with an increase in overall quality of life ($p = 0.04$) and improved physical wellbeing, with trend level significance ($p = 0.05$).[193]

The present study reported that considerable proportions of study participants in both intervention groups gained weight during phase I nutritional intervention. Thus it can be speculated, that weight gain resulting from the nutritional intervention partly explains the improvement in physical health and physical-mental health "activity-limitation" which was limited to the initial phase I intervention. One difference between the earlier studies that also evaluated quality of life and the present study is that participants in the earlier studies were not getting food supplements, yet these studies reported improvements in the quality of life in HIV infected patients on antiretroviral therapy alone. Thus an alternative explanation for the improvements in the HRQoL reported in both cohorts of the present study could be the effects related to the early responses to ART, which was introduced at the same time with and administered concurrently with supplementary feeding during the phase I intervention. Given the uncertainty regarding what was responsible for the improvements in the HRQoL during phase I intervention, weight gain resulting from supplementary feeding and/or the effects of the early responses to ART which was introduced together with the supplementary feeding, a randomised controlled trial with the inclusion of a "no food supplement" intervention arm, would have helped to understand better what was responsible for the improvements.

The finding in this study of a deteriorating HRQoL in participants who commenced ART with better HRQoL indicators, on one hand, and the enhanced quality of life in those initiating ART with poorer HRQoL indicators, on the other hand, is comparable to findings of some earlier studies which evaluated changes in HRQoL in ART patients.[202,204,205] A further analysis of the multicenter randomized clinical trial referred to in the previous paragraph compared the impact on quality of life of therapy with RTV/SQV versus RTV/SQV/stavudine, in asymptomatic and symptomatic HIV-infected patients who did or did not receive antiretroviral therapy before entry into the study.[218] The analysis revealed more favourable changes in cognitive and social function in symptomatic compared with asymptomatic patients, with symptomatic patients showing an improvement and asymptomatic patients showing a decline in function after baseline. A study to determine the effect of HIV protease inhibitors on quality of life among HIV infected individuals reported significant increases in health perception, physical, role and social functioning for individuals with low baseline measures, and a significant decline in mental health, physical health, role and social functioning over the study period for those with higher pre-treatment quality of life indicators.[220] The French APROCO cohort study reported a deterioration of HRQoL at 12 months in 27% of patients with a normal baseline HRQoL, while 29% of patients with a low baseline HRQoL achieved a normal HRQoL at 12 months.[221]

It has been shown in several earlier studies that despite optimal plasma HIV-1 RNA suppression and enhancement of immune function, a subgroup of ART-treated patients exhibit a paradoxical deterioration in their clinical status[206,207] a condition known as Immune Reconstitution Inflammatory Syndrome (IRIS).[208,209] Such ART-treated patients gain a striking capacity to mount an inflammatory response[210] against microbes that had either established a subclinical

infection or had been previously treated prior to ART commencement.[211] It can be speculated the deteriorating quality of life in participants who commenced ART with better HRQoL indicators partly suggests possible IRIS[208-211] particularly in individuals commencing ART with normal HRQoL. Medication side effects and contraindications to specific ART drugs are other possible causes for the deterioration of the HRQoL. These are likely to be reported by individuals with good baseline HRQoL measures than their counterparts who were already symptomatic with bad HRQoL measures at baseline.

4.6 The significant clinical events

4.6.1 Hospitalisations

There was no evidence that one form of supplementary feeding was superior to the other in reducing the number (percentage) of hospitalisations of study participants throughout the entire study follow-up period. Hospitalisations (percentage) in both intervention groups was highest during the initial 3.5-month phase I intervention, and significantly decreased in survivors in both intervention groups over the subsequent phase II study follow-ups.

By suppressing plasma HIV-1 RNA to undetectable levels and enhancing immune function to optimally protect against opportunistic infections and HIV-related malignancies,[22-24] it was expected the introduction of ART would reduce HIV-related morbidity and improve the prognosis of patients living with HIV/AIDS. Indeed a decline in HIV-related morbidity and hospitalisation rates following ART medication has been reported in earlier studies.[212-214] A prospective cohort study in 10 American HIV clinics reported a substantial decline in

hospitalisation rates for HIV-infected patients, mainly due to reductions in AIDS opportunistic infections.[212] A multi-centre French study showed a 35% drop in both hospitalisation days following ART medication.[213] Another cohort study to evaluate hospitalisation rates in HIV infected patients showed a statistically significant decline in crude and adjusted hospitalisation rates between 1995 and 1996, corresponding to the introduction of ART.[214]

Another possible explanation for the decreasing hospitalisation rates during phase I intervention, would be the better, more consistent availability of the preventive CTX during subsequent study follow-ups compared to study commencement. Nevertheless, only two-thirds of study participants were initiated on CTX during the entire study period. Of these only 234 individuals (70.4%) were initiated on CTX either before ART or concurrently with ART commencement. Thus it can be speculated the high rate of hospitalisations in study participants during phase I intervention may partly be explained by the absence of CTX to treat the undiagnosed opportunistic infections present at study enrolment or during phase I intervention. The decline in hospitalisation rates following completion of phase I intervention can also be explained by the high "early" mortality during phase I intervention, such that the majority of the ill study participants who may have required hospitalisation died "early" in the high early mortality during the phase I intervention.

4.6.2 Mortality

The trial registered an overall mortality rate of 27% of the total study enrolments over the 12-month study period. The majority of these deaths (79%) in this high risk study population occurred in the first 3.5 months of ART intervention. High early mortality rates are common in

ART programmes in sub-Saharan Africa.[11,12] One study from a rural Malawi reported a mortality rate of 26% during the first three months of ART in patients with severe malnutrition,[11] while another study from another rural Malawi site reported a mortality rate of 14.6% in the first six months of ART,[12] half that observed in the present study. The difference between the present study and the earlier one, is that the study had as a participation criteria wasting (BMI ≤18.5) and its participants initiated ART with severe wasting, an established risk factor for mortality in patients with HIV infection. Additionally there was an irregular availability of the preventive CTX during phase I of the study, suggesting that the undiagnosed opportunistic infections present at enrolment might have been an important cause of the high mortality rate. Indeed the regression analysis performed in this study indicated lack of CTX and severe wasting (BMI <16.0) as covariates to be statistically most strongly associated with "early mortality. Survival of study participants improved substantially after completion of the phase I intervention. For survivors of the phase I intervention, mortality was 7% during the 9- month post-supplementary feeding ART follow-ups, arguably after the anthropometric recovery following completion of the 3.5-month supplementary feeding and the ART medication, and the more consistent availability of the preventive CTX. Improved survival for HIV-infected patients following ART medication has been reported previously.[25,26]

4.6.2.1 Risk factors associated with "overall" (12-month study period), "early" (phase I intervention) and post-supplementary feeding (3.5 – 12.5 – month study follow-up period) mortality.

Patient characteristics associated with "overall" (12-month study period), "early" (3.5 month phase I intervention period) and the "post-supplementary feeding period" mortality differed. The

study reported severe wasting (BMI <16.0) and severe anaemia (haemoglobin concentration <8.0g/dl) at baseline, and rapid weight gain ≥10% of original body mass at 1.5 and at 2.5 month study follow-ups were covariates significantly associated with the "overall" study mortality, male sex, "no access" to the preventive CTX, severe wasting and a lower lean body mass at baseline and rapid weight gain ≥10% of the baseline body mass at 1.5 month study follow-ups as covariates significantly associated with the high "early" mortality, and a lower lean body mass and severe immune depletion (CD4 cell count <199 cells x 10^6/l) at commencement of phase II intervention, 3.5 month study follow-up, as covariates significantly associated with the "post-supplementary feeding" mortality. Value of each of the prognostic factors is discussed below.

4.6.2.1.1 The prognostic value of BMI, Fat-free body mass and weight gain

Several earlier studies have shown baseline BMI as a factor strongly associated with survival in patients with HIV infection,[10-15] reduced survival in those with wasting, and improved survival in those not wasted at baseline. This study also found severe wasting (BMI <16.0) at baseline as a factor strongly associated with the high "early" mortality after ART commencement and with "overall" study mortality. Thus, although weight gain was achieved by study participants in both intervention groups, the nutritional intervention did not have any short-term impact on the prognosis of individuals initiating ART with severe wasting (BMI < 16.0). However, survival in study participants who completed phase I intervention improved, with only 7% deaths occurring during the 9.5 months post-supplementary feeding study follow-up period. Thus, the short-term nutritional intervention helped to ameliorate wasting, an established risk factor for mortality in HIV infection in our study participants, with the resultant improved survival in the long-term ART patient care. This finding contributes to the increasing evidence of the utility of BMI at

baseline for assessing clinical prognosis and management of wasted HIV infected patients commencing ART.[10-15]

The finding of a lower fat-free body mass in predicting subsequent mortality ("Early" mortality which was high, and the "post-supplementary feeding" mortality) is fairly consistent with earlier body composition studies that have evaluated the prognostic value of fat-free body mass in individuals with HIV-associated wasting.[131,215] Kotler et al., demonstrated that loss of body cell mass as determined by potassium-40 isotope analysis was an important determinant of increased mortality in patients with advanced HIV disease.[132] A related body composition study showed a significant association between a higher lean body mass and better physical functioning, better general health perceptions and fewer days in bed over the previous month.[215] In another study that aimed to evaluate the association between the length of hospital stay in Geneva and Berlin patient hospital admission and high fat mass index, and low fat-free mass index, and the respective value of BMI and of fat-free mass index and fat mass index for nutritional assessment, increased length of hospital stay was associated with adiposity (high fat mass index) and low muscle mass.

The prognostic value of weight gain in ART patients has also been evaluated in some earlier studies.[216,217] A clinical cohort involving Cambodian and Kenyan adults initiated on ART with BMI <18.5 reported a higher mortality rate at 3 month follow-up in those with weight gain ≤5% than those with weight gain of 5-10%, and a higher mortality rate in those with weight gain ≤5% or weight gain 5-10% than those with weight gain >10%of the baseline body mass. At 6 months follow-up, the mortality rate was higher in those with weight gain ≤5% compared with those

with weight gain >10%.[216] Another clinical cohort in Boston and Rhode Island involving HIV infected individuals enrolled in a "Nutrition for Healthy Living" study reported a weight loss of ≥10% from baseline or the previous visit as significantly associated with a four- to six-fold increase in mortality compared gaining of weight.[217]

In contrast to these earlier reports, the present study reports a paradoxical association between good weight gain (weight gain ≥10% of the baseline body mass) at 1.5 and 2.5 month study follow-ups as opposed to poorer weight gain (weight gain <10% of the baseline body mass) or weight loss, with reduced survival of the HIV infected patients on ART. One possible explanation of this clinical paradox, is the exponential decay pattern of weight gain during recovery from wasting, rapid when an individual is severely wasted and decreases as an individual approaches a normal BMI.[189] The present study reported greater and rapid weight gains experienced by study participants with severe wasting (BMI <16) at ART initiation, compared to those with mild to moderate wasting (BMI ≥16) at ART initiation, on one hand, and severe wasting (BMI <16) at ART initiation as one of the factors associated with high early mortality. Taking the two observations into account, it can be speculated the paradoxical reduced survival in study participants with greater weight gains, was actually due to their severe wasting at baseline, than due to the rapid and higher weight gains they experienced after ART initiation and nutritional intervention. Thus while the percentage weight gains in those who died were higher than the percentage weight gains of survivors, their higher percentage weight gains were calculations with reference to their severe wasting at baseline, while their absolute weight gain values may not have been clinically significant to impact prognosis in the short-term. For instance, a patient initiated on ART with BMI 13.0 and, following ART and nutritional

intervention the severely wasted patient experiences a rapid higher weight gain with a consequent higher BMI increase to BMI 15.However, despite the remarkable impact of the intervention on the primary outcome, rapid weight gain, the patient (and similar patient cases) remain severely wasted, according to the classification of severe wasting, BMI <16, a condition associated with a poor prognosis in AIDS.

Alternatively, hyper-caloric feeding studies including use of appetite stimulants in wasted HIV-infected individuals,[191,218] suggest that while weight gain in HIV infected individuals is possible, the weight gain is predominantly fat with little effect on fat-free body mass. Thus while our study participants met two of the conditions associated with rapid weight gain during nutritional intervention, wasting and the nutritional intervention, it can be speculated that the rapid weight gain of ≥10% after just 1.5 and 2.5 months of intervention, was likely to have been mainly rapid fat re-deposition. The finding in this study of the significantly higher BMI and weight gains in individuals with severe wasting compared to those with mild to moderate wasting at baseline, without significant differences in the increases in fat-free body mass between the two sub-groups makes the case stronger. Additionally, although there is no evidence that it occurred in our study participants, it may also have been the consequence of fat redistribution (lipodystrophy), a metabolic side-effect of ART medication, while the lean body mass known to be a better predictor of survival in individuals with HIV-associated wasting may not have been repleted as efficiently as the fat. Together these findings are additional evidence to the findings of earlier body composition studies, that have consistently shown lean body mass depletion as strongly associated with decreased survival in patients with HIV-associated wasting compared to other more global body composition parameters such as weight gain, and that lean body mass repletion

of clinical significance takes longer than the intervention period in the design of the present clinical trial.

4.6.2.1.2 The prognostic value of haemoglobin concentrations

Anaemia is the common hematologic abnormality of HIV disease,[39,219-221] and it is suggested the pathogenesis of HIV-associated anaemia is likely to be multi-factorial in nature. This includes HIV infection of hematopoietic stem cells/erythroid progenitors, immune system–mediated haemolysis, aplastic anaemia, malignancies, blood loss, bone marrow infections and deficiency of erythropoietin,[222] all being clinical conditions that are likely to reduce survival of individuals with HIV associated anaemia. A EuroSIDA multicenter prospective observational cohort study of 6725 patients with HIV infection from across Europe reported a marked increase in the relative hazard of death for patients with anaemia versus patients with no anaemia. A further analysis of the study revealed that mild to severe anaemia were independently associated with clinical disease progression, compared with patients with no anaemia.[223] In a Tanzanian study to examine the role of anaemia in mortality and immunologic progression among a cohort of women with HIV disease, low haemoglobin was associated with an increased risk of mortality, independent of CD4 cell count, WHO clinical stage of disease, age, pregnancy, treatment arm in the vitamin study, and body mass index.[224] The finding in the present study of a lower haemoglobin status at baseline as a factor predicting mortality in ART patients contributes to the increasing evidence of the utility of the haemoglobin status for assessing clinical prognosis and management of HIV infected patients reported previously.

4.6.2.1.3 The prognostic value of CD4 cell count

The prognostic value of CD4 cell count has been evaluated in several earlier studies. A cross-sectional analytical study on risk factors for high early mortality in patients on antiretroviral treatment in a rural district of Malawi reported a linear trend in mortality with decreasing CD4 cell count.[11] A retrospective cohort analysis of the risk factors for early mortality in children on adult fixed-dose combination antiretroviral treatment in a central hospital in Malawi reported severe immunodeficiency as one of the factors significantly associated with 3-month mortality and 6-month mortality.[12] In a study on the prevalence, incidence and mortality associated with tuberculosis in HIV-infected patients initiating antiretroviral therapy in rural Uganda, low baseline CD4 cell count was one of the factors significantly associated with mortality. In a population-based analysis of antiretroviral therapy–naive HIV-positive individuals aged ≥18 years in British Columbia who initiated triple-drug therapy, patients with CD4 cell counts <50/μL were 6.7 times (95% CI 3.61-12.34) and those with CD4 cell counts of 50/μL to 199/μL were 3.4 (95% CI, 1.93-6.03) times more likely to die than those with counts of at least 200/μL.[225] In a prospective observational cohort study to investigate the relationship between CD4+ cell response after initiation of protease inhibitors and the occurrence of opportunistic infections and survival, multivariate analysis showed each 50/μL higher CD4+ cell count at baseline was associated with a 23% reduction [95% CI, 14–30] of risk, and each 50/μL increase in CD4+ cell count during follow-up was associated with a 9% reduction (95% CI, 2–15) of risk.[226] A large observational cohort from 21 Medicines' Sans Frontiers HIV/AIDS programmes taking 3TC/d4T/NVP reported CD4 cell count 15–50 cells/ml or < 15 cells/ml as one of the factors associated with mortality.[227]

In the present study, the multivariate Cox hazard modelling returns a CD4 cell count status <199/μL at 3.5 month study follow-up as a covariate predicting the "post-supplementary feeding mortality" mortality. The majority of study participants commenced ART with severe CD4 cell depletion, with WHO stages III and IV, clinically-symptomatic stages of HIV infection characterised by opportunistic infections[179] and were on supplementary feeding during phase I intervention, all conditions favouring rapid immune reconstitution following ART initiation. Thus the finding of a lower CD4 count at 3.5-month study follow-up in predicting "post-supplementary feeding" mortality imply treatment failure in study participants who died during the post-supplementary feeding study follow-ups; despite the baseline conditions for rapid immune reconstitution following ART,[63,62,20,175] i.e., severe pre-ART immune depletion,[63] pre-ART opportunistic infections exposure[62] and the nutritional intervention,[20,175] study participants who died failed to achieve immune-reconstitution to optimally protect them against the HIV-opportunistic infections and malignancies.

4.6.2.1.4 The prognostic value of cotrimoxazole

The prognostic value of access to the preventive CTX in ART medication has been evaluated earlier, notably in studies from Malawi and Uganda.[228-230] A study to assess the feasibility and effectiveness of voluntary counselling, HIV testing and adjunctive CTX in reducing mortality in a cohort of TB patients registered under routine programme conditions in a rural district of Malawi (77% of whom were HIV positive), the adjunctive CTX was shown to reduce mortality, whereby the adjusted relative risk of death in the intervention group compared with control group was 0.81 (p<0.001).[228]Another Malawian study reported a significantly reduced mortality rate the first 6 months of ART in patients receiving ART in clinics offering CTX, compared to

patients receiving ART in clinics not offering CTX (6-month mortality risk reduction = 40.7%).[229]In a study to assess the effect of CTX on morbidity, mortality, CD4-cell count, and HIV viral load among people with HIV infection in rural Uganda, CTX access was associated with a 46% reduction in mortality, lower rates of malaria, diarrhoea and hospital admission and beneficial effects on CD4-cell count and viral load.[230]

The present study observed a high mortality rate with most of the deaths occurring during the initial 3.5 months of ART commencement, and the regression analysis indicated lack of CTX access as the covariate statistically most strongly associated with "early" mortality after ART commencement. One difference between the present study and the previous reports was the irregular availability of CTX in Blantyre during the study period. This suggests that the invasive bacterial infections might have been an important cause of mortality, an observation consistent with some studies from the sub-Saharan Africa of early mortality on ART therapy.[231-233] I speculate that the high mortality rate in this study might also have been due to undiagnosed opportunistic infections present at enrolment. Tuberculosis is highly prevalent in Malawi and an important HIV co-infection.[118,119] It often presents atypically in patients with advanced immune suppression, and can give a clinical picture of wasting syndrome. It is an important cause of mortality in the first six months of ART in patients in sub-Saharan Africa.[13] At ART initiation, the emaciated patients might have benefited from more careful clinical screening for opportunistic infections, particularly tuberculosis. The effect of supplementary feeding on ART mortality might be more remarkable in a clinical setting where optimal management of opportunistic infections take place.

4.6.2.1.5. The prognostic value of sex

The study reported male gender as one of the covariates significantly associated with the high "early" mortality. This is comparable to the finding by the large observational cohort from 21 Medicines Sans Frontieres HIV/AIDS programmes offering 3TC/d4T/NVP which reported that male gender was significantly associated with early mortality independent of other factors.[227] However, two other studies have failed to demonstrate such gender differences in the prognosis of patients on ART medication. For instance in a longitudinal observational multicentre study across Italy to assess gender differences in the long-term clinical, virological and immunological outcomes during ART, no differences were found between genders in terms of virological and immunological outcomes during long-term ART.[234] A literature review on the potential effects of sex on the course of HIV infection found little evidence for sex differences in the rate of disease progression in the pre-ART and ART era, and no substantial sex difference in the benefit of antiretroviral therapy.[235] It is possible such inconsistencies in the prognostic value of gender in ART patients are largely influenced by several other confounding factors besides gender, such as significant interactions among variables of different study protocols.

4.7 Loss to follow-up

There was no evidence one form of supplementary feeding was superior to the other in improving study participant retention throughout the entire study follow-up period. A total of 46 (9.4%) of the enrolled study participants who failed to return for a scheduled study follow-up visit for a period exceeding two months[176] were reported as "lost to follow-up". However, the study clinic central registry indicated that 28 (60.8%) of these individuals had permanently

transferred out to other newly established ART facilities. Additionally active tracing revealed that a further 12 (26%) of these individuals had in fact died within one month of their last ART clinic visit, while one participant (2.1%) had stopped ART due to psychiatric problems. Five individuals (10.8%) could not be located despite attempts at active tracing, due to the general difficulties in tracing mobile patients in a congested Blantyre sub-urban environment. Thus, the true loss to follow-up in this study constituted a total of 33 individuals (6.7% of the enrolled study participants), of whom 28 individuals were permanently transferred out to other ART facilities, and five individuals who could not be located despite active tracing.

These outcomes are in many respects similar to those reported earlier in Malawi[11,12,177,178] and Kenya.[216] An ART study in a rural district of Malawi reported a total loss to follow-up of 5.5%, with 2.5% of the total sample being transfer-outs to other ART facilities and 3% being untraceable.[11] A related Malawian study involving children <15 years of age on a split-tablet adult fixed-dose combination ART reported a "loss-to-follow-up" rate of 8.6%.[12] Another Malawian study to determine true outcomes for patients on antiretroviral therapy who were "lost to follow-up" reported a loss-to-follow-up rate of 5%,[177] and in another Malawian clinical cohort study involving tuberculosis patients, a significant proportion of patients registered as defaulters with regard to treatment for tuberculosis had in fact died.[178] An ART cohort study involving Cambodian and Kenyan adults to determine the prognostic value of weight gain at 3 months of antiretroviral therapy on 3–6 months mortality, and at 6 months on 6–12 months mortality reported a loss to follow-up rate of 2.0% in the Cambodian cohort and 6.6% in the Kenyan cohort.[216] Similar trends in the true loss-to-follow-up have been reported in ART delivery programmes elsewhere in Africa, Asia and South America, where rates of lost to follow-up the

first year of ART were 12% in programmes with active follow-up and 19% in those with no active follow-up.[133]

4.8 Strengths and limitations of the study

4.8.1 Strengths of the study

The study design utilised randomization, the crucial component of high-quality controlled trials that eliminates selection bias in the selection of study participants. The generation of an unpredictable allocation sequence of the dietary assignments and concealment of this sequence from the investigators and study staff enrolling study participants and collecting outcome measures makes the presence of bias in this clinical trial very unlikely. Additionally the randomization process ensured equal numbers of study participants in both arms, with equal distribution of potential confounders in both intervention groups.

A two-tailed test was used in the calculation of the sample size, against the uncertainty whether the newly developed RUTF regimen would be superior over the traditional CSB in the management of wasted adult ART patients. Thus regardless of the direction hypothesised, i.e., RUTF feeding effecting greater increase in the BMI and fat-free body mass in wasted adults initiating ART than feeding with CSB, possibility of the relationship in both directions, RUTF and CSB nutritional interventions was tested for.

Most of the ART registrants (96% of study-eligible ART registrants during study period) who met the eligibility criteria for study participation were enrolled and participated in the study, with good participant retention. Thus a large proportion of patients participated in the study, making the risk of selection bias in this clinical trial small. The clinical trial was undertaken in the context of the current national recommendations for supplementary feeding for wasted HIV-infected patients on ART, and as the data comes from a public ART programme setting, the findings probably reflect operational realities on the ground. For instance anthropometric assessments, i.e., BMI, MUAC, and examining patients for active WHO defining diseases constitute part of routine clinical procedures in almost all ART clinics in Malawi. Thus such procedures do not add any additional workload for clinic staff. This is an important operational consideration for settings which are often overloaded and understaffed.

4.8.2 Limitations of the study

The trial, like most operational research projects faced several constraints

4.8.2.1 Rapid ART scale-up, and the lack of a "well-nourished" control group

In 2005, when the study was planned, the study clinic was the only public ART facility in Blantyre, with a capacity of only being able to take one hundred new ART registrants per month. Thus many ART eligible individuals had to be on a waiting list for a minimum period of six months before they were actually initiated on ART. Because of this, the original study protocol had included a pre- ART nutritional intervention for the ART-eligible wasted individuals on an "ART-initiation" waiting list, to compare outcomes of patients who initiate ART with normal

nutritional status with outcomes of their counterparts who initiate ART with wasting. However, with continued nation-wide public ART programme scale-up, the capacity of the study clinic for new ART registrants improved from 100 to 150 new ART registrants per month. Consequently the waiting period for the ART-eligible individuals to initiate treatment at the study clinic decreased substantially. This resulted in the pre-ART nutritional intervention study arm being deemed unethical, as it would have meant withholding ART-eligible patients from accessing the vital therapy until they completed the pre- ART nutritional intervention follow-up period.

4.8.2.2 Lack of a "no food" control group of study participants

The clinical trial did not have a control group of participants who did not receive supplementary food, thus the trial lacks directly comparable data on wasted ART patients not receiving supplementary feeding. Again, although included in the original study protocol, ethical considerations prevented us from collecting such data, because it was national policy to give supplementary food to wasted patients with HIV/ AIDS, and historical comparisons from the study area were not available as previous studies had not collected such information. Thus, it remains uncertain what outcomes would have been for study participants not randomised to supplementary feeding. Given the modest benefit of a specialised energy-dense food supplement, which was limited to improved anthropometric recovery, these results highlight the continued need for a randomised controlled trial with the inclusion of a "no food supplement" intervention arm, to understand what benefits supplementary feeding of any type confers.

4.8.2.3 Uncertain level of adherence to the study dietary assignments

Actual utilization of the study food supplements by study participants in their homes was not monitored. Food sharing is unavoidable in any scenario of supplementary feeding in a population with a largely food insecure background. Indeed focus group discussions with participants of the present study revealed sharing of the study food supplements by dependents and family members was common in both intervention groups. Thus the degree of adherence to dietary recommendations with regard to the study food supplements remains uncertain. The sharing of the study food supplements with family members was a potential study limitation, which had designed the amounts of the study food supplements to provide 50% of the daily estimated average requirement for energy of the study participants,[156] and safely assumed this nutritionally-vulnerable group of people would be receiving the other 50% from their habitual diet. However, this was a clinical effectiveness, as opposed to an efficacy trial, to determine which of the two food supplements lead to better outcomes when provided to ART patients, in an amount that can be sustained in an operational setting with limited resources.

4.8.2.4 Lack of a validation tool for the dietary diversity score

One of the tools the study utilized to assess the quality of study participants habitual diets is the 12-point dietary diversity score.[186] However, the reference on which the score is based, is only a discussion paper,[186] and may thus compromise interpretation regarding quality of the reported habitual dietary intakes of study participants. Some description of the validation trials on the dietary diversity score would have been important, given that it is an important contextual factor of study participants.

4.8.2.5 The sample size

The data do not show a survival benefit associated with either of the study food supplements, as the clinical trial was not powered to detect differences in survival of less than 10%. The sample size allowed detection of the difference in survival of 25% with 95% specificity and 80% power. Thus, it might have failed to detect a smaller survival benefit during the intervention period. Hence direct conclusions regarding the effect of the two study food supplements on survival are not possible. A larger clinical trial powered to show differences in survival rates of 1-5% is needed, and to detect such a modest difference, a sample size of about 3,000 participants would be needed, which was not practical in our setting, and also considering the cost of the RUTF.

4.9 Generalizability of study findings

Care and consideration must be exercised in assessing the generalizability of the present clinical trial findings to other settings in sub-Saharan Africa. The trial setting was atypical, as it was situated at a well organised, functioning major referral hospital in Malawi in an urban area. AIDS patients referred to this major hospital were more likely to have severe, advanced, complicated HIV disease requiring advanced care, and perhaps less likely to benefit from supplementary feeding. The case fatality rate in this study was higher than that reported in other ART studies from the sub-Saharan Africa. This was particularly the case when the study commenced in 2006. In contrast, the majority of ART delivery facilities in the sub-Saharan Africa including Malawi are in peripheral rural health centres with modest patient care facilities and resources. AIDS patients referred to such ART facilities are more likely to have less severe and less complicated HIV disease. In aetiological terms malnutrition (under-nutrition) is

considered “primary” when it is largely due to sub-optimal dietary quantity and quality, or “secondary” when it is largely a consequence of chronic infections.[19-21] Thus the performance of supplementary feeding in such settings caring for less complicated cases with a lower case fatality rate, and where poverty and food insecurity are more prevalent, is likely to be different from settings caring for patients with severe, advanced, complicated HIV disease requiring advanced care, and perhaps less likely to benefit from supplementary feeding. This warrants further operational research.

4.10 What was already known on the study topic?

HIV associated wasting remains a significant clinical problem in people living with HIV infection even in the era of ART. Thus supplementary feeding for wasted HIV infected individuals has become an increasing public health and political emphasis in recent years. Wasted HIV infected patients in sub-Saharan Africa are commonly given supplementary food. Programmatically the cost of supplementary feeding is considerable for HIV treatment programmes in sub-Saharan Africa where wasting is seen in some 50% of HIV infected patients.

4.11 What the present study adds

Short-term supplementary feeding with RUTF has modest clinical benefits; more rapid/ efficient anthropometric recovery in HIV infected individuals with pre-ART anthropometric compromise (under-nutrition), than those fed with CSB. No differences were observed in survival, CD4 count, HIV RNA viral load suppression, adherence to antiretroviral therapy or quality of life

between the two intervention groups. To my knowledge this clinical trial is unique; it is the first randomised controlled comparative clinical effectiveness trial to assess the performance of selected supplementary feeding strategies in wasted adult AIDS patients commencing ART, in a typically resource-limited setting where wasting in HIV infection is seen in 50% of treatment naïve patients. While there are several observational reports of nutrition support in ART programmes, there are no randomised controlled trials on nutrition intervention protocols in ART programmes. This sets the present clinical trial apart.

CHAPTER 5.0 CONCLUSIONS

Short-term supplementary feeding with an energy dense food supplement promotes better anthropometric recovery including improved BMI, fat-free body mass and MUAC gain, compared to feeding with CSB over a 3.5 month period. Higher BMI 3.5 months after the start of nutritional intervention and ART improved survival of patients one year thereafter. While supplementary feeding with RUTF can ameliorate an established risk factor for mortality, BMI, the effect on BMI is sustained only during the feeding intervention period, and there was no evidence that this advantage conferred any other benefits to ART patients during the nutritional intervention period, or for the 9 months thereafter, as HRQoL, ART adherence, survival and other clinical outcomes were similar between the two intervention groups.

CHAPTER 6.0 POLICY IMPLICATIONS OF THE STUDY FINDINGS

Based on current trends, even if rates of HIV transmission are reduced and ARVs become more widely available, many millions of people will continue to be infected with HIV,[1]TB,[118,119] and experience malnutrition.[16,117,123] The present study evaluated the value of supplementary feeding with two different dietary regimes in the public health response to AIDS in a typically resource-constrained setting in an era of increasing access to antiretroviral therapy. The study has provided information about the most effective dietary formulation and models for integrating nutritional support in ART programmes, RUTF, best practices for nutritional assessment and strategies to improve outcomes in adult ART programmes. To deliver an intervention that is effective in managing a life threatening disease such as HIV infection, health care practitioners must work within the health care system that delivers care appropriate to beneficiaries' needs. Thus nutritional guidelines should be developed in collaboration with guidelines for ART.

6.1 The two food supplements used in the clinical trial were well tolerated by the HIV infected adults on ART, and none of the study participants in either of the intervention groups had to stop supplementary feeding due to adverse effects or contraindications, suggesting that with responsible implementation, either of the two food supplements are a potential key component of a comprehensive ART response in resource limited settings. Nevertheless, feeding with the energy dense RUTF promoted better anthropometric recovery than feeding with CSB, including BMI and lean body mass - established independent predictors of survival in individuals with HIV associated wasting. -. Hence for programmatic decision making regarding integrating

nutrition interventions in ART programmes in resource-limited settings, RUTF-based intervention is probably the more effective strategy.

6.2 The World Health Organization (WHO) recommends increasing energy requirements by 30 percent for clinically symptomatic HIV adults. However it must be born in mind, that planning rations is only part of a larger process of programme design, and success of the programme depends on several factors, such as the intervention model, (i.e., therapeutic versus supplementary feeding or wet "on-the-spot" versus dry "take-home rations), the delivery channels, the beneficiaries' household food security situation, the duration of support, etc. Hence nutritional intervention programmes should be designed through a process that considers the needs of the beneficiaries, as well as the practical concerns that dictate the feasibility of implementing such interventions.

6.2.1 Typically, patients with active HIV disease (WHO stages III and IV) experience a combination of clinical conditions (including illness-associated anorexia) that may result in weight loss with eventual wasting and associated mortality if energy intakes are not increased or energy expenditures decreased. Thus for such high-risk groups, the "supervised" therapeutic feeding using the energy-dense RUTF formulation should be considered an integral part of in-patient care for the anorexic patient admitted for HIV-related illnesses or during convalescence between infective episodes, to ensure the intended beneficiary gets the recommended daily allowance for energy, including any additional demands. An added advantage to the suggested intervention model is that assistance would be available for patients too sick to eat, or patients unfamiliar with the non-traditional, specialised dietary regimen.

6.2.2 The finding in the present study, that nearly all study participants from both intervention groups reported sharing their study food supplements with dependents and family members has important implications. Food sharing is unavoidable in any scenario of supplementary feeding in a population with a largely food insecure background, such that patients receiving individual rations will share it with family members, resulting in inadequate nutritional support to meet the increased requirements for the intended patient. Thus special considerations have to be made, i.e., the overall household food security situation of the programme beneficiary should help determine whether the ration should be strictly based on the needs of the intended beneficially or the entire household of the beneficiary.

A combination of intervention models can be utilized in the programme design. For example "food-by-prescription",[236] i.e., the food supplement prescribed like medicine for the patient, which may be easier with the "specialised" medicinal energy-dense RUTF,[90,157] and where food insecurity affects the entire household "food rations" made available to the other household members, which may be appropriately done with the traditional CSB. The benefits of RUTF-based intervention over CSB-based intervention reported in the present study are arguably not overwhelming. In fact it is possible, that although feeding with RUTF was found to result in greater anthropometric recovery than feeding with CSB, given the greater sharing with family members reported in the CSB compared to the RUTF intervention, if the analysis accounted for this, it is possible CSB would be as good as, or even better than RUTF for study's primary outcomes. Hence a cost-benefit analysis between RUTF and CSB feeding should be considered. For instance for the same cost as RUTF, an entire family (including the intended beneficiary) could be substantially supported with CSB; in fact by helping household members maintain

productivity and income generating ability, provision of household rations as part of the "targeted" nutrition intervention package indirectly benefit the patient as well, or for the same cost as RUTF, CSB intervention can be given for three times longer.

6.2.3 Evidence is lacking and no consistency exists between different food aid agencies, regarding policy on the optimum duration for effective nutritional support possible in HIV care in the sub-Saharan Africa, and largely depends on individual programme's capacity. Within the context and limitations of the present study, supplementary feeding with a specialised energy dense food supplement promoted better anthropometric recovery including BMI and fat-free body mass in wasted HIV infected patients initiated on ART compared to feeding with CSB over a 3.5 month intervention period. A high "early" mortality was observed followed by substantial improvement in survival of the ART patients one year thereafter. Together these findings have important programmatic implications on the timing and duration of targeted nutritional interventions with regard to ART care.

6.2.3.1 Included in the pre-ART services in HIV care guidelines is the staging of the HIV disease progression in individuals with established HIV infection, and management of the various HIV-related opportunistic illnesses. The finding of a high "early" mortality despite the intervention in HIV infected individual who were initiated on ART with severe wasting (BMI < 16.0), and improved prognosis of the survivors following the 3.5-month supplementary feeding have very important programmatic implications; targeted supplementary feeding of individuals with a pre-ART anthropometric compromise (BMI <18.5) should be an integral part of the pre-ART care, alongside optimal management of opportunistic infections, to treat wasting before ART initiation, when patients are in a

fairly clinically stable condition to benefit from such initiatives, than having ART initiation as an admission criteria for supplementary feeding, as was the case with the present clinical trial.

6.2.3.2 The finding that fat-free body mass status remained a covariate significantly associated with the "post-supplementary feeding" mortality suggests that while the initial supplementary feeding improved anthropometric status including BMI and fat-free body mass, adequate fat-free body mass repletion of clinical significance may need a longer period of intervention than 3.5-month, before and / or after ART initiation.

6.3 About a quarter of the study participants were TB co-infected at ART initiation and study commencement. HIV and TB are important co-infections in sub-Saharan Africa,[118,119,123] and the two infections are independently associated with wasting, a clinical condition associated with early mortality in HIV infection. However, despite the overlapping epidemiology, to date national efforts to manage HIV,[179] and TB,[180] have largely been separate endeavours. Programmes to manage HIV-associated wasting will not realise their full potential if they fail to manage the competing cause of wasting in HIV infection. There is an urgent need for stronger HIV/TB collaborative activities, including integrating successful nutritional intervention models in the HIV/TB programmes, to control wasting more effectively and achieve shared goals of successful treatment.

6.4 Despite the proven importance of nutrition in the management of HIV disease, to date, there is very limited investment in the nutritional assessment capacity in many ART treatment

centres in Malawi. For instance proper nutritional monitoring and evaluation of AIDS patients is not part of the routine ART care. Instead the indicators used to monitor and evaluate the effectiveness of ART programmes, while equally important, are largely ART-specific,[167] i.e., the number of staff trained and accredited in use of ARV drugs, Given the proven prognostic value of the BMI in HIV infection, there is an urgent need to integrate routine anthropometric monitoring in HIV care, to detect and manage the HIV associated wasting timely.

Additionally, it is often assumed ART will ameliorate nutritional deficiencies. However evidence suggests this is not always the case.[237,238] While ART delays the clinical progression of HIV infection, and may thus reduce the risk of malnutrition, lipodystrophy (fat redistribution) is an established metabolic side effect of ART. Lipodystrophy masks on-going malnutrition of lean tissue wasting, body composition factor that has a stronger prognostic value for survival in patients with HIV-associated wasting than the total whole body weight. The finding in the present study of a lower fat-free body mass at baseline and at 3.5 month study follow-up being co-variants significantly associated with high "early" and "post-supplementary feeding" mortality, respectively, makes the case for best practices in nutritional assessments and referrals for adult HIV care strong; a more sophisticated anthropometric monitoring, i.e., body composition assessments using bioelectrical impedance integrated in ART delivery programmes is necessary, to detect and manage lean tissue wasting in HIV wasting timely.

6.5 The Malawi government has a task to address the high "early" mortality and improve the overall programme outcomes, particularly the credibility of the ART programme in the eyes of patients, health workers and the communities at large as it scales up the community-based ART

programmes. Identification of factors such as less and/or inconsistent CTX access, severe wasting (BMI <16.0) at baseline and rapid weight gain of ≥10 % following ART initiation in individuals with severe wasting (BMI <16.0) at baseline, lower fat-free body mass percentage of body composition, severe anaemia, severe immune depletion, etc. as strongly associated with "high" early mortality after ART commencement, on one hand, and the positive association observed between improvements in these prognostic factors following phase I intervention and improved survival one year after ART commencement, on the other hand, is a potentially important finding. Such factors could be important prognostic markers for national HIV monitoring, and patients with such conditions should be highlighted as "high-risk" groups that should trigger explicit, additional follow-up and care over the first weeks of ART initiation.

CHAPTER 7.0 TARGETS FOR FUTURE RESEARCH

7.1 While supplementary feeding is perceived as a potential key component of a comprehensive ART response to improve outcomes of individuals with HIV-associated wasting in resource limited settings, the cost to programmes of providing food support may be considerable. For instance while the RUTF and CSB provided in the present study cost $16.0 and $5.40, respectively, per patient per month, it must be born in mind that the cost of a food supplements is just a portion of the total cost of programme planning; Other expenses include staff to manage the feeding programme, i.e., screen patients for eligibility, dispense the food supplements, monitor patients' progress etc., and the various logistical challenges. Thus while the cost of actual food supplements are not substantial when overall costs of the ART programme is considered, the overall cost of an HIV feeding endeavour may well be. Hence formal cost-benefit analyses or effectiveness are required to determine whether HIV feeding strategies are cost effective when compared with other elements of clinical care given to those with HIV-associated wasting the sub-Saharan Africa.

7.2 Currently in Malawi the cost per kg of RUTF of the ingredients are as follows: milk powder $0.63, icing sugar $0.17, peanut butter $0.18, oil $0.18 and vitamins/minerals $0.26, a total of about $1.40/kg, compared to the fortified CSB which costs CSB $0.47/kg (Manary M, personal communication).The CSB intervention cost the study $5.40 per patient per month, while RUTF was three times as expensive, at $16 per patient per month. Thus while the study shows that RUTF is superior to CSB in effecting anthropometric recovery in wasted ART

patients, RUTF was a relatively expensive specialized food. As such, an area of concern is the sustainability of such an intervention in a typically resource-constrained ART delivery system like Malawi has, with about a third of all adult ART registrants wasted, and where sustained demand is likely. Further investigation of the alternative ingredients for this vital food formulation is required, to overcome this limitation.

The RUTF formulation used in the present clinical trial was a relatively expensive specialised dietary regimen which was 30% milk powder, a significant amount and the most expensive ingredient of the formulation. However one attractive notion about RUTF technology is the flexibility of the recipe, which can be adapted to incorporate less expensive ingredients and specific nutritional needs.[157] As such similar energy-dense specialised foods can be formulated without the milk ingredient, at a cost roughly 50% of the current RUTF cost (Manary M, personal communication). Additionally fortification levels of each nutrient are adaptable to compensate for the poor bioavailability of minerals in the alternative RUTF formulations where milk substitutes of low nutrient bioavailability are used. For instance a soy-based spread highly fortified with iron and minerals was tested to prevent anaemia and stunting in Saharawi children aged 3-6 years.[239] Modified cheaper RUTF formulations without milk powder would increase availability of the vital food supplement at virtually no additional cost compared to the milk-based RUTF formulation. Given the modest benefits reported with RUTF-based management of the wasted HIV infected patients, i.e., greater anthropometric recovery but lack of effect on morbidity and mortality in adult ART clients, clinical comparative effectiveness trials are needed to evaluate the value of the less expensive non-milk based RUTF formulations, before they are considered substitutes for the current milk-based RUTF formulation.

7.3 Evidence suggests that PI-containing regimens improve nutritional status of patients with HIV-associated.[237,238] Given this, the ART itself in the present clinical trial had the potential of contributing as much too at least one of the primary outcomes, increase in the BMI, as the supplementary feeding. The potential contribution of the PI-containing regimens in the other study primary outcome, increase in the fat-free body mass remain controversial as considerable evidence [94,191,218]suggests that the weight gain following ART is mainly derived from an increase in fat mass. However, due to ethical considerations the present clinical trial whose participants, wasted and from a largely from a food-insecure background, was not allowed to have a control group of participants not receiving supplementary food, to single out the effects of ART on the nutritional status of AIDS patients with HIV-associated wasting. Thus it remains uncertain what outcomes would have been for ART patients not receiving supplementary feeding. Given the modest benefit of the specialised energy-dense food supplement reported, which was limited to improved anthropometric recovery, this highlight the continued need for a randomised controlled trial with the inclusion of a "no food supplement" treatment arm, to understand what benefits supplementary feeding of any type confers. Given that RUTF is considered superior to CSB, perhaps looking at the duration of RUTF intervention, i.e., randomizing the wasted ART patients into different durations of intervention, may help isolate more substantially the role of supplementary feeding on the primary outcomes such as the BMI and body composition.

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APPENDICES

APPENDIX A STUDY ENROLLMENT FORM

Date ☐☐/☐☐/☐☐☐☐

Inclusion criteria

WHO stage III or IV or CD4 count < 200 cells/ mm^3	☐ Yes ☐ No
Body Mass Index (BMI) < 18.5	☐ Yes ☐ No
Age ≥ 18	☐ Yes ☐ No
Starting ARV therapy in QECH	☐ Yes ☐ No

Exclusion criteria

Involvement in a Supplementary Feeding Programme	☐ Yes ☐ No
Pregnancy / Breastfeeding	☐Yes ☐ No ☐NA
Patient eligible	☐ Yes☐ No

Study staff (initials) …….

STUDY NUMBER (If eligible) ☐☐☐

APPENDIX B CONSENT FORM AND PARTICIPANT INFORMATION SHEET



UNIVERSITY OF MALAWÎ

Principal

Prof. R.L. Broadhead, MBBS, FRCP, FRCPCH, DCH

College of Medicine

Private Bag 360

Chichiri

Blantyre 3

Malawi

Our Ref.:

Telephone: 677 245

677 291

Your Ref.:

Fax: 674 700

Telex: 43744

Study title: Randomized controlled trial comparing the impact of supplementary feeding with either ready-to-use food or corn-soy blend among malnourished anti-retroviral therapy clients in Malawi.

Sponsors: United States Agency for International Development (US AID – FANTA and the AIDS CARE Research in Africa (ACRiA) Joint Clinical Research Centre.

Investigator: MacDonald Joseph Ndekha M.Sc

Institution: University of Malawi College of Medicine

Day time and after hours telephone numbers: +265 09 205 448 / +265 09 922 682

Hello, my name is_____I would like to invite you to consider taking part in the research on the supplementary feeding protocols for adult AIDS patients undergoing antiretroviral therapy (ART), who are also underweight. Your participation in this study is entirely voluntary.

1.0 The purpose of the study; This study tries to determine the best form of nutritional support which when given together with the AIDS medicines enhances your recovery, and we are not sure whether a specialized nutrient-dense food supplement, is better than a cereal/legume supplement".

2.0 Procedures; The eligible participants will be the wasted adult AIDS patients starting ART. If you agree to participate, you will first be examined to see if you qualify for the study.

2.1 You will then be allocated, by a spin of a coin, to one of the two forms of nutritional support; the specialized nutrient-dense peanut-based ready-to-use food supplement, or the Cereal/legume food supplement. And since I will be assessing your health regularly, I will not know which treatment group you are in. The procedure helps ensure that the information gathered during the study is accurate.

2.3 Before receiving your assigned form of nutritional support;

2.3.1 You will be asked some questions about yourself, your home and your illness.
2.3.2 You will be weighed with a scale, measured with a height board, and have your body composition measured by a small machine attached to your body with safe and painless small sticky patches.
2.3.3 About 1 teaspoon of your blood sample will be drawn to measure the strength of your immunity, how severe your disease is, and your nutritional status.

2.3.3.1 Risks associated with blood drawing procedures;

The Venipunctures (i.e. drawing blood) are normally done as part of routine medical care. However, the procedure presents a slight risk of discomfort, and may result in bruising or bleeding at the puncture site and inflammation of the vein. There is also a slight possibility of infection. Your protection in this study is that materials will be available to maintain sterile conditions during the collection of blood samples, and only certified nurses/trained health personnel will collect the blood samples using universal precautions under sterile conditions. Patients will have the right to refuse the collection of these samples at any time during the study.

3.0 Unforeseen risks of the study foods supplements; The food supplements used in the study have been used in the standard treatment of childhood malnutrition in most hospitals in Malawi without any problem. However, it is possible some participants may be allergic or sensitive to components of the peanut-based ready-to-use food and the Corn-Soy Blend food supplements. In this study, symptoms of allergy will be monitored during follow-up visits, and should any such problem occur during your participation in the study, you should immediately contact me and the food will be discontinued.

4.0 The Benefits; There are no specific benefits to you from your participation in this study. But results of your participation in this study will help develop better treatment protocols for the adult AIDS patients like you, who are below their expected weight.

5.0 Alternative treatment available; The standard AIDS treatment is a combination of three antiretroviral drugs; nevirapine, stavudine and lamivudine, in a fixed dose to all eligible AIDS patients who express willingness and readiness to take ART adherently.

5.1 Benefits of the Standard alternative treatment;

If you decide not to take part in this study you will still receive the best current care, from your usual doctor. However, this may not include the study nutritional support.

5.2 Risks of the Standard alternative treatment;

Weight loss in AIDS can be caused by increased body demand for food without concomitant increase in dietary intake, diarrhoea, and other opportunistic infections. This increases mortality risk for any person fighting a chronic disease, such as HIV/AIDS, especially when accompanied by under nutrition.

6.0 The length of the study and the number of participants involved; The study will be performed at Queen Elizabeth Central Hospital ART clinic, in Blantyre, Malawi;

6.1 The study will involve 450 participants randomly allocated into two forms of nutritional support, 225 participants in each.

6.2 The period required for your participation is one follow-up visit per month in conjunction with the monthly ART clinic for 12 months. At each of these follow-up visits;

6.2.1. You will be asked about your quality of life, clinical symptoms and any clinical event indicative of a complication, such as hospitalisations, health centre visits, or new medications that have occurred in the previous month.

6.2.2 You will undergo weight, height and body composition measurements.

6.2.3 Blood samples of about 1 teaspoon each will be drawn upon admission, and after 3 months, thus a total of 2 teaspoons of blood will be collected over the course of the entire study.

6.2.4 A food frequency questionnaire about the foods you eat will be administered to you twice, upon your admission into the study, and after three months during your monthly ART clinic visit. These questions will take approximately 10 minutes to answer.

6.2.5 After 3 months of Nutritional support, I would ask you to join a 30-minute group discussion with about 10 other people who are also part of the study. This is to explore how you are using the study food supplements.

6.3 The nutritional support will be given for a total of 3.5 months.

6.4 An additional 7 months of follow-up will be conducted in the same manner with the other visits, using the same clinical assessments, except no study nutritional support will be distributed. Thus the total amount of time required for your participation will be 12 months.

7.0 Restrictions regarding participation in the study; If you are pregnant or breastfeeding or planning to become pregnant during the study period, you may not take part in this study.

7.1 Pregnancy is associated with weight gain which will be a confounding factor in the study primary outcomes (BMI, and fat free body mass),

7.2 Lactation is associated with an additional energy requirement of 500kcal/day. All these will make it difficult to assess the effect of a food supplement.

8.0 Interaction; Current decisions regarding supplementary feeding in AIDS patients are based on expert judgement rather than evidence. However, the decisions do not specify the right type of food supplement, which ART patients should receive the supplement or how much. To answer this question properly, it is important that you should not be registered with any other supplementary feeding programme. If you have to, please, inform me immediately. And if you are already on another supplementary feeding programme, it is important that you let me know, and how long you have been registered with that programme.

9.0 Rights as a participant in this study; Your participation in this study is entirely voluntary. You are free to decline participation or stop at any time without stating any reason, and those not participating will not be affected in their ability to receive ART and other normal clinic services to which they are entitled to. However you must inform me if you wish to stop taking the supplementary foods, so that I will supervise any discontinuation with your health as first priority. Other than non-participation, there are no alternatives.

10.0 Rights of a study doctor in this study; I retain the right to withdraw you from the study if circumstances arise (such as non-compliance with the protocol you have agreed to follow, if you did not give an accurate history or did not follow the guidelines and the regulations of the study facility, or non-tolerance of a study foods) which warrant doing so.

11.0 Emergency care and hospitalisation; This study is not intended for the purpose of diagnosing or treating any medical problems not specifically stated in the purpose of the study. If you feel you are injured because of the study, please contact me or the Human Studies Committee Chairman, and the study will strive to reduce, control and treat any complications from this research.

12.0 New findings; You will be informed of any significant new findings developed during the course of your participation in this research that may have a bearing on your willingness to continue in the study.

13.0 Financial arrangements; There is no cost to the participants; the research project will pay for all the food supplements, study procedures and reasonable medical expenses you may incur as a direct result of participation in this study, as determined by the sponsor and me.

13.1 You will not be paid to participate in this study.

14.0 Ethical approval; The study has been structured in accordance with the International recommendations guiding doctors in biomedical research involving human participants. A copy may be obtained from me should you wish to review it.

14.1 The study has been reviewed by the University of Malawi College of Medicine Research Ethics Committee, the Human Research Ethics Committee of the University of the Witwatersrand and the Human Studies Committee of the Washington University School of Medicine, and ethical approval has been granted by these Committees.

14.2 This study is sponsored by the United States Agency for International Development (US AID) – Food and Nutrition Technical Assistance, and the Aids Care Research in Africa (ACRiA) Joint Clinical Research Centre).

14.3 I do not have any financial or personal interests with these organisations that may bias my actions.

15.0 Source of additional information; For the whole study period, you will be under my care.

15.1 At any time between your visits you have any questions, please do not hesitate to contact me at my 24-hour telephone number +265 09 205 448

15.2 Doctors from this Department working on this study are: Dr. Mark Manary who may be contacted at +265 09 921 656, and Dr. Joep van Oosterhout who may be contacted at +265 09 922 682.

15.3 If you want any information regarding your rights as a research participant, or complaints regarding this research, you may contact Prof. Eric Borgstein, (Tel: +265 08 823 381), Chair of the University of Malawi College of Medicine Research Ethics Committee which is an independent committee established to help protect the rights of research participants.

16.0 Confidentiality; All reasonable measures to protect the confidentiality of your health record and identity will be taken.

16.1 Sample numbers will be recorded on patients' coded data sheets for the purposes of accurate analysis of results,

16.2 All hospital records, personal and research data will be kept strictly confidential, and no potentially identifying information will be recorded on the blood samples themselves.

16.3 Data that may be reported in scientific journals will not include any information that identifies you as a participant in this study.

16.4 However there is a possibility that your medical record, including identifying information, may be inspected and photocopied by domestic and foreign regulatory health authorities, like the Government Health Officials, University Human Studies Ethics Committee, as well as your personal doctor. These records will be utilised by them only in connection with carrying out their obligations relating to this clinical study.

16.5 Any information uncovered regarding your test results or state of health as a result of your participation in this study will be held in strict confidence.

16.6 You will be informed of any finding of importance to your health or continued participation in this study but this information will not be disclosed to any third party other than the ones mentioned above without your written permission. The only exception to this rule will be cases where a legal duty of notification of the Department of Health exists. In this case, you will be informed of my intent to disclose such information to the authorised state agency.

INFORMED CONSENT:

I hereby confirm that I have been informed by the study doctor, M. J. Ndekha, about the nature, conduct, benefits and risks of the clinical study on the Supplementary feeding protocols for the underweight HIV-infected adults on ART Protocol Number P 04 / 05 /350. I have also received, read and understood the above written information (Participant Information Leaflet and Informed Consent) regarding the clinical study. I am aware that the results of the study, including personal details regarding my sex, age, date of birth, initials and diagnosis will be anonymously processed into a study report. In view of the requirements of research, I agree that the data collected during this study can be processed in a computerised system by Mr. M. J. Ndekha, Dr. Mark Manary, Dr. Haroon Saloojee and Prof. John Pettifor.

I may, at any stage, without prejudice, withdraw my consent and participation in the study. I have had sufficient opportunity to ask questions and (of my own free will) declare myself prepared to participate in the study.

PARTICIPANT:

Printed Name Signature / Mark or Thumbprint Date and Time

I, .M. J. Ndekha, herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

STUDY DOCTOR:

Printed Name / Signature

TRANSLATOR/OTHERPERSON EXPLAINING INFORMED

CONSENT……DESIGNATION):

Printed Name Signature Date and Time

WITNESS (If applicable):

Printed Name

APPENDIX C PARTICIPANT DEMOGRAPHIC CHARACTERISTICS

PLEASE CIRCLE OR WRITE THE CORRECT ANSWER

Name_____Study number_____QECH ART number_____

Date of birth: _____/_____/_____ Age_____(yrs) Sex: M / F

Village / Township:_____

Direction to _____

_____

Name of identifiable guardian:_____

Total No. of people living with you in your household:_____Adults_____Children

Head of household: Myself Other (specify relationship)_____

Marital status: Married Single Widowed Other (specify)_____

Highest education attained: Some primary school, Primary School Leaving Certificate, Junior Certificate of Education, Malawi School Certificate of Education, University Degree, Other (specify)_____

Employment status: Unemployed Employed (specify)____Self employed (specify) _____

Number of people participate who in the economical support of your household:_____

Does the household posses any: Radio Bicycle Car Mattress Electricity

Source of drinking water: Borehole Public supply Stream Well

Roofing material your house made of: Harvey Tiles Tile Tin Thatch

APPENDIX D MASTER STUDY CLINIC FOLLOW-UP CHART

PLEASE CIRCLE OR WRITE THE CORRECT ANSWER

Hospital ART No_____Study number:_____Name:_____

Criteria for ART: WHO stage III WHO stage IV CD4<200

Dates of ART commencement:

1st-line regimen__/__/__Alternative 1st-line regimen__/__/__ 2nd-line regimen__/__/__Height___ ___ ___

Follow-ups	Date	Weight (kg)	MUAC (cm)	Waist (cm)	BIA		Food given	Blood drawn	Hospitalisations	Pregnancy check	Clinical comments
Enrolment											
0.5-mo											
1.5-mo											
2.5-mo											
3.5-mo											
6.5-mo											
9.5-mo											
12.5-mo											

Outcome status: Alive Dead Defaulted Stopped meds/food Transfer-out

3.5-month follow-up visit questions:

How long did the study food last: ____Days____Weeks _____Month

Did the food supplement last long enough: Yes No

APPENDIX E I CDC HRQoL – 14 HEALTHY DAYS MEASURE

STUDY NUMBER_____

1. 0 Health Days Core Module : CDC HRQoL – 4		
1.1 Would you say that in general your health is;	Excellent	1
	Very good	2
	Good	3
	Fair	4
	Poor	5
1.2 Now thinking about our physical Health, for how many days during the past 30 days was your physical health not good	A: Number of days	_____Days
	B: None	
	C: Don't know/not sure	
	D: Refused	
1.3 Now thinking about you're your mental health, which includes stress, depression, and problems with emotions, for how many days during the last 30 days, was your mental health not good.	A: Yes	_____Days
	B: None	
	C: Don't know/Not sure	
	D: Refused	
1.4 During the past 30 days, for about how many days did poor physical or mental health keep you from doing your usual activities, such as self-care, work, or recreation?	A: Yes	_____Day
	B: None	
	C: Don't know/Not sure	
	D: Refused	

APPENDIX E II CDC HRQoL – 14 HEALTHY DAYS MEASURE

STUDY NUMBER_____

Activity Limitation Module – 5		
1. Are you LIMITED in any way in any activities because of any impairment or health problem?	A: Yes	
	B: No	Go to Q1: Healthy Days Symptoms Module
	C: Don't know	Go to Q1 of Healthy Days Symptoms Module
	D: Refused	Go to Q1 of Healthy Days Symptoms Module
2. What is the MAJOR impairment or health problem that limits your activities?	A. Arthritis/rheumatism	
	B. Back or neck problem	
	C. Fractures / joint injury	
	D. Walking problem	
	E. Lung/breathing problem	
	F. Hearing problem	
	G. Eye/vision problem	
	H. Heart problem	
	I. Stroke problem	
	J. Hypertension/high blood pressure	
	K. Diabetes	
	L. Cancer	
	M. Depression/anxiety/emotional problem	
	N. Other impairment/problem	
	O. Don't know/Not sure	
	P. Refused	
3. For HOW LONG have your activities been limited because of your major impairment or health problem?	A. Days	
	B. Weeks	
	C. Months	
	D. Years	
	E. Don't know/Not sure	
	F. Refused	
4. Because of any impairment or health problem, do you need	A: Yes	
	B: No	
	C: Don't know	

the help of other persons with your PERSONAL CARE needs, such as eating, bathing, dressing, or getting around the house?	D: Refused
5. Because of any impairment or health problem, do you need the help of other persons in handling your ROUTINE needs, such as everyday household chores, doing necessary business, shopping, or getting around for other purposes?	A: Yes
	B: No
	C: Don’t know
	D: Refused

APPENDIX E III CDC HRQoL – 14 HEALTHY DAYS MEASURE

Healthy Days Symptoms Module - 5		
1. During the past 30 days, for about how many days did PAIN make it hard for you to do your usual activities, such as self-care, work, or recreation?	A: Yes	_____Days
	B: No	
	C: Don't know	
	D: Refused	
2. During the past 30 days, for about how many days have you felt SAD, BLUE, or DEPRESSED?	A: Yes	_____Days
	B: No	
	C: Don't know	
	D: Refused	
3. During the past 30 days, for about how many days have you felt WORRIED, TENSE, or ANXIOUS?	A: Yes	_____Days
	B: No	
	C: Don't know	
	D: Refused	
4. During the past 30 days, for about how many days have you felt you did NOT get ENOUGH REST or SLEEP?	A: Yes	_____Days
	B: No	
	C: Don't know	
	D: Refused	
5. During the past 30 days, for about how many days have you felt VERY HEALTHY AND FULL OF ENERGY?	A: Yes	_____Days
	B: No	
	C: Don't know	
	D: Refused	

APPENDIX F 24-HOUR DIETARY RECALL INTERVIEW

STUDY NUMBER_____

Food item / dish / beverage	Daily	Weekly	Monthly	Rarely

APPENDIX G STUDY BLOOD SAMPLES

Study period	Blood sample	Specimen storage	Laboratory test
Enrolment	2 - 3 ml EDTA	N/A	CD4 (FACS Count) and Full Blood Count
	2 - 3 ml Clotted	Serum at - 80^0 C	Serum albumin
	2 – 3 ml EDTA	Serum at - 80^0 C	N /A
3.5-mo follow-up	2 - 3 ml EDTA	N/A	CD4 (FACS Count) and Full Blood Count
	2 - 3 ml Clotted	Serum at - 80^0 C	Serum albumin
	2 – 3 ml EDTA	Serum at - 80^0 C	HIV viral load (Roche Amplicor®; Roche, Basel. Switzerland; detection level 48 copies/mL).

EDTA = ethylenediaminetetraacetic acid = purple top test tube.

APPENDIX H FOCUS GROUP DISCUSSION GUIDE

Think back to when you were identified as a beneficiary of the feeding programme; how is your life different after the supplementary feeding programme?

Which food supplement were you allocated on?

4. Have you been able to use the food supplements? (probe on the comments on taste and acceptability of either of the food supplements).

Have you encountered any problems in using any of the food supplements?

Did you do anything to counter any such problem?

Have you had any support/encouragement in using the food supplement? (explain the support and who provided the support).

Let us focus on what it means to take a food supplement at home (probe how the food supplement is used at home).

Do family members understand why you were given a food supplement at the hospital?

Did the food last until the next ration distribution? (probe why- for both yes and no?)

Think about the discussion we had today. The purpose of the discussion was to identify barriers of adherence to supplementary feeding programs. What advice would you have for the service providers?

Do you have any other comment regarding today's discussion?

APPENDIX I ART ADHERENCE INTERVIEW

STUDY NUMBER_____

1. Did you miss a Triomune® tablet *yesterday*?

Yes ☐ No ☐ don't know ☐

Did you miss a Triomune® tablet *last week*?

Yes ☐ No ☐ Don't know ☐

Did you miss a Triomune® tablet *last month*?

Yes ☐ No ☐ Don't know ☐

Did you *ever* miss a Triomune® tablet?

Yes ☐ No ☐ Don't know ☐

Did you have to stop your HIV drugs at any time during the whole period since you started HIV drugs?

Yes ☐ No ☐ Don't know ☐