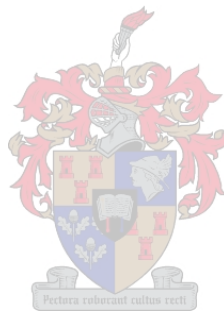


# **ART-related body composition changes in adult women in a semi-rural South African context.**

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**Assignment in partial fulfillment of the requirements for the degree of  
Master of Philosophy (Exercise Science)**

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**December, 2006**

**Declaration:**

**I, the undersigned, hereby declare that the work contained in this assignment is my own original work and that I have not previously in its entirety or in part submitted it at any university for a degree.**

**Signature:** .....

**Date:** .....

## Summary

The aim of this study was to investigate practical methods of monitoring AIDS related wasting and lipodystrophy in a resource-poor clinical setting with HIV infected women as the population group of interest. Measurement of body composition changes using anthropometry is both cost- and time-efficient. Various different skinfolds were taken and two different equations (the equations of Pollock *et al.* (1975) and Durnin and Womersley (1974) for calculating body fat were used to determine the most promising method or methods of monitoring body composition changes in a clinical setting.

Detailed anthropometric measurements were performed, as well as selected measurements for haematological parameters and quality of life (QoL) for a group of 8 participants on antiretroviral medication (ART group) and 6 participants who were not on treatment (TN group). New variables namely, intra-abdominal indicator (IAI) and a percent of ideal body mass to percent of ideal arm circumference ratio (%IBW:%IAC) were investigated as possible indicators of lipodystrophy. Although measurements were taken at various time-points, three specific time-points were chosen for data-analysis for the ART group and two time points for the TN group. These three time-points were, baseline (on the day of recruitment for TN participants and within one month before the initiation of treatment for ART participants), short-term (2 to 12 weeks after treatment initiation or the baseline measurement or for the ART and the TN participants) and long-term (within one and a half year of treatment initiation for the ART group).

ART and TN participants did not differ for many variables at baseline. The major differences between ART and TN were in measured and derived variables of the arm, especially percent of ideal arm circumference (%IAC) and upper arm fat area (UAFA), which were significantly lower in the ART group.

CD4<sup>+</sup> and QoL improved significantly for the ART participants from baseline to long-term. This was not associated with changes in muscle mass, but rather some fat mass variables. Participants on antiretroviral medication exhibited changes relating to abdominal obesity. It was concluded that antiretroviral therapy contributed greatly to the QoL of the

participants and it probably aided in the recovery from wasting for at least one participant in this study. Measures of the arm can be used in a rural clinical setting to effectively monitor patients with regard to AIDS related wasting. The new variables IAI and %IBW:%IAC could be helpful in the monitoring of lipodystrophy and should be investigated in future research.

## Opsomming

Die doelwit van hierdie studie is om praktiese metodes te ondersoek om VIGS-verwante uittering en lipodistrofie te meet in 'n plattelandse kliniese omgewing (waar hulpbronne dikwels beperk is) met MIV ge-infekteerde vroue as populasiegroep. Die gebruik van antropometrie om veranderinge in liggaamssamestelling te meet is beide koste- en tydeffektief. Verskeie velvoumetings is geneem en twee verskillende vergelykings (die vergelykings van Pollock *et al.* (1975) en Durnin en Womersley (1974)) is gebruik om liggaamsvetinhoud te bereken, met die doel om 'n belowende metode te vind om veranderinge in liggaamssamestelling te meet in 'n kliniese omgewing.

Verskeie antropometriese metings is geneem, sowel as uitgesoekte hematologiese en lewenskwaliteitsmetings (QoL) vir 'n groep van agt deelnemers wat antiretrovirale medikasie ontvang het (ART groep) en ses deelnemers wat nie hierdie behandeling ontvang het nie (TN groep). Nuwe veranderlikes (binnebuikindikator (IAI) en die verhouding van persentasie van ideale liggaamsmassa tot persentasie van ideale armomtrek ( $\%IBW:\%IAC$ )) is ondersoek as moontlike aanwysers van lipodistrofie. Drie spesifieke tydpunte vir die ART groep en twee tydpunte vir die TN groep is gekies uit die verskeie tydpunte waarby metings geneem is, nl. basislyn (gedefinieer as die dag wat TN deelnemers in die studie opgeneem is en 0 tot 4 weke voor die begin van behandeling vir die ART deelnemers), korttermyn (2 tot 12 weke nadat behandeling begin is of na die basislyn meting) en lang-termyn (binne een en 'n half jaar nadat behandeling begin is vir die ART groep).

By die basislyn tydpunt het min van die ART en TN deelnemers se gemete veranderlikes verskil. Die ART en TN groepe het hoofsaaklik verskil ten opsigte van veranderlikes wat betrekking het op die arm, veral persentasie van ideale armomtrek ( $\%IAC$ ) en bo-arm vet-area (UAFA). Hierdie twee veranderlikes was beduidend laer in die ART groep as in die TN groep.

$CD4^+$  seltelling en lewenskwaliteit tellings het beduidend verbeter vir die ART deelnemers van die basislyn tot die lang-termyn tydpunt. Hierdie veranderinge is nie samehangend met

veranderinge in spiermassa nie, maar eerder met sommige vetmassa veranderlikes. Deelnemers wat antiretrovirale medikasie ontvang het, het veranderinge getoon wat gedui het op 'n verhoogde neerlegging van vet in die buikarea. Ten slotte is bevind dat antiretrovirale medikasie bygedra het tot die verbeterde lewenskwaliteit van die deelnemers en dat dit waarskynlik ook die omkeer van uittering van ten minste een deelnemer aangehelp het. Daar is ook bevind dat armverwante metinge gebruik kan word in die plattelandse kliniese omgewing om pasiënte suksesvol te monitor ten opsigte van VIGS-verwante uittering. Die nuwe veranderlikes, IAI en %IBW:%IAC kan moontlik gebruik word om lipodistrofie-verwante veranderings te meet en die gebruik van hierdie veranderlikes behoort ondersoek te word in verdere navorsing.

## **Acknowledgements**

I would like to give special thanks to everyone in the department who helped me with advice and assistance (especially those who volunteered to be subjected to measurements and interviews while I was practicing data gathering techniques, as well as those who assisted from time to time in data gathering in the department and at the clinics).

I also wish to express sincerest gratitude towards everyone at Paarl HIV-clinic. I have great admiration for what you achieve there and I wish you the best for the future. Thank you Dr Grobbelaar for seeing opportunities where others see problems.

I am most grateful for the knowledge and advice of Drs. Smith and Nell and especially, Prof. Myburgh, without whom this project would have been impossible.

Deepest thanks also to Pieter, my family and friends for their endless patience and support.

## Abbreviations

%IAC	Percentage of ideal arm circumference
%IBW	Percentage of ideal body mass
AIDS	Acquired immune deficiency syndrome
AWS	AIDS wasting syndrome
BCM	Body cell mass
BIA	Bioelectric impedance analysis
BM	Body mass <sup>1</sup>
BMI	Body mass index (body mass (kg) / height <sup>2</sup> (m <sup>2</sup> ))
BW <sup>2</sup>	Body mass
BWL <sup>2</sup>	Body mass loss
%CD4	CD4 <sup>+</sup> count as a percent of total lymphocyte count
CNS	Central nervous system
D	Body density (g/mL)
DHEAS	Dehydroepiandrosterone-sulphate
DHHS	Department of Health and Human Services
DW	Refers to the equations of Durnin and Womersley (1974)
DXA	dual X-ray absorptiometry
ECM	Extracellular mass
ECW	Extracellular water
Fat%	Fat percentage
FDA	Food and drug administration (United States of America)
FFM	Fat free mass
FM	Fat mass
GI	Gastro-intestinal

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<sup>1</sup> Also referred to as body weight in some anthropometric calculations and tables.

<sup>2</sup> Accepted abbreviation for “mass” in anthropometry is “W” except for body mass index, hence abbreviations reflect common use in the literature (E.g. Kotler *et al.*, 1989; Melchior *et al.*, 1999; Nemecek *et al.*, 2000).



HAART	Highly active antiretroviral therapy
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
IAC	Ideal arm circumference
IAF	Intra-abdominal fat
IAI	Intra-abdominal indicator
IAI:H	Intra-abdominal indicator to hip ratio
IBW	Ideal body mass
ICW	Intracellular water
IL-6	Interleukin-6
Pol	Refers to the equations of Pollock <i>et al.</i> (1975)
LBM	Lean body mass
LBMI	Lean body mass index (lean body mass (kg) / height <sup>2</sup> (m <sup>2</sup> ))
LDL	Low density lipoprotein
MRI	Magnetic resonance imaging
mtDNA	Mitochondrial deoxyribonucleic acid
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
nSREBP	Nuclear sterol regulatory element binding proteins
PCM	Protein-calorie malnutrition
PI	Protease inhibitor
QoL	Quality of life
SCF	Subcutaneous fat
SKF	Skinfold thickness or skinfold thickness analysis
TB	The disease tuberculosis which is caused by <i>Mycobacterium tuberculosis</i>
TBK	Total body potassium
TBW	Total body water
TI	Treatment initiation
TN	Treatment naïve

TNF	Tumour necrosis factor
UAC	Upper arm circumference, also known as mid upper arm circumference (MUAC)
UAFA	Upper arm fat area
UAMA	Upper arm muscle area
W:H	Waist to hip ratio
WHO	World Health Organisation

<b>CONTENTS</b>	<b>PAGE</b>
<b>Declaration</b>	<b>2</b>
<b>Summary</b>	<b>3</b>
<b>Opsomming</b>	<b>5</b>
<b>Aknowledgements</b>	<b>7</b>
<b>Abbreviations</b>	<b>8</b>
<b>1. Introduction</b>	<b>13</b>
<b>2. Background to HIV/AIDS and ART</b>	<b>15</b>
<b>2.1. Clinical aspects of HIV/AIDS</b>	<b>15</b>
<b>2.1.1. The disease</b>	<b>15</b>
<b>2.1.2. Antiretroviral medicine</b>	<b>19</b>
<b>3. Literature review</b>	<b>24</b>
<b>3.1. Body composition changes with ART</b>	<b>24</b>
<b>3.1.1. The AIDS wasting syndrome (AWS)</b>	<b>24</b>
<b>a. Mechanisms of wasting</b>	<b>27</b>
<b>b. Interventions to reduce wasting</b>	<b>30</b>
<b>3.1.2. The lipodystrophy syndrome</b>	<b>33</b>
<b>3.2. Monitoring body composition changes</b>	<b>36</b>
<b>3.3. Quality of life</b>	<b>40</b>
<b>4. Methods</b>	<b>42</b>
<b>4.1. Ethical concerns</b>	<b>42</b>
<b>4.2. Participants</b>	<b>43</b>
<b>4.3. Rural and clinical setting</b>	<b>43</b>
<b>4.4. Data collection methods</b>	<b>44</b>
<b>4.5. Data analysis</b>	<b>46</b>

<b>5.</b>	<b>Results</b>	<b>50</b>
5.1.	Overview	50
5.2.	Baseline	54
5.3.	TN and ART group comparisons over time	58
5.4.	ART group: short and long-term changes	66
<b>6.</b>	<b>Discussion</b>	<b>75</b>
6.1.	Disease progression and wasting	76
6.2.	Lipodystrophy	86
6.3.	Conclusions	89
<b>7.</b>	<b>Appendices</b>	<b>91</b>
7.1.	Appendix A	91
7.2.	Appendix B	93
7.3.	Appendix C	103
7.4.	Appendix D	117
7.5.	Appendix E	132
<b>8.</b>	<b>References</b>	<b>134</b>

## **1. Introduction**

Untreated infection with the human immunodeficiency virus (HIV) leads to severe physical debilitation and disease culminating in the acquired immune deficiency syndrome (AIDS) and eventually, death. A joint report by the United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization (WHO) stated that an estimated 39.4 million people worldwide were living with HIV in 2004. An estimated 3.1 million deaths as a result of AIDS were also reported for 2004. Most of the people living with HIV are residents of Sub-Saharan Africa and numbered an estimated 25.4 million people in 2004. Compared to the next area of highest infection (South and South-East Asia with 7.1 million people living with HIV) this is indeed an astoundingly high prevalence. HIV/AIDS has become the largest cause of death in South Africa (Baleta, 2005).

The UNAIDS & WHO also reported that 57% of the people living with HIV in Sub-Saharan Africa were women (2004). Many factors were mentioned that could lead to an increased infection rate for women in this area. Social inequalities (accentuated by a lesser availability of education and lower social status for women), impoverishment, social distortions brought about by the migrant labour systems, intimate partner violence as well as a greater risk of infection in young women compared to men increase the vulnerability of women to becoming infected.

Furthermore, the whole society is affected by the high infection rate of women since they are often the main caregivers in the communities of Sub-Saharan African countries. The UNAIDS & WHO report stated that in South Africa, almost three quarters of AIDS affected households were headed by females, frequently with AIDS-related illnesses themselves. Illness and weakness result in a cycle of poverty and misfortune, impacting on a social as well as an economic level. Although, the situation was further aggravated by an absence of public access to antiretroviral drugs, these have become available at selected clinics in South Africa since 2004 (Baleta, 2003).

Therefore, it is important to investigate HIV infected women and the impact of antiretroviral treatment on this population in South Africa from multiple perspectives.

AIDS related wasting and lipodystrophy are two conditions that should be assessed. Monitoring could be done by appropriately trained exercise physiologists since information gained could potentially lead medical practitioners to recommend lifestyle changes. The aim of this study was to investigate practical methods of monitoring these two conditions in a resource-poor clinical setting with HIV infected women as the population group of interest. The criteria that were considered to define a practical method of measuring body composition changes in such a setting were that it should be cost- and time-efficient. Determining body composition using anthropometry may be a practical way of investigating changes in body composition related to wasting and lipodystrophy. A comprehensive battery of skinfold thicknesses were measured, along with various circumference measurements to determine the most promising subset for monitoring body composition changes in a clinical setting.

The literature review for this study is preceded by a general introduction to the disease progression and treatment of an HIV infection. Thereafter, AIDS related wasting, lipodystrophy, quality-of-life and methods of monitoring body composition are the focus points of the literature review.

## **2. Background to HIV/AIDS and ART**

The following general introduction to the disease and the treatment thereof is important when considering disease progression and the impact of antiretroviral treatment on the study population.

### **2.1 Clinical aspects of HIV/AIDS**

Acquired immune deficiency syndrome (AIDS) first emerged in 1981 in America as well as in Africa (Hooper, 2000). The virus that caused AIDS was isolated in 1983. Although it was initially referred to as the lymphadenopathy associated virus (LAV) or human T-lymphotropic virus III (HTLV-III), it was eventually named the human immunodeficiency virus (HIV) (Weatherall *et al.*, 1996).

#### **2.1.1 The disease**

HIV is a retrovirus of the lentivirus family, which is a subfamily of retroviruses. Retroviruses possess the unique ability to copy their viral RNA genome into strands of DNA using the reverse transcriptase enzyme. Based on genome organization and phylogenetic relationships, the virus can be divided into two types (HIV-1 and HIV-2) and subdivided into numerous subtypes (Janse van Rensburg, 2000). HIV-1 infection is the most prevalent, as HIV-2 infections are, for the most part, only found in West Africa (Weatherall *et al.*, 1996).

Transmission of the virus can occur as a result of sexual intercourse, direct blood-to-blood contact and through the use of contaminated needles. An infected mother can also pass the virus on to her infant through breastfeeding and during birth. The virus resides in CD4<sup>+</sup> lymphocytes and is therefore transmitted from person to person via these cells.

Cluster of differentiation (CD) refers to markers that bind to specific polypeptides on immune and some other cells (Roitt & Rabson, 2000). Therefore the CD4 marker indicates that cell-surface CD4 molecules are present. CD4 molecules are abundant on helper T-

cells, but macrophages and microglia also have low densities of these molecules on their surfaces (Roitt & Rabson, 2000).

The HIV glycoprotein, gp 120, binds to CD4 molecules when infecting a cell. After co-receptor binding and fusion of the viral membrane with the cell membrane, the virus enters the cell. The viral RNA is then converted to the corresponding DNA via reverse transcriptase. This DNA is integrated into the host genome where it can remain latent or be transcribed when the host cell is activated by cytokines or an antigen (Roitt & Rabson, 2000).

The progression of HIV infection can be divided into three stages. A primary viraemia develops four to eight weeks after infection and the virus is dispersed throughout the body during this stage (Weatherall *et al.*, 1996). This stage is associated with an immune response that typically produces cytotoxic T-cells and antibodies to the envelope proteins gp 120 and gp 41 and especially the nucleocapsid HIV protein p24 (Roitt & Rabson, 2000). The second stage is characterized by low viraemia as the HIV particles are mostly confined to lymphoid tissue. The person can be asymptomatic, or have only minor symptoms of infection. Generally, there is a gradual decrease in CD4<sup>+</sup> T-cells during the asymptomatic period. The duration of this period is highly variable, but it can last up to twelve years (Weatherall *et al.*, 1996).

The cause of the drop in CD4<sup>+</sup> T-cells cannot be fully explained. Although the HIV kills the cell directly once viral replication reaches high levels – some other factor (or factors) are thought to contribute to the decline of CD4<sup>+</sup> cells. Various hypotheses have been proposed, including the inhibition of new T-cell production, increased cytotoxic CD8<sup>+</sup> cells which play a role in the lysing of infected CD4<sup>+</sup> cells, an increased susceptibility to apoptosis and changes in the viral phenotype expression (Ribeiro *et al.*, 2006; Roitt & Rabson, 2000; Weatherall *et al.*, 1996).

Ultimately the falling number of CD4<sup>+</sup> T-cells will predispose the individual to development of opportunistic infections and the person will enter the third stage of the disease. If the disease is not treated, the person may only survive for about two to three



years with the “acquired immune deficiency syndrome” (AIDS), which will eventually result in death (Weatherall *et al.*, 1996).

Depending upon the geographical area, different definitions of AIDS are used (see Appendix A, Section 1). In developed countries a person will be diagnosed with AIDS if he or she has a proven HIV infection and a CD4<sup>+</sup> lymphocyte count less than 200 per  $\mu\text{L}$  irrespective of clinical manifestation (Weatherall *et al.*, 1996). In developing countries, where laboratory resources may be limited, other indicator diseases are used to diagnose AIDS.

Two staging systems to assist physicians in the assessment of their patients have been independently published by the WHO and the U.S. Centers for Disease Control (CDC). A 1989 version of the WHO classification system, shown in Table 1, describes 3 groups (A – C) based on laboratory measurements, co-classified into 1 of 4 groups (A1 – A4; B1 – B4; C1 – C4) based on clinical symptoms (Weatherall *et al.*, 1996).

In contrast, the 1993 version of the CDC classification system categorises the condition of a patient according to disease stage into one of three clinical categories (A indicates early disease, B late disease and C advanced disease). The CD4<sup>+</sup> count of the individual is also used to specify an immune category (category 1 represents a CD4<sup>+</sup> count of 500 cells/ $\mu\text{L}$  or more, category 2 represents a CD4<sup>+</sup> count of 200 cells/ $\mu\text{L}$  or more, but less than 500 cells/ $\mu\text{L}$  and category 3 signifies CD4<sup>+</sup> counts less than 200 cells/ $\mu\text{L}$ ) providing information about the disease progression. The lowest recorded CD4<sup>+</sup> count is used and a lower category cannot be reassigned if the patient’s CD4<sup>+</sup> count increases (Baylor College of Medicine, 2003).

This CDC classification system is clearly very similar to the WHO system, although it may be confusing since the numbering and lettering allocation is reversed. Letters A to C indicate a classification based upon haematological data and numbers are used to classify a person into a clinical group according to the WHO system, while the CDC classification system uses A to C to indicate disease stage and CD4<sup>+</sup> categories are given a number from 1 to 3.

Table 1: The WHO classification system for HIV infection (rewritten from Weatherall *et al.*, 1996).

Laboratory group			Clinical group			
	Lymphocyte count (x10 <sup>6</sup> /l)	CD4 <sup>+</sup> count (x10 <sup>6</sup> /l)	1	2	3	4
A	> 2 000	> 500	1A	2A	3A	4A
B	1 000 – 2 000	200 – 500	1B	2B	3B	4B
C	< 1 000	< 200	1C	2C	3C	4C
<b>Clinical group 1:</b>	Clinical group 1 of the WHO staging system represents those HIV-infected people who are asymptomatic or only have persistent generalized lymphadenopathy. They can also participate in normal physical activities.					
<b>Clinical group 2:</b>	Clinical group 2 represents the early stage disease when the person becomes symptomatic (but still retains normal physical activity) and body mass loss of less than 10 percent of body mass becomes apparent. Symptoms include recurrent upper respiratory tract infections and herpes zoster (shingles) infection occurring within 5 years.					
<b>Clinical group 3:</b>	A person will be classified with intermediate stage disease (group 3) when one or more of the following has occurred: a body mass loss of more than 10 percent of body mass, unexplained chronic diarrhoea for more than one month, unexplained prolonged fever for more than 1 month, oral candidiasis, oral hairy leucoplakia, pulmonary tuberculosis within 1 year, severe bacterial infections and/or being bedridden less than 50 percent of the day during the previous month.					
<b>Clinical group 4:</b>	A person will be classified with late stage disease when diagnosed with any of the AIDS-defining illnesses (as specified by the CDC – see appendix A, section 1) and/or this person has been bedridden for more than 50 percent of the day during the previous month.					

Of particular relevance to the current study are the facts that multiple infections, physical weakness, body mass loss and wasting are characteristic manifestations of the disease (see Table 1) and impact on the affected person's ability to lead a productive life. Poverty and limited access to resources may contribute to these manifestations and complicate the treatment choices thereof especially in the rural and semi-rural areas of South Africa. Clearly it is a debilitating disease and even though antiretroviral medicine has improved the quality of life of people suffering from the disease, the medicine itself may also impact negatively on the body composition of treated patients.

### 2.1.2 Antiretroviral medicine

At present there is no cure for an HIV infection and the design and testing of an effective vaccine is proving to be a time-consuming challenge. The main goal of current antiretroviral treatment (ART) is to reduce viral replication and levels (viral load) in the blood to allow the immune system to regain some of its lost function (Baylor College of Medicine, 2003). Therefore, one of the primary outcomes of ART is a reduced frequency of opportunistic infections and a general improvement in health. Antiretroviral therapy has prolonged the life expectancy of countless HIV-infected patients and consequently there are many living relatively normal lives with HIV and AIDS.

Although ART is generally effective in reducing viral load and improving health, there are many drawbacks to the treatment. The medicine has to be taken regularly for the rest of the HIV-infected individual's life and the patient who doesn't comply with a strict drug-taking regimen may potentially experience drug-resistance and treatment failure. Rigorous adherence to ART is therefore essential. Accessibility to water and food with which to take the medication, severe side-effects, multiple medications and interactions with other medicine are some of the additional obstacles that may influence adherence to treatment (Baylor College of Medicine, 2003).

The first drug to be developed (in 1985) against the HIV was zidovudine (3'-azido-3'-deoxythymidine). Yet, it was shown that treatment with zidovudine (also known as AZT, ACT and ZDV) as monotherapy is likely to lead to treatment failure due to the development of drug resistance. Since the development of additional drugs (like didanosine (dideoxyinosine, ddI) and zalcitabine (dideoxycytidine, ddC)) the use of combination therapy has been explored and found to be quite effective (Weatherall *et al.*, 1996).

At present, a host of different antiretroviral medicines are available. They can be classed into three groups: nucleoside reverse transcriptase (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs). As shown in Figure 1, the

groups indicate at which stage of viral replication the medicine acts (Baylor College of Medicine, 2003).

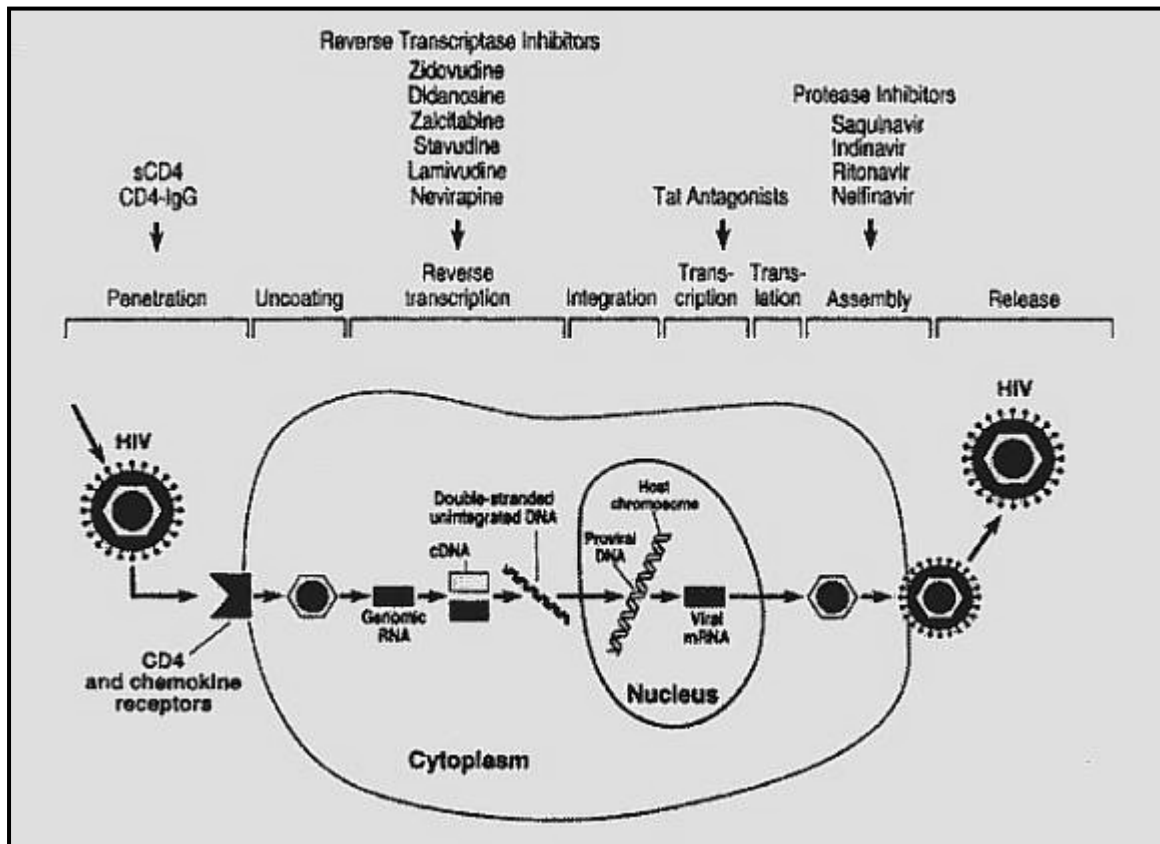


Figure 1: The sites of action of common antiretroviral medication in relation to the life cycle of the HIV (reproduced exactly from Baylor College of Medicine, 2003).

Either two or three different drugs are commonly used in combination therapy. The use of three different drugs is referred to as highly active antiretroviral therapy (HAART). HAART is believed to be the most effective therapy to suppress viral replication, but two-drug therapy has also been shown to increase survival and improve quality of life (QoL) (Baylor College of Medicine, 2003). Any treatment regimen should consist of at least two nucleoside reverse transcriptase inhibitors (NRTIs). One of these should be a thymidine analogue (such as d4T or ZDV), while the other should be a non-thymidine analogue (such as ddI, ddC or 3TC) (Baylor College of Medicine, 2003). A protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) can be added as the third drug (Baylor College of Medicine, 2003). A three NRTI therapy (referred to as a triple nucleoside

regimen) can also be used (Baylor College of Medicine, 2003; WHO, 2004). Table 2 summarizes the currently available antiretroviral drugs with their possible side effects.

**Table 2a:** Antiretroviral medications and side effects (adapted from Baylor College of Medicine, 2003).

Class	Antiretroviral drug	Possible side effects
NRTI	Didanosine (ddI); Videx	<u>Common</u> : nausea; vomiting; diarrhea; abdominal pain <u>Severe</u> : Peripheral neuropathy; electrolyte abnormalities; hyperuricemia; lactic acidosis with hepatic steatosis <u>Uncommon</u> : pancreatitis; increase liver function tests; retinal depigmentation
	Lamivudine (3TC); Epivir	<u>Common</u> : nausea; diarrhea; headache; fatigue; skin rash; abdominal pain <u>Severe</u> : pancreatitis; lactic acidosis with hepatic steatosis
	Zalcitabine (ddC); Hivid	<u>Common</u> : headache, malaise <u>Severe</u> : peripheral neuropathy; pancreatitis; hepatic toxicity; rash; oral ulcers; hematologic toxicity
	Zidovudine (ZDV); Retrovir	<u>Common</u> : hematologic toxicity; headache <u>Other</u> : myopathy; myositis; liver toxicity
	Stavudine (d4T); Zerit	<u>Common</u> : headache; nausea; vomiting; diarrhoea; skin rash; increase liver function tests <u>Severe</u> : peripheral neuropathy; pancreatitis; lactic acidosis with hepatic steatosis
	Abacavir; Ziagen	<u>Common</u> : nausea; vomiting; diarrhea; loss of appetite; malaise; headache; rash <u>Severe</u> : hypersensitivity (do not rechallenge)
	Tenofovir; Disoproxil; Fumarate; Viread	asthenia; headache; flatulence; nausea; lactic acidosis
	Zidovudine/Lamivudine; Combivir	lactic acidosis with hepatic steatosis
	Zidovudine/Lamivudine/Abacavir; Trizivir	lactic acidosis with hepatic steatosis
NNRTI	Delavirdine (DLV); Rescriptor	<u>Common</u> : headache; fatigue; nausea, vomiting, diarrhoea; rash
	Nevirapine (NVP); Viramune	<u>Common</u> : rash; sedative effects; headache; nausea; diarrhoea <u>Other</u> : increase liver function tests; rare-hepatitis
	Efavirenz	<u>Common</u> : rash; central nervous system (dizziness, etc) <u>Other</u> : increase liver function tests

In South Africa, Stavudine, Lamivudine and Efavirenz (kown as Stocrin in South Africa) are used as the first line of treatment, whereas Didanosine, Zidovudine and Combivir are

used in cases of treatment failure (insufficient viral suppression despite compliance) or other reason to alter treatment (e.g. lactic acidosis).

As shown in Tables 2a and 2b, an extensive range of side effects is associated with ART. Although some side effects like headache and nausea may only be experienced with the initiation of therapy, others can lead to toxicity. Side effects that persist and are not well tolerated can result in significant organ dysfunction related to toxicity (WHO, 2004). Toxicities observed in treated patients include neuropathy, pancreatitis, lipoatrophy, hepatotoxicity, severe but not life-threatening rash, life-threatening rash, persistent gastrointestinal (GI) intolerance, lactic acidosis, haematological toxicity, mitochondrial toxicity, myopathy, muscle wasting, anaemia and persistent central nervous system (CNS) toxicity (WHO, 2004; Baylor College of Medicine, 2003; Yarasheski & Roubenoff, 2001).

**Table 2b:** Antiretroviral medications and side effects (adapted from Baylor College of Medicine, 2003).

Class	Antiretroviral drug	Possible side effects
PI	Indinavir (IDV); Crixivan	<u>Common:</u> nausea; abdominal pain; headache; asymptomatic hyperbilirubinemia <u>Severe:</u> nephrolithiasis <u>Other:</u> spontaneous bleeding; hyperglycemia
	Nelfinavir (NFV); Viracept	<u>Common:</u> nausea; vomiting; diarrhoea; headache especially if receiving ZDV <u>Other:</u> asthenia; abdominal pain; rash; hyperglycemia
	Saquinavir (SQV), hard gelatin capsules; Invirase	<u>Common:</u> nausea; vomiting; diarrhoea; abdominal pain; headache <u>Other:</u> spontaneous bleeding; hyperglycemia
	Saquinavir (SQV); soft gelatin capsules; Fortovase	<u>Common:</u> nausea; vomiting; diarrhoea; abdominal pain; headache <u>Other:</u> spontaneous bleeding; hyperglycemia
	Ritonavir (RTV); Norvir	<u>Common:</u> nausea; vomiting; diarrhoea; abdominal pain; anorexia <u>Other:</u> circumoral paresthesias; increase liver function tests; spontaneous bleeding; pancreatitis; increase Triglyceride and Cholesterol; hyperglycemia
	Lopinavir/ritonavir; Kaletra	<u>Common:</u> nausea; vomiting; diarrhoea, headache <u>Other:</u> hyperglycemia; increase liver function tests
	Amprenavir; Agenerase	<u>Common:</u> headache; nausea; vomiting; diarrhoea; rash

HAART seems to be particularly associated with toxicities. Disturbances in lipid metabolism – leading to lipodystrophy, hyperlipidaemia, insulin resistance and hyperglycaemia – appear to be strongly associated with PI-based HAART (Calza *et al.*,

2003; Hui, 2003). However, PI-naïve patients treated with two NRTIs have also been shown to exhibit the same manifestations of a disrupted lipid metabolism (Galli *et al.*, 2002).

Therefore, although ART is a life-saving intervention that may improve the quality of life and survival rate of infected patients, it carries with it a range of possible complications.

### **3. Literature review**

The following literature review will focus on changes in body composition (whole body or regional muscle mass and fat mass) that may occur in HIV infected individuals. The mechanisms behind these changes as well as possible treatment options that have been explored are presented. The practicality of methods of monitoring these changes in a clinical setting is discussed. These issues will be discussed taking into account the role that health care professionals (especially exercise physiologists) can play in this regard.

#### **3.1 Body composition changes with ART**

Since wasting is directly associated with HIV/AIDS disease progression (Kotler *et al.*, 1989), nutrition was initially the main concern of paramedical health care professionals working with infected patients. The use of antiretroviral medications proved to be effective in reducing body mass loss and wasting (Dworkin *et al.*, 2003). However, it became apparent, as discussed in the previous section, that the toxic effects of HAART give rise to metabolic complications and lipid abnormalities. Patients reported experiencing a loss of fat in the face, arms and legs (Brinkman *et al.*, 1999; Carr *et al.*, 1998). Some would also experience a concomitant increase of waist circumference. An increased deposition of intra-abdominal fat has been implicated for this increase in girth (Miller *et al.*, 1998). The accumulation of adipose tissue in areas like the dorso cervical region of the neck and the breasts in the form of unencapsulated lipomas (similar to Madelung's syndrome) has also been observed with lipodystrophy (Salomon *et al.*, 2002; Brinkman *et al.*, 1999; Lo *et al.*, 1998). Therefore, ART may improve wasting, but it may cause detrimental changes in fat deposition.

##### **3.1.1 The AIDS wasting syndrome (AWS)**

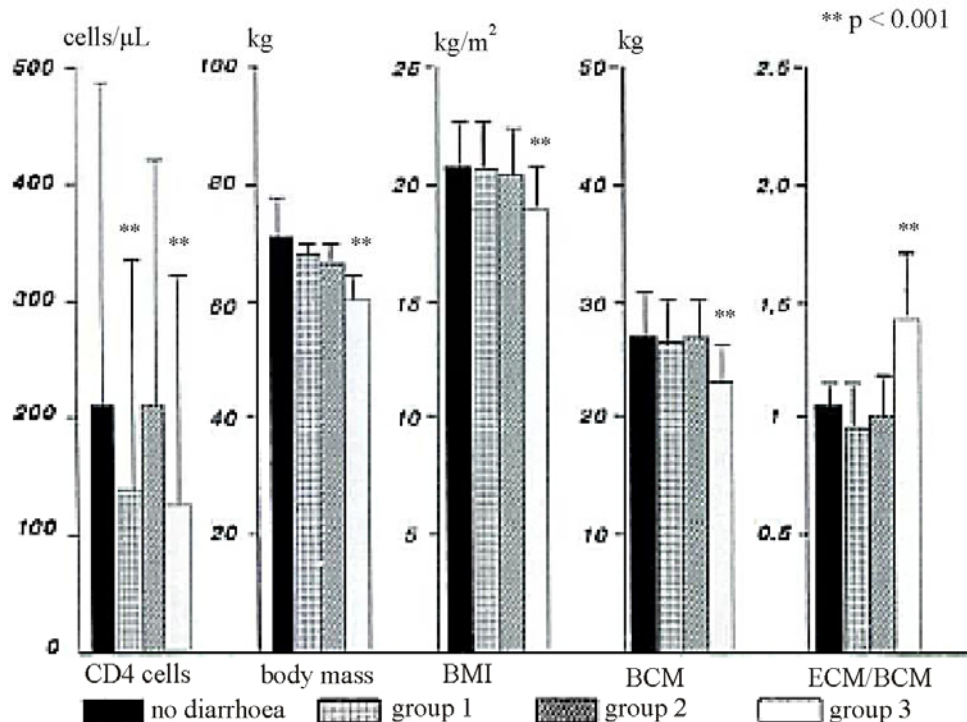
The HIV wasting syndrome is defined as involuntary body mass loss greater than 10% in addition to unexplained chronic diarrhoea for more than one month, or weakness and unexplained prolonged fever for more than one month (Baylor College of Medicine, 2003; Nemecek *et al.*, 2000; CDC, 1993). Other definitions of wasting that have been used are a



loss of more than 5% of body weight within six months with the loss sustained for more than a year and a body mass index that had fallen below 20 kg/m<sup>2</sup> (Wanke *et al.*, 2000). The HIV wasting syndrome is an AIDS defining condition (Baylor College of Medicine, 2003) and it is therefore also known as the AIDS wasting syndrome (AWS).

Kotler, *et al.* (1989) showed that the magnitude of body cell mass (BCM) depletion is related to the timing of death from wasting in AIDS. In this study, a regression line generated from the total body potassium (TBK) and anthropometric measurements of 43 patients indicated that body mass at 100 days before death is 90% of ideal body mass, but TBK (normalized for height, age and sex) extrapolated to only 71% of normal at 100 days. Since most potassium in the body is found in the non-adipose tissue cell mass, a measurement of TBK represents mainly the non-adipose tissue cell mass of the body (BCM). This study clearly demonstrated that a small perturbation in body mass can occur concomitantly with a greater change in BCM. The study also provided evidence that a critical level of body cell mass is needed for survival. If this pattern of wasting is typical of the AWS, it is clear that simply monitoring body mass is insufficient. Melchior *et al.* (1999) found lean body mass index (LBMI = lean body mass (kg) / height<sup>2</sup> (m<sup>2</sup>)), but not body mass loss, was an independent predictor of survival after controlling for other factors. Interventions that replete body cell mass are therefore critical for patients that suffer from the wasting syndrome.

It has been shown that a body mass loss greater than 10% prior to AIDS is associated with an increased risk of death (Palenicek *et al.*, 1995). Even a body mass loss between 5% and 10% has been shown to be associated with an increased risk of death and opportunistic complications (Wheeler *et al.*, 1998). Therefore, even slight body mass changes may be indicative of wasting. Ott and colleagues (1993) have demonstrated that there may be signs of malnutrition in patients with HIV as evidenced by a significantly increased ECM (extracellular mass) and ECM to BCM ratio compared to a control group, while BMI and body mass appear to be unaffected. The values of these variables are shown in Figure 2 for the HIV patient groups.



**Figure 2:** Results of CD4<sup>+</sup> cell count and body composition measurements of 193 male HIV infected patients at various disease stages. There were four patient groups, those with no diarrhoea (n = 114); mild diarrhoea (n = 42), mild to severe diarrhoea (n = 7) and those with severe or permanent diarrhoea (n = 30). P values are comparisons with the group of patients without diarrhoea (redrawn from Ott *et al.*, 1993).

The definition of wasting based on body mass is practical but may be too insensitive as patients with only a small body mass loss may actually be losing a greater amount of essential body mass. Nemechek and colleagues (2000) suggested that additional measurements of body composition should also be made when assessing patients. These authors suggested that body composition measurements should be made every 3 to 4 months. Bioelectric impedance analysis (BIA) and skinfold measurements were suggested as possible methods of measuring changes in body composition. In a review, Salomon *et al.*, (2002) also concluded that anthropometric measurements and BIA are practical solutions for measuring body composition changes in HIV patients. These measurements can enable clinicians and other health care workers to follow changes in BCM closely and assess patients more accurately.

Within the context of trying to understand HIV/AIDS in Sub-Saharan Africa, a drawback of the above-mentioned studies is that most of the study participants were men. Although the gender ratio of the cohort weren't mentioned by Kotler and co-workers (1989) in their publication, 95% of the participants were men in the study conducted by Melchior and colleagues (1999). Nevertheless, these two studies demonstrated the importance of considering LBM or BCM changes instead of BW when assessing the severity and impact of wasting. The studies done by Macallan *et al.* (1993) and Palenicek *et al.* (1995) had only male participants, while only 7.1% of the Wheeler *et al.* (1998) study participants were female. These three studies illustrated the importance of body mass loss and its relation to disease progression.

In the first instance, it would be important to know whether the observations made in all of the above studies can be applied to a female population. A decade after their ground-breaking study, Kotler *et al.* (1999) indicated that women lose proportionately more fat than men during HIV infection. Swanson *et al.* (2000) also presented evidence that suggested that HIV-infected women show a preferential loss of fat mass (FM) and a relative preservation of BCM. The authors of both studies suggested that a higher initial body fat content may predispose individuals to lose relatively more fat than LBM during wasting. Alternatively, the opposite may be true for men or wasting may be influenced by the sex hormone environment.

In addition, it would be important to know whether these observations apply to females in Sub-Saharan Africa where racial and socio-economic differences could influence disease progression and body composition changes.

#### **a. Mechanisms of wasting**

The underlying causes of the wasting process are often multiple. It has been shown that opportunistic infections, chronic diarrhoea, decreased dietary energy intake and also increased resting energy expenditure (REE) are correlated with body mass loss (Melchior *et al.*, 1999; Wheeler *et al.*, 1998). An altered metabolism, malabsorption of nutrients, increased cytokine levels, endocrine abnormalities and primary muscle disease have also

been implicated as possible underlying mechanisms of the wasting syndrome (Chang, *et al.* 1997). In a study that evaluated the deltoid muscle biopsy samples of 30 patients with the wasting syndrome (of which 26 were male), only 11 were found to have HIV-related myopathy (Miró *et al.*, 1997). The authors of this publication concluded that the AWS is a heterogeneous condition and not a true myopathy. Some of the endocrine abnormalities that have been shown to be associated with HIV infection include elevated concentrations of resting cortisol (which can lead to increased amino-acid catabolism) and decreased concentrations of dehydroepiandrosterone sulphate (DHEAS) (Christeff *et al.* 2000; De La Torre *et al.* 1997). While cortisol stimulates amino-acid catabolism, DHEA is anti-catabolic.

Cytokines may contribute to wasting and cachexia through various mechanisms (Chang *et al.*, 1998). In a review, Chang *et al.* (1998) stated that thyroid hormone and adrenal and gonadal homeostasis could be altered by cytokines during HIV infection, which may lead to hypermetabolism, anorexia and cachexia. Cytokines could play a role in stimulating the ubiquitin-proteasome pathway causing muscle proteolysis. Unfortunately the impact of cytokines on wasting in human subjects is difficult to study since they are rapidly internalized by cells. Cytokines also act in an autocrine manner and their concentration in the blood is therefore not necessarily reflective of their influence on body systems. Conflicting results have been found when circulating cytokine concentrations were measured in AIDS patients. Some studies found serum levels of the cytokine, tumour necrosis factor (TNF), to be elevated (Abad *et al.*, 2002; von Sydow *et al.*, 1994; Rautonen *et al.*, 1991; Lahdevirta *et al.*, 1988) while other studies failed to show high concentrations of TNF in the blood or any correlation between TNF concentrations and the magnitude of body mass loss in AIDS patients (Thea *et al.*, 1996; Reddy *et al.*, 1988). The serum concentrations of another cytokine, interleukin-6 (IL-6), have been found to be raised in AIDS patients in various studies (von Sydow *et al.*, 1991; Breen *et al.*, 1990; van Snick *et al.*, 1990). Differing results may be related to disease stage and treatment differences between the study populations. For example, those in the study by Thea *et al.* (1996) were not on ART, whilst Abad *et al.* (2002) have shown that wasting status could be related to cytokine concentrations.

Macallan and colleagues (1993) reported a close association between acute body mass loss episodes and opportunistic infections in males with stage 4 HIV infection. It should be noted that periods of body mass gain and stability were also shown in this longitudinal study that lasted between 1.2 months and 3 years. The median duration of body mass-stable episodes was 10 months while the median duration of body mass-gain was 3 months. Recovery of body mass may be incomplete or interrupted by a new acute body mass loss episode. Body mass gain did not necessarily lead to an improved prognosis as one of the individuals gained body mass virtually until death. Gained body mass may not be optimal as a patient may be gaining fat or fluid instead of lean body mass.

Different patterns of body mass loss are apparent from the study conducted by Macallan and colleagues (1993). Some patients experienced acute body mass loss events followed by periods of body mass gain, while others showed a chronic, relentless pattern of body mass loss. Nongastrointestinal infections were particularly associated with acute body mass loss events, while gastrointestinal disease (especially diarrhoeal diseases) was associated with chronic body mass loss. The authors suggested that the metabolic disturbance related to chronic body mass loss is similar to a malnutrition response (despite reduced metabolic rate), while acute body mass loss resembles the disturbances seen in catabolic states with increased metabolic rate. They also suggested that these different mechanisms can affect body composition, because of the tissue targeted during the wasting periods. It is therefore also important to record the rate of body mass loss as well as episodes of body mass gain or stability. This information can provide a better understanding of the type of body mass loss the individual is experiencing and how this body mass loss may be affecting body composition.

Roubenoff *et al.* (1997) proposed the use of three distinct terms that describe body composition changes to distinguish between the different underlying processes. They defined *sarcopenia* as the involuntary loss of skeletal muscle mass and reduced function, which may occur for various reasons including loss of alpha motor neurons in the spinal column, loss of endogenous growth hormone production, inadequate protein intake, dysregulation of catabolic cytokines (especially IL-6), loss of estrogen and androgen production and reduced physical activity. The term *cachexia* describes an involuntary loss

of body cell mass or fat free mass, without a large decrease in BW. This process might be due to an increased cytokine production which results in hypermetabolism. Roubenoff *et al.* (1997) defined *wasting* as characterized by a parallel decline in body mass and BCM. Therefore, wasting is always accompanied by cachexia, but cachexia does not necessarily lead to wasting. The authors suggested that an inadequate energy intake is necessary for the state of cachexia to develop into wasting, a process that is distinctive of advanced HIV-infection. It is therefore also possible for patients to maintain their body mass by adequate nutritional intake whilst experiencing a decrease in BCM, indicating the presence of cachexia but not wasting according to these definitions of Roubenoff *et al.* (1997).

#### **b. Interventions to reduce wasting**

Although many different factors may interact to cause wasting, nutritional status is clearly an important factor in progression of HIV-related wasting. After a review of the literature, Timbo and Tollefson (1994) concluded that the efficacy of nutritional supplementation should be investigated. McKinley *et al.* (1994) showed that nutrition intervention (dietary assessment, intake analysis, counseling and provision of supplements) by dietitians can improve nutritional status.

Berneis *et al.* (2000) demonstrated that oral nutritional supplementation combined with dietary counseling can diminish whole body protein catabolism and increase lean body mass in HIV infected subjects with modest to moderate malnutrition. Although positive effects of whey protein supplementation on body mass were found by Agin *et al.* (1999), these researchers also showed that the combination of supplementation and resistance exercise can lead to gains in body cell mass and fat free mass, whereas supplementation alone leads to increases of fat mass.

Resistance training has been shown to be an effective treatment to increase lean body mass, strength and functional status (Roubenoff & Wilson, 2001). Exercise may also have a positive effect on fat distribution, as shown by preliminary results of reduced trunk fat mass after 16 weeks of progressive resistance training with an aerobic component (Roubenoff *et al.*, 1999a). Roubenoff *et al.* (1999b) reported a lasting effect of increased lean body mass

up to 8 weeks after a resistance training programme was discontinued and normal activity was resumed. These results show that resistance exercise may be a feasible option for maintaining lean body mass. How this might be implemented in Sub-Saharan Africa remains to be investigated. Exercise physiologists could play an important role in this regard by monitoring patients' muscle function and assisting in educational programmes and exercise training sessions.

Androgen administration has been found to increase lean body mass and quality of life parameters (Gold *et al.*, 1996; Grinspoon *et al.*, 1998), but these studies did not take into account the possible influence of exercise during the study period. Therefore, it is not clear whether gains were from androgen administration alone, or also from exercise. Subsequently, the effect of testosterone administration in combination with resistance exercise was investigated (Grinspoon *et al.*, 2000) and the increases in skeletal muscle fibre size that were found were similar to those of the previous, less controlled study, suggesting a synergistic role of exercise. However, Bhasin *et al.* (2000) found that testosterone and exercise together did not produce greater gains than either intervention alone, suggesting that pharmaceutical intervention with anabolic agents is not a necessity for improved body composition even for HIV-infected men with low testosterone levels (less than 12.1 nmol/L). From these data it was concluded that, taking into account the longer-term effects of androgen treatment on endocrine metabolism, exercise alone might be the ideal long-term strategy to prevent or reverse muscle loss in HIV infected persons.

Most anabolic agents still need to be researched extensively before being approved by the Food and Drug Administration of the United States (FDA) for use as treatment for HIV-associated wasting. Only growth hormone has been granted accelerated approval by the FDA, although the dosing recommendations still need to be determined. A meta-analysis performed by Moyle *et al.* (2004) found that a dose of 6 mg recombinant human growth hormone per day had favourable effects on functional capacity and QoL. Possible side-effects from pharmacological doses of growth hormone include arthralgia, myalgia, diarrhoea and swelling and fluid retention in extremities. Oxandrolone (5 – 20 mg/day) is approved by the FDA as a short-term treatment for body mass loss as a result of chronic infection, trauma, prolonged use of corticosteroids or surgery. Nandrolone decanoate and



oxymetholone have been approved for the treatment of anaemia, but not wasting (Mulligan & Schambelan, 2002).

Shevitz *et al.* (2005) compared the effectiveness of nutrition intervention alone (nutritional counseling and an oral liquid supplement) or nutrition intervention with oral androgen (oxandrolone) administration or nutrition intervention with progressive resistance training (PRT) for treating AWS. Mid-thigh muscle cross-sectional area increased significantly in the oxandrolone and resistance training groups. Self-reported physical functioning improved significantly only with PRT and this intervention improved quality of life more than the other two interventions. PRT was found to be the most cost-effective intervention while oxandrolone administration proved to be the least cost-effective intervention. The calculation of the cost of PRT included the cost of nutrition intervention as well as gymnasium and personal training fees. Input in terms of transportation and time by the participants was also taken into account. This cost analysis may be inappropriate for Sub-Saharan Africa, since gymnasiums and related infrastructures are not widely available in this area. Researchers in South Africa should therefore explore other options of resistance training and investigate the cost and feasibility of implementing national exercise programmes or educational seminars for patients.

Although there are many treatment options for HIV associated wasting, it is important to be able to distinguish between the types of body mass loss (losing lean body mass versus fat mass) and the relevant underlying mechanisms, before effective treatment can be considered. Opportunistic infections, factors that limit food intake (relating to upper gastrointestinal tract pathology) and even psychiatric disorders need to be identified and addressed for exercise or nutritional support and supplementation to be successful (Williams *et al.*, 1999). Effective monitoring of body mass loss and body composition changes, considered together with clinical and laboratory evidence, provide information about important processes (like hypermetabolism or proteolysis) occurring in the body. Clinical markers proposed include the cytokines discussed before and creatinine and urea nitrogen (American Dietetic Association and Dietitians of Canada, 2004) to indicate proteolysis.



### 3.1.2 The lipodystrophy syndrome

During the late 1990s changes in the distribution of body fat became noticeable in patients taking HAART. Initially protease inhibitors (PIs) were implicated as the offending agent (Brinkman *et al.*, 1999), but similar lipid abnormalities have been shown in PI-naïve patients using two nucleoside reverse transcriptase inhibitors (NRTIs) (Galli *et al.*, 2002).

It has been hypothesized that PIs induce apoptosis of peripheral adipocytes by interfering with the *cis*-9-retinoic acid mediated stimulation of the retinoic X receptor which is involved in adipocyte differentiation (Carr *et al.*, 1998). Other possible avenues of metabolic disruption by PIs are the inhibition of lipoprotein receptor-related protein (involved in hepatic and endothelial clearance of chylomicrons and triglycerides) (Carr *et al.*, 1998), the suppression of the breakdown of nuclear sterol regulatory element binding proteins (nSREBP) in the liver and adipose tissue (potentially resulting in increased fatty acid and cholesterol biosynthesis in the liver, lipodystrophy and insulin resistance), suppression of proteasome mediated breakdown of nascent apolipoprotein B in the liver and the suppression of GLUT-4 expression in muscle and adipocytes (Hui, 2003).

NRTI's have been shown to inhibit DNA polymerase  $\gamma$  (responsible for mtDNA replication) (Lewis & Dalakas, 1995; Brinkman *et al.*, 1998). Brinkman *et al.*, (1999) have hypothesised that NRTI's cause mitochondrial toxicity. They proposed that this toxicity is the predominant cause of HAART-related lipodystrophy and that protease inhibitors then aggravate the condition. Currently lipodystrophy is "considered to be an adverse effect of antiretroviral therapy, not limited to a specific drug or class of drugs" (Malinkovic & Martinez, 2005).

The greatest obstacle for consensus on the aetiology of the lipodystrophy syndrome is probably the lack of a universally accepted definition. Defining the syndrome proved to be more difficult than initially supposed. To this date, there still is no practical definition for lipodystrophy (Milinkovic & Martinez, 2005). For a patient it simply involves the loss of fat in the face and arms, which may or may not be accompanied by an expanding waistline

or even the development of a “buffalo hump” (increased fat deposition in the dorsocervical area). These changes have profound social and clinical implications. It may force a person to disclose his or her status to enquiring friends and it may influence adherence to the drug regimen. The syndrome is also associated with metabolic abnormalities like dyslipidaemia, glucose intolerance, diabetes, hyperinsulinemia and insulin resistance (Salomon *et al.*, 2002; Brinkman *et al.*, 1999; Carr *et al.*, 1998). These features resemble the characteristics associated with the metabolic syndrome X.

Metabolic syndrome X has been described and studied since 1988, mainly in patients without HIV. It is a condition that frequently arises from a lifestyle that favours a high fat intake, chronic psychological stressors and low physical activity. Components of the syndrome include visceral and generalized obesity, fatty liver, hypertension, endothelial dysfunction, renal dysfunction, polycystic ovary syndrome, inflammation, hypercoagulability and atherosclerosis (Miranda *et al.*, 2005; Mehta & Reilly, 2004).

Although controversial, there are a few accepted definitions for this metabolic syndrome. These definitions commonly include the co-existence of conditions like glucose intolerance, central obesity, dyslipidaemia and hypertension. A body mass index (BMI) greater than 30, a waist circumference more than 102 cm for men or 89 cm for women or a waist-to-hip ratio more than 0.90 for men and 0.85 for women are some of the physical criteria that are considered to indicate the presence of metabolic syndrome X (Miranda, *et al.* 2005).

Such clear and practical definitions or criteria do not yet exist for the lipodystrophy syndrome. Instead, the subjective description of body fat changes based on reports from patients in combination with clinical evaluation are still used extensively to define lipodystrophy (Milinkovic & Martinez, 2005). A list of clinical aspects and observable characteristics has been compiled (see Table 3), but objective criteria still need to be formulated (Salomon *et al.*, 2002; Brinkman *et al.*, 1999).

The Lipodystrophy Case Definition Study generated a definition of lipodystrophy but it is too complex to use in clinical practice and therefore it does not qualify as a practical

definition of lipodystrophy (HIV Lipodystrophy Case Definition Study Group, 2003). This definition relies on parameters gathered from laboratory testing, anthropometry and radiology (computed tomography scanning and dual X-ray absorptiometry). Availability of equipment and the cost involved in obtaining the required parameters limit the application of this definition.

**Table 3:** Clinical aspects of the lipodystrophy syndrome (Salomon *et al.*, 2002; Rodwell *et al.*, 2000, Carr *et al.*, 1999).

<b>Fat accumulation</b> <ul style="list-style-type: none"> <li>▪ Abdominal obesity</li> <li>▪ Dorsocervical pad (“Buffalo hump”)</li> <li>▪ Cervical hypertrophy</li> <li>▪ Lipomas</li> <li>▪ Adipomasty</li> </ul>
<b>Fat loss</b> <ul style="list-style-type: none"> <li>▪ Face wasting (reduction or absence of subcutaneous tissue on the cheeks with sparing of the facial musculature)</li> <li>▪ Loss of subcutaneous fat of extremities</li> <li>▪ Loss of gluteal mass</li> </ul>
<b>Biological abnormalities</b> <ul style="list-style-type: none"> <li>▪ Glucose intolerance, diabetes, hyperinsulinemia and increased insulin resistance</li> <li>▪ Hypertriglyceridemia</li> <li>▪ Hypercholesterolemia: increased LDL cholesterol; decreased HDL cholesterol</li> </ul>

Some patients show only regional fat loss (lipoatrophy, usually of peripheral regions or face) or regional fat gain (lipohypertrophy, usually intra-abdominal or dorsocervical) (Carr *et al.*, 1999). Therefore, one may question the classification of the observed body fat changes as a single “lipodystrophy syndrome”. Is lipoatrophy a separate syndrome or a component of the lipodystrophy syndrome? This uncertainty makes the monitoring and assessment of the condition even more difficult. Carr *et al.* (1999) found that self-assessment, physical examination, measuring fasting triglycerides and C-peptide as well as the measurement of central adiposity with dual X-ray absorptiometry (DXA) to be useful in the diagnosis of the syndrome. Since DXA is an expensive and frequently unavailable technology in a typical rural clinic, I suggest that self-assessment and physical examination (which are subjective) should be combined with objective anthropometry measurements to assess and monitor lipodystrophy in South African clinics. Nurses and exercise

physiologists who have been trained in the methods of anthropometry, could perform these assessments.

### **3.3. Monitoring body composition changes**

The human body can be considered to be composed of various structural and functional compartments. There are cellular and non-cellular compartments, aqueous and non-aqueous compartments, as well as fat and non-fat compartments (Brooks *et al.*, 2001).

*Whole body:* Body mass (BW) can be divided into fat mass (FM) and fat free mass (FFM). Fat free mass includes the skeleton, water, muscle, connective tissue, organ tissues and teeth. FM can be divided into essential and non-essential fat. Essential fat is composed of the lipids that are incorporated into organs and tissues (cellular membranes, nervous tissue, mammary glands, heart, lungs, liver, etc.). Non-essential fat is excess fat stored in adipose tissue (Brooks *et al.*, 2001).

The metabolically active cellular component of FFM is referred to as the body cell mass (BCM). The extracellular component of fat free mass (ECM) contains solids (bone, fascia and cartilage) and fluids (plasma, lymph and interstitial fluid) (Wang *et al.*, 1992).

Fat free mass can be calculated by subtracting the FM from the BW. An indirect laboratory method of measuring body composition is hydrostatic weighing. This method is often seen as a “gold standard” and it has been used to develop equations so that body composition can be calculated from skinfold measurements (Brooks *et al.*, 2001).

Lean body mass (LBM) can be calculated by subtracting FM (as calculated from hydrostatic weighing) from body mass. Therefore, LBM and FFM are essentially the same body compartment but sometimes a small distinction is made between the two concepts. Bioelectric impedance analysis (BIA) is a technique that measures the conductivity of the body. When LBM is measured by bioelectrical impedance analysis, LBM corresponds with BCM, extracellular water (ECW) and intracellular water (ICW). This is because the aqueous compartments and lean tissue conduct electricity more rapidly than fat and BIA

measures how easily electricity flows through the body. Lean body mass then represents tissue that is highly conductive. When subtracting FM from BW, the result is usually referred to as FFM (Brooks *et al.*, 2001; Melchior *et al.*, 1999).

These are the most important categories and their relationships to each other:

$$\begin{aligned}\text{BW} &= \text{FM} + \text{FFM} \\ \text{FFM} &= \text{BCM} + \text{ECM} \\ \text{BW} &= \text{FM} + \text{BCM} + \text{ECM} \\ \text{LBM} &= \text{BCM} + \text{ECW} + \text{ICW}\end{aligned}$$

Laboratory methods of measuring body composition include dual X-ray absorptiometry (DXA), densitometry (also known as underwater or hydrostatic weighing), magnetic resonance imaging (MRI), neutron activation analysis and biochemical techniques (total body potassium (TBK) analysis, total body water (TBW) and inert gas absorption). Field test methods are usually validated against standard laboratory methods (hydrostatic weighing, TBK and DXA are considered gold standards). Anthropometry and skinfold measurements (SKF), ultrasound and BIA are considered to be field tests (Brooks *et al.*, 2001).

Bioelectric impedance analysis has been used extensively to measure body composition in HIV-infected populations (Wilson *et al.*, 2002; Forrester *et al.*, 2002; Swanson *et al.*, 2000; Kotler *et al.*, 1999; Bell *et al.*, 1997). Although this method is considered to be an acceptable alternative to DXA or TBK when resources are limited, it has been shown to produce highly variable estimations of FM and FFM in comparison to DXA and TBK among HIV-infected men and women with AIDS wasting (Corcoran *et al.*, 2000). Additionally, Corcoran and colleagues (2000) showed that FFM assessed by DXA was most highly correlated with TBK in men and women while BIA and skinfold thickness analysis were less well correlated with TBK. They showed a significant difference in the determination of FFM by BIA (using the standard RJL Systems Inc software) compared to DXA resulting in an overestimation of FFM by  $1.5 \pm 2.9$  kg for men ( $p < 0.001$ ) and  $2.0 \pm 2.6$  kg for women ( $p < 0.0001$ ). When compared to DXA, skinfold thickness analysis resulted in differences in FFM estimations that were on average less significant ( $1.2 \pm 3.4$

kg overestimation for women ( $p = 0.01$ ) and  $1.0 \pm 3.0$  kg underestimation for men ( $p = 0.02$ )) than those differences described above between BIA and DXA.

Estimating FM from skinfold thickness analysis resulted in an overestimation of  $1.3 \pm 3.0$  kg in men and an underestimation of  $1.0 \pm 3.3$  kg for women compared to DXA (Corcoran *et al.*, 2000), whereas BIA (with the RJL equation) underestimated the FM of men with  $1.1 \pm 2.8$  kg and  $1.8 \pm 2.5$  kg for women. Different equations used with BIA resulted in highly variable estimations of FFM and FM (overestimations of up to  $6.2 \pm 4.1$  kg and underestimations of up to  $5.9 \pm 4.2$  kg were shown). Body fatness also influenced the prediction of FFM by BIA in comparison to DXA. FFM was overestimated more in patients with greater body fat.

The above publication is especially relevant because all the participants were HIV-infected and showed signs of AIDS wasting (body mass  $< 90\%$  of ideal body mass and/or body mass loss  $> 10\%$  of original). The study clearly demonstrates that the results obtained from BIA measurements are highly variable and dependant upon the equation used. A disturbance in body water compartments (manifesting as a relative increase in extracellular water volume) has been linked to HIV-infection and AIDS wasting (possibly related to protein-calorie malnutrition (PCM)) (Paton *et al.*, 1998; Bell *et al.*, 1997). Such disturbances can influence determinations made by using TBK and BIA (Wang, *et al.*, 1992).

Selecting an appropriate method of measuring body composition is therefore a difficult task. In a resource-poor setting using TBK and DXA is virtually impossible, because of cost, space, additional facilities and the expertise needed to operate the equipment. Although BIA is easy to perform, the apparatus is expensive. Skinfold thickness analysis may be the ideal solution to assist in body composition measurements in resource-poor settings and rural clinics in South Africa because the equipment is much less expensive and the method is relatively easy to perform. However, the reliability coefficients (R) of skinfold measurements have been shown to be relatively large when different technicians performed the same measurements on the same subjects with less error when the same technician repeated the measurements on the same subjects (inter-observer variability (R) =

0.858-0.999; intra-observer variability (R): 0.979-0.999). Subsequent estimations of body composition exhibited comparatively higher reliability (inter-observer variability (R): 0.975-0.999; intra-observer variability (R): 0.995-0.999) (Klipstein-Grobusch *et al.*, 1997). Also, as illustrated in the Corcoran study (2000), skinfold thickness analysis can result in an over- or underestimation of FFM and FM in comparison to DXA, and although significant, these differences are usually less than one and a half kilogram. This difference will also be less important if the changes in FFM and FM are monitored over time instead of merely focussing on the absolute values of these variables. Therefore, it will have to be kept in mind that the same technician should perform all measurements on the same subject and that changes in the region of 1 kg are within measurement error for FFM.

*Regional:* Although skinfold thickness analysis can provide useful estimations of changes in FFM and FM they can also provide more detailed information on regional changes in fat distribution. The skinfold thickness values that were used in the above mentioned study were from the subscapular, biceps, triceps and supra-iliac sites and were consequently used to determine percentage of body fat by the equations of Durnin and Womersley (1974).

It is sometimes also useful to distinguish between subcutaneous fat (SCF) and intra-abdominal fat (IAF). Subcutaneous fat then represents non-essential fat in adipose tissue and IAF is the protective fat that surrounds the intestinal organs and therefore, if not excessive, it is a type of essential fat.

The technique of obtaining skinfold thickness measurements has to be learned and practised, but it requires some technical knowledge of standardized procedures (NHANES III, 1988). Nurses could be trained to perform this method relatively easily (as an additional skill to their existing clinical expertise) and it may assist greatly in the monitoring and diagnosis of patients. The measurement of circumferences at specific sites is another anthropometry method that is also simple to perform (provided the specific landmarks are understood) and could also be helpful with body composition assessments. Anthropometric measurements have the advantage that changes at specific sites can be monitored, which is especially of concern with iatrogenic lipodystrophy. Increases in waist girth and decreases in leg and arm circumferences could be valuable indicators when

lipodystrophy is suspected in patients. Exercise physiologists that are specifically trained to obtain skinfold thickness measurements and anthropometric circumferences can also make an important contribution in a clinical setting, especially with regard to lifestyle recommendations that may result from this information.

### **3.4 Quality of life**

The number and severity of HIV-related symptoms has been shown to be associated with a person's perceived quality of life (QoL) (Cleary *et al.*, 1993). The improvement in treatment options for HIV/AIDS has led to an increased interest in and assessment of QoL of infected individuals (Gielen *et al.*, 2001; Wu, *et al.* 1997).

The concept of QoL includes multiple aspects of life satisfaction (like sense of security, control over one's environment and spiritual fulfilment) that relate to physical functioning, mental health status and social role functioning (Gielen *et al.*, 2001). Questionnaires usually include various "dimensions" or aspects of QoL like global health perceptions, psychological functioning, self-care, mobility etc. (Burström *et al.*, 2001; Lenderking *et al.*, 1997).

The MOS-HIV questionnaire (HIV specific scales adapted from the Medical Outcomes Survey) is one of the most widely used questionnaires for the measurement of QoL, especially in the USA (Lenderking *et al.*, 1997; Wu *et al.*, 1997). Different versions of the questionnaire exist, varying in length, content and language. The different forms have been validated and shown to be reliable in various cities of the USA as well as London (Chan & Revicki, 1998; Wu *et al.*, 1997; Lenderking *et al.*, 1997; Carretero *et al.*, 1996).

Although the MOS-HIV has been used in South Africa (Wu *et al.*, 1997), there seems to be no available data describing its validation in a South African population. A European questionnaire (EQ-5D) has been translated (into Xhosa) and validated in a South African population (Jelsma, 2003). The original EQ-5D has been used extensively in various international studies including Japan, Canada and Zimbabwe (Burström *et al.*, 2001; Jelsma, 2003).



The assessment of QoL by health workers can assist in the monitoring of patients with regard to the impact of treatment (Chan & Revicki, 1998; Wu *et al.*, 1997). A QoL questionnaire can also be a powerful research tool since it is usually easy to administer and inexpensive. It can also expose unexpected findings, which may improve our understanding of effective treatment of patients. For example, the study conducted by Gielen *et al.*, (2001) showed a relationship between practicing more health promoting behaviours and improved mental health, physical functioning and overall quality of life. The participants of this study were all women (94% of which were African-American) and 54.5% of the study group did not have a high school diploma. A great number of these participants experienced sexual abuse and/or physical and/or sexual assault at some point in their lives. The researchers concluded that relatively straightforward lifestyle changes (like eating well, exercising and getting adequate sleep) can make a difference even in a complicated context involving HIV disease, poverty and oppression.

Resistance training and cycling has been shown to increase physical functioning and QoL in HIV-infected men and women (Agin *et al.*, 2001; Roubenoff & Wilson, 2001; Stringer *et al.*, 1998). Cardiovascular exercise and strength training have been suggested as possible treatment interventions for conditions like the AIDS wasting syndrome (AWS) and the metabolic abnormalities associated with antiretroviral therapy (Scevola *et al.*, 2003; Yarasheski & Roubenoff, 2001; Mars, 2000; Roubenoff *et al.*, 1999a). QoL, physical functioning and the HIV disease are therefore complexly interrelated and any study that investigates the impact of HIV disease on health or the treatment outcomes ART, should also include measurements of QoL.

Therefore, this study has included the measurement of QoL with an easy-to-use version of the EQ-5D questionnaire (as validated by Jelsma, 2003) in addition to the anthropometric measurements of body composition changes that may indicate AWS or lipodystrophy.

## **4. Methods**

### **4.1 Ethical concerns**

The protocol was evaluated and approved by the Ethics Committee of the University of Stellenbosch (Sub-committee C, Tygerberg campus). All relevant agencies and parties were contacted and consulted before the initiation of any measurements (including provincial and local administrators and government officials).

Participants were recruited with the assistance of support group leaders and medical staff who informed possible candidates about the project and consequently referred them to the investigator. Prejudice was still severe in the community that was investigated and the utmost discretion and confidentiality was observed at all times. HIV-related stigma meant that individuals could not disclose their status to many people and family members were often oblivious to their condition. It was therefore difficult to recruit a control group. Initially we attempted to recruit friends and family of our participants to serve as HIV-negative participants, but this was clearly not possible in the communities in our region. Alternative ethically acceptable strategies of recruiting appropriate controls were outside of the scope of the present study.

Before being accepted into the antiretroviral treatment (ART) programme, participants underwent thorough evaluation and counselling. Each patient needed to demonstrate that she had at least one family member or close friend that could assist the patient during times of disability and with the taking of medication. This “buddy” unfortunately also didn’t qualify as an appropriate control candidate since they were usually a poor match (being a husband or much older or younger).

Appendix C contains the information sheets and consent forms that were used. These forms were available in English and Afrikaans. An interpreter was used on the day of recruitment to explain the protocol in Xhosa in cases where the participant could not understand English or Afrikaans adequately.

## **4.2 Participants**

Participants were recruited from clinics in the Stellenbosch area at the end of 2003 with the help of health workers involved with HIV-counselling and support groups. In 2004, government-initiated programmes providing ART to selected HIV-infected patients were implemented at selected clinics. We recruited additional participants from one of these clinics situated in the semi-rural community of Paarl.

Therefore, some participants were enrolled into the study before ART was widely available, while other participants were enrolled while being assessed for qualification to enter a treatment programme.

Only South African non-Caucasian women were recruited to participate in the study. The only exclusion criterion was being pregnant, since it would influence body composition changes over time.

## **4.3 Rural and clinical setting**

Since there was no space to meet and assess participants at the Stellenbosch clinics, measurements of this group were performed at the University of Stellenbosch. Although the clinic at Paarl also had limited space, measurements were done at the clinic. Open offices were used as they became available, since all consultation rooms were shared between counsellors, doctors, nurses and a dietician.

Participants were reimbursed for travel expenses when they travelled for an appointment relating to the study. Some of the measurements at Paarl were performed concurrently with dates that the participants had to see a doctor or collect medicine.

The aim was to get at least one measurement every month for the first three months, a six-month follow-up measurement as well as a one-year follow-up measurement for every participant. Various participants missed several follow-up visits, whereafter new dates were scheduled. Thus, the participants' measurement dates do not follow a uniform

pattern, and for the purposes of data analysis their measurements were therefore divided into three main categories (baseline, short-term and long-term), which relate to the day of treatment initiation (TI) or the day of recruitment (R) into the study. These temporal categories are indicated in Table 4.

**Table 4:** Categories for time periods for which data are available.

<b>ART group</b>		
<b>Time Point</b>	<b>Description</b>	<b>Weeks since TI (mean <math>\pm</math> SD)</b>
Baseline	Within one month before the initiation of treatment	-4 to 0 weeks ( $-1 \pm 1$ )
Short-term	Within the first three months of TI	2 to 12 weeks ( $5 \pm 3$ )
Long-term	Within one and a half years of TI	42 to 65 weeks ( $52 \pm 7$ )
<b>TN group</b>		
<b>Time Point</b>	<b>Description</b>	<b>Weeks since R (mean <math>\pm</math> SD)</b>
Baseline	On the day of recruitment	0 weeks ( $0 \pm 0$ )
Short-term	Within the first three months after the day of recruitment	2 to 12 weeks ( $7 \pm 3$ )

**Abbreviations:** ART (antiretroviral treatment), TN (treatment naïve), TI (treatment initiation), R (day of recruitment).

#### **4.4 Data collection methods**

Detailed measurements of body composition were performed, whereas selected measurements were made for haematological parameters and quality of life (QoL).

*Body composition:* Participants removed all but their underclothes for all the anthropometric measurements except when height was determined, for which only shoes were removed. Body mass was determined on a scale accurate to the nearest 100 g (Tanita, Tokyo, Japan). A stadiometer was used to measure height and a Harpenden calliper (Baty British Indicators) for skinfold measurements. Measurements included nine skinfold measurements (at the biceps, triceps, sub-scapular, mid-axillary, iliac crest, supra-spinal, mid thigh, calf and abdominal landmarks) and five circumferences (mid-arm, waist, hip, thigh and calf circumferences), all made using standard techniques (NHANES III, 1988). The landmark sites were marked for each measurement on every occasion. All

measurements were made according to the guidelines specified by NHANES III, except for the waist circumference, which was taken midway between the lowest rib and the upper rim of the iliac crest.

*Haematology:* A registered nurse collected 5 ml blood from the cubital vein into EDTA-vacutainer tubes (BD systems, Plymouth, UK). The blood samples that were drawn in Stellenbosch were sent to a commercial pathology laboratory (PathCare) to determine CD4<sup>+</sup> cell count using the AffordCD4 method. Blood samples drawn at the Paarl clinic were sent to a national pathology laboratory at a government hospital (Tygerberg NHLS) for analysis. The CD4<sup>+</sup> cell counts for any given patient were always done at the same laboratory and the coefficient of variation between the two laboratories is less than 5 %.

The doctor consulting the patient at that time determined which blood parameters needed to be investigated according to the information needed for diagnosis and treatment. CD4<sup>+</sup> cell counts and total white cell counts were usually done at least once every six months and viral load was determined after being on treatment for approximately a year, but not in any of the cases at baseline. When enough clinical information was available for a particular patient, it was not always deemed necessary by the clinician to reassess the CD4<sup>+</sup> count before the initiation of treatment. Therefore, there are long intervals between the time of blood assessments and the actual anthropometry measurements for some of the participants.

*Quality of life:* A translated (original in English) and adapted QoL assessment tool (EQ-5D, hereafter called questionnaire) was used for three reasons. Firstly it is simpler than the MOS-HIV questionnaire (Wu *et al.*, 1997); secondly it was previously translated into appropriate languages for this study region (Jelsma, 2003) and thirdly there were only three rating levels (Burström *et al.*, 2001). The questionnaire was available in Xhosa, English and Afrikaans. The questionnaire had been developed and validated in all three languages at UCT Medical School according to accepted methods (Jelsma, 2003). For this study, pictures were added to the questionnaire to make it simpler and easier to explain to participants. The original, as well as the changed version, are included in Appendix C. The questionnaire requires the respondent to rate her perception of mobility, self-care, usual activities, pain or discomfort and depression or anxiety according to three levels of

experience (having no problems, some problems or a lot of problems). The participant was also required to specify an overall score out of a hundred, indicating what her state of health felt like on that day.

Community counsellors with basic counselling training, who regularly worked at the clinic, acted as interpreters. An interpreter assisted with the QoL questionnaire when it proved necessary.

#### 4.5 Data analysis

*Anthropometry calculations:* The equations provided by Frisancho (1981) were used to calculate the upper arm muscle (UAMA) and fat (UAFA) areas for the participants. These equations are given below for measurements in mm:

$$\text{UAMA} = [\{\text{upper arm circumference} - (\pi \times \text{triceps skinfold})\}^2] / 4\pi$$

$$\text{UAFA} = [\pi/4 \times (\text{upper arm circumference}/\pi)^2] - \text{UAMA}$$

Tables from the same publication were used to determine within which percentile categories these calculated parameters as well as the values for triceps skinfold and arm circumferences fell. These tables were also used to convert each participant's arm circumference to a percentage of ideal arm circumference (%IAC), using the value at the 50<sup>th</sup> percentile as reference value.

The equations of Durnin and Womersley (1974) (DW) were used to estimate average body density (D, g/mL) from four skinfolds (biceps, triceps, sub-scapular and supra-illiac). Body density was also estimated with an equation of Pollock *et al.* (1975) (Pol) using three skinfolds (triceps, thigh and supra-illiac) as well as the hip circumference. Both sets of equations were specifically developed for women and are given below:

The equations of Durnin and Womersley (1974):

$$D \text{ (DW)} = C - [M \times \text{Log}_{10} \times \sum \text{four skinfolds}]$$

$$\text{Where } C = 1.1599 \text{ (20 to 29 years) or } 1.1423 \text{ (30 to 39 years) or } 1.1333 \text{ (40 to 49 years) or } 1.1339 \text{ (50 and older)}$$

and M = 0.0717 (20 to 29 years) or 0.0632 (30 to 39 years) or 0.0612 (40 to 49 years) or 0.0645 (50 and older).

The equation of Pollock *et al.* (1975) (Pol):

$$D (\text{Pol}) = 1.1470292 - [0.0009376 \times \sum \text{three skinfolds}] + [0.000003 \times (\sum \text{three skinfolds})^2] - [0.0001156 \times \text{age in years}] - [0.0005839 \times \text{hip circumference in cm}]$$

Fat mass (FM) and fat free mass (FFM) were then calculated from the body density using the Siri (1956) equation:

$$\text{FM (kg)} = \text{Body mass (kg)} \times [(4.95/D) - 4.5]$$

$$\text{FFM (kg)} = \text{Body mass (kg)} - \text{Fat mass (kg)}$$

Additionally, each participant's body mass was expressed as a percent of ideal body weight (IBW) using the following formula (Baylor College of Medicine, 2003):

$$\% \text{IBW} = \text{Body mass (kg)} / \text{Ideal body mass (kg)} \times 100$$

$$\text{IBW} = 45.5 \text{ kg} + 0.9 \text{ kg/cm if height is over 152 cm}$$

Table 5 summarizes the anthropometric variables that are related to wasting and nutritional status, or lipodystrophy. The only variable in traditional anthropometry that is in part related to lipodystrophy is the waist to hip ratio. However, this variable does not account for fat distribution in sub-cutaneous vs. intra-abdominal sites. Therefore, I attempted to estimate the intra-abdominal circumference (the waist circumference without the layer of subcutaneous fat) by applying the same reasoning as when arm muscle circumference and area is estimated from arm circumference and triceps skinfold.

This approximation was based on the following assumptions: the trunk at the level of the waist is a circle, the abdominal skinfold measurement provides an estimation of 2x the thickness of the sub-cutaneous fat and that it is distributed similarly around the whole circle. This novel variable was termed the “intra-abdominal indicator” (IAI) and the following equation was used to calculate this variable:

$$\text{IAI (cm)} = [(\text{waist circumference (cm)} / 2\pi) - (\text{abdominal skinfold (cm)} / 2)] \times 2\pi$$

**Table 5:** Variables that were considered to be indicators of wasting status or manifestations of lipodystrophy, or both.

<b>Variables that relate to</b>	
<b>wasting and nutritional status</b>	<b>lipodystrophy</b>
Body mass (BM)	Waist to hip ratio (W:H)
Percent of ideal body mass (%IBW)	Intra-abdominal indicator (IAI)
Percent of ideal arm circumference (%IAC)	Intra-abdominal indicator to hip ratio (IAI:H)
Upper arm fat area (UAFA)	Upper arm fat area (UAFA)
Upper arm muscle area (UAMA)	
Thigh skinfold	
Thigh circumference	
Fat mass index (FMI)	
Fat free mass index (FFMI)	

The ratio between the IAI and the hip circumference was calculated, which could be considered similar to the waist to hip ratio but excluding estimated sub-cutaneous abdominal fat.

*Statistical analysis:* Prior to any group comparisons or assessments of change over time, descriptive statistics (mean  $\pm$ SD) for the whole group are presented for variables related to disease status. Statistical analysis of the data was performed with the assistance of a professional statistician. All statistical analyses were done with a computer software package (STATISTICA v.7, StatSoft, Inc., Tulsa, USA). A p-value of less than 0.05 was considered to indicate statistical significance. The analysis approach was designed to make three distinctly different comparisons:

(i) In order to determine if the ART and TN groups differed prior to treatment with antiretroviral medication, the baseline values of variables that relate to those mentioned in Table 5 of ART (participants who subsequently went on antiretroviral medication) and TN (participants not on treatment during this study) were compared using a Mann-Whitney U test because data was not normally distributed.



(ii) Thereafter, all the variables of the ART group and the TN group for baseline and short-term time points were compared using main effects ANOVA, to determine any main effect of time or group or both (interaction). A Bonferroni *post hoc* analysis was applied when significant differences were detected. Bootstrap means were calculated as deemed necessary by a statistician for one variable (frontal thigh), because of too many outliers. For some variables the change from baseline to short-term was also calculated prior to comparisons between the two groups. In these cases the two group comparisons were done using a Mann-Whitney U test.

(iii) Only for ART, changes over three time-points were also investigated in a separate analysis (repeated measures ANOVA, with Bonferroni *post hoc* test if applicable), to determine if differences existed between baseline, short-term and long-term time points.

## 5. Results

### 5.1 Overview

A total of 19 participants were recruited and participated in the study beyond the initial screening. A unique subject number was given to each participant to facilitate administration and the organization of data as well as ensuring the anonymity of the participants. For data analysis each subject was then assigned a group code, “EXCL” (the code given to participants who were excluded from the final analyses) or “TN” or “ART” respectively denoting groups belonging to the “treatment naïve” or “antiretroviral treatment” groups. All recruited participants, their group codes and essential information are shown in Tables 6a and 6b.

**Table 6a:** Descriptive information of participants excluded from further data analysis (EXCL 1-5).

Subject	Age (years)	Ethnicity	Date of TI	Baseline CD4 <sup>+</sup> (cells/μL)	Interval (days)	WHO stage	Body mass (kg)	%IBW (%)
EXCL1	43.9	Mixed descent / Afrikaans speaking	14-May-04	5	N/A	N/A	45.9	101
EXCL2	34.5	Mixed descent / Afrikaans speaking	none	116	N/A	N/A	35.4	N/A
EXCL3	33.6	Mixed descent / Afrikaans speaking	14-May-04	160	238	3	64.3	130
EXCL4	34.3	Black / Xhosa speaking	28-May-04	86	28	N/A	68.2	N/A
EXCL5	26.2	Black / Xhosa speaking	unknown	N/A	N/A	N/A	44.0	97
Mean	34.5			92			51.6	109
SD	±6.3			±65			±14.0	±18

Abbreviations: N/A – information not available; WHO – World Health Organization; TI – treatment initiation; %IBW – percent of ideal body mass. Interval indicates the number of days between blood drawing and baseline measurements.

One participant (EXCL2) passed away shortly after the first measurement, before receiving ART, due to lack of ability to overcome Tuberculosis (TB) despite treatment for this disease. Two participants (EXCL1, EXCL3) had already been on treatment for two weeks

by the time the first measurements were completed and were therefore excluded from the groups that were used for statistical analysis. One participant (EXCL4) declined further involvement in the study after the first measurements were done on the day of recruitment and was therefore also excluded from all except the data analyses in Tables 6a and 7. EXCL 5 could not be located for follow-up.

**Table 6b:** Descriptive information of participants belonging to the treatment naïve (TN 1-6) and antiretroviral (ART 1-8) groups.

<b>Subject</b>	<b>Age (years)</b>	<b>Ethnicity</b>	<b>Date of TI</b>	<b>Baseline CD4<sup>+</sup> (cells/<math>\mu</math>L)</b>	<b>Interval (days)</b>	<b>WHO stage</b>	<b>Body mass (kg)</b>	<b>%IBW (%)</b>
TN1	37.7	Black / Zulu speaking	15-Dec-03	65	32	N/A	60.8	134
TN2	29.3	Black / Xhosa speaking	unknown	235	92	N/A	57.0	98
TN3	36.4	Black / Xhosa speaking	18-Mar-04	217	24	N/A	77.5	167
TN4	34.2	Black / Xhosa speaking	none	673	24	N/A	95.0	158
TN5	36.0	Black / Xhosa speaking	unknown	778	4	N/A	79.8	149
TN6	29.9	Black / Xhosa speaking	8-Oct-04	190	115	4	57.3	114
ART1	34.0	Mixed descent / Afrikaans speaking	7-May-04	139	87	3	75.8	153
ART2	54.9	Black / Xhosa speaking	11-Jun-04	393	304	4	78.1	153
ART3	35.1	Black / Xhosa speaking	9-Jul-04	110	105	2	58.9	107
ART4	24.6	Black / Xhosa speaking	25-Jun-04	45	50	3-4	40.5	67
ART5	40.9	Mixed descent / Afrikaans speaking	30-Jul-04	126	14	4	45.0	99
ART6	22.7	Mixed descent / Afrikaans speaking	6-Aug-04	194	133	3	50.3	87
ART7	33.9	Black / Xhosa speaking	13-Aug-04	192	73	3	41.7	92
ART8	36.6	Black / Xhosa speaking	13-Aug-04	19	35	3	58.2	N/A
Mean	34.7			241	78		62.6	121
SD	$\pm 7.7$			$\pm 226$	77		$\pm 16.3$	$\pm 32$

Abbreviations: Refer to the Table 6a. Interval indicates the number of days between blood drawing and baseline measurements. The mean and SD at the bottom of the table represent those values calculated for TN as well as ART participants.

Shortly after baseline measurements, one participant (TN1) relocated to her previous home in KwaZulu Natal where she received ART upon arrival. Two other recruited participants (TN2, TN5) could not be contacted after two measurements and therefore it is assumed that they did not volunteer to have further measurements done. Near the end of the protocol, one participant (TN3) started ART at the Tygerberg Hospital Infectious Diseases clinic. Another participant (TN4) showed a slow disease progression – maintaining a high CD4<sup>+</sup> count and an absence of AIDS signs and symptoms. She was not enrolled into a treatment programme for the duration of the study. Finally, TN6 was enrolled for treatment. She was not used as a subject in the ART group, because more complete data were available for her first two measurement sessions pre-ART. Therefore, assessments that were done after she was enrolled into the treatment programme were excluded.

Despite the fact that 5 participants did not remain in the study (EXCL 1 to 5), their data are included in Table 7 to indicate the typical characteristics of subjects willing to have the majority of measurements done at least once (see Table 7).

**Table 7:** Descriptive statistics of all participants for selected variables on the day of recruitment.

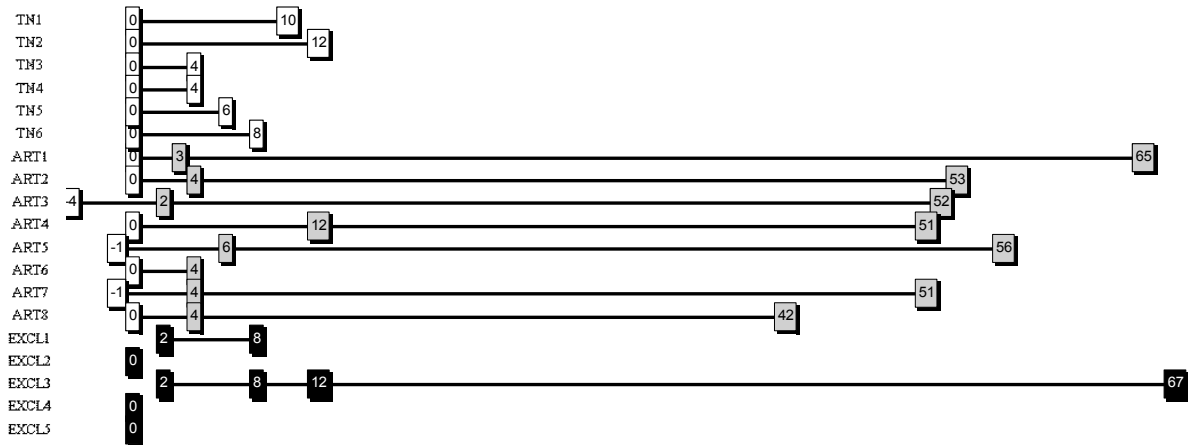
	<b>WCC</b> (cells/nL)	<b>QoL</b> (%)	<b>BMI</b> (kg/m <sup>2</sup> )	<b>Waist : Hip ratio</b>	<b>Triceps skinfold</b> (mm)	<b>Biceps skinfold</b> (mm)	<b>Body fat, DW</b> (%)	<b>UAC</b> (cm)
Median*	4.7	70	22.7	0.79	13.8	7.2	24.5	25.9
n	12	18	16	19	19	19	19	19
Min	2.6	20	14.3	0.64	3.8	2.4	8.4	16.6
Max	8.8	100	33.5	0.87	42.6	26.7	40.7	38.2

Abbreviations: WCC – total white cell count; QoL – overall quality of life score; BMI – body mass index; DW – from the equations of Durnin and Womersley (1974); UAC –upper arm circumference.

\* Due to skewed distribution of the data, median rather than mean is reported.

As mentioned in the Methods section, several appointments were missed or rescheduled for various participants. Therefore, the pattern of follow-up measurements appears to be somewhat inconsistent. Figure 3 is a graphic display of the time points at which measurements were done. Since the baseline time-point (week 0) for the ART group represents the date of treatment initiation and the first measurements were done before

starting treatment for some participants, the time-point for their first measurement is sometimes indicated with a negative number of weeks.



**Figure 3:** Time points for anthropometry measurements indicated as weeks since baseline measurement for TN and weeks since treatment initiation for ART. Group codes: TN1 to 6 represent the TN group, while ART1 to 8 represent the ART group and EXCL1 to 5 were subjects who were excluded due to inadequate data (no follow-up or no true pre-treatment baseline).

Ultimately, 8 participants were included in the group designated as the “ART” group (ART1-8: antiretroviral treated participants) and 6 participants were included in the “TN” group (TN1-6: treatment naïve participants). Baseline and short-term information was available for all subjects in the TN group. All the participants included in the ART group had true baseline information (before the initiation of treatment) and follow-up information for the short-term as well as long-term time points (as specified in the Methods section). One participant of the ART group did not have anthropometry data for the long-term time point and another ART participant’s height was never determined.

The rest of the Results section will be devoted to the findings of the statistical analyses relating to time and group comparisons. Section 5.2 presents the baseline data of both groups. Section 5.3 will present the results from ANOVA comparing the ART and the TN groups at baseline and short-term, while Section 5.4 will show the comparisons between baseline, short-term and long-term for the ART group.

## 5.2 Baseline

The descriptive statistics of selected variables of the ART and the TN groups are shown in Tables 8 and 9. Variables that relate to clinical aspects of the disease are shown in Table 8, while those variables that relate mainly to anthropometry are shown in Table 9.

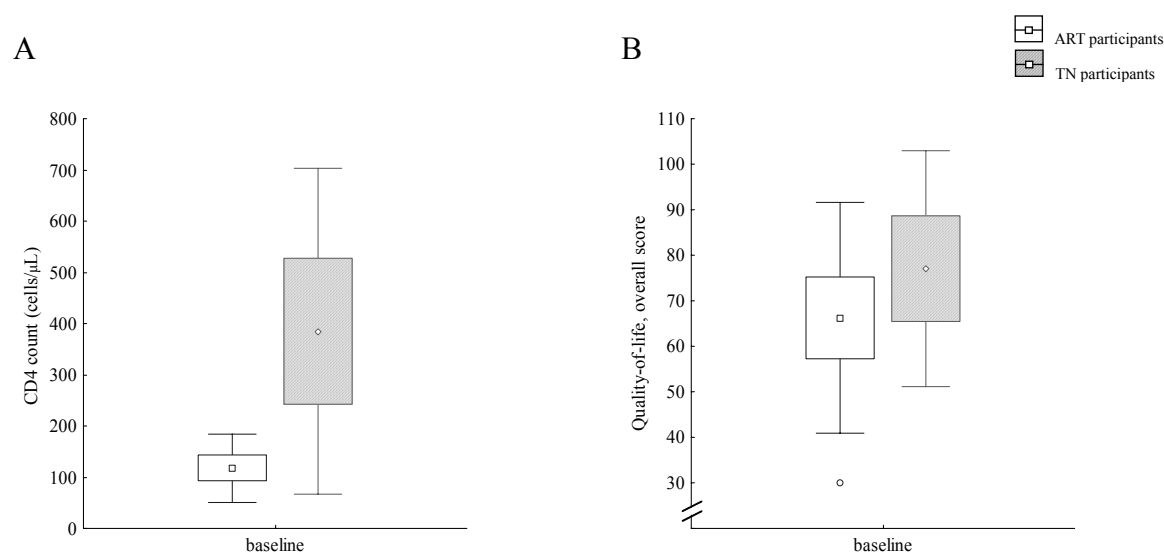
From Table 8 it may appear that body mass (BM) and body mass index (BMI) were different between the two groups, but there was only a trend ( $p = 0.09$ ). Percent of ideal body mass (%IBW) was also not significantly different ( $p = 0.12$ ).

**Table 8:** Descriptive statistics of selected variables at baseline for the TN and ART groups. These variables are important considerations during clinical evaluation.

Variable	TN		ART	
	Mean $\pm$ SD	n	Mean $\pm$ SD	n
Body mass (kg)	71.2 $\pm$ 15.4	6	56.1 $\pm$ 14.6	8
Body mass index (kg/m <sup>2</sup> )	28.2 $\pm$ 5.3	6	22.4 $\pm$ 6.4	7
Percent of ideal body mass (%)	137 $\pm$ 26	6	108 $\pm$ 33	7
CD4 <sup>+</sup> count (cells/ $\mu$ L)	384 $\pm$ 319	5	118 $\pm$ 67	7
CDC immune category	2 $\pm$ 1	5	3 $\pm$ 0 *	7
White cell count (cells/nL)	5.4 $\pm$ 2.2	5	5.1 $\pm$ 1.7	5

Statistical analysis by Mann-Whitney U-test: \*  $p < 0.05$ . Each participant's CD4<sup>+</sup> count was classified according to the CDC immune category where category 1 represents a CD4<sup>+</sup> count of 500 or more, category 2 represents a CD4 category of 200 - 499 and category 3 represents a CD4<sup>+</sup> count less than 200 (see section 2 (disease background) for more information about these categories).

The mean CD4<sup>+</sup> counts were not different at baseline ( $p = 0.09$ ), but the CDC immune category was significantly different between the two groups ( $p < 0.05$ ). The TN group exhibited large inter-individual variation for the baseline CD4<sup>+</sup> cell counts and both groups had large inter-individual variation for overall QoL scores (Figure 4). However, the means for both CD4<sup>+</sup> cell count and QoL scores were not significantly different between groups.



**Figure 4:** CD4 and QoL information for ART and TN groups at baseline and short term or long-term time points. The box plots represent mean  $\pm$  SE, while the whiskers indicate  $\pm$  SD. Outliers are represented by an open circle (  $\circ$  ).

The only anthropometry variables that were significantly different at baseline were the arm circumference (AC), percent of ideal arm circumference (%IAC) and upper arm fat area (UAFA) all of which were higher in the TN group ( $p < 0.05$ ) (Table 9). A few of the other variables shown in Table 9 approached statistical significance (p-value between 0.05 and 0.09). The p-values for biceps and triceps skinfolds both equaled 0.05. Waist circumference and upper arm muscle area (UAMA) also approached statistical significance with p-values of 0.07. In all these, TN tended to be higher than ART.

Fat free mass index as estimated by the Durnin and Womersley (1974) equation (FFMI, DW) was  $18.9 \text{ kg/m}^2 \pm 1.7$  for the TN group and  $16.3 \text{ kg/m}^2 \pm 2.4$  for the ART group. The corresponding values for fat mass index (FMI, DW) were  $9.3 \text{ kg/m}^2 \pm 4.1$  and  $6.0 \text{ kg/m}^2 \pm 4.0$  for the TN and ART groups respectively. Although none of the fat mass or fat free mass indices were significantly different between the two groups, the different equations for both FMI and FFMI resulted in dissimilar differences between the groups. The p-values for FMI and FFMI as estimated by the Pollock *et al.* (1975) equation (Pol) which included one lower body measurement, were 0.17 and 0.12 respectively, while the FFMI estimated by the Durnin and Womersley (1974) equation (DW) using only upper body measurements, approached statistical significance ( $p = 0.06$ ). In summary, the upper body appeared to

show signs of wasting of both muscle and fat in ART despite the fact that means for BMI and %IBW were normal.

**Table 9:** Descriptive statistics of measured and calculated anthropometry variables of the TN and ART groups at baseline.

	Variable	TN		ART	
		Mean $\pm$ SD	n	Mean $\pm$ SD	n
Measured variables	Arm circumference (cm)	32.1 $\pm$ 5.3	6	24.7 $\pm$ 5.3 *	8
	Biceps skinfold (mm)	16.6 $\pm$ 9.6	6	7.1 $\pm$ 5.0 †	8
	Triceps skinfold (mm)	27.3 $\pm$ 14.6	6	13.9 $\pm$ 8.8 †	8
	Thigh skinfold (mm)	38.4 $\pm$ 8.4	5	36.9 $\pm$ 13.9	8
	Thigh circumference (cm)	57.3 $\pm$ 6.9	6	48.1 $\pm$ 9.0	8
	Abdominal skinfold (mm)	22.6 $\pm$ 12.0	6	15.7 $\pm$ 9.9	8
	Waist circumference (cm)	81.3 $\pm$ 11.8	6	72.0 $\pm$ 7.8 †	8
	Hip circumference (cm)	105.6 $\pm$ 13.6	6	94.5 $\pm$ 14.4	8
Calculated variables	Percent of ideal arm circumference (%)	113 $\pm$ 18	6	87 $\pm$ 17 *	8
	Upper arm fat area (mm <sup>2</sup> )	3954 $\pm$ 2396	6	1699 $\pm$ 1317 *	8
	Upper arm muscle area (mm <sup>2</sup> )	4455 $\pm$ 821	6	3332 $\pm$ 938 †	8
	Fat mass index, Pol (kg/m <sup>2</sup> )	8.7 $\pm$ 3.9	5	6.0 $\pm$ 4.2	7
	Fat free mass index, Pol (kg/m <sup>2</sup> )	18.5 $\pm$ 2.4	5	16.4 $\pm$ 2.8	7
	Waist to hip ratio	0.77 $\pm$ 0.07	6	0.77 $\pm$ 0.08	8
	Intra-abdominal indicator to hip ratio	0.71 $\pm$ 0.08	6	0.72 $\pm$ 0.08	8
	Intra-abdominal indicator (cm)	74.2 $\pm$ 9.6	6	67.1 $\pm$ 4.8	8

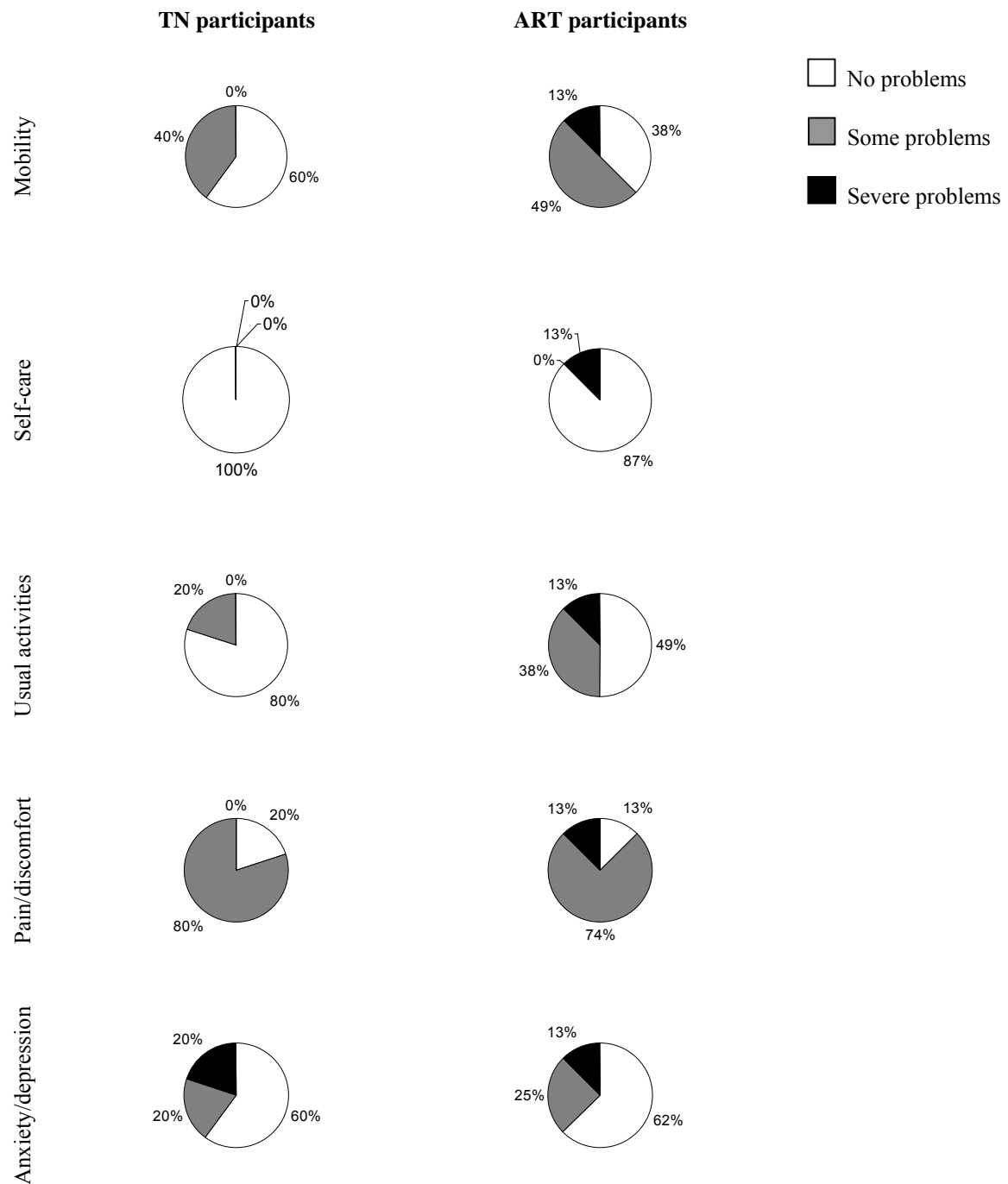
Statistical analysis by Mann-Whitney U-test: \*  $p < 0.05$ ; †  $p < 0.09$

Five QoL dimensions were assessed. Although overall score for QoL was used in this study as an indicator of general status along with clinical data, the individual dimensions are presented to indicate possible effects of wasting on factors such as mobility, self-care, etc.

Figure 5 shows pie charts of the percentages of TN and ART participants who reported no problems, some problems or severe problems for each the five QoL dimensions at baseline. Because of low subject numbers, no statistical analysis was done on the QoL data, however it seems as though the TN participants generally reported having fewer problems than the



ART participants with mobility and usual activities. Only for anxiety/depression did any of the TN subjects report a severe problem.



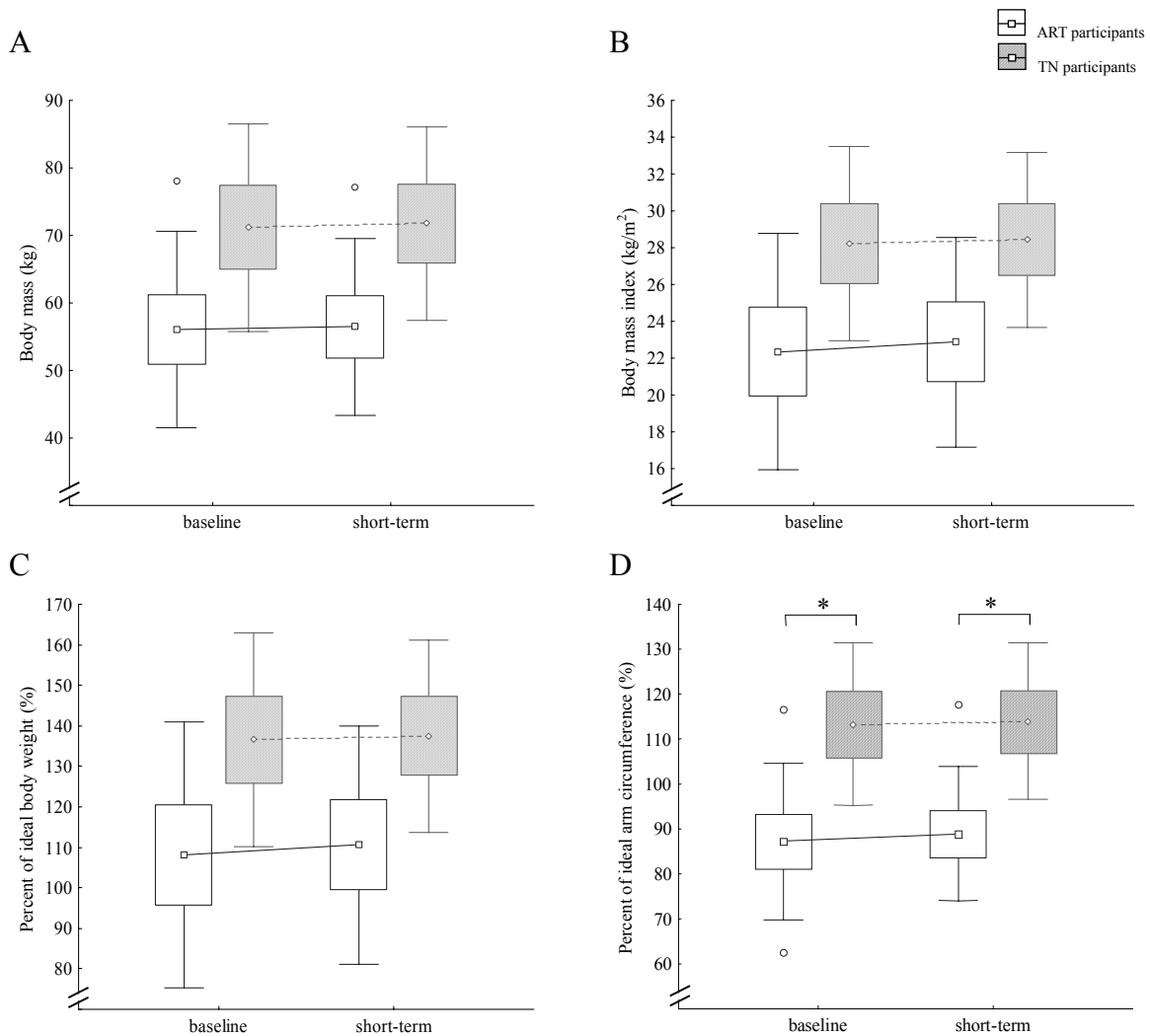
**Figure 5:** Pie charts representing the percentage of TN (n = 5) and ART (n = 8) subjects in each group who fitted into one of three categories for variables describing quality-of-life.

The results of the comparisons that were made between the groups at baseline and short-term will be presented in the next section.

### **5.3 TN and ART group comparisons over time**

The short-term time point was  $7 \pm 3$  weeks since the baseline measurement for the TN and  $5 \pm 3$  weeks since treatment initiation for ART. The variables used to assess immune and disease status ( $CD4^+$  count, CDC category and WC count) were not done by the clinic on a frequent basis. Quality of life assessments were also not done as frequently as the monitoring of body composition. Individual QoL data for the TN group were available, but for the ART subjects only 2 repeated their QoL questionnaire at the short-term time-point. This was because their clinical assessments took much longer and the QoL interview required an interpreter, who was not available at follow-up. However, since disease progression and treatment did not change for the TN subjects from baseline to short-term follow-up, I present these data as an indication of stability of the scores. The TN group's overall QoL score was  $77\% \pm 26$  vs.  $76\% \pm 19$  at baseline and short-term time points respectively. The Spearman rank order correlation coefficient for these 5 subjects was  $r = 0.92$ .

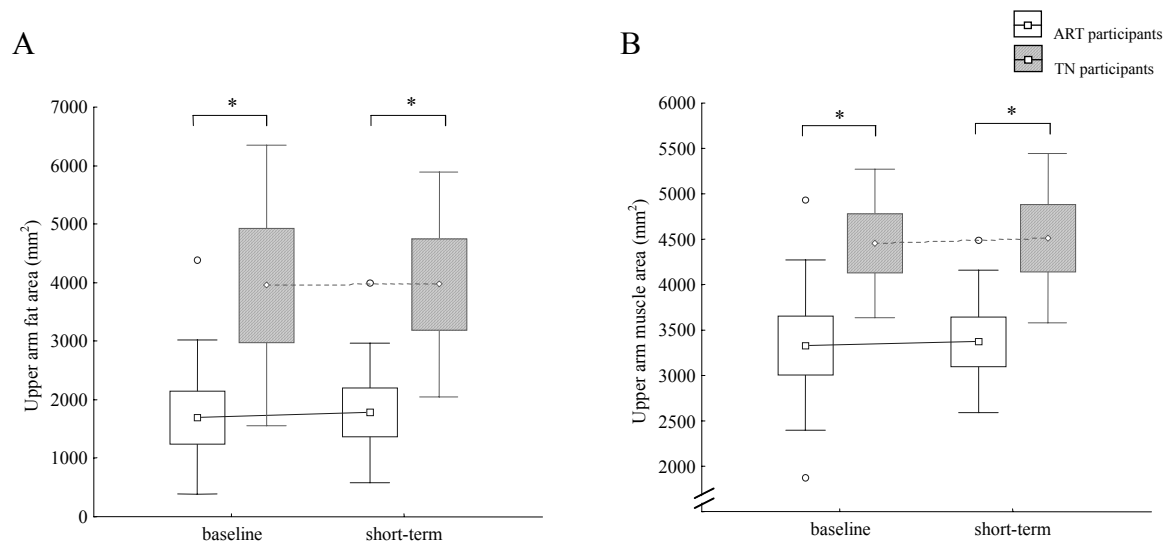
Figure 6 displays the body mass, BMI and %IBW for both groups at baseline and short-term time points and indicates no group differences and no significant changes over time. Although, there was a tendency for a group difference in body mass (Panel A;  $p = 0.07$ ), this tendency became clearly insignificant when corrections for height were made. The p-values for the difference in body mass index (BMI) and percent of ideal body mass (%IBW) were equal to 0.09 (Panel B) and 0.11 (Panel C) respectively. Nutritional or wasting status is also frequently assessed by determining the upper arm circumference and determining whether or not this deviates from published normal values (% ideal upper arm circumference, see Panel D).



**Figure 6:** Body mass, body mass index, percent of ideal body mass and percent of ideal arm circumference for ART and TN groups at baseline and short term time points. \* indicates statistical significance  $p < 0.05$ . The box plots represent mean  $\pm$  SE, while the whiskers indicate  $\pm$  SD. Outliers are represented by an open circle ( $\circ$ ).

In both groups it was possible to do regular anthropometry measurements so that for most variables the data set is complete for both baseline and short-term follow-up. The ART and TN groups were compared to determine if certain anthropometry variables were consistently different between the groups (main effect of group), changed similarly over time in both groups (main effect of time), or changed differently within the first three months of being on antiretroviral treatment compared to subjects who experienced little or no change in clinical status over a similar short time period (interaction between group and time).

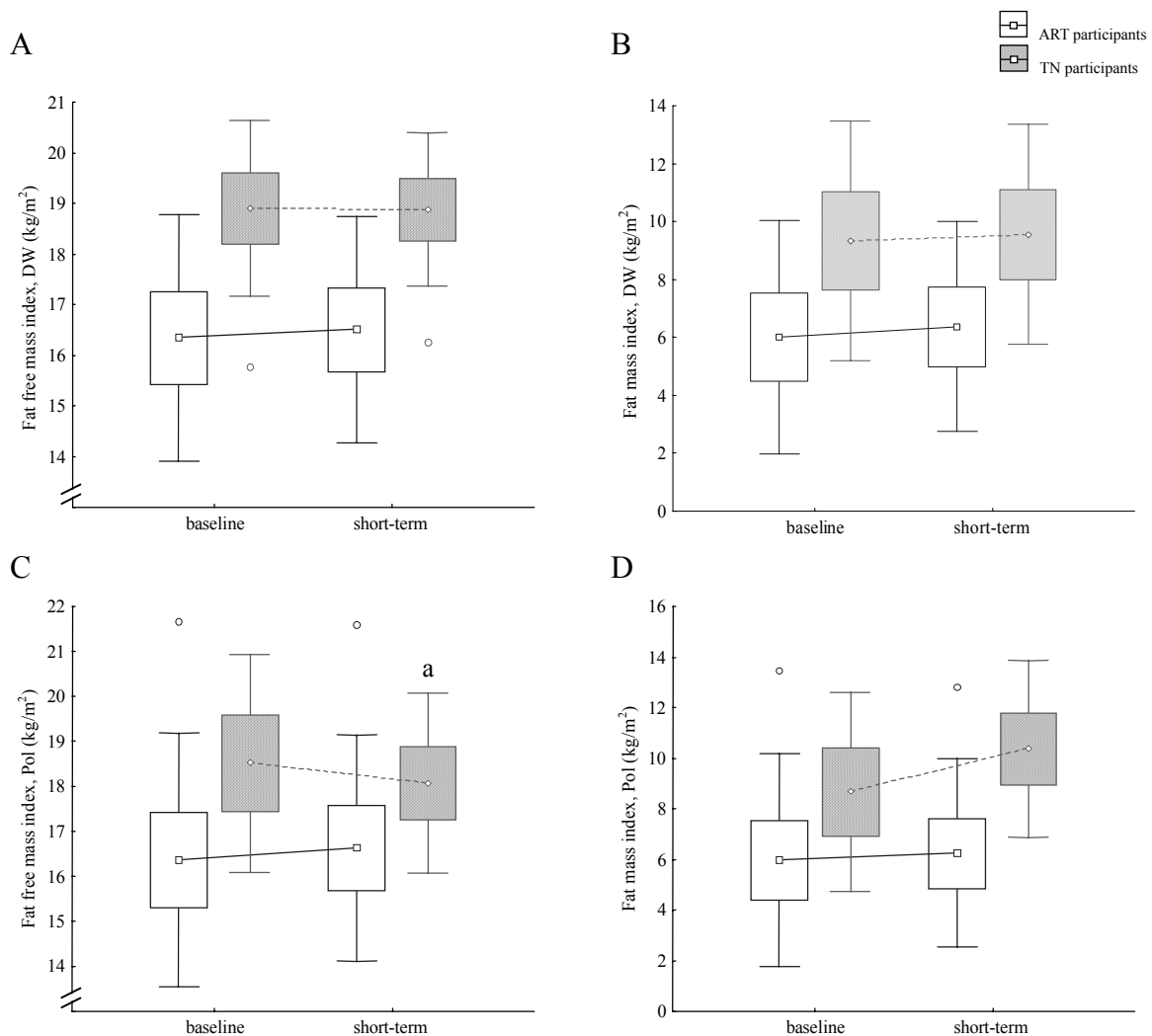
In contrast to the results of the Mann-Whitney U test (which found that only the %IAC and UAFA were different between the groups at baseline, see section 5.2), findings from the main effects ANOVA revealed more differences between the groups. As with the previous analysis the TN group had significantly higher %IAC (Figure 6, Panel D) and UAFA (Figure 7, Panel A) but there were also a main effects of group for UAMA (Figure 7, Panel B) and biceps and triceps skinfolds. All of these variables had a tendency to be different between groups with the previous analysis. For all these anthropometry variables TN had higher values than the ART group (Biceps: TN: baseline:  $16.6 \pm 9.6$  and short-term  $15.1 \pm 8.7$  vs. ART: baseline:  $7.1 \pm 5.0$  and short-term  $7.1 \pm 4.6$  mm; Triceps: TN: baseline:  $27.3 \pm 14.6$  and short-term  $27.4 \pm 10.6$  vs. ART: baseline:  $13.9 \pm 8.8$  and short-term  $14.7 \pm 8.0$  mm).



**Figure 7:** Upper arm muscle and fat areas at baseline and short term time points for ART and TN groups. \* indicate statistical significance  $p < 0.05$ . The box plots represent mean  $\pm$  SE, while the whiskers indicate  $\pm$  SD. Outliers are represented by an open circle (°).

Several whole body variables were calculated in order to estimate overall changes in body compartments, specifically fat free mass and fat mass. Since these variables are influenced by height, they are presented here as indexes relative to height squared as was previously done by Maia *et al.* (2005). No significant differences between the two groups were evident, although there was a tendency for FFMI to be lower in ART than TN (DW only,

Panel A,  $p = 0.05$ ). A comparison between Figure 7 and 8 reveals that UAMA and UAFA followed a pattern of change more similar to FFMI and FMI as estimated by the equations of Durnin and Womersley (DW) than when the equations of Pollock *et al.* (Pol) are used.

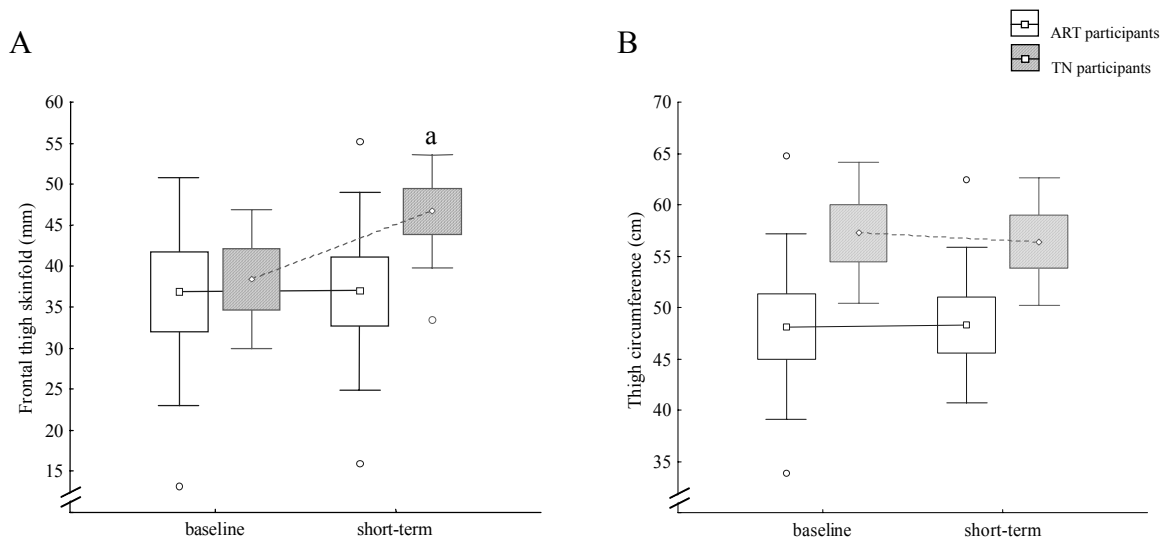


**Figure 8:** Fat mass index and fat free mass index as calculated by the equations of Pollock *et al.* (Pol) as well as by the equations of Durnin and Womersley (DW) for ART and TN groups at baseline and short term time points. The symbol, a, indicates a significant interaction effect ( $p < 0.05$ ). The box plots represent mean  $\pm$  SE, while the whiskers indicate  $\pm$  SD. Outliers are represented by an open circle (°).

However, the results generated from equations of Durnin and Womersley (DW) did not seem to show any changes over time for any of the groups, while those from the equations of Pollock *et al.* (Pol) indicate a significant group by time interaction for FFMI (see Figure

8, Panel C) and a trend for an increase in FMI for the TN group. The Pol equation uses thigh skinfold when calculating the fat mass, whereas the DW equation does not.

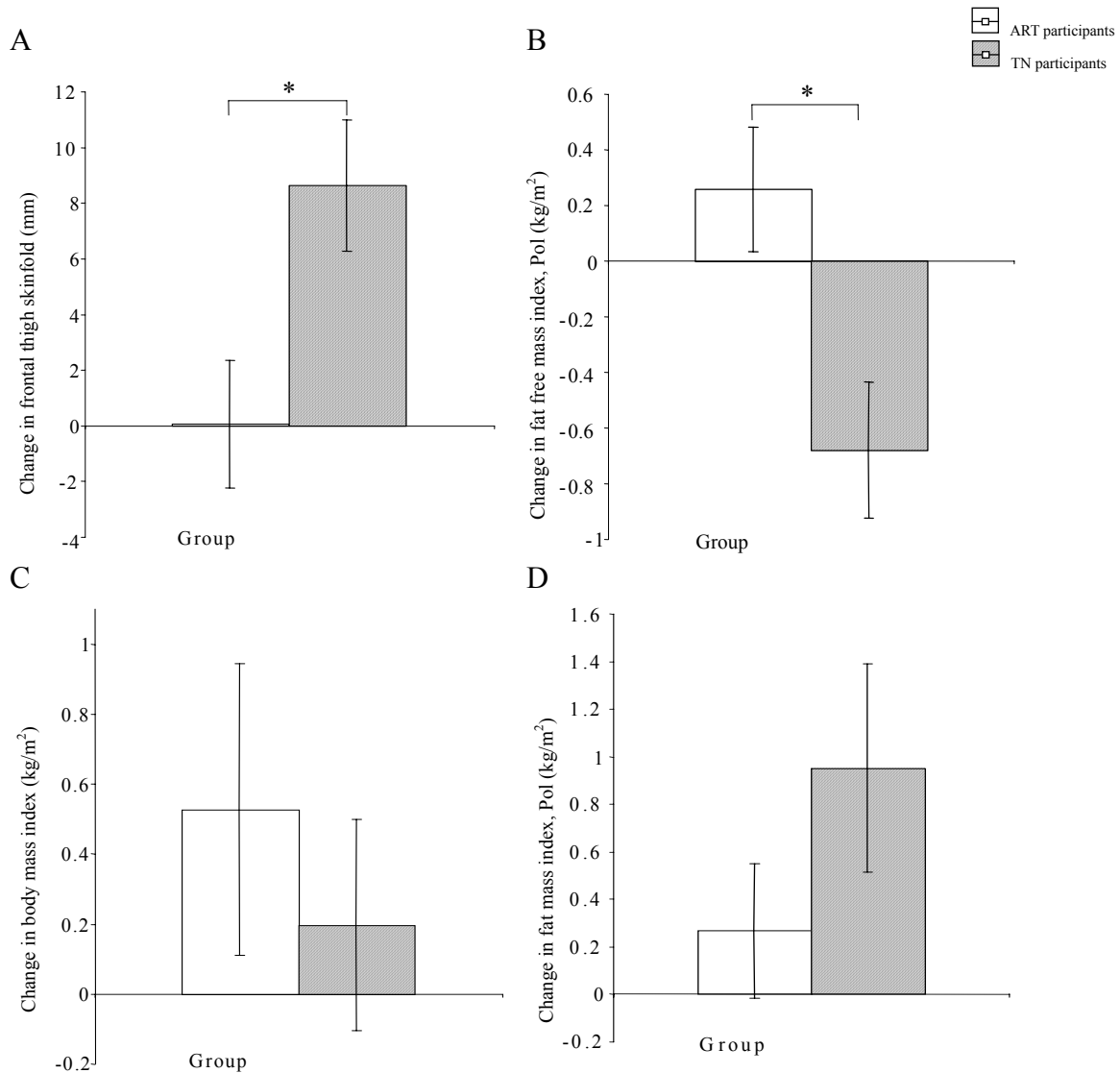
The data in Figure 9 indicate a significant interaction effect of group and time for the thigh skinfold (Panel A, main effect  $p < 0.05$ , *post hoc* difference at short-term  $p = 0.053$ ), but not for thigh circumference (Panel B). Thigh circumference tended to be different between the two groups, but this difference was not statistically significant (main effect  $p = 0.06$ ). However, the tendency for thigh circumference to decrease but thigh skinfold thickness to increase in TN could imply a decrease in thigh muscle mass. Indeed, this result is similar to the interaction effect between group and time for fat free mass corrected for height (FFMI, Pol) ( $p < 0.05$ ), displayed in Figure 8 Panel C.



**Figure 9:** Thigh skinfolds and circumferences at baseline and short term time points for ART and TN groups. The symbol, a, indicates a significant interaction effect ( $p < 0.05$ ). The box plots represent mean  $\pm$  SE, while the whiskers indicate  $\pm$  SD. Outliers are represented by an open circle ( $\circ$ ).

Another way of presenting these data, which removes the influence of individual differences in baseline body dimensions, is to calculate the change over time for each subject and then compare the two groups. The change in thigh skinfold was again significantly different between the two groups (Figure 10 Panel A). There was also a concomitant difference in fat free mass index (Pol) change. These significant changes were

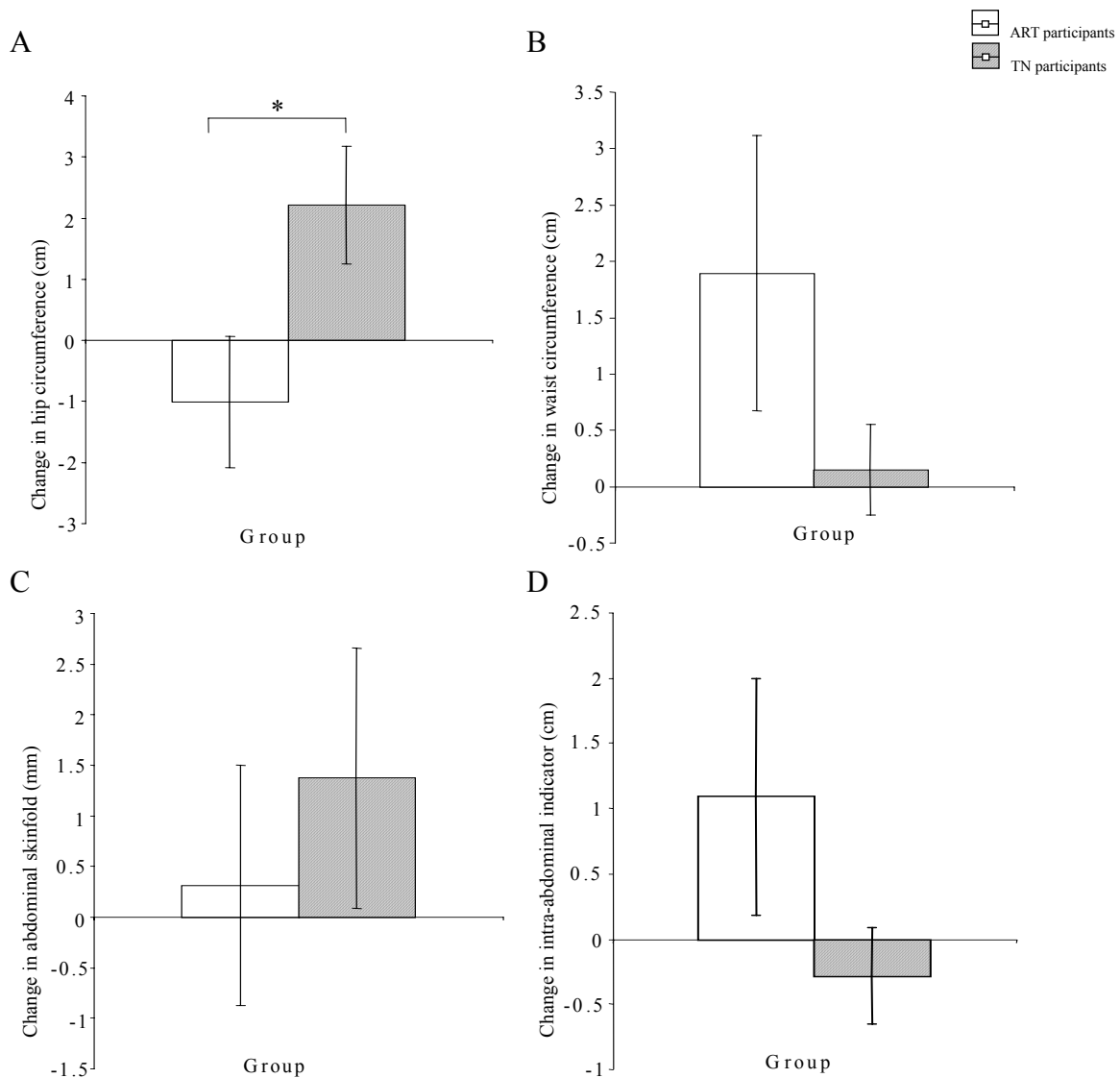
not reflected in BMI changes (Panel C), possibly because the change in FMI (Panel D) counteracted the change in FFMI.



**Figure 10:** Changes of variables from baseline to short-term that indicate body fat and muscle mass content for ART and TN groups. Vertical lines represent the SE and the symbol, \*, indicate statistical significance,  $p < 0.05$  (Mann-Whitney U test).

In summary, the ART group did not improve significantly for any variables that relate to nutritional status or wasting (body mass related variables, %IAC, UAFA, UAMA FMI and FFMI) over the short-term phase, even though this group had significantly lower values than the TN group for some of these variables at baseline. More dramatic changes were found for variables that may relate to lipodystrophy.

Initial ANOVA analysis showed that the interaction effect of group and time for the hip circumference approached statistical significance ( $p = 0.05$ ), but this difference was not verified with *post hoc* analysis. However, the Mann-Whitney U test revealed that the change in hip circumference was significantly different between the two groups during the short-term phase ( $p < 0.05$ ). Figure 11 illustrates comparisons between the groups for change in hip and waist circumference, abdominal skinfold and the calculated variable IAI.



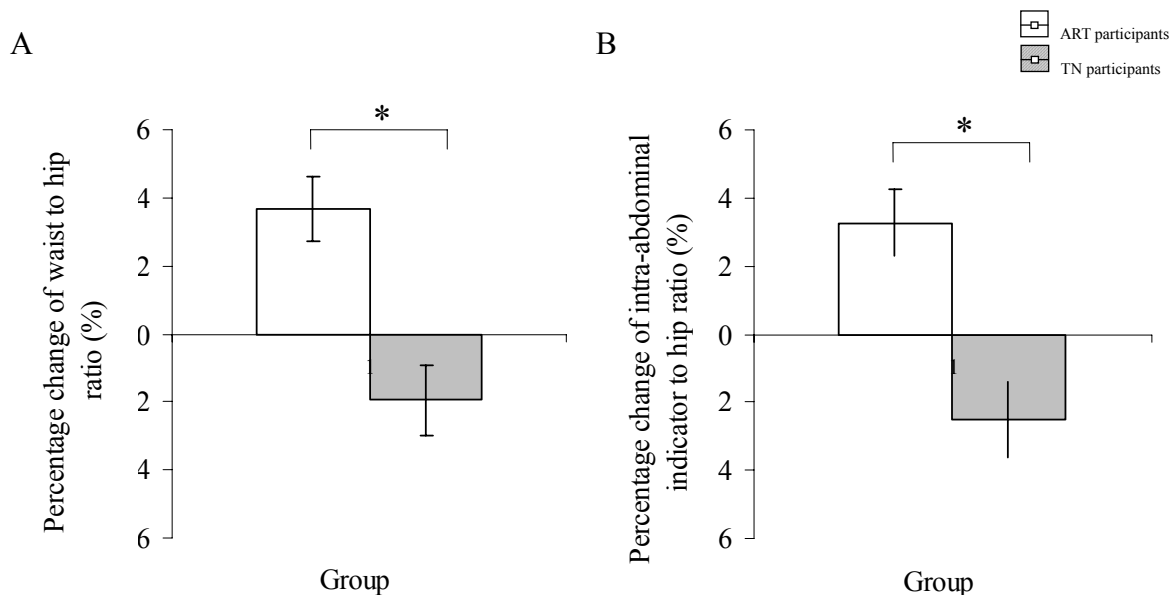
**Figure 11:** Changes of variables from baseline to short-term that relate to altered body fat deposition for ART and TN groups. Vertical lines represent the SE and the symbol, \*, indicate statistical significance,  $p < 0.05$  (Mann-Whitney U test).



Although the means for the two groups was significantly different for change in hip circumference (see Figure 11, Panel A), there was no difference between the two groups for change in waist circumference ( $p = 0.66$ ), or the change in abdominal skinfold. The ART group also appeared to exhibit a change in mean IAI (Panel D), but this was not significant ( $p = 0.45$ ). An increased waist circumference can be the result of an increase in IAI or abdominal skinfold or both.

However, the net effect of the variables presented in Figure 11 contributed to differences in the waist to hip ratio and the IAI to hip ratio. As shown in Figure 12 Panels A and B, the change in W:H and IAI:H were significantly different between the two groups ( $p < 0.01$ ; Mann-Whitney U test).

These differences were confirmed when a strong interaction effect of group and time was found for W:H ( $p < 0.005$ ) and IAI:H ( $p < 0.005$ ) with the ANOVA analysis. *Post hoc* analysis confirmed that W:H and IAI:H increased significantly ( $p < 0.05$ ) during the short-term phase in the ART group compared to the TN group.

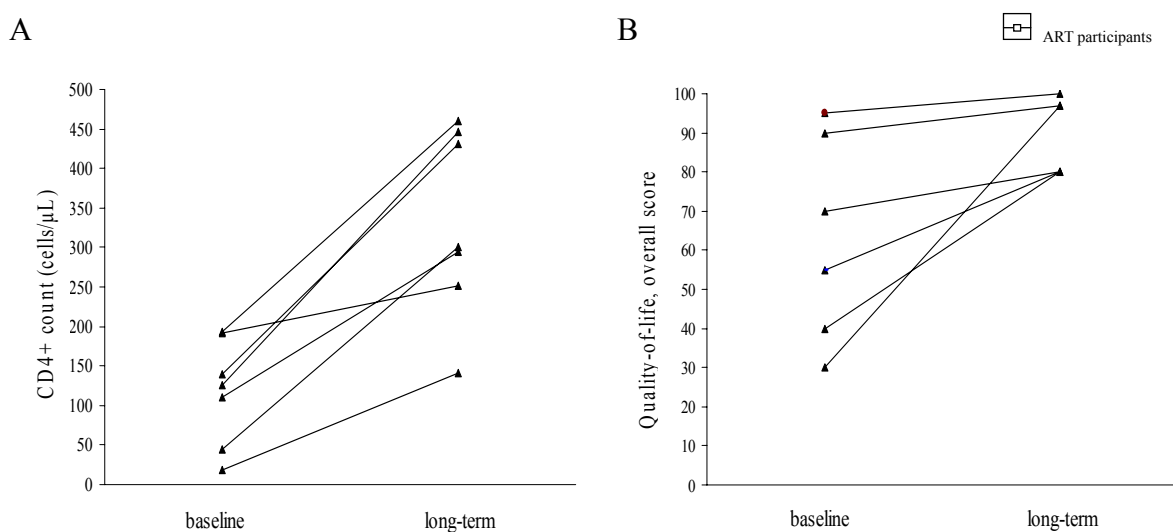


**Figure 12:** Changes of variables from baseline to short-term that relate to altered body fat deposition for ART and TN groups. Vertical lines represent the SE and the symbol, \*, indicate statistical significance,  $p < 0.01$  (Mann-Whitney U test).

The next section is devoted to the ART group only. The results from comparisons relating to short-term and long-term time points are presented.

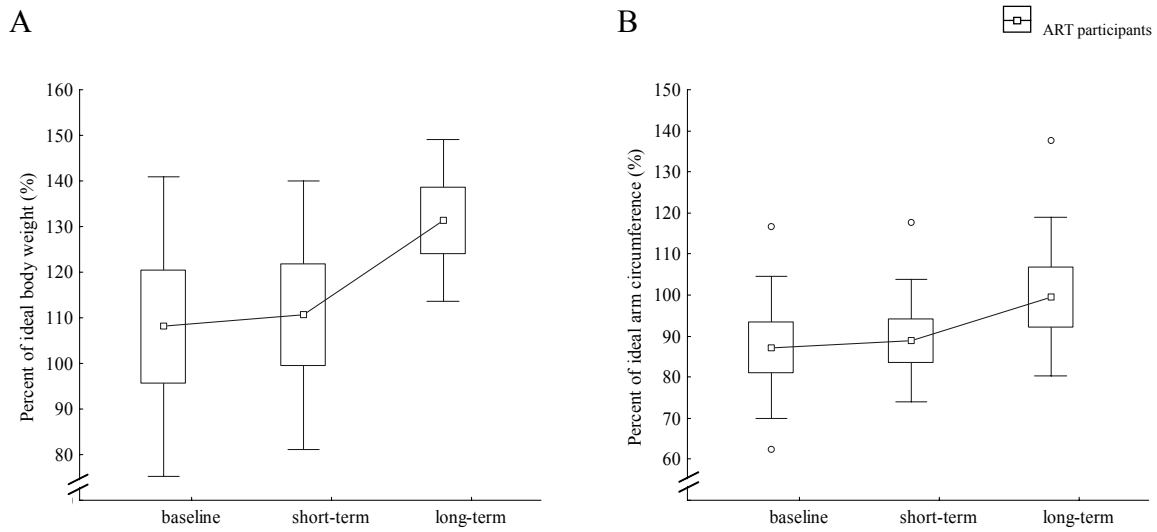
#### 5.4 ART group: short and long-term changes

Follow-up information for CD4<sup>+</sup> count and QoL was available for baseline the long-term time-point for the ART group. CD4<sup>+</sup> count and QoL improved significantly for the ART group ( $p < 0.05$ ) (Figure 13).



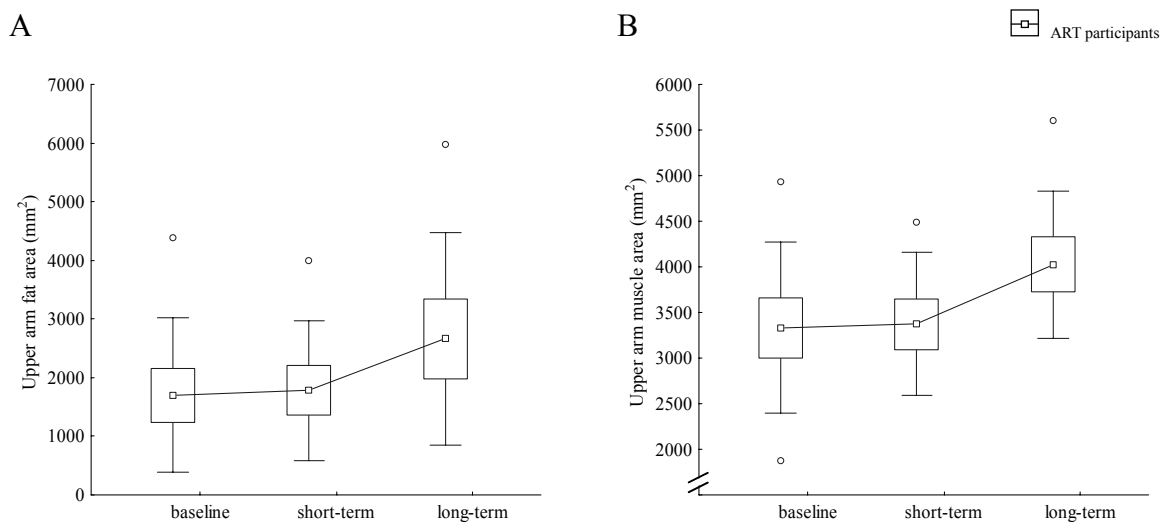
**Figure 13:** Individual CD4<sup>+</sup> counts and QoL scores for the ART group at baseline and long-term time points.

Although most variables showed an upward trend for the ART group (especially during the long-term phase, e.g. Figures 14 and 15), these trends were generally not significantly different at the short-term or long-term time points compared to the baseline time-point. When considering the variables that indicate nutritional status such as %IBW and %IAC, both follow an upward trend ( $p = 0.18$  and  $p = 0.29$  respectively) – especially after the short-term point. It can also be seen from Figure 14 that the inter-individual variation seemed to have decreased for percent of ideal body weight, but not for the variable that involved measurements of the arm (percent of ideal arm circumference).



**Figure 14:** Box plot representation of variables that indicate nutritional status the ART group at baseline, short term and long-term time points. The box plots represent mean  $\pm$  SE, while the whiskers indicate  $\pm$  SD. Outliers are represented by an open circle (°).

Arm fat (UAFA) and muscle (UAMA) area also tended to increase over time (especially after the short-term time-point) for the ART participants, although none of these increases proved to be statistically significant (ANOVA:  $p = 0.38$  and  $p = 0.21$ , respectively) (Figure 15).



**Figure 15:** Upper arm fat (UAFA) and muscle (UAMA) areas for the ART group at baseline, short term and long-term time points. The box plots represent mean  $\pm$  SE, while the whiskers indicate  $\pm$  SD. Outliers are represented by an open circle (°).

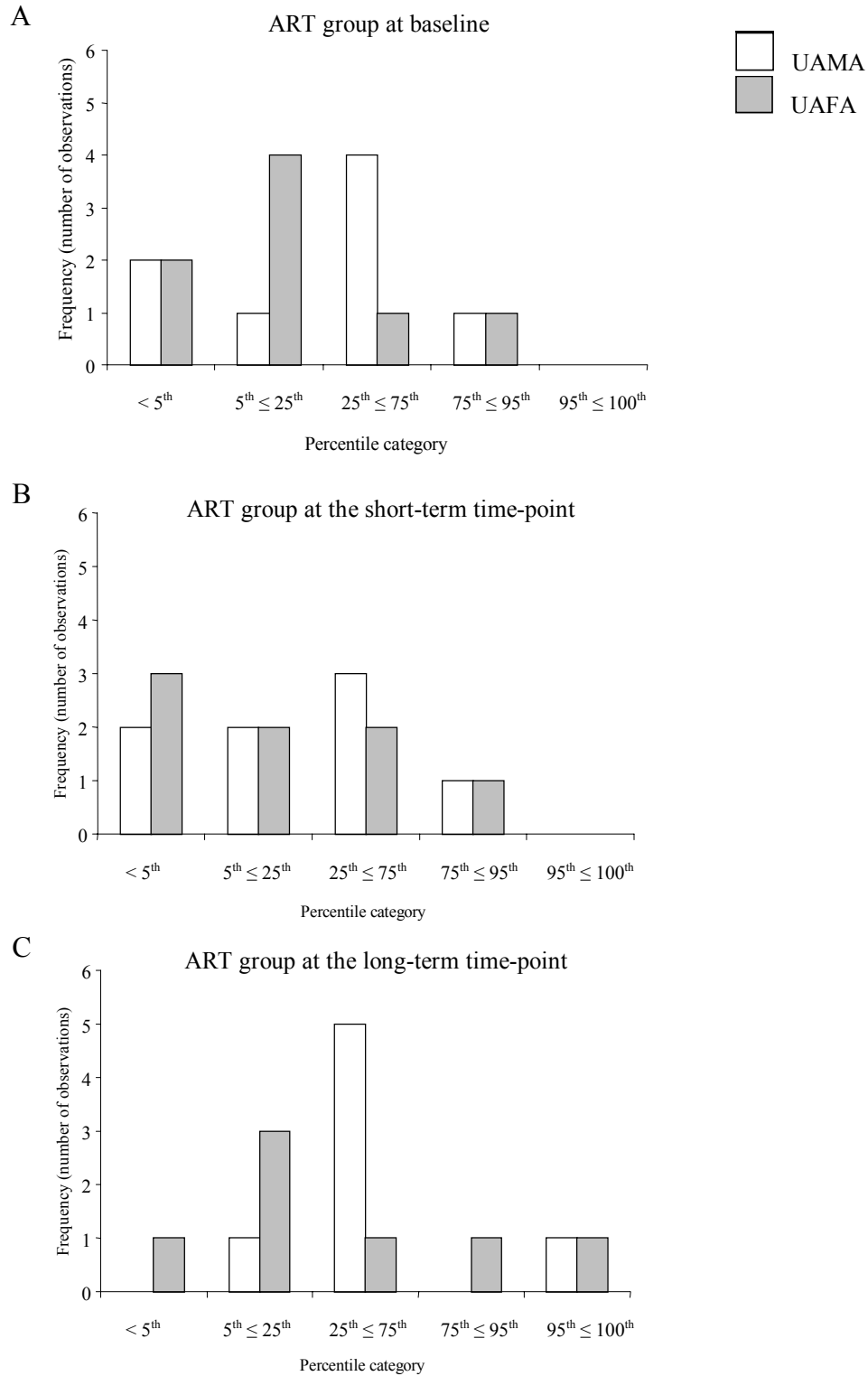
It is clear from the data in Figure 15 that outliers are present at each time point and the SD's are large. The outliers at baseline and short-term for UAFA are from participant ART1, while the outlier value at the long-term time-point represents participant ART4. There was also a dramatic shift for ART4 regarding UAMA values. ART4's UAMA value was the lower limit outlier at the short-term time-point and the higher limit outlier at the long-term time-point. The two higher limit outliers at baseline and short-term for UAMA represent data of participant ART2.

One method to descriptively display the data is to show the number of observations that fall into categories that relate to population percentile values. The calculated UAMA and UAFA of the participants were categorized according to percentile categories of Frisancho (1981) (see Figure 16).

At baseline most (50%) subjects' UAMA fitted into the main category (25<sup>th</sup> – 75<sup>th</sup> percentile). There were fewer UAMA and UAFA observations in the two lowest categories ("5<sup>th</sup> ≤ and < 25<sup>th</sup>" and the "less than 5<sup>th</sup>" category) at the long-term time-point compared to the baseline and short-term time points, suggesting an eventual improved nutritional status over time after initiation of ART in this small group of subjects.

Three participants had UAMA values that were classified below the 25<sup>th</sup> percentile at baseline. Two of these were below the 5<sup>th</sup> percentile. At the short-term time-point, one participant's nutritional status worsened and there were 4 observations below the 25<sup>th</sup> percentile. Yet, at the long-term time-point, only one participant's UAMA value was still classified below the 25<sup>th</sup> percentile, indicating improved arm muscle content for at least two participants.

Although less dramatic, there was also a shift to the right for the UAFA values over the long-term phase. One participant's UAFA value worsened during the short-term phase resulting in three observations below the 5<sup>th</sup> percentile at the short-term time-point. Only one observation remained in this category at the long-term time-point.



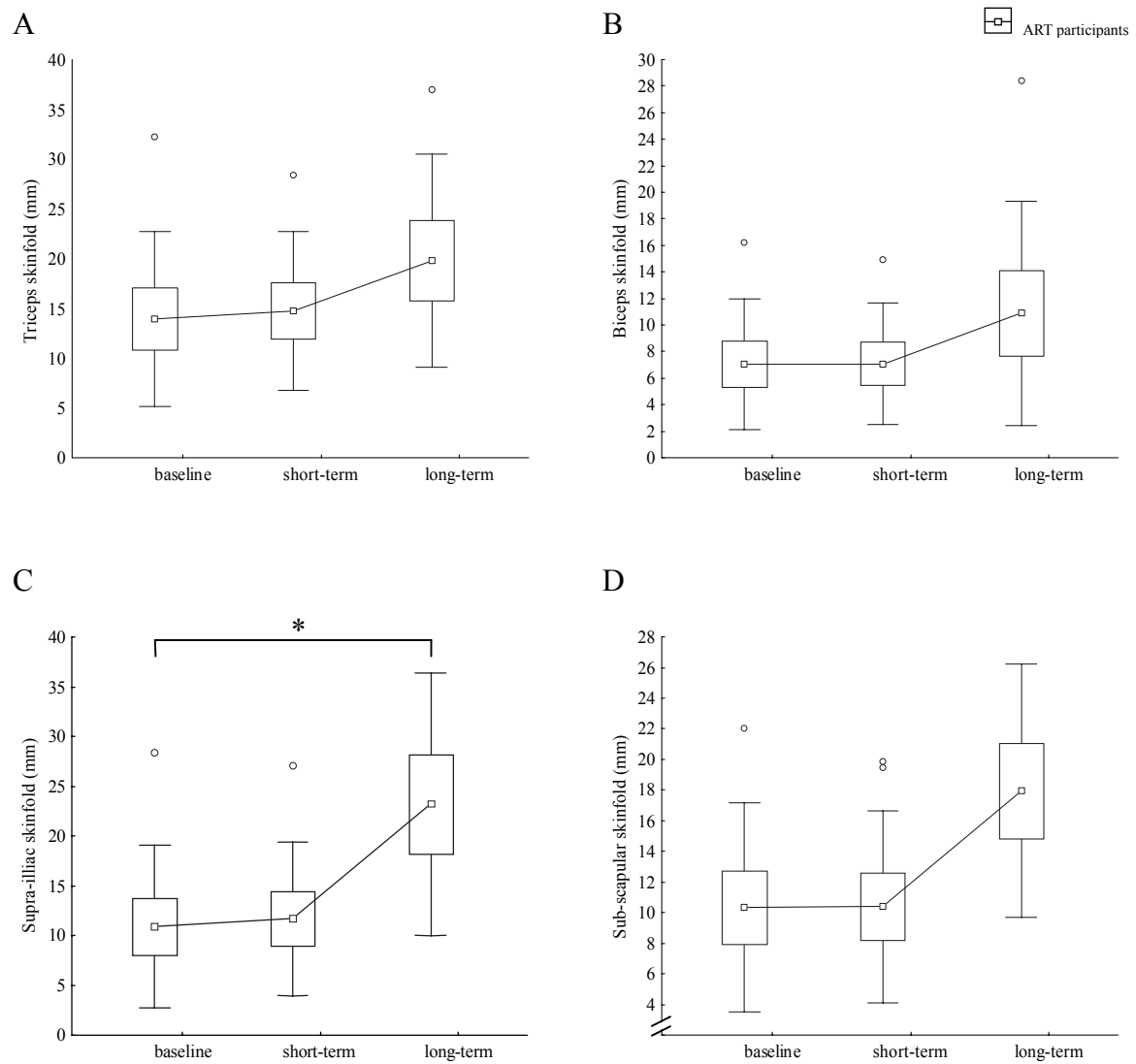
**Figure 16:** Histograms of upper arm muscle (UAMA) and fat (UAFA) areas according to population percentile categories for the ART group at baseline ( $n = 8$ ), short-term ( $n = 8$ ) and long-term ( $n = 7$ ) time points.

At the long-term time-point, there were more UAFA observations below the 25<sup>th</sup> and 5<sup>th</sup> percentile categories than for UAMA. While only one participant had a UAMA value less than the 25<sup>th</sup> percentile value (and no participant's UAMA was below the 5<sup>th</sup> percentile) at the long-term time-point, there were 4 UAFA observations lower than the 25<sup>th</sup> percentile and 1 of these was lower than the 5<sup>th</sup> percentile.

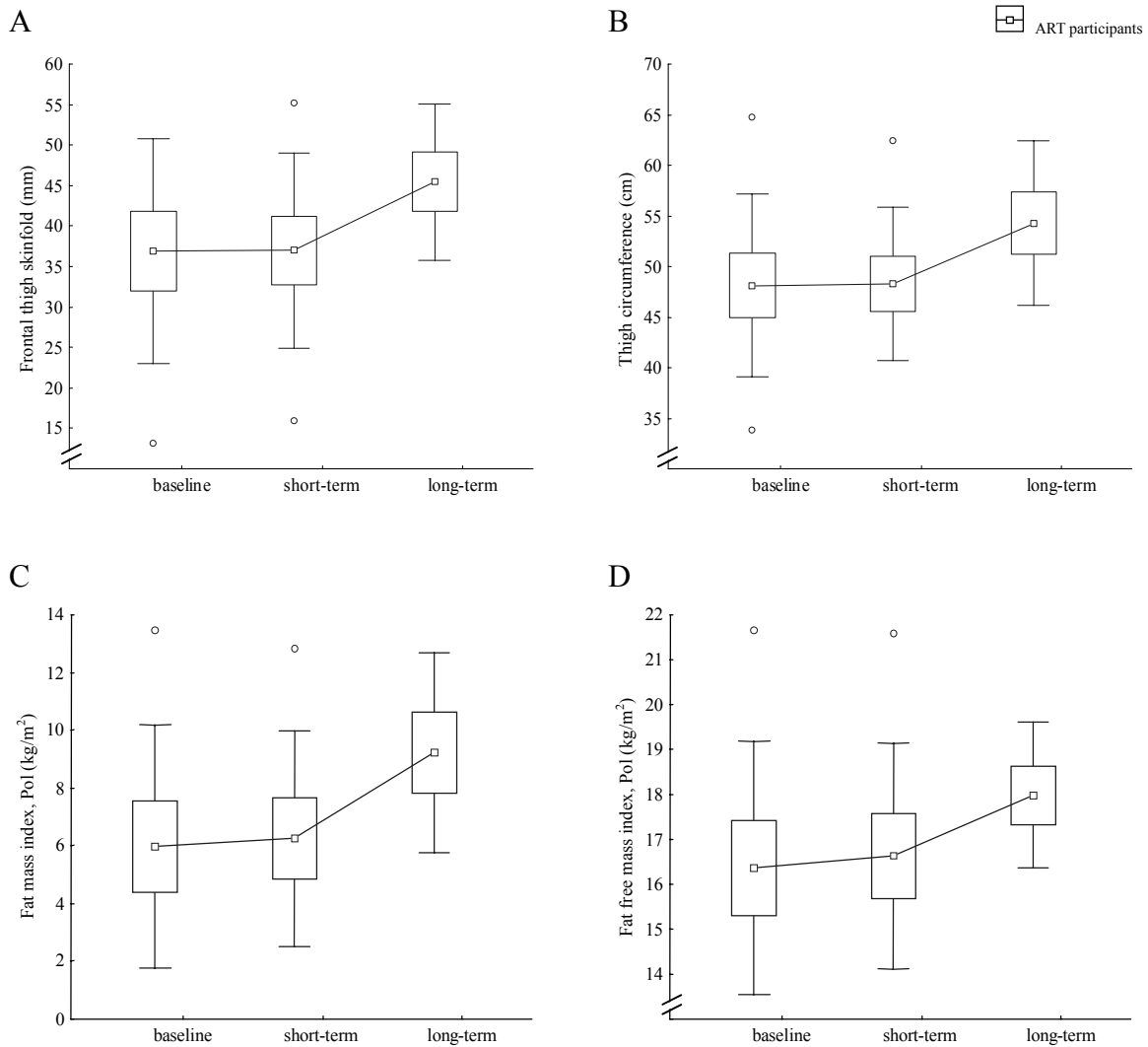
In summary, the ART group's UAMA values were generally higher than their UAFA values when compared to population percentiles. At least one participant showed a worsening of arm area measures at the short-term time-point while a general improvement was apparent for the whole group at the long-term time-point. Whether such a trend would occur in a larger cohort remains to be determined.

Despite the fact that upper arm fat mass appeared to be affected negatively by HIV status relative to population norms, Figure 17 suggests that there was a general increase in the triceps and biceps skinfold thickness from baseline and short-term to the long-term time-point. Similar trends were seen for other skinfold thicknesses, although only the supra-iliac skinfold at long-term was statistically significantly different ( $p < 0.05$ ) from the baseline value. The ART group's sub-scapular skinfold tended to change from baseline to long-term ( $p = 0.07$ ) and from short-term to long-term time-points ( $p = 0.08$ ) after performing a Bonferroni correction.

Figure 18 shows that the same upward trend is apparent for thigh skinfold and thigh circumference (although none of these variables changed significantly). Although both FMI (Pol) and FFMI (Pol) also followed an upward trend, these variables did not change significantly during the study. FMI and FFMI as calculated from the equations of Durnin and Womersley (1974) followed a similar trend to that of FMI (Pol) and FFMI (Pol) (data not shown).



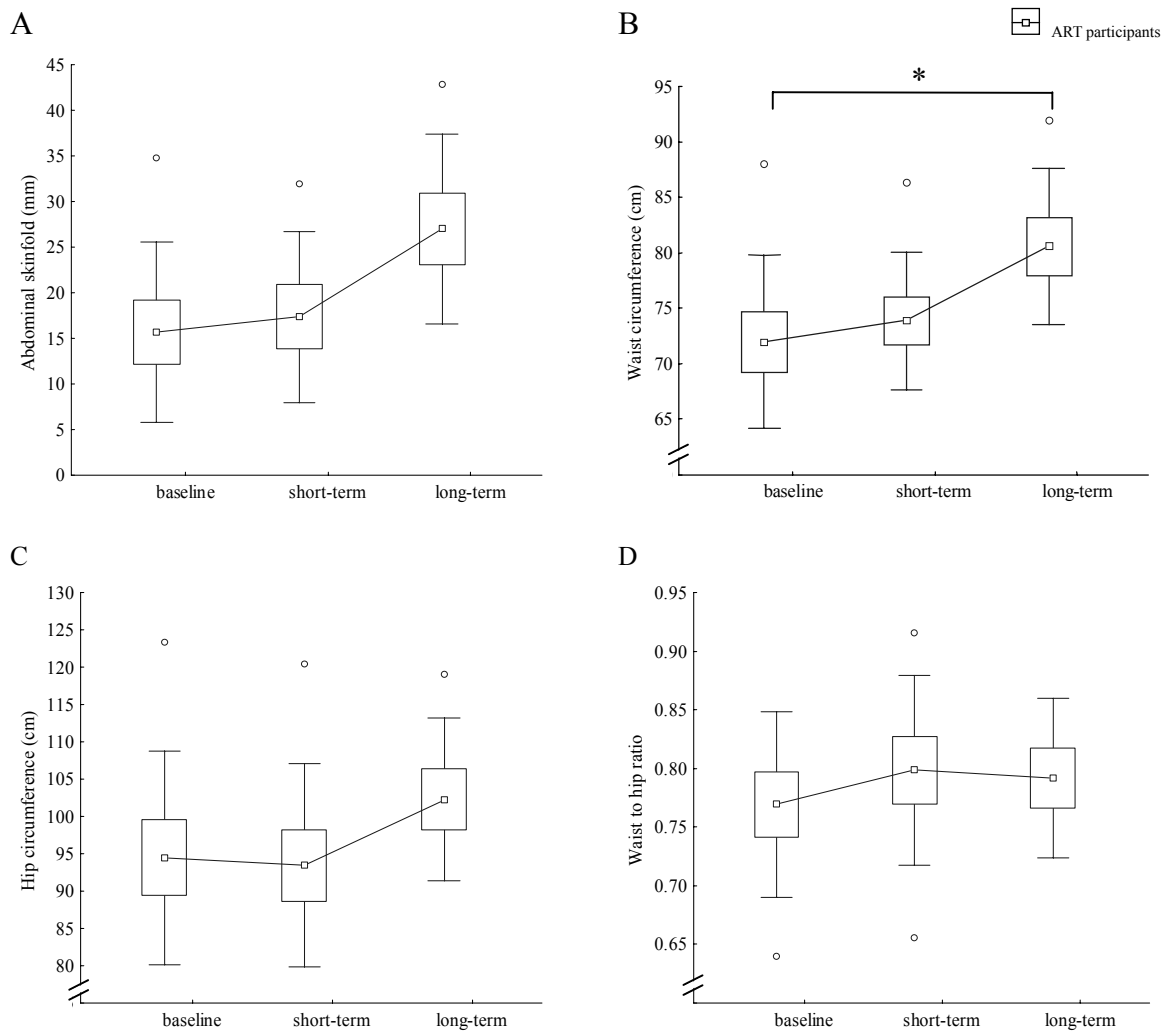
**Figure 17:** Skinfolds that are used to indicate changes in muscle and fat mass for the ART group at baseline, short term and long-term time points. \* indicates statistical significance,  $p < 0.05$ . The box plots represent mean  $\pm$  SE, while the whiskers indicate  $\pm$  SD. Outliers are represented by an open circle (  $\circ$  ).



**Figure 18:** Changes in muscle and fat mass for the ART group at baseline, short term and long-term time points. The box plots represent mean  $\pm$  SE, while the whiskers indicate  $\pm$  SD. Outliers are represented by an open circle (  $\circ$  ).

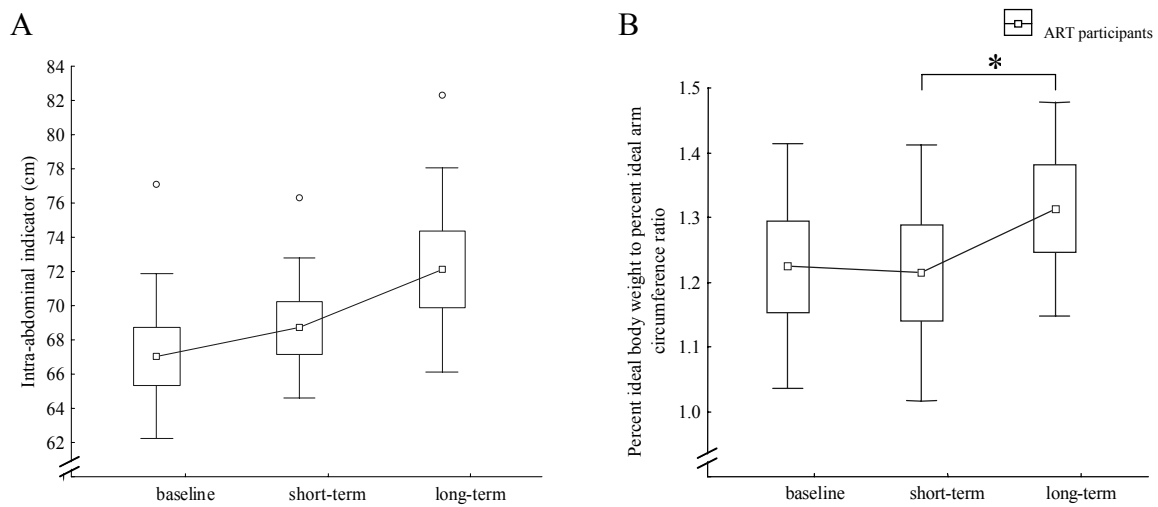
Figure 19 and 20 provide information about variables that are related to waist circumference, since changes in the latter may be a result of an altered fat deposition or an increase in intra-abdominal fat, or both. Although the waist circumference of the ART group did increase significantly from the baseline to the long-term time-point ( $p < 0.05$ ), hip circumference also appeared to be raised at the long-term time-point. Therefore, waist-to-hip ratio of the ART group appeared to deviate from the pattern of gradual increase that is evident for the other variables shown in Figures 14, 15 and 17.





**Figure 19:** Box plot representation of variables related to altered fat deposition for the ART group at baseline, short term and long-term time points. \* indicates statistical significance,  $p < 0.05$ . The box plots represent mean  $\pm$  SE, while the whiskers indicate  $\pm$  SD. Outliers are represented by an open circle (°).

In summary, several variables indicate increased fat mass; however, it is important to determine if increases in fat mass are evenly distributed or not. The intra-abdominal indicator measure showed a gradual non-significant trend toward an increase for the ART group ( $p = 0.12$ ) (Figure 20).



**Figure 20:** Box plot representation of additional measures that may indicate altered fat deposition for the ART group at baseline, short term and long-term time points. \* indicates statistical significance,  $p < 0.05$ . The box plots represent mean  $\pm$  SE, while the whiskers indicate  $\pm$  SD. Outliers are represented by an open circle (°).

However, taking into account the percentage of ideal body mass (%IBW) and percentage of ideal arm circumference (%IAC), %IBW/%IAC increased significantly from the short-term time-point to the long-term time-point. This indicates that the %IBW increased more than the %IAC over this time-period.

## Discussion

Undertaking longitudinal research in a semi-rural setting in a South African clinic presents numerous obstacles, some of which were known prior to the study e.g. requirement for cost-effectivity. The TN group was a poor control group since they were not a homogenous group with respect to disease stage and they were poorly matched to the ART group with regard to body mass and CD4<sup>+</sup> count. More suitable control groups should be used for future studies, including ethnically and socially relevant HIV-negative control groups.

The following points summarize the main findings.

- 1) Statistical analysis indicated that TN and ART participants did not differ significantly for many variables at baseline.
  - a. This was influenced by the large inter-individual variation in both groups as well as small group sizes.
  - b. The major differences between ART and TN were observed in measurements of the arm, especially %IAC and UAFA, which were significantly lower in ART at baseline because on average their disease progression was more advanced. Related to this is the fact that 6 of the 8 ART participants were categorized as having UAFA less than the 25<sup>th</sup> percentile.
- 2) CD4<sup>+</sup> count and QoL improved significantly for the ART participants from baseline to long-term. Associations with changes in muscle mass and fat mass variables were difficult to confirm due to low subject numbers.
- 3) A significant interaction effect between group and time was found for thigh skinfold and FFMI (Pol), but no significant improvements or declines were found for any variables related to wasting status for either group in the short term.
- 4) Participants on antiretroviral medication exhibited changes in abdominal anthropometric measurements or calculated variables:
  - a. ART vs. TN group comparisons at baseline and short-term:
    - i. The W:H and IAI:H of ART participants increased significantly compared to the TN group.
  - b. ART group comparisons at baseline, short-term and long-term:

- i. Supra-illiac skinfold increased significantly from baseline to long-term.
- ii. Two measures that may be related to lipodystrophy increased over time (waist circumference and %IBW:%IAC).

Disease progression and wasting will be discussed in the first section, while the second section will be devoted to lipodystrophy issues.

## 5.5 Disease progression and wasting

The most commonly used indicator of disease progression in an individual with HIV infection is the CD4<sup>+</sup> count (Weatherall *et al.*, 1996). Other indicators are viral load and CD4 to CD8 ratio (Ray *et al.*, 2006; Rodriguez *et al.*, 2006). A CD4<sup>+</sup> count below 350 cells/ $\mu$ L is considered to be one of the criteria that signify the need for treatment initiation in the USA (Baylor College of Medicine, 2003), although the value in South Africa is a count below 200 cells/ $\mu$ L. Although the CD4<sup>+</sup> counts of the two groups were not significantly different at baseline regarding ( $p = 0.09$ ), a large inter-individual variation was apparent for the TN group. Two of these participants could have qualified for treatment at the time of recruitment, but treatment was not yet available before 2004. Therefore, the participants that were recruited before 2004 were classified into the TN group, although that classification does not imply that they did not yet qualify for treatment. A difference did emerge however when the CD4<sup>+</sup> counts were categorised according to the CDC immune category. Therefore, the ART group was in fact as a whole at a more advanced stage of the disease than the TN group. The fact that the two groups differed with regard to measures of the arm, suggests that arm measures may be indicative of disease progression (discussed in more detail later in this section).

For four (29%) of the participants (including both the ART and the TN participants), the CD4<sup>+</sup> counts were determined more than 3 months before or after the anthropometry measurements were done. Therefore the TN and ART groups' CD4<sup>+</sup> counts at baseline may not be an accurate reflection of their clinical status at that time. For example, The CD4<sup>+</sup> counts of two ART participants were determined more than seven months prior to the

baseline anthropometry measurements. Their CD4<sup>+</sup> counts were 393 and 160 respectively. Considering the fact that they were included into the treatment programme, it is conceivable to surmise that their CD4<sup>+</sup> counts may have been lower at the baseline time-point, but lower values were not recorded in the patient files.

An American source of treatment guidelines recommended that (due to variability of CD4<sup>+</sup> counts) two to three baseline CD4<sup>+</sup> counts should be determined before initiating antiretroviral treatment (Department of Health and Human Services, 2005). It was also stated that CD4<sup>+</sup> counts should be taken every three to six months to monitor patients. As can be inferred from the previous paragraph – such practices are not always possible in developing countries at the level of rural clinics. Therefore, undertaking observational research in such a rural environment is often accompanied with certain restrictions and considerations relating to cost-effectiveness that are unique to the setting. In addition, the effectiveness of time utilisation and space availability are two other important considerations for conducting research in rural clinics.

Another factor that is related to disease progression is wasting status (Baylor College of Medicine, 2003). The loss of body mass is one of the criteria used in the WHO staging system (see section 2 for more information on this staging system). However, whether or not this is applicable in South Africa has never been investigated. As mentioned in the literature review, the HIV wasting syndrome is an AIDS defining condition called the AIDS wasting syndrome (AWS). It is also possible to have other AIDS-defining criteria in the absence of wasting. Several criteria defining the extent of wasting required to fulfil the definition have been developed: involuntary body mass (BM) loss greater than 10%, unexplained chronic diarrhoea for more than one month associated with BM loss, or weakness and unexplained prolonged fever for more than one month (Baylor College of Medicine, 2003; Nemechek *et al.*, 2000; CDC, 1992).

As discussed in the literature review, BM can provide useful information regarding the physiological status of an HIV-infected individual. BMI and %IBW are therefore also important variables, since they represent the BM after taking into account the height of the individual. Since the term malnutrition refers to the loss of structural body components,

one or more parameters of malnutrition can be used as complementary standards of objectively assessing wasting. Although, in terms of body measurements, malnutrition is most accurately reflected by the body cell mass (BCM) (Ott, *et al.* 1993), I examined more cost-effective accepted indicators of malnutrition (%IBW and threshold values that relate to arm variables) to assess wasting or lack thereof. Population percentiles were also used to compare the participants to a large database of individuals of a similar age group (Frisancho, 1981).

At baseline the percent of ideal body mass (%IBW) of the TN participants ranged from 98 to 176% with an average of 137%, while the ART group's %IBW ranged from 67 to 153% (refer to Table 5).

According to the definition of the AWS, a formal diagnosis can only be made by assessing body mass loss over time as well as taking into consideration the presence of associated conditions like diarrhoea, fever and weakness. In the absence of firm longitudinal data and community relevant controls it is difficult to make any assumptions on what the ideal body weight of the HIV-infected subjects in the study should be. Nonetheless, generalized norms are available for ideal body weight (Baylor College of Medicine, 2003), which were used to calculate an estimated IBW taking height into account.

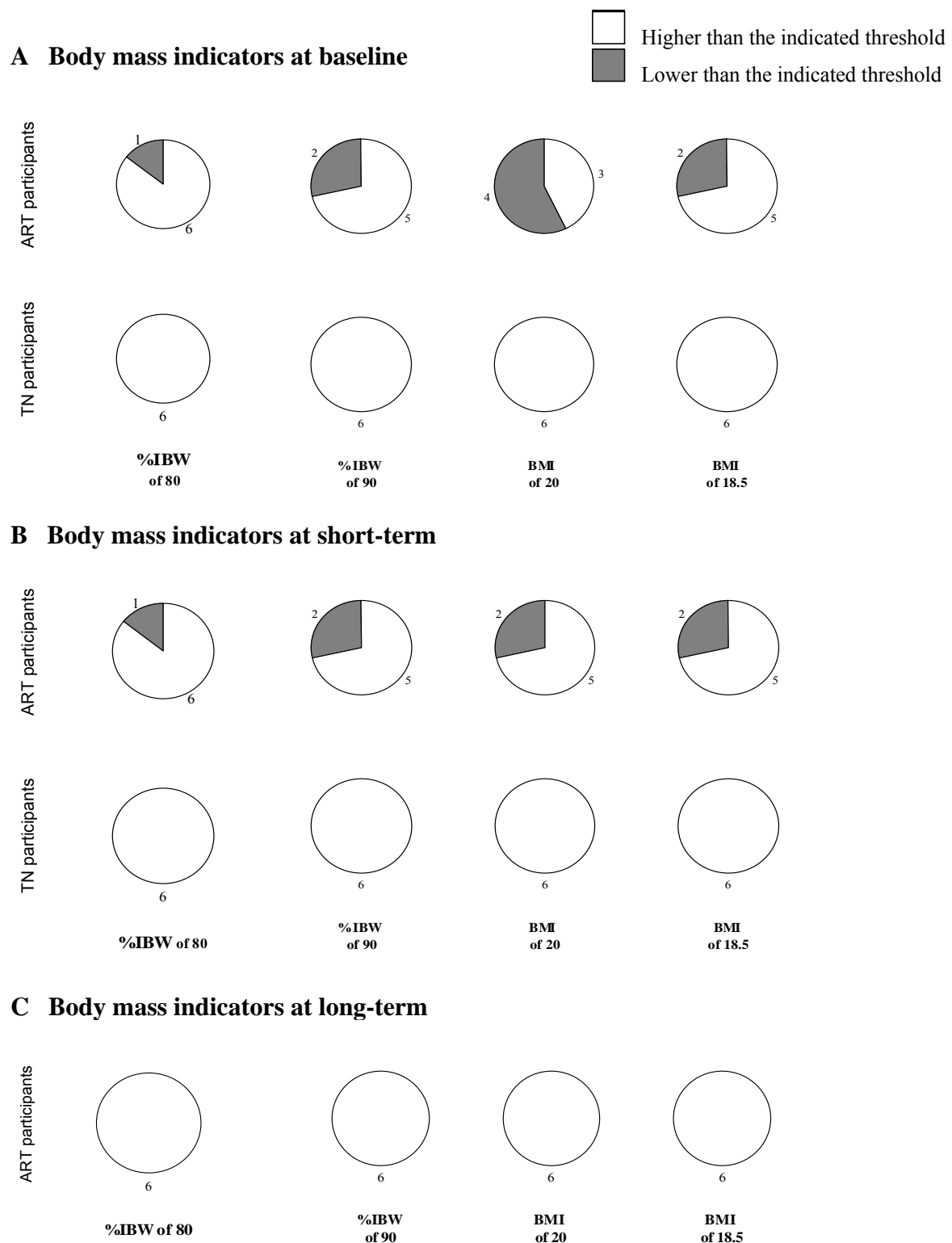
It should also be noted that many infected individuals have an initial body mass much greater than 100% (eight of the nineteen recruited participants had a %IBW greater than 110%). Individuals such as these could be undergoing wasting without having a body mass less than 10% of the ideal. For example, one participant was classified with late stage disease (WHO stage 4) and her calculated muscle area was below the 5<sup>th</sup> percentile threshold, but her body mass was only 1 percent below the ideal prescribed for a female of her height. Therefore, in a rural South African setting, taking only BM into consideration when evaluating a patient with regard to wasting is insufficient. However, recording accurate monthly BM measurements will have the benefit of providing longitudinal information although not specific to body compartments.

A body mass index below 18.5 has been suggested as a general threshold that may indicate being underweight for adults (WHO Technical Report, 2000). A body mass index less than 20 and a body mass less than 90% of estimated ideal body mass have been suggested to indicate malnutrition for an adult (Baylor College of Medicine, 2003). Another resource defined malnutrition as marginal when the BMI falls between 18.5 and 20, mild when the BMI falls between 16 and 17 and severe when it is below 16 (Weatherall, *et al.* 1996). According to these criteria, one of the ART participants can be said to have had severe malnutrition. One participant was mildly malnourished, while four of the ART participants had BMI's between 18.5 and 20. None of the TN participants' BMI's was below any of these limits.

The participant with severe malnutrition also exhibited the symptoms of diarrhoea and weakness. She was the only participant to be clinically diagnosed as being wasted by the medical staff at the clinic. Another participant weighed 58.2 kg at the time of recruitment. She reported experiencing occasional diarrhoea, fever, weakness and body mass loss.

The graphs shown in Figure 21 clearly indicate an improvement of BMI for the ART participants. Even though 50% of the ART participants had BMI under the "BMI of 20 threshold" at baseline, none of these participants were classified below any of the threshold values related to body mass relative to height at the long-term time-point. All the TN participants were above the thresholds at baseline as well as short-term, suggesting that none of the TN group were malnourished.

Another indicator of malnourishment is having a mid upper arm circumference (also referred to as MUAC, but abbreviated as AC for the current study) less than 22 cm (Weatherall, *et al.* 1996). The two groups differed in their %IAC as well as UAFA, but not any of the other anthropometry variables. This may indicate that a decrease in arm circumference (involving especially the arm fat) may be an early manifestation of advanced disease progression. Should this finding be replicated in a larger cohort, it may present the possibility of application in the rural clinics involved in monitoring patients.



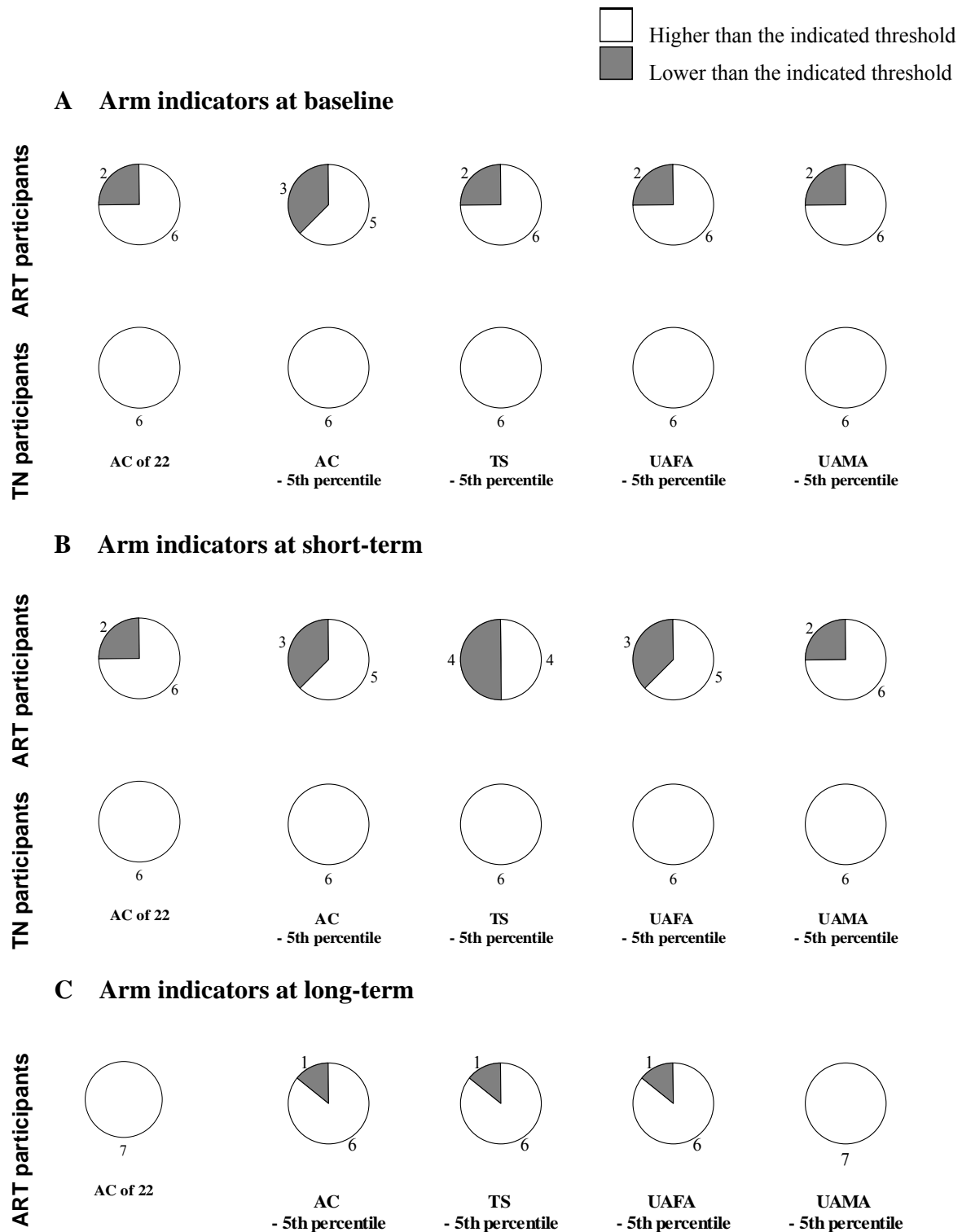
**Figure 21:** Variables related to BM in ART and TN groups at baseline (Panel A), short term (Panel B) and long-term (Panel C) time points. Estimated %IBW was calculated taking into account height (Baylor College of Medicine, 2003).



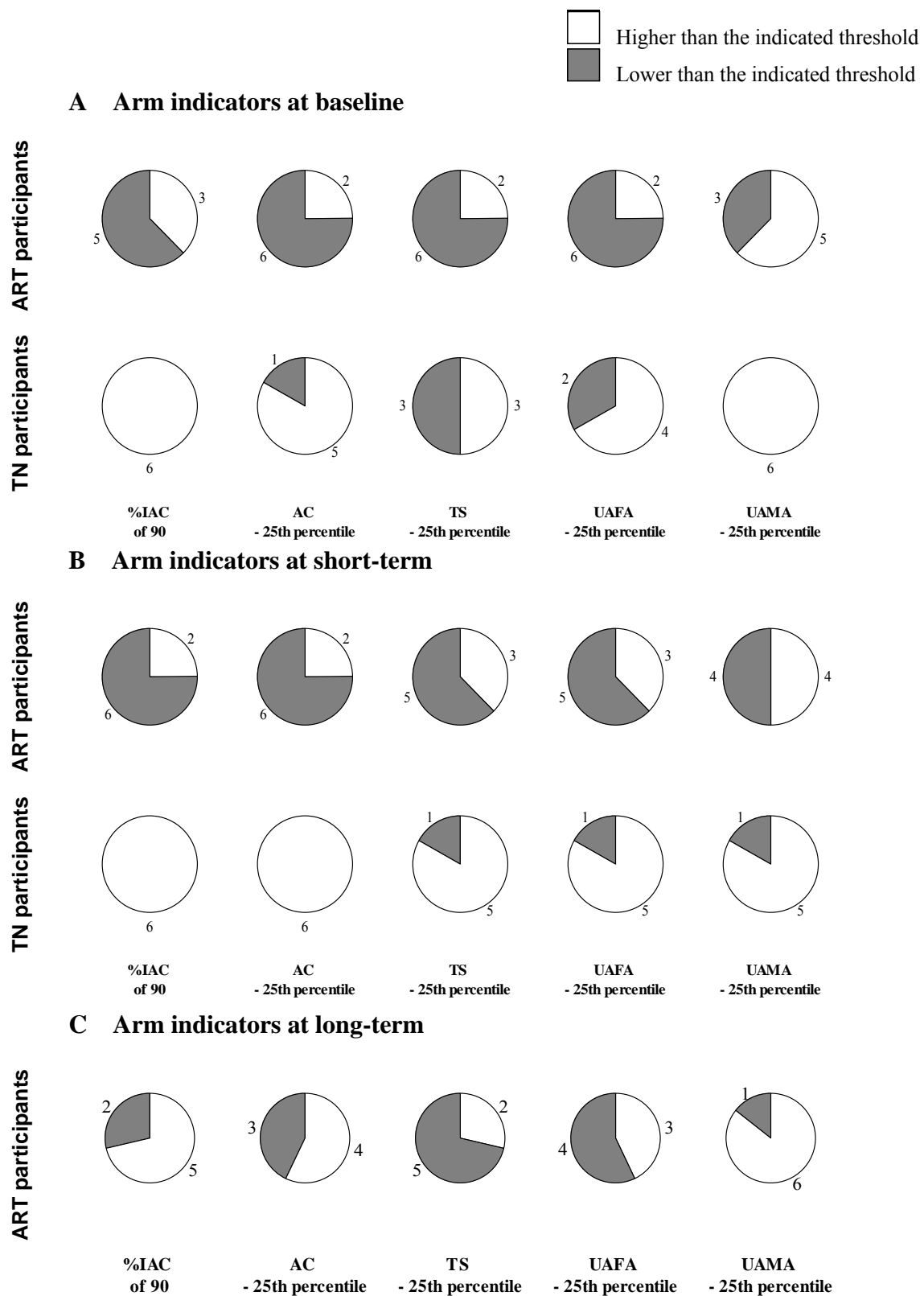
The %IBW, %IAC, UAFA and UAMA variables did not improve significantly for the ART group over time. Since the statistical analyses rely on means and standard deviations and because of the small subject numbers, it is also necessary to briefly discuss individual data. (See Appendix E for the graphs.) Although most of the ART participants showed a gradual increase for anthropometry variables and one ART participant showed a dramatic increase, two participants tended to have decreased values, especially at the long-term time-point. These observations indicate the requirement for greater subject numbers in order to subdivide subjects according to groups with different responses.

Classifying the ART and TN groups according to their arm anthropometry values (Figures 22 and 23) revealed the same pattern as that shown in Figure 21. Three of the four ART participants with low BMI values also had arm muscle area values below the 25<sup>th</sup> percentile threshold, while all four of them had arm circumference and fat area values below the 25<sup>th</sup> percentile threshold. It seems that the “BMI of 18.5” and “%IBW of 90” criteria lead to a more similar classification to the “AC of 22” criterion than does the criterion of “BMI of 20”. Using a BMI of 20 as threshold value is possibly therefore not selective enough.

The same conclusion could be made about using a threshold of less than the 25<sup>th</sup> percentile to classify percentile values of arm circumference (AC), triceps skinfold (TS), upper arm fat area (UAFA) and upper arm muscle area (UAMA). The population standards are not generated exclusively from individuals living a rural or semi-rural lifestyle and also not individuals from the population groups in this study. This might be the reason why so many participants (even from the TN group) are classified below the chosen threshold in Figure 23. Those that are included into the less than 25<sup>th</sup> percentile but not the 5<sup>th</sup> percentile are possibly erroneously included into a class that indicates malnutrition. Alternatively, it could be a more sensitive indicator of future manifestation of malnutrition.



**Figure 22:** Variables related to the arm indicating the number of subjects in the lowest 5<sup>th</sup> population percentile or with an arm circumference of 22 cm in ART and TN groups at baseline, short-term and long-term time-points.



**Figure 23:** Variables related to the arm indicating the number of subjects in the lowest 25<sup>th</sup> population percentile or an %IAC of 90 in ART and TN groups at baseline, short-term and long-term time-points.

It is possible that participants may experience wasting before it is becoming apparent from BM status. In a clinical setting, follow-up measurements would be vital for such patients (especially those not on treatment yet) to establish whether they are merely thin or are starting to experience wasting and a decline in health. After conducting a study that compared the measurements of South African youths with youths from other ethnic groups, Eckhardt *et al.* (2003) suggested that anthropometry measurements should be considered in conjunction with BMI when assessing body composition and that these assessments can be influenced by ethnicity.

Performing anthropometry measurements on the arm is a simple and cost-effective assessment that can be made on a routine basis. At baseline triceps skinfold thickness correlated positively with CD4<sup>+</sup> count in ART and TN subjects combined ( $R = 0.71$ ;  $p = 0.02$ ). This and other related variables should be investigated in a larger study group. Values obtained from measuring the arm circumference and subcutaneous fat content could provide important objective additional information about the nutritional status of the patient. This indirect evaluation of the nutritional status of the patient in conjunction with clinical evidence could provide the necessary information to confirm wasting at an early stage.

The TN participants in our study did not exhibit a decrease in arm measures during the short-term phase. Long-term changes may however be different. Nevertheless, some of the TN participants' arm variables were below the 25<sup>th</sup> percentile threshold (Figure 23) but not the 5<sup>th</sup> percentile threshold (Figure 22). Therefore, using the 25<sup>th</sup> percentile (or a threshold between 5 and 25) as threshold level to indicate nutritional status may serve as an early warning sign of future malnutrition. This could only be assessed by further longitudinal studies with ethnically diverse study groups.

A closer look at the QoL data can provide further indication regarding the status of the ART and TN participants. Figure 4B indicates an outlier in the ART group with a particularly low overall QoL score. Although the sample size was too small to perform meaningful statistical analysis on the sub-divisions of QoL, some information can be gained from looking at the pie charts shown in Figure 5. One ART participant was

consistently reporting severe problems, but this subject did not coincide with the subject with the lowest (outlying) overall score. This indicates that the overall score is perceived differently from the more specific questions.

The TN participants did exhibit some problems with all except the self-care QoL dimension. After a closer look, it was clear that these problems were not experienced only by subjects who actually already qualified for ART, but were not receiving it. It is possible that these problems are unrelated to the progression of the HIV-infection, or that the observations arose out of experimental error (e.g. difficulty in asking questions through translation). However, if some of the TN participants did experience problems with mobility, pain, performing usual activities and anxiety (as indicated in Figure 5) as a result of the HIV-infection, it is possible that they were already experiencing some side effects of wasting or some other condition related to disease progression. Alternatively the diagnosis itself may have caused sufficient anxiety to disrupt QoL.

In summary, using anthropometry variables of the arm to observe patients may present an alternative way of monitoring wasting. It is a practical cost- and time-effective method that nurses could easily do in rural clinics. Population reference values could be supplied to clinics as wall charts to make the process easier. Although the information supplied by publications such as Frisancho (1981) can be used initially, reference values relevant to South African populations should eventually be produced and used. Further research is merited, especially an investigation into the predictive value of using a threshold between the 5<sup>th</sup> and 25<sup>th</sup> percentile that could foretell future malnutrition in patients.

It is interesting to note that those measures that relate specifically to fat (TS and UAFA) tend to have a greater frequency below the chosen thresholds than UAMA. It is possible that this indicates a preferential loss of fat instead fat free mass similar to that seen in other studies (Kotler *et al.*, (1999); Swanson *et al.*, (2000)).

It is also recommended that future research should include measurements of QoL and physical functioning. Such observations should be interpreted in relation to anthropometric measurements since important recommendations can be made from such information. For

example, it is possible that those patients that manage to stay active can maintain their muscle mass better than those individuals that do not. Therefore, I have made a preliminary investigation into possible ways of assessing physical functioning in a resource-poor and space-limited clinical setting (refer to Appendix B).

## **Lipodystrophy**

Lipodystrophy results in the preferential deposition of fat in the intra-abdominal area. Less fat is deposited in peripheral areas like the arms and legs, or fat may be mobilized from these areas. Therefore, the fat deposited in the intra-abdominal area could be a result of redistribution (McDermott *et al.*, 2001) of existing fat in the body (patients who were not malnourished before these changes) or the preferential deposition of “new” fat in intra-abdominal areas in patients who gained body mass after being malnourished.

Mechanisms for targeting of peripheral fat in patients include the impairment of the mitochondrial DNA polymerase  $\gamma$  (with NRTI administration) and inhibition of the cytochrome P450-3A isoform (with PI administration) that may interfere with retinoic acid binding and lead to impaired adipocyte function, adipocyte differentiation, decreased storage of triglycerides, insulin resistance and apoptosis (Hirsch & Battegay, 2002). Further research into whether or not women differ from men in their responses to ART should be done.

In order to exclude possible confounding effects of body mass loss (e.g. causing a decrease in arm fat) only weight stable patients were included in some of the lipodystrophy studies mentioned in the literature review (Rodwell *et al.*, 2000; Carr *et al.*, 1999; Gervasoni *et al.*, 1999). Therefore, these studies only investigated the redistribution of existing fat reserves. However, in a different study, patients with lipodystrophy have also shown a highly significant loss of body mass ( $p = 0.0005$ ) in comparison to a control group (Carr *et al.*, 1998).

Change in waist circumference represents the cumulative effect of the change in IAI and abdominal skinfold. The pattern of changes of the TN group's IAI and abdominal skinfold

suggests that the change of the one variable negated the changes of the other variable, resulting in a relatively unchanged waist circumference.

However, changes in waist circumference could also be accompanied by changes in hip circumference, thus one or both of these variables could influence the parameters of W:H and IAI:H. The significant increase of W:H and IAI:H observed in the ART group compared to the TN group may be a result of an increased deposition of intra-abdominal fat. In a group where some participants started out as being malnourished and subsequently improved their nutritional status, it is difficult to establish to what extent this increase is influenced by changes relating to “gaining weight”, as opposed to redistribution of fat mass.

If the subcutaneous fat had increased more in the abdominal area than the gluteal area, this could explain the increased W:H observed. It would however not explain an increase in IAI:H. IAI exhibited a gradual non-significant increase over time (Figure 20, Panel A). A combined effect of an increase in body mass and a redistribution of body fat with fat now being stored intra-abdominally and subcutaneously (only the latter expected with normal weight gain) may have contributed to the increase in waist circumference observed in the ART participants over the long-term.

“Gluteal wasting” has also been reported to be associated with lipodystrophy (Salomon *et al.* 2002; Carr *et al.* 1999; Gervasoni *et al.* 1999); therefore there could be opposing effects on the hip circumference. An increase in body mass could lead to an increase in hip circumference, while peripheral wasting could result in a decreased hip circumference. The use of dual X-ray absorptiometry (DXA) to measure total or regional fat content could be a useful method in assessing the redistribution of body fat (HIV Lipodystrophy Case Definition Study Group, 2003).

The female body also tends to store fat more easily in the gluteal area than some other areas of the body (Blaak, 2001), which could mask the manifestation of lipodystrophy in women. Therefore, it is possible that lipodystrophy should be investigated in a different way in men and women. Using arm anthropometry variables to indicate lipodystrophy could also offer

an alternative method of monitoring lipodystrophy-related changes. However, being able to discriminate such changes from the changes seen in wasting will pose a significant challenge.

**Table 9:** Body composition changes associated with wasting and lipodystrophy.

Variable	Change as a result of		
	wasting	recovering from wasting	lipodystrophy
Waist circumference	↓	↑	↑
Intra-abdominal indicator	↓	↑	↑
Hip circumference	↓	↑	↓
Arm circumference	↓	↑	↓
UAMA	↓	↑	-
UAFA	↓	↑	↓

↑ symbolize an increase; ↓ symbolize a decrease; - indicates that there is no plausible effect on this variable.

Body composition changes of HIV-infected patients are therefore complex and multifaceted (Table 9). This may be why no statistically significant changes were observed for the ART participants with regard to the waist and intra-abdominal indicator to hip ratios when these data were analyzed over the long-term. Other possible explanations are that the statistical power (group size) was too small or that even the long-term time point is still an early time point for lipodystrophy to develop in patients taking ART. The longitudinal study conducted by Galli *et al.*, (2003) found evidence of fat accumulation and combined forms (simultaneous evidence of fat loss and fat accumulation) in HIV<sup>+</sup> women receiving antiretroviral therapy after 12 months of observation, with more observations (especially lipoatrophy) after 24 months.

It is also possible that a patient could be experiencing only lipoatrophy, without the concomitant increase in waist circumference. In the study conducted by Rodwell *et al.* (2000), which investigated patients with a clinically abnormal reduction or absence of subcutaneous tissue in the cheeks, data revealed that 6 of 14 participants exhibited decreased fat in the cheeks without an enlarged abdomen. Five of the participants exhibited



clinically abnormal absence or reduced fat in the legs and arms without an enlargement in the abdomen. Another study (Carr, *et al.* 1998) showed that patients receiving protease inhibitors had lower arm and leg fat mass but similar central abdominal fat mass compared to control patients.

Figures 22 and 23 illustrate that there is still some evidence for sub-optimal arm fat reserves at the long-term time point, while arm muscle areas compared better to healthy population values. It is possible that this could be a manifestation of peripheral arm fat loss in some participants as a result of lipodystrophy. Therefore, changes in arm fat mass (interpreted according to population reference values (Frisancho, 1981)) could also be used as an additional measure when assessing lipodystrophy. Once again, more participants were included under the 25<sup>th</sup> percentile threshold than the 5<sup>th</sup> percentile threshold and it is possible that the 25<sup>th</sup> percentile is too lenient to be clinically relevant. Subsequent studies should investigate the use of arm fat percentile values as an additional variable when assessing lipodystrophy. However, this should be done in conjunction with arm muscle area to take into account the possibility that wasting could be affecting the arm fat instead.

In our study there was a greater increase in %IBW than %IAC which may be a normal manifestation of “gaining weight” or it may also be an indicator of lipodystrophy. Patients who are weight stable, yet show an increase in %IBW to %IAC ratio may be experiencing peripheral wasting and fat redistribution. The changes in this ratio (%IBW:%IAC) could therefore also be a helpful variable when assessing lipodystrophy and should be considered in future studies.

### **6.3 Conclusions**

The increased CD4<sup>+</sup> counts of the ART participants and the information gained from the QoL questionnaires suggest that their health improved. The general trend of increasing skinfold and other anthropometric values suggests that the ART group gained body mass, which consisted of both fat and fat free mass. If the sample size had been larger, more of these variables might have shown a statistically significant increase. Antiretroviral therapy seemed to contribute greatly to the QoL of the participants and it probably aided in the

recovery from wasting for at least one participant in this study. Attempts to understand changes in the anthropometry of the arm could lead to recommendations for use in a clinical setting to effectively monitor patients in future.

This study found some evidence of lipodystrophy even though a very small sample group was investigated. Two new calculated variables (IAI and %IBW:%IAC) were derived and investigated that could make the monitoring of lipodystrophy easier. These variables are not tested or validated and should be included in future studies to examine the feasibility of using them in a clinical environment.

Finally, continuation of this study could add to the literature on responses to ART in Southern Africa. It is possible that different ethnic groups can exhibit different metabolic responses which can lead to different changes in body composition (Punyadeera *et al.*, 2001). Although studies that investigate different metabolic responses and differences in body composition in specific ethnic groups from Southern Africa are available (van der Merwe *et al.*, 1998; Punyadeera *et al.*, 2002; Kruger *et al.*, 2004), I could not find any studies that specifically investigates the effect of ART on the body composition of South African women. Such investigations would be important since it has been shown that obese South African black women are more insulin resistant than obese South African white women (van der Merwe *et al.*, 2000), which could predispose these black women to develop type 2 diabetes (van der Merwe *et al.*, 2001). Other metabolic differences like higher concentrations of leptin and free fatty acids have also been shown in obese South African black women (van der Merwe *et al.*, 1999). A better understanding of how these processes differ between ethnic groups may lead to improved treatment and lifestyle interventions in South African populations.

## Appendices

### 7.1. Appendix A

#### Defining AIDS

The following definitions were taken from Weatherall *et al.* (1996).

The 1987 CDC (Centers for Disease Control) definition of AIDS states that it is an illness characterized by one or more ‘indicator’ diseases. When the following indicator diseases are diagnosed in the absence of another cause of immune deficiency even without laboratory evidence of HIV infection – they are considered to be indicative of AIDS:

- Candidiasis: oesophageal, pulmonary
- Cryptococcosis: extrapulmonary
- Cytomegalovirus disease: disseminated
- Herpes simplex virus infection
- Mucocutaneous ulceration lasting longer than 1 month
- Pulmonary or oesophageal infection
- Kaposi’s sarcoma: patient aged under 60
- Primary cerebral lymphoma: child aged under 13
- *Mycobacterium avium*: disseminated
- *Mycobacterium kansasii*: disseminated
- *Pneumocystis carinii* pneumonia
- Progressive multifocal leucoencephalopathy
- Cerebral toxoplasmosis

If there is laboratory evidence of HIV infection and the following indicator diseases are either definitively or presumptively diagnosed (regardless of the presence of other causes of immune deficiency) – a diagnosis of AIDS can be made:

Diseases diagnosed definitively:

- Recurrent/multiple bacterial infections: child aged under 13
- Coccidioidomycosis: disseminated
- HIV encephalopathy
- Histoplasmosis: disseminated
- Isosporiasis: diarrhoea persisting for longer than 1 month
- Kaposi's sarcoma at any age
- Primary cerebral lymphoma at any age
- Non-Hodgkin's lymphoma: diffuse undifferentiated B-cell type, or unknown phenotype
- Any disseminated mycobacterial disease caused by other than *Mycobacterium tuberculosis*
- *Mycobacterium tuberculosis*: extrapulmonary
- *Salmonella septicaemia*: recurrent
- HIV wasting syndrome

Diseases diagnosed presumptively:

- Candidiasis: oesophageal
- Cytomegalovirus retinitis with loss of vision
- Kaposi's sarcoma
- Lymphoid interstitial pneumonia: child aged under 13
- Mycobacterial disease (acid-fast bacilli, species not identified by culture): disseminated
- *Pneumocystis carinii* pneumonia
- Cerebral toxoplasmosis

Since 1993 another definition of AIDS has been used in the United States. According to this definition any person with a proven HIV infection with a CD4<sup>+</sup> lymphocyte count of less than 200 cells/ $\mu$ l is diagnosed with AIDS (irrespective of clinical manifestation). Three new AIDS-indicator diseases were also added to the above list. These are pulmonary tuberculosis, recurrent bacterial pneumonia in adults and invasive cervical cancer.

The World Health Organization (WHO) also proposed other definitions for use in developing countries. These include the Bangui (for use in sub-Saharan Africa) and Caracas (the Pan American Health Organisation and the WHO Global Programme for South America) definitions (WHO, 2004).

## **7.2. Appendix B**

### Physical activity:

Disease can lead to a decrease in physical activity and it is possible that this decrease in activity can impact negatively on conditions like wasting and lipodystrophy. It is important for future researchers to investigate the interaction between disease, physical activity and QoL in HIV/AIDS, since these three aspects probably interact in a reciprocal and complex manner.

Although I originally wanted to measure the physical mobility and fitness of the participants in this study, it became clear early on that there were a few obstacles unique to a clinical environment in South Africa that would make this endeavour difficult. At the time of doing this study, this population group was unfamiliar with researchers conducting studies and they were reluctant to join in the project. Although the participants that eventually joined this study did so voluntarily after all their questions were answered and the project was discussed at great length before starting any measurement, they were still inherently hesitant to participate in unfamiliar activities. Therefore I focussed on measurements like anthropometry (which more closely resembles a nurse or doctor's consultation). I did however perform a few tests that could give an indication of muscular and cardiovascular physical fitness. These tests were easy to perform and the participants were not hesitant to participate in these tests, since care was taken in the design of the tests to exclude actions or equipment they were not familiar with. All the participants of the "study group" that participated in exercise tests had been on ART for at least 9 months. Two of the tests (the Bottle Test and the Grip Strength Test) were also carried out by a "control group" of 76 female students who were between the ages of 20 and 25 years.

Bottle Test:

Existing muscular endurance tests that require the participant to do sit-ups, chin-ups, push-ups dips and squats were thought to be too unfamiliar to be performed by this population. Some of these tests also require the use of expensive equipment, which makes them less feasible for implementation in a South African clinic setup. The “Bottle Test” was designed to be a practical test for a clinical environment, requiring no expensive equipment or specific skill for performing the test.

The test consists of incremental workloads to exhaustion. Instead of traditional weights, filled 1-litre water bottles (each weighing 1 kg) were put inside two strong shopping bags. At first, each bag contained 3 bottles (3 kg), after which bottles were added for each subsequent level with increments of 3 kg per bag. To perform the test, the test subject was required to sit upright on a chair with no armrests, while holding the arms flexed at an angle of 90° at the elbow. The test administrator then held the bags so that the participant could easily get a hold on them, one in each hand. A timer was started when the test administrator transferred the weight of the bags to the hands of the participant. The test administrator recorded the duration that the participant could hold the bags while maintaining an angle of 90° at the elbow for that arm. (Separate scores were recorded for the right and the left arm.) The administrator stopped the participant if a time of 3 minutes were reached, signifying the completion of that level. After a rest lasting 5 minutes and adding 3 bottles to each bag, the next level was then attempted. Once a participant could not reach a time of 3 minutes, the test was completed.

A score was determined by calculating the total of the points generated during each level per arm. The maximum number of points that can be achieved per level is 3 points. For example, participant X completed level 1 and held onto the bags for 1 min and 30 seconds (right (R) arm) and 1 min 12 seconds (left (L) arm) during level 2. Her score was:

$$\begin{aligned}\text{Level 1} &= (180 \text{ seconds achieved} / 180 \text{ seconds maximum}) \times 3 \\ &= 3 \text{ points}\end{aligned}$$

R arm:

$$\begin{aligned}\text{Level 2} &= (90 \text{ seconds achieved} / 180 \text{ seconds maximum}) \times 3 \\ &= 1.5 \text{ points}\end{aligned}$$

L arm:

$$\begin{aligned}\text{Level 2} &= (72 \text{ seconds achieved} / 180 \text{ seconds maximum}) \times 3 \\ &= 1.2 \text{ points}\end{aligned}$$

Total score R arm:

$$= 4.5$$

Total score L arm:

$$= 4.2$$

The first 10 subjects of the control group performed the Bottle Test twice, after which we found the results to be repeatable. Thereafter, the participants of the control group were only required to do the test once. Furthermore, the muscle action required resemble a biceps curl, which the majority of the controls had performed at some point in their lives. All the participants of the control group advanced to stage 2 and 10 participants attempted stage 3 for at least one arm. Three individuals of this group wanted to repeat the test on the same day to try to better their score. Their scores remained relatively unchanged also indicating repeatability in a healthy population, as shown below:

Table i:

Subject	First attempt R arm	Second attempt R arm	First attempt L arm	Second attempt L arm
1	4.2	4.1	3.5	3.6
2	3.8	3.7	3.7	3.6
3	3.8	4.0	4.0	3.8
Coefficient of Variation	5.9%	5.3%	6.7%	3.1%

Eight individuals of the HIV-infected participants that were recruited for this project took part in this test. Five of these participants repeated the test again one week later. On both occasions they were required to do the test twice (after resting for at least 1 hour in between). The first attempt served as a familiarisation phase because the testing situation

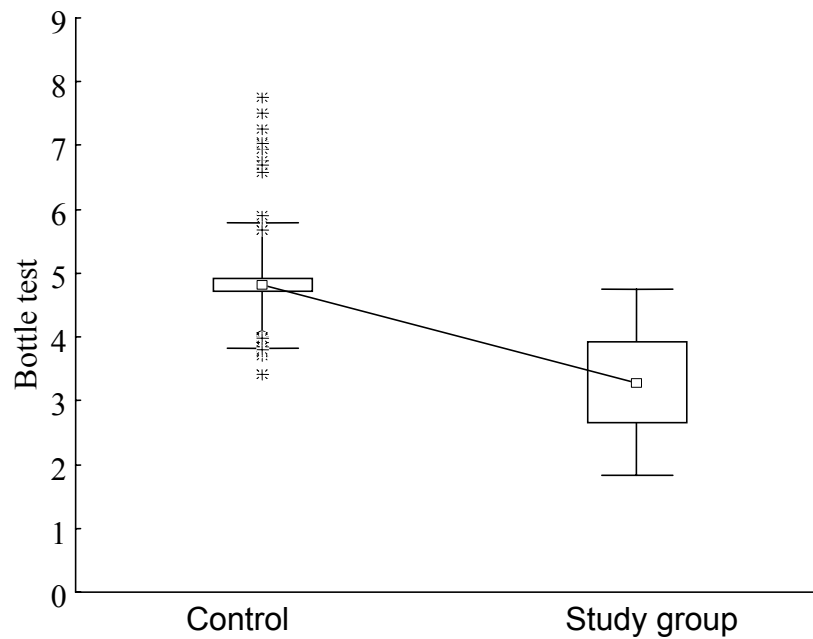
was unfamiliar to the participants as confirmed by visual assessment. The score of the second attempt was recorded as that week's score.

The results for the right arms are shown in Figure i. The two graphs show a comparison between the results of the first and second week's test scores with the test scores of the control group. For both situations, the study group scores were significantly lower ( $p < 0.05$ ) than the scores of the control group (revealed by a Mann-Whitney U test). However, the variability for the scores of the second week (Figure i Panel B) was remarkably less than for the first week (Figure i Panel A). This probably indicates a learning-effect, since three of the participants (i.e. 60%) had higher scores for the second week's test. The Bland-Altman plot shown in Figure ii provides additional evidence that a learning-effect occurred, since the upward trend to the right indicates that those participants with a low average score had improved scores for the second week. The results for the left arm showed the same pattern (of lower subject group scores compared to the control group and less variability for the scores of the second week) as for the right arm (data not shown).

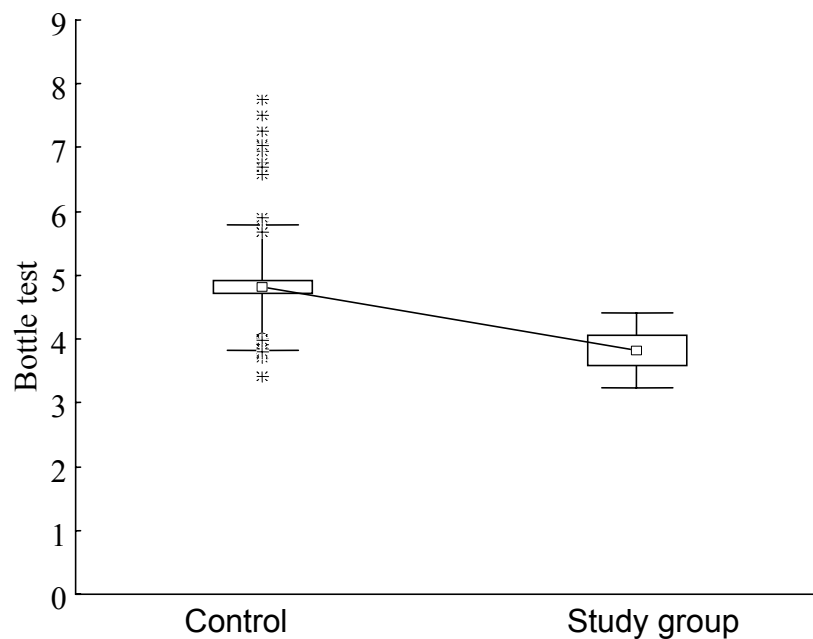
Even though this new "Bottle Test" showed a learning effect, I believe it would be worthwhile to investigate its use in future since the study group had significantly lower scores than the control group. It is possible that this difference reflects physical disability in the study group as a result of the HIV condition. Therefore, I believe that this test (or a similar test) should be tested for validity and in a HIV infected population. The test is very simple and doesn't take a lot of time to perform. The materials would also be very easy to acquire in a resource-poor setting. I would suggest modifying the test to be validated so that it would include an activity that more closely reflects the participant's daily lifestyle (like picking up a certain amount of bags with bottles and putting them onto a table of standard height and recording heart rate, time and rating of perceived exertion on a three-level scale (easy, moderate and difficult)).



A



B



**Figure i:** Week 1 (Panel A) and week 2 (Panel B) scores of the right arm of the study group (n = 5) compared to the control group (n = 76). The box plots represent mean  $\pm$  SE, while the whiskers indicate  $\pm$  SD. Extreme outliers are represented by a star (\*) while the middle points in the boxes signify the means.

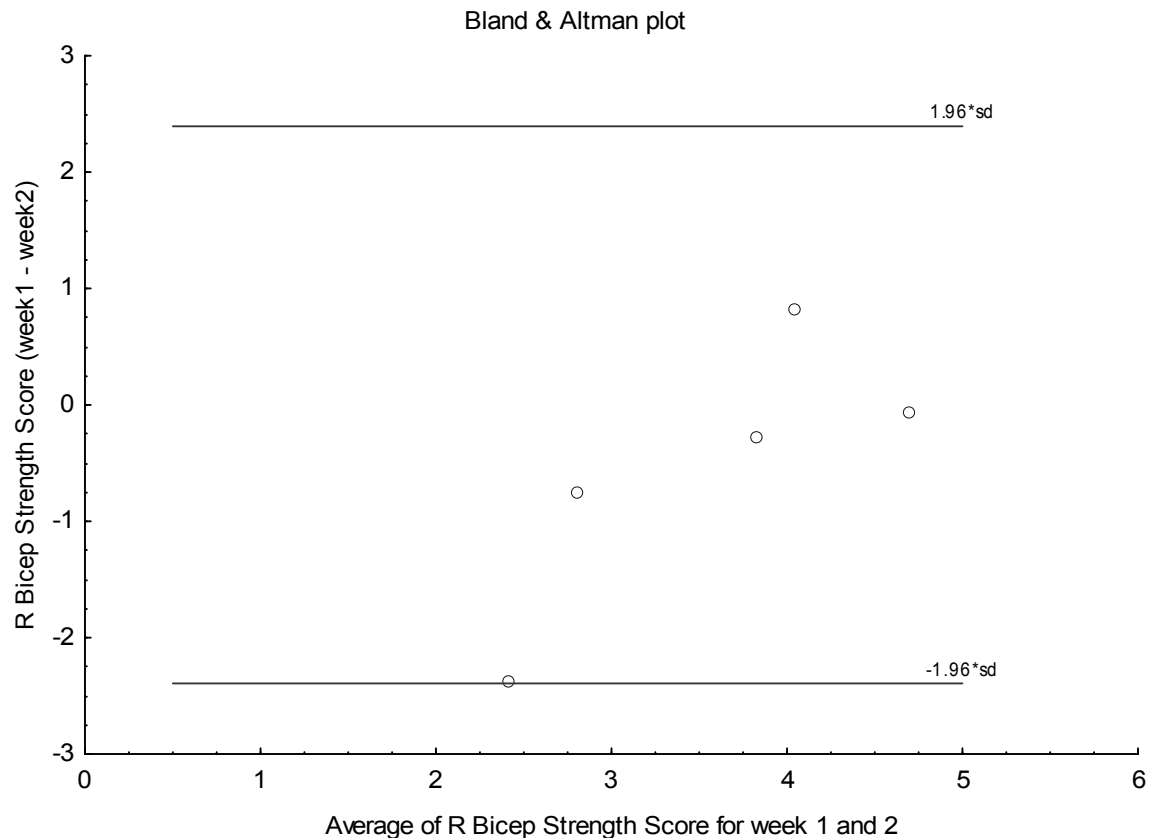
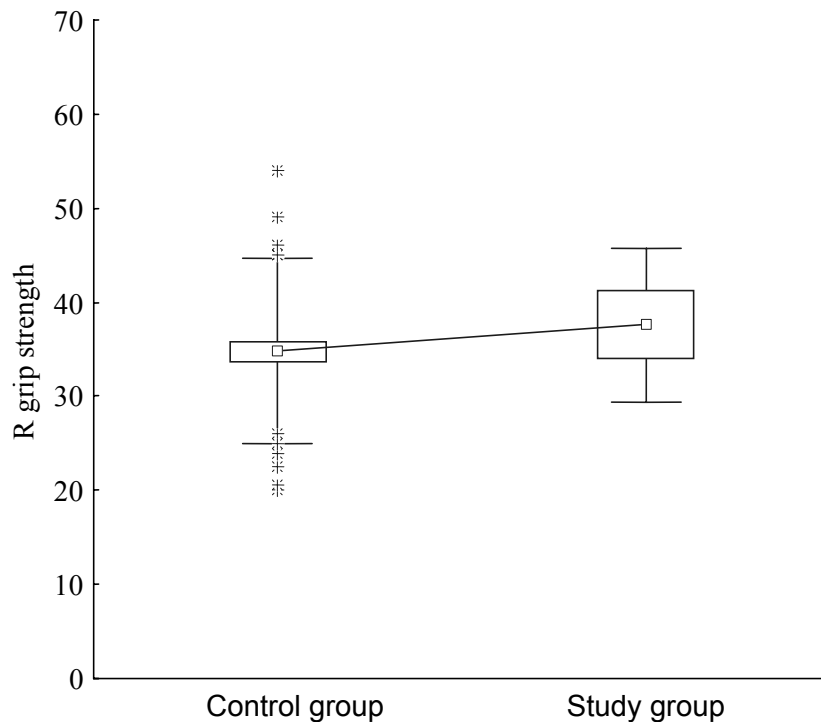


Figure ii: Bland-Altman plot of week 1 and week 2 right arm scores of the study group.

### Grip Strength Test:

I also determined the grip strength with a grip dynamometer of both the study and the control group. Reliability coefficients greater than 0.90 have been reported by others for this test of hand grip strength (Johnson & Nelson, 1979).

The right hand grip strength measurements (in kg) of the two groups are shown in Figure iii. Although the grip strength of 9 participants of the study group were determined, only the five that were included in the graphs of Figures i ii are included in this graph. A comparison of the two groups revealed no significant difference with the Mann-Whitney-U test (the same was true for the left grip measurements (data not shown)).



**Figure iii:** Right hand grip strength measurements of the control group (n = 76) and the study group (n = 5). The box plots represent mean  $\pm$  SE, while the whiskers indicate  $\pm$  SD. Extreme outliers are represented by a star (✱) while the middle points in the boxes signify the means.

Although it is possible that the grip strength test is too insensitive to detect differences between a healthy group and a group affected by HIV, it is also possible that grip strength was unaffected in this study group. A study with more participants and different tests of muscle function and strength may show differences between two such groups.

#### Step test:

It was decided that the existing cardiovascular fitness tests would be too difficult to administer in the environment that this particular project were done. The commonly used walk tests (like the 12-minute Field Performance Test and the One-Mile Walk Test) require a considerable distance in a straight line or a large circular route (Maud & Foster, 1995). This was not available at some of the clinics where we performed measurements, and I also feared a high dropout rate from the study if I were to require them to do such tests.

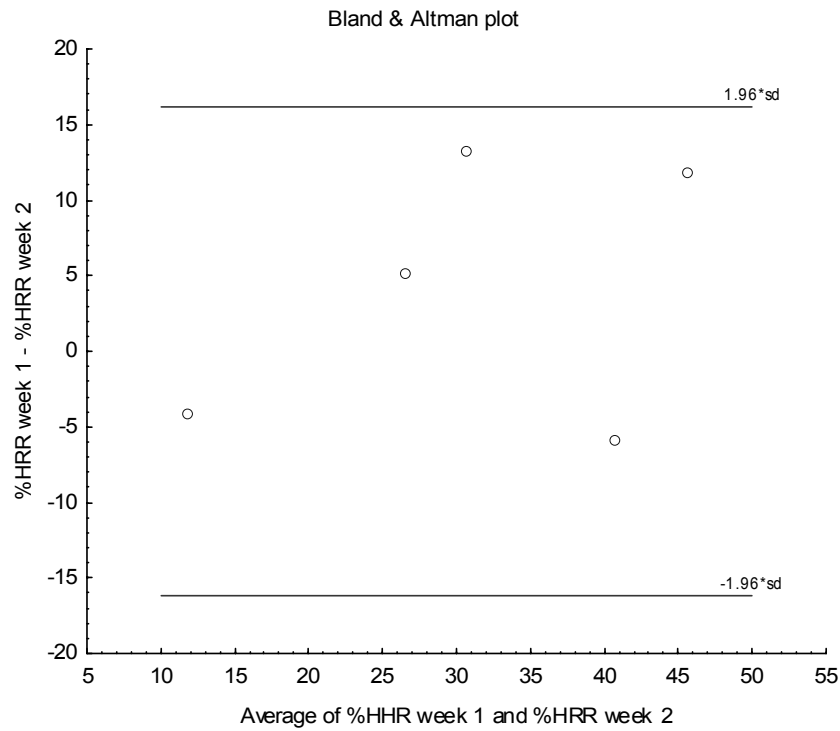
Step tests would be easier to administer, since it doesn't require a lot of space and a step would be easy to acquire or manufacture. Unfortunately, step tests (like the Harvard Step Test and the OSU Step Test) require the participant to perform the exercise at a specified cadence with the aid of a metronome (Johnson & Nelson, 1979). It quickly became apparent that this specific population group had great difficulty with this requirement since they lacked the coordination, skill and experience to perform a step test at a specified cadence. Therefore, the self-paced step test developed by Petrella and colleagues (2001) was used. The participants were required to step up and down two small steps 20 times. The time it took them to perform these 20 steps (T) as well as their heart rates immediately before and after the test were recorded. Their resting heart rate was also recorded upon arrival at the clinic (after sitting for at least five minutes), before the step test was performed. The percent of heart rate reserve (%HHR) was calculated for each test with the following formula:

$$\%HHR = (\text{post-step HR} - \text{HR at rest}) / ((\text{HR}_{\text{max}}) - \text{HR at rest}) \times 100$$

$$\text{where } \text{HR}_{\text{max}} = 220 - \text{age}$$

Although seven participants of the study group performed this test at least once, only five of them repeated the test one week later. As with the Bottle Test, they performed the test once to familiarize themselves with the protocol. After a rest of at least one hour, they repeated the test. The time and post-step heart rate of this second test was used as the score for the step test. Bland-Altman plots were used to illustrate the %HHR (Figure iv Panel A), post-step HR (Figure iv Panel B) and the time it took the participant to perform 20 steps (Figure v).

A



B

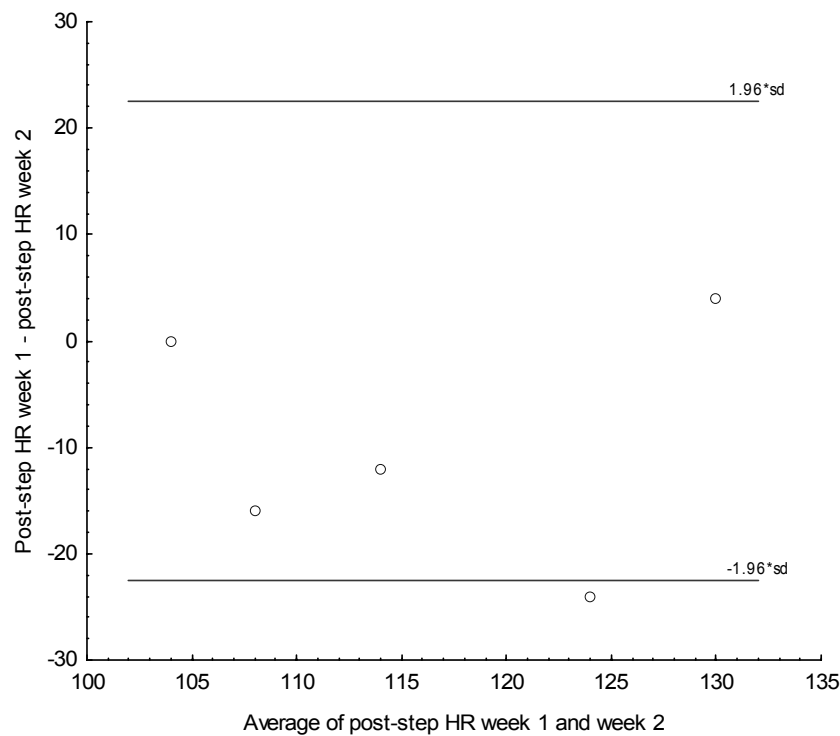
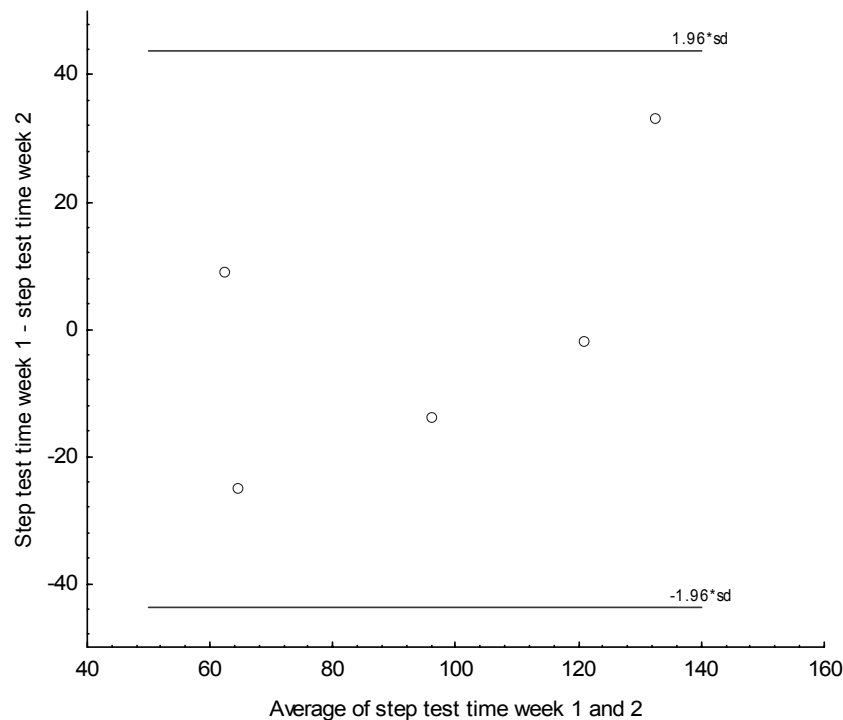


Figure iv: Percent of heart rate reserve and post-step heart rate for 5 individuals of the study group.



**Figure v:** The time it took the participant to perform 20 steps (T) for 5 individuals of the study group.

The differences between the %HRRs of week 1 and 2 were small (less than 10%) compared to the post-step HR. The post-step HR was 24, 16 and 12 beats/min higher respectively for three participants during the second week compared to the first week. Adjusting for resting HR by using the %HHR variable is therefore probably a better indicator of the individual heart rate response to activity. It appears as though there is an upward trend for T (Figure v). Although this sample is too small to make any conclusions from this graph, this could indicate that those with a high average time between the two weeks improved their time for the second week by completing the test in a shorter time. This could then indicate a greater efficiency to perform the task and a possible learning-effect.

Therefore, although the self-paced step test was very easy to perform in a clinical setting, further research is necessary to examine its validity and reliability in a South African population.

### 7.3. Appendix C

*Information sheets and consent forms:*

**The University of Stellenbosch  
Department Physiological Sciences  
Subject Information Sheet**

**Project Title:**

Body composition changes in HIV-positive females after initiating antiretroviral treatment, in comparison with CD4-count matched HIV-positive females not receiving ART.

**Coordinator:**

Prof K H Myburgh

E-mail: khm@sun.ac.za

**Project researchers:**

Ms PC de Bruto (Master's student)  
(Supervisors: KH Myburgh, C Smith)

Telephone: (021) 808 4564

**Collaborator:**

Dr. Grobbelaar

Telephone: (021) 872 1711

You are cordially invited to take part in a research study of which the aim is to monitor the quality of life and selected physiological parameters of HIV-positive people.

#### **Background**

There are various changes that can happen in the body as a result commencing antiretroviral treatment. Fat distribution, body mass and metabolic changes can occur which may have an influence on quality of life and daily activities.

During this study, certain parameters (CD4 count, body mass, body composition) will be assessed over a six month time period. The aim of this assessment is to improve the researcher's understanding of the course and impact of the disease and its treatment. This knowledge is necessary to develop effective treatment principles and the information gained from the study will also be used to design subsequent studies. The eventual aim is to develop practical programs with guidelines and recommendations which could help improve the quality of life of HIV positive people.

#### **Procedures**

The study will take place at the T. C. Newman Community Hospital under the supervision of Dr N.Grobbelaar.

If you decide to take part in the study, you will have to visit the hospital at least eleven times. Eight of these visits will coincide with your regular clinic visits and therefore you will only have to come to the clinic for three additional visits. You will receive compensation to the amount of sixty rand to compensate for the travel expenses of these three visits.

If you decide to participate, the following measurements and procedures will be carried out at the clinic:

- 1) Blood samples (one sample of 10 ml – approximately two teaspoons – per occasion) will be taken after three months and after six months, by the medical doctor treating you.

- 2) Ten skinfold measurements will be taken in the following areas: triceps (the back of the upper arm), subscapular (upper back), biceps (the front of the upper arm), iliac crest (just above the hip, on the side), supra-spinal (the side), abdominal (on the front), frontal thigh (the front of the upper leg), medial calve (the side of the calve), mid axial (on the side, between the arm and hip) and pectoral (on the front at the arm and chest junction). These measurements are taken with a calliper, which “pinches” the skin slightly (no pain is felt with this procedure). All these measurements will be taken in privacy.
- 3) You will be weighed (with an electronic scale) and your height will be measured. The circumferences of the upper arm, waist, hip, thigh and calve will also be measured.
- 4) You will be asked to complete a quality of life questionnaire and you will be interviewed privately by the researcher to assist you in doing this. The questionnaire will also be filled in at home at regular times. The researcher will also ask questions about what you ate the previous day and your normal eating habits. All information gained will be regarded as highly confidential.
- 5) You will be required to perform an exercise test on a treadmill. The treadmill test begins by walking slowly. The speed and gradient of the treadmill will be adjusted and you will be asked to exercise until you are close to total fatigue (about 90 % of your maximum ability, which we calculate). This exercise test will take about ten to twenty minutes. Your heart rate will be monitored before and during the exercise test, and a medical doctor will be on standby for the duration of the test.
- 6) The researchers are interested in energy utilisation, daily activity level and metabolic tempo. These factors will be measured with a heart rate monitor which you will wear for three days while you continue with your normal daily activities. The heart rate monitor fits like a belt around the chest under your clothes and is not uncomfortable or even noticeable.

In addition, if you agree to the procedure, Computed Tomography (CT) scans will be done at the Stellenbosch MediClinic (transport will be organised for you from the Paarl Hospital). Scans of the abdomen and mid-thigh will be performed at Stellenbosch MediClinic by a radiographer and assessed by Dr R de Villiers (a radiologist). Before doing the procedure, the radiologist will inform you of any side-effects or danger involved in having the scans taken of you. From these scans the researchers will be able to view the relative amounts of muscle to fat mass in the scanned areas.

The main advantage of taking part in this study, is that your body composition will be monitored regularly and free of charge. At the end of the study, you will also receive information on how to change your eating habits to improve your health. The only disadvantage that we foresee, from participating in this study, is that you will have to make a few extra trips to the clinic and that your regular visits to the clinic may take longer than usual. The only risk is the very small dose of radiation which you will be subjected to when you go for a computed tomography scan, but this procedure is not a prerequisite for participation in the project, so you are free to decline taking part in this specific procedure.

Blood samples will be collected by the medical staff from a vein in the forearm on two occasions, over and above the amount necessary for usual diagnosis and treatment of your illness. Ten milliliter blood (which is approximately the same volume as two teaspoons) will be taken per occasion. The only side effect that can result from this procedure is occasionally a small bruise and tenderness.

Fifty HIV-positive subjects will participate in this study.

This project has been evaluated and approved by the Sub-Committee C Ethics Committee of the University of Stellenbosch.

**Important:**



You are free to withdraw from the study at any time without any explanation. Your participation or lack of participation will in no way influence any other activities at the Hospital, and you will be treated without prejudice should you choose not to participate or to withdraw. Your withdrawal will not influence your future medical treatment in any way.

All information regarding the tests, your illness and treatment thereof, will be kept confidential and publication or presentations of the results at conferences will not reveal your identity. However, we will be pleased to discuss the results with you at the end of the study.

Any further questions that you may have relating to the experiment will be answered in full by either the co-ordinator Prof KH Myburgh (021 808 3149) or the project investigator: Me PC de Bruto (021 808 4564).

**The University of Stellenbosch  
Department Physiological Sciences  
Consent Form**

**Project Title:**

Body composition changes in HIV-positive females after initiating antiretroviral treatment, in comparison with CD4-count matched HIV-positive females not receiving ART.

**STATEMENT BY SUBJECT**

I, the undersigned.....

[ID .....] of .....(address)

**A:** I confirm that:

1. I was invited to participate in the above-mentioned study that is being performed by the Department Physiological Sciences of the University of Stellenbosch.
2. It has been explained to me that:
  - 2.1 The aims of this study will be to determine:  
Changes and associations between body mass and composition, immune parameters, physical activity and quality of life of HIV-positive subjects over the time period of six months.
  - 2.2 The following procedures will be followed:
    - (a) Anthropometrical measurements at each occasion (eight times). These will include skinfold thickness measurements with a Harpenden caliper, body and limb circumferences with a measuring tape and body mass on an electronic scale.
    - (b) Heart rate will be measured with a heart rate monitor. These measurements will be taken while lying down, sitting and standing as well as walking and slow running on a treadmill. This protocol will be performed twice.
    - (c) Ten milliliter blood will be taken on two occasions by a nurse or medical doctor.
    - (d) A short and confidential questionnaire will be completed regularly at home. This takes about ten minutes per occasion.
    - (e) A private and confidential interview will be conducted on three occasions.
    - (f) Computed Tomography scans will be done on two occasions during which I will be exposed to minimal radiation, should I choose to take part in this particular procedure. The radiation dose of each scan is approximately equivalent to that of one X-ray procedure. This procedure is not a prerequisite for participation in the study.
  - 2.3 It is expected that this project would be completed on a total of 50 subjects. The project will ideally be completed over a period of 26 weeks. There will be a total of at least 11 visits to the clinic over a period of 26 weeks. Each visit will last about 1 to 3 hours.
3. I have been informed of any possible side effects, discomfort or risk involved from my participation in this study.
4. All the possible advantages of the study were explained to me.
5. I have been informed that the information collected will be treated as confidential. Every subject and his/her information will be represented by a code and thus no name will be associated with the individual results. The results will be used for a scientific project,

publication and/or thesis, but my identity will not be revealed.

6. Results of the entire project, as well as my own individual results, will be made available to me during/after completion of the project.
7. I have been informed that I may refuse to participate in this study (also that I may discontinue participation at any time) and that such refusal or discontinuation would not be to the disadvantage of my future treatment at this institution. I also understand that the investigator may withdraw myself from the study should he/she feel that it would be in my best interest.
8. No pressure has been placed on me to consent to my participation in this study and I understand that I may withdraw from the study at any time without being penalised.
9. Participation in this study holds no additional costs for me.
10. I understand that it may be known that HIV related research is conducted during the times I visit the Hospital and although my HIV status will be known only to the researchers, I understand that other people may associate me with the HIV related research.
11. I will not hold Drs. Van Wageningen & Partners Inc. responsible for any loss or injury incurred as result of the CT scanning procedure, but I am aware that the University of Stellenbosch has insurance available should loss or injury occur.

**B:** I hereby freely consent to participate in the abovementioned study.

Signed at .....

on ..... 200....

.....  
Subject signature or right thumb print

.....  
Witness

**STATEMENT BY OR ON BEHALF OF INVESTIGATOR**

I, ....., declare that:

1. the information given in this document was explained to ..... (*Name of the patient*) by me;
2. I encouraged him/her/them to ask me any questions should there be anything that was unclear;
3. that this conversation was conducted in Afrikaans/English and that no translator was used/ that this conversation was translated in Xhosa by

Dr/Mr/Mrs.....

Signed at .....on .....200....

.....  
Investigator/investigator's representative      Witness

**\* Delete if not relevant**

**Exercise Science Laboratory  
Department of Physiological Sciences  
University of Stellenbosch.**

**Project Title:**

Body composition changes in HIV-positive females after initiating antiretroviral treatment, in comparison with CD4-count matched HIV-positive females not receiving ART.

**Statement of understanding:**

1. I have read and signed the attached informed consent.
2. I understand I will receive the results of the research I requested.

Signed at ..... on .....200  
.....  
(place) (date)

.....  
.....  
*Signature of patient/participant* *Signature of witness*

**Die Universiteit van Stellenbosch  
Departement Fisiologiese Wetenskappe  
Proefpersoon Inligtingstuk**

**Projektitel:**

Liggaamskomposisie veranderinge van MIV-positiewe vroue met die aanvang van antiretrovirale behandeling.

**Koördineerder:** Prof K H Myburgh

**E-pos:** khm@sun.ac.za

**Projek Navorsers:**

Ms PC de Bruto (Master's student)  
(Supervisors: KH Myburgh, C Smith)

**Telephone:** (021) 808 4564

**Medewerker:**

Dr. Grobbelaar

**Telephone:** (021) 872 1711

U word vriendelik uitgenooi om deel te neem aan 'n navorsingstudie waarvan die doel is om lewenskwaliteit en sekere fisiologiese parameters van MIV-positiewe persone te monitor.

**Agtergrond**

Daar verskeie liggaamlike veranderinge wat kan plaasvind met die aanvang van antiretrovirale behandeling. Liggaamsmassa en vetverspreiding kan verander, asook metaboliese veranderinge wat die lewenskwaliteit en daaglikse aktiwiteitsvlakke kan beïnvloed.

Hierdie studie sal sekere parameters (byvoorbeeld; CD4-telling, massa en liggaamssamestelling (relatiewe vet en spiermassa)) monitor oor ses maande sodat 'n beter begrip van die verloop en impak van die siekte en die behandeling daarvan verkry kan word. Sulke kennis is nodig om effektiewe behandeling te ontwikkel en die verkrygte inligting sal gebruik word om verdere studies te ontwerp met die uiteindelijke doel om suksesvolle programme te ontwikkel en te implimenteer om die lewenskwaliteit van MIV-positiewe persone te verbeter.

**Prosedures**

Die studie sal plaasvind by die T. C. Newman Hospitaal vir gemeenskapsgesondheid, onder toesig van Dr N.Grobbelaar.

Daar sal van u verwag word om die hospitaal op minstens elf geleenthede te besoek. Agt van hierdie besoeke sal met u gereelde kliniekbeseke saamval, dus sal u slegs vir drie ekstra geleenthede na die kliniek toe kom. U sal 'n bedrag van sestig rand ontvang as vergoeding vir die reiskoste vir hierdie drie besoeke.

Indien u besluit om deel te neem, sal die volgende metings en prosedures uitgevoer word by die kliniek:

- 1) Bloedmonsters (een monster van 10 ml – ongeveer twee teelepels – per geleentheid) sal geneem word by die kliniek na drie maande en weer na ses maande.
- 2) Tien velvoudiktes sal geneem word van die volgende areas: trisept (boarm aan die agterkant), subskapulêr (boonste deel van die rug), bisept (boarm aan die voorkant), illiakruin (net bo die heupe aan die sy), supraspinaal (die sy), abdominaal (aan die voorkant), frontale dy (voorkant van die bobeen), mediale kuit (die binnesy van die kuit), midaksilla (die sy, tussen die arm en heup) en pektoraal (aan die voorkant waar die arm en die bors bymekaarkom). Die metings sal met 'n kaliper geneem word, wat die vel

liggies “klem” en ‘n knypgevoel – sonder pyn – word ondervind. Al hierdie metings sal in privaatheid geskied.

- 3) Beide u liggaamsmassa (op ‘n elektroniese massaskaal) en u lengte sal gemeet word. Omtreksmetings (met ‘n maatband) sal geneem word van die boarm, middel, heup, bobeen en kuit).
- 4) U sal gevra word om ‘n vraelys in te vul onder die toesig van een van die navorsers, asook by die huis op gereelde tye. Die navorser sal in ‘n private onderhoud vir u vrae vra ten opsigte van wat u die vorige dag geëet het en wat u normaalweg eet. Alle inligting verkry sal as hoogs vertroulik geag word.
- 5) Daar sal van u verwag word om ‘n oefeningstoets te voltooi op ‘n trapmeul. Die toets op die trapmeul en begin met ‘n stadige stap tempo. Die spoed en helling van die trapmeul sal verstel word en daar sal van u verwag word om die toets te doen tot voor totale uitputting (ongeveer 90% van maksimale vermoë soos bereken deur die navorsers). Die oefentoets sal ongeveer tien tot twintig minute neem. U harttempo sal geneem word voor en tydens die oefentoets. ‘n Mediese dokter sal die toets bystaan.
- 6) Die navorsers stel belang in u energieverbruik, daaglikse aktiwiteit en metaboliese tempo. U sal ‘n harttempo monitor vir drie dae by die huis en werk moet dra, terwyl u voortgaan met normale daaglikse aktiwiteite. Die harttempo monitor pas soos ‘n lyfband om die borskas onder die klere en is nie ongemaklik om te dra nie.

Indien u bereid is, sal rekenaartomografie skandering gedoen word van die middel en bobeen. Die prosedure word uitgevoer in Stellenbosch Medi-Clinic deur ‘n radiograaf en geëvalueer word deur Dr R de Villiers (‘n radioloog). Die radiograaf sal u vooraf inlig omtrent enige nuwe-effekte of gevare betrokke by die skandering. Hierdie skandering sal die navorsers in staat stel om die relatiewe spier- tot vetmassa in die betrokke areas waar te neem. U sal (moontlik saam met ongeveer drie ander projekdeelnemers) na Medi-Clinic geneem word in ‘n bus wat deur die Universiteit gereel word.

Die grootste voordeel van deelname aan hierdie studie is dat u liggaamskomposisie gereeld gemonitor sal word teen geen persoonlike onkoste nie. Aan die einde van die studie sal u inligting verkry omtrent u eetgewoontes en hoe u dit kan verander om u gesondheid te verbeter. Die enigste nadeel wat ons voorsien van deelname aan hierdie studie, is dat u ‘n paar ekstra besoeke aan die kliniek sal moet maak en dat u gereelde besoeke aan die kliniek moontlik effens langer sal neem as gewoonlik. Die enigste risiko is dat u aan ‘n baie klein dosis bestraling blootgestel sal word tydens die neem van die rekenaartomografie skandering, maar hierdie prosedure is nie ‘n vereiste vir deelname aan die studie nie. U kan dus kies om nie aan hierdie spesifieke prosedure deel te neem nie.

‘n Suster of mediese dokter sal bloed vanuit ‘n aar in u voorarm trek by twee geleenthede bykomend tot die geleenthede waarvan die doel diagnose en behandeling is. Tien milliliter bloed (wat ongeveer gelykstaande is aan twee teelepels) sal getrek word per geleentheid. Daar is geen nuwe-effekte nie, behalwe – in sommige gevalle – vir ‘n klein kneusplekkie.

Vyftig MIV-positiewe proefpersone sal deelneem aan hierdie studie.

Hierdie projek is deur die Subkomitee C Etiese komitee van die Universiteit van Stellenbosch geëvalueer en goedgekeur.

### **Belangrik:**

U is vry om te enige tyd van die studie te onttrek sonder om ‘n verskoning te gee. U sal sonder benadeling behandel word, indien u sou besluit om nie deel te neem nie of om te onttrek. Indien u sou onttrek, sal dit nie enige ander aktiwiteite by die hospitaal beïnvloed nie. Toekomstige mediese behandeling sal nie beïnvloed word indien u onttrek uit die studie nie.

Alle inligting aangaande die toetse, jou siekte en die behandeling daarvan, sal as vertroulik hanteer word, en u identiteit sal nie bekend gemaak word met publikasie of met die aanbieding van resultate nie. Nietemin sal ons graag die resultate met u bespreek aan die einde van die studie.

Enige verdere vrae wat u in verband met die eksperiment mag hê, sal ten volle deur die koördineerder Prof K H Myburgh (021 808 3149) of projeknavorser: Me PC de Bruto (021 808 4564) beantwoord word.



**Universiteit van Stellenbosch  
Departement Fisiologiese Wetenskappe  
Toestemmingsvorm**

**Projektitel:**

Liggaamskomposisie veranderinge van MIV-positiewe vroue met die aanvang van antiretrovirale behandeling.

**VERKLARING DEUR DEELNEMER**

Ek, die ondergetekende, .....

[ID .....] van .....(adres)

**A:** Ek bevestig dat:

1. Ek uitgenooi is om deel te neem aan bogemelde navorsingsprojek wat deur die Departement Fisiologiese Wetenskappe van die Universiteit van Stellenbosch onderneem word.
2. Daar aan my verduidelik is dat:
  - 2.1 Die doelwitte van hierdie studie is:

Om die veranderinge en onderlinge verwantskappe van liggaamsmassa, liggaamssamestelling, immuun parameters, fisiese aktiwiteit en lewenskwaliteit van MIV-positiewe deelnemers te monitor oor die tydperk van ses maande.
  - 2.2 Die volgende prosedures sal gevolg word:
    - (a) Antropometriese metings by elke geleentheid (agt keer): Velvoudiktes gemeet met 'n diktemeter, liggaamssomtrekke met 'n maatband, en liggaamsmassa met 'n elektroniese skaal.
    - (b) Harttempo met 'n harttempo monitor en uitgeasemde gasse met 'n gasmasker gekoppel aan 'n gas-analiseerder sal bepaal word. Hierdie metings sal geneem word terwyl 'n lêende, sittende, staande posisie ingeneem word, asook tydens loop en draf op 'n trapmeul. Hierdie protokol word twee keer uitgevoer.
    - (c) Die trek van tien milliliter bloed by twee geleenthede deur 'n suster of mediese dokter.
    - (d) Die invul van 'n kort en vertroulike vraelys by die huis op gereelde tye wat ongeveer tien minute sal neem.
    - (e) 'n Privaat en vertroulike onderhoud by drie geleenthede.
    - (f) Twee geleenthede van rekenaartomografie skandering waartydens ek per geleentheid aan 'n minimale bestralingsdosis, ongeveer gelykstaande aan die dosis van een X-straal prosedure, blootgestel sal word. Hierdie prosedure is nie 'n voorvereiste vir deelname aan die studie nie.
  - 2.3 Dit word verwag dat hierdie projek voltooi sal word met 'n totaal van 50 proefpersone. Ideaal gesien sal die projek oor 'n periode van 26 weke afgehandel word. Daar sal 'n totaal van ten minste 11 besoeke aan die kliniek wees oor 'n periode van 26 weke. Elke besoek sal ongeveer 1 tot 3 uur duur.
3. Ek is ingelig oor enige moontlike nuwe-effekte, ongemak of nadelige effekte van deelname aan hierdie studie.
4. Al die moontlike voordele van die studie is verduidelik.
5. Inligting ingesamel in hierdie studie sal vertroulik wees. Geen naam sal geassosieer word met individuele resultate nie, want elke proefpersoon sal deur 'n nommer onbekend aan hulle verteenwoordig word. Die resultate sal gebruik word vir 'n wetenskaplike werkstuk, publikasie

of tesis, maar my identiteit sal nie bekend gemaak word nie.

6. Tydens/na afhandeling van die projek sal resultate aan my beskikbaar gestel word aangaande die volledige projek, sowel as my eie individuele resultate sodra die projek voltooi is.
7. Ek is meegedeel dat ek mag weier om deel te neem aan hierdie projek (asook dat ek te enige tyd deelname daaraan mag staak) en dat sodanige weiering of staking nie op enige manier my huidige/toekomstige behandeling by hierdie inrigting of die hospitaal sal benadeel nie. Ek verstaan ook dat die navorser my van die projek mag onttrek indien dit in my belang geag word.
8. Daar geen dwang op my geplaas is om toe te stem tot my deelname aan hierdie projek nie en dat ek besef dat ek deelname te enige tyd mag staak sonder enige penalisasie.
9. Deelname aan die projek geen addisionele koste vir my inhou nie.
10. Ek verstaan dat dit bekend mag wees dat daar MIV-verwante navorsing plaasvind in die tye wat ek die kliniek besoek en selfs al is my MIV-status onbekend, begryp ek dat ander persone my mag assosieer met die MIV-verwante navorsing.
11. Ek sal nie Drs. Van Wageningen & Vennote Ing. verantwoordelik hou vir enige verlies of besering as gevolg van die skandering prosedure nie. Ek is wel daarvan bewus dat die Universiteit van Stellenbosch versekering beskikbaar het indien verlies of besering sou plaasvind.

**B** Ek stem hiermee vrywillig in om deel te neem aan die bogemelde projek.

Geteken te ..... op ..... 200....

.....  
Deelnemer se handtekening of regter duimafdruk

.....  
Getuie

#### **VERKLARING DEUR OF NAMENS NAVORSER**

Ek, ....., verklaar dat ek:

1. die inligting vervat in hierdie dokument aan .....(Naam van die deelnemer) verduidelik het;
2. hom/haar/hulle versoek het om vrae aan my te stel indien daar enigiets onduidelik was;
3. dat hierdie gesprek in Afrikaans, Engels, plaasgevind het en dat geen tolk gebruik is nie/\*dat hierdie gesprek in Xhosa getolk is deur

Dr/Mnr/Me.....

Geteken te ..... op .....20....

.....  
Navorser/Navorser se verteenwoordiger

.....  
Getuie

**\* Haal deur indien nie relevant nie**

**Projektitel:**

Liggaamskomposisie veranderinge van MIV-positiewe vroue met die aanvang van antiretrovirale behandeling.

**Verklaring van begrip:**

1. Ek het die aangehegte ingeligte toestemming gelees en geteken.
2. Ek verstaan ek sal die resultate van die navorsing wat ek aangevra het ontvang.

Geteken te ..... op ..... 20.....  
(plek) (datum)

.....  
Handtekening van pasiënt/deelnemer      Handtekening van getuie

## **7.4. Appendix D**

*Quality of life questionnaires:*

***EQ - 5D***

**Health Questionnaire**

**South African English version**

By placing a tick in one box in each group below, please indicate which statements best describe your own state of health TODAY.

**Mobility**

- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

**Self-Care**

- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

**Usual Activities** (*e.g. work, study, housework, family or leisure activities*)

- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

**Pain/Discomfort**

- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

**Anxiety/Depression**

- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

---

Compared with my general  
level of health over the past 12 months,  
my state of health today is:

- Better ☐ PLEASE TICK
- Much the same ☐ ONE

Worse



BOX

To help people say how good or bad their state of health is, we have drawn a scale on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale, in your opinion, how good or bad your own health is today. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your state of health is today.

**Your own  
state of health  
today**

Best  
imaginable  
state of health

100

90

80

70

60

50

40

30

20

10

0

Worst  
imaginable  
state of health

Because all replies are anonymous, it will help us to understand your answers better if we have a little background data from everyone, as covered in the following questions.

1. Have you experienced serious illness?
 

Yes	No	
<i>yourself</i>	<input type="checkbox"/>	<input type="checkbox"/>
<i>in your family</i>	<input type="checkbox"/>	<input type="checkbox"/>
<i>while caring for others</i>	<input type="checkbox"/>	<input type="checkbox"/>

PLEASE TICK  
APPROPRIATE  
BOXES
  
2. What is your age in years ?
  
3. Are you male or female?
 

Male	Female	
<input type="checkbox"/>	<input type="checkbox"/>	

PLEASE TICK  
APPROPRIATE  
BOX
  
4.
 

<i>I smoke</i>	<input type="checkbox"/>	
<i>I used to smoke</i>	<input type="checkbox"/>	
<i>I have never smoked</i>	<input type="checkbox"/>	

PLEASE TICK  
APPROPRIATE  
BOX
  
5. Do you now, or did you ever, work in health services or social welfare?
 

Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	

PLEASE TICK  
APPROPRIATE  
BOX

If so, in what capacity? .....
  
6. Which of the following best describes your main activity?
 

<i>self employed</i>	<input type="checkbox"/>	
<i>in formal employment</i>	<input type="checkbox"/>	
<i>retired</i>	<input type="checkbox"/>	
<i>homemaker/domestic worker</i>	<input type="checkbox"/>	
<i>student</i>	<input type="checkbox"/>	
<i>seeking work</i>	<input type="checkbox"/>	
<i>other (please specify)</i>	<input type="checkbox"/>	.....
  
7. What was the highest grade that you attained at school?
  
8. Do you have a diploma or equivalent?
 

Yes	No	
<input type="checkbox"/>	<input type="checkbox"/>	

PLEASE TICK  
APPROPRIATE  
BOX
  
9. If you know the area/suburb in which you stay, please write it here.....



# ***EQ - 5D***

**Gesondheidsvraelys**

**Afrikaanse veergawe**  
***(Afrikaans version)***

Dui asseblief aan watter stellings u eie gesondheidstoestand vandag die beste beskryf deur 'n regmerk in een blokkie by elkeen van die onderstaande groepe te maak.

### **Beweeglikheid**

Ek het geen probleme om rond te loop nie ☐

Ek het sommige probleme om rond te loop ☐

Ek is beperk tot die bed ☐

### **Selfversorging**

Ek het geen probleme om myself te versorg nie ☐

Ek het sommige probleme om myself te was of aan te trek ☐

Ek is nie in staat om myself te was of aan te trek nie ☐

### **Gewone Aktiwiteite** (bv. werk, studeer, huiswerk, familie- of ontspanningsaktiwiteite)

Ek het geen probleme om my gewone aktiwiteite uit te voer nie ☐

Ek het sommige probleme om my gewone aktiwiteite uit te voer ☐

Ek is nie in staat om my gewone aktiwiteite uit te voer nie ☐

### **Pyn/ Ongemak**

Ek het geen pyn of ongemak nie ☐

Ek het matige pyn of ongemak ☐

Ek het uiterste pyn of ongemak ☐

### **Angstigheid/ Neerslagtigheid**

Ek is nie angstig of neerslagtig nie ☐

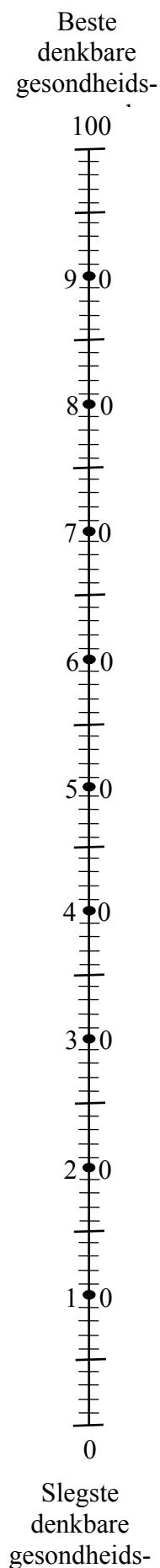
Ek is matig angstig of neerslagtig ☐

Ek is uiters angstig of neerslagtig ☐

Om mense te help om te sê hoe goed of sleg hul gesondheidstoestand is, het ons 'n skaal (baie soos 'n termometer) geteken waarop die beste gesondheidstoestand wat u u kan verbeel, gemerk is met 100 en die slegste gesondheidstoestand wat u u kan verbeel, gemerk is met 0.

Ons wil graag hê dat u op hierdie skaal aandui hoe goed of sleg u eie gesondheid vandag na u mening is. Doen dit asseblief deur 'n streep te trek vanaf die blokkie hieronder (waar dit sê: “u eie gesondheidstoestand vandag”) tot by enige punt op die skaal wat aandui hoe goed of sleg u gesondheidstoestand vandag is.

**U eie**  
gesondheids-  
toestand  
vandag



Omdat alle antwoorde naamloos is, sal dit ons help om u antwoorde beter te verstaan indien ons 'n bietjie agtergrondinligting oor almal het, soos in die volgende vrae gedek.

1. Het u ernstige siekte ondervind?	Ja	Nee	
<i>in uself</i>	<input type="checkbox"/>	<input type="checkbox"/>	MERK ASSEBLIEF TOEPASLIKE BLOKKIES
<i>in u familie</i>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>in die versorging van andere</i>	<input type="checkbox"/>	<input type="checkbox"/>	
2. Wat is u ouderdom in jare?	<input type="text"/>		
3. Is u:	Manlik	Vroulik	MERK ASSEBLIEF TOEPASLIKE BLOKKIE
	<input type="checkbox"/>	<input type="checkbox"/>	
4. Is u:			MERK ASSEBLIEF TOEPASLIKE BLOKKIE
<i>'n huidige roker</i>	<input type="checkbox"/>		
<i>'n voormalige roker</i>	<input type="checkbox"/>		
<i>iemand wat nog nooit gerook het nie</i>	<input type="checkbox"/>		
5. Werk u nou, of het u ooit in die gesondheids- of maatskaplike dienste gewerk?	Ja	Nee	MERK ASSEBLIEF TOEPASLIKE BLOKKIE
Indien wel, in watter hoedanigheid? .....	<input type="checkbox"/>	<input type="checkbox"/>	
6. Watter van die volgende beskryf u hoofaktiwiteit die beste?			MERK ASSEBLIEF TOEPASLIKE BLOKKIE
<i>in diens wees of vir uself werk</i>	<input type="checkbox"/>		
<i>afgetree</i>	<input type="checkbox"/>		
<i>huiswerk</i>	<input type="checkbox"/>		
<i>student</i>	<input type="checkbox"/>		
<i>soek werk</i>	<input type="checkbox"/>		
<i>ander (spesifiseer asseblief)</i>	<input type="checkbox"/>	.....	
7. Het u onderwys voortgegaan na die minimum skoolverlatersouderdom (15 jaar oud / Graad 9 / Standaard 7)?	Ja	Nee	MERK ASSEBLIEF TOEPASLIKE BLOKKIE
	<input type="checkbox"/>	<input type="checkbox"/>	
8. Het u 'n graad of 'n diploma?	Ja	Nee	MERK ASSEBLIEF TOEPASLIKE BLOKKIE
	<input type="checkbox"/>	<input type="checkbox"/>	
Indien u u poskode ken, sal u dit asseblief hier neerskryf			
<input type="text"/>			

# ***EQ - 5D***

**Iphepha lemibuzo ngezempilo**

**(Inguqulelo yesiXhosa saseMzantsi Afrika  
*Xhosa Version*)**

Beka uphawu kwibhokisi ibenye kwiqela ngalinye echaza imeko yempilo yakho namhlanje, kwezi bhokisi zilandelayo.

**Musa ukuphawula ngaphezulu kwebhokisi enye kwiqela ngalinye.**

***Ukuhamba***

- Andinangxaki zokuhamba ☐
- Ndinazo ingxakana zokuhamba ☐
- Ndingumlwelwe obopheleleke ebhedini ☐

***Ukuzinonophela isiqu***

- Andinangxaki zokuzinonophela ☐
- Ndinazo ingxakana zokuhlamba okanye ukuzinxibisa ☐
- Andikwazi ukuzihlamba okanye ukuzinxibisa ☐

**Izinto zesiqhelo** (Umsebenzi, Ukufunda izifundo

Umsebenzi wasekhaya, Usapho, Ezolonwabo)

- Andinangxaki nokuzenzela izinto zesiqhelo ☐
- Ndinazo iingxakana zokuzenzela izinto zesiqhelo ☐

**Andikwazi kuzenzela izinto zesiqhelo**



***Iintlungu / Ukungaziva kakuhle***

- Andinazintlungu okanye ukungaziva kakuhle ☐
- Ndinentlungwana okanye ukungaziva kakuhle okungephi ☐
- Ndinentlungu ezigqithileyo okanye ukungaziva kakuhle okugqithileyo ☐

***Ukuxhalaba / Ukudakumba***

- Andinaxhala okanye andidakumbanga ☐
- Ndibuxhalaba okanye ndibudakumba ☐
- Ndixhalabe gqitha okanye ndidakumbe gqitha ☐

**Xa ndithelekisa umgangatho wobunjani**

bempilo yam jikelele kwezi nyanga  
 zili-12 zidlulileyo imeko yempilo yam  
 namhlanje:

Eyona meko entle  
 yempilo onokuyiqikelela

Ingcono  
 Ibufana  
 Imandundu

☐ Phawula
 ☐ ibhokisana
 ☐ efanelekileyo

Ukunceda abantu ukuze baxele okokuba imeko yabo yempilo intle okanye imandundu na sizobe isikali (esifana nethemometha). Eyona meko entle yempilo iphawulwe ngo-100, eyona meko imandundu iphawulwe ngo-0.

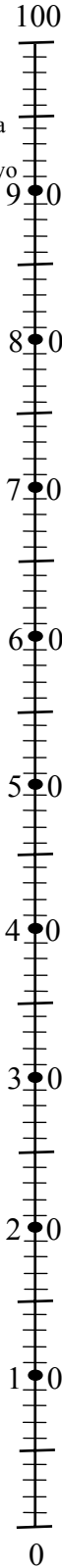
Singathanda ubonise kwesi sikali ngokoluvo lwakho ukuba impilo yakho intle okanye imandundu kangakanani namhlanje.

Nceda wenze oku ngokuzoba umgca osuka ebhokisini engezantsi ukuya kulo ndawo esikalini ibonisa ukuba imeko yempilo yakho intle okanye imbi kangakanani namhlanje.

Imeko yempilo yakho namhlanje

>

Ibhokisi



Eyona meko imandundu yempilo

Njemgoko kunganyanzelekanga ukuba ubhale igama lakho, kodwa ke kuyakunsinceda siqonde ngcono iimpemduko ukuba sinolwazana lwemvelaphi kulowo nalowo umntu njengoko zichatshazelwe kule mibuzo ilandelayo

- |  |                          |                          |                                    |
|--|--------------------------|--------------------------|------------------------------------|
| 1. Ukhe wabanamava okugula kakhulu na? | Ewe                      | Hayi                     |                                    |
| Wena                                   | <input type="checkbox"/> | <input type="checkbox"/> |                                    |
| Kusapho lwakho                         | <input type="checkbox"/> | <input type="checkbox"/> | Phawula ibhokisana ezifanelekileyo |
| Xa ukhathalele abanye                  | <input type="checkbox"/> | <input type="checkbox"/> |                                    |

2. Mingaphi iminyaka yakho?

- |       |                          |                          |                                  |
|-------|--------------------------|--------------------------|----------------------------------|
| 3. U- | Yindoda                  | Libhinqa                 |                                  |
|       | <input type="checkbox"/> | <input type="checkbox"/> | Phawula ibhokisana efanelekileyo |

- |                            |                          |  |                                  |
|----------------------------|--------------------------|--|----------------------------------|
| 4. Uyatshaya               | <input type="checkbox"/> |  |                                  |
| Wawutshaya                 | <input type="checkbox"/> |  |                                  |
| Ungumntu ongazange atshaye | <input type="checkbox"/> |  | Phawula ibhokisana efanelekileyo |

- |   |                          |                          |                                  |
|---|--------------------------|--------------------------|----------------------------------|
| 5. Usebenza, okanye ukhe wasebenza kwiinkonzo zezempilo okanye ezentlalontle? | Ewe                      | Hayi                     |                                  |
|   | <input type="checkbox"/> | <input type="checkbox"/> | Phawula ibhokisana efanelekileyo |

Ubusenzani?.....

- |  |                          |  |                                  |
|--|--------------------------|--|----------------------------------|
| 6. Koku kulandelayo kokuphi okuchaza ngcono okwenzayo? |                          |  |                                  |
| Uyaphangela okanye uyazisebenzela                      | <input type="checkbox"/> |  |                                  |
| Udla umhlalaphantsi                                    | <input type="checkbox"/> |  |                                  |
| Umsebenzi wasekhaya                                    | <input type="checkbox"/> |  | Phawula ibhokisana efanelekileyo |
| Umfundi  | <input type="checkbox"/> |  |                                  |
| Ufuna umsebenzi  | <input type="checkbox"/> |  |                                  |
| Okunye (Chaza)   | <input type="checkbox"/> |  |                                  |

7. Leliphi ibanga ofikelele kulo esikolweni?.....

- |                                |                          |                          |                                  |
|--------------------------------|--------------------------|--------------------------|----------------------------------|
| 8. Unesidanga okanye i-diploma | Ewe                      | Hayi                     |                                  |
|                                | <input type="checkbox"/> | <input type="checkbox"/> | Phawula ibhokisana efanelekileyo |

9. Ukuba uyayazi ikhowudi yeposi yakho nceda uyibhale apha



## Modified QoL questionnaire - English

By placing a tick in one box in each group below, please indicate which statements best describe your own state of health TODAY.



**Mobility**

**1**

- ☐ I have no problems in walking about
- ☐ I have some problems in walking about
- ☐ I am confined to bed



**Self-Care**

**2**

- ☐ I have no problems with self-care
- ☐ I have some problems washing or dressing myself
- ☐ I am unable to wash or dress myself



**Usual Activities**

**3**

(e.g. work, study, housework, family or leisure activities)

- ☐ I have no problems with performing my usual activities
- ☐ I have some problems with performing my usual activities
- ☐ I am unable to perform my usual activities



**Pain/Discomfort**

**4**

- ☐ I have no pain or discomfort
- ☐ I have moderate pain or discomfort
- ☐ I have extreme pain or discomfort

**Anxiety/Depression**

**5**

- ☐ I am not anxious or depressed
- ☐ I am moderately anxious or depressed
- ☐ I am extremely anxious or depressed

Best  
imaginable  
state of health

100

**6**

90

80

70

60

50

40

30

20

10

0

Worst  
imaginable  
state of health

## Modified QoL questionnaire - Afrikaans

Dui asseblief aan watter stellings u eie gezondheidstoestand VANDAG die beste beskryf deur 'n regmerk in een blokkie by elkeen van die onderstaande groepe te maak.



### Beweeglikheid 1

- ☐ Ek het geen probleme om rond te loop nie
- ☐ Ek het sommige probleme om rond te loop
- ☐ Ek is beperk tot die bed



### Selfversorging 2

- ☐ Ek het geen probleme om myself te versorg nie
- ☐ Ek het sommige probleme om myself te was of aan te trek
- ☐ Ek is nie in staat om myself te was of aan te trek nie



### Gewone Aktiwiteite 3

(bv. werk, studeer, huiswerk, familie- of ontspanningsaktiwiteite)

- ☐ Ek het geen probleme om my gewone aktiwiteite uit te voer nie
- ☐ Ek het sommige probleme om my gewone aktiwiteite uit te voer
- ☐ Ek is nie in staat om my gewone aktiwiteite uit te voer nie



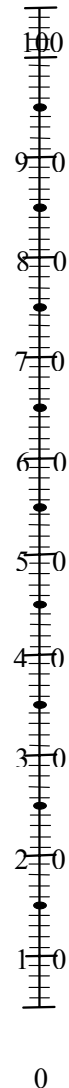
### Pyn/ Ongemak 4

- ☐ Ek het geen pyn of ongemak nie
- ☐ Ek het matige pyn of ongemak
- ☐ Ek het uiterste pyn of ongemak

### Angstigheid/ Neerslagtigheid 5

- ☐ Ek is nie angstig of neerslagtig nie
- ☐ Ek is matig angstig of neerslagtig
- ☐ Ek is uiters angstig of neerslagtig

Beste denkbare  
gesondheidstoestand



Slegste denkbare  
gesondheidstoestand

## Modified QoL questionnaire - Xhosa

Beka uphawu kwibhokisi ibenye kwiqela ngalinye echaza imeko yempilo yakho namhlanje, kwezi bhokisi zilandelayo.

**Musa ukuphawula ngaphezulu kwebhokisi enye kwiqela ngalinye.**



**Ukuhamba**

**1**

- ☐ Andinangxaki zokuhamba
- ☐ Ndinazo ingxakana zokuhamba
- ☐ Ndingumlwelwe obopheleleke ebhedini



**Ukuzinonophela isiqu**

**2**

- ☐ Andinangxaki zokuzinonophela
- ☐ Ndinazo ingxakana zokuhlamba okanye ukuzinxibisa
- ☐ Andikwazi ukuzihlamba okanye ukuzinxibisa



**Izinto zesiqhelo**

**3**

(Umsebenzi, Ukufunda izifundo

Umsebenzi wasekhaya, Usapho, Ezolonwabo)

- ☐ Andinangxaki nokuzenzela izinto zesiqhelo
- ☐ Ndinazo iingxakana zokuzenzela izinto zesiqhelo
- ☐ Andikwazi kuzenzela izinto zesiqhelo



**Iintlungu / Ukungaziva kakuhle**

- ☐ Andinazintlungu okanye ukungaziva kakuhle
- ☐ Ndinentlungwana okanye ukungaziva kakuhle okungephi
- ☐ Ndinentlungu ezigqithileyo okanye ukungaziva kakuhle okugqithileyo

**Ukuxhalaba / Ukudakumba**

**5**

- ☐ Andinaxhala okanye andidakumbanga
- ☐ Ndibuxhalaba okanye ndibudakumba
- ☐ Ndixhalabe gqitha okanye ndidakumbe gqitha

Eyona meko entle yempilo anokuyilona

**6**

100

90

80

70

60

50

40

30

20

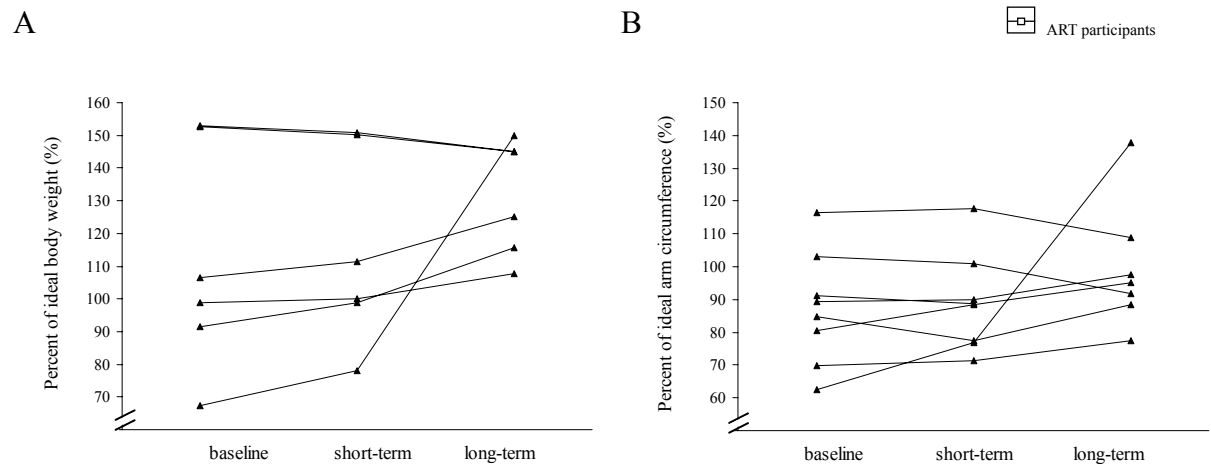
10

0

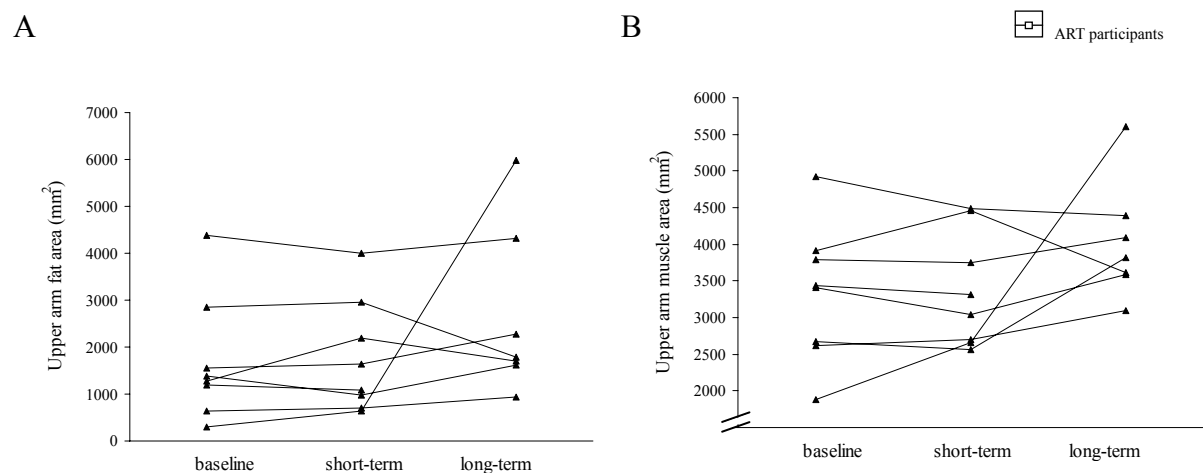
Eyona meko imandundu yempilo

## 7.5. Appendix E

The individual changes of ART participants for some variables that relate to nutritional status are shown in the graphs below.



**Figure vi:** Individual data-points of %IBW and %IAC for the ART group at baseline, short term and long-term time points.



**Figure vii:** Upper arm fat (UAFA) and muscle (UAMA) areas as individual data-points for the ART group at baseline, short term and long-term time points.



## 8. References

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