THE IMPACT OF HIV INFECTION ON THE PHYSICAL ACTIVITY LEVELS, FUNCTIONAL INDEPENDENCE AND EXERCISE CAPACITY IN A GROUP OF SOUTH AFRICAN ADULTS TAKING OR NOT TAKING ANTIRETROVIRAL MEDICATION

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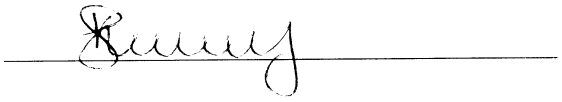
Declaration

I, Kirsten Liza Kinsey, declare that this dissertation is my own work. It is being submitted for the degree of Master of Science (Medicine) in Applied Physiology in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



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Publications and Presentations

Part of this work in support of this dissertation has appeared in the proceedings of the 34th Meeting of The Physiological Society of South Africa (September 2006).

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Abstract

Human Immunodeficiency Virus (HIV), a chronic medical condition characterized by cycles of wellness and illness, has the potential to decrease the physical activity levels and functional independence of infected individuals. Although antiretroviral therapy has been credited with improving and maintaining the immune status of infected patients by increasing cluster of differention 4 (CD4) count and suppressing viral load, the short- and long-term side effects of antiretroviral medication and the possible negative impact of these side effects on physical well-being have not yet been fully investigated. Therefore, I assessed the relationship between CD4 count, habitual physical activity levels and functional independence in a group of HIV positive South African adults either taking or not taking antiretroviral medication. I also compared the aerobic capacity, muscle strength and physical activity levels (activity counts) of age-matched black HIV negative females and HIV positive females who were taking antiretroviral medication.

For the first part of the study, a Lifestyle and Physical Activity Questionnaire was completed by 186 black* male and female HIV positive outpatients who were recruited from a Johannesburg based antiretroviral roll out site. Of these patients, 121 were on first line antiretroviral treatment (median time of seven months), and 65 patients were not taking any medication. The questionnaire, as well as recording HIV history and current CD4 count, assessed each patient's ability to independently perform one or more tasks of daily living as well as his/her monthly occupational, household and recreational physical activity levels. From the subjects' responses, a total metabolic equivalent (MET) score for one month was calculated. The second part of the study assessed the full blood counts, aerobic capacity (submaximal bicycle ergometer test), lower limb strength (isokinetic dynamometry), hand grip strength (hand dynamometer) and seven day physical activity counts (actigraphy) of ten HIV positive black females recruited from the same Johannesburg antiretroviral roll out site. All of these patients had been taking first line antiretroviral treatment for a median time period of seven months. Ten HIV negative age-matched black females acted as their controls.

From the questionnaire, significant correlations were observed between CD4 count and length of time on antiretroviral medication ($P < 0.0001$; r = 0.45), and between CD4 count and total monthly physical activity level ($P = 0.0067$; r = 0.20). Patients who considered themselves functionally independent had a significantly higher CD4 count that those patients who required help from others ($P = 0.0031$). The second part of the study revealed no significant difference in aerobic capacity, lower limb muscle strength (peak torque), handgrip strength and seven day physical activity counts between the female HIV positive patients and HIV negative controls.

My results show that the use of antiretroviral medication (median time of seven months) increases CD4 count which translates into an increased habitual physical activity level and greater sense of functional independence. I have also shown that HIV positive females who are taking antiretroviral medication have an aerobic capacity, leg strength, handgrip strength and physical activity count which is not statistically different to their HIV negative counterparts. In this sample, the side effects associated with the administration of antiretroviral medication did not negatively impact on physical well-being. However, more research needs to be conducted on the possible physical activity limiting side effects of longer term antiretroviral medication administration, which may limit habitual physical activity levels.

* Footnote: Race does not refer to any biological attributes but rather to the compulsory classification of people into the Population Registration Act. Although the act has been amended, these categories are still powerful and commonly used by the South African Government and statistical services.

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List of Abbreviations

3TC	Lamivudine
AIDS	Acquired Immune Deficiency Syndrome
ARV	Antiretroviral
AWS	AIDS Wasting Syndrome
AZT	Zidovudine
CD4	Cluster of differention 4
CNS	Central Nervous System
D4T	Stavudine
ddl	Didanosine
DoH	Department of Health
EE	Energy expenditure
EFV	Efavirenz
HAART	Highly Active Antiretroviral Therapy
HDL	High Density Lipoproteins
HIV	Human Immunodeficiency Virus
LPV	Lopinavir
MET	Multiple of average resting metabolic rate
NNRTI	Non-nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NVP	Nevirapine
PA	Physical activity
PCP	*Pneumocystis carinii* pneumonia
PI	Protease Inhibitor
RTV	Ritonavir
SA	South Africa
SSA	Statistics South Africa
TB	Tuberculosis
UNAIDS	Joint United Nations Programme on HIV/AIDS
WHO	World Health Organisation

Chapter 1 – Introduction

1.1 Literature Review

Human immunodeficiency virus (HIV) is a human retrovirus and is believed to be the causative organism of Acquired Immune Deficiency Syndrome (AIDS) (Griffen, 2003; Fauci *et al.*, 1994). First being identified in 1981, HIV continues to be a rapidly growing epidemic, with approximately 37.8 million people worldwide living with the disease (UNAIDS, 2004). The World Health Organisation (WHO) estimated that 40.3 million people were living with HIV disease at the end of 2005 (WHO, 2006). This number continues to grow, regardless of improvements in treatment and prevention campaigns.

HIV and AIDS is a pandemic with cases reported from every continent (Fauci *et al.*, 1994). However, sub-Saharan Africa has the highest incidence of HIV/AIDS in the world. In 2003, an estimated 2.3 million people in this region died of HIV/AIDS. At the same time an estimated 3.2 million people acquired the infection in the same area (Stewart *et al.*, 2004). The Joint United Nations Programme on HIV/AIDS (UNAIDS) and WHO estimated that 25.8 million people in the sub-Saharan region were living with HIV at the end of 2005 (WHO, 2006). However, it is thought that the percentage of adults infected with HIV in this region has remained stable in recent years (UNAIDS, 2004).

1.1.1 HIV in South Africa

At the end of 2002, it was estimated that there were 5.3 million South Africans living with HIV, with a population prevalence rate of 21.5% (UNAIDS, 2004). South Africa (SA) is said to have a higher population of people infected with HIV than any other country (WHO, 2006). By February 2003, approximately 30 000 people were receiving antiretroviral (ARV) treatment. Provision was mainly to individuals who had medical aid coverage through the private health sector and to some individuals receiving treatment through non-profit organizations (Stewart *et al.*, 2005). It was further estimated that approximately 500 000 South Africans

had AIDS defining illnesses and were in need of ARV treatment. In November 2003, the South African government released their "Operational Plan for Comprehensive HIV and AIDS Care and Treatment". The Operational Plan focuses on providing comprehensive care, including ARV medication in order to provide care to all South Africans and permanent residents who require it. This plan outlines a multi-sector response to the epidemic, and recognizes the crucial role of ARVs in the treatment of people with HIV/AIDS (Stewart *et al.*, 2005). By August 2004, the Department of Health (DoH) estimated that ARV treatment was being provided to 11 253 patients, with the number increasing substantially to 19 500 patients by the end of October 2004. The Department of Health indicated that almost 30 000 patients were on treatment by February 2005 (Stewart *et al.*, 2005). However, it is unclear whether these figures include both private and public health sectors. Also, these figures provided by the Department of Health differ considerably from the estimates reported by WHO. At the end of 2004, WHO estimated that between 40 000 and 67 000 South Africans were receiving treatment (Dorrington *et al.*, 2004). It was also stated that the number of individuals receiving ARV treatment rose to between 178 000 and 235 000 by the end of 2005 (WHO, 2006). The exact number of people receiving ARV treatment in SA is still unknown. From the information released by the Department of Health it is estimated that only approximately 21,5% HIV positive individuals in SA were receiving treatment at the end of 2004. Due to the lack of access to ARV medication, it might be worth considering alternative therapies for increasing wellness and quality of life in HIV positive individuals not receiving ARV medication.

1.1.2 Clinical symptoms of HIV infection

HIV disease is characterized by a large immunodeficiency caused by a progressive quantitative and qualitative loss of the CD4 subset of T lymphocytes (Eichner *et al.*, 1994; Fauci *et al.*, 1994). Although the CD4 T cell is the predominant cell type that is infected with HIV, almost any human cell which expresses the CD4 molecule is capable of binding to and becoming infected with

HIV. The decline in the CD4 cell count results in an increased loss of integrity of the immune system and the development of a wide variety of clinical signs and symptoms.

It was recognized early that CD4 T cells are the main targets of HIV infection and that a substantial reduction in the number of CD4 cells is required for the development of AIDS (Fahey *et al.*, 1990). HIV disease can therefore be divided into specific stages on the basis of the amount of immunosuppression. These stages are an early stage (CD4 cell count > 500 cells per mm^3), an intermediate stage (CD4 cell count between 200 and 500 cells per mm^3), and an advanced stage (CD4 cell count < 200 cells per mm^3) (Fauci *et al.*, 1994). In early HIV infection, immunological status (i.e., CD4 cell count) is one of several factors that have been established as prognostic of risk for progression to AIDS (Chlebowski *et al.*, 1989). The majority of AIDS defining opportunistic infections occur within the advanced stage.

WHO classifies HIV/AIDS into four clinical stages (WHO, 2005), based on signs and symptoms with which HIV positive patients present. These four clinical stages are shown in Table 1.1.

The staging system below relies more on clinical conditions for classification of HIV. For the purposes of this text, separate sections will deal with primary infection, asymptomatic latent disease, symptomatic latent disease and AIDS.

Table 1.1 Summary of World Health Organisation (WHO) Clinical Staging of HIV/AIDS for adults and adolescents (adapted from Department of Health, 2003: Standard Treatment Guidelines and Essential Drugs List for South Africa).

Primary HIV Infection - Seroconversion

Asymptomatic

Acute retroviral syndrome (flu-like illness)

Clinical stage 1

Asymptomatic for approximately 8 – 10 years

HIV replication rate is high but immune system still capable of containing the infection

Persistent generalized lymphadenopathy (PGL)

Performance Scale 1: asymptomatic, normal activity

Clinical stage 2

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

Minor mucocutaneous manifestations (recurrent oral ulcerations, fungal nail infections)

Recurrent respiratory tract infections

Herpes zoster within last five years

Performance scale 2: symptomatic, normal activity

Clinical stage 3

Conditions where a presumptive diagnosis can be made of clinical signs or simple investigations

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

Unexplained chronic diarrhea for longer than one month

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

Oral candidiasis

Pulmonary tuberculosis (TB) diagnosed in last two years

Severe presumed bacterial infections (e.g. pneumonia, meningitis)

Conditions where confirmatory diagnostic testing is necessary

Unexplained anemia (< 8g/dl) and or neutropenia (< 500/mm3) and thrombocytopenia (< 50 000/mm^3) for more than one month

Performance Scale 3: bedridden less than 50% of the day during the last month

Clinical stage 4

Conditions where a presumptive diagnosis can be made of clinical signs or simple investigations

HIV wasting syndrome: body mass loss of more than 10% of body body mass, plus either the following persisting for more than one month: Unexplained chronic diarrhea, chronic weakness, unexplained prolonged fever

Recurrent severe or radiological bacterial pneumonia

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

Extrapulmonary TB

Kaposi's sarcoma

Conditions where confirmatory diagnostic testing is necessary

Extrapulmonary cryptococcosis including meningitis

Disseminated non-tuberculous mycobacteria infection

Progressive multifocal leukoencephalopathy (PML)

Performance scale 4: bedridden for more than 50% of the day during the last month

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1.1.3 Opportunistic infections associated with HIV

HIV disease may present with opportunistic or secondary infections due to lowered immune competence (Kotler *et al.*, 1985). These infections are a late complication of HIV infection, for the most part occurring in patients with a CD4 cell count of less than 200 cells per mm^3 (Fauci *et al.*, 1994). Opportunistic infections are the leading cause of morbidity and mortality in patients infected with HIV.

Virtually every organ system in the body is vulnerable to disease either as a direct consequence of HIV infection, or secondary to other infections or neoplastic conditions (Fauci *et al.*, 1994). While the majority of these diseases are due to opportunistic infections, there are also a variety of clinical problems for which no specific pathogens are clearly identified. Pulmonary disease is seen in virtually every patient. Pneumonia is the most common manifestation of pulmonary disease. Sinusitis is a common respiratory tract complication of HIV disease, and is seen at all stages of infection. Gastrointestinal disease is a common feature of HIV infection and is most frequently due to a secondary infection. Infections of the small and large intestine are among the most significant gastrointestinal

problems in HIV infected individuals and usually present with diarrhoea, abdominal pain, occasional fever, and in severe cases, body mass loss.

Pneumocystis carinii is one of the most common infections associated with advanced HIV infection (Wilkin *et al.*, 1999; Fauci *et al.*, 1994). Another protozoal infection associated with HIV is toxoplasmosis, the most common secondary central nervous system (CNS) infection in patients with advanced HIV disease or AIDS (Fauci *et al.*, 1994). Tuberculosis (TB) is a common bacterial opportunistic infection with HIV (Grimwood, 2004). TB is likely the leading cause of death among HIV-infected persons (Stewart *et al.*, 2004; Department of Health, 2003). TB accounted for an estimated 30% of all AIDS related deaths in 1999 (Statistics SA, 2005). Fungal infections include oral and vaginal *Candida* (thrush). These types of infections are seen early in the course of HIV infection, indicating the onset of clinically apparent immunodeficiency (Fauci *et al.*, 1994). A variety of neoplastic and premalignant diseases occur with increased frequency in HIV infected patients, including Karposi's sarcoma and lymphoma (Fauci *et al.*, 1994).

Hematological problems, such as anemia, neutropenia and thrombocytopenia, are common throughout the course of HIV infection and occur as a direct result of HIV, as a manifestation of opportunistic infections and as a side effect of therapy (Fauci *et al.*, 1994). Renal disease may be associated with HIV infection, and although it is often the result of a drug-induced injury, a significant portion of patients infected with HIV develop renal disease. This type of renal disease is designated as HIV-associated nephropathy. Dermatological problems include seborrheic dermatitis, eosinophilic pustular folliculitis, and several minor cutaneous infections.

Prophylactic medication is used to treat opportunistic infections (Griffen, 2003). The following conditions are indicated before opportunistic infections can be treated with prophylactics (DoH, 2003):

- WHO Clinical stage 3 or 4 for HIV infection and disease in adults and adolescents
- CD4 cell count less than 200 cells per mm^3

Prophylaxis is discontinued if the CD4 cell count increases to more than 200 cells per mm^3 on ARV therapy (DoH, 2003).

1.1.4 Physiology of HIV infection

HIV infection is associated with various physiological symptoms or manifestations. As the disease progresses, various metabolic syndromes are observed (Stringer *et al.*, 2001). These syndromes include body mass loss and muscle wasting and are discussed below. Some metabolic syndromes can be attributed to use of ARV medication.

Severe body mass loss and body wasting is a major component of HIV infection (Hellerstein *et al.*, 1990; Chlebowski *et al.*, 1989; Kotler *et al.*, 1985). In HIV infection, each component of the energy-balance equation (caloric intake, total energy expenditure (EE), resting EE, dietary expenditure and energy expended in activity) may be disturbed (Grunfeld *et al.*, 1992). Opportunistic infections and their associated symptoms (including anorexia, nausea, vomiting, malabsorption, and diarrhea) limit food intake and intensify resting energy demands, increasing nutritional needs (DoH, 2003), so that body mass cannot be maintained. The effect of the wasting process on morbidity plays a major role in the decreased quality of life of these patients (Hellerstein *et al.*, 1990). For undernourished HIV-infected people, the resulting trend of inadequate nutritional intake, inability to maintain body mass and lean tissue mass, micronutrient deficiency and increased susceptibility to opportunistic infections accelerates the development of AIDS (DoH, 2003).

AIDS wasting syndrome (AWS) is defined as the loss of body mass from decreased calorie intake, decreased appetite, and starvation. AWS is diagnosed when there is an involuntary loss of greater than ten percent body mass (Stringer

et al., 2001). Loss of body mass from inadequate calorie intake usually occurs during serious opportunistic infections when appetite is impaired. Increased production of cytokines (such as tumor necrosis factor, which has been associated with the presence of severe infections and may result in abnormal metabolism) has also been suggested to contribute to malnutrition and subsequent body mass loss (Grunfeld *et al.*, 1992; Chlebowski *et al.*, 1989). Diarrhoea and malabsorption are additional contributory factors common to AWS.

Severe body mass loss is a major component of the clinical syndrome in patients with HIV (Chlebowski *et al.*, 1989). Body mass loss of more than ten percent of pre-infection body mass during the course of HIV infection is associated with increased mortality and adverse outcomes (Stringer *et al.*, 2001; Bhasin *et al.*, 2000; Kotler *et al.*, 1985). However, lean body mass loss is a more reliable estimate of the degree of wasting than is body mass (Grunfeld *et al.*, 1993). Body fat content is not a reliable marker of wasting as some patients may lose lean body mass with little loss of fat (Grunfeld *et al.*, 1992).

Cachexia is defined as the loss of lean body mass despite adequate or even increased caloric intake and is likely to be associated with hypermetabolism inflammation caused by increased levels of cytokines (Grunfeld *et al.*, 1992). Resting energy expenditure (EE) or metabolic rate is increased during acute infection and is thought to significantly contribute to body mass loss (Grunfeld, *et al.*, 1992). It has been concluded that the loss of lean body mass in men infected with HIV is dependent on the percentage body fat before the body mass loss (Forrester *et al.*, 2002). This type of loss of lean body mass, especially muscle, is associated with active viral replication and opportunistic infections, and can be treated with appropriate ARV therapy (Stringer *et al.*, 2001).

Sarcopenia, also called muscle wasting, occurs with AWS and cachexia and results in decreased lean body mass. Sarcopenia can also result from muscle myopathy caused by the effect of a specific ARV treatment called nucleoside reverse transcriptase inhibitors (NRTIs) on mitochondrial function. Sarcopenia

can also result from myositis or it may be related to an HIV-induced myopathy (Stringer *et al.*, 2001).

Decreased muscle mass causes a decrease in the overall functional status of HIV infected individuals, including decreased exercise performance, aerobic capacity and lower-body muscle strength (Grinspoon *et al.*, 1996). Weakness and fatigue are among the most troubling and debilitating symptoms reported by these patients (Hellerstein *et al.*, 1990). Inactivity and the accompanying symptoms also lead to a decrease in muscle mass and the inability to restore muscle mass after bouts of wasting, resulting in a loss of functional capacity. Therefore, the role of regular exercise in preventing this loss of lean body mass, and subsequent functional capacity, becomes more important. Physical activity (PA) is required for the maintenance of muscle mass (Grunfeld *et al.*, 1992), as it prevents the loss of muscle function that accompanies a sedentary lifestyle (Jones *et al.*, 2001). Maintaining a pattern of regular exercise is helpful for maintaining muscle mass and strength (Willardson, 2004). Resistance exercise in particular has demonstrated increased muscle protein synthesis, as well as decreased myostatin (protein product of the gene that regulates muscle growth). High levels of myostatin have been associated with muscle wasting in AIDS patients. Therefore exercise is important for restoring muscle size and strength through increases in muscle protein synthesis and motor unit synchronization.

1.1.5 Treatment of HIV

Treatment of patients with HIV infection not only requires a comprehensive knowledge of the disease process itself, but also the patient's psychological ability to deal with the problems of a chronic, life-threatening illness. Although the infection cannot be cured, chances of survival and quality of life have been improved with the use of specific antiretroviral (ARV) therapy and antimicrobial treatment and prophylactic medication (Griffen, 2003; Fauci *et al.*, 1994).

The provision of ARV therapy has been credited with having a significantly positive effect on the lives of people living with HIV/AIDS (Stewart *et al.*, 2004). ARV therapy targets HIV at various points of its cycle. The primary goals of ARV treatment are maximal and persistent suppression of viral load, restoration and preservation of immunologic function, improvement of quality of life, and reduction of HIV-related morbidity and mortality (Department of Health, 2003). When taking ARV therapy, a patient should experience fewer HIV-related illness, his/her CD4 cell count should rise and remain above the baseline count, and the patient's viral load should become undetectable (<400 copies per mm^3) and remain undetectable (Grimwood, 2004). ARV therapy also leads to substantial body mass gain (Grunfeld *et al.*, 1992). It has been demonstrated that combination ARV therapies significantly delay the progression of HIV and improve survival (Smith *et al.*, 2001). However, HIV mutates rapidly and can become resistant to drugs but this is less likely to happen when combinations of different classes of ARV drugs, known as highly active antiretroviral therapy (HAART) are used (Griffen, 2003; Stringer *et al.*, 2001). HAART is usually initiated when viral load rises late in the course of infection.

The Department of Health (2003) has set criteria which have to be met before ARV treatment can be initiated in adults. These criteria include:

- CD4 cell count $\leq$ 200 cells per mm^3 and symptomatic, irrespective of stage, or
- WHO stage IV AIDS defining illness, irrespective of CD4 cell count, and
- Patient prepared and ready to take ARVs adherently.

The provision of ARV drugs in developing countries such as South Africa has been limited because of a number of factors, most importantly the high cost of these medications (Stewart *et al.*, 2004). The choices of ARV regimes are limited because of the limited availability of approved drugs in South Africa and resource restrictions. Two regimes are recommended for use in the South African public sector (Grimwood, 2004). Table 1.2 shows the regimes followed in South Africa.

Each regime consists of one or more nucleoside reverse transcriptase inhibitors (NRTI), non-nucleoside reverse transcriptase inhibitors (NNRTI) and protease inhibitors (PI) (Safrin, 2001). NRTIs act by competitive inhibition of HIV-1 reverse transcriptase and can also be incorporated into the growing viral DNA chain and cause termination of the viral DNA. NRTI drugs include Zidovudine (AZT), Didanosine (ddI), Lamivudine (3TC) and Stavudine (d4T). NNRTIs bind directly to a site on the viral reverse transcriptase that is near to but distinct from the binding site of NRTIs. The binding of NNRTIs to the enzyme's active site results on the blocking of RNA- and DNA-dependent DNA polymerase activities. NNRTIs include Nevirapine (NVP) and Efavirenz (EFV). Protease Inhibitors (PI) prevent new waves of infection by preventing the production of mature infectious virions during HIV replication. Ritonavir and Lopinavir are examples of PIs. Each drug used in the treatment regimes of HIV is discussed in more detail below.

Table 1.2 Antiretroviral (ARV) Treatment Regimes used in South Africa.

Regime	Drugs	Indications
1a **First line regime**	**Stavudine (d4T)** **Lamivudine (3TC)** **Neverapine**	• **Men** • **Women of childbearing potential** • **Pregnant women** • **Conditions where Efavirenz is contraindicated**
1b **Alternate first line regime**	**Stavudine (d4T)** **Lamivudine (3TC)** **Efavirenz**	• **Persons who develop Neverapine intolerance** • **Persons who have evidence of hepatoxicity** • **Other conditions where Neverapine is contraindicated**
2 **Second line regime**	**Zidovudine (AZT)** **Didanosine (ddI)** **Lopinavir** **Ritonavir**	• **Persons who 'fail' regime 1a or 1b** • **First line in patients who have evidence of Neverapine resistance before ARV initiation**

Adapted from Department of Health, 2003: *Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa*. Department of Health, South Africa.

Patients with advanced HIV disease, particularly those with a CD4 cell count of less than 50 cells per mm^3, may become ill with an immune reconstitution illness during the first few weeks of ARV use (Grimwood, 2004). Immune reconstitution illnesses occur when an improving immune function reveals a

previously latent opportunistic infection i.e., an infection that was present in the patient's body but was not clinically evident. They may have signs and symptoms of sweats, loss of body mass, cough, persistent fever and shortness of breath. TB is a common immune reconstitution illness in South Africa. However, immune reconstitution illnesses are not indicative of drug failure or drug side effects, and ARV treatment should be continued.

A patient's best chance of a good clinical outcome is when the first line treatment is successful. A second line regimen, while still being effective, is often less effective than the first line, as the virus may have developed resistance to a specific class of drugs (Department of Health, 2003). Development of resistance to a specific ARV agent may result in resistance to other drugs within the same class and can significantly limit future treatment options (Stewart *et al.*, 2004). If the second line of drug treatment fails, then salvage therapy, which is a highly specialized and expensive treatment, may have to be considered. Salvage therapy is not currently available in the South African public sector because of the high cost and limited clinical benefit.

Use of ARV therapy usually results in a reduction of viral load to undetectable levels and an increase in CD4 cell counts, with a concomitant restoration of immune competence (Griffen, 2003). Suppression of HIV replication plays an important role in prolonging life as well as improving the quality of life of patients with HIV infection (Fauci *et al.*, 1994). HAART has been associated with a reduction in the severity of body mass loss and malnutrition and an improvement in the immune status of HIV positive patients (O'Brien *et al.*, 2005). ARV therapy has resulted in dramatic decreases in the mortality and morbidity from HIV infection (Stringer *et al.*, 2001). There is a increased prevalence of persons living with HIV disease, primarily as a result of improvements in ARV therapy and subsequently fewer opportunistic infections (Clingerman, 2003). As a result, more consideration must be given to the long-term health of individuals infected with HIV, especially because HIV infection and treatment may increase the risk of other common diseases such as heart disease, diabetes and

hypercholesterolemia (Stringer *et al.*, 2001). However, there is also the risk of drug toxicity and the development of drug resistance to ARV therapy. Therefore, the HIV positive patient can consider complimentary therapies, such as exercise and nutrition, to maintain the integrity of his/her immune system should drug toxicity develop.

Aside from the positive effect of slowing HIV disease progression, ARV therapy has been associated with troubling symptoms such as fatigue, dyspnoea (shortness of breath) and undesirable body mass change (Smith *et al.*, 2001). A new set of metabolic and body composition abnormalities have arisen in HIV infected patients, in association with ARV therapy (Hellerstein, 2001; Jones *et al.*, 2001; Stringer *et al.*, 2001). Metabolic dysregulation, such as lipodystrophy (lipohypertrophy and lipoatrophy), a condition associated with abnormal fat distribution as well as glucose intolerance, diabetes mellitus and hyperlipidemia are more common in patients who are on HAART, as well as a syndrome that includes lactic acidosis which may reflect tissue mitochondrial toxicity (Hellerstein, 2001).

Although HAART has been known to reduce the severity of body mass loss, it may also be associated with unwanted changes in body composition known as lipodystrophy (O'Brien *et al.*, 2005; DoH, 2004; Grimwood, 2004). Lipodsytrophy is a syndrome associated with physical and metabolic changes in the body and is characterized by a reduction in subcutaneous fat in the face, arms, legs and buttocks, and an increase in visceral fat in the abdomen, back of neck and breasts. Lipohypertrophy is the deposition of fat just behind the neck ("buffalo hump") or visceral abdominal fat deposition. Conversely, lipoatrophy may occur with loss of adipose tissue in the face, arms or legs. Lipohypertrophy and lipoatrophy may be observed in the same patient. Plasma triglyceride concentrations are elevated in patients with AIDS and somewhat elevated in HIV positive patients (Grunfeld *et al.*, 1992), and is thought to be due to slowing of triglyceride clearance. Many of these abnormalities in lipid metabolism may act as risk factors for coronary artery disease (Jones *et al.*, 2001). Lipid abnormalities

(dyslipidemia) are primarily reported with the use of PIs but have also been reported with the usage of NRTIs and NNRTIs (DoH, 2004; Grimwood, 2004). Increases in total cholesterol are usually due to administration of PIs. NNRTIs are also known to increase total cholesterol but have also been reported to increase high density lipoproteins (HDL), particularly Efavirenz. Lifestyle modifications such as increased PA levels, proper nutrition and body mass loss have been recommended by the DoH as important measures to prevent or decrease lipid abnormalities (DoH, 2004; Grimwood, 2004).

HIV infection and PI treatment are associated with impaired lipid metabolism, including elevations in triglycerides and cholesterol, similar to the changes observed with type 2 diabetes in individuals who are not HIV infected (DoH, 2004; Cade *et al.*, 2003; Hellerstein, 2001; Stringer *et al.*, 2001). Impaired glucose metabolism, such as glucose intolerance, has been associated with PI treatment, and the degree of insulin resistance has been significantly associated with the degree of lipodystrophy (Cade *et al.*, 2003; Stringer *et al.*, 2001).

Gastrointestinal or abdominal discomfort is the most commonly reported ARV side effect and may occur earlier on in therapy (DoH, 2004). Common complaints include abdominal discomfort, nausea and vomiting, loss of appetite, diarrhoea, abdominal pain, pancreatitis, constipation and heartburn.

The use of NRTIs is also reported to be associated with distal symmetric polyneuropathy (Department of Health, 2004). Distal symmetric polyneuropathy is characterized by injury or loss of primary afferent fibers, resulting in distal axonal degeneration (Verma et al., 2005), and usually presents with distal symmetric distribution and sensorimotor paralysis. Numbness or burning dysesthesia of the distal extremities occurs at times with sharp, shooting pains or continuous severe burning. These symptoms of distal symmetric polyneuropathy can lead to gait difficulties and sleep disturbances, which may have a significant impact on quality of life. The pain may become so severe that patients develop

contact sensitivity to bed sheets or socks or feel sensations of pain when touched by non-painful stimuli e.g., cotton wool, a condition known as allodynia.

Abnormal patterns of gaseous exchange have been noted in HIV positive patients, resulting in reduced exercise capacity (Pothoff *et al.*, 1994). HAART has been known to disrupt normal mitochondrial functions, by causing pathological changes in mitochondrial structure (mitochondrial swelling, cristae disruption) and damaging and decreasing the number of mitochondrial DNA and RNA. The use of NRTIs also results in a deficiency of specific mitochondrial enzymes essential for ATP production via oxidative phosphorylation (Cade *et al.*, 2004). Delayed recovery and larger depletion of phosphocreatine following muscular exercise have also been reported with NRTI use. These alterations in mitochondrial function may be a contributor to muscle oxygen extraction-utilization limitation in most individuals treated for HIV infection (Cade *et al.*, 2003). It is this muscle oxygen extraction-utilization limitation that has been identified as a mediator of diminished aerobic capacity and would likely limit participation in physical activity.

Lactic acidosis is a rare but life threatening condition and usually occurs in one to 20 months after the start of NRTI therapy (Department of Health, 2004). Clinical symptoms are not specific and include fatigue, nausea, vomiting, abdominal pain, body mass loss and dyspnea. These symptoms may occur acutely or gradually over time.

The recognition of these new adverse effects associated with ARV therapy requires health care professionals to pursue more aggressive symptom management strategies (Smith *et al.*, 2001). The pharmacological approach to symptom management in HIV patients is not without risk. Patients may not wish to add other medications to an already complex regime. Therefore, there is a need for alternative strategies to manage the disease as well as the adverse effects associated with ARV use. It may be considered more appealing to use alternative therapies than conventional medical treatment that is often perceived as

unpleasant, and even toxic (Singh *et al.*, 1996). Therefore the popularity and use of nontraditional therapies among patients with HIV infection has grown enormously.

Scientific advances are occurring at an extremely rapid pace in the area of HIV research, especially with regards to treatment of opportunistic diseases, and vaccine development (Fauci *et al.*, 1994; Chlebowski *et al.*, 1989). Despite these advances, the HIV pandemic is growing in magnitude world wide and the cost in human life and suffering is staggering (Fauci *et al.*, 1994). Even with the development of HAART, the pandemic is confounded by socioeconomic factors and unequal access to health care (Brown *et al.*, 1997). Physicians and other health care workers are in the unusual position of caring for HIV-infected individuals within the framework of a rapidly evolving scientific and clinical discipline. Therefore, physicians and health care workers are continually implementing alternative therapies, such as physical activity (PA) and exercise, lifestyle modifications and nutrition, as a strategy to manage the disease. With the role of HAART in prolonging the life of HIV-infected individuals, HIV is being increasingly referred to as a chronic disease, and both drug and non-drug therapies should be offered to mitigate the long term risk of the metabolic complications of HIV and HAART.

1.1.6 Physical Activity and HIV

For most people who are able to access and tolerate HAART, HIV has become a chronic condition characterized by cycles of illness and wellness, which has led to a potential increase in the prevalence and impact of disability of people living with HIV infection (O'Brien *et al.*, 2005). Persons living with HIV disease experience a range of disease impacts. These impacts include limitations in physical and role functioning i.e., the ability to perform physical activities without assistance or to carry out social roles such as employment (Crystal *et al.*, 2000). Functional ability (or the restriction of it) is a major factor in determining if a person is capable of independent living (Mathie *et al.*, 2004). A person's level of

functional ability has a significant impact on quality of life. Individuals infected with HIV are living longer lives compared to similar populations in history, but with physical, psychological and social challenges, which all affect quality of life (Rusch *et al.*, 2004). HIV disease can deprive an individual of his or her physical resources, such as mobility, muscular strength, joint flexibility, endurance and energy (Clingerman, 2003). There is a high prevalence of fatigue and lack of endurance in HIV positive patients, many of whom face challenges with daily activities (Rusch *et al.*, 2004). It has been established that HIV infection compromises pulmonary function even in the early stages of the disease (Pothoff *et al.*, 1994), which may be a contributing factor to the fatigue experienced by HIV positive patients. Alternative strategies for the management of HIV-infection and its related metabolic syndromes need to be considered because of the changing course of HIV. A number of non-nutrient based strategies, such as physical activity and exercise, are available to physicians for improving endurance and increasing lean body mass, and thus functional status, in HIV infected individuals (Hellerstein, 2001).

Physical activity (PA) may help manage HIV-related stress and improve aerobic capacity and cardiopulmonary and immune function in HIV positive patients. Physical activity (PA) is defined as any bodily movement produced by the skeletal muscles resulting in energy expenditure (EE), in the form of heat loss, above the resting levels (Shepard, 2003; Meijer *et al.*, 1991; Casperson *et al.*, 1986). Physical activity (PA) has both physiological and behavioural aspects (Baranowski et al., 1992). From a physiological perspective, PA is a component of total EE, which also includes resting EE, energy expended with food digestion and growth. From a behavioural perspective, PA can be viewed within several frameworks, e.g., recreational, rehabilitative, developmental or health related.

Of the most relevant interest is habitual PA i.e., activity that is performed on a daily basis, and is composed of the following domains: leisure time, gardening or yardwork, household chores, transport or moving from place to place, and occupational physical activity (Booth, 2000). High levels of habitual PA are

considered an essential component of a healthy lifestyle (Ridgers *et al.*, 2005; Hardman, 1999). Regular participation in moderate PA is an essential component of a healthy lifestyle (Padden, 2002). Moderate PA enhances immunity (by increasing CD4 cell counts or by slowing CD4 cell count decline) and may even lower the risk of some infections (Mustafa *et al.*, 1999; Mackinnon, 1994). For patients with metabolic syndrome, increasing PA is encouraged (Wigle, 2006). PA has the potential to improve the body composition of HIV positive patients suffering from HIV related lipodystrophy (Roubenoff *et al.*, 1999). High levels of habitual PA positively influence a number of conditions including osteoporosis, obesity, hypertension and diabetes (Blair, 1993). Since functional status and well being are highly valued by patients with chronic conditions (Stewart *et al.*, 1989), PA may contribute to the maintenance of functional status and improvement in the physical and mental well-being of people infected with HIV. Psychological benefits of PA include positive changes in mood, relief from tension, depression and anxiety, and increased ability to mentally cope with daily activities (Padden, 2002).

1.1.7 Exercise as a subcategory of physical activity

As mentioned above, PA is defined as any bodily movement produced by skeletal muscles that result in energy expenditure (EE). However, exercise is a subcategory of PA and is defined as planned, structured movement undertaken to improve or maintain one or more aspects of physical fitness (Shepard, 2003; Casperson *et al.*, 1986). Exercise is one fundamental management strategy used by health care professionals to address impairments, activity limitations and participation restrictions in the HIV positive population (O'Brien *et al.*, 2005). Exercise is considered an attractive option because it is inexpensive (Bhasin *et al.*, 2000), and it is known that exercise is an effective method used to reduce risk factors and morbidity of cardiovascular and other chronic diseases as well as to improve mental health (Jones *et al.*, 2001; Mustafa *et al.*, 1999). Exercise is also used to address unwanted changes in body mass and body composition in HIV positive people (O'Brien *et al.*, 2005) by either maintaining muscle mass

associated with HIV infection or by preventing abnormal fat distribution caused by ARV use.

Long term survivors of HIV infection have attributed their longevity to various lifestyle modifications, including changing exercise habits (Eichner *et al.*, 1994). The Department of Health's Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa (2003) states that HIV positive patients who are early in the course of their infection will benefit primarily from good nutrition, stress reduction and behavioural modification. Increasing PA and exercise levels as part of this behavioural modification can maintain the quality of life of these patients as well as contribute to stress reduction. Combined aerobic and resistance exercise has been suggested to contribute to the modification of blood lipid concentrations, preventing the deposition of fat (Jones *et al.*, 2001). It has also been shown that performing constant or interval aerobic exercise, or a combination of aerobic and progressive resistance exercise interventions at least three times per week for at least four weeks appeared to be safe and may lead to clinically important improvements in cardiopulmonary fitness, body body mass and composition for medically stable HIV positive adults (O'Brien *et al.*, 2005). Improvement in muscle strength and flexibility, cardiopulmonary function, decrease in depression, anxiety and anger, and increase in CD4 cell count following exercise training in HIV infected individuals has been reported (Mustafa *et al.*, 1999). Exercise may therefore be associated with slower HIV disease progression as well as improved mental well being, and may prove to be an important adjunctive therapy in future HIV disease management (Mustafa *et al.*, 1999).

Submaximal aerobic exercise is used as a therapy to improve functional status and stimulate the immune system in HIV-infected individuals. Aerobic exercise has been used in managing signs and symptoms of other chronic illnesses and is widely used in health promotion and rehabilitation programmes to improve physical endurance (Smith *et al.*, 2001). Therefore, aerobic exercise may be an effective alternative in the treatment of certain signs and symptoms associated

with HIV infection. HIV-infected individuals who have participated in aerobic exercise programmes have demonstrated improved aerobic capacity, functional status, lean body mass, body mass, mood and quality of life (Stringer *et al.*, 2001).

Aerobic exercise has been shown to have no harmful effects on the immune system of an HIV infected individual (Stringer *et al.*, 2001). The changes observed with immune function were small and not clinically significant. However, the lack of detrimental effect is important. Therefore regular aerobic exercise can be recommended without hesitation as an important complimentary therapy.

Although aerobic exercise has been shown to improve the functional capacity of HIV-infected individuals, it is not associated with substantial skeletal muscle hypertrophy (Zinna *et al.*, 2003). Aerobic exercise primarily alters the enzyme activity of mitochondrial and cytosolic proteins while resistance exercise is responsible for increasing contractile protein mass. Therefore, resistance exercise is combined with aerobic exercise to improve muscle size and strength of HIV-infected individuals.

Resistance exercise is used as a medical therapy to increase lean body mass (Hellerstein, 2001). Progressive resistance exercise is a type of exercise that involves strengthening of muscle tissue that may include, but is not limited to activities such as isotonic strengthening exercises, and isometric strengthening exercises (O'Brien *et al.*, 2005).

Resistance exercise has been associated with significant gains in muscle strength, size and body body mass, counteracting the effects of AWS and cachexia in HIV-infected individuals (Bhasin *et al.*, 2000). Pharmacological interventions of anabolic agents such as testosterone supplementation have received attention (Hellerstein *et al.*, 1990). Such supplementation has been shown to improve muscle mass and strength (Bhasin *et al.*, 2000). However, the effects of testosterone interventions and resistance exercise were not additive, indicating

that resistance exercise can be as effective, but much less expensive with fewer side effects, as testosterone supplementation in managing the muscle wasting and loss of strength associated with HIV infection (O'Brien *et al.*, 2005; Bhasin *et al.*, 2000). Progressive resistance exercise interventions, with or without aerobic exercise also contribute to improvements in psychological status for HIV positive adults (O'Brien *et al.*, 2005).

Exercise has been known to reduce risk factors and morbidity of cardiovascular and other chronic diseases as well improve mental health. In general, exercise has been shown to improve muscle strength and flexibility, cardiopulmonary function, decrease depression, anxiety and anger, and increase CD4 lymphocytes (Mustafa *et al.*, 1999). The stress of a positive HIV test and living with HIV has been shown to alter immune function and exercise training has been suggested to attenuate some of the psychological and immunological effects of this stress (Eichner *et al.*, 1994). LaPerriere *et al.* (1994) and Jonsdottier *et al.* (1997) suggest that exercise training reduces depression and anxiety, increases the release of endogenous opiates (endorphins) and decreases stress hormone levels, and normalizes the immune system as a result of increased number and function of natural killer cells and lymphocytes. The endorphins are also associated with improved pain tolerance and mood state (Schwarz et al., 1992) indicating that exercise can be used in the management of HIV related pain. It has also been shown that HIV infected people who participate in regular exercise have a more positive perception of their health than those who do not participate regularly (Munro *et al.*, 1998). Therefore, exercise training has been implied to be beneficial from both a psychological and immunological perspective (Eichner *et al.*, 1994). Exercise, especially moderate activity, may be associated with slower HIV disease progression, and may prove to be an important supportive therapy in HIV disease management (Mustafa *et al.*, 1999).

A regime of combined aerobic and resistance training can be effective in enhancing functional capacity (strength and aerobic endurance), reducing subcutaneous fat, total cholesterol, triglyceride concentrations and increasing body mass (Jones *et al.*, 2001). The usefulness of exercise additional to

conventional HAART may rest on its potential to decrease the body composition and lipoprotein disturbances associated with adherence to HAART.

A holistic approach to treating and living with HIV and AIDS, including ARV treatment, as well as lifestyle modification (increased PA and exercise levels, and improved nutritional status), is a key factor for success in living a longer, healthier life with the disease. The health benefits of PA and exercise in the management of HIV are well documented. However, it is unknown if people infected with HIV are currently participating in these health promoting PA behaviours in order to better manage the disease. The role of PA epidemiology therefore becomes more important. The descriptive epidemiology of PA as an individual behaviour provides insights into the types and amounts of PA performed by members of a population (Casperson, 1989). Therefore, physical assessment techniques should be employed in order to better understand the type, frequency and duration of PA undertaken by HIV infected individuals. It is this information that contributes to the development, implementation, and evaluation of policy designed to promote a more active and healthy society (Dominguez-Berjon *et al.*, 1999; Bernstein *et al.*, 1998; Casperson, 1989).

1.1.8 Physical Activity Assessment Techniques

Assessment of habitual physical activity (PA) is an imperative task to determine descriptive information about different populations (Iltis *et al.*, 2000). Measurement of PA needs to include accurate estimates of energy expenditure (EE) and the ability to determine the manner in which an individual expends energy during the day (Matthews *et al.*, 1995). The assessment of habitual PA behaviours of a specific population, however, is challenging, because people are active in different ways, at different times, at many locations, and for different reasons (Sallis *et al.*, 1985). PA is based on individual habits and the pattern of activity among individuals varies based on the day, week or time of year (Freedson *et al.*, 2000; Sallis *et al.*, 1985). It is also a difficult behaviour to

assess because it involves several variable aspects such as type, intensity, duration and frequency (Brage *et al.*, 2003; Sallis *et al.*, 1985).

Some of the most commonly used methods to estimate PA and EE are recall questionnaires, activity diaries, interviews, direct observations and time-motion analysis, heart rate monitoring, movement sensors, and direct and indirect calorimetry (Ramirez-Marrero *et al.*, 2005; Montoye, 2000; Bernstein *et al.*, 1998). The selection of a measurement approach depends on the purpose of the study (Tudor-Locke *et al.*, 2001).

PA questionnaires are currently the most practical and widely used method for the assessment of PA in epidemiologic research (Tudor-Locke *et al.*, 2001; Bernstein *et al.*, 1998; Aaron *et al.*, 1995; Washburn *et al.*, 1990) because of their ease of administration and distribution. They require no technical equipment, are less expensive and do not interfere with subjects' usual activity. PA questionnaires are generally retrospective and require recall of specific activities over a specific time frame. The information gained from the questionnaire is converted to an estimate of caloric expenditure (Tudor-Locke *et al.*, 2001) or multiples of the average resting metabolic rate (METS) (Shepard, 2003; Ainsworth *et al.*, 2000; Lamb *et al.*, 1990). A MET is defined as the ratio of work metabolic rate to a standard metabolic rate of 1.0 (4.184kJ per kg per hr). Therefore, 1 MET is considered a resting metabolic rate obtained during quiet sitting. However, care must be taken when interpreting MET scores, because increments of energy expenditure may not be uniform across all populations (Shepard, 2003). Although METS (multiples of average resting metabolic rate) will be the same across all populations, conversion into EE (according to Ainsworth *et al.*, 2000) for comparitive purposes between HIV positive and HIV negative populations will be invalid because HIV positive patients are hypermetabolic, and have a significantly higher resting EE (Macallan *et al.*, 1995; Suttman *et al.*, 1993; Grunfeld *et al.*, 1992; Hellerstein *et al.*, 1990). Therefore, more research into this field is required.

A limitation of using a questionnaire to assess PA is that questionnaires are subjective in nature. Self report of PA is susceptible to inaccuracy and/or imprecision as these instruments are dependent on subjects' ability to recall or report PA (Freedson *et al.*, 1998). Subjects are likely to recall vigorous, structured activity with a high degree of accuracy, but are not as good at recalling frequent, moderate intensity activities such as walking (Basset *et al.*, 2000). It has been suggested that activities such as walking are the major contributors to PA in normal life, as most people spend a large amount of time walking for their work or for leisure activities (Levine *et al.*, 2001; Terrier *et al.*, 2001; Meijer *et al.*, 1991). An inability to accurately recall such activities would result in inaccurate quantification of PA. Another limitation with this method of PA assessment is that reporting of PA performed may be influenced by the perceived desirability of a given response (Klesges *et al.*, 1990) as well as inaccurate perception of one's activity behaviour (Freedson *et al.*, 2000). Most individuals overestimate their PA when left alone to determine their level of exertion in specific activities (Conway *et al.*, 2002). A third limitation is that lifestyle activity is generally less structured than more vigourous bouts of exercise and therefore may be harder to code and recall on self-report instruments (Welk *et al.*, 2000). Lifestyle activities also encompass a wide range of intensities, and can also be accumulated throughout the day, making it difficult to obtain an accurate measure of the amount, intensity or duration of activity. Hence there are difficulties associated with addressing frequency, intensity and duration of lifestyle activity.

Questionnaires are practical for obtaining data on large samples and are therefore well suited to surveillance and screening (Tudor-Locke *et al.*, 2001). However, to eliminate many problems associated with self-report measures, it is necessary to explore alternative methods that do not rely on the individuals' ability to recall activity or on the quality of the questionnaire (Freedson *et al.*, 1998). Motion sensors, such as accelerometers, have the potential to eliminate these problems and offer the most promise for precisely quantifying PA behaviour.

Advances in technology have generated an increased interest in objective monitoring of PA using body worn motion sensors or activity monitors, for example, accelerometers and pedometers (Le Masurier *et al.*, 2003; Hendelman et al., 2000). Activity monitors were developed in response to the lack of reliability of self-report measures such as questionnaires and activity diaries, the intrusiveness of direct observation, and the complexity of heart rate monitoring (Puyau *et al.*, 2002). Objective monitoring of physical activity by activity monitors is now supported by technology that is capable of capturing free-living PA information (Mathie *et al.*, 2004; Tudor-Locke *et al.*, 2002), and allows for the continuous and precise measurement of PA intensity (Brage *et al.*, 2003). An activity monitor is an electronic instrument that picks up motion or acceleration of a limb or trunk, depending on where the monitor is attached to the body (Freedson *et al.*, 2000). Every movement requires acceleration and deceleration of the trunk or body segments. An activity monitor records acceleration changes to evaluate EE as well as the amount of PA performed. The activity monitor will best measure human motion (and estimate EE accurately) when the monitor is attached to the body part responsible for the motion and optimally aligned with the motion itself (Heil, 2006). Under free-living conditions, activity monitors attached to the ankle or wrist are probably far more likely to record motions not relating to the activity being performed (e.g. fidgeting). Therefore, the most common site for activity monitor placement is on the hip.

An activity monitor allows for the assessment of movements of the body in order to get a quantitative measure of physical activity (Meijer *et al.*, 1991). The most common commercially available activity monitors can be described as uniaxial (sensing motion in a single plane), or triaxial (sensing motion in all three planes) (Heil, 2006). However, the Actical® (Mini Mitter Company Inc, Oregon) activity monitor is described as omnidirectional that is most sensitive in a single plane and less sensitive in other planes. As a result, these devices have the ability to detect concurrent activity data, expressed as activity counts on a minute-by-minute basis for weeks at a time with minimal intervention from the researcher (Metcalf *et al.*, 2002; Tudor-Locke *et al.*, 2002; Basset, 2000). These activity counts are the

result of duration, frequency and intensity of movement, sampled at set intervals (Heil, 2006; Mathie *et al.*, 2004; Powell *et al.*, 2003; Puyau *et al.*, 2002; Tudor-Locke *et al.*, 2001; Eston *et al.*, 1998). The capacity to store activity counts over small time periods permits the evaluation of patterns of activity within a day or over several days (Freedson *et al.*, 1998).

Activity monitors have been validated against indirect calorimetry and calibrated in terms of resting metabolism equivalents (METS) (Puyau *et al.*, 2002). METS per minute is a useful measure as it emphasizes movement, independent of body size (Jacobs *et al.*, 1993). It further emphasizes that interpretation of amount of PA in kilocalories per day, or kilocalories per kilogram body mass per day includes assumptions of the relation of EE to body size. However, variation in the estimate of resting metabolic rate is not taken into account. As discussed above, conversion of METS obtained from the PA monitoring by activity monitors of HIV positive patients, into EE, will be incorrect due to the higher resting EE in the HIV positive population (Macallan *et al.*, 1995; Suttman *et al.*, 1993; Grunfeld *et al.*, 1992; Hellerstein *et al.*, 1990). However, these activity monitors can be used to monitor parameters that are sensitive to changes in health or functional status, by monitoring the amount of hourly and daily physical activity and the amount of time spent resting during the day and at night (Mathie *et al.*, 2004).

The small size, ease of use and objectivity of activity monitors make them a promising tool to assess PA and EE (Swartz *et al.*, 2000). They provide a convenient tool for assessing PA outside the laboratory setting in a free living environment: they are relatively simple to use, unobtrusive by not impeding movement, compatible with most daily activities and are well tolerated by subjects, allowing for little subject influence (Mathie *et al.*, 2004; Welk *et al.*, 2004; Freedson *et al.*, 2000; Hendelman *et al.*, 2000; Fehling *et al.*, 1999; Sequeira *et al.*, 1995).

A limitation of activity monitors is that they are unable to detect the metabolic cost associated with standing, upper body movements, static work, vertical lift

and changes in gradient (Basset, 2000). Also, if the activity monitors are positioned or angled in slightly different ways when taken off and reattached to the body, a measurement error occurs (Welk *et al.*, 2004). These differences are likely when monitors are worn under free-living conditions as it is harder to standardize positions on the hip and maintain proper orientation of the monitor during field-based monitoring over several days.

Therefore, the best option for objectively monitoring physical activity is to use a combination of indirect and direct assessment techniques i.e. using a self-report questionnaire in conjunction with an accelerometer.

1.1.9 Summary

Early on in the HIV disease process, individuals may appear physically asymptomatic yet may experience psychosocial symptoms such as sadness, stress, anxiety, and fear. As HIV disease progresses in severity and symptoms increase, individuals face multiple lifestyle changes and eventual debilitation. People living with HIV experience high levels of depression, body impairments, activity limitations and participation restrictions. Physical inactivity places all people, including persons living with HIV disease, at a higher risk for other acute and chronic conditions and can prevent them from achieving their highest level of wellness. Developing and maintaining a healthy lifestyle can help counteract the negative effects of HIV disease. However, little is known about current health promoting PA behaviours of people living with HIV disease. Type, frequency and duration of PA behaviours for this specific population are absent in the empirical literature. Also, previous studies have focused on the immunological response of people infected with HIV rather than on how HIV infection impacts on their ability to exercise or perform various types of PA. This study focused on identifying the association between HIV infection and habitual PA behaviours, functional independence and exercise capacity in a group of HIV positive adults who were either taking ARV medication or who were not taking ARV medication. The results of this study can be used in the development,

implementation, and evaluation of health policies which outline specific interventions to promote a more active and healthy HIV positive population.

1.2 Aims of Study

The aim of this study was to determine the impact of HIV infection on the habitual physical activity levels, functional independence and exercise capacity, in a group of HIV positive South African adults either taking or not taking antiretroviral medication.

The objectives of the study were:

a) To assess the relationship between CD4 cell count (a marker of HIV disease progression), habitual physical activity levels and functional independence in an HIV positive South African adult population either taking or not taking antiretroviral medication.

b) To compare the aerobic capacity, lower limb muscle strength, handgrip strength and physical activity count of age-matched HIV negative black females and HIV positive black females who are taking antiretroviral medication.

Chapter 2 – Materials and Methods

2.1 Introduction

The purpose of this study was to determine the impact of HIV infection on the habitual physical activity levels, functional independence and exercise capacity, in a sample of HIV positive South African adults either taking or not taking antiretroviral (ARV) medication. Therefore the study was composed of two parts. Firstly, a Lifestyle and Physical Activity questionnaire was used to determine the relationship between CD4 cell count, habitual physical activity levels and functional independence in a group of HIV positive outpatients either taking or not taking ARV medication. Secondly, a group of HIV positive female outpatients, who were taking ARV medication, and a group of HIV negative age-matched control subjects completed a physiological exercise testing protocol which assessed their aerobic capacity, lower limb muscle strength, handgrip strength and physical activity counts.

2.2` Lifestyle and Physical Activity Questionnaire

2.2.1 Patients

A total of 200 HIV positive outpatients from the antiretroviral roll out site at Helen Joseph Hospital (Auckland Park, Johannesburg) were approached to complete a Lifestyle and Physical Activity Questionnaire. This was considered a convenient sample as these patients regularly present themselves at the clinic for monthly check ups and to receive treatment if needed. As the majority of the patients completing the questionnaire were black, the nine patients who were Caucasian or coloured were excluded as this sample did not have any sample power. One scholar was also excluded due to her age. The data from four questionnaires were not used as CD4 cell counts were not available. Therefore, the data from one hundred and eighty six black male (n=47) and female (n=139) HIV positive outpatients were used to assess the current habitual PA levels in this population. The gender imbalance is representative of the patient demographics at this clinic. The patients were between 20 and 60 years of age (35.2 ± 7.9; mean ± SD). The experimental protocol was approved by the University of the Witwatersrand Committee for Research on Human Subjects (Protocol Number M050525; Appendix A). All patients gave written consent before completing the

questionnaire. Two multilingual interviewers assisted patients in completing the questionnaire correctly. The questionnaire was completed anonymously, with reference numbers being used for identification purposes.

2.2.2 Questionnaire

The questionnaire used in this study assessed the habitual physical activity levels of HIV positive black South African adults (Appendix B). The questionnaire was developed from three previously validated questionnaires namely the Modifiable Activity Questionnaire (Kriska *et al.*, 1990), Minnesota Leisure-Time Physical Activity Questionnaire (Taylor *et al.*, 1978) and the Baecke Questionnaire of Habitual Physical Activity (Baecke *et al.*, 1982). The questionnaire was divided into six sections. Section A contained questions regarding the patient's demographic information, including gender, age, race and home language, as well as socioeconomic information, including employment status, income, education, residence and amenities available in his/her residence. Section B gathered information about the patient's HIV status and included questions regarding diagnosis, current CD4 cell count, if and what antiretroviral medication was used and for how long, side effects from medication since commencement of ARV treatment and the occurrence of opportunistic infections in the past 12 months. Section C dealt with the patient's inactivity, by determining the level of independence of each patient as well as energy used in inactive situations, such as sleeping and watching television. Section D contained questions regarding the patient's activity levels in his/her occupation. This section was not completed if the patient was unemployed. Section E gathered information about the physical activity levels within the patient's household, and required the patient to determine the length and frequency that specific domestic duties were performed in his/her house. Section F of the questionnaire dealt with physical activity from a recreational perspective, independent of occupation and housework. The patient was required to recall the length and frequency of certain recreational activities.

From the questionnaire, a metabolic equivalent (MET) which is a proxy for the intensity level of physical activity performed in the last month was calculated

(Ainsworth *et al.*, 2000). The number of hours accumulated each day for a specific activity was multiplied by the number of times each activity was performed in one week. Hours per week were multiplied by 4.3 weeks in order to determine the number of hours each activity was performed per month. The result obtained was multiplied by the metabolic cost of the activity expressed as a multiple of one resting MET (one MET is defined as the metabolic cost of sitting quietly) (Ainsworth *et al.*, 2000).

For example, the MET hour score for one month for a patient who ran for one hour, five days a week was calculated as follows:

Hours per week = number of hours per day × number of days per week
= 1 hour per day × 5 days per week
= 5 hours per week

Hours per month = number of hours per week × 4.3 weeks per month
= 5 hours per week × 4.3 weeks per month
= 21.5 hours per month

The metabolic equivalent of running is 8 METS, therefore:

Met hours per month = hours per month × metabolic equivalent
= 21.5 hours per month × 8 METS
= 172 MET hours per month

A total MET hour score for one month was calculated by summing the METS obtained for each activity. Determining the total MET hour score for one month allowed for the evaluation of the contributions of various types of physical activity to energy expenditure.

2.2.3 Statistical Analysis

Data are shown as mean ± standard deviation unless otherwise stated. Spearman's correlations were done to determine the relationships between CD4 cell count and length of time on ARV medication, CD4 cell count and total habitual physical activity, CD4 cell count and degree of functional dependency as well as the relationship between total habitual physical activity and length of time on ARV medication and total habitual physical activity and degree of functional dependency.

Mann-Whitney tests were done to determine differences between the CD4 cell count of the male and female patients, the CD4 cell count of patients taking and not taking ARV medication and the CD4 cell count of patients considering themselves either functionally independent or dependent. Mann-Whitney tests were also used to determine differences between the total habitual physical activity levels of the male and female patients, and the total habitual physical activity levels of patients taking and not taking ARV medication.

Kruskal-Wallis tests were done to determine differences in CD4 cell count and differences in total habitual physical activity between patients experiencing no side effects from ARV medication use, patients experiencing one side effect, two side effects, three side effects and four or more side effects from ARV medication use.

For all statistical analysis, significance was set at $P < 0.05$.

2.3 Physiological Evaluation

2.3.1 Participants

A convenience sample of ten HIV positive black female outpatients were recruited from the antiretroviral roll out site based at Helen Joseph Hospital to participate in the study. The patients were all taking ARV medication and were aged between 20 and 45 years of age (34.0 ± 5.7; mean ± SD). The experimental protocol was approved by the University of the Witwatersrand Committee for

Research on Human Subjects (Protocol Number M051127; Appendix A). All subjects gave written consent for participation. Before commencement of the exercise testing sessions, the patients were questioned on their health to ensure they had not suffered from any infections in the past three months and were not taking any chronic medication, other than ARV medication, nor suffered from any orthopedic or joint problems.

Ten HIV negative age-matched black females were recruited to participate as control subjects. The control subjects were between the ages of 20 years and 45 years of age (32.5 ± 5.4; mean ± SD). Subjects were medically screened to ensure they were healthy and able to exercise. The experimental protocol was approved by the University of the Witwatersrand Committee for Research on Human Subjects (Amended Protocol M051127; Appendix A). All subjects gave written consent for participation. HIV negative status was confirmed with an ELISA diagnostic HIV test, with analysis performed by the National Health Laboratory Service based at Johannesburg General Hospital, Parktown, Johannesburg. Pre- and post-HIV test counseling was provided to each control subject by a qualified HIV counselor and registered nurse. All the control subjects followed the same study procedures as the HIV positive patients.

2.3.2 Blood Analysis

Patients were required to have a blood test one week before participating in the exercise tests. The blood sample was analysed by the National Health Laboratory Service at Johannesburg General Hospital, Parktown, Johannesburg for current CD4 cell count, full blood count and glycated hemoglobin (HbA1c). Glycated hemoglobin was assessed to provide an indication of glucose levels over a three month period. In addition, a finger prick lactate test was performed using an Accusport Lactate Machine (Model 1488767, Boehringer Mannheim GmbH, Manneheim, Germany) to determine the random resting lactate levels of each patient. Lactate was used as an indirect assessment of detecting lactic acidosis. Blood samples were obtained in the morning, in a non-fasted state.

2.3.3 Activity Monitor

Each patient received an Actical® Version 2.0 activity monitor (Mini Mitter Company Inc, Oregon) to wear for one full week (five week days and two weekend days) in order to objectively measure physical activity levels over that specific period of time. The Actical®, an omnidirectional accelerometer, is a small match-box sized device (28×27×10 mm) and weighs 17 g. It was worn around the waist, underneath the patients clothing, slightly medial to the left anterior superior iliac spine and provided a quantifiable measure of physical activity without hindering movement. The Actical® was worn at all times, except when the patient bathed or swam. Patients were educated on how to reattach the actical after it had been removed for bathing purposes. Physical activity counts were expressed as a percentage of the maximum count measured for the Actical® over the seven days.

2.3.4 Anthropometry

The anthropometric assessment followed the protocol as stated by the MOGAP procedure (Norton *et al.*, 1996). The patients' height was measured to the closest millimeter using a Seca wall-mounted stadiometer (Seca, Hamburg, Germany). Body mass to the closest 0,05g was measured in minimal clothing and without shoes using a Mettler TE Industrial Precision digital scale (Mettler Instrumente AG, GreiFensee, Switzerland). Body mass index was calculated as body mass (kg) divided by height^2 (m^2). The circumference of the waist was measured at the level of the narrowest point between the lowest costal border and the iliac crest. Hip circumference was taken at the level of the greatest posterior protuberance of the buttocks approximately corresponding anteriorly to the level of the symphysis pubis. Both circumferences were measured using a standard non-distendable measuring tape. Waist:hip ratio (WHR) was calculated as waist circumference (cm) divided by hip circumference (cm).

2.3.5 Aerobic capacity

The YMCA Submaximal Bicycle Ergometer Protocol (Golding *et al.*, 1989) was used to determine the physical work capacity of each patient. The bicycle used

was a Monark friction-braked, cadence dependent cycle ergometer. The subject was seated on the cycle ergometer so that the knee angle formed was approximately 120 degrees with the pedal at the dead bottom centre in the 6 o'clock position. A gentle warm up of five minutes was performed to allow the patients to become familiar with the testing equipment as well as for the bike to be set up to accommodate each subject correctly. Pedal cadence was set at between 50 and 60 revolutions per minute, with each subsequent workload lasting four minutes. The first workload was set at 25 watts (150kg.m.min^{-1}). This workload was performed for four minutes until a steady state heart rate was achieved. Subsequent workloads were then set according to Table 2.1.

Table 2.1 Subsequent workloads of the YMCA Submaximal Protocol

Heart Rate [a]	< 80 bpm	80-89 bpm	90-100 bpm	> 100bpm
Workload 2	750kg.m.min^{-1} [*] 125 watts [#] 2.5kg [$]	600kg.m.min^{-1} 100 watts 2.0kg	450kg.m.min^{-1} 75 watts 1.5kg	300kg.m.min^{-1} 50 watts 1.0kg
Workload 3	900kg.m.min^{-1} 150 watts 3.0kg	750kg.m.min^{-1} 125 watts 2.5kg	600kg.m.min^{-1} 100 watts 2.0kg	450kg.m.min^{-1} 75 watts 1.5kg
Workload 4	1050kg.m.min^{-1} 175 watts 3.5kg	900kg.m.min^{-1} 150 watts 3.0kg	750kg.m.min^{-1} 125 watts 2.5kg	600kg.m.min^{-1} 100 watts 2.0kg

[a] Subsequent workloads are chosen dependent on the heart rate response to the first workload of 25 watts (or 150kg.m.min^{-1}) i.e., if the patients heart rate was less than 80 beats per minute, a second workload of 125 watts (or 750kg.m.min^{-1}), using a weight of 3.0kg as resistance.

[*]Represents the workload in kilogram meters per minute. On a Monark cycle ergometer, the flywheel travels 6 meters per pedal revolution. Resistance is set with a weighted pendulum, and the workload is calculated as follows:

Workload = resistance in kg × revolutions per minute × revolutions per minute

[#] represents the power output of the workload in watts (1 watt = 6kg.m.min^{-1})

[$] represents the weight of the weighted pendulum (i.e. resistance) in kg

Heart rate was measured using a Polar S610 Heart Rate Monitor (Polar Electro Oy, Kempele, Finland). The test was terminated once the patient could not maintain the pedal cadence and could not continue with the test. Predicted

maximal oxygen uptake was then calculated using an extrapolation graph by plotting power output (in kilogram meters per minute or $kg.m.min^{-1}$) and the corresponding heart rate achieved for each workload. From the graph, the workloads at a heart rate of 150bpm and 170bpm were also calculated.

Patients were asked to rate their perceived exercise exertion on a scale of one (1) to ten (10) using the OMNI-Cycle Scale of perceived exertion for adults (Robertson *et al.*, 2004). This rating of perceived exertion was used as a marker for level of difficulty and provided a subjective indication of the amount of tiredness experienced by the subject.

2.3.6 Muscle Strength and Endurance

Muscle strength of the quadriceps and hamstring muscles of the dominant leg of each patient was measured using a Cybex II isokinetic dynamometer (Cybex, Ronkonkoma, New York, USA). The dominant leg was defined as the one preferred for daily activities, for example, kicking a soccer ball. The cycle ergometer test was used as the warm up before the isokinetic testing. Patients were taken through a stretching routine of the calves, hamstrings and quadriceps. A brief warm up was allowed on the Cybex to allow each patient to familiarize herself with the equipment. The quadriceps and hamstrings were isolated by stabilizing the waist and thigh of the non-dominant leg. Gravity correction was done by allowing compensation for gravity assisted knee flexion. Range of motion for the test was between zero and 90 degrees. Patients were given a warm up by performing one repetition each at 25%, 50% and 75% of maximum knee extension and flexion as well as two maximal repetitions which were done at a speed of 60 degrees per second. A rest period of 90 seconds was allowed before commencement of the strength test protocol which consisted of four maximal repetitions at a speed of 60 degrees per second.

Hand grip strength of the dominant hand was measured using a Jamar Hand dynamometer (Sammons Preston Inc, Bolingbrook, Illinois). The dominant hand was defined as the one preferred for daily activities such as writing. Grip strength

was measured in a standing position with the shoulder adducted and neutrally rotated and the elbow in full extension. Results were recorded in kilograms. The patients performed three maximal attempts and the highest value was recorded.

2.3.7 Statistical Analysis

Data are shown as mean ± standard deviation unless otherwise stated. Unpaired student t-tests were done to determine for significant differences between the anthropometric and physiological variables of the HIV positive patients and the HIV negative controls. The anthropometric variables included age, height, mass, body mass index (BMI), and waist hip ratio (WHR), and the physiological variables included relative maximal oxygen consumption, lower limb muscle strength (peak torque of hamstrings and quadriceps), handgrip strength and physical activity count.

Chapter 3 – Lifestyle and Physical Activity Questionnaire

3.1 Introduction

This chapter presents the results of the Lifestyle and Physical Activity Questionnaire, including demographic information and HIV history of the patients, their use of antiretroviral (ARV) medication, details of their habitual physical activity levels as well as their functional independence.

3.2 Demographic Information

A total of 186 black outpatients from an ARV roll out site in Johannesburg completed the questionnaire. Of this group 25% were male and 75% were female. The mean ± SD age of the patients (both males and females) was 36 ± 8 years. The mean ± SD age of the male patients was 36 ± 7 years and of the female patients was 35 ± 8 years. A breakdown of the socioeconomic status of the patients including employment status, income per month, educational qualification and area of residence is shown in Table 3.1.

Table 3.1: Socioeconomic characteristics of the patients (both genders)

Socioeconomic Variable		**n**	**%**
Employment status	Unemployed	101	54
	Employed	85	46
Income per month	No income	101	54
	Less than R1000	30	16
	Between R1000-R5000	51	27
	Between R5000-R10000	4	2
Highest educational qualification	No education	9	5
	Lower than Grade 7	25	13
	Between Grade 7 – Grade 11	83	45
	Grade 12	64	34
	Post matric certificate	5	3
Area of residence	Homeless	1	1
	Traditional village	22	12
	Informal township	21	11
	Formal township	93	50
	Low income housing	3	2
	Middle class suburb	20	11
	Upper class suburb	26	14

3.3 HIV History

The majority of the patients (49%) had been diagnosed with HIV for one year or less before completing the questionnaire. Of the remaining patients, 17% had

been diagnosed between one and two years before completing the questionnaire, 10% had been diagnosed with HIV for more that two years, 7% for more than three years, 4% for more the four years, and 12% for more that five years. The remaining 1% of the patients did not know when they had been diagnosed with HIV. At the time of the study, the CD4 cell count range of the patients was 3 to 1031cells/mm^3, with a median CD4 cell count of 195 cells/mm^3. The male patients had a significantly lower median CD4 cell count (median = 135 cells/mm^3; range = 9 to 475 cells/mm^3) than the female patients (median = 203 cells/mm^3; range = 3 to 1031 cells/mm^3) (*P = 0.024*, Mann-Whitney test).

3.4 Use of Antiretroviral (ARV) Medication

A total of 121 (65%) patients were on ARV medication. The majority of patients were on first line treatment, consisting of Lamivudine and Stavudine (both nucleoside reverse transcriptase inhibitors) and either Efavirenz or Nevirapine (both non-nucleoside reverse transcriptase inhibitors), depending on whether the patient was on reliable contraception. Of the 121 patients who were taking ARV, 30 (25%) were male and 91 (75%) were female. No significant association was found between gender and ARV use (*P = 0.86*, Fishers Exact test). The length of time these patients had been receiving ARVs ranged from two weeks to 32 months (median = 7 months). As seen in Figure 3.2, there was a positive correlation between CD4 cell count and length of time on ARV medication (Spearman's correlation, $P < 0.0001$, r = 0.45).

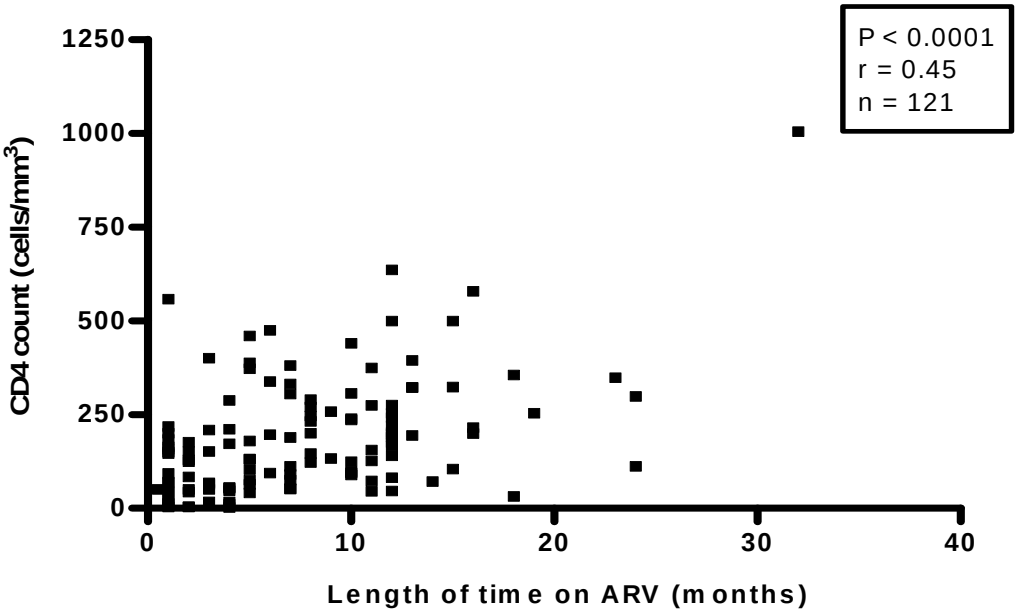

Figure 3.1: The correlation between CD4 cell count and length of time on ARV medication (Spearman's correlation, *P < 0.0001*; r = 0.45)

The most common side effects experienced by patients using ARV medication are shown in Figure 3.3. There was no significant difference in the CD4 cell counts of the patients who had not experienced side effects from ARV medication use and patients who experienced one, two, three and four side effects from medication use (*P = 0.79*, Kruskal-Wallis test).

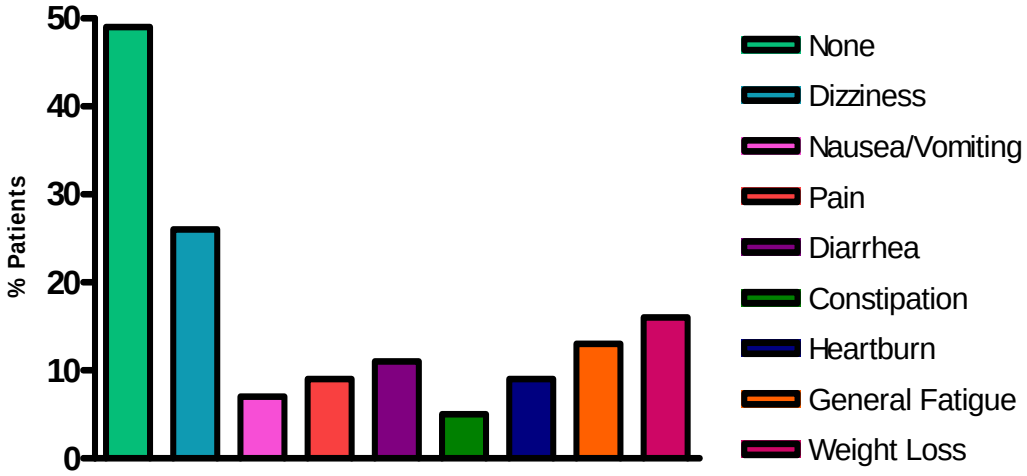

Figure 3.2: The percentage of patients who experienced side effects from ARV use (n = 121).

Of the patients using ARV medication, 84% believed that use of ARV medication increased their habitual physical activity levels, 3% believed that the use of the medication decreased their habitual physical activity levels, and 14% felt no change in their habitual physical activity levels. There was, however, a significant association between use of ARV medication and patients reporting sleep disturbances (*P = 0.019*, Fishers Exact test).

3.5 Habitual Physical Activity Information

Table 3.2 shows the contributions of the various types of physical activities [inactivity (sleep, relaxation), occupational, household and recreational] to total habitual physical activity levels in the male and female patients. The scores presented in the table are in MET hours per month. There was no significant difference in any of the contributions to or in **total** habitual physical activity levels between the male and the female patients (*P = 0.19*, Mann-Whitney test).

Table 3.2: Contribution of the various types of physical activity levels (MET hours*/month) to the total monthly habitual physical activity levels in the male and female patients

Activity	Males	Females
Inactivity	342 ± 99	349 ± 103
(sleep, relaxation)	(n = 47)	(n = 139)
Occupational	688 ± 265	706 ± 379
	(n = 21)	(n = 64)
Household	76 ± 55	159 ± 114
	(n = 34)	(n = 132)
Recreational	114 ± 139	99 ± 104
	(n = 26)	(n = 62)
Total	770 ± 420	869 ± 443
	(n = 47)	(n = 139)

Data is shown as mean ± SD

n = number of patients who participated in that specific activity

* The above scores represent multiples of one MET. One MET is defined as the energy expenditure for sitting quietly, which for the average adult is approximately 3.5ml of oxygen per kg body body mass per minute (Ainsworth *et al.*, 2000).

The relationship between CD4 cell count (cells/mm3) and total habitual physical activity level is shown in Figure 3.4. There was a positive correlation between CD4 cell count and total habitual physical activity (Spearman's correlation, *P = 0.0067*, r = 0.20; Figure 3.4). There was no significant difference in the CD4 cell counts when the total habitual physical activity levels were separated into low (0 to 500 MET hours per month), low to medium (500 to 1000 MET hours per month), medium (1000 to 1500 MET hours per month) and high categories (greater than 1500 MET hours per month) (*P = 0.095*; Kruskal-Wallis test).

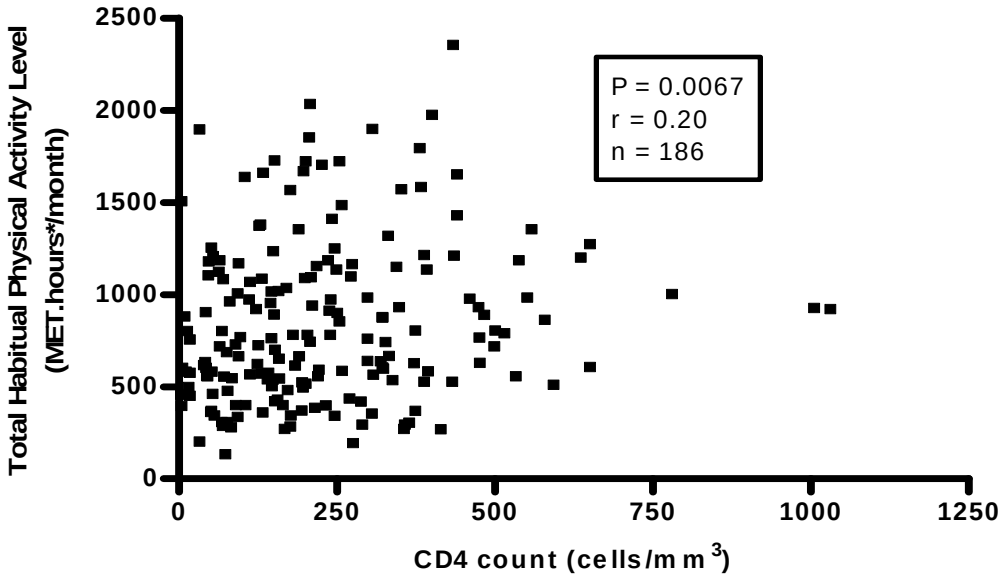

Figure 3.3: The correlation between CD4 cell count (cells/mm^3) and total habitual physical activity levels (MET hours*/month) for the male and female patients (n = 186) (Spearman's correlation, *P = 0.0067*, r = 0.20)

* The scores in the above figure represent multiples of one MET. One MET is defined as the energy expenditure for sitting quietly, which for the average adult is approximately 3.5ml of oxygen per kg body body mass per minute (Ainsworth *et al.*, 2000).

There was no significant correlation between total habitual physical activity level and length of time on ARV medication (Spearman's correlation, *P = 0.83*, r = -0.020). There were no significant differences in the total habitual physical activity levels of patients who had not experienced side effects from ARV medication use and patients who had experienced one side effect, two side effects, three side effects and four side effects (*P = 0.66*, Kruskal-Wallis test).

3.6 Functional Dependency

Of the total 186 patients, 12 patients (7%) reported difficulty independently performing one or more of the tasks of daily living listed in the questionnaire, and were as such classified as being functionally dependent on others for help.

Patients who considered themselves functionally independent i.e., not needing help, had a significantly higher CD4 cell count than patients who did not think they were functionally independent (*P = 0.0031*, Mann-Whitney test; Figure 3.5). There was a significant correlation between CD4 cell count and degree of subjective functional dependency (Spearman's correlation, *P = 0.0024*, r = -0.22).

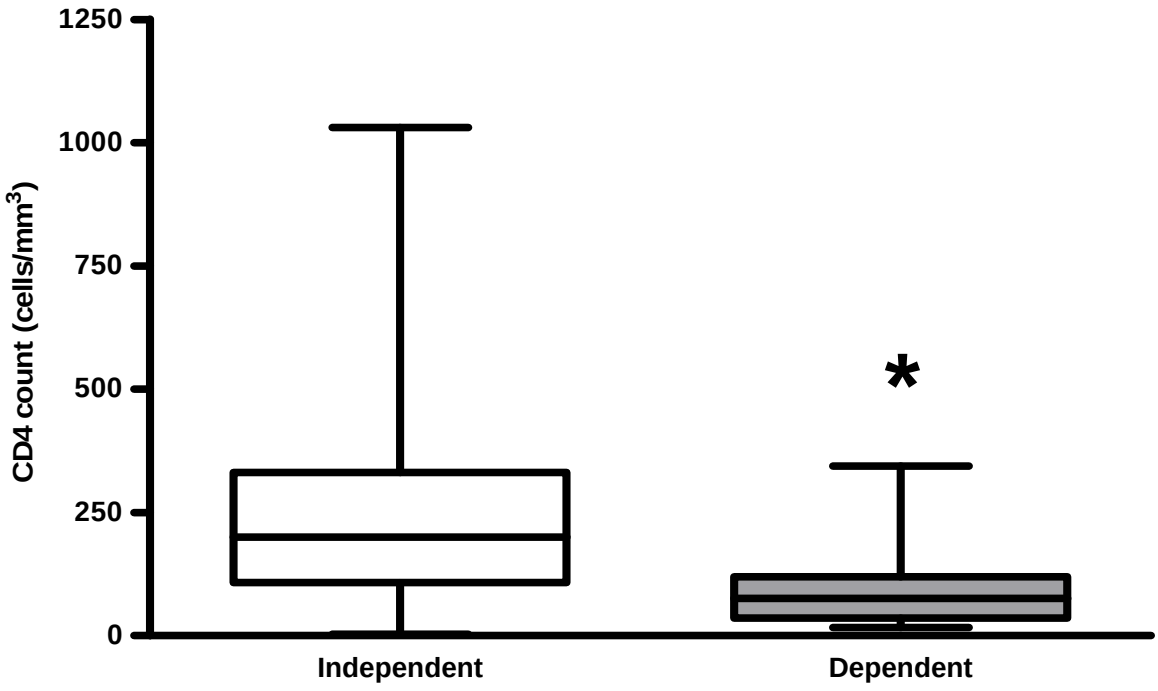

Figure 3.4: A box and whisker representation of the CD4 cell counts (cells/mm^3) of the patients who were functionally independent (n = 174) and functionally dependent on others for help (n = 12). The patients who were functionally dependent on others for help had a significantly lower CD4 cell count (* *P = 0.003*)

There was no significant difference between the total habitual physical activity levels of the patients who were functionally independent and dependent on others

for help (*P = 0.12*, Mann-Whitney test) and no significant correlation between total habitual physical activity levels and subjective functional dependency (Spearman's correlation, *P = 0.12*, r = -0.11).

Chapter 4 – Physiological Evaluation

4.1 Introduction

This chapter presents the findings of the physiological evaluation of a sample of HIV positive black female patients and HIV negative black female age-matched controls. The subjects' physical characteristics, blood analysis, aerobic capacity, muscle strength and habitual physical activity counts are presented.

4.2 Physical Characteristics

Ten HIV positive black females (aged 34 ± 6 years) recruited from an ARV roll out site in Johannesburg participated in this study. The patients were receiving first line treatment consisting of a combination of Lamivudine, Stavudine and Efavirenz, and had been taking these medications for a time period ranging from two months to 84 months (median = 7 months). Ten black age-matched HIV negative females (aged 32 ± 6 years) acted as their controls. Table 4.1 describes the physical characteristics of the HIV positive patients and HIV negative control subjects.

Table 4.1: Physical characteristics of the HIV positive patients and HIV negative controls

	HIV positive patients	HIV negative controls
Height (m)	1.59 ± 0.07	1.57 ± 0.05
Mass (kg)	68.5 ± 13.0	73.7 ± 15.7
BMI * (kg/m^2)	26.9 ± 3.3	29.7 ± 5.1
WHR #	0.81 ± 0.08	0.75 ± 0.11

Data are presented as mean ± SD

* BMI = Body Mass Index: calculated as mass (kg)/height^2 (m)

WHR = Waist Hip Ratio: calculated as waist circumference (cm)/hip circumference (cm)

There was no significant difference in the physical characteristics between the HIV positive patients and HIV negative controls (Unpaired t-test, $P > 0.05$)

4.3 Blood Analysis

The blood analysis results for the HIV positive patients and HIV negative controls are presented in Table 4.2.

Table 4.2: Blood test results of the HIV positive patients and HIV negative controls

	HIV positive patients	HIV negative controls	Reference Ranges
Hemoglobin (g/d*l*)	13.6 ± 1.3	13.7 ± 0.9	14.3 – 18..3
Hematocrit (%)	40 ± 3	41 ± 2	43.0 – 55.0
Resting Lactate (mmol/*l*)	2.2 ± 0.9	1.9 ± 0.4	2.0 -5.0
Glycated hemoglobin (%)	5.4 ± 0.3	5.9 ± 0.3[#]	< 7%
CD4 cell count (cells/mm^3)	246 ± 124	819 ± 194 [*]	500 - 2010

Data are presented as mean ± SD

[#] P = 0.0011

[*] P < 0.0001

The HIV negative control subjects had a significantly higher percentage glycated hemoglobin (HbA1c) than their HIV positive counterparts (*P = 0.0011*, t = 3.87, df = 18, Unpaired t-test). The HIV positive patients had a significantly lower CD4 cell count than the HIV negative control subjects (*P < 0.0001*, t = 7.86, df = 18, Unpaired t-test).

4.4 Aerobic Capacity

The predicted relative maximal oxygen uptake (VO_{2max}) of the HIV positive patients was not significantly different to that of the HIV negative controls (*P = 0.26*, t = 1.16, df = 18, Unpaired t-test; Figure 4.1).

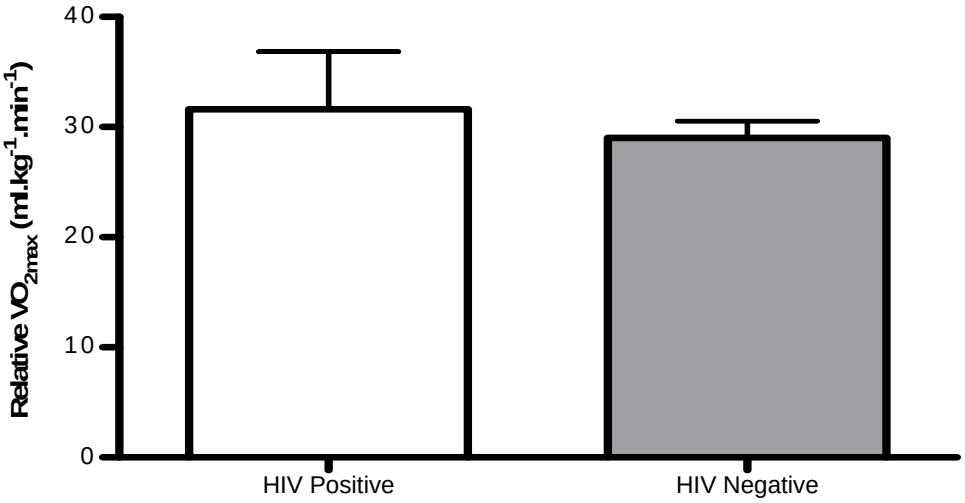

Figure 4.1: The predicted relative maximal oxygen uptakes (VO_{2max}, $ml.kg^{-1}.min^{-1}$) of the HIV positive patients and HIV negative controls (mean + SD).

4.5 Muscle Strength

The peak torque (Nm) of the hamstring and quadriceps muscles of the HIV positive patients and HIV negative controls are shown in Figures 4.2 and 4.3 respectively. No significant difference was found between the mean hamstring muscle peak torque (Nm) of the HIV positive patients (70.38 Nm) and the HIV negative controls (76.80 Nm) (*P = 0.22*, t = 1.27, df = 17, Unpaired t-test; Figure 4.2).

No significant difference was found between the mean quadricep muscle peak torque of the HIV positive patients (118.46 Nm) and the HIV negative controls (123.0 Nm) (*P = 0.87*, t = 0.16, df = 18, Unpaired t-test; Figure 4.3).

The mean handgrip strength of the HIV positive patients (35.69 kg) was not significantly different to the mean handgrip strength of the HIV negative controls (34.45 kg) (*P = 0.52*, t = 0.66, df = 18, Unpaired t-test).

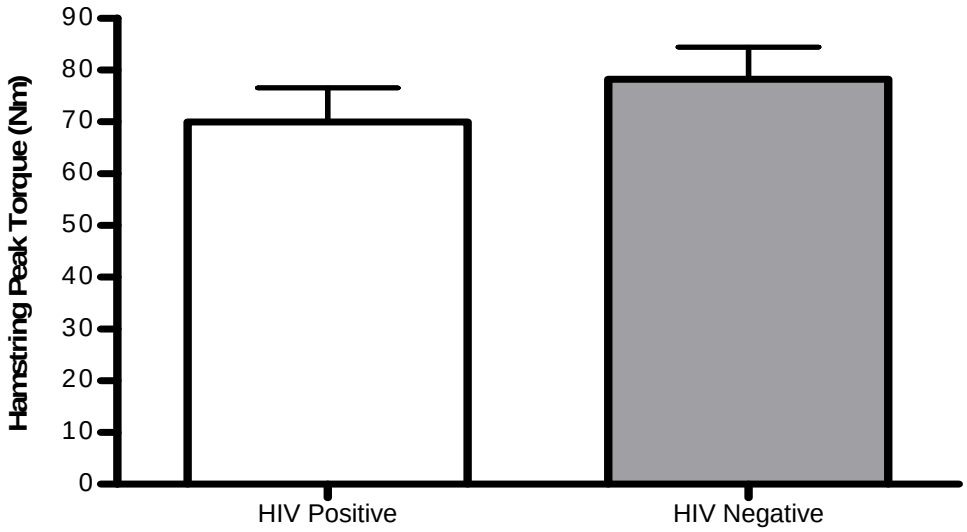

Figure 4.2: The hamstring muscle peak torque (Nm) of the HIV positive patients and HIV negative controls (mean + SD).

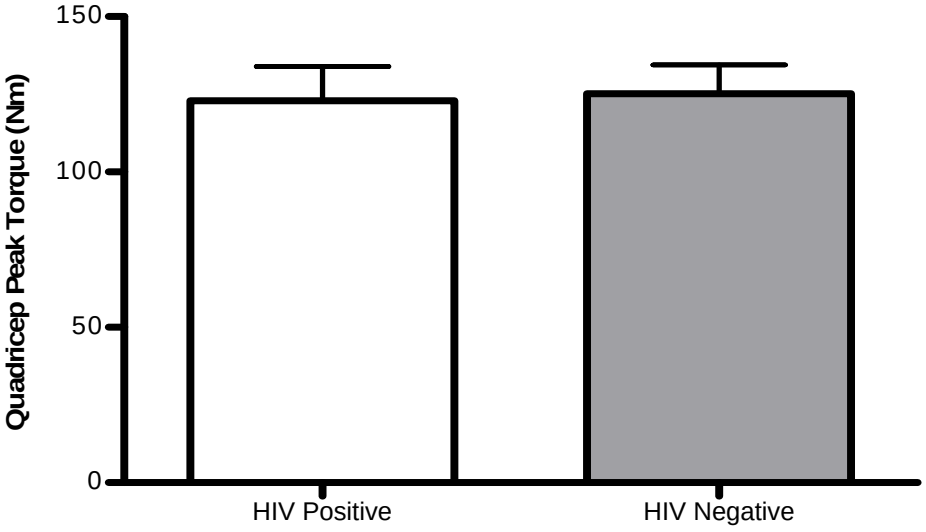

Figure 4.3: The quadricep muscle peak torque (Nm) of the HIV positive patients and HIV negative controls (mean ± SD).

4.6 Physical Activity Count

The seven day physical activity counts, expressed as a percentage of the maximum count for each individual, are shown in Figure 4.4. There was no significant difference between the physical activity counts of the HIV positive patients and HIV negative controls (*P = 0.55*, t = 0.61, df = 18, Unpaired T-test). The physical activity count includes the hours when the HIV positive patients and HIV negative controls were awake and asleep.

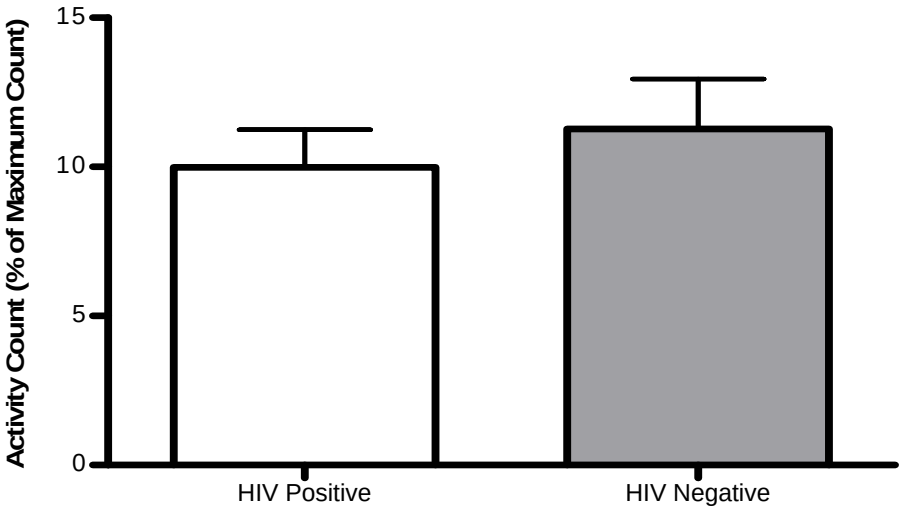

Figure 4.4: The seven day physical activity counts (% of maximum count for that individual) of the HIV positive patients and HIV negative controls (mean + SD). There was no significant difference in the activity counts between the HIV positive patients and HIV negative controls (*P = 0.55*).

Chapter 5 – Discussion and Conclusions

5.1 Discussion

The purpose of this study was to determine the association between HIV infection, and use of antiretroviral (ARV) medication on habitual physical activity (PA) levels, functional independence as well as measured exercise capacity and measured activity counts, in a sample of HIV positive South African adults. This chapter discusses and contextualizes the results of the Lifestyle and Physical Activity Questionnaire as well as the results of the Physiological Evaluation.

A convenience sample of black HIV positive patients who frequented an antiretroviral (ARV) roll out site within the Johannesburg area was recruited to participate in this study. A total of 186 HIV positive male and female patients completed the questionnaire, and a total of 10 HIV positive females participated in the physiological evaluation. The majority of the patients fell into a lower socio-economic bracket and were unemployed. Those that were employed reported a monthly income of between R1000 and R5000. The majority of patients had obtained a matric certificate and resided within a formal township.

The study assessed firstly, using a Lifestyle and Physical Activity Questionnaire, the relationship between CD4 cell count (a marker of immune status), amount of habitual physical activity (PA) and degree of subjective independence in a group of black male and female HIV positive out-patients (n = 186). These patients were recruited from an antiretroviral (ARV) roll out site within the Johannesburg area and were either not taking ARV medication (n = 65), or had been on the ARV medication (n = 121) for a time period ranging from two weeks to 32 months (median time = 7 months). As far as I am aware, this study is the first to assess this relationship in a SA population and forms a valuable foundation for further investigation, particularly the relationship between long term ARV medication use (greater than three years) and physical well-being in HIV positive individuals.

Analysis of the questionnaire showed that there was a positive and significant correlation between CD4 cell count and length of time on ARV medication, implying that the long term use of ARV medication, albeit only for a median time of seven months in these patients, improves CD4 cell count and helps maintain immune status. The positive and significant correlation between CD4 cell count and total habitual physical activity (PA) levels suggests an association between CD4 cell count and total habitual habitual PA. Furthermore, patients who considered themselves to be functionally independent, and not requiring help from others in performing tasks of daily living, had a significantly higher CD4 cell count than those patients who needed help to perform these tasks. Therefore, my results show that the use of ARV medication, albeit only for a median time of seven months in my patients, is associated with a higher CD4 cell count (an indicator of slower HIV disease progression) which translates into an increased total habitual PA level and greater sense of functional independence.

ARV therapy, as with any other drug therapy, is associated with acute and chronic drug administration side effects which could decrease physical well being and impact negatively on functional independence. Despite the literature reporting the possible physical activity limiting side effects associated with the use of ARV medication, and many of my patients experiencing one or more of these side effects within the past year or since commencing ARV administration, 85% of these patients still believed that the use of ARV medication increased their total habitual PA levels. Furthermore, the total habitual PA levels of the patients who had experienced one or more side effects from ARV administration and those patients who had not experienced any side effects, were not statistically different. Therefore, these results highlight the benefit of ARV medication, despite side effects, in improving immune status, increasing PA levels and maintaining functional independence in HIV positive patients. The patients in my study had only been using ARV medication for a relatively short time (median time of seven months; range: two weeks to 32 months), and therefore more research would need to be done to determine whether the often more serious side effects associated

with longer administration of ARV medication would begin to have a negative impact on physical well-being.

In the second part of my study, I assessed the full blood counts, aerobic capacity, lower limb and handgrip strength, and seven day physical activity (PA) counts of ten HIV positive black females recruited from the same Johannesburg ARV roll out site. All these patients were on first line ARV treatment consisting of Stavudine, Lamivudine and Efavirenz and had been taking ARV medication for a time period ranging from two months to 84 months (median time = 7 months). Ten HIV negative age-matched black females acted as their controls. My results show no significant differences in hemoglobin, hematocrit, and resting blood lactate levels between the two groups. The HbA1c (glycated hemoglobin) level, an indicator of plasma glucose concentration over a time period of approximately three months, was significantly lower in the HIV positive patients compared to the HIV negative controls. However, both groups' HbA1c results were within the normal range. The body mass index (BMI), although high in both groups, and waist hip ratio (WHR) were not statistically different between the two groups. I have also shown that the aerobic capacity (predicted VO_2 max) and lower limb and hand muscle strength of the two groups were not significantly different. Although a small representation of the HIV positive population, my results show that the patients who are infected with HIV and have been taking ARV medication for a median time of 7 months are as aerobically and muscularly strong as their HIV negative counterparts. In addition, the seven day PA counts (actigraphy) of the HIV positive patients were not statistically different to those of the HIV negative controls, suggesting that they were as physically active as the HIV negative controls. My results could suggest that either the HI virus does not negatively impact on physical well being until much later in the progression of the disease, or that the use of ARV medication, although only short term in this group, has slowed down the disease progression, and maintained physical well being. If the latter is true, the documented side effects of ARV medication, as reported in the literature and in the questionnaire, have not negatively affected physical well being in these HIV positive patients. However, as suggested

previously, more research to determine if side effects from longer ARV use will negatively impact on physical well-being is needed.

The results obtained from my two studies are not representative of the South African HIV positive population in its entirety. As stated by the constitution, HIV positive patients have a right not to disclose their HIV status, and therefore access to an HIV positive population was limited to a sample from a major public HIV clinic within the Johannesburg area who fell into a lower socio-economic bracket. Therefore, my study did not include HIV positive patients from the private health sector nor did it include patients from different racial, cultural and socio-economic backgrounds other than this specific black population group.

Although the sample size of the questionnaire based study was relatively small, the use of a questionnaire was still the easiest and least expensive and time consuming technique to assess the habitual physical activity levels in this population. The Lifestyle and Physical Activity Questionnaire was developed to compare the habitual physical activity behaviours between different population groups, and not to assess the habitual physical activity levels in an HIV positive population only. Since the questionnaire was used to obtain exploratory data, it was not validated specifically in an HIV positive population and as such is a limitation of the study. Validation of a questionnaire required comparison of the results to that of a control group i.e., HIV negative participants, which was beyond the scope of this study, both ethically and logistically.

Another limitation of this method of assessment is the subjective nature of a self-reported questionnaire. Questionnaire responses are dependent on a patient's bias, his/her inaccurate perception of the frequency and intensity of physical activity performed as well as his/her ability to recall the exact volume of physical activity performed. Also, patients are influenced by the perceived desirability of their responses i.e., what would be considered a good answer? As a result, most patients will overestimate the amount of physical activity performed. Another limitation is that every day tasks which contribute to habitual physical activity,

such as walking and domestic activities, are easily overlooked as many patients perceive physical activity as being structured exercise, rather than any type of bodily movement resulting from skeletal muscle contraction. Therefore, physical questionnaires are valuable in obtaining data from large population groups but are limited in their accuracy.

For comparative purposes, physical activity information gained from the questionnaire used in this study was converted to an estimate of caloric expenditure or multiples of resting metabolic rate (METS). One MET is defined as the energy expended during quiet sitting and is the ratio of work metabolic rate to a standard resting metabolic rate of 1.0 (4.184kJ per kg per hr) (Ainsworth *et al.*, 2000). Although METS (multiples of average resting metabolic rate) will be the same across all populations, conversion into actual energy expenditure for comparison purposes between HIV positive and HIV negative populations cannot be accomplished accurately because of the higher resting energy expenditure (EE) and hypermetabolic nature of HIV positive patients (Macallan *et al.*, 1995; Suttman *et al.*, 1993). More research into this field is required and as such, this study did not compare the total habitual physical activity levels (MET hours per month) between HIV positive and HIV negative individuals. Furthermore, because potential HIV negative controls subjects would have to be asked to disclose their HIV status, or many costly HIV tests and counseling sessions would have to be performed to determine their status, I was ethically and financially unable to administer the questionnaire to HIV negative control subjects. As such, the questionnaire was only completed by HIV positive patients and did not compare the habitual physical activity levels between HIV positive patients and HIV negative control subjects.

A physiological evaluation was therefore completed which investigated the aerobic capacity, lower limb muscle strength, hand grip strength and physical activity counts (actigraphy) in a group of black HIV positive females and a group of age-matched HIV negative control subjects. A limitation of the physiological evaluation was the small sample size. HIV positive patients who were

approached were reluctant to participate in the study for various reasons. It was also difficult to obtain HIV negative control subjects, firstly, because some subjects were afraid and therefore unwilling to take an HIV test, and secondly, due to the difficulty of finding HIV negative black females who were age-matched to the HIV positive patients. Post hoc analysis revealed that approximately 30 more subjects would be required to see significant differences in aerobic capacity, muscle strength and physical activity counts between the two groups, and not necessarily greater in the HIV negative controls. Although the HIV positive patients and HIV negative controls did not complete the Lifestyle and Physical Activity Questionnnaire, a limitation in the study, I was able to objectively measure their physical activity counts using activity monitors (actigraphy), a novel technique which is as reliable, if not more accurate, than questionnaire based activity studies. Indeed, this study is the first to use activity monitors to objectively measure physical activity counts in HIV positive patients. Another limitation of this study was the use of a submaximal bicycle ergometer test. The majority of patients had not been on any form of bicycle before participation in this study and therefore struggled to maintain peddle cadence during the test. However, this was true for both groups and the use of this test was not biased toward a specific group. A better alternative for future studies would be the six minute walk test (American Thoracic Society, 2002; Solway *et al.*, 2001) to assess aerobic fitness of individuals not comfortable using a stationary cycle ergometer. The six minute walk test is also a better reflection of the functional exercise level required for daily physical activities.

Despite these limitations, my study has still made significant inroads into the assessment of total habitual physical activity habits and exercise capacity of HIV positive individuals. ARV medication is used to improve the immune status of HIV infected individuals by increasing and stabilizing CD4 cell count and decreasing HIV viral load to undetectable levels (Grimwood, 2004; Department of Health, 2003). I have shown that the use of ARV medication, despite side effects, results in a higher CD4 cell count, and a higher habitual physical activity level and greater functional independence. Furthermore, HIV positive women

who are taking ARV medication have an aerobic capacity, muscle strength and physical activity count which is not statistically different to their HIV negative peers.

South Africa is said to have more people infected with HIV than any other country (WHO, 2006), a statistic which places a great financial and social burden on the infrastructure of the country. HIV infection is associated with various physiological symptoms and manifestations. Various metabolic syndromes are observed as the disease progresses (Stringer *et al.*, 2001), which can severely decrease physical activity levels and functional independence. A major component of HIV infection is severe body mass loss and body wasting (Hellerstein *et al.*, 1990; Chlebowski *et al.*, 1989; Kottler *et al.*, 1985) and the morbidity of the wasting process plays a major role in the decreased quality of life of these patients (Hellerstein *et al.*, 1990). The subsequent decreased muscle mass causes a decrease in the overall functional status of individuals infected with HIV, including decreased exercise performance, aerobic capacity and lower body muscle strength (Grinspoon *et al.*, 1996). Weakness and fatigue are among the most troubling and debilitating symptoms reported by HIV positive patients (Hellerstein *et al.*, 1990), and can certainly decrease functional independence and decrease quality of life. However, in my study, the female HIV positive patients showed no signs of severe body mass loss or body wasting and their aerobic capacity, muscle strength and physical activity counts were not significantly different to their age-matched counterparts. Perhaps the HI virus does not negatively impact on physical well-being until much later in the progression of the disease, or the use of ARV medication, albeit only short term in this group, and not without side effects, has improved immune status and physical well-being.

In this study, 65% of the patients who completed the questionnaire, and all the patients who participated in the physiological evaluation, were taking ARV medication. Although ARV medication is used specifically to increase CD4 cell count and to decrease the HIV viral load in patients infected with the disease, the

South African Department of Health has set criteria which have to be met before ARV treatment can commence (Department of Health, 2003). Only patients who have a CD4 cell count of less than 200 cells/mm^3 or lower, or are symptomatic qualify for ARV treatment. Once ARV treatment has been started, patients will take the medication for life to prevent drug resistance, despite an increase in their CD4 cell count, suppression of viral load and increased health and well being (Griffen, 2003). The results of my questionnaire show that use of ARV medication is associated with enhanced immunity which has a positive impact on total physical activity levels and functional independence. Bopp *et al.* (2004) showed that an inverse relationship exists between mean physical activity levels and viral load, suggesting increased activity levels has beneficial effects on viral load of HIV infected individuals. Furthermore, the female HIV positive patients who were taking ARV medication had an aerobic capacity, lower limb muscle strength, hand grip strength and seven day physical activity count which were not statistically different to their age-matched HIV negative counterparts.

The majority of patients in this study were on first line treatment, consisting of Lamivudine and Stavudine (nucleoside reverse transcriptase inhibitors or NRTI) and either Efavirenz or Nevirapine (non-nucleoside reverse transcriptase inhibitors or NNRTI). The side effects associated with the use of ARV medication have been well documented in the literature. ARV therapy has been associated with troubling symptoms such as fatigue, dyspnoea (shortness of breath) and metabolic and body composition abnormalities (Hellerstein, 2001; Jones *et al.*, 2001; Stringer *et al.*, 2001) as well as gastrointestinal pain, nausea, vomiting, diarrhea, loss of appetite, constipation and heartburn (Department of Health, 2004).

Nucleoside reverse transcriptase inhibitors (NRTI) have been associated with side effects such as diarrhea, pancreatitis, and lactic acidosis. Short term side effects associated with NNRTIs include dizziness, insomnia, abnormal dreams and hallucinations (with Efavirenz) and nausea and vomiting (with Nevirapine). These side effects are considered short term and resolve themselves after a few

weeks on ARV therapy. ARV therapy, especially combination therapy using NRTIs, has also been shown to disrupt normal mitochondrial functioning (Cade *et al.*, 2004), which negatively impacts on ATP production via oxidative phosphorylation. This limitation in oxygen delivery to working muscles has been identified as a mediator of diminished aerobic capacity, and can increase exercise intolerance. Distal symmetric polyneuropathy, another side effect of ARV medication, is characterized by a loss of primary afferent fibers, resulting in distal axonal degeneration and symptoms of pain and paraesthesia in the distal extremities and can cause gait difficulties (Verma *et al.*, 2005). The symptoms of distal axonal degeneration and decreased muscle oxygen delivery, as well as the other side effects of ARV medication, can lead to decreased levels of PA, decreased functional independence and poor quality of life. However, in my study, the median time the patients were taking ARV medication was seven months, by which time most of the short term side effects associated with NRTI and NNRTI use had been resolved. No difference in aerobic capacity, muscle strength and physical activity counts were seen between the HIV positive patients and HIV negative controls who participated in the physiological evaluation. These results suggest that the use of ARV medication is beneficial in improving and maintaining the functional capacity of HIV positive patients, despite the short term side effects.

The long term side effects associated with ARV medication use include unwanted changes in body composition (lipodystrophy), impaired glucose metabolism (glucose intolerance and insulin resistance which can lead to the development of diabetes mellitus) and impaired lipid metabolism (dyslipidemia), including elevated tryglycerides and cholesterol (Department of Health, 2004; Cade *et al.*, 2003; Stringer *et al.*, 2001; Grunfeld *et al.*, 1992). These symptoms are mainly associated with the use of protease inhibitors (PIs) but have also been associated with NRTIs and NNRTIs (Department of Health, 2004; Grimwood, 2004). Lipodystrophy manifests after approximately two years, diabetes mellitus after four years and dyslipidemia after five years (Chow *et al.*, 2006).

No evidence of body wasting or lipodystrophy was observed in the HIV positive patients who were taking ARV medication. This result is reflected in the BMI and WHR values obtained for these patients. Although the BMI could be considered high by normal standards, these values are not uncommon in black females. However, more accurate anthropometric protocols should be employed over a period of time to assess body composition changes. Glycated hemoglobin (HbA1c) is used as an indicator of the average plasma glucose concentration over a period of approximately three months and is used as a clinical tool in the diagnosis of diabetes mellitus (Marshall *et al.*, 2000; McCane *et al.*, 1994). In the physiological evaluation, the HIV positive patients had a significantly lower HbA1c level than the HIV negative controls, even though both results were within the normal range of 4.3% to 6.3% (Peters *et al.*, 1996). An HbA1c level of over 7% is recommended as the cut off for diagnosing diabetes. However, the HIV positive patients who participated in this research had only been taking ARV medication for a median time of seven months where it is unlikely that the long term side effects of ARV medication use would have manifested in that time period. Also, fasting cholesterol levels were not measured which would provide some indication of the lipid metabolism of the HIV positive patients taking ARV medication. It is difficult to determine if these long term side effects associated with ARV medication use will impact negatively on the habitual physical activity levels and functional status of these patients. Therefore a longitudinal study monitoring the effects of long term adverse drug reactions on habitual physical activity levels and functional capacity should be conducted.

5.2 Conclusion

HIV is a rapidly growing epidemic despite high profile prevention campaigns and treatment advances. People living with HIV are said to experience high levels of body impairments, activity limitations and participation restrictions. With the introduction of antiretroviral (ARV) therapy, people infected with HIV have an improved immune function as well as a better quality of life. However, little is known about the effect of HIV disease on a person's habitual physical activity

levels as well as the effect of ARV use on exercise capacity and functional independence. The results of my study have shown that the use of ARV medication improves the immune status of HIV infected individuals (reflected by a higher CD4 cell count), which translates into higher habitual physical activity levels and a greater sense of functional independence. In addition, I have also shown that the use of ARV medication results in no physiological difference with regard to exercise capacity, muscle strength and measured physical activity counts between HIV positive patients and their HIV negative counterparts. This result suggests that patients infected with HIV who are taking ARV medication are not at a disadvantage when performing tasks of daily living requiring some degree of endurance and are able to maintain their functional independence.

5.3 Recommendations for future work

This study provides a valuable foundation for future studies investigating the relationships between HIV infection and the physical well being of patients infected with HIV. It is recommended that future studies focus on the effects of long term ARV use (greater than three years) on the habitual physical activity levels and functional well being of patients infected with HIV. Therefore, a longitudinal study which follows patients over a long period of time starting from diagnosis and commencement of ARV treatment, should be conducted in order to effectively assess the impact of long term ARV medication side effects on the functional status of patients infected with HIV.

When assessing the relationship between HIV infection and physical activity levels, it is recommended that potential confounders, such as age, gender, socioeconomic status, stage of disease, prevalence of opportunistic infections, etc. be taken into account. This would enable a more accurate assessment of the factors that contribute to physical activity in this population. Also, assessing the socioeconomic status of HIV positive individuals (and the South African population as a whole) is a complex issue with regard to income *vs*. area of residence etc. it is recommended that more detailed questions with regard to

socioeconomic data be asked to provide a more representative picture. Investigation of the mechanisms of how HIV infection affects a patient's ability to remain functionally independent is also suggested for future work.

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Appendix A

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Kinsey

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M050525**
PROJECT	A Comparison Between the Physical Activity Levels of HIV Postive Patients with Different CD4 Counts
INVESTIGATORS	Ms K Kinsey
DEPARTMENT	School of Physiology
DATE CONSIDERED	05.05.27
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 05.06.20 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor: Ms I Chantler

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to th Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Kinsey

CLEARANCE CERTIFICATE	**PROTOCOL NUMBER M051127**
PROJECT	The Relationship between Exercise Capacity and Habitual Physical Activity in an HIV Positive SA Adult Population taking....
INVESTIGATORS	Ms K Kinsey
DEPARTMENT	School of Physiology
DATE CONSIDERED	05.11.25
DECISION OF THE COMMITTEE*	Approved unconditionally

Unless otherwise specified this ethical clearance is valid for 5 years and may be renewed upon application.

DATE 05.11.25 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable

cc: Supervisor : Ms J Chantler

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10005, 10th Floor, Senate House, University.
I/We fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee. **I agree to a completion of a yearly progress report.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

University
of the Witwatersrand,
Johannesburg

Human Research Ethics Committee (Medical)
(formerly Committee for Research on Human Subjects (Medical)
Secretariat: Research Office, Room SH10005, 10th floor, Senate House • Telephone: +27 11 717-1234 • Fax: +27 11 339-5708
Private Bag 3, Wits 2050, South Africa

4 May 2006

Ms K Kinsey
School of Physiology
Faculty of Health Sciences
University

Dear Ms Kinsey

RE: PROTOCOL M051127

This letter serves to confirm that the Chairman of the Human Research Ethics Committee (Medical) has approved the amendment to the abovementioned protocol. Copy attached.

Yours sincerely,

Anisa Keshav (Ms)
Secretary
Human Research Ethics Committee (Medical)

Appendix B

LIFESTYLE AND PHYSICAL ACTIVITY QUESTIONNAIRE

Please answer the following questions by crossing (X) the right block or writing down your answer in the space provided.

Example of how to complete this questionnaire
Gender
If you are female

Male	1
Female	X

SECTION A – BACKGROUND INFORMATION

This section of the questionnaire refers to background information. All results will be treated with absolute confidentiality. Thank you for taking the time to fill in this questionnaire.

1. Gender

Male	1
Female	2

2. Age (in complete years)

3. Race

Black	1
White	2
Coloured	3
Indian/Asian	4

4. Home language

English	1
Afrikaans	2
Zulu	3
Sotho	4
Xhosa	5
Tswana	6
Swazi	7
Ndebele	8
Venda	9
Tsonga	10
Other (please specify) _____	11

5. Are you employed?

Yes	1
No	2

6. If yes, what is your occupation?

_____

7. How much do you earn per month?

More than R20 000	1
R10 000 – R20 000	2
R5000 – R10 000	3
R1000 – R5000	4
Less than R1000	5
I do not earn a salary	6

8. What is your highest educational qualification?

Post-graduate degree(s)	1
Bachelor degree(s)	2
Post Matric certificate/diploma	3
Grade 12 (Matric, Std 10)	4
Grade 8 (Std 6) – Grade 11 (Std 9)	5
Grade 1 – Grade 7 (Std 5)	6
I did not go to school	7

9. How would you describe the area in which you permanently live?

Upper class suburb	1
Middle class suburb	2
Low income housing project	3
Township (formal settlement)	4
Township (informal settlement)	5
Traditional village	6
I am homeless	7

10. Which of the following amenities do have in your permanent home?

Running water	1
Electricity	2
Flushing toilet inside your house	3
Flushing toilet outside your house	4
Working oven	5
Working microwave	6
Working television	7
Working radio	8
Working car	9

SECTION B – HIV INFORMATION

THIS INFORMATION IS TO BE OBTAINED FROM PATIENT RECORDS

11. When where you first diagnosed with HIV?

0 – 6 months	1
6 months – 1 year	2
1 – 2 years	3
2 – 3 years	4
3 – 4 years	5
4 – 5 years	6
More than 5 years	7
Unknown	8

12. When was your last blood test to determine your CD4+ count?

In the last 3 months	1
3 months – 6 months ago	2
6 months - 1 year ago	3
1 – 2 years ago	4
2 – 3 years ago	5
3 – 4 years ago	6
More than 4 years ago	7
Unknown	8

13. What is the patient's current CD4+ count (in cells/mm^3)

_____

14. Are you currently on any of the following anti-retroviral medication?

I am not on any medication	1
3TC (Lamivudine)	2
Combiver (Lamivudine + Zidovudine)	3
Crixivan (Indinavir)	4
Forte-Vase (Saquinavir)	5
Invi-Rase (Saquinavir mesylate)	6
Kaletra (Lopinavir + Ritonavir)	7
Norvir (Ritonavir)	8
Ritrovir (Zidovudine)	9
Stavir (Stavudine)	10
Stocrin (Efavirenz)	11
Videx (Didanosine ddI)	12
Viramune (Nevirapine)	13
Zerit (Stavudine)	14
Ziagen (Abacavir)	15
Other (please specify) _____	16

15. If you are on antiretroviral treatment, for how long have you been taking the medication (in months)?

_____

16. Have you suffered from any of the following side effects since using anti-retroviral medication?

I have not had any side effects from the medication	1
Dizziness	2
Nausea and/or vomiting	3
Abdominal discomfort/pain	4
Diarrhea	5
Constipation	6
Heart burn	7
General fatigue	8
Body mass loss	9
Any kind of body pain (please specify) _____	10
Other (please specify) _____	11

17. Do you think that the antiretroviral treatment has increased or decreased your physical activity levels?

Increased activity levels	1
No change in activity levels	2
Decreased activity levels	3

18. Have you suffered from any of the following conditions in the past year?

I have not been sick in the past year	
Pneumonia	1
Tuberculosis	2
Herpes	3
Hepatitis	4
Bacterial respiratory infections	5
Kaposi's sarcoma	6
Other (please specify) _____	7

19. Have you suffered from any of the following symptoms as the result of being sick in the past year?

Fatigue	1
Sleepiness	2
Depression	3
Decreased appetite	4
Lack of interest in appearance/grooming	5
Decreased social behaviour	6

20. Do you think that your physical activity levels have increased or decreased as a result of being sick in the past year?

Decreased activity levels	1
No change in activity levels	2
Increased activity levels	3

SECTION C – INACTIVITY

This section deals specifically with any condition or situation which results in inactivity.

21. Have any of the conditions listed in questions 16 and 18 caused you to spend more than one week in a bed or chair?

No	1
Yes	2

21.1 If yes, for how many weeks were you in a bed or chair?

1 week	1
2 – 4 weeks	2
4 – 6 weeks	3
6 – 8 weeks	4
More than 8 weeks	5

22. Do you have difficulty doing any of the following activities as a result of being HIV positive?

Getting in or out of bed or a chair	1
Walking across a small room without resting	2
Walking for 10 minutes without resting	3
Dressing yourself	4
Washing/bathing yourself	5
Getting in or out of a car/bus/taxi	6
Working in your occupation	7
Participating in recreational activity	8

23. Approximately how many hours do you sleep at night?

I do not sleep at night	
1 – 2 hours	1
2 – 4 hours	2
4 – 6 hours	3
6 -8 hours	4
8 – 10 hours	5
10 -12 hours	6
More than 12 hours	7

24. Approximately how many hours do you sleep during the day?

I do not sleep during the day	1
1 – 2 hours	2
2 – 4 hours	3
4 – 6 hours	4
6 -8 hours	5
8 – 10 hours	6
10 -12 hours	7
More than 12 hours	8

25. Do you think that your sleep is affected in any way by your HIV status?

Yes	1
No	2
No opinion	3

26. In general, how many hours per day, during the week (Monday to Friday) do you spend watching television, listening to the radio or reading?

1 – 2 hours	1
2 – 4 hours	2
4 – 6 hours	3
6 -8 hours	4
8 – 10 hours	5
10 -12 hours	6
More than 12 hours	7

27. In general, how many hours per day, during the weekend (Saturday and Sunday) do you spend watching television, listening to the radio or reading?

1 – 2 hours	1
2 – 4 hours	2
4 – 6 hours	3
6 -8 hours	4
8 – 10 hours	5
10 -12 hours	6
More than 12 hours	7

SECTION D – OCCUPATIONAL ACTIVITY

This section focuses on any activity performed as a result of your occupation. Only answer this section if you are employed.

28. How many days per week do you work?

1 day per week	1
2 days per week	2
3 days per week	3
4 days per week	4
5 days per week	5
6 days per week	6
7 days per week	7

29. How do you travel to work?

Walk	1
Bicycle	2
Car/bus/taxi/train	3
I stay at my employer's residence	4
Other (please specify) _____	5

29.1. If you walk or cycle to work, at what pace do you walk or cycle?

Brisk/fast	1
Moderate/medium	2
Leisurely/slow	3

29.2. If you walk or cycle to work, how long does it take you to get to work and back home again?

Less than 1 hour	1
1 – 2 hours	2
2 -3 hours	3
3 - 4 hours	4
More than 4 hours	5

30. Approximately how many hours do you spend traveling per day, by car, bus, taxi or train?

Less than 1 hour	1
1 – 2 hours	2
2 – 4 hours	3
4 – 6 hours	4
6 -8 hours	5
8 – 10 hours	6
10 -12 hours	7
More than 12 hours	8

31. At work, for how many hours do you sit per day?

Less than 1 hour	1
1 – 2 hours	2
2 – 4 hours	3
4 – 6 hours	4
6 -8 hours	5
8 – 10 hours	6
10 -12 hours	7
More than 12 hours	8

32. At work, for how many hours do you stand per day?

Less than 1 hour	1
1 – 2 hours	2
2 – 4 hours	3
4 – 6 hours	4
6 -8 hours	5
8 – 10 hours	6
10 -12 hours	7
More than 12 hours	8

33. At work, for how many hours do you walk?

Less than 1 hour	1
1 – 2 hours	2
2 – 4 hours	3
4 – 6 hours	4
6 -8 hours	5
8 – 10 hours	6
10 -12 hours	7
More than 12 hours	8

34. At work, do you lift heavy loads?

Never	1
Seldom	2
Sometimes	3
Often	4
Always	5

35. After work, are you tired?

Never	1
Seldom	2
Sometimes	3
Often	4
Always	5

36. Do you think that you are more tired after work than you were when you were HIV negative?

Yes	1
No	2

SECTION E – HOUSEHOLD ACTIVITY

This section focuses on any activity that you do in your house.

37. Please mark any of the following household activities which you do regularly. Please fill in the following information:
- Minutes per day (1 – 180min)
- Days per week (1 – 7 days)
- Weeks per month (1 – 4 weeks)
- Months per year (1 – 12 months)

No	Activity	Min/day	Days/wk	Wks/mnth	Mnths/yr
Eg	**Cooking**	**20**	**7**	**4**	**12**
1	Sweeping floors				
2	Heavy cleaning eg windows				
3	Mopping				
4	Washing dishes – standing				
5	Vacuuming				
6	Cooking – standing				
7	Food shopping – walking				
8	Ironing				
9	Scrubbing floors				
10	Carrying water				
11	Carrying wood				
12	Hanging up washing				

SECTION F – RECREATIONAL ACTIVITY

This section refers to any recreational or leisure time activity in which you have participated in the last year.

38. Please mark any of the following recreational activities in which you have regularly participated in the past year. Please fill in the following information:

- Minutes per day (1 – 180min)
- Days per week (1 – 7 days)
- Weeks per month (1 – 4 weeks)
- Months per year (1 – 12 months)

No	Activity	Min/day	Days/wk	Wks/mnth	Mnths/yr
eg	**Soccer**	**30**	**3**	**4**	**6**
1	Bicycling for pleasure				
2	Circuit training (gym)				
3	Body mass training (gym)				
4	General health club exercise				
5	Running (treadmill)				
6	Rowing (machine)				
7	Ballet/modern dancing				
8	Aerobics				
9	Fishing				
10	General gardening				
11	Carpentry				
12	Jogging				
13	Running				
14	Badminton				
15	Basketball				
16	Bowls				
17	Boxing				
18	Cricket				
19	Rugby				
20	Golf (walking, carrying clubs)				
21	Golf (using golf cart)				
22	Gymnastics				
23	Hockey				
24	Horseback riding				
25	Judo, karate etc				
26	Orienteering				
27	Soccer				
28	Squash				
29	Tennis				
30	Volleyball				
31	Hiking				
32	Rock climbing				
33	Walking for pleasure				
34	Canoeing/ rowing for pleasure				
35	Sailing				
36	Skipping				
37	Swimming slowly				
38	Swimming fast				
39	Water aerobics				
40	Playing with children				

39. Do you think your physical exercise habits have been negatively affected by your HIV status?

No	1
Yes	2

40. Are you interested in participating in an exercise test at the Wits Exercise Lab?

Yes	1
No	2

41. If you would like us to contact you if you require more information, please provide a telephone number or email address in the space provided below. Your details will remain confidential.

Telephone number _____

Email address _____

Postal Address _____

_____

Thank you for taking the time to fill in this questionnaire.