

Impact of highly active antiretroviral therapy (HAART) on  
body composition and other anthropometric measures of  
HIV-infected women in a primary healthcare setting  
in KwaZulu-Natal: a pilot study

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## Declaration

By submitting this thesis electronically, I declare that the entirety of the work contained therein is my own, original work, that I am the owner of the copyright thereof and that I have not previously in its entirety or in part submitted it for obtaining any qualification.



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## **Abstract**

### **Background and objectives:**

An understanding of the effect of HAART on different aspects of health, including nutritional status, of HIV-infected individuals in South Africa is needed to ensure that appropriate population-specific guidelines and policies can be developed. This study aimed to investigate the impact of HAART on nutritional status, focusing on changes in anthropometric measures, and to explore the relationship between these measures and immunological and virological response to HAART.

### **Methods:**

A prospective study of 30 adult females was carried out at a clinic in Cato Manor, KwaZulu-Natal. Anthropometric measurements, including weight, mid-upper arm circumference (MUAC), waist circumference, hip circumference, body mass index (BMI) and waist-to-hip ratio (WHR), were performed at baseline and 12 and 24 weeks after commencing HAART. Laboratory values, including CD4 lymphocyte count, viral load, albumin and haemoglobin as well as bioelectrical impedance analysis data, including lean body mass (LBM), fat mass (FM) and body fat percentage (BF%), were collected at baseline and after 24 weeks on HAART.

### **Results:**

Overall, there was a statistically significant increase in all anthropometric measures, except WHR and LBM. The mean weight change was  $3.4 \pm 5.8$  kg ( $p=0.006$ ). Fifty percent of the subjects had a BMI above normal at baseline and mean BMI increased from  $25.6 \pm 5.7$  kg/m<sup>2</sup> to  $27.3 \pm 5.6$  kg/m<sup>2</sup> ( $p=0.007$ ). Seventy percent of subjects gained weight, 18.5% had a stable weight and 11.1% lost weight. The weight gain in most subjects was attributable to a gain in FM while in subjects who lost weight, the loss consisted mainly of LBM. Some patients with stable body weight experienced

changes in the relative proportions of fat and lean mass. Six patients showed evidence of disproportionate gains and losses in body circumference measurements which may be indicative of fat redistribution. Subjects with lower CD4 lymphocyte counts experienced greater increases in weight, BMI, FM and BF%. The strongest correlation was observed with FM ( $r_s=-0.53$ ;  $p=0.00$ ). Greater increases in weight, BMI, MUAC, waist circumference, hip circumference, FM and BF% were seen in those with lower baseline haemoglobin. Baseline viral load and albumin did not correlate significantly with changes in any anthropometric variables. Change in CD4 count was only significantly associated with baseline MUAC ( $r_s=0.40$ ;  $p=0.04$ ). Change in viral load was significantly correlated with baseline weight, LBM, FM, BF% and MUAC with the strongest correlation being with weight ( $r_s=0.44$ ;  $p=0.01$ ). No significant association was found between anthropometric changes and changes in CD4 count and viral load between baseline and the 24-week visit.

### **Conclusion:**

Overall, subjects experienced a significant increase in most anthropometric measures. There appears to be a relationship between some anthropometric and laboratory measures but this needs clarification. The findings of this study demonstrate the value of including circumference measurements and body composition techniques as part of nutritional status assessment and demonstrate the need for studies to determine the prevalence and significance of overweight and obesity in the HIV-infected population. Research is needed to determine the best methods of bringing about the most favourable anthropometric changes to enhance the health of patients on HAART.

## Opsomming

### Agtergrond en doelwitte:

Begrip van die effek van HAART op verskillende aspekte van gesondheid, insluitende voedingstatus, van MIV-geïnfekteerde individue in Suid-Afrika is nodig om te verseker dat toepaslike populasie-spesifieke riglyne en beleide ontwikkel kan word. Die doel van die studie was om die impak van HAART op voedingstatus te ondersoek, met fokus op veranderinge in antropometriese metings, en om die verhouding tussen hierdie metings en die immunologiese en virologiese respons tot HAART te bepaal.

### Metodes:

'n Prospektiewe studie van 30 volwasse vroue was uitgevoer by 'n kliniek in Cato Manor, KwaZulu-Natal. Antropometriese metings, insluitende gewig, bo-armomtrek (BAO), middelomtrek, heupomtrek, liggaamsmassa indeks (LMI) en middel-tot-heup verhouding (MHV) was uitgevoer by basislyn sowel as 12 en 24 weke na aanvang van HAART. Laboratorium waardes, insluitende CD4 limfosiet telling, virale lading, albumien, hemoglobien en bio-elektriese impedansie analyse data, insluitende maer liggaamsmassa (MLM), vetmassa (VM) en liggaamsvet-persentasie (LV%), was versamel by basislyn en na 24 weke op HAART.

### Resultate:

Oor die algemeen was daar 'n statistiese beduidende toename in alle antropometriese meetings, behalwe MHV en MLM. Gemiddelde gewigsverandering was  $3.4 \pm 5.8 \text{ kg}$  ( $p=0.006$ ). Vyftig persent van vroue het 'n LMI bo normaal gehad (basislyn) en gemiddelde LMI het toegeneem van  $25.6 \pm 5.7 \text{ kg/m}^2$  tot  $27.3 \pm 5.6 \text{ kg/m}^2$  ( $p=0.007$ ). Sewentig persent van vroue het gewig opgetel, 18.5% het 'n stabiele gewig gehandhaaf en 11.1% het gewig verloor. Gewigstoename in meeste vroue kon

toegeskryf word aan 'n toename in VM terwyl in vroue wat gewig verloor het, het die verlies hoofsaaklik bestaan uit MLM. Sommige pasiënte met stabiele liggaamsgewig het veranderinge ondervind in die relatiewe proporsies van vet en maer massa. Ses pasiënte het bewyse getoon van disproporsionele toenames en verliese in liggaamsomtrek-metings wat 'n indikasie van vet herdistribusie mag wees. Pasiënte met laer CD4 limfosiet tellings het groter toenames in gewig, LMI, VM en LV% ondervind. Die sterkste korrelasie was waargeneem met VM ( $r_s = -0.53$ ;  $p = 0.00$ ). Groter toenames in gewig, LMI, BAO, middelomtrek, heupomtrek, VM en LV% was gesien in pasiënte met laer basislyn hemoglobien. Basislyn virale lading en albumien het nie beduidend gekorreleer met veranderinge in antropometriele veranderlikes nie. Verandering in CD4 telling was slegs beduidend geassosieer met basislyn BAO ( $r_s = 0.40$ ;  $p = 0.04$ ). Verandering in virale lading was beduidend gekorreleer met basislyn gewig, MLM, VM, LV% en BAO, met die sterkste korrelasie met gewig ( $r_s = 0.44$ ;  $p = 0.01$ ). Geen beduidende assosiasie was gevind tussen antropometriele veranderinge en veranderinge in CD4 telling en virale lading tussen basislyn en die 24-week besoek nie.

### **Gevolgtrekking:**

Oor die algemeen het pasiënte 'n beduidende toename in die meeste antropometriele metings ondervind. Dit wil voorkom asof daar 'n verhouding tussen sommige antropometriele en laboratorium metings is maar dit benodig uitklaring. Bevindinge van hierdie studie demonstreer die waarde van die insluiting van omtrek-metings en liggaamsamestelling tegnieke as deel van voedingstatus evaluering en demonstreer die behoefte aan studies om die prevalensie en belang van oorgewig en vetsug in die MIV-geïnfekteerde populasie te bepaal. Navorsing is nodig om die beste metodes te bepaal wat die mees gunstige antropometriele veranderinge teweeg sal bring ten einde die gesondheid van pasiënte op HAART te verbeter.

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### List of Abbreviations

3TC	lamivudine
ABW	actual body weight
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
AZT	zidovudine
ARV	antiretroviral
BIA	bioelectrical impedance analysis
BMI	body mass index
BCM	body cell mass
BF%	body fat percentage
CBV	combivir
d4T	stavudine
EFV	efavirenz
FFM	fat free mass
FM	fat mass
HAART	highly active antiretroviral therapy
HIV	human immunodeficiency virus
IRIS	immune reconstitution inflammatory syndrome
LBM	lean body mass
MTCT	mother to child transmission
MUAC	mid-upper arm circumference
NCDs	non-communicable diseases
NHLS	National Health Laboratory Services
NNRTI	non-nucleoside reverse transcriptase inhibitor

NRTI	nucleoside reverse transcriptase inhibitor
NSP	national strategic plan
NVP	nevirapine
PBW	previous body weight
PMTCT	prevention of mother to child transmission
PI	protease inhibitor
RNA	ribonucleic acid
SANAS	South African National Accreditation System
TB	tuberculosis
TBW	total body water
WHO	World Health Organization
WHR	waist-to-hip ratio

## List of Definitions

### Antiretroviral (ARV)

An antiretroviral is a medication which can be taken to prevent viral replication, for example replication of the Human Immunodeficiency Virus (HIV).<sup>1</sup>

### Bioelectrical impedance analysis (BIA)

A technique for measuring body composition which uses a battery operated unit, connected to the body by electrodes, to pass a small electric current through the body. A measurement of the impedance to the current in the body is then obtained and is used to estimate total body water and calculate fat-free mass and body fat using regression equations.<sup>2</sup>

### Body cell mass (BCM)

The mass of the metabolically active cells in the body.<sup>3</sup>

### Body mass index (BMI)

An index, calculated by dividing body weight in kilograms by the height squared in metres ( $\text{weight}/\text{height}^2$ ), used to categorise individuals as underweight, normal, overweight and obese.<sup>2</sup>

### Fat free mass (FFM)

The FFM of the body includes the muscle, bone and water as well as any other parts of the body that do not contain any fat or lipid.<sup>2</sup>

### Fat mass (FM)

The FM includes all the fat and lipid found in the body, both the essential and non-essential.<sup>2</sup>

### Highly active antiretroviral therapy (HAART)

Highly active antiretroviral therapy, also known as potent combination antiretroviral therapy, refers to the use of a combination of three or more antiretroviral drugs, to control replication of the human immunodeficiency virus and halt disease progression. Regimens usually consist of antiretroviral drugs from more than one class and commonly include one non-nucleoside reverse transcriptase inhibitor (NNRTI) with two nucleoside reverse transcriptase inhibitors (NRTIs) or a protease inhibitor (PI) with two NRTIs.<sup>1,4</sup>

### Lean body mass (LBM)

The fractions of the body consisting of muscle, water and bone as well as the essential lipid or fat in the body, together make up the lean body mass.<sup>2</sup>



## **CHAPTER 1: INTRODUCTION AND STATEMENT OF PROBLEM**

According to a recent report released by Statistics South Africa there were an estimated 5.3 million people living with the Human Immunodeficiency Virus (HIV) in South Africa in mid-2007.<sup>5</sup> The prevalence rate among adults between the ages of 20 and 64 years in South Africa is approximately 17.9%.<sup>5</sup> KwaZulu-Natal is the province that has been hardest hit by the pandemic with an HIV prevalence of 28% in adults between the ages of 20 and 64 years in mid-2006. HIV and Acquired Immunodeficiency Syndrome (AIDS)-related deaths are the leading cause of death in South Africa.<sup>6</sup>

The HIV and AIDS and STI Strategic Plan for South Africa, 2007 – 2011 aims to use a multi-sectoral approach to “reduce the number of new HIV infections by 50% and reduce the impact of HIV and AIDS on individuals, families, communities and society by expanding access to appropriate treatment, care and support to 80% of all people diagnosed with HIV”.<sup>7</sup> Nutrition is an important component of the comprehensive care and treatment package that needs to be provided and it is important that research in this area is undertaken to ensure that the nutritional interventions used are appropriate, feasible and effective.

The advent of antiretroviral therapy (ART), and especially highly active antiretroviral therapy (HAART), has dramatically altered the course of this devastating disease but many questions related to the management of patients on HAART remain unanswered. Knowledge of the effect of HAART on the health, including the nutritional status, of HIV-infected individuals in South Africa is needed. Changes in

the body composition and anthropometric measures of patients on HAART in South Africa remain to be investigated and an understanding of the way in which these changes affect the immunologic and virologic response to HAART as well as the overall health of patients will allow for improved decision-making and patient management.

This research project serves as a preliminary exploratory study to determine the impact of HAART on the nutritional status of HIV-infected adult females in a primary healthcare setting in KwaZulu-Natal, South Africa, focusing on the effect on body composition and other anthropometric measures. This study will also investigate the relationship, if any, between anthropometric measures and immunological and virological parameters.

## CHAPTER 2: REVIEW OF RELATED LITERATURE

### 2.1. Introduction

The relationship between poor nutritional status and disease progression in individuals infected with HIV is well known<sup>8,9</sup> and although morbidity and mortality associated with HIV/AIDS have decreased significantly since the advent of ART, malnutrition and wasting continue to be a problem in patients receiving HAART.<sup>10,11,12</sup> The loss of lean body mass (LBM) in particular, remains a concern in patients on HAART as it is associated with a poor prognosis and decreased survival.<sup>12</sup>

On the other end of the spectrum, overweight and obesity in South Africa are on the increase. A recent study found that a large proportion of a community in rural KwaZulu-Natal, South Africa, were overweight even though the prevalence of HIV in the area was very high, indicating that the HIV positive population may not be precluded from the obesity epidemic.<sup>13</sup>

The health risks associated with overweight and obesity in the general population are well known and include Type 2 diabetes mellitus, hypertension, dyslipidaemia, respiratory difficulties and osteoarthritis<sup>14</sup> but the effect of overweight and obesity more specifically on the health of individuals infected with HIV, especially in the era of HAART, is largely unknown.

Numerous studies have explored the changes in nutritional parameters in patients receiving ART in developed countries, but results have varied and research in developing countries has been limited.<sup>15-19</sup> To date, and to the principal investigator's

knowledge, no research on this topic in the South African population has been published in the peer-reviewed literature. With access to ART in South Africa increasing, there is a need for research in the context of the primary healthcare setting to investigate the impact of ART on nutritional status, a vital component of health, and to allow for appropriate population-specific guidelines and policies to be developed.

## **2.2 Antiretroviral therapy in South Africa**

The South African Government ARV (Antiretroviral) Roll-out Programme was initiated in July 2004 with the primary aim of decreasing HIV-related morbidity and mortality with the use of HAART.<sup>20</sup> The South African ARV Programme is being implemented at numerous public hospitals nationally and is being expanded to include primary healthcare clinics as well. Many individuals in South Africa also access HAART through the private sector, including through private hospitals, doctors and programmes run by non-governmental organizations.

It is estimated that in mid-2006 there were 225 000 people 14 years and older receiving HAART in South Africa.<sup>6</sup> One of the main goals of the National Strategic Plan (NSP) is to start 1.53 million people (1.38 million adults and 152 000 children) on HAART during the 5-year time frame between 2007 and 2011.<sup>7</sup>

As a result of the strong link between good nutritional status and the health of HIV-infected persons,<sup>8,16,21</sup> part of the care provided to patients on the ARV Programme in South Africa is the assessment of nutritional status and the provision of dietary advice and support, including food parcels and supplements. Making sure that

patients are provided with the most appropriate nutritional interventions depends largely on ensuring that a comprehensive nutritional assessment is performed, including anthropometric, biochemical, clinical and dietary assessment.<sup>12,22</sup>

### **2.3. Weight loss and wasting in HIV-infected individuals**

It is well known that malnutrition in HIV-infected individuals has a negative impact on immune system function; disease progression; quality of life; the ability to tolerate medication and survival.<sup>10</sup> Wasting is common and is associated with a poor prognosis, largely due to the predominant loss of LBM.<sup>23</sup> Patients who experience significant unintentional weight loss or weight loss that occurs at a rapid rate, irrespective of their body mass index (BMI), require increased attention as they are at greater risk of morbidity and mortality.<sup>24</sup>

HIV disease progression has been found to occur more rapidly in patients with a BMI <20 kg/m<sup>2</sup> as evidenced by a faster decline in CD4 lymphocyte count.<sup>25</sup> Melchior *et al.*<sup>21</sup> investigated the factors associated with poor survival in HIV-infected individuals and concluded that lean body mass index, calculated as the ratio of LBM in kilograms to height in metres squared, is a significant independent predictor of survival. Research has also shown that survival is significantly reduced in patients with a body cell mass (BCM) less than 30% of their body weight.<sup>10</sup>

Loss of LBM in HIV-infected individuals can occur in the absence of significant weight loss due to increases in body fat and body water.<sup>11</sup> For this reason, the importance of including not only body weight, height and BMI in the assessment and monitoring of

patients, but more specific measures of body composition as well, has been recognised.<sup>10,11,22</sup>

The proportions of fat and lean body mass lost during wasting are largely determined by the body fat content prior to illness.<sup>3,16,24</sup> Patients with a greater body fat content tend to lose more fat mass than LBM during periods of weight loss compared with patients with lower body fat contents who seem to lose more LBM than fat mass (FM).<sup>10</sup>

Studies have also shown that the proportions of fat mass and lean mass lost in individuals with HIV differ by sex. Women lose more fat than lean mass during wasting and tend to preserve lean body mass until the more advanced stages when significant loss of body cell mass also occurs. Muscle wasting has been shown to occur earlier in men with less fat loss taking place.<sup>3,9,26</sup>

## **2.4 Overweight and obesity in HIV-infected individuals**

Obesity in South Africa is on the rise and the large proportion of the population already affected is alarming. Overweight and obesity are particularly prevalent in women and according to data taken from the World Health Organization (WHO) Global InfoBase approximately 32.0% of South African women are overweight, defined as having a BMI  $\geq 25 < 30 \text{ kg/m}^2$  and 35.2% are obese defined by a BMI  $\geq 30 \text{ kg/m}^2$ .<sup>27</sup>

Overweight and obesity are of concern as they are associated with the development of numerous non-communicable diseases (NCDs) and other comorbid conditions,

including type 2 diabetes mellitus, hypertension, dyslipidaemia, chronic musculoskeletal problems and certain types of cancer.<sup>14</sup>

Although there has been much discussion and research on the subject of weight loss and wasting in HIV-infected individuals, fewer studies have been undertaken to describe overweight and obesity in this population.

Some researchers have found a high prevalence of overweight among HIV-infected individuals, even amongst those in the later stages of the disease.<sup>28</sup> There have been various reports of favourable associations between higher BMIs and various outcome measures, such as lower viral loads and slower disease progression in patients not receiving ART.<sup>25,28,29</sup> A study carried out by Shor-Posner *et al.*<sup>29</sup> revealed that individuals with a BMI of  $\geq 27$  were significantly less likely to experience a 25% decrease in CD4 lymphocyte count compared with individuals with a BMI of  $< 27$  over an 18-month study period. Obesity was also found to be associated with improved survival time with all of the obese patients surviving the duration of the study while 16.7% of the individuals with a BMI  $< 27$  died of HIV-related causes.<sup>29</sup>

The majority of the studies on this topic have been undertaken in developed countries before the advent of HAART. Research is needed in the context of the primary healthcare setting of developing countries to determine the prevalence and significance of overweight and obesity in the HIV positive population in the era of HAART, including whether or not BMI influences the immunologic and virologic responses of patients on HAART.

## **2.5 Assessment of body composition and other anthropometric measures**

Various methods exist for measuring body composition, such as dual-energy X-ray absorptiometry, underwater weighing, isotope dilution, computed tomography and magnetic resonance imaging. However, the cost and expertise required make most of these methods unsuitable for routine use or for use in research undertaken in the primary health care setting.<sup>10</sup>

Anthropometry, including mid-upper arm circumference (MUAC), skinfold thicknesses, waist circumference,<sup>10</sup> waist-to-hip ratio (WHR) as well as bioelectrical impedance analysis (BIA)<sup>12,22</sup> are more cost effective and practical methods for use in these settings. BIA can be used to obtain reliable estimates of body composition in individuals with many disease conditions, including HIV, particularly for monitoring changes in body composition over time provided that suitable population-specific equations are used.<sup>10</sup>

The use of anthropometry is not without its limitations which include inaccuracy due to incorrect technique, unreliability due to intra- and inter-observer variability and the lack of population-specific reference data.<sup>2</sup> Anthropometric assessment is however a very valuable component of nutritional status assessment and some of the limitations can be addressed through the use of standardised methods and equipment and through good training and practice, for example in the location of the anatomical landmarks used for measurements.<sup>2</sup>



## **2.6 HAART and changes in anthropometric measures and body composition**

Many studies have reported an improved state of health and well-being among those receiving HAART,<sup>11</sup> but according to Wanke *et al*,<sup>10</sup> muscle wasting continues to be a problem for many patients and the use of HAART has also brought about new concerns related to nutritional status. One of these is the complication of lipodystrophy syndrome that occurs in many patients.<sup>10</sup>

Lipodystrophy syndrome is the term used to describe the abnormal body fat changes and alterations in metabolic parameters, such as dyslipidaemia and insulin resistance, that can develop in patients receiving ART. The abnormal body fat changes that can occur include peripheral lipoatrophy and central lipohypertrophy. Patients with peripheral lipoatrophy typically experience fat loss from the extremities, buttocks and face while abdominal fat accumulation, increase in breast size and development of dorsocervical fat pads have been reported in those with central lipohypertrophy.<sup>30</sup>

Lipoatrophy and lipohypertrophy do not necessarily occur simultaneously and various risk factors for their development have been identified. The use of thymidine Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs), in particular stavudine (d4T), and less commonly zidovudine (AZT), as well as older age, longer duration of therapy, white race and severe disease, as evidenced by lower CD4 lymphocyte count and higher viral load, have all been associated with the development of lipoatrophy. Risk factors for the development of lipohypertrophy include the use of protease inhibitors, lower CD4 lymphocyte counts, higher viral load, female gender, older age and longer duration of ART.<sup>30</sup>

It is crucial to use measures of body composition to distinguish between patients with lipoatrophy in the absence of muscle wasting and those with maintenance of fat mass but depletion of LBM as well as to identify patients with co-existing lipoatrophy and depletion of LBM.<sup>16</sup> This will assist in making decisions regarding treatment and the most appropriate interventions to be used.

It has been suggested that some anthropometric measurements and indices, such as waist and hip circumferences, WHR<sup>12</sup> and MUAC can be used as practical and inexpensive means of identifying fat redistribution in patients.<sup>10</sup>

A recent prospective study of 190 HIV-infected adults, 85% of whom were men, found that the patients differed in their response to a nevirapine-based HAART regimen with 22% losing weight, others gaining weight and some maintaining their weight over the 6-month follow-up period. Body fat and body cell mass (BCM) were measured by BIA and it was found that the weight lost and gained by the patients was composed of proportional decreases or increases in both fat and BCM.<sup>31</sup>

Silva *et al*,<sup>32</sup> found that if the weight of patients increased on HAART, the increase was mostly a result of an increase in FM rather than LBM.<sup>32</sup> Another study concluded that patients who lost weight while on HAART maintained their muscle mass despite reductions in FM.<sup>16</sup>

Some researchers have reported significant increases in total body water (TBW), which is indicative of LBM, in patients on ART,<sup>33</sup> while others have found only modest increases in body weight and LBM.<sup>18</sup> Ferrando *et al*<sup>15</sup> conducted a longitudinal

cohort study and concluded that potent ART regimens were associated with an increase in BCM, expressed as the ratio of BCM to height<sup>2</sup>, but no significant changes in body weight or FM were reported.<sup>15</sup> Several studies have also reported changes occurring in patients on ART which are characteristic of lipodystrophy.<sup>17,19,34</sup>

The results of studies investigating the effect of ART on body composition have varied and limited definitive conclusions have been drawn. Few longitudinal studies have been carried out and the methodology used in studies has differed considerably. The majority of the studies have been done on males with a small number focusing specifically on females. Very little has been done in the context of the primary health care setting in developing countries and no known studies are available in the peer-reviewed literature involving patients receiving HAART in South Africa. Drawing conclusions from research involving patients on ART is also complicated by the fact that numerous drugs and regimens have been used in different studies and the effects of these drugs can differ significantly.

## **2.7 Relationship between anthropometric measures and virological and immunological parameters**

Various studies have explored the relationship between body composition changes and immunological and virological parameters but, as stated by Wanke *et al*, “data from studies have not clearly demonstrated that there is an association between suppression of HIV and either maintenance of nutritional status or the return of nutritional status to a normal level”.<sup>35</sup>

In the study carried out by Saghayam *et al*<sup>31</sup>, which documented weight changes in a group of patients receiving a nevirapine-based HAART regimen, no correlation between body weight changes and immunologic response, as measured by CD4 lymphocyte count, was observed. Significant increases in CD4 lymphocyte count were seen in patients irrespective of whether they lost weight, gained weight or maintained their weight after the 6-month study period.<sup>31</sup>

Shikuma *et al*<sup>18</sup> found initial increases in LBM to be greater in patients with baseline CD4 lymphocyte counts below 200 cells/mm<sup>3</sup> and viral loads of  $\geq 100\,000$  copies/ml compared with those with higher CD4 counts and lower viral loads, but by 48 weeks the difference was no longer significant. Patients who achieved HIV-1 RNA loads of  $< 500$  copies/ mL displayed greater increases in body weight.<sup>18</sup> A recent study which followed a cohort of 622 patients, with a baseline BMI of  $< 25$  kg/m<sup>2</sup>, reported no significant association between increases in BMI and virological success, defined as an undetectable viral load which in this case was below 300 copies/mL, after 6 months of HAART.<sup>36</sup>

In a study by Schwenk *et al*,<sup>33</sup> no association was found between improved CD4 count and viral load and changes in body composition.<sup>33</sup> In contrast, Mwamburi *et al*<sup>37</sup>, found an association between a reduction in CD4 count and weight loss but viral load was not significantly associated with weight change in patients on HAART.<sup>37</sup> There is no consensus on the relationship, if any, between anthropometric measures and virological and immunological parameters in patients on HAART highlighting the need for more research in this area.

## **2.8 Conclusion**

Making HAART available in the public sector has changed the face of HIV/ AIDS in South Africa, but along with the improvements in the health and well-being of many patients, comes the need for information regarding the effect of HAART on the various aspects of health, and importantly the long-term health, of these patients.

Nutritional status, including optimal body composition, is an important component of health in HIV-infected individuals and the close link between the maintenance of a good nutritional status and immune function, highlights the need for research in this area.<sup>8,21</sup> Obtaining a more in-depth understanding of the effect of HAART on anthropometric measures, including body composition, is necessary to ensure that appropriate interventions are developed and implemented when necessary. Enhancing our knowledge of the significance of changes in anthropometric measures and body composition in relation to patient morbidity, drug toxicity and side-effects is also necessary.

This exploratory research project will serve as a pilot study to investigate the changes in body composition and other anthropometric measures of HIV-infected women after the initiation of HAART in the context of the primary healthcare setting of South Africa. It will also explore the relationship, if any, between anthropometric measures and morbidity, immunological and virological parameters.

## **CHAPTER 3: METHODOLOGY**

### **3.1. Aim**

To study the early changes, occurring within the first 24 weeks of commencing therapy, in anthropometric measures and body composition of HIV-infected women receiving HAART in a primary healthcare setting in KwaZulu-Natal and to investigate associations between anthropometric measures and morbidity, virological and immunological parameters.

### **3.2. Objectives**

#### **3.2.1. Primary objectives**

- To study the impact of HAART on anthropometric measures, including weight, MUAC, waist circumference and hip circumference of HIV-infected women.
- To study the impact of HAART on the BMI and WHR of HIV-infected women.
- To study the changes in the LBM, FM and body fat percentage (BF%) of HIV-infected women on HAART as determined by BIA.

#### **3.2.2. Secondary objectives**

- To correlate baseline CD4 lymphocyte count, viral load, serum albumin, haemoglobin, WHO stage and Karnofsky Score with changes in anthropometric measures, including weight, BMI, MUAC, waist circumference, hip circumference, WHR, LBM, FM and BF%, after 24 weeks of HAART.
- To correlate baseline weight, BMI, MUAC, LBM, FM and BF% with CD4 lymphocyte count response and virological response as well as with changes in levels of haemoglobin and serum albumin after 24 weeks of HAART.

- To correlate changes in weight, BMI, LBM, FM and BF% with changes in CD4 lymphocyte count, viral load and serum albumin after 24 weeks of HAART.
- To obtain basic information from subjects, at the 24-week visit, on changes, if any, in appetite, portion sizes and number of meals and/ or snacks per day since the initiation of HAART.
- To keep a record of any subjects who, according to records of self-reported HAART adherence in the patient files, are identified as having sub-optimal adherence.

### **3.3. Study design**

A longitudinal, observational study was carried out.

### **3.4. Study population and sampling**

The study sample for this research project was drawn from patients on the Mother to Child Transmission (MTCT)-Plus Programme. The MTCT-Plus programme is an internationally-funded programme that provides comprehensive care and treatment for HIV-infected women and their families. In KwaZulu-Natal the MTCT-Plus Programme is being implemented from a Municipal primary healthcare clinic, known as the Umkhumbane Community Health Centre.

The clinic is situated in Cato Manor, which is approximately seven kilometres from the Central Business District of Durban and has an estimated population of 123 000.<sup>38</sup> The majority of the patients on the MTCT-Plus Programme reside in the Cato Manor urban informal settlements which are in close proximity to the clinic. Here the homes consist of shacks and low-cost housing, many without running water,

electricity or a water-borne sewage system. Unemployment levels in the community are high and for many families survival is a struggle as poverty is rife.<sup>39</sup> IsiZulu is the first language spoken by most of the patients on the MTCT-Plus Programme.

**Inclusion criteria:**

- Females 18 years of age or older, who started HAART for the first time between March 2007 and October 2007.
- Eligible for HAART according to the MTCT-Plus protocol which follows the WHO guidelines<sup>40</sup> which state that an individual is eligible to commence HAART if they have:
  - A CD4 lymphocyte count of below 200 cells/mm<sup>3</sup>
  - WHO clinical stage 4 disease irrespective of CD4 lymphocyte count
  - WHO clinical stage 3 disease and CD4 count 200 – 350 cells/mm<sup>3</sup>
- ARV-naïve, except for prevention of mother to child transmission (PMTCT) prophylaxis taken during pregnancy.

**Exclusion criteria:**

- Planning to relocate or transfer to another treatment site within the next 6 months.
- Pregnant or recent pregnancy (delivery in the previous 8 weeks).
- Any malignancies other than Kaposi's Sarcoma.

No control group was used in this study as it is unethical to withhold HAART from eligible patients. In view of the fact that South African data on anthropometric and body composition changes in adults on HAART is lacking, this study was designed



as a pilot study to provide information which would inform a larger study and it was determined that a sample size of 30 would be used. This represented approximately 10% of the female population on HAART at the Umkhumbane Community Health Centre at the time the study commenced. This was taken to be a realistic estimate based on the programme enrollment register and taking into consideration the 24 week follow-up period. The first 30 females who were starting HAART; met the eligibility criteria; and were willing to participate in the research were enrolled into the study.

### **3.5. Ethical considerations**

The study protocol was approved by the Committee for Human Research at Stellenbosch University (Project number: N07/06/139) (Appendix 1). The Bioethics Committee of the Faculty of Medical Sciences, Nelson R Mandela School of Medicine, University of KwaZulu-Natal gave approval for the project to be undertaken at the research site used by Professor Anna Coutsooudis for a study that is on-going at the clinic and the necessary amendments were made to her study protocol "Pilot programme: Implementing care and anti-retroviral therapy to HIV-infected mothers (and their families) in resource constrained settings" (Ref: E121/02) (Appendix 2).

Patients who are enrolled into the MTCT-Plus Programme are required to sign written informed consent, which includes consent for all blood tests and other procedures (Appendix 3). Many of the patients had been enrolled in the programme for some time and therefore it was only necessary for them to sign a separate consent form for this research project explaining the anthropometric measurements and BIA (Appendix 4). The study consent form was attached to the existing MTCT-Plus

consent and kept in the patients' files. Copies of the consent forms were also given to the subjects. The patient information sheet and consent form were translated into Zulu and a Zulu-speaking counselor assisted with translations and answering questions when necessary. (Appendix 5)

A study number was allocated to each patient and at no time were the names of the subjects disclosed to anyone other than the researchers and clinic staff involved in patient management. Subject confidentiality and privacy were protected by ensuring that no names appeared on the forms. Measurements and assessments were done in a private consultation room.

### **3.6. Study procedures**

Adult females who were eligible to start HAART according to the WHO criteria and who met all the inclusion criteria had the details of the research project clearly explained to them by the principal investigator and were then asked to sign the written informed consent to participate in the study. The information was explained in the patient's language of preference and a translator was used when necessary.

The subjects were followed up over a period of 24 weeks from the day they started HAART. The personnel responsible for the data collection included the principal investigator (a registered dietitian), an enrolled nurse, a Zulu-speaking counsellor and a medical doctor.

Baseline socio-demographic information was obtained from the MTCT-Plus database used at the clinic and by means of a standardised recording form which was

administered by the principal investigator (Appendix 6). Questions included, date of birth, age, number of previous pregnancies, date of last pregnancy (if applicable), education level, employment, availability of electricity and piped water in the home and history of or current tuberculosis (TB). A question on the history of unintentional weight loss was also included and where possible, an estimate of the amount lost over the previous six months was obtained either from the patient or the file. The percentage of weight lost or gained over the past six months was calculated using the formula:

$$\text{Percentage weight change (lost/ gained)} = (\text{PBW} - \text{ABW}) \div \text{PBW} \times 100$$

Where previous body weight (PBW) is the weight six months ago and actual body weight (ABW) is the weight on day of starting HAART.

The patients were then categorised according to the weight change as either “lost weight”, “gained weight” or “weight stable”. Weight was considered stable if an individual had gained or lost one kilogram or less over the past six months. Patients in the “lost weight” group and the “gained weight” group were then further categorised into different groups according to the percentage of weight lost or gained. The categories included “<5%”, “5–10%” and “>10%” change.

A standardised follow-up form was placed in each patient’s file and was completed at 12-week intervals during routine clinic visits (Appendix 7). This form included space to record the additional measurements that are not performed routinely at the appointments, including mid-upper arm circumference, waist circumference and hip

circumference, as well as questions regarding the presence of nutrition-related symptoms and the use of nutritional supplements. Nutrition-related symptoms referred to symptoms that are known to have an impact on nutritional status, including diarrhoea, nausea, vomiting, mouth sores, difficulty swallowing and loss of appetite. Contact numbers were obtained whenever possible to assist with tracing subjects.

### **Anthropometric measurements**

Anthropometric measurements included weight, height, MUAC, waist circumference and hip circumference. To eliminate error due to inter-observer variability and enhance reliability all anthropometric measurements were performed by the principal investigator. Anthropometric measurements were practiced on 10 individuals prior to the start of the data collection. The principal investigator practiced performing the measurements on each individual following the procedures that would be employed in the study.

Anthropometric measurements were performed at baseline and at 12-week intervals thereafter. Standardised techniques and the same equipment were used for all measurements. The weight, height, MUAC, waist and hip circumference measurements were taken in duplicate and the mean of the two measurements was used. To enhance precision, if the two measurements differed by more than 0.1 kg for weight or by more than 0.5 cm for height and circumference measurements, the measurements were repeated.<sup>41</sup>

Weight was measured using an electronic scale and measurements were recorded to the nearest 0.1 kg. Subjects were weighed without shoes and with only light clothing whenever possible.<sup>2</sup> Height was measured using a stadiometer (SECA 225) and was recorded to the nearest 0.1cm. Subjects were measured without shoes and standing in an upright position. The head was positioned in the Frankfort horizontal plane and the subject was asked to relax their shoulders and stand with their arms at their sides.<sup>2</sup>

Mid-upper arm circumference was measured using a flexible, inelastic tape measure (SECA) and was taken on the right side for all subjects. The mid-point between the top of the acromion process of the scapula and the olecranon process of the ulna was located and a mark was made using a marking pen. The MUAC was then measured to the nearest 0.1cm with the arm hanging freely at the subject's side.<sup>42</sup>

Waist circumference was measured to the nearest 0.1cm using a flexible, inelastic tape measure (SECA) with the subject standing in an upright position with their feet together and arms relaxed at their sides. The measurement was taken with the tape measure positioned around the abdomen at the mid-point between the lowest rib and the iliac crest after the subject had gently exhaled.<sup>42</sup> Hip circumference was measured using a flexible, inelastic tape measure (SECA) and was recorded to the nearest 0.1cm. Hip circumference was measured as the maximal circumference over the buttocks.<sup>42</sup>

In some cases measurement of the waist and hip circumferences necessitated the removal of the outer layer of clothing, especially in the case of subjects wearing jeans

or pants with pockets, to improve the accuracy of the measurements. This was only done if the subject was comfortable to do so. If not, the dietitian recorded that the measurement was taken with bulky clothing, which may have hindered the accuracy of the measurement.

The BMI was calculated by dividing the weight of the subject by their height squared ( $\text{kg/m}^2$ ) and the WHR was calculated by dividing the waist circumference by the hip circumference. The measurements obtained as well as these indices, were then used to classify the individuals according to the WHO cut-off values.<sup>14</sup> Patients were classified into the following BMI categories: underweight ( $<18.5 \text{ kg/m}^2$ ); normal weight ( $18.5\text{-}24.9 \text{ kg/m}^2$ ); overweight ( $25.0\text{-}29.9 \text{ kg/m}^2$ ) and obese ( $>30 \text{ kg/m}^2$ ). A WHR greater than 0.85 can indicate accumulation of abdominal fat and a waist circumference of  $\geq 80 \text{ cm}$  and  $\geq 88\text{cm}$  can be used to identify individuals at increased risk and substantially increased risk of cardiovascular disease respectively.<sup>14</sup> Abdominal obesity increases the risk of developing insulin resistance, hypertension, hyperlipidaemia and Type 2 diabetes mellitus.<sup>2</sup>

BIA was performed at baseline and 24 weeks after starting HAART using a quad-frequency analyser (Bodystat® QuadScan 4000 Hydration/ Body Composition Monitoring Unit, Isle of Man, British Isles). To enhance reliability, all the assessments were performed by the principal investigator and the analyser was calibrated before each analysis using the calibrator supplied by the manufacturer. Measurements were performed according to the manufacturer's instructions using standardised procedures and electrode placement. The skin surfaces on which the electrodes were placed were cleaned with an alcohol swab to ensure good adhesion and the

disposable electrodes were then attached to the wrist, hand, ankle and foot on the right side of the body. Measurements were done with the subject lying supine, with limbs slightly abducted and analysis was performed after the subject had been lying in the supine position for five minutes.( Bodystat<sup>®</sup> QuadScan 4000 User's Guide)

It is recommended that to enhance accuracy of measurements subjects do not eat or drink anything during the four hours preceding the BIA,<sup>10</sup> therefore when subjects attended the clinic appointment approximately four weeks prior to the visit at which HAART was initiated, they were advised not to eat or drink anything on the morning of their next visit. Patients were also advised at their 20-week visit to fast on the morning of the 24-week visit. Where possible, subjects were also contacted telephonically to remind them to fast. Subjects were also asked to remove all jewellery before the assessment.<sup>10</sup> A standardised form was used to record the BIA measurements (Appendix 8).

It cannot be assumed that the equations built into the analyser by the manufacturer are suitable for use in black African HIV-infected females in South Africa. An ancillary study attached to the same study population (principal investigator Dr. Gurpreet Kindra), developed a prediction equation based on the deuterium dilution method. Dilution techniques are considered to be the reference method for body composition assessment.<sup>43</sup> Linear regression analysis was used to develop and validate the prediction equation. The correlation coefficient was 0.873 showing a good fit between the values obtained from the equation using impedance values from the BIA and the deuterium dilution method. The study is ongoing and has not yet

been published, however the equations were used with the permission of the principal investigator.

The subjects' impedance values at 50 kHz and 100 kHz obtained from the BIA were then used in the following prediction equation to calculate LBM:

$$\text{LBM} = (0.777 \times H^2/Z_{50}) + (0.152 \times W) + (0.018 \times Z_{100}) - 10.062$$

Where  $H^2$  is height squared in  $\text{cm}^2$ ;  $Z_{50}$  is impedance at frequency 50 kHz;  $W$  is weight in kg;  $Z_{100}$  is impedance at 100 kHz.

FM was calculated by subtracting the LBM from total body weight. Body fat percentage was calculated by dividing the body fat mass by the total body weight and multiplying the value by 100.

### **Laboratory methodology**

All laboratory tests for patients on the MTCT-Plus Programme are done routinely by the Provincial laboratories at Inkosi Albert Luthuli Central Hospital and King Edward VIII Hospital. These are both National Health Laboratory Service (NHLS) laboratories which have been accredited by the South African National Accreditation System (SANAS). Viral loads were performed by *in vitro* NASBA® HIV-1 assay using the NucliSens Easy-Q-HIV-1 Viral Load Method (bioMérieux SA, Boxtel, Netherlands) and CD4 lymphocyte counts were done by flow-cytometry using the BD Facscalibur Method (Becton Dickinson, San Jose, CA, USA). Blood samples were drawn for analysis at baseline and 24 weeks after the initiation of HAART according to the MTCT-Plus programme protocol. The CD4 lymphocyte counts, plasma HIV



ribonucleic acid (RNA) or viral loads, haemoglobin and serum albumin results were obtained from the patient files and recorded on a standardised form (Appendix 7).

Baseline blood values that were recorded were those that were obtained up to a maximum of 8 weeks prior to the initiation of HAART or up to a maximum of 2 weeks after the initiation of HAART. A viral load of less than 25 copies/ mL was considered undetectable as this is the lower detection limit of the Nuclisens Easy-Q-HIV-1 Viral Load Assay. An albumin level within the range of 35 to 50 g/l/L was defined as normal and a lower cut-off value of 11.5 g/dL was used for haemoglobin.<sup>44</sup>

Using the guidelines proposed by the Department of Health and Human Services Panel on Antiretroviral Guidelines for Adults and Adolescents, a significant change in CD4 count was defined as an increase of approximately 30% and an optimal virological response was defined as achieving an undetectable viral load after 24 weeks on HAART.<sup>4</sup>

### **Clinical Assessment**

A clinical assessment was carried out on a 4-weekly basis by the MTCT-Plus clinician and included WHO staging (Appendix 9) as well as examination for signs and symptoms of opportunistic infections, the presence of comorbid conditions, side-effects and drug-related toxicity. The Karnofsky Performance Score was also used to assess the health status of patients.

The Karnofsky score is a tool used to rate a patient's functional status on a scale, in increments of 10%, between 0 and 100% (Appendix 10). The patient is given a

score based on their signs and symptoms as well as their ability to carry out daily activities as determined by clinical observation and questions asked by the clinician.<sup>18</sup>

The findings of the clinical assessments were obtained from the patient files as well as the MTCT-Plus database. To ensure ease of data entry for analysis, the anthropometric measurements, the information from the follow-up form in the patient file and from the clinical assessment was entered into a standardised summary form which was kept in a separate file (Appendix 11). Drug regimens as well as any drug switches or regimen changes were also recorded for each subject (Appendix 9). The HAART regimens used by the MTCT-Plus Programme are those that are consistent with the WHO guidelines, details of which can be found elsewhere.<sup>40</sup>

All of the patients on the study were prescribed the first-line HAART regimen which is based on a combination of one Non-nucleoside Reverse Transcriptase Inhibitor (NNRTI) with two Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTI) and consisted of either nevirapine (NVP) with zidovudine (AZT) and lamivudine (3TC), efavirenz (EFV) with AZT and 3TC or stavudine (d4T), 3TC and EFV depending on the characteristics of the patient.

Patients were prescribed AZT, 3TC and NVP unless they were on rifampicin-containing TB medication in which case EFV was used instead of NVP to prevent drug-drug interactions. In the case of patients with anaemia, AZT is contraindicated and d4T was used instead. Patients who were not using a reliable method of contraception were prescribed NVP as EFV is potentially teratogenic.<sup>40</sup> The dosages

are as follows: AZT, 300 mg every 12 hours; 3TC, 150 mg every 12 hours; d4T, 30 mg every 12 hours; NVP, 200 mg once daily for 14 days, then 200 mg every 12 hours and EFV, 600 mg once daily. AZT and 3TC are prescribed as a single combination tablet, namely Combivir (CBV). Patients with poor adherence were identified from records of self-reported adherence in the patient files.

### **Questionnaire for 24-week follow-up visit**

A brief standardised questionnaire was administered at 24 weeks. Each subject was asked a series of questions to establish whether or not there had been any significant changes in their diet since starting HAART. The questionnaire also included questions on socio-demographic variables to determine whether or not there had been any changes in the variables assessed at baseline, for example employment status (Appendix 7). The questions were asked by the principal investigator with the aid of a translator when necessary. The questionnaires were discussed with the MTCT-Plus counselors prior to the start of the study to ensure that the questions were clear and easily understood.

### **3.7. Analysis of data**

Continuous variables were summarised using means and standard deviations and were compared using paired t-tests. The mean change in variables between baseline and the 12- and 24-week visit was calculated by subtracting the mean value at baseline from the mean value at the 12- and 24-week visit. Categorical data were summarised using proportions and percentages. For analysis purposes subjects with an undetectable viral load were assigned a viral load of 24 copies/ ml or  $1.4 \log_{10}$  copies/ml. Subjects were also categorised according to their body weight changes

between baseline and the 24-week visit as follows: weight loss, weight gain or weight stable, as well as according to their body composition changes into the following categories: gained fat mass, gained lean mass, lost fat mass, lost lean mass or stable.

Correlation analysis was performed to investigate the relationship between continuous variables and was expressed using Spearman's correlation coefficient. The relationship between continuous variables and nominal variables was investigated by analysis of variance (ANOVA) or the Mann-Whitney or Kruskal-Wallis test as appropriate. The maximum-likelihood (ML) chi-square test was used to compare two nominal variables. A  $p$ -value of less than 0.05 was considered statistically significant. The statistical analyses were carried out by a statistician using STATISTICA, version 8.<sup>45</sup>

## CHAPTER 4: RESULTS

### Baseline sample characteristics

A total of 30 patients were enrolled into the study. The participants were all of black African ethnicity and had a mean age ( $\pm$  SD) of  $30.9 \pm 5.6$  years. Table 4.1a and Table 4.1b present the baseline characteristics of the 30 females enrolled into the study, including the baseline socio-demographic, nutritional, laboratory and clinical parameters. The HAART regimens prescribed at baseline are also shown.

Information on weight changes that occurred during the six months prior to the commencement of HAART was available for 27 of the subjects. Of these, 11 (40.7%) had lost weight unintentionally, seven (25.9%) had gained weight and nine (33.3%) had a body weight that had remained stable. Two patients lost more than 10% of their body weight, three lost between 5-10% and six lost less than 5% of their body weight (Table 4.1a).

The most common nutrition-related symptom was loss of appetite which was reported by 46.7% (n=14) of the subjects. Diarrhoea, mouth sores, oral thrush and difficulty swallowing were also relatively common with 30.0% (n=9), 26.7% (n=8), 23.3% (n=7) and 23.3% (n=7) suffering from these symptoms respectively. According to the WHO clinical disease classification, 43.3% (n=13) of the patients had stage 1 disease, 16.7% (n=5) had stage 2, 36.7% (n=11) had stage 3 and only 3.3% (n=1) had stage 4 disease. (Table 4.1b)

**Table 4.1a: Baseline socio-demographic, anthropometric and laboratory characteristics of the 30 females enrolled into the study**

Characteristics	Subjects (n = 30)
Age (years)	30.9 ± 5.6
Education (years)	9 ± 3
Employed	16 (53.3)
No piped water in home	11 (36.7)
No electricity in home	14 (46.7)
Previous pregnancy	30 (100)
Number of previous pregnancies	
1	6 (20.0)
2	15 (50.0)
3 or more	9 (30.0)
History of weight loss (in last 6 mths) (n = 27)	11 (40.7)
< 5 %	6 (54.5)
5 - 10 %	3 (27.3)
> 10 %	2 (18.2)
Initial HAART Regimen	
AZT, 3TC, NVP	17 (53.3)
AZT, 3TC, EFV	8 (26.7)
d4T, 3TC, EFV	5 (16.7)
Weight (kg)	63.7 ± 16.0
BMI (kg/m <sup>2</sup> )	25.6 ± 5.7
< 18.5 (underweight)	2 (6.7)
18.5 - 24.9 (normal weight)	13 (43.3)
25 - 29.9 (overweight)	9 (30.0)
= 30 (obese)	6 (20.0)
MUAC (cm)	28.3 ± 5.1
Waist circumference (cm)	84.5 ± 11.6
Hip circumference (cm)	98.6 ± 13.2
WHR	0.86 ± 0.05
Waist circumference = 80 cm	9 (30.0)
Waist circumference = 88 cm	9 (30.0)
WHR > 0.85	17 (56.7)
LBM (kg)	41.9 ± 5.7
FM (kg)	21.8 ± 11.2
BF%	32.2 ± 9.7
CD4 cell count (cells/mm <sup>3</sup> )	164 ± 69
< 50	4 (13.3)
50 - 99	1 (3.3)
100-199	15 (50)
≥ 200	10 (33.3)
Viral load, (log <sub>10</sub> copies/mL)	4.5 ± 1.2
Haemoglobin (g/dL)	11.1 ± 2.1
Serum albumin (g/L)	29 ± 8

**Note:** Data are number (%) of patients or mean ± SD. HAART, highly active antiretroviral therapy; AZT, zidovudine; 3TC, lamivudine; NVP, nevirapine; EFV, efavirenz; d4T, stavudine; BMI, body mass index; MUAC, mid-upper arm circumference; WHR, waist-to-hip ratio; LBM, lean body mass; FM, fat mass; BF%, body fat percentage.

**Table 4.1b: Baseline clinical characteristics of the 30 females enrolled into the study**

Characteristics	Subjects (n = 30)
<b>Tuberculosis</b>	
Never	20 (66.7)
Past	4 (13.3)
Current	6 (20.0)
<b>Symptoms (nutrition-related)</b>	
Diarrhoea	9 (30.0)
Nausea	5 (16.7)
Vomiting	2 (6.7)
Mouth sores	8 (26.7)
Oral thrush	7 (23.3)
Difficulty swallowing	7 (23.3)
Loss of appetite	14 (46.7)
<b>WHO Clinical Stage</b>	
Stage 1	13 (43.3)
Stage 2	5 (16.7)
Stage 3	11 (36.7)
Stage 4	1 (3.3)
<b>Karnofsky score</b>	
100%	17 (56.7)
90%	8 (26.7)
80%	4 (13.3)
50%	1 (3.3)

**Note:** Data are no.(%) of patients. WHO, World Health Organization

### **Anthropometric and laboratory parameters at baseline**

The mean values for the anthropometric measures, including weight, BMI, MUAC, waist and hip circumferences, WHR, LBM, FM and BF%, as well as the laboratory parameters of the subjects at baseline are shown in Table 4.1a. The mean weight ( $\pm$  SD) of the subjects at baseline was  $63.7 \pm 16.0$  (range: 40.5 – 109.6 kg), the mean BMI ( $\pm$  SD) was  $25.6 \pm 5.7$  kg/m<sup>2</sup> (range: 14.5 – 37.8 kg/m<sup>2</sup>) and the mean BF% ( $\pm$  SD) was  $32.2 \pm 9.7$  % (range: 7.1 – 48.0%).

The number of subjects in each BMI category is also indicated in Table 4.1a. Only two (6.7%) of the subjects were underweight (BMI <18.5 kg/m<sup>2</sup>) at baseline while 13 (43.3%) were normal weight (BMI 18.5–24.9 kg/m<sup>2</sup>), nine (30.0%) were overweight (BMI 25–29.9 kg/m<sup>2</sup>) and six (20.0%) were obese (BMI >30 kg/m<sup>2</sup>). Nine subjects (30.0%) had a waist circumference ≥80 cm and nine had a waist circumference ≥88 cm. Seventeen (56.7%) had a WHR greater than the cut-off of 0.85.

The mean (± SD) CD4 lymphocyte count, viral load, serum albumin and haemoglobin levels at baseline were  $164 \pm 69$  cells/mm<sup>3</sup>,  $4.5 \pm 1.2$  log<sub>10</sub> copies/mL,  $29 \pm 8$  g/L and  $11.1 \pm 2.1$  g/dL respectively. Eighteen (60.0%) of the patients had a serum albumin level under the lower limit of 35 g/L and 12 (40.0%) had a haemoglobin level less than the lower cut-off value of 11.5 g/dL.

Interestingly baseline CD4 lymphocyte count was not significantly correlated with any of the anthropometric measures at baseline but a significant inverse correlation was found between baseline viral load and all baseline anthropometric measures, except LBM (Table 4.2). Albumin level and Karnofsky score at baseline were modestly but significantly correlated with all baseline anthropometric measures. There was also a statistically significant relationship found between WHO stage at baseline and all anthropometric measurements at baseline, except LBM, and between haemoglobin level at baseline and all anthropometric measurements at baseline, except LBM (Table 4.2).



**Table 4.2: Relationship between laboratory measures, WHO stage and Karnofsky score at baseline with anthropometric measures at baseline.**

Anthropometric measure	CD4 cell count		Viral load		Haemoglobin		Albumin		WHO Stage		Karnofsky Score	
	$r_s$	$p$ -value	$r_s$	$p$ -value	$r_s$	$p$ -value	$r_s$	$p$ -value	$r_s$	$p$ -value	$r_s$	$p$ -value
Weight	0.31	0.09	<b>-0.49</b>	<b>0.01</b>	<b>0.48</b>	<b>0.01</b>	<b>0.59</b>	<b>0.00</b>	<b>-0.46</b>	<b>0.01</b>	<b>0.67</b>	<b>0.00</b>
BMI	0.27	0.15	<b>-0.43</b>	<b>0.02</b>	<b>0.47</b>	<b>0.01</b>	<b>0.60</b>	<b>0.00</b>	<b>-0.50</b>	<b>0.01</b>	<b>0.65</b>	<b>0.00</b>
LBM	0.26	0.17	-0.34	0.06	0.36	0.05	<b>0.43</b>	<b>0.02</b>	-0.19	0.31	<b>0.48</b>	<b>0.01</b>
FM	0.34	0.07	<b>-0.53</b>	<b>0.00</b>	<b>0.51</b>	<b>0.00</b>	<b>0.65</b>	<b>0.00</b>	<b>-0.55</b>	<b>0.00</b>	<b>0.68</b>	<b>0.00</b>
BF%	0.28	0.14	<b>-0.53</b>	<b>0.00</b>	<b>0.49</b>	<b>0.01</b>	<b>0.62</b>	<b>0.00</b>	<b>-0.60</b>	<b>0.00</b>	<b>0.64</b>	<b>0.00</b>
Waist circumference	0.25	0.19	<b>-0.42</b>	<b>0.02</b>	<b>0.56</b>	<b>0.00</b>	<b>0.59</b>	<b>0.00</b>	<b>-0.54</b>	<b>0.00</b>	<b>0.72</b>	<b>0.00</b>
MUAC	0.32	0.08	<b>-0.46</b>	<b>0.01</b>	<b>0.49</b>	<b>0.01</b>	<b>0.58</b>	<b>0.00</b>	<b>-0.48</b>	<b>0.01</b>	<b>0.67</b>	<b>0.00</b>

**Note:** WHO, World Health Organization; BMI, body mass index; LBM, lean body mass; FM, fat mass; BF%, body fat percentage; MUAC, mid-upper arm circumference

**Results of follow-up visits**

Twenty-seven of the 30 patients completed the 24-week follow-up period. Two patients died before their 12-week visit and one was classified as lost-to-follow up after 20 weeks as she did not arrive for her appointment. Attempts to trace the patient were unsuccessful and no information on her whereabouts or health could be obtained. There were no significant differences in the baseline characteristics of the patients that completed the 24-week follow-up and those that did not.

Only one patient required an ARV drug change during the course of the study. This occurred two weeks after commencing HAART when the patient was diagnosed with TB which necessitated a switch from NVP to EFV. Five subjects had sub-optimal HAART adherence during the course of the study as determined from the self-reported assessment of adherence routinely recorded in the patient files.

None of the patients received nutritional supplements for any significant time period during the study as the supply of supplements from the South Africa Government at the clinic was inconsistent and patients eligible for the supplements did not receive them.

There was an overall improvement in nutrition-related symptom with fewer subjects reporting diarrhoea (7.4% vs. 30.0%), nausea (11.1% vs. 16.7%), vomiting (3.7% vs. 6.7%), mouth sores (3.7% vs. 26.7%), oral thrush (3.7% vs. 23.3%), difficulty swallowing (7.4% vs. 23.3%) and loss of appetite (22.2% vs. 46.7%) after 24 weeks on HAART. The majority of the patients had Karnofsky scores of 100% for the duration of the study with very little variation in the scores between baseline and the

24 week visit. At baseline 17 subjects (56.7%) had a Karnofsky score of 100% at versus 19 (70.4%) at the 24-week visit, eight (26.7%) had a score of 90% versus five (18.5%) at the 24-week visit and five (16.7%) had a score of less than 90% versus three (11.1%) at baseline. Two patients were hospitalised during the study period, both of them two weeks after the commencement of HAART, most likely due to Immune Reconstitution Inflammatory Syndrome (IRIS) and the ensuing effects.

The results of the questionnaire administered at the 24-week follow-up visit to determine any dietary changes after the initiation of HAART showed that 22 (81.5%) of the subjects who completed the 24-week follow-up, reported an increase in appetite since starting HAART. Twenty (74.1%) reported increased portion sizes and 11 (40.7%) reported an increase in the number of meals and/ or snacks they had per day. Sixty-three percent of the patients were employed at the end of the study period compared with 53.3% at baseline.

### **The effect of HAART on anthropometric and laboratory measures of patients**

The mean weight, BMI, MUAC, waist and hip circumferences and WHR at baseline and 12 and 24 weeks after the initiation of HAART are displayed in Table 4.3. The values for LBM, FM and BF% at baseline and after 24 weeks of HAART, as determined by BIA, are also presented as well as the mean changes for each of the anthropometric measures, between baseline and the 12-week visit and between baseline and the 24-week visit.

Overall, there was a statistically significant increase in all anthropometric measures after the initiation of HAART, except for WHR and LBM (Table 4.3). The mean weight

( $\pm$ SD) at baseline, after 12 weeks and after 24 weeks was  $63.7 \pm 16.0$  kg,  $66.0 \pm 15.9$  kg and  $68.2 \pm 15.0$  kg respectively. This was an average weight change of  $1.9 \pm 3.7$  kg ( $p = 0.011$ ) from baseline to 12 weeks and  $3.4 \pm 5.8$  kg ( $p = 0.006$ ) from baseline to 24 weeks. At the 24-week visit, nine (33.3%) subjects had a waist circumference  $\geq 80$ cm and 11 (40.7%) had a waist circumference  $\geq 88$  cm. Ten (37.0%) subjects had a WHR  $> 0.85$ .

The mean CD4 lymphocyte counts, viral loads, haemoglobin and serum albumin levels of the subjects at baseline and after 24 weeks on HAART are shown in Table 4.3. The changes in these parameters are also displayed. Overall the subjects experienced a mean ( $\pm$  SD) increase in CD4 lymphocyte count of  $120 \pm 114$  cell/mm<sup>3</sup> ( $p = 0.000$ ) and a mean decrease in viral load of  $2.7 \pm 1.2$  copies/mL ( $p = 0.000$ ) between baseline and the 24 week follow-up visit. Serum albumin levels also increased significantly after 24 weeks on HAART ( $29 \pm 8$  g/L to  $35 \pm 6$  g/L;  $p = 0.000$ ). The mean haemoglobin level at the 24 week visit did not differ significantly from the level at baseline ( $11.1 \pm 2.1$  g/dL to  $11.5 \pm 1.1$  g/dL;  $p = 0.340$ ).

Four (15.0%) of the patients who completed the follow-up period did not have undetectable viral loads at the 24-week visit. Twenty-two patients (81.5%) achieved a satisfactory immunological response to HAART. Four (15.0%) experienced a drop in CD4 lymphocyte count and one had an increase of less than 30% from baseline which is not considered to be a clinically significant increase.<sup>4</sup>

Discordant immunological and virological responses were seen in some patients. The five patients who did not achieved a satisfactory immunological response all had

undetectable viral loads and the four who did not have an undetectable viral load after 24 weeks all had satisfactory CD4 lymphocyte count increases.

**Table 4.3: Anthropometric and laboratory measures at baseline and after 12 and 24 weeks on HAART**

Variable	At baseline (n = 30)	12-week visit (n = 28)	Change	<i>p</i>	24-week visit (n = 27)	Change	<i>p</i>
Weight (kg)	63.7 ± 16.0	66.0 ± 15.9	1.9 ± 3.7	0.011	68.2 ± 15.0	3.4 ± 5.8	0.006
BMI (kg/m <sup>2</sup> )	25.6 ± 5.7	26.6 ± 5.7	0.8 ± 1.5	0.012	27.3 ± 5.6	1.4 ± 2.5	0.007
MUAC (cm)	28.3 ± 5.1	29.2 ± 4.8	0.7 ± 1.7	0.028	29.8 ± 4.4	1.1 ± 2.1	0.009
Waist circumference (cm)	84.5 ± 11.6	86.9 ± 11.3	2.3 ± 3.9	0.004	88.3 ± 11.2	3.3 ± 6.4	0.012
Hip circumference (cm)	98.6 ± 13.2	101.0 ± 13.4	2.1 ± 4.2	0.016	102.1 ± 11.8	2.6 ± 4.9	0.011
WHR	0.86 ± 0.05	0.86 ± 0.05	0.01 ± 0.02	0.178	0.86 ± 0.07	0.01 ± 0.04	0.294
LBM (kg)	41.9 ± 5.7	-	-	-	43.0 ± 6.2	0.7 ± 3.2	0.262
FM (kg)	21.8 ± 11.2	-	-	-	25.2 ± 9.5	2.7 ± 4.5	0.005
BF%	32.2 ± 9.7	-	-	-	35.7 ± 7.0	3.0 ± 5.2	0.006
CD4 cell count (cells/mm <sup>3</sup> )	164 ± 69	-	-	-	282 ± 154	120 ± 114	0.000
Viral load (log <sub>10</sub> copies/mL)	4.5 ± 1.2	-	-	-	1.7 ± 0.8	-2.7 ± 1.2	0.000
Haemoglobin (g/dL)	11.1 ± 2.1	-	-	-	11.5 ± 1.1	0.4 ± 1.9	0.340
Serum albumin (g/L)	29 ± 8	-	-	-	35 ± 6	4.6 ± 5.7	0.000

**Note:** Data are mean ± SD; - = not assessed at 12 week visit.

HAART, highly active antiretroviral therapy; BMI, body mass index; MUAC, mid-upper arm circumference; WHR, waist-to-hip ratio; LBM, lean body mass; FM, fat mass; BF%, body fat percentage.

Although the majority of the subjects gained weight (n=19; 70.4%) after 24 weeks on HAART, three (11.1%) lost weight and five (18.5%) had a body weight that remained stable. In those that gained weight the average weight gain was  $5.6 \pm 5.3$  kg ( $p = 0.000$ ) (range: 1.2 – 24.7 kg). The subjects that lost weight lost an average of  $4.6 \pm 1.6$  kg ( $p = 0.037$ ) (range: 2.9 – 6.0 kg) by the 24-week visit. The group of subjects that gained weight experienced significant increases in waist circumference, hip

circumference, LBM, FM and BF% while in the group that lost weight the changes in these measures were not statistically significant. Table 4.4 shows the changes observed in anthropometric and laboratory measures after 24 weeks of HAART for each weight change category. A statistically significant improvement in CD4 lymphocyte count was found in the weight stable group ( $p = 0.015$ ) and the group that gained weight ( $p = 0.000$ ) but not in the group that lost weight ( $p = 0.503$ ). Viral load decreased significantly in all of the groups.

Of the 19 patients who gained weight between baseline and the 24-week visit, the majority of the patients ( $n=13$ ; 68.4%) gained FM and six (31.6%) gained mostly LBM. Three of the five patients with a stable body weight lost FM and gained LBM while the proportions of FM and LBM remained stable in the other two. In the three patients that lost weight after commencing HAART, the weight loss consisted mainly of LBM.

Six patients had evidence of disproportionate gains and losses in body circumference measurements. Three patients experienced an increase in waist circumference and a simultaneous decrease in hip circumference and three patients experienced an increase in waist circumference with a simultaneous decrease in hip circumference and MUAC.

The mean values for anthropometric measurements at baseline and after 24 weeks, according to BMI category at baseline, are presented in Table 4.5. The changes in weight, CD4 lymphocyte count and viral load according to BMI category are presented graphically in Figures 4.1, 4.2 and 4.3 respectively.

**Table 4.4. Changes in anthropometric and laboratory measures after 24 weeks on HAART by weight change category**

Characteristic	Total (n = 27)	<i>p</i>	Weight loss group (n = 3)	<i>p</i>	Weight stable group (n = 5)	<i>p</i>	Weight gain group (n = 19)	<i>p</i>
Weight (kg)	3.4 ± 5.8	0.006	-4.6 ± 1.6	0.037	-0.5 ± 0.7	0.163	5.6 ± 5.3	0.000
BMI (kg/m <sup>2</sup> )	1.4 ± 2.5	0.007	-1.8 ± 0.6	0.038	-0.2 ± 0.3	0.266	2.3 ± 2.3	0.000
Waist circumference (cm)	3.3 ± 6.4	0.012	-2.5 ± 2.6	0.238	-0.3 ± 0.8	0.518	5.2 ± 6.8	0.004
Hip circumference (cm)	2.6 ± 4.9	0.011	-3.7 ± 2.9	0.161	-0.6 ± 1.3	0.322	4.4 ± 4.6	0.001
LBM (kg)	0.7 ± 3.2	0.262	-4.8 ± 3.8	0.159	1.2 ± 1.2	0.093	1.5 ± 2.7	0.031
FM (kg)	2.7 ± 4.5	0.005	0.2 ± 3.4	0.927	-1.7 ± 1.4	0.063	4.2 ± 5.2	0.001
BF%	3.0 ± 5.2	0.006	2.8 ± 5.4	0.461	-1.8 ± 1.2	0.033	4.2 ± 5.2	0.002
CD4 cell count (cells/mm <sup>3</sup> )	120 ± 114	0.000	49 ± 104	0.503	154 ± 84	0.015	123 ± 122	0.000
Viral load (log <sub>10</sub> copies/mL)	-2.7 ± 1.2	0.000	-3.1 ± 1.0	0.031	-3.5 ± 0.2	0.000	-2.5 ± 1.3	0.000
Haemoglobin (g/dL)	0.4 ± 1.9	0.340	0.0 ± 2.1	0.980	-0.8 ± 0.8	0.086	0.7 ± 2.1	0.140
Serum albumin (g/L)	4.6 ± 5.7	0.000	7 ± 3	0.070	2 ± 4	0.380	5 ± 6	0.003

**Note:** Data are mean ± SD. Weight loss group if lost > 1kg; weight stable group if weight changed by 1kg or less; weight gain group if gained >1 kg. HAART, highly active antiretroviral therapy; BMI, body mass index; LBM, lean body mass; FM, fat mass; BF%, body fat percentage.

The subjects in the normal weight BMI category gained a statistically significant amount of weight ( $5.9 \pm 7.4$  kg;  $p = 0.025$ ) while those in the underweight, overweight and obese categories did not ( $4.5 \pm 1.6$  kg;  $p = 0.161$ ;  $0.8 \pm 4.1$  kg,  $p = 0.605$  and  $1.8 \pm 3.5$  kg,  $p = 0.281$  respectively) (Figure 4.1).

CD4 lymphocyte count improved significantly in the normal weight ( $77 \pm 96$ ,  $p = 0.024$ ), overweight ( $200 \pm 142$ ;  $p = 0.005$ ) and obese ( $127 \pm 51$ ,  $p = 0.002$ ) groups but not in the underweight group ( $22 \pm 28$ ,  $p = 0.470$ ) (Figure 4.2). Viral load decreased by  $2.7 \pm 1.1$  ( $p = 0.000$ ) in the normal weight group,  $2.3 \pm 1.4$  ( $p = 0.002$ ) in the overweight group,  $2.8 \pm 1.0$  ( $p = 0.001$ ) in the obese group and  $4.3 \pm 0.7$  ( $p = 0.070$ ) in the underweight group (Figure 4.3). Two subjects changed from being normal weight at baseline to being overweight after 24 weeks and one changed from being normal weight to obese after 24 weeks. A statistically significant increase in LBM was only seen in the obese group while FM only increased significantly in the normal weight group.

Table 4.6 shows the changes in anthropometric and laboratory measures for the subjects receiving the different HAART regimens. FM and BF% increased significantly in the d4T, 3TC and EFV group but not in the other two regimen groups. The mean BMI in the AZT, 3TC, NVP group was  $28.2 \pm 5.9$  kg/m<sup>2</sup>, in the AZT, 3TC, EFV group it was  $27.9 \pm 5.5$  kg/m<sup>2</sup> and in the d4T, 3TC, EFV group it was  $24.2 \pm 5.4$  kg/m<sup>2</sup>.



**Table 4.5: Anthropometric and laboratory measures of subjects at baseline and after 24 weeks on HAART by BMI category at baseline**

Variable	Baseline				24-week visit							
	BMI < 18.5 (underweight) n = 2	BMI 18.5 - 24.9 (normal weight) n = 13	BMI 25 - 29.9 (overweight) n = 9	BMI = 30 (obese) n = 6	BMI < 18.5 (underweight) n = 2	<i>p</i>	BMI 18.5 - 24.9 (normal weight) n = 11	<i>p</i>	BMI 25 - 29.9 (overweight) n = 8	<i>p</i>	BMI = 30 (obese) n = 6	<i>p</i>
Weight (kg)	41.4 ± 1.2	55.0 ± 6.5	66.6 ± 5.8	88.3 ± 11.5	45.8 ± 0.4		60.9 ± 7.0		67.3 ± 6.3		90.0 ± 11.3	
Weight change (kg)					4.5 ± 1.6	0.161	5.9 ± 7.4	0.025	0.8 ± 4.1	0.605	1.8 ± 3.5	0.281
BMI (kg/m <sup>2</sup> )	16.4 ± 2.6	22.1 ± 1.6	27.3 ± 1.7	34.4 ± 2.5	18.1 ± 2.2		24.6 ± 3.2		27.6 ± 2.3		35.2 ± 2.8	
BMI change (kg/m <sup>2</sup> )					1.7 ± 0.4	0.111	2.5 ± 3.2	0.028	0.3 ± 1.6	0.580	0.7 ± 1.4	0.271
LBM (kg)	36.3 ± 1.9	38.5 ± 2.7	44.0 ± 4.5	49.0 ± 5.3	36.6 ± 0.2		39.6 ± 2.3		42.8 ± 3.3		51.7 ± 6.5	
LBM change (kg)					0.3 ± 2.1	0.869	1.1 ± 2.9	0.239	1.2 ± 3.8	0.384	2.7 ± 2.0	0.021
FM (kg)	5.1 ± 3.1	16.5 ± 4.9	22.5 ± 5.1	39.3 ± 6.9	9.2 ± 0.6		21.3 ± 5.8		24.6 ± 4.2		38.3 ± 5.9	
FM change (kg)					4.1 ± 3.7	0.358	4.8 ± 5.5	0.016	2.0 ± 2.5	0.054	-0.9 ± 2.6	0.413
BF%	12.2 ± 7.1	29.5 ± 5.9	33.7 ± 6.4	44.4 ± 2.7	20.1 ± 1.1		34.5 ± 5.8		36.3 ± 3.8		42.5 ± 2.9	
BF% change					8.0 ± 8.3	0.403	4.9 ± 5.5	0.014	2.6 ± 3.5	0.075	-1.8 ± 1.5	0.034
CD4 cell count (cells/mm <sup>3</sup> )	65 ± 57	165 ± 73	158 ± 85	191 ± 21	87 ± 28		242 ± 115		358 ± 215		318 ± 48	
CD4 cell count change (cells/mm <sup>3</sup> )					22 ± 28	0.470	77 ± 96	0.024	200 ± 142	0.005	127 ± 51	0.002
Viral load (log <sub>10</sub> copies/mL)	5.7 ± 0.7	4.5 ± 1.1	4.0 ± 1.4	4.3 ± 1.0	1.4 ± 0.0		1.8 ± 1.0		1.7 ± 0.9		1.5 ± 0.2	
Viral load change (log <sub>10</sub> copies/mL)					-4.3 ± 0.7	0.070	-2.7 ± 1.1	0.000	-2.3 ± 1.4	0.002	-2.8 ± 1.0	0.001

**Note:** Data are mean ± SD

HAART, highly active antiretroviral therapy; BMI, body mass index; MUAC, mid-upper arm circumference; WHR, waist-to-hip ratio; LBM, lean body mass; FM, fat mass; BF%, body fat percentage; WHO, World Health Organization

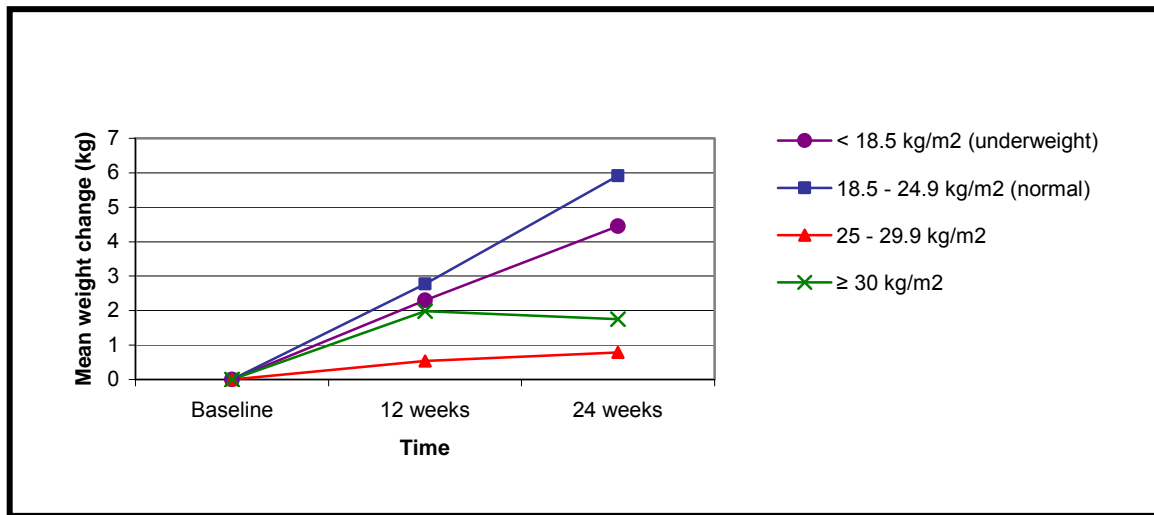


Figure 4.1: Mean change in weight from baseline according to baseline BMI category

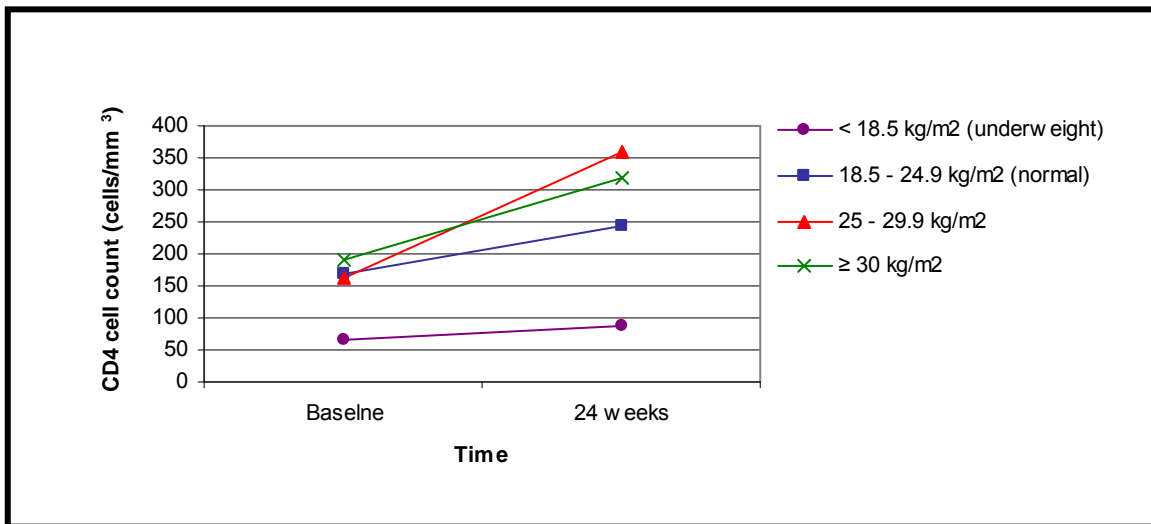


Figure 4.2: Mean change in CD4 lymphocyte count from baseline according to baseline BMI

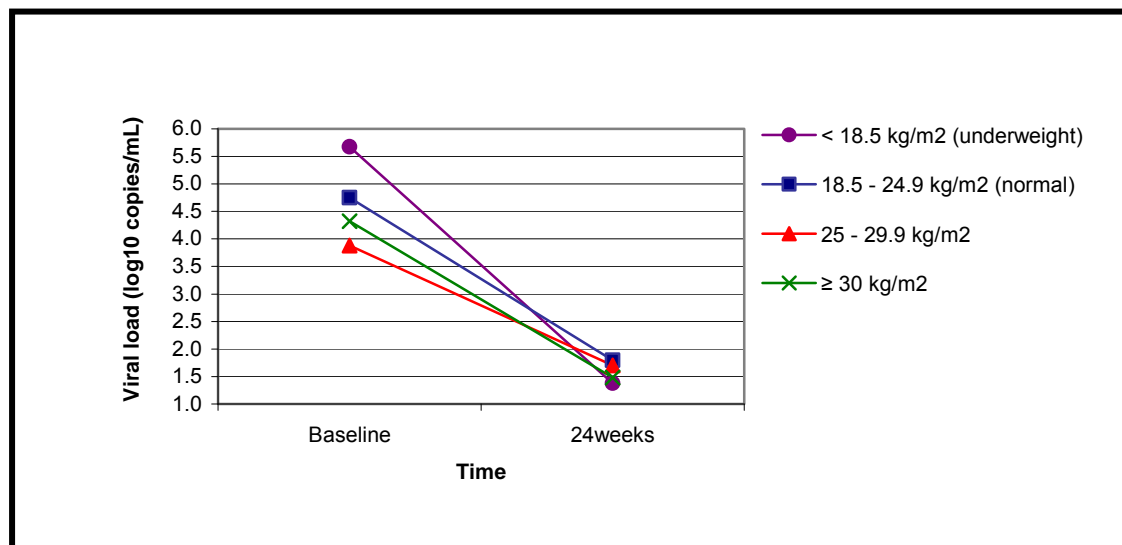


Figure 4.3: Change in viral load after commencement of HAART according to BMI category at baseline

### **Relationship between laboratory parameters at baseline and changes in anthropometric measures after 24 weeks of HAART.**

A weak but statistically significant negative linear correlation was found between CD4 lymphocyte count at baseline and changes in weight ( $r_s = -0.40$ ;  $p = 0.04$ ), BMI ( $r_s = -0.40$ ;  $p = 0.04$ ) and BF% ( $r_s = -0.41$ ;  $p = 0.02$ ) between baseline and after 24 weeks on HAART but not between changes in MUAC, waist circumference, hip circumference, WHR or LBM. A significant modest correlation was found between baseline CD4 lymphocyte count and change in FM ( $r_s = -0.53$ ;  $p = 0.00$ ).

For baseline haemoglobin, the correlation with changes in weight, BMI, MUAC, waist circumference, hip circumference, BF% was also weak but significant ( $r_s = -0.46$ ;  $p = 0.02$ ,  $r_s = -0.44$ ;  $p = 0.02$ ,  $r_s = -0.45$ ;  $p = 0.02$ ,  $r_s = -0.41$ ;  $p = 0.03$ ,  $r_s = -0.43$ ;  $p = 0.03$ , and  $r_s = -0.39$ ;  $p = 0.04$  respectively). The correlation was strongest between baseline haemoglobin and change in FM ( $r_s = -0.57$ ;  $p = 0.00$ ).

Changes in weight that occurred after the initiation of HAART seem to differ according to whether haemoglobin at baseline was below normal or within the normal range with those with low haemoglobin levels having greater increases in weight,  $6.0 \pm 7.6$  kg (95% CI, 0.9 – 11.1) versus  $1.6 \pm 3.4$  kg (95% CI, -0.2 – 3.3). This difference was statistically significant ( $p = 0.049$ ). Changes in FM and MUAC also differed significantly ( $p = 0.008$  and  $p = 0.024$  respectively) between those with a low haemoglobin ( $5.3 \pm 5.2$  kg and  $2.2 \pm 0.6$  cm) and those with a normal haemoglobin level at baseline ( $0.8 \pm 2.9$  kg and  $0.4 \pm 0.5$  cm).

**Table 4.6: Changes in anthropometric and laboratory measures between baseline and 24 weeks according to HAART regimen**

Variable	AZT, 3TC, NVP (n = 15)	<i>p</i>	AZT, 3TC, EFV (n = 7)	<i>p</i>	d4T, 3TC, EFV (n = 5)	<i>p</i>
Weight (kg)	1.9 ± 3.6	0.065	2.1 ± 3.5	0.176	8.6 ± 10.6	0.146
BMI (kg/m <sup>2</sup> )	0.8 ± 1.4	0.052	-0.8 ± 1.4	0.172	3.6 ± 4.7	0.160
Waist circumference (cm)	1.3 ± 2.1	0.033	3.0 ± 4.2	0.114	9.5 ± 12.9	0.174
Hip circumference (cm)	0.6 ± 2.7	0.385	2.4 ± 3.8	0.150	7.4 ± 8.1	0.111
LBM (kg)	0.3 ± 2.8	0.659	1.4 ± 1.8	0.086	0.3 ± 5.9	0.902
FM (kg)	1.6 ± 3.7	0.130	-0.7 ± 2.0	0.425	8.2 ± 5.6	0.031
BF%	1.9 ± 4.7	0.162	-0.1 ± 1.6	0.829	10.1 ± 4.1	0.005
CD4 cell count (cells/mm <sup>3</sup> )	193 ± 103	0.000	57 ± 77	0.097	35 ± 27	0.042
Viral load (log <sub>10</sub> copies/mL)	-2.4 ± 1.1	0.000	-2.6 ± 1.3	0.002	-3.9 ± 0.8	0.000
Haemoglobin (g/dL)	0.0 ± 1.2	0.916	-1.0 ± 1.4	0.129	3.3 ± 1.3	0.004
Serum albumin (g/L)	5 ± 6	0.010	1 ± 3	0.587	10 ± 4	0.003

**Note:** Data are mean ± SD. HAART, highly active antiretroviral therapy; AZT, zidovudine; 3TC, lamivudine; NVP, nevirapine; EFV, efavirenz; d4T, stavudine; BMI, body mass index; LBM, lean body mass; FM, fat mass; BF%, body fat percentage.

There was no significant correlation between changes in any of the anthropometric measures with baseline viral load or with baseline serum albumin levels. WHO stage at baseline was also not associated with changes in anthropometric measures occurring after the initiation of HAART.

Baseline CD4 lymphocyte count was not correlated with any of the anthropometric measures at the 24-week visit. Baseline viral load was significantly correlated with the following anthropometric measures at the 24-week visit: weight ( $r_s = -0.45$ ;  $p = 0.02$ ), LBM ( $r_s = -0.44$ ;  $p = 0.02$ ), FM ( $r_s = -0.40$ ;  $p = 0.04$ ) and MUAC ( $r_s = -0.45$ ;  $p = 0.02$ ).

Baseline haemoglobin did not correlate significantly with any anthropometric measurements at the 24-week visit while baseline albumin levels correlated with the following anthropometric measures at the 24-week visit: weight ( $r_s = 0.47$ ;  $p = 0.01$ ), BMI ( $r_s = 0.47$ ;  $p = 0.01$ ), LBM ( $r_s = 0.40$ ;  $p = 0.04$ ), FM ( $r_s = 0.49$ ;  $p = 0.01$ ), BF% ( $r_s = 0.41$ ;  $p = 0.03$ ) and MUAC ( $r_s = 0.47$ ;  $p = 0.01$ ).

Baseline WHO stage was significantly associated with weight ( $r_s = -0.46$ ;  $p = 0.02$ ), BMI ( $r_s = -0.50$ ;  $p = 0.01$ ), FM ( $r_s = -0.55$ ;  $p = 0.00$ ), BF% ( $r_s = -0.58$ ;  $p = 0.00$ ), waist circumference ( $r_s = -0.52$ ;  $p = 0.01$ ) and MUAC ( $r_s = -0.44$ ;  $p = 0.02$ ) at the 24-week visit. The relationship between Karnofsky score at baseline and all anthropometric measurements at the 24-week visit was statistically significant and correlations were as follows: weight ( $r_s = 0.64$ ;  $p = 0.00$ ), BMI ( $r_s = 0.58$ ;  $p = 0.00$ ), LBM ( $r_s = 0.55$ ;  $p = 0.00$ ), FM ( $r_s = 0.62$ ;  $p = 0.00$ ), BF% ( $r_s = 0.56$ ;  $p = 0.00$ ), waist circumference ( $r_s = 0.61$ ;  $p = 0.00$ ) and MUAC ( $r_s = 0.67$ ;  $p = 0.00$ ).

### **Relationship between baseline anthropometric measures and changes in laboratory parameters after 24 weeks on HAART.**

Change in CD4 lymphocyte count between baseline and 24 weeks was not significantly associated with any of the baseline anthropometric measurements, except for MUAC with which there was a modest but significant positive correlation ( $r_s = 0.40$ ;  $p = 0.04$ ).

Change in viral load between baseline and 24 weeks showed a significant correlation in a positive direction with the following baseline anthropometric values: weight ( $r_s = 0.44$ ;  $p = 0.01$ ), LBM ( $r_s = 0.37$ ;  $p = 0.04$ ), FM ( $r_s = 0.43$ ;  $p = 0.02$ ), BF% ( $r_s = 0.38$ ;  $p = 0.04$ ) and MUAC ( $r_s = 0.41$ ;  $p = 0.02$ ).

The only baseline anthropometric measure that was correlated with change in serum albumin after commencing HAART was BF% ( $r_s = -0.41$ ;  $p = 0.03$ ).

Correlation analysis of baseline anthropometric measures, including baseline weight, BMI, MUAC, LBM, FM and BF%, with immunological response (an optimal response being a significant rise in CD4 lymphocyte count of 30% from baseline value) and virological response (an optimal response being an undetectable viral load) after 24 weeks of HAART, showed no association.

A significant difference was found between patients with a haemoglobin value in the normal range after 24 weeks of HAART and those with a haemoglobin level below normal with respect to their BMI, MUAC, FM and BF% at baseline. Those with a haemoglobin level below 11.5 g/dL had lower BMI values ( $23.4 \pm 5.0 \text{ kg/m}^2$  vs.  $28.3 \pm$

5.7 kg/m<sup>2</sup>;  $p = 0.031$ ), lower MUAC values ( $26.3 \pm 4.2$  cm vs.  $30.9 \pm 5.1$  cm;  $p = 0.031$ ), lower FM ( $17.8 \pm 9.6$  kg vs.  $26.8 \pm 11.5$  kg;  $p = 0.033$ ) and lower BF% ( $28.8 \pm 10.4$  % vs.  $36.5 \pm 7.8$  %;  $p = 0.037$ ) before commencing HAART.

No differences were found between those with an albumin level below the cut-off of 35 g/dL compared with those with an albumin level within the normal range at week 24 with respect to their baseline weight, BMI, MUAC, LBM, FM or BF%.

Chi-square tests to investigate whether or not a difference existed in the immunological and virological response to HAART according to BMI category was carried out. No significant relationships were found between baseline BMI category and likelihood of achieving an undetectable viral load or a significant improvement in CD4 from baseline (taken to be a 30% change in a positive direction from baseline value).

#### **Relationship between changes in anthropometric measures and changes in laboratory parameters after 24 weeks of HAART.**

Correlation analysis found no significant linear association between changes in weight, BMI, MUAC, waist circumference, hip circumference, WHR, LBM, FM or BF% between baseline and the 24 week follow-up visit and changes in CD4 lymphocyte count, viral load or serum albumin. Only BF% showed a trend towards a positive correlation with change in serum albumin which approached statistical significance ( $r_s = 0.38$ ;  $p = 0.05$ ).

## CHAPTER 5: DISCUSSION

### **Changes in anthropometric measures after the initiation of HAART**

Overall the patients who participated in this study underwent significant changes in the most of the anthropometric measures assessed. Mean weight, BMI, MUAC, waist circumference, hip circumference, FM and BF% all increased significantly after the initiation of HAART. Only mean WHR and LBM did not increase significantly. Shikuma *et al*<sup>18</sup> and Mallon *et al*<sup>19</sup> reported increases in LBM after the initiation of HAART but the reasons for this observation were not examined. LBM has been found to be associated with improved functional performance in patients receiving HAART<sup>18</sup> and therefore identifying ways of improving lean mass in HIV-infected individuals receiving HAART may prove valuable. The high BF% and the absence of a significant increase in LBM in these subjects may indicate a lack of participation in behaviour that would promote a reduction in body fat and gain in LBM, such as involvement in physical activity.

In accordance with the results of the study by Saghayam *et al*<sup>31</sup>, some patients gained weight, some lost weight and in some body weight remained stable during the 24 week follow-up period. Some of the patients gained considerable amounts of weight after just 24 weeks on HAART. Although a thorough assessment of dietary changes was beyond the scope of this study, the results of the questionnaire administered at the 24-week visit did show that the majority of the subjects reported an increase in appetite and portion size which may have contributed to the increase in body weight experienced by the majority of the subjects.



The majority of the weight gain in most patients was attributable to increased FM and this is consistent with the findings of the study by Silva *et al.*<sup>32</sup> Accumulation of fat, and especially accumulation of fat in the abdominal area, are known to be associated with increased risk of NCDs in the general population<sup>14</sup> but the implications of increased FM for the health of patients receiving HAART in South Africa requires investigation.

Wasting remains a problem for some patients even after the commencement of HAART and this was evident in this study.<sup>10,12</sup> In the three patients that lost weight, the loss was composed mostly of LBM and this is well known to be prognostically unfavourable.<sup>12</sup> In this study, despite the loss of lean mass all three subjects achieved viral suppression by the 24-week visit. One experienced a reduction in CD4 lymphocyte count but the other two had adequate CD4 lymphocyte count responses. Two of the three patients that lost weight were known to live in food insecure households and the other reported that she lost weight intentionally.

Some patients had a stable body weight for the duration of the study but experienced changes in the relative proportions of fat and lean mass. Possible explanations for the improvement in LBM include improvements in muscle mass as a result of an increase in activity levels associated with an overall improvement in health after starting HAART or dietary changes.

Another noteworthy observation was the disproportionate change in circumference measures seen in some patients. These changes may be indicative of fat redistribution, during which it is common for patients to experience fat loss from the

buttocks and extremities and/ or an increase in abdominal fat mass.<sup>23</sup> This finding highlights the usefulness of circumference measurements. Although d4T is most commonly implicated, abnormal body fat changes have also been reported in patients taking AZT.<sup>30</sup> In this study, none of the patients with disproportionate changes were receiving a regimen containing d4T.

The above-mentioned findings all signify the importance of examining body composition in addition to the measurement of body weight in the assessment of nutritional status.

The results of this study illustrate that changes in body composition and other anthropometric measures may differ according to HAART regimen, BMI category and weight change category, but this should be examined in future studies with larger samples as the small number of subjects in this study does not allow for any definitive conclusions to be drawn.

### **Relationship between anthropometric measures and laboratory measures**

The investigation for relationships between various laboratory parameters and anthropometric measures revealed some interesting associations. Comparison of the results with those of other studies that have investigated the relationship between anthropometric measures and laboratory measures, including CD4 lymphocyte count and viral load, is not easily accomplished due to the different study designs and methodology used.

In this study, subjects with a higher viral load, lower haemoglobin level and higher WHO stage at baseline had a significantly lower weight, BMI, MUAC, waist circumference, FM and BF% at baseline compared with those who had lower viral loads, higher haemoglobin levels and lower WHO stage. Only albumin level and Karnofsky score at baseline showed a statistically significant association with all anthropometric measures, including LBM, at baseline.

From the results, it can be seen that CD4 lymphocyte count and haemoglobin level at baseline appear to have a role in the changes that occur in some anthropometric measures after the initiation of HAART but not others. Subjects with lower CD4 lymphocyte counts experienced greater increases in weight, BMI, FM and BF%. Larger increases in weight, BMI, MUAC, waist circumference, hip circumference, FM and BF% were seen in those with lower baseline haemoglobin levels. The finding that patients with more severe immunosuppression at baseline experienced greater increases in body weight on HAART is supported by the results of the study by Shikuma *et al.*<sup>18</sup> Viral load and serum albumin at baseline were not associated with any anthropometric changes between baseline and the 24-week visit.

Subjects that had a haemoglobin level within the normal range after 24 weeks on HAART had a higher BMI, MUAC, FM and BF% at baseline compared with those who did not. Haemoglobin has been found to be a significant marker of disease progression and a good indicator of prognosis.<sup>44</sup> The above finding may therefore be explained by the fact that those with a normal haemoglobin level at week 24 generally had normal haemoglobin levels at baseline indicating that they may have been less ill at the time of starting HAART and less likely to have experienced

significant weight loss. The relationship between anthropometric status at baseline and achievement of viral suppression, a significant improvement in CD4 lymphocyte count or a normal serum albumin level at week 24 was not significant. This may be due to the fact that very few of the subjects in this study were nutritionally compromised at baseline and almost all of the subjects achieved viral suppression and a significant increase in CD4 cell count. The number of subjects that failed to have adequate immunological and virological responses was too small to allow for comparison of between those that did and did not have a satisfactory response.

In the current study, no significant correlation was found between changes in any of the anthropometric measures with changes in CD4 lymphocyte count or viral load. Previous studies have reported conflicting results. In a study by Mwamburi *et al*<sup>37</sup> changes in CD4 lymphocyte count were associated with changes in weight but changes in viral load were not. Other researchers have reported a positive correlation between viral load decreases and increases in weight.<sup>18,32</sup> Subjects that had not achieved an undetectable viral load by week 24 had still experienced increases in weight and BMI. This is substantiated by the results of a study by Messou *et al*<sup>36</sup> which concluded that changes in BMI cannot predict virological response.

### **Overweight and obesity**

A considerable proportion of the subjects (50.0%) enrolled into this study had a BMI above the upper limit of the normal range at baseline. The mean BMI of the patients at baseline was  $25.6 \pm 5.7 \text{ kg/m}^2$  and this increased to  $27.3 \pm 5.6 \text{ kg/m}^2$  by the 24-week visit. These values lie within the overweight range of 25 – 29.9  $\text{kg/m}^2$ . This is

consistent with data from other studies which have found a high prevalence of overweight and obesity in HIV-infected populations and is cause for concern.<sup>28,29</sup>

Firstly, because of the well known health risks associated with overweight and obesity in the general population, which include Type 2 diabetes mellitus, hypertension and dyslipidaemia and secondly because this may mean that a large proportion of HIV-infected individuals may not seek care and healthcare professionals may not identify them for HIV testing as a result of the common misconception that they are “healthy”, when in fact they may already be eligible for HAART.<sup>46</sup> Also, the stigma associated with HIV is still rife and needs to be addressed as the desire to gain weight to avoid being stigmatised for appearing thin and ill is still expressed by many patients, even those who have a normal or above normal BMI.

Although the risks of overweight and obesity in the HIV-infected population specifically are not known, it seems prudent to ensure that patients are cautioned against excessive weight gain due to the association between overweight and obesity and adverse health outcomes in the general population. The optimal nutritional advice to be given to overweight and obese HIV-infected patients remains to be determined and the effects of weight loss, even if it is intentional, on the health of patients on HAART in South Africa requires investigation.

## **CHAPTER 6: CONCLUSION, RECOMMENDATIONS AND LIMITATIONS**

### **CONCLUSION**

In summary, the results of this pilot study demonstrate that significant changes in various anthropometric measures occur in some, but not all patients after the initiation of HAART. Overall, patients seem to experience an increase in most anthropometric measures and there appears to be a relationship between some anthropometric measures and immunological and virological parameters.

The findings of this study demonstrate the value of including circumference measurements and body composition assessment techniques as part of the assessment of nutritional status. These measurements would not necessarily need to be done at every visit but may prove useful in decisions regarding patient management if performed at regular intervals, such as 6 monthly or even on an annual basis.

The issue of overweight and obesity warrants attention and studies are urgently needed to determine the prevalence and significance of overweight and obesity in HIV-infected individuals in South Africa in the era of HAART. This information should then be used to develop appropriate guidelines which should be incorporated into the documents that are available to guide healthcare workers in the management of patients. Many of the guidelines and policy documents available, as well as information available to patients in the form of pamphlets, make little, if any mention of the issue of overweight and obesity with the focus being on underweight individuals and wasting.

As the patient load at most ARV clinics increases while there is a drive to meet the goals of the NSP, there is a need for research to be conducted to enable the development of population-specific guidelines and policies to guide the management of these patients.

Patients who lose weight on HAART may need to be monitored closely and possible causes of the weight loss need to be identified and managed appropriately. Food insecurity is still a huge problem and with the dramatic food price increases more households will become food insecure. A concerted effort needs to be made to ensure that suitable and sustainable interventions are available for patients in need.

Another important area requiring research is the relationship between weight loss, whether intentional or not, in patients on HAART and immunological and virological outcome. The optimal weight loss strategy for overweight and obese patients who express the desire to lose weight also remains to be determined.

The long-term aim of ART is to enable patients to enjoy not only better health but more productive lives and an optimal nutritional status is fundamental to survival, health and quality of life.

## **RECOMMENDATIONS AND LIMITATIONS**

The sample for this study was drawn from a population that is not necessarily representative of the HIV-infected population receiving HAART in the primary healthcare setting of South Africa. Only females were included in the study and the results cannot therefore be generalised to male patients.

Due to the small sample size, the investigator was unable to control for potential confounding factors, such as the baseline characteristics of the subjects and morbidity factors which included TB and the presence of nutrition-related symptoms such as diarrhoea. Another limitation is the fact that the impact of sub-optimal adherence to HAART was not analysed. The changes that were observed may therefore have been independently associated with other factors not analysed. Future studies should adjust for these variables during analysis.

Larger studies should also stratify patients according to their HAART regimens, BMI categories and their weight change category (weight stable, weight loss or weight gain) as the results of this pilot study show that important differences may exist according to these characteristics. The methods used in this pilot study and the information generated can be used to guide the planning and design of future studies to investigate the changes in nutritional status after the commencement of HAART.

A thorough assessment of changes in dietary intake after the initiation of HAART was beyond the scope of this study but it is an important component of comprehensive nutritional status assessment and should be examined in future studies. The questionnaire administered at the 24-week visit was used only to obtain a rough estimate of dietary changes since the commencement of HAART and due to time constraints and the complexity of the study, face and content validity of the questionnaire were not tested.



Assessment of physical activity levels is also an important aspect that should be considered for future research and including the measurement of metabolic parameters, such as blood glucose and lipid levels, and investigating the relationship between anthropometric measures and these metabolic parameters, would be valuable. The use of supplements prior to HAART being initiated should also be assessed.

Larger studies of longer duration should be carried out to examine the changes in anthropometric measures that occur after the initiation of HAART and to more clearly describe the relationship between anthropometric measures and virological and immunological parameters. The anthropometric changes that occur are likely to be multifactorial and the reasons for these changes require investigation. Further research should also be undertaken to evaluate the prevalence and risk factors for lipodystrophy syndrome in South Africa.

Once a more thorough understanding of the anthropometric changes that occur after the initiation of HAART is obtained, research should be undertaken to determine the best methods of bringing about the most favourable anthropometric changes to enhance the health and quality of life of patients on HAART.

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## Appendix 1

17 July 2007

Ms FM Esposito  
C/o Mrs J Visser  
Division of Human Nutrition  
Dept of Interdisciplinary Health Sciences

Dear Ms Esposito

RESEARCH PROJECT : "IMPACT OF HIGHLY ACTIVE ANTI-RETROVIRAL THERAPY (HAART) ON BODY COMPOSITION AND OTHER ANTHROPOMETRIC MEASURES OF HIV-INFECTED WOMEN IN A PRIMARY HEALTHCARE SETTING IN KWAZULU-NATAL: A PILOT STUDY"

PROJECT NUMBER : N07/06/139

*It is my pleasure to inform you that the abovementioned project has been provisionally approved on 16 July 2007 for a period of one year from this date. You may start with the project, but this approval will however be submitted at the next meeting of the Committee for Human Research for ratification, after which we will contact you again.*

Notwithstanding this approval, the Committee can request that work on this project be halted temporarily in anticipation of more information that they might deem necessary to make their final decision.

*Please note that a progress report (obtainable on the website of our Division) should be submitted to the Committee before the year has expired. The Committee will then consider the continuation of the project for a further year (if necessary). Annually a number of projects may be selected randomly and subjected to an external audit.*

In future correspondence, kindly refer to the above project number.

I wish to remind you that patients participating in a research project at Tygerberg Hospital will not receive their treatment free, as the PGWC does not support research financially.

The nursing staff of Tygerberg Hospital can also not provide extensive nursing aid for research projects, due to the heavy workload that is already being placed upon them. In such instances a researcher might be expected to make use of private nurses instead.

Yours faithfully

**CJ VAN TONDER**  
**RESEARCH DEVELOPMENT AND SUPPORT (TYGERBERG)**  
Tel: +27 21 938 9207 / E-mail: cjvt@sun.ac.za

CJVT/pm



## Appendix 1

>>> "Herselman, Marietjie, Prof <mgh@sun.ac.za>" <MGH@sun.ac.za> 2007/07/19 09:51 AM >>>

Dear Prof Coutsooudis,

### Use of the March data set

The Postgraduate Programme Committee convened an ad hoc meeting on 17 July to consider your request that Francesca uses the data she has already collected since March for her thesis. The Committee agreed to this request, provided the protocol that was approved by the Ethics Committee of Stellenbosch University (US) is the same as the protocol that was used for her study. If there is a difference, she will not be able to make any statements on the protocol being approved by the US Ethics committee in any forthcoming publications.

I trust this information clarifies the issues raised.

May I wish you success with your research programme and Francesca's contribution to it.

Best Regards,

Marietjie

### **Marietjie Herselman**

Associate Professor and Acting Head: Division of Human Nutrition,  
Dept of Interdisciplinary Health Sciences, Faculty of Health Sciences, PO Box 19063, Tygerberg 7505, South Africa

**Tel:** +27 21 938 9256 **Mobile:** 082 8212430 **Fax:** +27 21 933 2991

**E-mail:** [mgh@sun.ac.za](mailto:mgh@sun.ac.za)

Dear Prof Herselman

Thank you very much for convening an ad hoc committee meeting so speedily to consider the request that Ms Esposito be allowed to use the data she has been collecting since the protocol was approved by the UKZN. I wish to confirm that the protocol approved by UKZN is indeed the same protocol that she is using for her masters research project and would therefore appreciate it if the University of Stellenbosch provides Ms Esposito approval to include all the data she has collected since March 2007. Written, informed consent was provided by all patients enrolled in the study.

## Appendix 2



**Department of Paediatrics and Child Health  
Room 257, DDMRI Building  
Nelson R Mandela School of Medicine  
Private Bag 7  
Congella 4013  
South Africa**

**Phone: 27-31-2604489**

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**19 March 2007**

**Francesca Esposito  
Dietetics Dept  
Stellenbosch University**

Dear Francesca

Re: research project "Impact of HAART on anthropometric measures and body composition of HIV positive women in a primary health care setting in KwaZulu-Natal"

This is to inform you that the ethics committee has approved amendments to my study to enable you to undertake the above research proposal – please see attached letter. You therefore now have ethical clearance to undertake your study.

Yours sincerely

A handwritten signature in black ink, appearing to read "A. Coutsooudis".

Prof Anna Coutsooudis

## Appendix 2



19 March 2007

Professor A Coutsoodis  
Paediatrics  
Nelson R Mandela School of Medicine

Dear Professor Coutsoodis

**PROTOCOL: Pilot programme: Implementing care and anti-retroviral therapy to HIV infected mothers (and their families) in resource constrained settings. A Coutsoodis, Paediatrics. Ref: E121/02**

Your letter dated 6 February 2007 in response to our query raised on 01 February 2007 has been noted and approved by a sub-committee of the Biomedical Research Ethics Committee. Your Protocol Amendment dated 16 November 2006 has been approved to allow you to include dietary intake assessment and body composition measures of adult patients on HAART.

A full sitting of the Committee will be advised of this decision at the next meeting to be held on 10 April 2007.

Yours sincerely

Suraiya Buccas  
Ethics Research Administrator

## Appendix 3

### **The MTCT Plus Programme/ iKhaya Lempilo: Providing care (including antiretrovirals) for HIV infected mothers and their families**

#### **INVITATION TO PARTICIPATE IN THE CARE PROGRAMME:**

You are invited to participate in a care programme to improve the quality of life of HIV infected mothers and their families. You have been asked to participate in this programme because you have been tested and shown to have a positive HIV test and we believe that by your participation in this programme we can assist you to have a better quality of life.

In order to decide whether or not you wish to be part of this programme you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the research study, which a member of the care team will discuss with you. This discussion will go over all the points of this care programme: its purpose, the procedures that will be performed, any risks of the procedures, and possible benefits. Once you understand the study, you will be asked if you wish to participate. If so, you will be asked to sign this form. This process is known as informed consent.

#### **PURPOSE OF THE STUDY:**

The purpose of this programme is to provide care and treatment of HIV infected mothers and their families and to record all the benefits to those on treatment as well as any side effects. In order to check if the treatments are safe we will do clinical examinations as well as blood tests. All this information will be carefully recorded and used to recommend to the government what, and how care and treatment for HIV infected people should be introduced in the public health system.

#### **BACKGROUND:**

Treatment with antiretroviral drugs in wealthy countries which can afford the expensive drugs has been shown to improve the health of HIV infected people. The price of drugs has been reduced considerably because of the pressure that the world has put on the drug companies. This has made it possible for us to now offer treatment to some people. Before the government can implement it for everyone they need to see how effective the treatment will be in South African people and if there are any serious side effects. Another problem is that the virus that causes AIDS is a very dangerous virus because it can quickly become resistant to the drugs and escape their effect – this happens if the level of drug in your blood is too low because you have not taken your medication at the right time every day. If a person feels that they cannot keep to the schedule of drugs your health team will advise you to wait until you are ready to be able to take the drugs at the right time and every day. They will help you develop ways of keeping to your schedule.

## Appendix 3

### DESCRIPTION OF PROCEDURES:

After the programme has been carefully explained to you, if you agree to participate in this programme you will be asked to provide written informed consent. During the screening visit you will also be asked what medications you are taking, about your medical history, and you will be given a brief physical exam. You may be excluded from the anti-retroviral drug treatment part of the programme if you have a medical condition, which could make it unsafe for you to receive these drugs. However you will receive all the other aspects of care to help you have a healthier life.

Once you have entered the programme you will have a second visit (for women this will be at the 6 week postpartum visit); at this visit blood tests will be performed so that we can check the level of your body's immunity so we can determine if you need to be started on anti-retroviral medication. You will have about 1½ tablespoons of blood drawn at this time. These blood tests will be repeated every 6 months. You will also receive medication-taking training.

If you are a woman, able to have children, you will be asked about your contraception methods and we will suggest tubal ligation as the best option as some of the drugs may be harmful for an unborn baby and a new pregnancy will put a strain on you and not give you the full benefit of the drugs which are given to you to keep you healthy for longer.

Each month, you will receive additional medication taking training to prepare you in case you need to start taking anti-retroviral drugs. When the number of white blood cells (which fight infection) in your blood drop to very few cells you may commence taking anti-retroviral drugs which will stop the virus from replicating and therefore will stop the virus from destroying your white blood cells. You need to know that not everyone whose white blood cell count drops will be able to start treatment because we have a limit on funds and only 50 people a year will be able to receive drugs. Because of the danger of not adhering to the drugs we have to have certain criteria to allow people to go onto drugs so that only those who will benefit from the drugs will go onto drugs – these are:

- Live near to the clinic
- Have disclosed your status to one other person who will be able to support you emotionally
- Be prepared to have home visits from our counselors to assist you with adhering to your drugs
- If you are a woman you will need to be on contraception, preferably have a tubal ligation

You need to know however that if you and/or the team decide that you will not take drugs you will still remain part of the programme and will receive all other aspects of care that are available such as psychological, emotional, and spiritual support. In addition you will be able to visit the clinic on any day to see the doctor or counselors.

If you are started on anti-retroviral treatment you will also have blood tests every 6 months to check the health of your liver, so that we can be sure that the drugs are

## Appendix 3

not affecting your liver and we will continue checking the white blood cell count to check that the drugs are improving your immunity.

Once you are commenced on anti-retroviral drugs you will be provided with the medication for life.

### **RISKS OR DISCOMFORTS:**

If you are receiving anti-retroviral drugs you will receive licensed medications, each of which may have side effects and toxicities. Each patient will be individually assessed and a combination of drugs will be suggested for them. You will be explained the side effects of each drug you are given and if you experience any side effects you must report to the clinic for a check-up or phone the emergency number you will be given.

You will have periodic blood tests. Taking blood may cause some discomfort, bleeding, or bruising where the needle enters the body, and, in rare cases, fainting or bleeding.

### **RISKS OF PREGNANCY:**

Some drugs may have an effect on the developing child in early pregnancy and thus becoming pregnant prior to or during taking this medication is strongly discouraged. Therefore, women of childbearing potential (that is, not surgically sterile or post menopausal) who participate in this study must practice effective birth control or we would recommend tubal ligation.

### **POTENTIAL BENEFITS:**

This programme will benefit you directly as you will receive treatment for any infections which you may develop e.g. TB, candida, pneumonia and you may also receive drugs for the treatment of HIV/AIDS. In addition, you will receive training in medication taking. You will also be given psychological, emotional, spiritual and nutritional support and will be assisted in finding out if there are any social services you may access. Finally you will have the satisfaction of contributing to our understanding of the proper way to treat people with HIV/AIDS.

### **CONFIDENTIALITY:**

Your confidentiality will be protected to the extent of legal requirements and clinical research practice. All records will be kept in locked files and/or within limited access, code protected computer files, available only to investigators, study personnel and study monitors.

Any publication or presentation of study results will not identify you by name.

**IN CASE OF DRUG COMPLICATIONS:**

In the event of any complications from drugs, medical care will be available by the research staff of the Umkhumbane Clinic. For any complications which require hospitalization we will organize for you to be hospitalized at King Edward Hospital or McCord's Hospital.

**VOLUNTARY PARTICIPATION:**

You are free to decide whether or not you wish to participate in this programme and may withdraw from the programme at any time. You are also free to decide to participate in all aspects of the programme and there is no pressure on you to take drugs if you prefer not to. Your decision not to participate or to withdraw will not affect your relationship with the sisters and doctors at Umkhumbane Clinic or King Edward Hospital. You should however bear in mind that should you withdraw from the programme while you are receiving anti-retroviral treatment it would not be a good idea as the virus will develop resistance to being treated with the medication when you decide to restart treatment.

**INVOLUNTARY WITHDRAWAL:**

You may be discontinued from study participation for the following reasons:

- a. If the study doctor or your primary care provider decides it is not in your best interest to continue.
- b. If you do not follow programme procedures or miss clinic appointments.
- c. If you do not follow clinic policies or are disruptive to the programme.

**QUESTIONS:**

We have used some technical terms in this form. Please feel free to ask anything you don't understand and to consider this research and the consent form carefully - as long as you feel is necessary-before you make a decision. If you have questions you can contact the programme director, Prof Anna Coutsooudis (083 788 6363), or the study clinician, Dr Gurpreet Kindra (082 9631921), or the counsellor, Mrs Thembi Ngubane (031-2615675).

If you have any concerns about the project you may contact the Medical School Research Ethics Committee – contact person Suraiya Buccas on 031-2604769.

## **PARTICIPANT INFORMATION LEAFLET AND CONSENT FORM**

### **TITLE OF THE RESEARCH PROJECT:**

The impact of highly active anti-retroviral therapy (HAART) on anthropometric measures and body composition of HIV positive women in a primary healthcare setting in KwaZulu-Natal.

**REFERENCE NUMBER:** N07/06/139

**PRINCIPAL INVESTIGATOR:** Francesca Mary Esposito

**ADDRESS:** MTCT-Plus Programme  
Umkhumbane Clinic  
25 Kalanden Road  
Durban  
KwaZulu-Natal

**CONTACT NUMBER:** Clinic: 031-2615675 or Cell: 083 408 3360

You are being invited to take part in a research project. Please take some time to read the information presented here, which will explain the details of this project. Please ask the study staff any questions about any part of this project that you do not fully understand. It is very important that you are fully satisfied that you clearly understand what this research entails and how you could be involved. Also, your participation is **entirely voluntary** and you are free to decline to participate. If you say no, this will not affect you negatively in any way whatsoever. You are also free to withdraw from the study at any point, even if you agree to take part.

This study has been approved by the Committee for Human Research at Stellenbosch University and by the University of KwaZulu-Natal Ethics Committee and will be conducted according to the ethical guidelines and principles of the international Declaration of Helsinki, South African Guidelines for Good Clinical Practice and the Medical Research Council (MRC) Ethical Guidelines for Research.

### **What is this research study about?**

The study will be investigating the effect of anti-retroviral therapy (ARVs) on health. It is important for us to know whether taking ARVs causes changes in nutritional status, including changes in the fat and muscle in the body over 6 months from the time you start ARVs. By participating in the study you will help us to collect important information that is needed to help improve the management and care of patients on ARVs.

### **Procedures:**

This study does not involve any invasive procedures and we will mostly be using the information that is usually collected during your follow-up visits to the clinic. You will not need to have any additional visits other than your usual appointments.



We will only be taking a few additional measurements at each visit, namely mid-upper arm circumference, waist circumference and hip circumference. These measurements involve using a tape measure to measure around the top of your arm, around your waist and around your hips.

We will also do another assessment to see how ARVs affect muscle and fat changes in the body. This assessment is called bioelectrical impedance analysis (BIA), and will be done once before starting ARVs and 6 months after starting ARVs. This measurement only takes about 15 minutes and is done using a special machine which is not harmful and does not cause any pain.

**Are there in risks involved in your taking part in this research?**

There are no health risks associated with any of the measurements that will be done. Some of the measurements may require your shirt to be pulled up or removed to take the upper arm, hip and waist measurements and these measurements will be done in a private consulting room. Your privacy will be ensured at all times.

**Who will benefit by you taking part in this research?**

By participating in the study we will ensure that you receive all the care and support you need while taking ARVs. We will inform you of the outcomes of the study and you will receive nutritional intervention if it is determined to be needed. By you participating in this study it will help us to get the information we need to provide good quality care to patients on ARVs.

**Confidentiality:**

The information that we collect from you will be treated as confidential and your identity will remain anonymous. Access to your medical records will be strictly controlled and only the health care providers at MTCT-Plus Programme, Cato Manor will have access to the information.

**Access to findings:**

Only the researcher will have access to the information collected however we will ensure that the meaning of all the measurements taken and the information collected will be explained to you. How will the outcome of the study be known to the participants? You will be contacted when the results of the study are available and will then be invited to the clinic to have the results explained to you by the researcher.

**Voluntary participation/ refusal/ discontinuation:**

Participation in this study is voluntary and it is your decision whether or not you wish to be involved. You may discontinue participation any time and should you choose to refuse to participate or discontinue this will not influence the quality of your treatment and care in any way. The investigator may withdraw you from the study should she feel that it would be in your best interest.

**Are there any costs involved?**

Participating in this study will not result in any expenses for you.

### Declaration by participant

By signing below, I ..... agree to take part in the above-mentioned study.

I declare that:

- I have read or had read to me the above information about the research and it is written and was explained to me in a language with which I am fluent and comfortable.
- I have had a chance to ask questions and all my questions have been adequately answered.
- I understand that taking part in this study is **voluntary** and I have not been pressurised to take part.
- I may choose to leave the study at any time and will not be penalised or prejudiced in any way.
- I may be asked to leave the study before it has finished, if the researcher feels it is in my best interests, or if I do not follow the study plan, as agreed to.

Signed at (*place*) ..... on (*date*) .....

.....  
Signature of participant

.....  
Signature of witness

### Declaration by investigator

I (*name*) ..... declare that:

- I explained the information in this document to .....
- I encouraged her to ask questions and took adequate time to answer them.
- I am satisfied that she adequately understands all aspects of the research, as discussed above
- I made use of a translator when necessary.

Signed at (*place*) ..... on (*date*) .....

.....  
Signature of investigator

.....  
Signature of witness

**Declaration by translator**

I (*name*) ..... declare that:

- I assisted the investigator to explain the information in this document to (*name of participant*) ..... using the language medium of isiZulu.
- We encouraged her to ask questions and took adequate time to answer them.
- I conveyed a factually correct version of what was related to me.
- I am satisfied that the participant fully understands the content of this informed consent document and has had all her questions satisfactorily answered.

Signed at (*place*) ..... on (*date*) .....

.....  
Signature of translator

.....  
Signature of witness

- You may contact the Committee for Human Research at 021-938 9207 if you have any concerns or complaints that have not been adequately addressed by the researcher.

## **INCWAJANA YOLWAZI NEFOMU YEMVUME YOBAMBE IQHAZA**

### **ISIHLOKO SEPROJEKTHI YOCWANINGO**

Umthelela wemishanguzo (Ama-ARV) ekondlekeni kwabesifazane abanesandulela-ngculazi emtholampilo kwaZulu-Natal.

**INOMBOLO YEREFARENSI:** N07/06/139

**INHLOKO YOCWANINGO:** Francesca Mary Esposito

**IDILESI:** MTCT-Plus Programme  
Umkhumbane Clinic  
25 Kalanden Road  
Durban  
KwaZulu-Natal

**INOMBOLO:** Tel 031-2615675

Uyamenywa ukuthi uzoba yingxenye yeprojekthi yocwaningo. Uyacelwa ukuthi uzinike isikhathi sokufunda lolulwazi olungezansi oluchaza ngeprojekthi. Kusemqoka ukuthi uqonde yonke into ngakho uyacelwa ukuthi ubuze ngezinto ongaziqondi.

Leprojekthi igunyazwe yikomiti lobulungiswa (Ethics) laseNyuvesi yaKwaZulu-Natal kanye ne-Stellenbosch Nyuvesi.

### **Ngabe iprojekthi yocwaningo iyini?**

Iprojekthi yocwaningo izobheka umphumela wemishanguzo (ama-ARV) esimweni sokondlekeni komzimba, kumbandakanya nezinguquko emanonini nasemisisheni emzimbeni. Ngokubamba iqhaza kulolucwaningo uyosisiza siqoqe ulwazi olusemqoka oludingekayo ukusiza ukuphucula ukunakekelwa kweziguli ezisebenzisa imishanguzo.

### **Ingqubo:**

Ngazo zonke izikhathi uvakashele emtholampilo siyokukala, okuyoba ukukusebenzisa ithephu ukukala ingalo yakho ngenhla, sizungeze ukhalo sizungeze izinqulu. Ulwazi luyoqoqwa ngezinsuku zakho eziwayelekile ebezihleliwe zokubonwa futhi ngeke kudingeke ezinye ezehlukile zokuvakashela emtholampilo.

Okunye ukukalwa kuyodinga ukuba uphakamise noma ukhumule ngenhla ukuze kukalwe ngenhla kwengalo, ezinqulwini nasokhalweni kodwa siyoqinisekisa ukuthi ufihlekile ngazo zonke izikhathi.

Ukuqinisekisa ukuthi kukaleka ngakho ungase ucelwe ukuba ukhumule ezinye zezimpahla/izingubo kodwa izingubo zangaphansi ziyohlala emzimbeni ngaso sonke isikhathi.

Siyophinda sihlola izingunqoko emisipheni nasemanonini emzimbeni. Lokukuhlola kubizwa nge bioelectrical impedance analysis (BIA-ukuhlaziywa kokuqokethwe umzimba okwenziwe ngomshini oyisipesheli), eyokwenziwakanye ngaphambili kokuthi uqale ukuthatha imishwanguzo, nangemuva kwezinyanga ezi-6 uyiqalile nangemuva kwezinyanga eziwu-12 waqala imishwanguzo (ama-ARV). Lokhu kukalwa kuthatha imizuzu ewu-10 kuphela kanti kwenziwa ngomshini oyisipesheli ongenabungozi futhi ongenzi buhlungu.

### **Ngabe akhona yini amathuba obungozi uma uyingxenye yalolucwaningo?**

Awekho amathuba obungozi empilweni axhumene nanoma ikuphi ukukalwa okuyokwenziwa.

### **Ngubani oyohlomula ngokubamba kwakho iqhaza kulolucwaningo?**

Ngokubamba kwakho iqhaza kulolucwaningo kuyosisiza ukuthola ulwazi esiludingayo ukuze sikwazi ukunakekela kahle iziguli ezisebenzisa imishanguzo.

#### **Imfihlo:**

Ulwazi esiyoluthola kuwe luyogcinwa luyimfihlo futhi ngeke waziwe ukuthi ungubani. Ukuthola amarekhodi akho kuyolawulwa.

#### **Ukuthola imiphumela**

Siyiqinisekisa ukuthi okuchazwa ukukalwa okwenziwe nolwazi olutholakele uyachazelwa ngakho.

### **Ukuzinikela ukubamba iqhaza/ukunqaba/nokuyeka**

Uyobamba iqhaza ngokuzinikela futhi ukhululekile ukuzikhethela ukubamba iqhaza. Uma ukhetha ukungalibambi, lokhu ngeke kube nomthelela omubi nanoma ingayiphi indlela. Futhi ukhululekile ukuhoxa ocwaningweni noma inini.

### **Ngabe kukhona ekuyodingeka ngikukhokhile?**

Ukubamba iqhaza kulolucwaningo ngeke kugcine kukudalele izindleko.

#### **Isifungo sobambe iqhaza**

Ngokusayina ngezansi, mina.....  
ngiyavuma ukuba yingxenye yeprojekthi yocwaningo oludalulwe ngenhla.

Ngiyafunga ukuthi:

- Ngifundile noma ngifundelwe imininingwana ngocwaningo futhi ibhaliwe yachazwa ngolimi engilijwayele nengikhululekile ngalo

- Ngilitholile nethuba lokubuza imibuzo nemibuzo yami iphendulwe ngendlela.
- Ngiyaqonda ukuthi uyazikhethela ukuba yingxenywe yaleprojekthi futhi angizange ngicindezelwe ukuthi ngibambe iqhaza.
- Ngingazikhethela ukulishiya ucwaningo noma inini ngeke ngihlawuliswe noma ngibandlululwe nangayiphi indlela.

Isayinwe (indawo) .....ngomhlaka.....

.....

Sayina obambe iqhaza

.....

Sayina ufakazi

### Isifungo somcwaningi

Mina.....

- Ngichazile ngalolulwazi kulelipheshana ku.....
- Ngimunikile ithuba lokuthi abuze imibuzo
- Ngisebenzisa umchazi uma kunesidingo

Isayinwe (indawo) .....ngomhlaka.....

.....

Sayina umcwaningi

.....

Sayina ufakazi

### Isifungo somchazi

Mina.....

- Ngimsizile umcwaningi ngokumchazela ngesi Zulu.....
- Ngamkhuthaza ukuthi abuze imibuzo
- Ngikhululekile ngokuthi uzwire konke achazelwe khona

Isayinwe (indawo) .....ngomhlaka.....

.....

Sayina umchazi

.....

Sayina ufakazi

- Uma unemibuzo noma izinkinga ngaleprojekthi ungathintana nekomidi kulenamba 021-9389207.

## BODY COMPOSITION AND HAART STUDY

### SOCIO-DEMOGRAPHICS AND BASELINE DATA

**CODE:** Yes = ✓ No = X

[illegible]

**BODY COMPOSITION AND HAART STUDY**

Study No.: .....

CODE: Yes = Y; No = N

Height: 1st.....cm; 2nd .....cm

Date	Weight (kg)		BMI	MUAC (cm)		Waist Circum (cm)		Hip Circum (cm)		D	N	V	L O A	Mouth Sores	Difficulty Swallow	Any Nutrition Suppl

HAART Regimen: 1) ..... 2) .....

Reason for drug switches or regimen changes (if any): .....

**LABORATORY RESULTS**

CD4		VL		HB		Alb	
Date	Result	Date	Result	Date	Result	Date	Result

**QUESTIONNAIRE - 24 WEEKS**

DIETARY CHANGES		YES	NO	REASON
1	Increased portion/ meal size?			
2	Decreased portion/ meal size?			
3	Increased appetite?			
4	Decreased appetite?			
5	Increased variety of foods eaten?			
6	Decreased variety of foods eaten?			
7	Number of meals you eat increased?			
8	Number of meals you eat decreased?			
SOCIO-DEMOGRAPHIC CHANGES		YES	NO	REASON
1	Are you employed?			
2	Do you have electricity in your home?			
3	Do you have piped water in your home?			



## BODY COMPOSITION AND HAART STUDY

### Bioelectrical Impedance Analysis

Study No.: .....

Height: .....

Date	Baseline: .....	24 weeks: .....
Weight (kg)		
Age (years)		
Time		
TBW (lt)		
TBW%		
FM (kg)		
BF%		
LBM (kg)		
Impedance: 5 kHz		
Impedance: 50 kHz		
Impedance: 100 kHz		
Impedance: 200 kHz		

## **Revised WHO Clinical Staging of HIV/AIDS for Adults and Adolescents**

### **Clinical Stage 1**

Asymptomatic

Persistent generalized lymphadenopathy (PGL)

### **Clinical Stage 2**

Moderate unexplained weight loss (<10% of presumed or measured body weight)

Recurrent respiratory tract infections (RTIs, sinusitis, bronchitis, otitis media, pharyngitis)

Herpes zoster

Angular cheilitis

Recurrent oral ulcerations

Papular pruritic eruptions

Seborrhoeic dermatitis

Fungal nail infections of fingers

### **Clinical Stage 3**

Severe weight loss (>10% of presumed or measured body weight)

Unexplained chronic diarrhoea for longer than one month

Unexplained persistent fever (intermittent or constant for longer than one month)

Oral candidiasis

Oral hairy leukoplakia

Pulmonary tuberculosis (TB) diagnosed in last two years

Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia)

Acute necrotizing ulcerative stomatitis, gingivitis or periodontitis

Unexplained anaemia (< 8 g/dl), and or neutropenia (<500/mm<sup>3</sup>) and or thrombocytopenia (<50 000/ mm<sup>3</sup>) for more than one month

### **Clinical Stage 4**

HIV wasting syndrome

Pneumocystis pneumonia

Recurrent severe or radiological bacterial pneumonia

Chronic herpes simplex infection (orolabial, genital or anorectal of more than one month's duration)

Oesophageal candidiasis

Extrapulmonary TB

Kaposi's sarcoma

Central nervous system (CNS) toxoplasmosis

HIV encephalopathy

Extrapulmonary cryptococcosis including meningitis

Disseminated non-tuberculous mycobacteria infection

Progressive multifocal leukoencephalopathy (PML)

Candida of trachea, bronchi or lungs

Cryptosporidiosis

Isosporiasis

Visceral herpes simplex infection

Cytomegalovirus (CMV) infection (retinitis or of an organ other than liver, spleen or lymph nodes)

Any disseminated mycosis (e.g. histoplasmosis, coccidiomycosis, penicilliosis)

Recurrent non-typhoidal salmonella septicaemia

Lymphoma (cerebral or B cell non-Hodgkin)

Invasive cervical carcinoma

Visceral leishmaniasis

**KARNOFSKY PERFORMANCE SCORE**

Normal health	100%
Minor symptoms	90%
Normal activity with some effort	80%
Unable to carry out normal activity, able to care for oneself	70%
Requires some help with personal needs	60%
Disabled	50%
Requires considerable assistance, medical care	40%
Severely disabled, in hospital	30%
Very sick, active support needed	20%
Moribund (near death)	10%

## BODY COMPOSITION AND HAART STUDY

## SUMMARY FOLLOW-UP FORM

Study Number: .....

Y = Yes; N = No

[illegible]