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Preliminary investigation into the exercise endurance of HIV infected school going children aged seven to ten years

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PRELIMINARY INVESTIGATION INTO THE EXERCISE ENDURANCE OF HIV INFECTED SCHOOL GOING CHILDREN AGED SEVEN TO TEN YEARS

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg in partial fulfilment of the requirements for the degree of Master of Science Physiotherapy.

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ABSTRACT

HIV is a global epidemic with the majority of people infected living in Sub-Saharan Africa. The era of Highly-Active Antiretroviral Therapy has resulted in HIV infected children living longer lives and more commonly reaching school going age. These children are expected to participate at the same level as their peers despite the numerous effects that HIV and HAART have on the body. The aim of this cross sectional comparative study was to compare the exercise endurance of a group of HIV infected children to that of their uninfected peers.

Sixty children aged between seven and ten years were enrolled in the study; 30 HIV infected children and 30 children not infected with HIV. Children were assessed using the six minute walk test (6MWT) according to American Thoracic Society guidelines.

The two groups were well matched in terms of socio-economic status, gender and age. Statistically significant differences were found when comparing anthropometric measurements of height and weight with HIV infected participants being shorter and weighing less than their non-infected peers. The distance walked in the 6MWT was significantly reduced in the HIV infected participants with these children walking 57.86 metres less than the non-infected participants. It was also found that HIV infected children had significantly lower heart rates at all stages of testing. Correlations were found between the distance walked in the 6MWT and average and maximum heart rates.

This study confirms that the exercise endurance of a group of HIV infected children is significantly reduced when compared to their age matched non-infected peers. It indicates the need for further investigation into the exercise endurance in HIV-infected children in a larger more representative sample of the population. Further investigation into the possible benefits of the prescription of exercise programmes in children needs to be done.

DECLARATION

I, Alison – Jane Walker, declare that this research report is my own unaided work except for the persons listed in my acknowledgements. It is being submitted in partial fulfilment of the requirements of the degree of Master of Science, Physiotherapy, at the University of Witwatersrand. It has not been submitted before for any other degree or examination in any other university.

Signed this day in Johannesburg



Signature

27 / 08 / 2014

Date

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LIST OF ABBREVIATIONS

3TC	Lamivudine
6MWT	Six Minute Walk Test
ABC	Abacavir
ADL's	Activities of Daily Living
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
AZT	Zidovudine
BMD	Bone Mineral Density
BMI	Body Mass Index
BP	Blood Pressure
BPM	Beats per minute
CNS	Central Nervous System
CRC	Chronic Radiographic Changes
D4T	Stavudine
EFV	Efavirenz
HAART	Highly-Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HR	Heart Rate
NVP	Nevirapine
SATS	Oxygen saturation
TDF	Tenofovir

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CHAPTER 1: INTRODUCTION

HIV is a global epidemic with the number of people living with the disease being estimated at 33.3 million people in 2009. This number was 23% higher than in 1999 (World Health Statistics 2011 report). In South Africa, amongst children aged 0-14 years, it was estimated that there were 63 600 new HIV infections in 2011 (Statistics South Africa: P0302, 2011). South Africa started its Highly-Active Antiretroviral Therapy (HAART) rollout in 2004 and by 2010 it was estimated that 105 123 children (<15 years) were receiving antiretroviral therapy (Statistics South Africa: P0302, 2011). In a group of South African children, early HAART has been shown to reduce early infant mortality by 76% and HIV progression by 75% when compared to deferred therapy (only initiated when CD4 count decreases below 20% or 25% in a child under 1 year) (Violari et al, 2008). This reduction in paediatric mortality rate and improvement in survival rates has resulted in a greater number of children infected with HIV reaching school going age (Kapogiannis et al, 2011). These children have to cope with the demands of schooling as well as live with the many negative effects that HIV has on the body.

Despite the success of HAART in reducing the mortality rate, adverse events with its usage are common and may affect patient adherence (Max and Sherer, 2000). These include nausea, vomiting, diarrhoea, headache, anaemia as well as myopathy and peripheral neuropathy (Max and Sherer, 2000). Non-infectious complications of HIV infection and combination HAART have become increasingly evident (Reekie et al, 2011). HIV infection also causes changes to occur in many body systems.

The musculoskeletal system is affected with a loss of skeletal muscle mass and wasting with associated impairment of strength (Grinspoon and Mulligan, 2003). There is also a higher bone metabolism rate with a consequent negative impact on bone mineral density (Mora et al, 2007).

HIV encephalopathy is common in children infected with HIV as it is known to invade the central nervous system (CNS) early in infection (Van Rie et al, 2007). Frequent and often significant developmental delays have been reported in a number of South African studies (Govender et al, 2011; Abubakar et al, 2008; Baillieu and Potterton, 2008 and Potterton, 2007).

HIV is known to cause changes in the defence mechanisms of the lungs and the respiratory tract, therefore contributing to an increased risk for lung complications (Shellito, 2004). Mortality from acute lung disease was high in the early years of the AIDS epidemic. In more recent years, early diagnosis, chemoprophylaxis and improved treatment of these conditions have lowered the mortality rates (Zar, 2008). However, in the era of HAART and chemoprophylaxis a wide range of chronic HIV associated lung diseases are being observed. These include lymphocytic interstitial pneumonia (LIP) as well as recurrent or persistent pneumonia due to bacterial, mycobacterial, viral, fungal or mixed infections (Zar, 2008). These children are reported to have a greater risk of developing bronchiectasis (Berman et al, 2007).

Cardiomyopathy is a World Health Organisation HIV clinical stage four disease (WHO Press, 2007) and is one of the leading causes of non-infectious death among HIV infected children (Patel et al, 2012). The P²C² Study group have published numerous articles. In one by Starc et al (2002), during five year follow-ups of HIV-infected children, cardiac dysfunction occurred in 18% to 39% of them and was associated with an increased risk of death. The presence of cardiovascular risk factors may be the result of HAART or due to the chronic viral infection of HIV. In another report describing the cumulative incidence of cardiac abnormalities in HIV infected children over a period of two years, 19.1% of children presented with cardiac impairment (Starc et al, 1999).

Due to the chronic nature of HIV in the HAART era as well as the related risks mentioned above, there has been an increased interest in the safety and efficacy of exercise programmes in this population. These studies have shown positive outcomes in the exercising groups in terms of strength and fitness when compared to a non-exercising group (Miller et al, 2010;

O'Brien et al, 2010). There is however very limited literature on the actual effects HIV has on a person's exercise endurance. A study by Hand et al (2008) reported a 25% or greater reduction in age predicted functional aerobic capacity in adults, while Keyser et al (2000) found a 42% reduction in expected capacity in a group of adolescents, indicating a functional aerobic impairment with a decreased ability to perform routine activities of daily living. Decreased VO2 peak, body strength and flexibility were also found in a group of HIV infected children when compared to non-infected controls (Somarriba et al, 2013).

Problem Statement

The effect that HIV has on the exercise endurance of infected children has not been investigated in South Africa.

Aim of Study

The aim of the study was to investigate the exercise endurance of HIV infected school going children aged seven to ten years.

Objectives of the Study

- To establish the exercise endurance of a group of children aged seven to ten who are *infected* with HIV using the six minute walk test.
- To establish the exercise endurance of a group of children aged seven to ten who are *not infected* with HIV using the six minute walk test.
- To compare:
    - The exercise endurance of children infected with HIV with that of children not infected
    - Cardiovascular data between the two groups
- To determine whether there is any relationship between CD4 count, length of time using anti-retroviral therapy and anthropometric measurements on the exercise endurance of children infected with HIV.

Significance of the Study

There has been no research investigating exercise endurance in HIV infected children in South Africa. This study reports on findings from a group of South African school going children aged seven to ten years.

Exercise programmes have been found to be beneficial in HIV infected adults but little is known about its effects with children. Physiotherapy services may need to be increased to this group of children to include a more holistic approach to their treatment.

Conclusion

There have been very limited studies done investigating the effect of HIV on exercise endurance and none done on South African children. The aim of this study was therefore to determine the effect that HIV has on the exercise endurance of HIV infected children aged seven to ten years when compared to their non-infected age-matched peers.

CHAPTER 2: LITERATURE REVIEW

This chapter will look at the epidemiology of HIV/AIDS. It will then discuss the general effects HIV has on the body and focus more specifically on the cardiovascular and pulmonary systems. Various forms of exercise testing will be reviewed with a closer look at the six minute walk test.

Literature was sourced through searches on the following databases: PubMed, CINAHL, ScienceDirect and Cochrane Collaboration. Keywords used: HIV, HAART, exercise, six minute walk test, children, cardiovascular, pulmonary.

2.1 Epidemiology

HIV/AIDS is a global epidemic with the number of people living with HIV continuing to grow. The World Health Organisation (WHO, 2011) estimated that 33.3 million people were living with HIV in 2009. This was 23% higher than in 1999. Of these people it was estimated that 3.3 million of them were children under the age of 15 years (UNAIDS, 2013). In South Africa the overall HIV prevalence rate was estimated to be approximately 10.6% with the total number of people living with HIV estimated at 5.38 million in 2011. It was estimated that amongst children aged 0-14 years there were 63 600 new HIV infections in 2011 (Statistics South Africa: P0302, 2011).

Highly Active Antiretroviral Therapy (HAART) first became available in developed countries in 1996. In 2009 it was estimated that six million people globally were receiving HAART, however, treatment-coverage rates remained low in low to middle income groups (WHO, 2011). South Africa started its rollout in 2004 and by 2010 it was estimated that 105 123 children (<15 years) were receiving HAART (Statistics South Africa: P0302, 2011). The life-prolonging effects of HAART have contributed greatly to the increasing number of people living with HIV (WHO, 2011).

HAART is defined as using a combination of at least three drugs from at least two different HIV drug classes. The, 2013 World Health Organisations consolidated guidelines, recommends initiating HAART in all children under five years and in children five to ten years with WHO clinical stage three or four or with a CD4 cell count less than or equal to 500 cells/mm³. The first line regimen of HAART for children three to ten years old is as follows:

- Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI):

  - Efavirenz (EFV) is the preferred drug with Nevirapine (NVP) being the alternative.

- Nucleoside Reverse Transcriptase Inhibitor (NRTI):

  - Abacavir (ABC) and Lamivudine (3TC) or
  - Zidovudine (AZT) or Tenofovir (TDF) and 3TC

Drug combinations including Stavudine (D4T) can be used under special circumstances, these may include 'situations where preferred or alternative regimens may not be available or suitable because of significant toxicities, anticipated drug-drug interactions, drug procurement and supply management issues, or for other reasons' (World Health Organisation, 2013). A well known adverse effect of treatment with NRTI's is peripheral neuropathy. A prospective follow-up study by Dragovic and Jevtovic (2003) reported that the risk of peripheral neuropathy is almost twice as high when D4T is used alone or in combination with didanosine (another NRTI drug). It was for this reason that it was concluded that its usage should be discouraged. Kaletra is a protease inhibitor containing lopinavir and ritonavir.

A number of studies have found that the use of HAART significantly reduces mortality rates in children and adolescents. In a study conducted in the United States observing children from 1996-2006 it was estimated that there was a 76% lower mortality rate amongst HIV infected children and adolescents when using HAART regimens as opposed to non-HAART regimens (Patel et al, 2008). Another study on children in the United States by Kapogiannis et al (2011) found that six year survival rates of children infected with HIV increased from 57% in the no/monotherapy era to 91% in the HAART era.

However more than 90% of children receiving HAART are living in resource limited areas (Edmonds et al, 2012). Common in these environments are multiple factors which may have adverse effects on treatment outcomes such as; delayed presentation to care facilities as well as a higher incidence of concurrent infectious and non-infectious conditions including under-nutrition (Edmonds et al, 2012). In a study conducted in a resource poor area, The Democratic Republic of Congo, HAART reduced the rate of mortality by 75% when compared to no HAART (Edmonds et al, 2012). In a group of South African children early HAART has been shown to reduce early infant mortality by 76% and HIV progression by 75% when compared to deferred therapy (only initiated when CD4 count decrease below 20% or 25% in a child under one year) (Violari et al., 2008). Even though this early intervention shows good results, the difficulties in continuing treatment for life need to be considered. The limitations of the available drugs, the long-term toxicity of HAART, the risk of resistance to HAART, adherence issues and limited resources need to be considered (Violari et al, 2008). Despite the use of HAART there are still significantly higher mortality rates in HIV infected children when compared to non-infected children. In the United States in 2005, a 50 fold higher mortality rate was reported in HIV infected children (Kapogiannis et al 2011).

HIV was once considered a progressive fatal disease, however in the era of HAART it has now become a chronic treatable condition in adults as well as children (Mothi et al, 2011). This reduction in paediatric mortality rate and improvement in survival rates has resulted in a greater number of children infected with HIV reaching school going age (Kapogiannis et al 2011). These children have to cope with the demands of schooling as well as live with the many negative effects that HIV has on the body.

We will now look further into the general effect as well as more specific effects that HIV as well as HAART have on the body, cardiovascular and pulmonary systems.

2.2 Effect of HIV and HAART in general

HIV infection may affect a person in numerous ways. The WHO has developed a clinical staging classification system for HIV infection based on the patients' signs and symptoms.

Clinical stage 1: Children are asymptomatic or may have persistent generalised lymphadenopathy. CD 4 count is > 500/mm³ in children older than five years.

Clinical stage 2: Children exhibit symptoms such as hepatosplenomegaly, extensive human papilloma virus infection, papular pruritic eruptions, recurrent oral ulcerations and herpes zoster. CD 4 count 350 – 490/mm³

Clinical stage 3 and 4: A presumptive diagnosis can be made on the basis of these clinical signs. Stage 3 includes moderate unexplained malnutrition, unexplained persistent diarrhoea, oral candidiasis, severe recurrent bacterial pneumonia and pulmonary TB. CD 4 count 200 – 349/mm³. Stage 4 includes unexplained severe wasting, chronic herpes simplex infection, Kaposi's sarcoma and HIV encephalopathy. CD 4 count <200/mm³ (Interim WHO clinical staging of HIV/AIDS, 2005)

From this grading system it is evident that HIV has an impact on many body systems and increases susceptibility to infection through the lowering of the patients' immune system.

Despite the success of HAART in reducing mortality rate, adverse events with its usage are common and may affect patient adherence (Max and Sherer, 2000). The most commonly occurring adverse events noted with the use of NRTI's are nausea, vomiting, diarrhoea, headache, anaemia as well as myopathy and peripheral neuropathy. Diarrhoea, nausea, vomiting and skin rash are also common with the use of protease inhibitors (Max and Sherer, 2000). NNRTI's have reported short term side effects of rash and neuropsychiatric symptoms of vivid dreams, insomnia and hallucinations which usually resolve within four weeks (Drake, 2000). On a positive note, the initiation of HAART in children has been shown to produce a continued increase in weight and height with those with more severe disease attaining better growth catch-up than those with mild or moderate HIV-infection (Guillen et al, 2007).

Non-infectious complications of HIV infection and combination ART have become increasingly evident (Reekie et al, 2011). HIV infection also causes changes to occur in many body systems. The following are common examples of these complications and the effects that HAART has on them:

2.2.1 Musculoskeletal Effects

Loss of skeletal muscle mass and wasting (involuntary weight loss >10% ideal body weight) are common in people infected with HIV, even in the era of HAART (Scott et al, 2007). Wasting, especially loss of metabolically active lean tissue, has been associated with accelerated disease progression and impairment of strength and functional status (Grinspoon and Mulligan, 2003). Only two pilot studies were found investigating the effect of HIV on muscle strength in children. The first, a study by Ramos et al (2012) found that preadolescent HIV subjects had a significantly reduced aerobic power output when compared to seronegative control subjects. There were however no significant differences between groups in terms of their muscle strength (this testing was only done for the knee extensors). The second pilot study conducted by Humphries et al (2014) recruited children aged four to eight years. A handheld dynamometer was used for testing the shoulder, elbow, hip and knee joints. The study compared children already receiving HAART with those not yet initiated and found that those receiving HAART were significantly weaker than those not receiving HAART. It was also noted that, in the group receiving HAART, no significant correlation was found between length of time receiving HAART and muscle strength or CD4 count and muscle strength.

Another possible factor that may be responsible for the finding of reduced muscle force production in people with HIV is that of impairment of central activation (i.e. There may be a decrease in the ability to activate the available muscle mass, in the absence of wasting) (Scott et al, 2007). This may be due to impaired oxygen extraction or utilisation by the working muscles or due to central nervous system disease which is discussed later.

The initial immune reaction induced by HIV infection is known to alter osteoblast and osteoclast activity. This activity is critical for the regulation of bone turnover with a high bone metabolism rate leading to a net decrease in bone formation (Mora et al, 2007). Clinically this is seen as an increased risk for fractures (Bonjoch et al, 2010). Bone mineral density (BMD) has also been investigated in the era of HAART. In a retrospective observational study by Bonjoch et al (2010), of 671 adult patients, 47.5% were diagnosed with osteopaenia while osteoporosis was diagnosed in 23% of patients with the rate of osteoporosis increasing with duration of infection and length of time on ART. A longitudinal study by Mora et al (2004) followed 32 HIV infected children aged six to seventeen years. They were compared to 381 comparable healthy individuals. BMD was measured at the lumbar spine and whole skeleton and was found to be significantly lower at baseline in the HIV infected subjects. There was also a significantly lower annual increase in BMD when followed up after one year.

Other possible factors responsible for these differences in BMD in children have been reported and include; delayed growth and puberty, nutritional and hormonal factors, chronic inflammation and physical inactivity (Jacobson et al, 2010; Mora et al, 2004).

2.2.3 Cancers

People with HIV/AIDS are at high risk for developing certain cancers. One of the characteristic complications of HIV clinical stage four, as seen above, is Kaposi sarcoma. The severe immunodeficiency associated with this stage was linked to the increasing numbers of cases seen. Non-Hodgkin lymphoma and invasive cervical carcinoma were also added to this group of AIDS-defining malignancies.

Following the introduction of HAART a decreased prevalence of severe immunodeficiency has been noted with a resulting rapid reduction of AIDS-defining malignancies. It has however been accompanied by an increase in the chance of developing non-AIDS defining malignancies (Alvaro-Meca et al, 2011; Franceschi et al, 2010). This may, in part, be due to

the improvement in life expectancy, accompanied by only partial reconstitution of immune status, allowing cancers with a long latent period to present clinically (Clifford et al, 2005).

A study in the United States by Patel et al (2008) compared cancer incidence among HIV infected persons with that of the general population between 1992 and 2003. The incidence of a number of non-AIDS defining cancers was significantly higher amongst the HIV infected population. These included anal, vaginal, Hodgkin lymphoma, renal, liver, lung and leukaemia. In a case control study of HIV infected children conducted in Spain between 1999 and 2008 it was found that the highest rates of cancer diagnoses were for non-Hodgkin lymphoma, malignant neoplasm of bone and articular cartilage, and Hodgkin lymphoma, with the overall rate of diagnosis about eight times higher than that of the HIV-negative group. It was reported that the rate of AIDS defining malignancies significantly decreased from the early-period HAART (1997-1999) to the late-period HAART (2003-2008) while the rate of non-AIDS defining malignancies increased (Alvaro-Meca et al, 2011). A similar result was found in an Italian study where an observational population study was conducted on perinatally HIV-infected children from 1985 to 2004. Overall cancer rates remained similar in the early HAART era (1996-1999) when compared to pre-HAART but showed a significant decline in the late-HAART era (2000-2004) (Chiappini et al, 2007).

2.2.4 Central Nervous System Disease

HIV-1 is known to invade the central nervous system (CNS) early in infection with neurodevelopmental abnormalities having been documented complications of HIV infection since the first reports of paediatric AIDS in the 1980's (Van Rie et al, 2007). HIV infects the immature brain in children and manifests as static or progressive encephalopathy often occurring before there is any significant immunosuppression (Van Rie et al, 2007). HIV encephalopathy may present clinically with features including loss of or failure to attain developmental milestones, impaired brain growth and motor deficits (Patel et al, 2009). The disease in children may present as rapidly progressive and fatal while others present with stable phases interspersed with short phases of neurological deterioration (Patel et al, 2009).

HIV encephalopathy was highly prevalent in the pre-HAART era with reports of greater than 50% of children showing signs of neurologic involvement (Epstein et al, 1986). However, in a large paediatric prospective US cohort observed from 1993-2006, a 10-fold decrease was found in the incidence of HIV encephalopathy with the use of HAART decreasing the risk by 50% compared to no HAART use (Patel et al, 2009). A second US study reported a decline in the rate of HIV encephalopathy from 31% in 1992 to less than two percent in 2000 in HIV infected children (Chiriboga et al, 2005).

Sub Saharan Africa is home to 2.9 million children of the 3.3 million infected (UNAIDS, 2013), however the initiation of HAART in these countries was delayed and in South Africa the public sector treatment program only commenced in April 2004. Access to therapy remained low in the early years and was often only initiated after neurologic disease was recognised (Govender et al, 2011). There are also a number of environmental factors, common in developing countries, which have been associated with neurodevelopmental delay. These include; 'maternal drug and alcohol use, poverty, low maternal income and poor quality of the home environment' (Van Rie et al, 2007). Children with poor nutrition are also more likely to present with developmental delay (Govender et al, 2011).

There have been a number of studies investigating the extent of developmental delay in HIV infected children in Sub-Saharan Africa. In a systematic review of seven studies done in Sub-Saharan Africa investigating motor and mental development, consistent findings of delay in motor development in HIV-positive children was found in all age groups (Abubakar et al, 2008). In a South African based study by Govender et al (2011) seventy-eight children between the ages of three months and twelve years were assessed for neurological deficits. Fifty nine percent of children were found to have abnormal neurological examinations and 30 percent of children fulfilled the diagnostic criteria for HIV encephalopathy. This finding was statistically more common in those children who were not initiated on HAART. Sixteen percent and six percent also had cortical visual impairment and sensorineural hearing impairment respectively. In a study by Baillieu and Potterton (2008) of 40 antiretroviral therapy naïve children, significant delay in motor development was found in 77.5% of children aged between 18 and 30 months with the mean motor developmental age 9.65 months below the mean chronological age. Another South African study by Potterton (2007)

carried out a randomised control trial with 122 children during the period when HAART became available at the study hospital. At baseline, before the initiation of HAART, developmental scores showed that 78 percent of children had delayed cognitive impairment while 87 percent had delayed motor development. A home management programme was prescribed by a physiotherapist to the experimental group, with both groups being reassessed a final time 12 months later. The experimental group showed a significantly greater improvement in developmental scores but still remained well below normal ranges.

2.2.5 Haematological Abnormalities

HIV infection of lymphocytes, monocytes and macrophages is responsible for the occurrence of numerous blood defects (Moroni and Antinori, 2003). Anaemia is the most common haematological abnormality seen in HIV infected patients (Moroni and Antinori, 2003). In a global systematic review by Calis et al (2008) the overall prevalence of mild or moderate anaemia in HIV-infected children ranged between 22% - 94% and 3% - 82% respectively. A study conducted in Uganda tested 257 HAART naïve children and found anaemia present in 57.6 percent (mild anaemia 62.2%, moderate anaemia 32% and severe anaemia 4.8%) of participants. It was also reported that treatment with HAART improved anaemia in most HIV infected individuals without the need for anaemia specific additional treatments (Ruhinda et al, 2012). In children, it may present with weakness, fatigue, tachypnea and congestive cardiac failure (Calis et al, 2008). Poorer outcomes in former iron deficient anaemic or chronically iron-deficient adolescents compared to those without anaemia are reported in terms of motor and cognitive scores as well as social problems, anxiety and depression despite iron therapy that corrected their anaemia in infancy (Walker et al, 2007)

2.3 HIV and the pulmonary system

HIV is known to cause changes in the defence mechanisms of the lungs and the respiratory tract, therefore contributing to an increased risk for lung complications (Shellito, 2004). Lung cells that are infected with HIV include the alveolar macrophages, neutrophils, T lymphocytes and fibroblasts- with CD4+ lymphocytes recently being shown to be long term reservoirs for the infection (Twigg et al, 2008). These cells undergo alterations which results

in impaired abilities to release cytokines in response to infection, thereby minimising the inflammatory response and the ability to initiate adaptive immunity (Shellito, 2004). HAART has been found to significantly decrease the HIV load in the vascular compartment and lymph nodes and brings the percentage and total number of lymphocytes to within normal limits at six months post initiation (Twigg et al, 2008).

There are a large number of lung complications that are associated with HIV infection, which includes infectious and non-infectious mechanisms. In the pre-HAART era and even today, in patients who don't have access to care, opportunistic infections and neoplasms are the most commonly occurring lung complications (Grubba et al, 2006). In a respective review by Marolda et al (1991) of HIV infected children admitted to two hospitals in New York City between 1982 and 1988, before the use of ART, 79% presented with pulmonary problems. *Pneumocystis jiroveci* pneumonia (PJP) was reported as the most common cause of pulmonary disease with bacterial pneumonia and lymphoid interstitial pneumonia also occurring frequently.

A study conducted in South Africa by Da Cunha et al (2013) recruited 125 children under the age of seven years who were admitted to hospital with a respiratory condition and infected with HIV/AIDS. Only 36 of these children were already receiving HAART prior to admission. Respiratory conditions were categorised into eight groups with 69% of patients presenting with more than one condition and being classified as having a high burden of disease. A higher burden of disease was reported amongst patients already using HAART. This was however thought to have been due to the referral system to the tertiary hospital at which the study was conducted with more severe cases being seen, as well as the fact that children receiving HAART for short and long periods were analysed in the same group. Bacterial pneumonia was found in two thirds of children with PJP and Tuberculosis (TB) being reported in 23% and 50% respectively. The greater percentage of bacterial pneumonia cases compared to PJP was considered to be largely due to the improved prophylactic measures.

Mortality from acute lung disease was high in the early years of the AIDS epidemic. In more recent years, early diagnosis, chemoprophylaxis and improved treatment of these conditions have lowered the mortality rates (Zar, 2008). With improving survival of HIV infected children, there is now an increasing frequency in the number of children presenting with chronic radiographic lung changes (CRC) (Zar, 2008). The P²C² Study (Pediatric Pulmonary and Cardiovascular Complications of Vertically Transmitted HIV Infection) is a prospective multicentre study which followed up on 805 infants between 1990 and 1997. This study found a cumulative incidence in CRC of 32.8% by four years old, with the most common findings being an increase in bronchovascular markings and/or reticular densities (Norton et al, 2001).

In the era of HAART and chemoprophylaxis a wide range of chronic HIV associated lung diseases are being observed. Some of these manifestations are occurring as a result of the increased immune response soon after HAART is commenced. This is known as Immune Reconstitution Inflammatory Syndrome (IRIS) (Grubba et al, 2006). Patients present with increasing lymphadenopathy, new clinical and radiological respiratory signs and fever (Zar, 2008). Other manifestations are being seen due to the prolonged patient survival which allows for other processes to occur following lengthened immunosuppression (Grubba et al, 2006). These include:

- Lymphocytic interstitial pneumonia (LIP) which presents with chronic lymphocytic infiltration of the lungs. Symptoms are a chronic cough and mild tachypnea with recurrent episodes of acute lower respiratory tract infections (Zar, 2008).
- Recurrent or persistent pneumonia due to bacterial, mycobacterial, viral, fungal or mixed infections (Zar, 2008).

Children with a history of the above conditions are reported to have a greater risk of developing bronchiectasis (Berman et al, 2007). In a South African study by Masekela et al (2011), 35 children aged 6-18 years with symptoms suggestive of, and a radiological diagnosis of, bronchiectasis were followed up for one year. Induced sputum sample results revealed haemophilus influenza and parainfluenzae to be the most dominant organisms. Seventy five percent of the study population also had a prior diagnosis of TB. It was hypothesized that 'the presence of an aggressive immune response against pathogens may trigger airway inflammation and subsequent bronchiectasis' (Masekela et al, 2011).

TB is the most common opportunistic infection in HIV infected people worldwide (Swaminathan, 2004). In 2009 South Africa ranked third in the world in terms of the number of incident cases of TB and fourth in the number of drug-resistant cases (Lawn and Zumla, 2011). It is the most common cause of mortality in HIV infected individuals in Sub-Saharan Africa with approximately 80% of active TB cases in KwaZulu Natal, South Africa, being co-infected with HIV (Gandhi et al, 2006). Diagnostic errors and delayed diagnosis of TB are common in HIV infected children because of its overlapping clinical and radiographic features with other lung diseases (acute pneumonias and chronic lung diseases such as bronchiectasis) which are difficult to distinguish from TB (Swaminathan, 2004).

Although TB predominantly affects the lungs it may cause disease in any organ in the body and needs to be considered as a differential diagnosis in numerous clinical presentations (Lawn and Zumla, 2011). Pulmonary TB is associated with lung remodelling, with healed cavitation, fibrosis and bronchiectasis, which is a major cause of lung disease (Dheda et al, 2005). The development of TB has also been associated with increased HIV replication and increased viral loads (Swaminathan, 2004).

2.4 HIV and the cardiovascular system

Cardiomyopathy is a WHO HIV clinical stage four disease (WHO Press, 2007) and is one of the leading causes of non-infectious death among HIV infected children (Patel et al, 2012). Possible mechanisms for this disease have been proposed including; direct infection of cardiac myocytes by HIV; increased production of proinflammatory cytokines within the myocardium with cardiomyocyte apoptosis and ventricular remodelling or mitochondrial toxicity induced by NRTI (Patel et al, 2012).

HIV and its related metabolic complications are common in individuals receiving HAART. These complications include: disturbances in lipid metabolism with associated increases in triglyceride and cholesterol levels; glucose metabolism with associated insulin resistance, impaired glucose tolerance and hyperglycaemia (Galli et al, 2001); as well as altered fat distribution with loss of subcutaneous fat and a relative gain in central fat (Grinspoon and

Carr, 2005). This pattern of metabolic changes resembles those of the so-called metabolic syndrome X, which is known to increase the risk of cardiovascular disease in the HIV negative population (Kuritzkes and Currier, 2003; Galli et al, 2001). HIV infection alone has been reported to decrease high density lipoprotein cholesterol early on in disease progression and later a decrease in low density lipoprotein cholesterol. This, together with hypertriglyceridemia, is known to increase the risk of atherosclerosis (Galli et al, 2001). These results are more widely reported in adults but were found to be true for a group of children investigated by Miller et al (2008). When compared to a group of HIV negative children it was found that children infected with HIV had significantly higher triglyceride levels and lower levels of high density lipoprotein cholesterol (Miller et al, 2008).

A large multicenter cohort study was conducted by Lipshultz et al (2013) which included the following participants: Perinatally HIV-infected children receiving HAART (n=325) aged 7-16 years between 2007 and 2009; HIV-exposed but uninfected children (n=189) aged 7-16 years between 2007 and 2009, and HIV-infected (mostly HAART-unexposed) historical paediatric controls from the National Institutes of Health–funded P²C²-HIV Study (n=70) aged seven years or older and born before 1985. Echocardiograms were conducted on the majority of the children and it was found that 44% of the children from the P²C²-HIV study met the definition for cardiomyopathy whereas less than 1% of children in the other two groups met the definition. In the P²C²-HIV cohort, increased LV mass, dimension, wall thickness, and wall stress and decreased LV fractional shortening and contractility all predicted mortality. The findings of this study suggest an overall cardioprotective effect of long-term HAART.

The Paediatric AIDS Clinical Trials Group (PACTG) followed up children from 1993 – 2007. They reported a six-fold decrease in the incidence of cardiomyopathy in the HAART era (1996-2007) when compared to the pre-HAART era (1993-2005), but even so, when compared to the US-based Pediatric Cardiomyopathy Registry the annual incidence is 40 times higher in HIV infected children (Patel et al, 2012).

2.5 HIV, endurance and exercise

A number of studies were found investigating HIV in terms of the effects it has on a person's functional aerobic capacity and their ability to perform activities of daily living. There are a greater number of studies done with adult HIV infected participants than there are with children. In these adult studies it has been found that the rate of decrease in heart rate in the first two minutes of recovery following cessation of exercise is predictive of mortality in adult men and that recovery during the second minute is predictive of coronary artery disease (Lipinski et al, 2004). HIV infection, as well as the metabolic complications that may accompany HAART usage, are known risk factors for cardiovascular disease. Heart rate recovery in these patients is significantly delayed at 1.5 and two minutes when compared with HIV uninfected controls (Cade et al, 2008). This study also reported a higher baseline heart rate and lower peak exercise heart rate in the HIV infected participants. A study by Hand et al (2008) reported a 25% or greater reduction in age predicted functional aerobic capacity in adults while Keyser et al (2000) found a 42% reduction in expected capacity, in a group of adolescents, indicating a functional aerobic impairment with a decreased ability to perform routine ADL's. However, in the first study, following a six week exercise programme the participants improved to 1.2% above age predicted norms.

In a study conducted on adolescents where peak exercise testing was done, it was found that the HIV infected participants had significantly lower peak oxygen consumption and peak heart rate at volitional exhaustion than their age matched peers (Cade et al, 2002). They were reported to have a clinically significant functional aerobic impairment. There have been several mechanisms proposed for decreased aerobic capacity and functional aerobic impairment. These include: pulmonary dysfunction, anaemia, deconditioning, cardiovascular dysfunction and peripheral muscle oxygen extraction-utilisation limitation (Stringer, 2000). In the study by Cade et al (2002) each of these mechanisms were explored. The authors however remained inconclusive, but stated the lack of cardiac output measurements as being a limitation to their study. Cade et al (2008) reported that the difference in peak exercise heart rates found suggest that HIV infected individuals on HAART have evidence of early cardio-autonomic dysfunction and may be at greater risk for cardiovascular disease. There were no similar studies found in HIV infected children.

The chronic nature of HIV in the HAART era as well as the related risks mentioned above has led to the investigation of the safety and efficacy of exercise programmes in this population. A group of 34 HIV infected children aged six years and older completed a 24 session hospital supervised exercise training programme conducted by Miller et al (2010). A strong positive relationship was found in terms of strength, flexibility, cardiorespiratory fitness and lean body mass with no adverse events being reported. A review by O'Brien et al (2010) of 14 randomised control trials of exercise programmes in adults with HIV reported: conflicting results in regards to CD4 count and viral load changes; significant improvements in VO2 max, exercise time and time to fatigue as well as significant improvement in strength outcomes in those groups following exercise programmes compared to non-exercising controls. The limitations in both of these reviews noted small sample sizes and large withdrawal rates with a need for further research.

In addition to the numerous adverse effects of HAART medication discussed previously, patients also often rate anxiety, depression and fatigue highly in their list of associated symptoms, with a resulting compromised quality of life (Ciccolo et al, 2004). Numerous studies have been done with participants suffering from known chronic illnesses with these similar symptoms and have shown that exercise is a useful approach to manage them (Ciccolo et al, 2004). In a review by Ciccolo et al (2004) of research investigating the effect of exercise in the HIV population, found that various exercise programmes resulted in improvement of symptoms and reported quality of life (QoL). Many of these studies had small sample sizes. In the review mentioned above by O'Brien et al (2010) the various studies found significant improvements in QoL questionnaire scores, depression as well as mood and life satisfaction in the exercising participants.

Exercise programmes have been shown to have many beneficial effects for the HIV infected adult and are an appropriate intervention for reducing the many modifiable risk factors for cardiovascular disease (Jaggers et al, 2013). It is considered an appropriate additional therapy for health promotion in these patients (Neto et al, 2013). There was however again very little literature found for its appropriate use in children.

2.6 Exercise tests

'Cardiorespiratory fitness can be quantitatively measured in the exercise physiology laboratory as aerobic capacity' (Oursler et al, 2006). The gold standard measurement of aerobic capacity is the rate of oxygen utilisation per minute at maximum exercise effort (Bassett and Howley, 2000). This is recorded as VO2max. VO2peak is also often used as 40-50% of healthy adults don't achieve VO2max with testing (Oursler et al, 2006).

Progressive exercise protocols conducted on a cycle ergometer or treadmill are popular methods of exercise testing in children and adults (Nixon et al, 1996). From review of the literature, graded exercise testing on a motorized treadmill using the modified Bruce treadmill protocol was used most often to conduct VO2 testing in HIV infected adults (Beans et al, 2013; Oursler et al, 2009; Oursler et al, 2006) and children (Somarriba et al, 2013). However, in a report by Cooper (1995), the concern was raised that maximal exercise tests do not represent the types of physical activity in which children usually participate.

In more recent years there has been increasing interest in more simple exercise tests that do not require the technology utilised in the above mentioned methods and which are more closely related to daily activities (Wise and Brown, 2005). Functional walk tests are exercise tests that measure a person's functional status and their ability to perform activities of daily living and provide a measure of response to treatment (Solway et al, 2001). In 1968, Cooper developed the 12 minute running test which was then modified to the **12 minute walking test** to assess impairments in people with respiratory disease. The patients had difficulty in completing this test and it was then found that results from the six-minute walk test (**6MWT)** were highly correlated to those in the 12 minute test (Wise and Brown, 2005). The 6MWT is now the most widely used walking test and will be discussed in detail in the next section. The other known walking tests will be discussed briefly.

The **incremental shuttle walk test** has reported widespread use in Europe. It is a 'progressive exercise test that uses a taped metronome to coach patients to perform incrementally faster walking speeds to the point of intolerance' (Wise and Brown, 2005). An

advantage of this test is that it is externally paced and therefore does not require the patient's ability to strategise or perform self-pacing (Wise and Brown, 2005).

Poor performance in the **400 metre long distance corridor walk test** has been associated with a higher risk of mortality, occurrence of cardiovascular disease and mobility limitation and was reported to be a useful substitute for treadmill testing in older adults (Newman et al, 2006).

In a review of five studies, the **2-minute walk test** was validated as a similar measure as the 6MWT for exercise tolerance in patients with chronic disease. It was also found to be a reliable test and had moderate to strong associations with measures of oxygen consumption (Solway et al, 2001).

Other performance based tests that have been used to test disability in the HIV population include: Berg balance scale, timed up and go test, functional reach test, one-leg standing with eyes closed test, five-times sit-to-stand test, grip strength test in adults (Richert et al, 2011; Terzian et al, 2009) and hand held dynamometry, sit-up and sit-and-reach tests in children (Humphries et al, 2014; Somarriba et al, 2013).

2.7 The six minute walk test

The timed six minute walk test (6MWT) was developed in 1963 by Balke to evaluate functional capacity. The 6MWT measures the distance an individual can walk in six minutes on a hard, flat surface, with the goal being to walk as far as possible in the time given (ATS Guidelines, 2002). It provides a global evaluation of all the body systems involved during exercise including 'pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units and muscle metabolism' (ATS Guidelines, 2002). The 6MWT assesses the patient at a submaximal level of function as they are able to choose the level of intensity at which they perform the test. This may however provide a better reflection of functional exercise level as most activities of daily living are performed at a submaximal level of exertion (ATS Guidelines, 2002).

Height, weight, age, gender and ethnic background are documented factors that can affect the distance walked in the 6MWT (Ulrich et al, 2013; Enright, 2003). Review of the literature found eight studies that report on reference values or equations for the 6MWT in children. There are currently standard references for healthy Chinese children aged seven to sixteen years (Li et al, 2007), Austrian caucasian children aged three to eighteen years (Geiger et al, 2007), Indian children aged seven to twelve years (D'silva et al, 2012), UK children aged four to eleven years (Lammers et al, 2008), seven to eleven year old children in the United States of America (Klepper and Muir, 2011), six to twelve year old children in Brazil (Priesnitz et al, 2009) and five to seventeen year old children in Switzerland (Ulrich et al, 2013). Another study by Saad et al (2009) was conducted on children in North Africa, Tunisia, aged six to sixteen years. They reported that the available published reference values were not reliable predictions of the six minute walk distance in their population.

Reference equations were published in the following studies:

- Saad et al (2009): 6-MWD (m) = 4.63 x height (cm) - 3.53 x weight (kg) + 10.42 x age (years) + 56.32].
- Ulrich et al (2013): (1) 6MWD (m) = 11.89 x age (y) + 486.1 and (2) 6MWD (m) = 391.9 x height (m) – 2.41 x weight (kg) + 140.2.
- Priesnitz et al, 2009): 6MWD (m) = 145.343 + [11.78 x age (years)] + [292.22 x height (m)] + [0.611 x diff. HR (bpm)] - [2.684 x body weight (kg)].
- Li et al (2007): 6MWD (m) for males = 554.16 + (difference in heart rate x 1.76) + [height (cm) x 1.23], and 6MWD (m) for females = 526.79 + (difference in heart rate x1.66) + [height (cm) x 0.62].
- Geiger et al (2007): 6MWD (m) for males = 196.72 + (39.81 x Age) - (1.36 x Age^2) + (132.28 x Height), and 6MWD (m) for females = 188.61 + (51.50 x Age) - (1.86 x Age^2) + (86.10 x Height).

In addition to age, weight and height the above studies also documented blood pressure, heart rate, peripheral arterial oxygen saturation, leg length, subjective feeling of dyspnoea, forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF) and forced vital capacity (FVC) in varying combinations. There were no reference values or equations found for South African children.

In a study by Hassan et al (2010), the 6MWT was performed in three groups of children with haemophilia, juvenile idiopathic arthritis and spina bifida respectively. Their results were compared with the reference values established by Li et al (2007) and Greiger et al (2007) and it was found that all three groups had significantly reduced walking distances with those with spina bifida being the most reduced achieving 60-62% of the predicted values.

The 6MWT is used in patients with chronic disease to assess functional exercise capacity and is currently the most popular functional walk test used for clinical or research purposes (Hassan et al, 2010). It has also been shown to be reproducible and suitable to perform in children or adolescents with cystic fibrosis with mild and moderate bronchial obstruction (Cunha et al, 2006) (Gulmans et al, 1996). The 6MWT has been shown to be a valid and reliable test for assessing exercise tolerance and endurance in healthy children (Li et al 2005), children with mild to moderate cystic fibrosis (Gulmans et al, 1996), congenital heart disease (Moalla et al, 2005), children undergoing assessment for asthma control (Yüksel et al, 2012) and obese children undergoing cardiorespiratory assessment during weight-loss programmes (Elloumi et al, 2011). Nixon et al (1996) suggest that it may be an effective test for assessing exercise tolerance and oxyhemoglobin desaturation in chronically ill children awaiting heart or lung transplantation.

Very few studies were found investigating HIV and the 6MWT in adults. None were found for children. A study by Beans et al (2013) compared 45 HIV-infected men, with no history of cardiovascular disease, with 37 uninfected age matched controls. They found no difference in the performance of the 6MWT between these two groups. However, Richert et al (2011) detected poor performance in 23.6% of their 324 HIV-infected adult subjects when compared with a known reference formula for the 6MWT, while Oursler et al (2006) found that the mean distance walked was only reduced by 8% when compared to expected values.

2.8 Conclusion

This chapter has reviewed the literature and discussed the epidemiology of HIV as well as the many effects that HIV and HAART have on the systems of the body and its impact on endurance and exercise. It has provided background on the various tests available to test aerobic capacity with a focus on the one that will be used in this study. It is hoped that this background provides rationale for the present study.

CHAPTER 3: METHODS

This chapter will discuss the location, ethical considerations, study design, subjects, materials and measurements, procedure for data collection and data analysis.

3.1 Location

This study was conducted in Kabokweni, Mpumalanga. Themba Hospital is a secondary hospital serving an estimated population of 244 192 people (StatsSA 2011 Census). There are 19 clinics served by this hospital. The Bambanani Wellness Clinic was opened in April 2004. This clinic provides out-patient services to children and adults living with HIV/AIDS and serves approximately 2000 patients per month. Patients are referred to the clinic, undergo adherence classes and are initiated on HAART. Once the doctor is satisfied with their progress they may be down referred to the surrounding clinics for follow up. Some patients remain for follow up at the Bambanani Wellness Clinic if their nearest clinic is known to be poorly resourced or if the doctor chooses to monitor the patient at the Wellness clinic.

Sandzile Primary School is located two kilometres away from Themba Hospital and had 987 pupils in 2013. The Kabokweni area was a former homeland and is to this day a low income earning area. The children at the Bambanani Wellness clinic as well as at Sandzile Primary School are of a low socio economic status. The majority of children are reported to walk to school each day. The majority of homes have access to electricity, however, there is an inconsistent supply of water to the area. Most households rely on collecting water in Jo-Jo tanks or other containers when their water is turned on once or twice a week.

3.2 Ethical Considerations

Ethical clearance was obtained from the Human Research Ethics Committee of the University of the Witwatersrand, Johannesburg (M121159) (see appendix I). Permission was obtained from the Mpumalanga Department of Health's Provincial Research and Ethics Committee as well as from Themba Hospital's medical manager and manager of the Bambanani Wellness Clinic. Permission was also obtained from the schools circuit manager as well as the principal of Sandzile Primary School.

Informed consent (see appendix II) was obtained from all primary caregivers as well as informed assent (see appendix III) from each participant. All participant information was made anonymous by assigning a study number to each child which was recorded on all documentation and only accessed by the principal researcher. Gender was coded on the data collection sheet so that age and gender together could not be seen as an identifier. All parents/guardians and children were aware that they were allowed to withdraw from the study at any stage with no negative consequences.

3.3 Study Design

This was a cross sectional comparative study comparing the exercise endurance of a group of HIV infected children to that of their uninfected peers. Thirty HIV infected children between the ages of seven and ten years were tested at Themba Hospitals, Bambanani Wellness Clinic where they were receiving their medication. A group of uninfected children of the same age group and of similar socio-economic background were tested at Sandzile Primary School which is in close proximity to the hospital.

3.4 Subjects

HIV Infected Participants: Children aged seven to ten years attending the Bambanani Wellness Clinic for initiation or repeat prescription of HAART treatment and who were enrolled at a school at the time of the study were invited to participate. Children were excluded if they had a:

- Raised temperature >37°C,
- Respiratory rate >24 breaths/minute,
- Oxygen saturation level < 90% on the day of testing,
- or if they were unable to walk independently.

Data collection stopped once 30 consecutive children, for whom consent was obtained, had been tested.

Non-Infected Participants: Children from one Grade-3 and one Grade-4 class at Sandzile Primary School where recruited for the study. Consent forms were sent home with the children. The information sheet informed the parents/guardians that they did not need to return the consent form if they answered 'yes' to any of the three questions on the parent/guardian questionnaire. These questions were as follows:

- Has your child been admitted to hospital in the last three months?
- Does your child have a known chronic illness?
- Does your child have to take any medication every day?

Thirty children were randomly selected from the returned signed consent forms. Children were again excluded from the study if they had a:

- Raised temperature > 37°C,
- Respiratory rate >24 breaths/minute,
- Oxygen saturation level < than 90% on the day of testing.

HIV status was not tested in this group of children, however none of the children in this group presented with obvious clinical features of HIV infection.

3.5 Materials and Measurements

3.5.1. Immunology and Virology

The most recent CD4 count was recorded on the data collection sheet for those children tested at the Bambanani Wellness Clinic. Children are initially tested six months after initiation of HAART and thereafter annually or at the discretion of the doctor.

3.5.2. Anthropometric and Cardiovascular

Each child's weight and height was measured using a digital scale designed to measure height and weight (ADAM: Digital Physician Scale (MDW-250L). They were all instructed to take their shoes and jerseys off while these measurements were made. The children put their shoes back on for the walking test and performed it with a short sleeve t-shirt on.

Blood pressure was measured using a digital electronic sphygmomanometer (Rossmax Medical, Automatic Upper Arm Blood Pressure Monitor. Model: AK 150) with a paediatric cuff. The blood pressure cuff was placed on the left upper arm.

A Polar heart rate monitor was used. The strap was tightly secured around each participant's chest just below the nipple line. The watch was worn by the participant throughout the testing procedure. The watch records the number of beats per minute during the test and then provides a maximum HR and average HR for each participant once the watch is stopped at the end of their test.

A finger-tip pulse oximeter (BCi Finger Oximeter Smith Medical 3420Y) was also worn throughout the test. This was placed on the right index or middle finger.

All measurements were taken by the principal investigator.

3.5.3. Six Minute Walk Test

The 6MWT measures the distance an individual can walk in six minutes on a hard, flat surface, with the goal being to walk as far as possible in the time given (ATS Guidelines, 2002). A 30 metre distance was marked on a hard, flat surface with orange cones at five metre intervals. The turn-around points were clearly marked with two cones. Each participant sat quietly in a chair for at least 10 minutes before the test was performed. The test was thoroughly explained to the participant using the ATS guidelines (see Appendix V) and the principal investigator then demonstrated one lap of the course to ensure they understood where and how to turn around at the end of each lap. The principal investigator held the stopwatch and gave the standardised phrases of encouragement at one minute intervals and marked each lap on the data collection sheet.

3.6 Procedure

No pilot study was conducted during this research as the validity and reliability of all outcome measures are well established.

HIV Infected Participants: The principal researcher visited the Bambanani Wellness Clinic as often as possible to screen for children who met the inclusion criteria. There were a number of days where there were no children within the age limits. There were also a number of children who were too ill to be tested, were too shy, came to the hospital with someone other than the primary caregiver or whose primary caregiver did not consent to their child undergoing testing. When a primary caregiver did give consent, and their child gave assent, he or she was included in the study. HIV information was recorded from their hospital files. The most recent CD4 count was recorded, in some cases this result was more than six months old.

Non – Infected Participants: 100 consent forms were given to one Grade 3 and one Grade 4 class. The consent form informed the primary caregivers that they did not need to return the form if they did not want their child to participate or if they answered yes to any of the

screening questions. Seventy eight were received back, six of them had one or more screening questions answered 'yes', 19 of them had incomplete information. Eight children were too old to be included in the study. Random selection of children was done with the 45 remaining consent forms. On the day of testing each child was screened to ensure that they met the inclusion and exclusion criteria. The test was then explained to them and they were asked to sign an assent form. None of the children refused to participate.

Each child who participated in the study had their height and weight measured. Their blood pressure was tested before, immediately after and five minutes post-test. This was done with the child seated on a chair with both feet on the floor. A Polar heart rate monitor was secured around their chests and a finger-tip pulse oximeter was worn for the duration of the test and readings taken as above. All information was recorded on the data collection sheet (see appendix IV) by the primary researcher. The 6MWT was completed by each child. Standard words of encouragement were given according to the ATS guidelines. The number of laps walked by each child was recorded by the principle researcher and the total distance walked was calculated.

3.7 Data Analysis

The study recruited 60 children (30 HIV infected and 30 presumed Non-Infected) between seven to ten years of age. A sample size calculation using the 6MWT as the primary outcome yielded a sample size of 14. As this was a very small sample size it was decided to use the central limit theorem and increase the size to 30 per group.

Data was analysed using STATA (version 11 for windows) with the level of significance for all statistical tests set at $p=0.05$.

Descriptive statistics were used to describe the demographic information of the participants. The two groups were compared using student t test. Pearson's correlation and a multiple regression analysis were performed to determine which variables had an effect on the distance walked.

This data is presented in tables to show the means and standard deviations, frequencies and percentages.

3.8 Conclusions

This chapter has discussed the location, ethical considerations, study design, subjects, materials and measurements, procedure for data collection and data analysis. The results of this study will be presented in the following chapter.

CHAPTER 4: RESULTS

This chapter will present the results of this study. The 6MWT was conducted with 60 children; 30 known HIV infected children and 30 presumed non-infected children. Demographic and anthropometric data will be presented first followed by the results from the 6MWT. Descriptive statistics were used to analyse the data and will be shown in tables using frequencies and percentages or means and standard deviations.

4.1 Demographic Data

The HIV infected and HIV non-infected groups were compared using the student t test. This data is reflected in table 4.1 and 4.2. The information was obtained from the patients files in the HIV infected children and from the parent/guardian questionnaire (Appendix III) and from the Data Collection Sheet (Appendix V).

Table 4.1 Demographic data of the HIV infected and non-infected groups

Variable	**HIV Infected n=30**(%)	**HIV Non-Infected n=30** (%)	**Total**
Females	11 (36.7)	16 (53.3)	27
Males	19 (63.3)	14 (46.7)	33
Total	30	30	60

(Values presented are frequencies and percentages)

Table 4.2 Demographic data of the HIV infected and non-infected groups

	HIV Infected n=30		HIV Non-Infected n=30		p-Value
	Mean	**SD**	**Mean**	**SD**	
Age (months)	106.7	12.7	107.4	8	0.78
Male	105.9	11.47	108.71	8.76	0.45
Female	108	15.1	106.31	7.46	0.7

(Values presented are means and standard deviations)

Tables 4.1 and 4.2 shows that there were no significant differences for gender or age between the two groups; thus showing that the groups were well matched.

4.2 Anthropometric and Cardiovascular Data

Anthropometric data (height, weight, BMI, HR, BP and SATS) were recorded for each child on the day of testing. HR, BP and SATS were measured pre-test, immediately post-test and five minutes post-test. The average and maximum HR's were also recorded.

Table 4.3 Anthropometric data for HIV infected and non-infected groups

Variable	**HIV Infected (n=30)**	**HIV Non-Infected (n=30)**	**p-Value**
Height (metres)			
Total (30)	1.21 (0.08)	1.3 (0.08)	0.00
Male	1.19 (0.07)	1.31 (0.08)	0.00
Female	1.23 (0.93)	1.30 (0.08)	0.03
Weight (kilograms)			
Total (30)	23.87 (4.61)	28.44 (6.39)	0.00
Male	23.88 (3.25)	26.81 (4.38)	0.04
Female	23.86 (6.52)	29.86 (7.6)	0.04
BMI	16.28 (1.77)	16.64 (2.79)	0.56

(Values presented are means and standard deviations)

Table 4.3 shows significant differences between the two groups in terms of height (p=0.00) and weight (p=0.00) with the HIV infected group being on average 9 cm shorter and 4.57 kg lighter than the non-infected group. There was no significant difference found for BMI between the two groups.

Table 4.4 Cardiovascular data during the 6MWT

Variable	**HIV Infected**	**HIV Non-Infected**	**p-Value**
Pre-test			
HR (beats per minute)	86.57 (10.49)	92.27 (11.59)	0.05
Male	84.47 (9.76)	87.36 (11.16)	0.44
Female	90.18 (11.2)	96.56 (10.48)	0.14
BP (mmHg)			
Systolic	109 (11.89)	105 (12.48)	0.20
Diastolic	72 (8.18)	67 (10.28)	0.02
SATS (%)	97.07 (1.57)	97.93 (0.94)	0.01
Immediate Post-test			
HR	132.1 (20.86)	149 (16.98)	0.00
Male	132.8 (22.51)	142.8 (15.66)	0.16
Female	130.9 (18.63)	154.4 (16.66)	0.00
BP			
Systolic	112 (13.92)	119 (15.23)	0.06
Diastolic	76 (10.95)	74 (11.1)	0.63
SATS	97.1 (1.94)	96.8 (1.27)	0.48
5 minutes Post-test			
HR	93.63 (10.15)	99.1 (11.25)	0.05
Male	91.9 (10.7)	92.57 (9.34)	0.85
Female	96.64 (8.77)	104.81 (9.73)	0.04
BP			
Systolic	103 (9.48)	107 (12.39)	0.18
Diastolic	71 (8.28)	70 (11.53)	0.61

SATS	97.6 (1.1)	97.4 (0.77)	0.50
Average HR	133.3 (15.04)	151.8 (18.2)	0.00
Male	133.11 (15.14)	146.79 (14.61)	0.01
Female	133.64 (15.6)	156.19 (20.28)	0.01
Maximum HR	145.77 (16.52)	165.83 (16.76)	0.00
Male	144.68 (15.83)	159.36 (16.94)	0.16
Female	147.64 (18.27)	171.5 (14.87)	0.00

(Values presented are means and standard deviations)

Table 4.4 demonstrates significant differences in pre-test (p=0.05), immediate post-test (p=0.00), five minutes post-test (p=0.05) as well as average (p=0.00) and maximum HR (p=0.00) between the two groups. These findings are less significant when males and females are analysed separately with males showing less difference in HR readings between the two groups. HR was significantly lower in the HIV infected group at all stages of testing. The difference between resting heart rate and immediate post-test heart rate was 45.53 bpm and 56.73 bmp in the HIV infected and non-infected groups respectively, while the difference between maximum HR was 20.06 bpm. No consistent significant differences were found for BP and SATS.

4.3 Medical Information for HIV Infected group

CD4 counts show the state of the immune system with the WHO defining a CD 4 count <200/mm³ indicates clinical stage four HIV infection and CD4 count > 500/mm³ indicates clinical stage one. Medical information was obtained from each participants hospital file and recorded on the data collection sheet (see Appendix V).

Table 4.5 Distribution of CD4 count

	WHO clinical stage	HIV infected participants n (%)
CD4 < 200/mm³	Four	2 (6)
CD4 200 – 349/mm³	Three	3 (10)
CD4 350 – 490/mm³	Two	1 (3)
CD 4 > 500/mm³	One	24 (80)

(Values presented are frequencies and percentages)

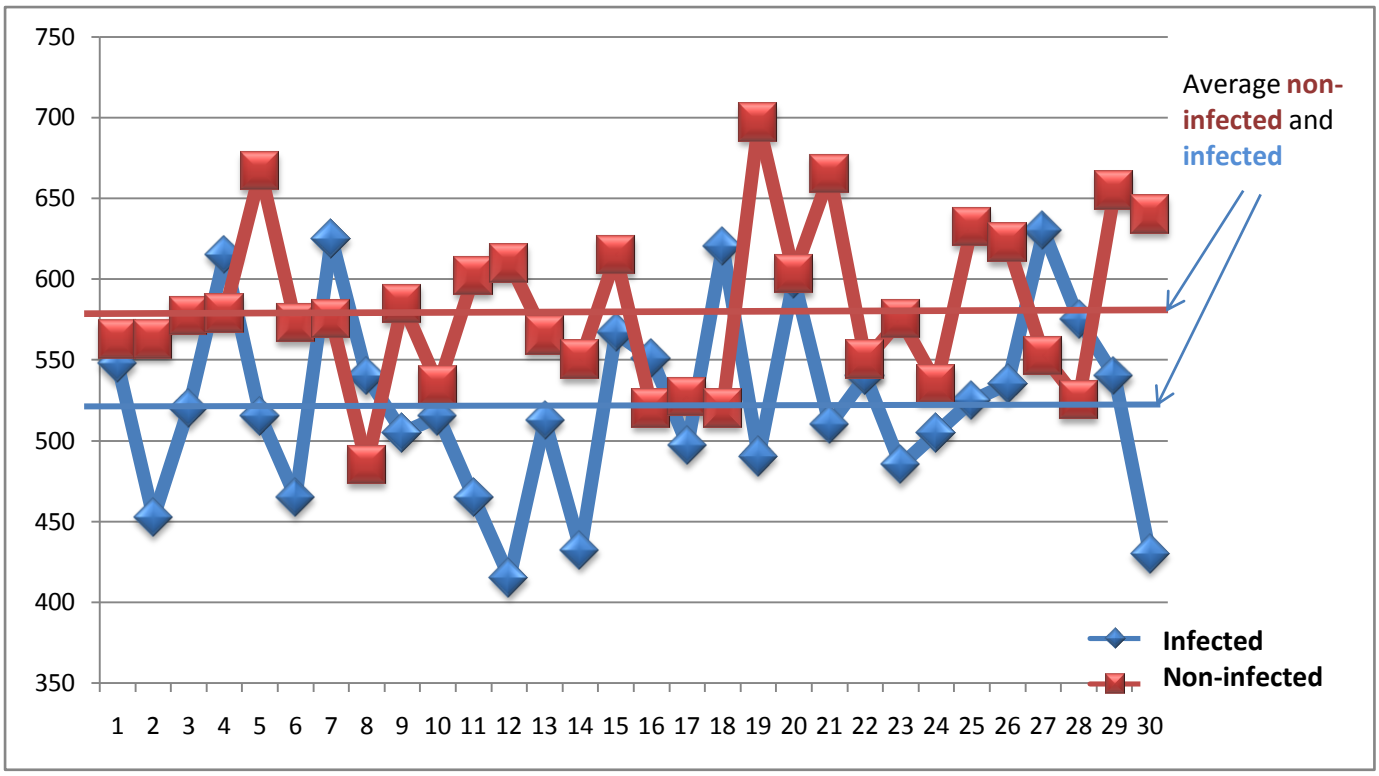
Table 4.5 shows the number of HIV infected participants in each CD4 count category. The majority of the participants (80%) had CD4 counts indicating stage one disease. According to the WHO, in children over five years of age, clinical stage one is defined as children that are asymptomatic or who have persistent generalised lymphadenopathy.

The average time that children had been on HAART was 38 months (SD 19.73) with a range of six to 91 months. All children were receiving HAART except for one who had been initiated previously but had defaulted and was at the clinic to be reinitiated.

The most common drug combinations were D4T, 3TC and EFV (n=11, 38%) and ABC, 3TC and EFV (n=10, 34%).

4.4 Six Minute Walk Test

The following graph shows the distance walked by each participant in the 6MWT. The non-infected participants are shown in red and the infected participants in blue. The average distance for each group is demonstrated by the horizontal line.



Graph 4.1 Six minute walk test results

Graph 4.1 shows the distribution of each participants 6MWD. The solid horizontal lines show the difference between the two groups mean walking distance with the red line showing the non-infected participants average at 582.03m and the blue line showing the HIV infected participants average at 524.17m.

Table 4.6 Six minute walk test results

Variable	**HIV Infected** (SD)			**HIV Non-Infected** (SD)			**p-Value**
6MWD	524.17 (57.9)			582.03 (50.9)			0.00
	Male	Female	p-Value	Male	Female	p-Value	
	524.21 (60.2)	524.09 (56.5)	0.996	592.82 (59.5)	572.59 (41.6)	0.285	

(Values presented are means and standard deviations)

Table 4.6 demonstrates a significant difference (p=0.00) in the distance walked between the two groups, with the HIV infected group walking an average of 57.86 metres less than the

non-infected group. It also shows that the difference in distance walked between males and females in each group is insignificant. Male non-infected participants did however walk an average of 20.23 meters further than the non-infected female participants.

Table 4.7 Six minute walk test results by gender

		HIV Infected	**HIV Non-Infected**	**p-Value**
6MWD	Male	524.21 (60.2)	592.82 (59.5)	0.00
	Female	524.09 (56.5)	572.59 (41.6)	0.02

(Values presented are means and standard deviations)

Table 4.7 shows a significant difference between the distances walked in HIV infected males (p=0.00) and females (p=0.02) when compared to their non-infected gender matched peers. HIV infected males and females walked an average of 68.64 metres and 48.5 metres less than the non-infected participants respectively.

Table 4.8 Six minute walk test results for each age group

	7 years	**n**	**8 years**	**n**	**9 years**	**n**	**10 years**	**n**
HIV-Infected								
Total	487.1 (52.07)	7	531.57 (47.83)	7	541.7 (65.05)	10	529.58 (56.18)	6
Male	470.5 (58.46)	4	547.2 (44.54)	5	537.13 (66.76)	8	522.5 (17.68)	2
Female	509.17 (41.56)	3	492.5 (38.9)	2	560 (77.78)	2	533.13 (71.54)	4
Non-Infected								
Total	556.5 (31.82)	2	565.36 (45.58)	11	591.5 (52)	16	665	1
Male		0	566 (54.92)	7	612.08 (55.67)	6	665	1
Female	556.5 (31.82)	2	564.25 (29.82)	4	579.15 (48.29)	10		0

(Values presented are means and standard deviations)

Table 4.8 shows the breakdown of the distance walked for each age group. In the non-infected participants it shows an increasing trend overall as well as in each gender group. The

HIV infected participants show a similar trend overall except for a decline between the nine and ten year old age categories. This pattern is not seen as clearly when looking gender specifically with females increasing between seven and eight and then decreasing between the subsequent age groups. In males there is a decrease seen between seven and eight and increase between eight and nine and then a decrease again between nine and ten years.

A Spearman's rho test was performed to determine whether there were any variables that correlated to the distance walked in the 6MWT.

Table 4.9 Spearman's Correlation for 6MWD

6MWD	HIV Infected		HIV Non-Infected	
	r-value	p-value	r-value	P-value
Age	0.19	0.33	0.50	0.01
Height	0.25	0.19	0.17	0.38
Weight	0.16	0.40	0.13	0.51
Average HR	0.38	0.04	0.58	0.00
Maximum HR	0.40	0.03	0.65	0.00
CD4 count	0.30	0.12	n/a	n/a
Length of time on ARV's	0.17	0.37	n/a	n/a

(r=spearman's rho)

Table 4.9 shows results for a Spearman's correlation test for various variables, with the distance walked in the 6MWT. Moderate correlations were found for maximum heart rate and 6MWD in the HIV infected group and for age, average and maximum heart rate in the non-infected group.

A multiple regression analysis was done for factors in the HIV-infected population which may impact on the distance walked in the 6MWT. It revealed no correlations between any of the variables.

4. 5 Conclusion

The findings from this study show that the two groups were well matched in terms of gender and age. The HIV infected children were significantly shorter and weighed significantly less than their non-infected peers.

This study found that children aged seven to ten years who are infected with HIV walked significantly shorter distances on the six minute walk test than their uninfected peers. There was a difference of 57.86m walked between the two groups. The heart rates recorded in the HIV infected participants were also significantly lower.

There were moderate correlations found for maximum heart rate and 6MWD in the HIV infected group and for age, average and maximum heart rate in the non-infected group.

This study demonstrates a lower level of exercise endurance, specifically in the ADL activity of walking, in the HIV infected participants aged seven to ten years. These results will be discussed further in the following chapter.

CHAPTER 5: DISCUSSION

As a group, HIV infected children aged seven to ten years performed significantly worse than HIV non-infected children when tested with the six minute walk test (p=0.00). No similar studies have been conducted with HIV infected children but the results found were consistent with those found in children with chronic conditions (Greiger et al, 2007) and well as HIV infected adults (Richert et al, 2011).

This chapter will give explanation for the study design used, discuss the results and compare the findings to those of previous studies. It will also discuss the limitations, implications and recommendations for future studies.

5.1 Study Design

This study investigated the difference in exercise endurance between HIV infected children, aged seven to ten years old, and their uninfected peers. This age range was chosen as all eight studies reporting on reference values or equations for the 6MWT in children incorporated this age group (Ulrich et al, 2013; D'silva et al, 2012; Klepper and Muir, 2011; Priesnitz et al, 2009; Saad et al, 2009; Lammers et al, 2008; Geiger et al, 2007 and Li et al, 2007). It would therefore make it possible to compare the results with those of the above mentioned studies. Ten years was chosen as the upper age limit so as to limit the effect that puberty may have had on the children in the study. The 6MWT was chosen as a suitable tool to assess exercise endurance as it provides a global evaluation of all the body systems involved during exercise including 'pulmonary and cardiovascular systems, systemic circulation, peripheral circulation, blood, neuromuscular units and muscle metabolism' (ATS Guidelines, 2002). The 6MWT is used in patients with chronic disease to assess functional exercise capacity (Yüksel et al, 2012; Elloumi et al, 2011; Moalla et al, 2005 and Gulmans et al, 1996) and is currently the most popular functional walk test used for clinical or research purposes (Hassan et al, 2010).

HIV status was not tested in the HIV non-infected group for logistical reasons and due to the lack of acceptability of asking parents/guardians for this permission. The parent/guardian questionnaire was designed to try and eliminate known HIV infected children from the HIV non-infected group. It was hoped that by excluding children who had been admitted to hospital in the previous three months, were known with a chronic illness or had to take medication on a daily basis, there would be minimal chance of including an HIV infected child in the HIV non-infected group. As a consequence, the HIV non-infected group may have included a small number of participants that were infected with HIV.

5.2 Comparison of the groups

5.2.1 Demographics

Age, gender and ethnic background are documented factors that can affect the distance walked in the 6MWT (Ulrich et al, 2013; Enright, 2003). There were no significant differences between the groups for gender and age. All participants were of the same ethnic background. These factors were therefore not considered as possible reasons for the differences seen between the two groups in this study.

5.2.2 Anthropometric Measurements

Height and weight are also known factors which can affect the distance walked in the 6MWT (Ulrich et al, 2013; Enright, 2003). Significant differences were found when comparing weight and height between the two groups. The HIV infected participants had an average height 9cm shorter and an average weight 4.5kg lighter than their uninfected peers.

These results are similar to other studies who found that HIV infected children from birth to twelve years of age had significant differences in anthropometric measurements compared to their unexposed and exposed but uninfected peers (Humphries et al, 2014; Musoke et al, 2010; Shet et al, 2009 and The European Collaborative Study, 2003).

Significantly lower heart rates were found in the HIV infected group in this study at all stages of testing. Few studies report on this parameter in their results. Of the three studies found (Beans et al, 2013; Richert et al, 2011; Oursler et al,2006), where the 6MWT was used in HIV infected adults, only one reported on HR findings. In this study, by Beans et al (2013), comparing HIV-infected men to age matched uninfected controls, maximum HR was tabulated, but not discussed further, as there was no significant difference between the two groups. This study did however exclude any person with known cardiovascular disease. In the studies by Cade et al (2002) and Cade et al (2008) maximal treadmill testing with late adolescents and maximal cycle ergometer testing with adults was performed respectively. In the group of late adolescents a difference of 18 bpm was found between peak HR in the HIV infected group and the control group with the infected group having a significantly lower average peak HR (Cade et al, 2002), while in the adult group a difference of 15 bpm in peak HR was found, again with the HIV infected group having the lower average reading (Cade et al, 2008). This was similar to the findings in the current study where a difference in maximum heart rate of 20.06 bpm was found with the average in the HIV infected group again being significantly lower. There has been very little discussion surrounding the possible reasons for this lower HR being reported. Some of the reasons that have been postulated for decreased aerobic capacity include pulmonary dysfunction, anaemia, deconditioning, cardiovascular dysfunction and peripheral muscle oxygen extraction-utilisation limitation (Stringer, 2000) and cardio-autonomic dysfunction (Cade et al, 2008). The current study did not perform any specific testing for the above mentioned outcomes and can therefore not establish a reason for the finding of a decreased HR in the HIV infected participants.

In the non-infected participant group, females had heart rates that were in the region of 10 beats per minute faster than males at all testing periods (Pretest: 9.2; Immediate post test: 11.6; 5 min post test: 12.24; Average: 9.4 and Maximum: 12.14). Of the studies that reported on male and female heart rates Ulrich et al (2013); Saad et al (2009); Geiger et al (2007) and Li et al (2007), all reported higher heart rates in their female populations. This was found to be true too, although to a lesser extent, in the HIV infected participants in this study (Pretest: 5.71; 5 min post test: 4.74; Average: 0.53 and Maximum: 2.96) except at the immediate post test reading where males averaged 1.9 bpm faster.

5.2.3 Medical Information for HIV Infected group

CD4 counts were obtained from the files of all HIV infected children. Unfortunately some of the results were older than six months due to the testing policy at the Bambanani Wellness Clinic. All children were receiving HAART except one who had defaulted treatment and was at the clinic to be reinitiated.

The most common drug combinations were D4T, 3TC and EFV (n=11, 38%) and ABC, 3TC and EFV (n=10, 34%). ABC, 3TC and EFV is a known first line regimen for children with D4T (Stavudine) being prescribed under special circumstances such as 'significant toxicities, anticipated drug-drug interactions or for other reasons' (World Health Organisation, 2013). D4T is however known to significantly increase the risk of peripheral neuropathy and for this reason its use is discouraged (Dragovic and Jevtovic, 2003). There were a large percentage of children in this study receiving a HAART regimen that included D4T. Undiagnosed peripheral neuropathy may have contributed to the decreased distance walked in the HIV infected participants.

5.2.4 Six Minute Walk Test

This study demonstrates that the 6MWD of HIV-infected children is significantly reduced when compared with healthy subjects. There are no known similar studies done with HIV infected children. Only one adult study conducted testing with an HIV infected and uninfected group (Beans et al, 2013). This study reports that to their knowledge theirs was the first to use the 6MWT to compare these two groups in adults. Their results showed a 14m difference in distance walked favouring the HIV infected group. This is in contrast to the current study where a 57.86 m difference was found, with non-infected participants walking the greater distance. Richert et al (2011) and Oursler et al (2006) reported on poor performance on the 6MWT in their HIV infected adult populations but this was only determined by using known reference formulae.

More studies were found where VO2 peak was used as the measure of cardiorespiratory fitness with peak exercise treadmill testing being done. Lower VO2 peak results were reported in studies with HIV infected children (Somarriba et al, 2013), adolescents (Cade et al, 2002; Keyser et al, 2000) and adults (Oursler et al, 2006) demonstrating substantial reductions in aerobic capacity in all age groups.

When using the reference equations provided by previous studies for predicted walking distances the percentage of predicted distance in this study were as follows;

Non-infected participants: 98.6% (males and females combined) (Priesnitz et al, 2009); 90% (males and females combined) (Saad et al, 2009); 96% (males) and 94% (females) (Geiger et al, 2007); 73% (males) and 81% (females) (Li et al, 2007) and 98% (1) and 100% (2) (males and females combined) (Ulrich et al, 2013) of predicted distance respectively.

HIV infected participants: 92.4% (males and females combined) (Priesnitz et al, 2009); 84% (males and females combined) (Saad et al, 2009); 87% (males) and 86% (females) (Geiger et al, 2007); 67% (males) and 78% (females) (Li et al, 2007) and 89% (1) and 94% (2) (males and females combined) (Ulrich et al, 2013) of predicted distance respectively.

This shows that the healthy population in this study is more comparable to the population tested by Ulrich et al (2013), a group of children in Switzerland, than to a group of children in Tunisia, Africa. This points to the need for a standard reference equation for South African children specifically.

Trends in terms of the distance walked, when comparing males and females, has shown that males generally walk slightly greater distances than females. This may be due to their greater muscle mass or their ability to attain higher levels of physical activity (Li et al, 2007). Li et al (2007) found that males averaged 38.2m more than females while D'silva et al (2012) found a difference of 121.8m favouring males. Saad et al (2009), Ulrich et al (2013) and Klepper and Muir (2011) divided their participants into their respective age categories, with the general trend being towards males walking longer distances, except in the 6-7 year, 8 year and 9 year old categories in each study respectively where females walked slightly greater distances. In the current study this trend was seen in the non-infected participants with the difference in distance walked being 20.23 metres and with a greater distance for males in

each age category. In the HIV-infected group there was only a 12 centimetre difference between males and females and, when looking at each age category individually, males only walked a greater distance in the eight year old category in the HIV infected group, whereas the average distance walked was greater for females in the seven, nine and ten year old groups.

There is also a general trend found for the distance walked in the 6MWT to increase with increasing age (Ulrich et al, 2013; Priesnitz et al, 2009; Saad et al, 2009 and Lammers et al, 2008). This was seen in the non-infected participants with an increase of 8.86m between seven and eight years, 26.14m between eight and nine years and 73.5m between nine and ten years. This was also seen in the HIV-infected participants with an increase of 44.47m between seven and eight years and 10.13m between eight and nine years. There was however a decrease of 12.12m in the distance walked between nine and ten year olds. A moderate correlation (r=0.50) was found for age and 6MWD in the non-infected population but a poor correlation (r=0.19) was found in the HIV infected group.

Height is also known to impact on the distance walked in the 6MWT. Taller people may have a larger stride length and therefore walk greater distances (Li et al, 2007). Among all anthropometric measurements, height was reported to have the strongest correlation to the distance walked in the 6MWT in the study by Li et al (2007). They also developed reference centile curves based on this parameter. Height also showed significant correlations in most other reference studies (Ulrich et al, 2013; D'silva et al, 2012; Priesnitz et al, 2009; Saad et al, 2009; Lammers et al, 2008 and Geiger et al, 2007). In the current study HIV infected participants were significantly shorter than their non-infected peers. There was however a lack of correlation found for height and the distance walked, in both HIV infected (r=0.25) and non-infected (r=0.17) participants.

Another significant correlation that has been reported on is heart rate (Ulrich et al, 2013; Priesnitz et al, 2009; Geiger et al, 2007 and Li et al, 2007). In the current study moderate correlations were found for average (r=0.38; p=0.04) and maximum (r=0.40; p=0.03) heart rate and 6MWD in the HIV infected group and for average (r=0.58; p=0.00) and maximum

(r=0.65; p=0.00) heart rate in the non-infected group. All mean heart rate readings fell within the normal ranges for their age.

5. 3 Limitations

- The medical history was not included on the data collection sheet. A detailed medical examination would have been beneficial to determine the extent of cardiorespiratory, musculoskeletal and neurological complications as well as complications related to the side effects of HAART.

- The 6MWT was the only test used in this study. A wider variety of tests could be included in further studies such as The Activity Scale for Kids (ASK).

- There is a current lack of normative data for the 6MWT in South African children thereby limiting the interpretation of the current findings.

- Due to the protocols at the Bambanani Wellness Clinic the CD4 count is taken only yearly in children who are deemed stable on HAART. This resulted in 12 participants CD4 count readings being more than six months old.

- The small study sample in a single centre made the generalisation of study findings difficult.

5. 4 Implications for clinical practice

HIV infected children are more at risk for decreased exercise endurance than their uninfected peers. With the increasing availability of HAART in Sub-Saharan Africa, these children are more likely to have a life expectancy similar to their uninfected peers. Exercise programmes have been shown to be safe and beneficial in increasing the exercise endurance in the paediatric population (Miller et al, 2010 and O'Brien et al, 2010). Physiotherapy departments

are frequently under-resourced in the rural areas and often do not manage to provide this service.

5. 5 Recommendations

- Multidisciplinary management of children infected with HIV should be common practice, and involve allied health professionals. Each child should have a baseline endurance test done on initial presentation to the hospital or clinic. Testing should also include muscle strength as well as a neurological assessment.
- Physiotherapy services need to be advocated for with an increase in the services provided to patients especially in rural areas. Each child should receive an exercise programme suited to their needs. This may require an initial period of supervised training after which follow up of a home programme should be done.
- Awareness should be increased amongst physiotherapists about the importance of their role within this patient group. This should be done at University level.

5.6 Suggestions for further research

A reference formula for the 6MWT should be formulated for use with South African children specifically. This will allow for a more accurate comparison when studying different populations.

If a similar study to this is conducted then a detailed medical examination would help determine the extent and influence of pre-existing cardiac and pulmonary deficits.

CHAPTER 6: CONCLUSION

The purpose of this cross sectional comparative study was to compare the exercise endurance of a group of HIV infected children to that of their uninfected peers using the six minute walk test according to standardised ATS guidelines.

The two groups were well matched in terms of socio-economic status, gender and age. Statistically significant differences were found when comparing anthropometric measurements of height and weight as well as in the participants heart rates when comparing the two groups. The distance walked in the 6MWT was significantly less in the HIV infected participants when compared to their non-infected peers.

This study demonstrates a lower level of exercise endurance in the HIV infected participants. Multidisciplinary management including physiotherapy should be mandatory for these children with exercise programmes being designed and monitored for each HIV infected child.

This is the first known study of this kind. The study sample was relatively small and further research should be done to confirm these findings. A standard reference equation for the 6MWT in South African children should be formulated to more easily determine the impact of disease.

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APPENDIX I: ETHICAL CLEARANCE

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
Division of the Deputy Registrar (Research)

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
R14/49 Miss Alison J Walker

CLEARANCE CERTIFICATE	**M121159**
PROJECT	Preliminary Investigation into the Exercise Endurance of HIV Infected School Going Children Aged Seven to Ten Years
INVESTIGATORS	Miss Alison J Walker.
DEPARTMENT	Department of Physiotherapy
DATE CONSIDERED	30/11/2012
DECISION OF THE COMMITTEE*	Approved unconditionally

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

DATE 31/01/2013 **CHAIRPERSON** .....
(Professor PE Cleaton-Jones)

*Guidelines for written 'informed consent' attached where applicable
cc: Supervisor : Dr J Potterton

DECLARATION OF INVESTIGATOR(S)
To be completed in duplicate and **ONE COPY** returned to the Secretary at Room 10004, 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...

MPUMALANGA PROVINCIAL GOVERNMENT

Building No.3
No. 7 Government Boulevard
Riverside Park Extension 2
Nelspruit
1200
Republic of South Africa

Private Bag X 11285
Nelspruit, 1200
Tel: 013 766 3429
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Department of Health

Litiko Letemphilo | Umnyango WezaMaphilo | Departement van Gesondheid

Enquiries: Themba Mulungo (013) 766 3511

28 February 2013

Ms. Alison Walker
10 Hillside Manor
3 Sonbesie Road
Nelspruit
1200

Dear Ms. Alison Walker

APPLICATION FOR RESEARCH & ETHICS APPROVAL: PRELIMINARY INVESTIGATION INTO THE EXERCISE ENDURANCE OF HIV INFECTED SCHOOL GOING CHILDREN AGED SEVEN TO TEN YEARS

The Provincial Research and Ethics Committee has approved your research proposal in the latest format that you sent.

Kindly ensure that you provide us with the soft and hard copies of the report once your research project has been completed.

Kind regards

Mr. Molefe Machaba
Research and Epidemiology

28/02/2013
Date

We care Do you?
Siyanakekela

MPUMALANGA
A Pioneering Spirit

APPENDIX II: INFORMED CONSENT

University of Witwatersrand

Informed consent

Hello, my name is Alison Walker and I am a Masters Physiotherapy student at the University of Witwatersrand. I am currently working at Themba Hospital, Kabokweni.

I am doing a project to find out if HIV has an effect on the fitness of children aged 7 - 10 years.

I would like to ask for your permission to include your child in this project.

The project involves a once off walking test where your child will be asked to walk between two markers for 6 minutes. Your child will sit quietly for 10 minutes before the test. Their height, weight, heart rate, blood pressure and oxygen saturation will be measured. Your child will then be asked to walk at an easy speed for 6 minutes. Once finished, their heart rate, blood pressure and oxygen saturation will be measured again. The test will be done at Themba hospital and the total time for the whole test will be 20 minutes.

Your child's hospital file will be used to get information about the anti-retroviral therapy they are taking.

Risks: Your child may get tired and out of breath during the walking test. They will be told before the test that they can stop for a rest at any time if they are feeling too tired. The hospitals facilities will be available if there is any emergency.

Benefits: No direct benefits

The results of the project will be available if you are interested in finding out more

Taking part in the project is voluntary; you are free to say no at any time. Your child's treatment at the clinic will continue as normal even if you do not want him/her to take part in the project. The project will be explained to your child and they will be asked to sign another form if they want to take part.

Confidentiality: Efforts will be made to keep all data and information private. Your child's name will not appear on any records. No one will be able to link your child's name to the data collected or to their hospital file except the researcher (Alison Walker). All information will be kept privately in a sealed box for 3 years before being discarded.

Contact Information:

Researcher: Alison Walker: 083 497 0610

Department of Physiotherapy, University of Witwatersrand: 011 717 3702

REC chair – Professor P Cleaton Jones: 011 717 1234, for reporting of ethical complaints or problems

Consent:

I have carefully read the information document/had it read to me.
I understand the aim and procedures involved in this project.
I understand that at any time I may withdraw my child from the study.
I understand that there are no monetary rewards for participating in the study.
I hereby give permission for my child to participate in this study.

Name (in full) of child/participant: _____

Name (in full) of parent/guardian:_____

Signature of parent/guardian: _____

Relationship to child: _____

Name (in full) of witness: _____

Signature of witness: _____

Date: _____

University of Witwatersrand

Informed consent – (Imvumo yokwatiswa nge njongoyemsebenti/lucwaningo)

Sakubona, ligama lami ngingu – Alison Walker, ngenta tifundvo tami letiphakeme tebudokotela bematsambo enyumvesi yase-Witwatersrand. Ngisebenta eThemba esibhedlela, Kabokweni.

Ngenta lucwaningo lokutfola kutsi sifo sagawulako singaba nemtselela lonjani ekukhuleni kwemntfwana loneminyaka lesikhambisa kuya kwelishumi

Ngitsandza kucela imvumo yokusebentisa lomtfwanakho kulolucwaningo

Lolucwaningo lufaka ekhatsi kuhamba kwemntfwana wakho emkhatsini kwemamaki lamabili, emaminitsi lasitfupha. Umntwana wakho utawuhlala phansi emaminitsi lalishumi ngembi kweluhlolo. Utawukalwa budze, sisindvo, kushaya kwenhlitiyo, kugijima kwengati ne-oxygen engatini. Umntfwana wakho utawucelwa kutsi ahambe ngesivinini lesikahle, emaminitsi lasitfupha. Uma acedza, kusebenta kwenhlitiyo, kugijima kwengati ne lizinga le-oxygen litokalwa. Loluhlolo lutochutjwa esibedlela eThemba, lutotsatsa emaminitsi lamashumi lamabili.

Tingoti letingavela: Umntfwana wakho kungenteka adzinwe aphelelwe ngumoya kuloluhlolo lwekuhamba. Batowatiswa ngembi kwekucala luhlolo, kutsi bangema, baphumule uma bativa badziniwe.

Tinsita lesibhedlela titabakhona uma kunesidzingo lesiphutfumako.

Tindzuzo: Kute

Imiphumela yaloluhlolo iyatfolakala, uma unesifiso sekwati.

Kutsatsa indzima kuloluhlolo ukwenta ngekufuna. Uvumelekile kwala nobe kunini. Uma uvuma umntfwana wakho utakuchazelwa kabanti ngaloluhlolo bese utawucelwa kutsi asayine lelinye liphepha lekutsi naye uyavuma.

Kwelashwa kwemntfwanakho kutochubeka ngalokujwayelekile noma angala kungenela loluhlolo

Imfihlo: Imizamo itawentiwa kutsi imininingwane ifihlwe. Ligama lemntfwana wakho angeke livetwe emibhalweni. Akekho longahlanganisa ligama lemntfwana wakho nemininingwane yaloluhlolo ngaphandle kwemcwaningi (Alison Walker). Imininingwane yonkhe itawujcinwa ebhokisini lelivaliwe iminyaka lemitsatfu ngembi kwekube ilahlwe.

Imininingwane yekuchumana:

Umcwaningi: Alison Walker: 083 497 0610

Department of Physiotherapy, University of Witwatersrand: 011 717 3702

REC chair – Professor P Cleaton Jones: 011 717 1234, kokubikwa gwetinkinga nobe kukhononda

Sivumelwano

Ngifundzisisile leliphepha lemphiko/bangifundzele

Ngiyavisisa injongo neluhlelo lwaleluhlolo.

Ngiyavisisa kutsi ngingamkhipha umntfwana wami nobe kunini kuloluhlolo.

Ngiyavisisa ayikho indzuzo ngetimali lekhona kuloluhlolo.

Ngako-ke ngiyamvumela umntwana wami kutsi angatsatsa indzima kuloluhlolo .

Ligama (Leliphelele) lemntfwana/umdlali: _____

Ligama(Leliphelele) lemtali/umgadzi wemntfwana: _____

Kusayina kwemntali/umgadzi wemntwana: _____

Buhlobo nemtfwana: _____

Ligama (Leliphelele) lwa fakazi: _____

Kusayina Kwafakazi: _____

Lusuku: _____

University of Witwatersrand

Informed consent

Hello, my name is Alison Walker and I am a Masters Physiotherapy student at the University of Witwatersrand. I am currently employed at Themba Hospital, Kabokweni.

I am doing a project to find out the fitness of healthy children and to compare it to children with chronic illnesses.

I would like to ask for your permission to include your child in this project. Please read this form before signing. Please also complete the attached questionnaire. If your child has a known chronic illness or is taking any long term medication, your child should not take part in the study so you do not need to give consent. You are welcome to contact me to ask any questions you may have.

The project involves a once off walking test where your child will be asked to walk between two markers for 6 minutes. Your child will sit quietly for 10 minutes before the test. Their height, weight, heart rate, blood pressure and oxygen saturation will be measured. Your child will then be asked to walk at an easy speed for 6 minutes. Once finished, their heart rate, blood pressure and oxygen saturation will be measured again. The test will be conducted at their school and the total time for the whole test will be 20 minutes.

Risks: Your child may get tired and out of breath during the walking test. They will be told before the test that they can stop for a rest at any time if they are feeling too tired.

Benefits: None

The results of the project will be available if you are interested in finding out more

Taking part in the project is voluntary; you are free to say no at any time. If you do give permission the project will be explained to your child and they will be asked to sign another form only if they want to take part.

Confidentiality: Efforts will be made to keep all data and information private. Your child's name will not appear on any records. No one will be able to link your child's name to the data collected except the researcher (Alison Walker). All information will be kept privately in a sealed box for 3 years before being discarded.

Contact Information:

Researcher: Alison Walker: 083 497 0610

Department of Physiotherapy, University of Witwatersrand: 011 717 3702

REC chair – Professor P Cleaton Jones: 011 717 1234, for reporting of ethical complaints or problems

Parent/Guardian Questionnaire

Child's Name: _____

Date of Birth of child: _____

Has your child been admitted to hospital in the last 3 months? Yes or No (circle one)

Does your child have a known chronic illness? Yes or No (circle one)

(Examples of chronic illness: Lung problems, heart problems)

Does your child have to take any medication every day? Yes or No (circle one)

If yes, please write the names down and what it is for:

_____

_____

_____

Consent:

I have carefully read the information document/had it read to me.
I understand the aim and procedures involved in this project.
I understand that at any time I may withdraw my child from the study.
I understand that there are no monetary rewards for participating in the study.
I hereby give permission for my child to participate in this study.

Name (in full) of child/participant: _____

Name (in full) of parent/guardian:_____

Signature of parent/guardian: _____

Relationship to child: _____

Name (in full) of witness: _____

Signature of witness: _____

Date: _____

University of Witwatersrand

Informed consent – (Imvumo yokwatiswa nge njongoyemsebenti/lucwaningo)

Sakubona, ligama lami ngingu – Alison Walker, ngenta tifundvo tami letiphakeme tebudokotela bematsambo enyumvesi yase-Witwatersrand. Ngisebenta eThemba esibhedlela, Kabokweni.

Ngenta tifundvo tekucwaninga kutsi bantfwana labaphilile bacinelele kanganani, nabacatsaniswa nebantfwana labaphila nekugula.

Ngitsandza kucela imvumo yakho kufaka umntfwana wakho kulelucwaningo. Ngicela ufundze leliphepha ngembhi kweku sayina. Ngicela uphindze ugwalise lemibuto lenamatselisiwe. Uma ngabe umntfwana wakho uphila netifo letitsite nobe utsatsa emaphilisi amihlayonkhe, umntfwana wakho angatsatsi indzima kulolucwaningo, akudzingeki kutsi unikele imvumo, uvumelekile kungitsindza kungibuta imibuto lonayo.

Lolucwaningo lufaka ekhatsi kuhamba kwemntfwana wakho emkhatsini kwemamaki lamabili, emaminitsi lasitfupha. Umntwana wakho utawuhlala phansi emaminitsi lalishumi ngembi kweluhlolo. Utawukalwa budze, sisindvo, kushaya kwenhlitiyo, kugijima kwengati ne-oxygen engatini. Umntfwana wakho utawucelwa kutsi ahambe ngesivinini lesikahle, emaminitsi lasitfupha. Uma acedza, kusebenta kwenhlitiyo, kugijima kwengati ne lizinga le-oxygen litokalwa. Loluhlolo lutochutjwa esikolweni sabo, lutotsatsa emaminitsi lamashumi lamabili.

Tingoti letingavela: Umntfwana wakho kungenteka adzinwe aphelelwe ngumoya kuloluhlolo lwekuhamba. Batowatiswa ngembi kwekucala luhlolo, kutsi bangema, baphumule uma bativa badziniwe.

Tindzuzo: Kute

Imiphumela yaloluhlolo iyatfolakala, uma unesifiso sekwati.

Kutsatsa indzima kuloluhlolo ukwenta ngekufuna. Uvumelekile kwala nobe kunini. Uma uvuma umntfwana wakho utakuchazelwa kabanti ngaloluhlolo bese utawucelwa kutsi asayine lelinye liphepha lekutsi naye uyavuma.

Imfihlo: Imizamo itawentiwa kutsi imininingwane ifihlwe. Ligama lemntfwana wakho angeke livetwe emibhalweni. Akekho longahlanganisa ligama lemntfwana wakho nemininingwane yaloluhlolo ngaphandle kwemcwaningi (Alison Walker). Imininingwane yonkhe itawuqcinwa ebhokisini lelivaliwe iminyaka lemitsatfu ngembi kwekube ilahlwe.

Imininingwane yekuchumana:

Umcwaningi: Alison Walker: 083 497 0610

Department of Physiotherapy, University of Witwatersrand: 011 717 3702

REC chair – Professor P Cleaton Jones: 011 717 1234, kokubikwa gwetinkinga nobe kukhononda

Mibuto yemtali/logadza umntwana ***(leli liphepha libuyiswe ngumntfwana)***

Ligama lemntfwana _____

Lilanga lekutalwa lemntfwana: _____

Ingabe umntfwana uke walaliswa esibedlela kuletinyanga letintsatfu letengcile?

Yebo nebo cha (dvwebela yinye)

Ingabe umntfwana wakho unato tifo lenitatiko laphilanato? Tifo laphila nato: tifo tesifuba, tifo tenhlitiyo

Yebo nebo cha (dvwebela yinye)

Ingabe akhona maphilisi lanatfwa ngumntfwana wakho onkhe malanga?

Yebo nebo cha (dvwebela yinye)

Uma kunjalo, bhala emegama alamaphilisi:

_____

_____

Sivumelwano

Ngifundzisisile leliphepha lemphiko/bangifundzele
Ngiyavisisa injongo neluhlelo lwaleluhlolo.
Ngiyavisisa kutsi ngingamkhipha umntfwana wami nobe kunini kuloluhlolo.
Ngiyavisisa ayikho indzuzo ngetimali lekhona kuloluhlolo.
Ngako-ke ngiyamvumela umntwana wami kutsi angatsatsa indzima kuloluhlolo .

Ligama (Leliphelele) lemntfwana/umdlali: _____

Ligama(Leliphelele) lemtali/umgadzi wemntfwana: _____

Kusayina kwemtali wemntali/umgadzi wemntwana: _____

Buhlobo nemtfwana: _____

Ligama (Leliphelele) lwa fakazi: _____

Kusayina Kwafakazi: _____

Lusuku: _____

APPENDIX III: INFORMED ASSENT

University of Witwatersrand

Informed assent

Information Document for Participants

Hello, my name is Alison and I am a physiotherapist doing a project to see how fit children are.

I would like to ask you if you would like to do a special test with me to see how fit you are. If you would like to do the test we will be doing a few things that I have listed below together. You are allowed to say no at any time even if we have already started the test.



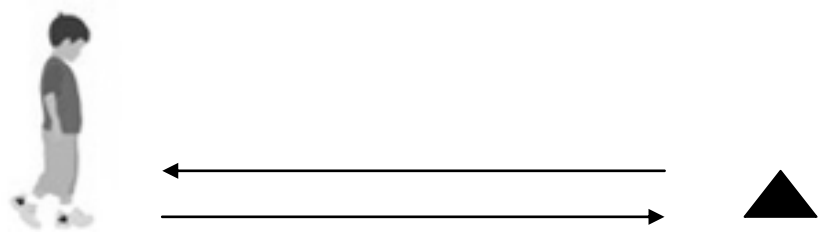
I will measure your weight and height. You will then sit quietly in a chair for 10 minutes.

I will put a strap around your arm to measure how strong your heart is. I will also put a strap around your chest to see how fast your heart is beating. I will measure the amount of oxygen in your blood by putting a small machine on your finger





I will then ask you to walk for 6 minutes between two markers. You should try to walk as far as possible during this time. If you feel tired you will be allowed to rest until you can carry on. If you want to stop the test you at any time you can tell me.



Consent

I know what I will have to do in this test.

I know that I can stop and rest if I feel tired. I know that I can stop the test at any time.

I would like to take part in this study.

Name (in full) of child/participant: _____

Name written by child (or verbal): _____

Witness: _____

Date: _____

University of Witwatersrand

Sivumelwano

Liphepha lesivumelwano

Sakubona, ligama lami ngingu-Alison, ngingudokotela wematsambo, ngenta lucwaningo lekuhlola kucinelela kwebantfwana

Ngifisa kukubuta kutsi ungafisa yini kubayincenye yekucwaninga kutsi ucinelele nganani. Uma ngabe ufisa kuba yincenye yaloluhlolo, sitowenta letintfo letimbalwa letibhalwe ngentasi. Uvumelekile kwala nobe sesicalile luhlolo



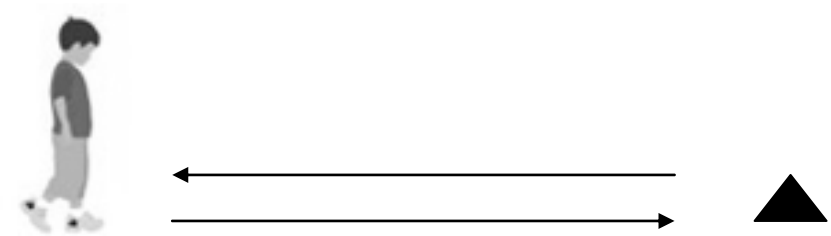
Ngitokukalo sisindvo nebudze. Utohlala phantsi emaminitsi lalishumi.

Ngitofaka sibopho emkhonweni, kutokala kutsi inhlitiyo icinelele nganani. Ngitofaka lesinye sibopho esifubeni, kukala kutsi inhlitiyo ishaya nganani. Ngitokala lizinga le-oxygen engatini yakho ngekufaka lomshini esandleni sakho





Ngitokucela kutsi uhambe maminitsi lasitfupha emkhatsini kwemamaki lamabili. Uzame kuhamba libanga lelidze kulesikhatsi. Uma utiva udziniwe uvumelekile kuphumula uze ukhone kuqubeka futsi. Uma ufisa kuyekela lolucwaningo ungangitjela nobekunini.



Sivumelwano

Ngiyavisisa kutsi yini lekumele ngikwente kule lucwaningo.

Ngiyati kutsi ngingema ngiphumule nangitiva ngikhatsele. Ngiyati kutsi nginga yekela noma kunini.

Ngifuna kubakhona kulelicwaningo.

Ligama (leliphelele) lemntwana/lemdlali: _____

Ligama lemntwana libhalwe phansi: _____

Fakazi: _____

Lisuku: _____

APPENDIX IV: DATA COLLECTION SHEET

Data Sheet **(Group 1)**

Participant study number: _____ Date: _____

Gender: 1 2

Age: _____ years _____ months

Height: _____ cm

Weight: _____ kg BMI: _____

ART information: yes or no

Date Initiated: _____

Most recent CD4 count and/or viral load (date) _____

ART Medication list:

_____

_____

Additional Medication (current)

_____

_____

	Pre-test	Post-test (immediate)	Post-test (5 minutes)
BP	/	/	/
HR			
SATS			

Lap Counter: ____ ____ ____ ____ ____ ____ ____ ____ ____

____ ____ ____ ____ ____ ____ ____ ____ ____ ____ ____

____ ____ ____ ____ ____ ____ ____ Total Laps:_____

Total Distance (m): _____

Paused or stopped during test: Y N Reason: _____

During test: Average HR: _____ Max HR: _____

Any other comments:

_____

_____

_____

Data Sheet **(Group 2)**

Participant study number: _____ Date: _____

Gender: 1 2

Age: _____ years _____ months

Height: _____ cm

Weight: _____ kg BMI: _____

	Pre-test	Post-test (immediate)	Post-test (5 minutes)
BP	/	/	/
HR			
SATS			

Lap Counter: ____ ____ ____ ____ ____ ____ ____ ____ ____

____ ____ ____ ____ ____ ____ ____ ____ ____ ____ ____

____ ____ ____ ____ ____ ____ ____ Total Laps:_____

Total Distance (m): _____

Paused or stopped during test: Y N Reason: _____

During test: Average HR: _____ Max HR: _____

Any other comments:

_____

_____

_____

APPENDIX V: AMERICAN THORACIC SOCIETY GUIDELINES

Testing guidelines used: As recommended by the American Thoracic Society (2002)

1. A “warm-up” period before the test should not be performed.

2. The participant should sit at rest in a chair, located near the starting position, for at least 10 minutes before the test starts. During this time, check for contraindications, measure pulse and blood pressure, and make sure that clothing and shoes are appropriate

3. Pulse oximetry is optional. If it is performed, measure and record baseline heart rate and oxygen saturation (SpO2). Make sure the readings are stable before recording. Note pulse regularity and whether the oximeter signal quality is acceptable.

4. Instruct the participant as follows:

“The object of this test is to walk as far as possible for 6 minutes. You will walk back and forth in this hallway. Six minutes is a long time to walk, so you will be exerting yourself. You will probably get out of breath or become exhausted. You are permitted to slow down, to stop, and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you are able. You will be walking back and forth around the cones. You should pivot briskly around the cones and continue back the other way without hesitation. Now I’m going to show you. Please watch the way I turn without hesitation.” Demonstrate by walking one lap yourself. Walk and pivot around a cone briskly. “Are you ready to do that? Remember that the object is to walk AS FAR AS POSSIBLE for 6 minutes, but don’t run or jog. Start now, or whenever you are ready.”

5. Position the participant at the starting line. You should also stand near the starting line during the test. Do not walk with the participant. As soon as the participant starts to walk, start the timer.

6. Do not talk to anyone during the walk. Use an even tone of voice when using the standard phrases of encouragement. Watch the participant. Do not get distracted and lose count of the laps. Each time the participant returns to the starting line, mark the lap on the worksheet. Let the participant see you do it.

After the first minute, tell the participant the following (in even tones): “You are doing well. You have 5 minutes to go.”

When the timer shows 4 minutes remaining, tell the participant the following: “Keep up the good work. You have 4 minutes to go.”

When the timer shows 3 minutes remaining, tell the participant the following: “You are doing well. You are halfway done.”

When the timer shows 2 minutes remaining, tell the participant the following: “Keep up the good work. You have only 2 minutes left.”

When the timer shows only 1 minute remaining, tell the participant: “You are doing well. You have only 1 minute to go.”

Do not use other words of encouragement (or body language to speed up).

If the participant stops walking during the test and needs a rest, say this: “You can lean against the wall if you would like; then continue walking whenever you feel able.” Do not stop the timer. If the participant stops before the 6 minutes are up and refuses to continue (or you decide that they should not continue), wheel the chair over for the participant to sit on, discontinue the walk, and note on the worksheet the distance, the time stopped, and the reason for stopping prematurely.

When the timer is 15 seconds from completion, say this: “In a moment I’m going to tell you to stop. When I do, just stop right where you are and I will come to you.”

When the timer rings (or buzzes), say this: “Stop!” Walk over to the participant. Consider taking the chair if they look exhausted. Mark the spot where they stopped by placing a bean bag or a piece of tape on the floor.

7. If using a pulse oximeter, measure SpO2 and pulse rate from the oximeter and then remove the sensor.

8. Record the total number of laps from the tick marks on the worksheet.

9. Record the additional distance covered (the number of meters in the final partial lap) using the markers on the wall as distance guides. Calculate the total distance walked, rounding to the nearest meter, and record it on the worksheet.

10. Congratulate the participant on good effort and offer a drink of water.