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Notice 1

Notice 2

PHYSICAL ACTIVITY FOR PEOPLE LIVING WITH THE HUMAN IMMUNODEFICIENCY VIRUS

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Contents

Highly active antiretroviral therapy (HAART) has transformed human immunodeficiency virus (HIV) into a chronic, relatively manageable illness for those who can access medical care. Despite increased life expectancy, however, HIV remains a serious illness, as problems associated with the virus and its treatments contribute to a reduced quality of life and a significant burden of disease. Patients face issues of aging and frailty, including an increased risk for the development of cardiovascular disease (CVD) and a range of metabolic, morphological and psychological problems.

Physiotherapists and other health care providers have advocated for the use of exercise training interventions and increased physical activity participation in HIV infection to help manage many physical and psychological complications. However, the effects of long term physical activity in this context are largely unknown. This Thesis will aim to determine whether long term physical activity is associated with improved health outcomes for people living with HIV and will focus on clinical endpoints relevant to chronic, treated HIV infection.

Increasing knowledge of patterns of physical activity behaviours in this patient group and understanding factors that may contribute to low levels of physical activity is also important. This knowledge may allow HIV health care providers to target physiotherapy referrals to those who are most likely to benefit from physical activity interventions. Specific strategies can be developed to target interventions and reduce inactivity (and the associated poorer health outcomes).

The current research was undertaken in five main parts:

> 1. Measurement of the prevalence of physical activity in an ambulatory HIV-infected population.
>
> 2. Validation of a well recognised physical activity measurement tool for use in HIV-infected populations.
>
> 3. A systematic evaluation of existing evidence on the effects of exercise training on morphological and metabolic outcomes in HIV-infected populations.

4. Description of long term physical activity/cardiovascular fitness and an exploration of relationships between long term physical activity/cardiovascular fitness and body composition, body image and CVD risk, in HIV-infected individuals.

5. Evaluation of the relationship of body composition and joint health (knee structure) in HIV-infected individuals.

The description and measurement of physical activity behaviours in populations with chronic, treated HIV infection has been the subject of few studies. The proportion of HIV-infected individuals who meet physical activity recommended guidelines is also unknown. Chapter 2 measured the physical activity prevalence of an ambulatory HIV-infected population and determined the proportion of individuals meeting the Centers for Disease Control (CDC) and the American College of Sports Medicine (ACSM) physical activity guidelines. The majority of HIV-infected participants (73.8%) met recommended physical activity guidelines, however 1:4 participants engaged in suboptimal levels of physical activity.

There is a current lack of practical and reliable physical activity measurement instruments that have been validated for clinical and research purposes in populations with HIV infection. Chapter 3 investigated the validity of the International Physical Activity Questionnaire (IPAQ) long form, a well recognised physical activity measurement tool. The IPAQ long form is a simple, inexpensive, easily to administer questionnaire. It has been extensively used in healthy and disease specific populations, however its application in HIV-infected populations has not previously been evaluated. There was significant correlation between physical activity measured by the IPAQ and accelerometry, however problems of over-reporting and its poor ability to identify inactive individuals are of concern.

To our knowledge, a systematic review on the effects of exercise training on metabolic and morphological complications has not previously been performed. Chapter 4 represents a systematic review of published randomised controlled trials (RCTs) on the topic and aims to elucidate the latest evidence for the role of exercise interventions in managing these important complications of HIV and its treatment. Few RCTs were found and their quality varied. Aerobic exercise decreased adiposity and improved

certain lipid subsets while progressive resistive exercise increased body weight and peripheral limb girths. A combination of both types of training did not provide additional benefits.

There is a relative lack of data regarding the optimal role of long term physical activity in managing HIV-infected patients in the era of HAART. Chapter 5 aimed to improve our understanding of the relationships between long term physical activity/cardiovascular fitness and important HIV clinical outcomes. Truly evidence-based health recommendations and interventions require knowledge of the effects of sustained, habitual physical activity, as well as an understanding of the determinants of and barriers to participation in physical activity in the relevant patient population. This data will facilitate optimal prescription of physical activity and assist in the future development of evidence-based physical activity guidelines for this group. An improved ability to target patients who could benefit most from physiotherapy intervention has also been achieved. Both physical activity and cardiovascular fitness did not change substantially over one year; however a suboptimal level of physical activity participation was identified. Cardiovascular fitness was associated with improved body composition, while improving physical activity levels were associated with improved perceived body image. Despite convincing evidence that physical activity and cardiovascular fitness are associated with reduced CVD risk in the general population, our findings were inconclusive. Finally, being in a permanent relationship was correlated with higher levels of physical activity.

The problem of obesity is increasing in the HIV setting and it is a well recognized risk factor for osteoarthritis (OA) in the general population. It is plausible that the morphological complications discussed in Chapter 4, particularly recent problems of obesity, overweight and central fat accumulation observed in HIV- infected individuals may also result in an increased incidence of OA. A rising prevalence of bone health issues, including osteopenia and osteoporosis in the HIV-infected population has recently been observed. Chapter 6 explored a cross sectional sample of HIV-infected individuals and looked at the relationship between body composition and knee structure abnormalities. Total body and android fat mass were inversely related to average knee cartilage volume in ambulant, HAART-treated HIV-infected adults. This Chapter discusses these findings as novel implications for musculoskeletal health of chronic, treated HIV infection.

This Thesis examined the relationships between long term physical activity/cardiovascular fitness and important HAART-related complications over a one year period. It defined the prevalence of long term physical activity in a local cohort of HIV-infected individuals and validated a well recognised physical activity measurement instrument. Existing RCTs on the effects of exercise training on metabolic and morphological complications were systematically reviewed and the risk of OA in this population is discussed after a novel finding. This Thesis contributed to an increased understanding of the plausible role of both physical activity and exercise training in the optimal management of chronic, treated HIV infection. It has also identified priority areas for future study in this area.

Published Journal Articles

1. **Fillipas S,** Cherry CL, Cicuttini FM, Smirneos L and Holland AE. The effects of exercise training on metabolic and morphological outcomes for people living with HIV: a systematic review of randomised controlled trials. *HIV Clinical Trials 2010*; 11, 270-82.

2. **Fillipas S**, Cicuttini FM, Holland AE and Cherry CL. The International Physical Activity Questionnaire overestimates moderate and vigorous physical activity in HIV. The Journal of the Association of Nurses in AIDS Care. *Journal of Nurses in AIDS Care* 2010; 21, 173-181.

3. **Fillipas S**, Bowtell-Harris CA, Oldmeadow LB, Cicuttini FM, Holland AE and Cherry CL. Physical activity uptake in patients with human immunodeficiency virus: who does how much? *International Journal of STD and AIDS* 2008; 19, 514-518.

Submitted journal articles

1. **Fillipas S**, Cicuttini FM, Holland AE and Cherry CL. Physical activity participation and cardiovascular fitness in people living with HIV: a one- year longitudinal study. *Submitted HIV Medicine* May 2011.

2. **Fillipas S,** Tanamas S, Davies-Tuck ML, Wluka AE, Wang Y, Holland AE, Cherry CL and Cicuttini FM. The relationship between body composition and knee structure in patients with Human Immunodeficiency Virus. *Submitted J Rheumatology* May 2011.

Published abstracts

1. **Fillipas S,** Holland AE, Cherry CL and Cicuttini FM. The effects of exercise training on metabolic and morphological outcomes for people living with HIV: a

systematic review of randomised controlled trials. *XV111 International AIDS Conference*, Vienna July 2010.

2. **Fillipas S**, Cicuttini FM, Holland AE and Cherry CL. The International Physical Activity Questionnaire overestimates moderate and vigorous physical activity in HIV. *Proceedings from the Australian Physiotherapy Association Conference,* October 1st-5th, 2009.

3. **Fillipas S**, Bowtell-Harris CA, Oldmeadow LB, Cicuttini FM, Holland AE and Cherry CL. Physical activity uptake in patients with human immunodeficiency virus: who does how much? *HIV Clinical Trials*, 9, Suppl 1, pg 47, 2008.

4. **Fillipas S**, Bowtell-Harris CA, Oldmeadow LB, Cicuttini FM, Holland AE and Cherry CL. Physical activity uptake in patients with human immunodeficiency virus: who does how much? *The Australian Journal of Physiotherapy,* 54, 1, March, pgS1, 2008.

Conference presentations

1. **Fillipas S,** Holland AE, Cherry CL and Cicuttini FM. The effects of exercise training on metabolic and morphological outcomes for people living with HIV: a systematic review of randomised controlled trials. *Proceedings from the 23nd Australian Society of HIV Medicine Conference, October 20-22nd 2010.*

2. **Fillipas S,** Bowtell-Harris CA, Cicuttini FM, Holland AE and Cherry CL. The International Physical Activity Questionnaire overestimates moderate and vigorous physical activity in HIV. *Proceedings from Alfred Week Oct 2009.*

3. **Fillipas S,** Bowtell-Harris CA, Cicuttini FM, Holland AE and Cherry CL. The International Physical Activity Questionnaire overestimates moderate and vigorous physical activity in HIV. *Proceedings from the 22nd Australian Society of HIV Medicine Conference,* September 9th -12th, Brisbane, 2009.

4. **Fillipas S**, Bowtell-Harris CA, Oldmeadow LB, Cicuttini FM, Holland AE and Cherry CL. Physical activity uptake in patients with human immunodeficiency virus: who does how much? Higher Degree by Research Week, Monash University. August 19th 2008.

5. **Fillipas S**, Bowtell-Harris CA, Oldmeadow LB, Cicuttini FM, Holland AE and Cherry CL. Physical activity uptake in patients with human immunodeficiency virus: who does how much? *Proceedings from the American Conference for the Treatment of HIV (ACTHIV)* May 2007.

6. **Fillipas S**, Bowtell-Harris CA, Oldmeadow LB, Cicuttini FM, Holland AE and Cherry CL. Physical activity uptake in patients with human immunodeficiency virus: who does how much? *Proceedings from Alfred Week* 2006.

7. **Fillipas S**, Bowtell-Harris CA, Oldmeadow LB, Cicuttini FM, Holland AE and Cherry CL. Physical activity uptake in patients with human immunodeficiency virus: who does how much? *Proceedings from the 18th Annual Australasian Society of HIV Medicine Conference. Melbourne,* October 12-15th 2006.

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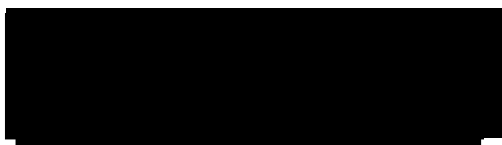
Lastly, I would also like to thank my Manager Mr Jim Sayer, who supported my research efforts from the outset and my colleagues at the Alfred Hospital for providing support and encouragement.

Declaration

I hereby declare that this Thesis contains no material which has been accepted for the award of any other degree or diploma, except where due reference is made in the text of the Thesis.

To the best of my knowledge, this Thesis contains no material previously published or written by another person except where due reference is made in the text of the Thesis.

Signed

Dated 17.04.2011

PART A: General Declaration

Monash University
Monash University Graduate School

General Declaration

In accordance with Monash University Doctorate Regulation 17/ Doctor of Philosophy and Master of Philosophy (MPhil) regulations the following declarations are made:

I hereby declare that this thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

This thesis includes 3 original papers published in peer reviewed journals and 2 publications currently undergoing peer-review. The core theme of the thesis is "Physical activity in human immunodeficiency virus". The ideas, development and writing up of all the papers in the Thesis were the principal responsibility of myself, the candidate, working within the Department of Epidemiology and Preventive Medicine under the supervision of Professor Flavia Cicuttini, Associate Professor Catherine Cherry and Associate Professor Anne Holland.

The inclusion of co-authors reflects the fact that the work came from active collaboration between researchers and acknowledges input into team-based research.

In the case of Chapters 2 to 6 my contribution to the work involved collection of the majority of clinical data, performing all data entry and playing a major role in all statistical analyses and taking the main role in manuscript preparation. Specifically:
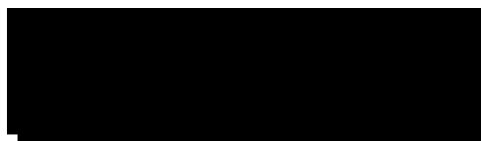
Thesis chapter	Publication title	Publication status*	Nature and extent of candidate's contribution
2	Physical activity uptake in patients with human immunodeficiency virus: who does how much?	Published	Consent, data collection, data synthesis and analysis, writing the manuscript
3	The International Physical Activity Questionnaire overestimates moderate and vigorous physical activity in HIV.	Published	Consent, data collection, data synthesis and analysis, writing the manuscript
4	The effects of exercise training on metabolic and morphological outcomes for people living with HIV: a systematic review of randomised controlled trials.	Published	Search strategies, abstract review, quality review, data extraction and analysis, writing the manuscript
5	Physical activity participation and cardiovascular fitness in people living with HIV : a one-year longitudinal study	Currently undergoing peer review	Consent, data collection, data synthesis and analysis, writing the manuscript

| 6 | The relationship between body composition and knee structure in patients with human immunodeficiency virus | Currently undergoing peer review | Consent, data collection, data synthesis and analysis, writing the manuscript |

[* For example, 'published'/ 'in press'/ 'accepted'/ 'returned for revision']

I have renumbered sections of submitted or published papers in order to generate a consistent presentation within the thesis.

Signed: ████████████████

Date: 17.04.2011

Abbreviations

ACSM	American College of Sports Medicine
AE	Aerobic exercise
BIS	Body Image Scale
BMI	Body Mass Index
BRFSS	Behavioural Risk Factor Surveillance System
CD4	CD4 Cell Count
CDC	Centres for Disease Control
CVD	Cardiovascular disease
CVF	Cardiovascular fitness
DAD	Data Collection on Adverse events of Anti-HIV Drugs
HAART	Highly Active Anti Retroviral Therapy
HDL-chol	High density lipoprotein cholesterol
HIV	Human immunodeficiency virus
IPAQ	International Physical Activity Questionnaire
Kj	Kilojoules
Kcal	Kilocalories
LDL-chol	Low density lipoprotein cholesterol
LDS	Lipodystrophy
MET	Metabolic equivalents
MLTPAQ	Minnesota Leisure Time Physical Activity Questionnaire
MRI	Magnetic resonance imaging
OA	Osetoarthritis

MSM	Males who have sex with males
PA	Physical activity
PRE	Progressive resistive exercise
RCT	Randomised controlled trial
TC	Total cholesterol
TG	Triglycerides
VL	HIV RNA viral load
VO_{2max}	Maximal oxygen uptake
WHR	Waist to Hip Ratio

Chapter 1   Introduction

1.1 Organisation of Thesis

Chapter 1 gives an overview of this Thesis including its organisation, followed by a literature review, and the aims of this Thesis.

Chapter 2-6 presents the results of this Thesis.

Chapter 7 presents an overall discussion that integrates the finding of this Thesis and future directions.

Chapter 8 provides a conclusion that summarises the main findings.

1. 2 Human Immunodeficiency Virus in the Highly Active Antiretroviral Therapy Era

More than 33.3 million people worldwide are living with HIV[1]. The introduction of HAART, a combination of potent antiretroviral agents that inhibit HIV replication via multiple mechanisms, has resulted in a dramatic reduction in the mortality associated with HIV in the developed world[2-3]. However, HIV infection continues to cause a significant burden of disease, even in countries like Australia where HAART is readily available. In particular, disorders of ageing and frailty, including cardiovascular and metabolic problems are all substantially increased among those with treated HIV[4]. Patients may also be affected by morphological complications associated with the virus and its treatment[5]. Despite increased longevity, people living with HIV experience significant chronic illness and a reduction in quality of life.

Cardiovascular disease is a major problem among people living with HIV[6]. The Data Collection on Adverse events of Anti-HIV Drugs (DAD) study group, the largest observational cohort of HIV-infected patients, demonstrated that HAART resulted in a 26% relative increase in the rate of myocardial infarction for each year of use[7]. Both HIV infection and exposure to HAART can contribute to the development of coronary artery disease and induce risk factors, including dyslipidemia, disorders of glucose metabolism, and central fat accumulation[5, 8]. Cardiovascular events in HIV-infected individuals are strongly associated with traditional risk factors such as older age, male gender, cigarette smoking, hypertension, family history of heart disease and hypercholestolaemia[9]. In addition to all this, it is clear that individuals with HIV are at increased CVD risk over and above that attributable to their traditional risk factors, and this excess risk increases with increasing time on HAART[7].

A metabolic syndrome, also referred to as lipodystrophy, characterized by a combination of morphological and metabolic changes, is one of the most common and problematic complications of HAART and is a major clinical issue for patients with HIV[5, 10-11]. One or more of several metabolic abnormalities are typically associated with this syndrome including elevated total cholesterol (TC), elevated triglycerides (TG), low levels of high-density lipoprotein cholesterol (HDL-chol), insulin resistance and type 2 diabetes mellitus[5]. Abnormalities in body composition are also a common feature

of this syndrome and have been reported in 40 to 50 percent of ambulatory HIV-infected patients[12]. Changes in both central and peripheral fat stores (increased visceral adiposity, subcutaneous fat atrophy of the face and extremities, hypertrophy of the posterior cervical fat pad; *buffalo hump*) have been well documented. The sequelae of these body composition changes on patient's psychological status can be debilitating and can have a negative impact on patient's self esteem and perceived body image[13].

People living with chronic HIV infection are also susceptible to a range of musculoskeletal diseases. Opportunistic bone infections, osteonecrosis, osteopenia and the risk of osteoporosis have been described[14]. Both HIV infection and HAART have been associated with disorders of bone health, with studies reporting a greater prevalence of low bone mineral density and a higher fracture rate than the general population[15-16]. HIV infection is now believed to be an independent risk factor for reduced bone mineral density[14].

Increased attention has been directed toward non-pharmacological interventions to help manage HIV infection and its complications. Pharmacological interventions may ameliorate some HAART-related problems, but their use is associated with financial costs, adherence issues and potential toxicities. Safe, effective, non-pharmacological interventions are needed to address the clinical complications relevant in the HAART era, particularly the myriad of metabolic and morphologic abnormalities and the associated CVD risk. Exercise training has been shown to improve many physical and psychological outcomes in the general population and reduces chronic disease risk[17]. The therapeutic use of exercise training has also been studied in other chronic disease populations including cancer, heart failure, chronic obstructive pulmonary disease, osteoarthritis, depression, schizophrenia and chronic fatigue syndrome[18-27] and it is possible that it may have a beneficial role in managing the current issues facing HIV-infected patients[28-29].

1.3 Definitions: Exercise Training, Physical Activity and Cardiovascular Fitness

To assist with the interpretational framework of this Thesis, the terms 'exercise' ,'physical activity' and 'cardiovascular fitness' need defining. Physical activity and exercise are distinct phenomena, however they are often confused and used interchangeably[30]. In fact, exercise is a subset of physical activity. Both physical activity and exercise share a number of commonalties, for example, both involve bodily movements produced by skeletal muscles and both are positively correlated with physical fitness[30]. Importantly, physical activity is a complex behaviour that varies greatly in its effect on health-related outcomes and its determinants and may require different approaches for intervention and promotion. Conversely, physical fitness is not necessarily related to bodily movements but is a set of attributes that people have or achieve. Five measurable components of physical fitness have been identified including cardiorespiratory endurance, muscular endurance, muscular strength, body composition, and flexibility[30]. Clear and precise definitions of these related terms are required for understanding the works in this Thesis.

Caspersen CJ et al 1985 defines physical activity as "as any bodily movement produced by skeletal muscles that results in energy expenditure. The amount of energy required to accomplish an activity can be measured in kilojoules (kj) or kilocalories (kcal); 4,184kj is essentially equivalent to 1 kcal *(I)*".

Exercise is defined by the same author as "physical activity that is planned, structured, repetitive and purposive in the sense that improvement or maintenance of one or more components of physical fitness is an objective" while physical (cardiovascular) fitness is "a set of attributes that are either health or skill related"[30].

1.4 The Measurement of Physical Activity

The accurate measurement of physical activity behaviour is required to describe physical activity prevalence rates among populations, determine dose-response relationships between physical activity and health outcomes, identify correlates and determinants of physical activity and evaluate the effectiveness of interventions designed to increase activity levels[31].

Physical activity measurement is a challenging area for both clinical and research purposes[30, 32]. No single assessment method of physical activity is able to record the complete spectrum of variables that encompass this multi-faceted behaviour including energy expenditure, cardiovascular endurance and strength[32].

A range of assessment methods have been utilised to assess physical activity exposure, including standardised questionnaires, pedometers, accelerometers, indirect calorimetry and doubly labelled water[33]. Objective methods of measuring physical activity have gained increasing recognition over recent years in an attempt to address the methodological issues of subjective methods. Objective methods are based on more direct and physiological measures and include measures of energy expenditure using direct calorimetry with doubly labelled water , measures of activity with motion sensors (pedometers , accelerometers) and measures of cardiovascular fitness [maximal oxygen uptake (VO_{2max})][33]. Objective methods are usually more expensive and difficult to administer, however they do provide the ability to quantify the amount and intensity of physical activity [33]. In particular, the accelerometer is currently the method of choice in much physical activity research and is highly accepted as the criterion measure in validation studies of physical activity tools[34].   Accelerometers quantify physical activity behaviours and are relatively easily to administer however limitations have been described. For example, the underestimation of energy expenditure secondary to the accelerometer's inability to accurately measure all types of physical activity such as water based activities, weight training and bicycling[34].

Questionnaires are the most common assessment technique used and are considered the most feasible measurement method of physical activity in epidemiological studies[35]. Standardised questionnaires can provide useful information, provided the right

measurement instruments are chosen and used correctly[35]. The advantages of self-report measures are their relatively low cost, population acceptability and convenience. However, as with many self-report measures, physical activity self-reporting can be flawed with methodological problems[36]. Self-reporting physical activity through standardised questionnaires can be cognitively challenging and can be harder for some populations including the elderly, children and those with chronic illnesses[37]. Measurement error problems due to poor recall and over reporting have also been identified as major issues[35].

The International Physical Activity Questionnaire (IPAQ) has recently been developed to allow international comparisons of physical activity data and facilitate global surveillance[38]. Eight versions of the self report questionnaire have been developed, including short (Appendix 1) and long versions (Appendix 2). Modes for administration of the questionnaire can be either self administered or by telephone interview. Also, two reference periods are available including 'usual week' or 'last seven days' .The main evaluation study of the IPAQ involved several stages of developing and testing and included data from 14 centres and 12 countries[38]. This important study found the questionnaire to be valid and reliable and reported no significant differences between the validity and reliability of both the short and long versions. The study also found the short version to be feasible to administer and that some investigators and respondents found this version to be more acceptable[38]. In contrast, the long version is recommended for research purposes where the collection of more detailed information on physical activity is required[38].

1.4.1 The Measurement of Physical Activity in the Context of HIV

Knowledge about levels and patterns of physical activity is limited amongst populations with HIV infection, in part due to the difficulty of accurately measuring this complicated behaviour. Validated and reliable assessment tools for use in this context would facilitate a greater understanding of the role of physical activity and its benefits for this population. Specifically, better assessment would provide more accurate surveillance estimates of the prevalence of physical activity in people living with HIV, the identification of inactive /sedentary individuals (and outcomes associated with

inactivity) and improved assessment of the efficacy of physical activity on managing side effects and complications of HIV and HIV treatments.

Existing studies of physical activity in HIV-infected populations have typically relied on questionnaires designed for use in general populations. For example, Clingerman et al 2003[39] used the Behavioural Risk Factor Surveillance Survey (BRFSS), Domingo et al 2003[40] used the Minnesota Leisure Time Physical Activity Questionnaire (MLTPAQ) and Smit et al 2006[41] used the Paffenger Survey.

Few attempts have been made to assess the performance of physical activity self-assessment instruments among people with HIV. Florindo et al 2006[42] compared objective physical activity measures with the Baecke's questionnaire in 30 HIV-infected adults. The Baecke questionnaire assesses habitual physical activity (occupational, leisure, leisure and locomotion) relating to the previous 12 months[43]. Validity was determined by comparing responses with measurements of VO_{2max}, peak workload, and energy expenditure in 30 subjects, whilst reliability was determined by testing and retesting 29 subjects at intervals of 15-30 days. The study found the Baecke questionnaire to be valid for the evaluation of habitual physical activity among people living with HIV.

The well recognised International Physical Activity Questionnaire (IPAQ) was developed specifically to address the need for an international, standardised, valid and reliable tool[38]. Both the long and short versions have been used in healthy[38, 44] and increasingly in disease specific populations[45-46]. An important advantage of the IPAQ is that it can provide an estimate of total habitual physical activity, specifically providing information on the type (leisure, work, transport, domestic/gardening) , frequency (average number of sessions per specified time period), duration(average time spent per session) and intensity (metabolic cost)[38].

The validity and reliability of the Spanish version of IPAQ was evaluated among Hispanic adults with treated and untreated HIV infection living in Puerto Rico[47] . The Spanish version of the IPAQ short form was found to overestimate physical activity, demonstrating reasonably poor validity correlation coefficients (ρ -0.3 to 0.28), but better test- retest reliability (ρ 0.32 to 0.75)[47]. The authors also reported a low sensitivity (ability to detect insufficiently active individuals) (23%) and a high specificity (87%). This study provides useful data on a non–English version of the IPAQ in an Hispanic

population but has limited generalisability to other groups affected by HIV infection. More work is needed to determine the validity of the IPAQ, in particular the English-version and other physical activity self-report tools among populations with treated HIV infection.

In summary, the measurement of physical activity poses many challenges. In epidemiological research, physical activity standardised questionnaires represent an acceptable, convenient and low cost method of measuring this important health promoting behaviour. Many valid and reliable questionnaires have been developed for use in other contexts, but their application in the HIV-infected population has not been well evaluated. The study by Ramirez-Marreo et al 2008[47] is of great importance, as it attempted to validate the IPAQ instrument that is increasingly being preferred by researchers. The measurement properties of the more detailed English version of the IPAQ long form in HIV-infected subjects would add to the study by Ramirez-Marrero et al 2008 and have not previously been explored. The validation and evaluation of physical activity questionnaires in this population is much needed.

1.5 The Measurement of Cardiovascular Fitness

Maximal oxygen uptake is considered the best criterion measure for assessing cardiovascular fitness[48]. Despite the high validity and reliability of maximal exercise testing, it is not always the most suitable method of choice when evaluating cardiovascular fitness. Maximal exercise tests may be contraindicated for patients who are limited by dyspnoea, fatigue or pain[49]. Furthermore, the high costs, possible risk of injury to participants and the high level of participant motivation/cooperation needed to perform the test often make this type of testing unsuitable[50].

Submaximal exercise testing can be a useful alternative for individuals with limitations to performing maximal exercise testing[50]. Many different types of submaximal exercise tests are available including step tests, ergometers and treadmill tests. This type of testing can be used to predict VO_2 max and to assess functional problems and outcomes of interventions[50]. This type of evaluation can categorise an individual's fitness level and can monitor responses to endurance training programs. Despite the wide adoption of

such testing amongst physiotherapists, submaximal exercise tests remain largely underdeveloped[50]. Problems associated with under or over-stressing have been reported which may lead to invalid conclusions and incorrect interpretation (ceiling or floor effects)[50].

Submaximal exercise testing has been safely used in chronic diseases including chronic heart failure[51 52-53],cancer[54] and interstitial lung disease[55]. This type of exercise testing has also been recommended in any patient group with functional limitations and in older adults[50]. With respect to chronic HIV infection, submaximal exercise testing has been utilsed[56-57], however its validity and reliability have not been formally tested.

1.6 Physical Activity Participation in HIV-Infected Populations

Despite strong evidence for health benefits of physical activity for those with chronic diseases, including those living with HIV infection, little is known about physical activity participation rates in people living with HIV. To date, very few studies have attempted to measure and describe participation levels in physical activity in this chronic illness[39, 41]. Some physical activity information is also available from epidemiological studies that have explored relationships between various HIV- related health outcomes and assessed physical activity as an independent variable[58-61].

Clingerman et al 2003[39] evaluated physical activity behaviours of 78 HIV-infected adults (mean age 40.4 years SD 8.33). Physical activity was measured using the Behavioural Risk Factor Surveillance System (BRFSS). The BRFSS evaluates leisure and occupational physical activity including walking and moderate, vigorous, and strengthening physical activity behaviours. Results showed that walking was the most popular type of activity preferred by participants. This study also revealed that fewer participants performed sufficient activity to meet the frequency and duration recommendations described by *Healthy People 2010*[62] compared to the general population. *Healthy People 2010*[62] classifies individuals as participating in regular moderate physical activity if they participate in moderate activities five or more times per week for at least 30 minutes, or vigorous activities three or more times per week for

at least 20 minutes. This study's results are limited by the choice of physical activity measurement tool (the BRFSS which has not been validated for use in those with HIV), its small sample size and the inclusion of very few female participants. Furthermore, the majority of participants were African American, possibly limiting the generalisability to other ethnic groups.

A study by Smit et al 2006[41] compared physical activity behaviour in HIV-negative and HIV-positive injection drug users (total n=324). Physical activity was measured using a modified Paffenbarger physical activity questionnaire. This questionnaire collects information on daily number of stairs climbed and number of blocks walked, frequency of weekly regular exercise and strength training and an estimation of the duration of various activity levels during weekdays and weekends including sleeping, exercise and work related activites[63]. Findings revealed that vigorous activity was lower among HAART-treated than HIV-infected participants not on treatment (p= 0.0025) and also tended to be lower than HIV-negative participants (p= 0.11). Energy expenditure in vigorous activity was also lower among HAART-treated participants than both HIV-negative and HIV-positive participants not on treatment. It was concluded that HAART-treated, HIV-positive participants spend less time in vigorous activity independent of recent injection drug use. This study's limitations included its cross-sectional design and the use of a physical activity measurement tool that had not been validated for use in the context of HIV. Additionally, generalisabiltiy may be limited due to a very high proportion of African-American participants and of the fact that only injection drug users were studied.

The data provided from the few studies published on the physical activity behaviours of people living with HIV provide some preliminary information, however much is still unknown. Comparisons between these studies are limited due to methodological and population differences. To move forward in this area, a simple and validated physical activity tool is needed to facilitate the collection of standardised physical activity data across a diverse range of HIV-infected populations over time.

1.6.1. Determinants of Physical Activity in People Living with HIV Infection

Most of the available evidence describing physical activity patterns among HIV-infected populations suggest that this group's activity levels are suboptimal[39, 41, 64]. Although these basic prevalence data are important, a furthered understanding of factors associated with physical activity participation in HIV is greatly needed. Better evidence on determinants of physical activity would contribute to an enhanced understanding of how to intervene to help promote and sustain lifelong healthy behaviour patterns in those living with chronic HIV infection.

In the general population, determinants of physical activity have been broadly categorised as personal, program-related and environmental[65]. Age, gender, socioeconomic status and education have been consistently associated with physical activity levels[65-66]. For example, groups identified at highest risk of inactivity are black females, overweight, less educated and older people[65]. Furthermore, psychosocial factors influencing women's participation in physical activity may be different to males who have sex with males (the group most affected by HIV in Australia). Motherhood and the associated parenting responsibilities have been identified as potential barriers for women[67]. Physical and social environmental factors have also been associated with participation levels in physical activity and evidence has suggested that social support is important in the adoption and maintenance of physical activity in older people[68] and in those with chronic diseases[69].

Very little work has been undertaken to identify determinants of physical activity among individuals with HIV. A cross-sectional study explored the relationship between social, cognitive and physical health factors and adherence to a three month supervised exercise program in HIV-infected adults[70]. Physical health factors included CD4 cell counts, self-report assessments of physical symptoms, and physicians' examinations and these were found to be predictors of adherence to the structured exercise program. Conversely, a study by Petroczi et al 2010[57] also examined adherence to a 10 week, twice weekly exercise program and determined that physical heath factors were not associated with exercise adherence, but found perceived well being to be important[71]. A

cross-sectional study evaluating factors associated with the use of complimentary therapies examined factors associated with the use of exercise training[72]. This study found younger age, higher education and income to be associated with the use of complimentary therapies (including exercise). Future research endeavours need to address the relative lack of knowledge in this area. Specifically, identifying barriers and obstacles to physical activity for a diverse group of people living with HIV can assist in planning interventions to increase the uptake of this behaviour.

1.7 The Role of Physical Activity in People Living with HIV Infection

The benefits of short-term exercise training for HIV-infected individuals have been well documented[28-29]. Most studies performed to date have evaluated a structured exercise program [either aerobic exercise, progressive resistive exercise or a combination of both], over a short period of time (four weeks to six months) and share some commonly measured endpoints based on physiological and psychological health outcomes. Short-term therapeutic exercise studies have shown increased cardiovascular fitness[56, 73-79], increased strength[80-83], enhanced psychological parameters[74, 84-87], improvement in immune indices[74, 78] and improvements in some aspects of quality of life[56, 73, 77]. There is some suggestion that improvements in metabolic and morphological complications observed in HIV-infected individuals can also occur[81, 88-91] and that CVD risk can be reduced[92]. In addition, it has been shown that exercise training in HIV-infected individuals is safe and does not significantly decrease CD4 counts[73, 79] or increase circulating HIV RNA[73].

While papers on the effects of exercise training in HIV-infected populations have been published as early as 1990[74], results were not systematically reviewed until 2001[93]. The original review evaluating the effects of aerobic exercise interventions by Nixon et al 2001[93], was recently updated and concluded that aerobic exercise is safe and beneficial for people living with HIV[28]. Fourteen RCTs were included and findings suggested that thrice weekly constant or interval aerobic exercise, or a combination of constant aerobic exercise and progressive resistive exercise, for at least five weeks, may improve some aspects of cardiovascular fitness, body composition and psychological status in individuals with HIV[28].

O'Brien et al 2004[29] systematically reviewed the effects of progressive resistive exercise in HIV–infected individuals. This Cochrane Library Review was updated in 2009, however no changes to the content were deemed necessary. Seven RCTs were included and results suggested that thrice weekly progressive resistive exercise or a combination of progressive resistive exercise and aerobic exercise, for at least four weeks appears to be safe and may improve some body composition and cardiovascular fitness parameters[94]. Other systematic reviews[95] and narrative review papers[96-99] have also been published and have shown that exercise and physical activity confer positive health benefits for people living with HIV.

Importantly, there is an absence of current, evidence- based physical activity guidelines for populations with HIV infection. Existing exercise training recommendations are based on pre-HAART data[100-101] or provide recommendations that neglect level of immunosupression and other disease specific details[28-29]. Physical activity guidelines relevant to HAART-treated patients require knowledge of the effects of sustained, habitual physical activity, as well as an understanding of the determinants and barriers to participation in physical activity.

In summary, evidence for the benefits of sustained physical activity participation and exercise training is scanty in this population. There has been great interest in studying the effects of long term physical activity on health outcomes in healthy populations for decades[102-104]. Sustaining exercise over a two year period has also been associated with improved health and well being for those with chronic conditions including diabetes, depression and hypertension[105]. Despite these data being available in other populations, there is insufficient information on the longitudinal patterns of physical activity among those living with HIV and the relationships between long term physical activity and newly emerging HIV health outcomes such as body composition, body image and CVD risk.

1.7.1 The Role of Physical Activity in Managing Cardiovascular Disease Risk, Metabolic and Morphological Complications of HIV and HIV-Associated Treatments

Current guidelines for the non-pharmacological management of dyslipidaemia in HIV-infected individuals are largely based on those used in HIV-negative individuals. Recommendations include cigarette smoking cessation, dietary advice and the uptake of physical activity[106]. Lifestyle interventions, including the use of physical activity, have been advocated by many as a first-line treatment to reduce CVD risk and to manage lipodystrophy[106-107], but population-specific data to support these recommendations are limited. Scevola D et al 2003[107] recommended that exercise training should be used as a medical treatment to reduce metabolic complications and reduce the use of lipid lowering medications. In the general population, physical activity has been shown to be beneficial in reducing the risk of CVD through its effect on numerous modifiable risk factors, including dyslipidemia, insulin resistance and obesity[108].Furthermore, prospective epidemiological studies of physical activity have consistently documented a reduced incidence of CVD events in the more physically active[109] and fit[110] participants. Published studies provide some suggestion of similar benefits from exercise and physical activity in the context of HIV. But these data are limited, particularly in terms of the role of exercise and physical activity in those using HAART.

Few review papers on the effects of exercise on metabolic and morphological outcomes in people living with HIV have been published. A narrative review paper by Malita et al 2005[97], included eleven studies that evaluated the effects of aerobic exercise , PRE and a combination of both types of exercise training on body composition and body fat distribution in HIV- infected individuals. Duration (8 to 16 weeks) and study designs varied, including cross-sectional and interventional studies. The review concluded that combined aerobic exercise and progressive resistive exercise in HIV-infected individuals with lipodystrophy is more effective in reducing body fat and increasing lean muscle mass than aerobic exercise or progressive resistive exercise interventions in isolation. The included studies in this review were published in the early years of HAART, hence the results may not be applicable to more recent HAART regimens. The authors also identified that the review was subject to limitations and suggested that

future studies should be of more rigorous design, with more precise measurements of body composition and better subject characterisation.

Most RCTs evaluating the effects of exercise training on body composition parameters in HIV-infected individuals were conducted prior to the routine use of HAART[78-80, 85]. The relevance of these data to HAART-treated populations are therefore limited. The few RCTs on exercise training conducted during the HAART era[56, 111-114] explored mainly body composition effects and provided limited information on the effects on metabolic parameters. Collectively these studies found that exercise training can improve some morphological complications seen in chronic, treated HIV infection, whilst little attention had been paid to clinically important metabolic issues. Furthermore, the non-randomised pilot studies evaluating morphological and metabolic complications conducted during the HAART era offer inconclusive and conflicting results[81, 89, 91, 115].

Very few studies have evaluated habitual physical activity behaviour among populations with treated HIV and its effect on metabolic and morphological parameters and as far as we know, no review papers have been published. A cross-sectional study explored the relationship between habitual physical activity and central body fat distribution[42]. The physical activity behaviour of 220 HAART-treated, HIV-infected adults was recorded using the Baecke's physical activity questionnaire (self report physical activity over the preceding 12 months). Leisure time physical activity was inversely associated with central subcutaneous fat and was at the limits of significance with waist to hip ratio (WHR) measures. Participants performing walking or cycling as leisure time activities or as the means of travelling to work, shopping or school had lower measures for central fat.

A cross-sectional study examined the relationship between physical activity and body fat redistribution in 150 HAART-treated, HIV-infected adults[40]. Specifically, this study evaluated the metabolic disturbances associated with HAART. Physical activity behaviour, over the last 12 months was recorded using the Spanish version of the MLTPAQ (previously validated in Spanish HIV- negative individuals[116]). Although this study did not provide any detailed description of physical activity, nor did it use a validated physical activity tool for use in this population, it did find a protective role for

physical activity, where inactive participants had reduced subcutaneous fat, increased central subcutaneous fat and increased WHR.

Lastly, another cross sectional study compared levels of physical activity with body composition and other variables among 68 physically active and inactive HIV-infected adults in Puerto Rico[117]. Time spent in leisure and occupational time was measured using The Seven-Day Physical Activity Recall during the previous week[118]. Average daily energy expenditure associated with self-reported physical activity was estimated using The Compendium of Physical Activities[119]. Participants were classified as active if they expended at least 300 kcal/day. Active individuals had lower total subcutaneous fat and central fat than individuals deemed inactive and also had higher life satisfaction scores. This study quantified physical activity using a self-report questionnaire, with no objective physical activity assessment and no information regarding the validity and reliability of the physical activity questionnaire used. Additionally, generalisability of findings may be due to only Hispanic individuals being included in the study.

1.7.2 The Role of Physical Activity on Perceived Body Image in People Living with HIV infection

Morphological changes associated with HIV infection and HAART profoundly affect body image and influence health-related quality of life[13, 120]. Research on the relationship between exercise and perceived body image in HIV- negative cohorts has found that exercise is associated with improvements in body image. Indeed, a recent meta-analysis concluded that exercise is positively associated with perceived body image[121]. Evidence to support a similar relationship between exercise and perceived body image in HIV-infected individuals is sparse. As far as we know, there has only been one published RCT evaluating the effects of an exercise training program on body image perception in HIV-infected adults[112]. This study evaluated the effects of a six month supervised aerobic exercise program on various quality of life measures, including perceived body image. One hundred HAART-treated, HIV–infected African adults, all of whom had moderate to severe lipodystrophy took part in the study. Quality of life was measured using The WHO Quality Of Life -BREF[122] and body image was assessed with the inclusion of an extra domain developed by the authors. This domain

aimed to obtain additional data related to participants' fears of HIV status being revealed by body composition changes and other psychosocial factors associated with body fat abnormalities. Results suggested that perceived body image significantly improved in the exercise group compared with the non-exercise group ($p<0.001$). Although this is an important finding, perceived body image was assessed using an instrument that had not been validated in people living with HIV. Also, results may not be generalisable to all HAART-treated patients, with the study limited to those in Sub-Saharan Africa and to patients with moderate to severe lipodystrophy.

Summary

The limited data available suggest that both physical activity and exercise training may have health benefits for HIV-infected individuals. Results seen with short duration exercise interventions suggest that exercise training may ameliorate certain morphological complications associated with HIV infection and its treatment, however data on the effects on metabolic complications are conflicting. Furthermore, data on the effects of habitual physical activity on body image are lacking. Information on the relationships between longer term patterns of physical activity and clinically relevant outcomes for the HAART-treated HIV patient need further study.

1.8 Aims of this Thesis

The aims of this Thesis were to document the prevalence of physical activity uptake among Australian adults living with HIV and to investigate relationships between physical activity and clinically relevant problems faced by individuals with HIV using HAART, including:

1. CVD risk

2. Body composition

3. Body Image

To address these aims, the following studies were undertaken:

1. A cross-sectional physical activity study was undertaken by offering a brief survey to all patients attending a hospital-based Infectious Diseases clinic over a month period (see Chapter 2)

2. A 12-month cohort study of HAART-treated adults with HIV was performed. Habitual physical activities, including cardiovascular fitness responses, and HAART-relevant outcomes were monitored. Sub-studies including the same participants were undertaken to address the validity of the physical activity measurement tool (n=30), the association between body composition and joint health (n=35 and 18 controls) and a systematic review is also presented (see Chapters 3, 4 and 6).

The results of these studies will provide a better understanding of the effects of exercise training and physical activity participation in adults with HAART-treated HIV. They will also provide further evidence for the role of both exercise training and physical activity in the management of some of the common complications seen in adults with treated HIV. Finally, this work can assist in the future development of evidence-based, disease-specific physical activity guidelines.

Chapter 2 Physical Activity Uptake in Patients with Human Immunodeficiency Virus

Despite the strong evidence for health benefits of physical activity, physical activity behaviours have been poorly monitored and described in HIV-infected populations. Furthermore, it is not known how well individuals with HIV meet recommended physical activity guidelines.

Physical activity patterns in this group of patients have been studied in a small number of papers[39, 41, 64], however Australian data are lacking. Limited information available from some of these studies suggests that when HIV-infected individuals are compared to the general population, they are less likely to meet recommended physical activity guidelines[39, 64].

The paper presented within this Chapter describes the prevalence of physical activity in HIV-infected patients attending an Infectious Diseases clinic in a Melbourne hospital. It also compares the prevalence of physical activity in HIV-infected individuals with general infectious diseases patients. The proportion of patients meeting CDC/ACSM recommended physical activity guideline is also described.

> 2.1 **Fillipas S**, Bowtell-Harris CA, Oldmeadow LB, Cicuttini FM, Holland AE and Cherry CL. Physical activity uptake in patients with human immunodeficiency virus: who does how much? **International Journal of STD and AIDS.** 19:514-518, 2008.

Two hundred and sixty one out of 347 eligible patients (75.2% response rate) completed the study. One hundred and ninety one HIV-infected and 70 general infectious diseases individuals participated. Mean age of the two groups was similar, but HIV-infected respondents were more likely to be male (p<0.0001) (consistent with the demographics seen in the clinic's population). Almost three-quarters of HIV-infected respondents (73.8%) (n=142) and two thirds of general infectious diseases respondents (65.8%) (n=46) reportedly met recommended physical activity guidelines. No differences

between proportions of respondents meeting guidelines according to age, gender and self reported HIV-status were found (p>0.05).

Although the majority of respondents reportedly met internationally recognised physical activity guidelines, 1:4 patients living with HIV failed to meet these recommendations. These findings are of significance, given the established health benefits of regular physical activity and exercise participation. Future endeavours are warranted to ascertain determinants of physical activity in those with HIV-infection. Identifying barriers to participation will facilitate the development of appropriate interventions to improve the uptake of physical activity.

Declaration for Thesis Chapter 2

Declaration for Thesis Chapter 2: Physical Activity Uptake in Patients with Human Immunodeficiency Virus

Declaration by candidate
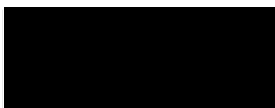
In the case of Chapter 2 the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Consent, data collection, data synthesis and analysis, writing the manuscript	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Christine Bowtell-Harris	Data collection, revision of manuscript	
Leonie Oldmeadow	Revision of manuscript	
Flavia Cicuttini	Study concept and design, revision of manuscript	
Anne	Revision of manuscript	

Holland		
Catherine Cherry	Revision of manuscript	

Candidate's Signature	███████████████	Date 17. 4. 2011
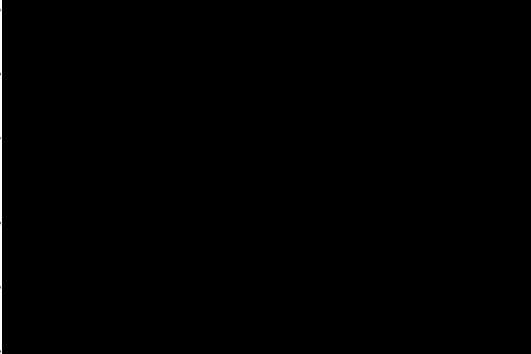
Declaration by co-authors

The undersigned hereby certify that:

(1) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(2) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(3) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(4) there are no other authors of the publication according to these criteria;

(5) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(6) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	The Alfred Hospital, Melbourne

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

		Date
Signature 1		12/4/11
Signature 2		6/4/2011
Signature 3		3/411
Signature 4		15/4/11
Signature 5		15/4/11

Physical activity uptake in patients with HIV: who does how much?

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Summary: Regular physical activity is recommended for patients with human immunodeficiency virus (HIV) to help manage their disease. However, to date, little is known about levels of uptake of this advice. This study describes daily physical activity in HIV antibody-positive patients attending a public hospital infectious diseases clinic, compares them with those of patients attending the clinic for general infectious diseases and investigates compliance with the recommendations of the Centres for Disease Control and Prevention and American College of Sports Medicine physical activity guidelines. During April 2006, 261 patients completed the International Physical Activity Questionnaire short form. One hundred and ninety-one reported being HIV antibody-positive. Results showed that 1:4 HIV antibody-positive and 1:3 HIV antibody-negative respondents failed to meet the recommended guidelines. These findings are of concern, given the evidence-based benefits of regular physical activity. Further work is needed to identify barriers to participation and interventions that can improve uptake.

Keywords: International physical activity questionnaire, exercise, inactivity, AIDS, physical activity

INTRODUCTION

Physical activity provides significant health benefits for the general population[1] and for those with chronic diseases, such as the human immunodeficiency virus (HIV).[2-5] Physical activity is a safe, non-pharmacological intervention for the HIV antibody-positive patient, who may be burdened with complex drug regimens and associated side-effects. Physical activity improves aerobic fitness[6-8] and quality of life,[7,9,10] increases strength[11-15], decreases fatigue[12,16], enhances self-efficacy[17] and reduces depression and anxiety.[18-20] Recently, physical activity has been shown to contribute to better management of the metabolic and morphological complications associated with lipodystrophy in the HIV antibody-positive patient and to reduce cardiovascular disease (CVD) risk.[21-25] Despite the strong evidence for health benefits of physical activity in this patient group, it is not known how well this advice is being implemented and whether the levels of uptake are sufficient to achieve the promised health benefits.

Current guidelines, developed by the Centres for Disease Control (CDC) and the American College of Sports Medicine (ACSM) recommend that adults engage in at least 30 minutes of moderate-intensity physical activity on at least five days per week or at least 20 minutes of vigorous-intensity physical activity at least three days per week.[1] Physical activity is defined as 'any bodily movement produced by skeletal muscles that results in energy expenditure'.[26] Moderate-intensity physical activity is an activity performed between three and six metabolic equivalent tasks (METs) and vigorous activity is performed at greater than six METs, where one MET is the amount of energy expended during one minute of rest.[1] In the absence of any specific recommendations for infectious diseases or HIV populations, the CDC/ACSM guidelines provide a reasonable starting point to evaluate compliance.

Collecting physical activity data that is valid and reliable is difficult because of the wide variety of measurement tools available.[27] More recently, a tool, the International Physical Activity Questionnaire (IPAQ) has been developed to be used in studies involving both healthy and disease-specific populations[28-30], providing some degree of standardization and comparability.

The main aim of this study is to describe levels of physical activity using the IPAQ, in patients with HIV attending one infectious diseases outpatient clinic in Melbourne, to compare them with those patients with general infectious diseases and to investigate compliance with the physical activity guidelines described by the CDC/ACSM.

METHODS

This study used a four-week cross-sectional design. Voluntary, anonymous completion of a physical activity questionnaire was sought from all consenting adults (18 years and older) who attended the Infectious Diseases (ID) clinic of The Alfred hospital, Melbourne, Australia between 1 and 30 April 2006. This clinic is both a statewide service for HIV antibody-positive

patients and a clinic for patients with general infectious diseases. Nearly 90% of HIV antibody-positive and 75% of general infectious diseases patients agreed to complete the questionnaire. During the study period, the mean age of all respondents was 45.7 years. Three-quarters of the HIV antibody-positive group were on highly active antiretroviral treatment (ART). The median CD4 count and HIV viral load (VL) were 368 cells/mm^3 and 50 log$_{10}$ copies, respectively. The study was approved by The Alfred hospital's Human Ethics Committee.

Self-reported data on gender, age and HIV status were collected. Those reporting to be HIV-infected were classified as HIV antibody-positive and those reporting to be negative or unsure of their status were classified as HIV antibody-negative.

Physical activity data were collected using the self-administered, usual week version of the IPAQ Short Form, which is detailed elsewhere.[27,31] The IPAQ usual week version was selected over the last seven days version because general infectious diseases patients were more likely to have had a recent acute illness, than HIV antibody-positive patients whose condition is predictably more stable.

The IPAQ Short Form evaluates physical activities, performed in everyday life in the four domains of leisure, work, transport and domestic/gardening. It asks about three specific types of activity: vigorous, moderate and walking and scores the frequency (days) and duration (minutes) for each. A total weekly energy expenditure was calculated (MET-minutes/week) by multiplying the time spent in vigorous-moderate-intensity and walking activities by an average MET, expressed in MET-minutes/week. The minutes per week for vigorous, moderate intensity and walking activity were multiplied by a factor of 8, 4 and 3.3, respectively.[27]

Responses on the IPAQ can be stratified into three categories defined as follows:[31] low (inactive) – individuals who did not meet criteria for moderate or high categories; moderate – individuals who performed three or more days of vigorous activity of at least 20 minutes per day or five or more days of moderate-intensity activity or walking of at least 30 minutes per day or five or more days of any combination of walking, moderate- or vigorous-intensity activities achieving a minimum of at least 600 MET-minutes/week; vigorous – individuals who performed either vigorous-intensity activity on at least three days and accumulating at least 1500 MET-minutes/week or seven or more days of any combination of walking, moderate- or vigorous-intensity activities achieving a minimum of at least 3000 MET-minutes/week.

Frequency and duration of activities performed for >10 min continuously during one usual week were documented. Time spent in sitting was also recorded as an indicator of time spent in a sedentary activity.

The data were then used to determine how many respondents met the physical activity guidelines as described by the CDC/ACSM. Respondents were classified as having met the guidelines provided they performed at least 30 minutes, at least five days per week of moderate-intensity activity or at least 20 minutes, at least three days per week of vigorous-intensity activity.

Statistical analyses

Statistical analyses were performed using SPSS version 11.5 (SPSS, Inc., Chicago, IL, USA). Figures were created using Stata 9.1 (StataCorp, College Station, TX, USA). Comparisons

Table 1 Characteristics of respondents

Variables	Total	HIV-positive	HIV-negative
Patient group (*n*)	261	191	70
Age mean (range)	43.3 (18–81)	43.9 (20–73)	41.8 (18–81)
Male gender (*n*/%)	226/86.6*	177/92.7†	49/70

*Two HIV-positive respondents were transgender (classified as non-male)
†HIV-positive respondents were more likely to be male ($P < 0.0001$)

between HIV-positive and -negative respondents were performed using the Mann-Whitney U test for continuous variables. Categorical data were analysed using chi-square test.

RESULTS

Two hundred and sixty-one out of 347 eligible patients (75.2% response rate) completed the study. One hundred and ninety-one respondents self-reported that they were HIV antibody-positive. This represents nearly 90% of known HIV-infected patients attending the clinic during April 2006. The HIV antibody-negative group ($n = 70$) included patients with an acute infectious process, for example, cellulitis, pneumonia.

Respondent characteristics are listed in Table 1. Mean age of the two groups was similar, but those in the HIV antibody-positive group were more likely to be male ($P < 0.0001$), consistent with the demographics of the overall population of HIV seen in this clinic.

Physical activity described by the IPAQ

For the total group, 72% participated in moderate to high levels of physical activity and 28% were physically inactive (Table 2). Participation was not different when age and gender were considered. There was, however, a trend for HIV antibody-positive patients to participate at more vigorous levels and for longer durations with greater energy when compared with the HIV antibody-negative group (Figures 1 and 2). The frequency with which respondents engaged in each intensity of physical activity (Figure 3), as well as the time spent sitting did not differ between patient groups.

Walking was the most frequent activity reported by both the HIV antibody-positive (90.1%) and -negative (84.3%) patient groups.

Compliance with the CDC/ACSM physical activity guidelines

Almost three-quarters of HIV antibody-positive respondents ($n = 142$) (73.8%) and two-thirds of HIV antibody-negative

Table 2 International physical activity questionnaire categories

Activity group	HIV-positive *n* (%)	HIV-negative *n* (%)
Low	49 (25.7)	24 (34.3)
Moderate	63 (33.0)	23 (32.9)
High	79 (41.3)	23 (32.9)

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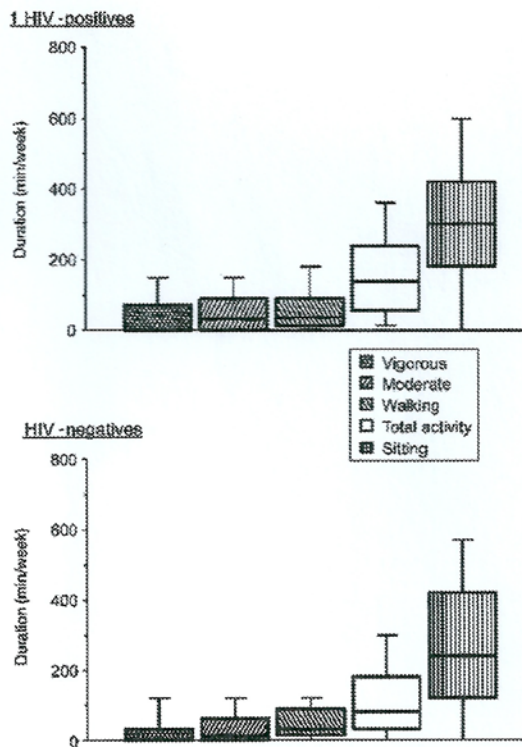
Figure 1 Duration (minutes/week) in each intensity of physical activity by HIV status. The graph above represents HIV-positive and the graph below HIV-negative respondents. Time spent in vigorous activities (P 0.034) and total time spent in all activities (P 0.010) were different according to HIV status
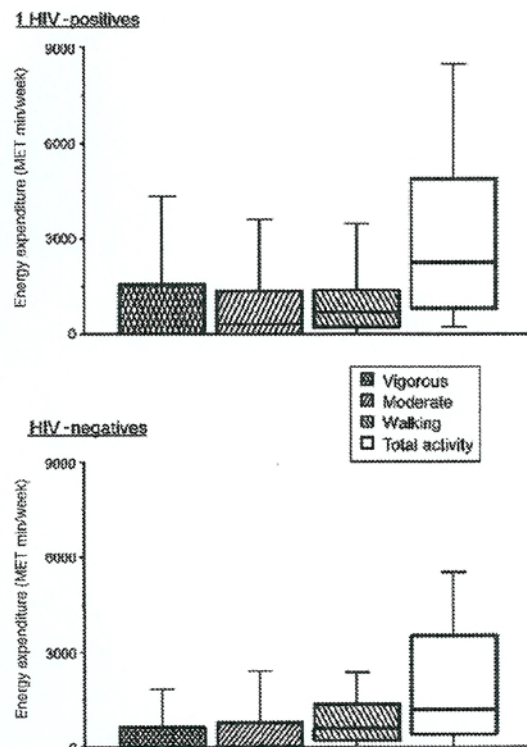
Figure 2 Energy expenditure (in MET-minutes/week) in each intensity of physical activity by HIV status. The graph above represents HIV-positive and the graph below HIV-negative respondents. Vigorous (P 0.028), moderate (P 0.046) and total energy expended (P 0.019) were different according to HIV status

respondents ($n = 46$) (65.8%) did meet the recommended guidelines. There were no differences between the proportions of respondents who met the guidelines according to age, gender or self-reported HIV status ($P > 0.05$).

DISCUSSION

This small, preliminary study is the first to report levels of physical activity in ambulatory infectious diseases patients attending a public hospital outpatient clinic in Melbourne. Our findings show that the majority of patients with infectious diseases participate in recommended levels of physical activity. However, given the strong evidence base for health benefits from regular physical activity for all and particularly HIV infection, the finding that one in four HIV antibody-positive patients are not meeting the minimum recommendations may be a concern.

Others have attempted to describe levels of physical activity in individuals with HIV[32-35] and comparisons are limited because of the various physical activity questionnaires used

and the differences in the sociodemographic profile of the patients. However, one study by Clingerman (2003) compared activity levels of 78 HIV-infected individuals to the Healthy People 2010 recommendations (same criteria as ACSM/CDC guidelines) and found (as we did) that 31 (40%) did not meet the recommendations.

We also found that HIV antibody-positive patients engaged in higher levels of vigorous physical activity than those attending for other infections. They were also more likely to be male. Generally, men are more likely to engage in vigorous activity[36], which may explain our finding. We found no association between age and physical activity levels. This is different from the general population, where age is an important determinant of physical inactivity. Older adults tend to do less moderate to vigorous activity and are less likely to meet the CDC/ACSM guidelines.[36] The HIV antibody-positive respondents reported higher levels of physical activity, spending more time and expending more energy in weekly physical activity than the HIV antibody-negative group. These differences could be attributable to HIV-infected individuals being more likely to take an active participation in their chronic disease
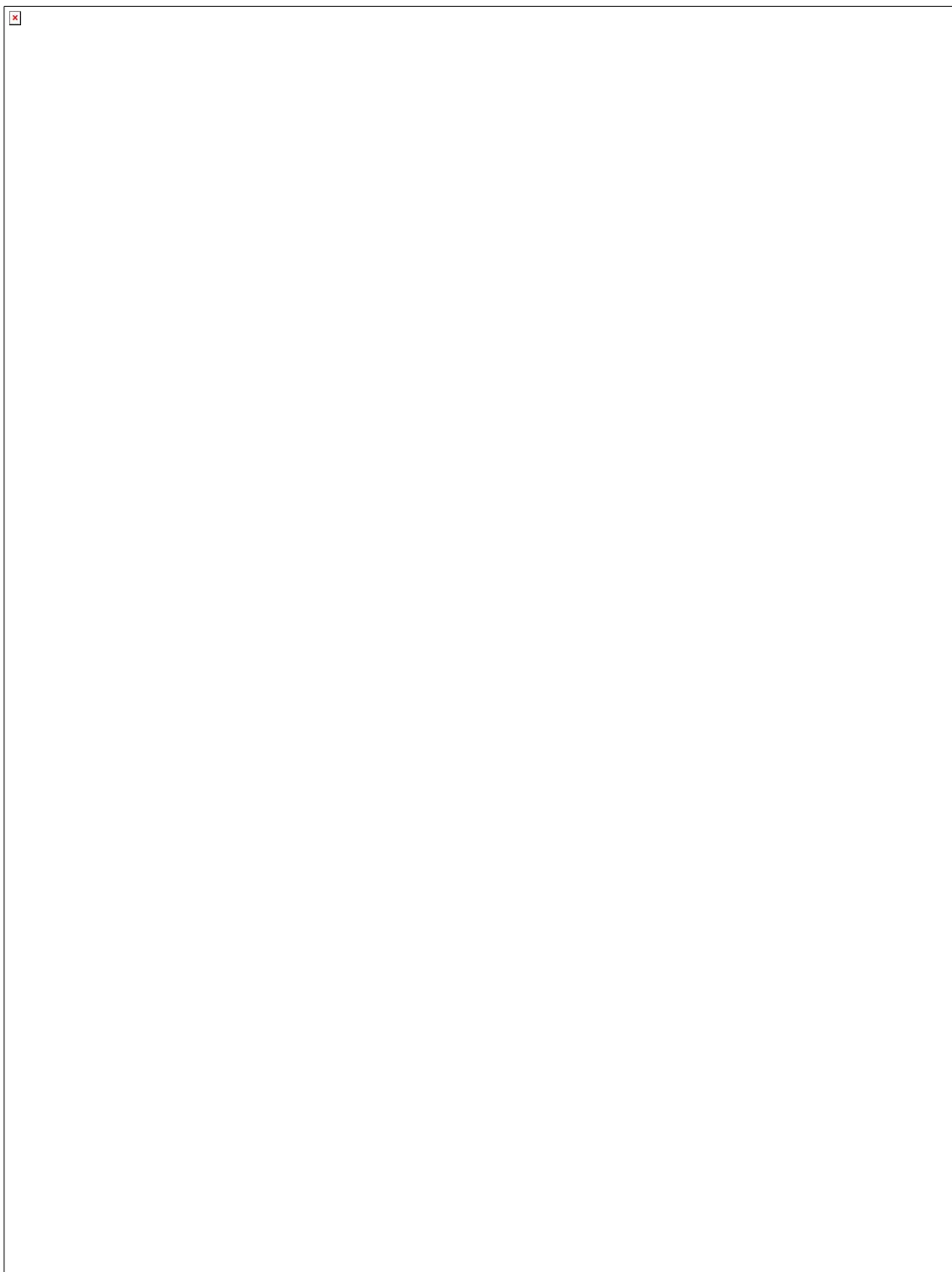
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Chapter 3 The International Physical Activity Questionnaire Overestimates Moderate and Vigorous Physical Activity in Individuals with Human Immunodeficiency Virus

Growing recognition of the importance of physical activity in the management of many HIV-related complications has resulted in an urgent need for valid and reliable physical activity measurement tools[42, 47]. Accurate data on physical activity may be helpful in the long-term monitoring of HIV infection and HAART-related side effects. It is therefore necessary to determine feasible and practical methods for assessing habitual physical activity within this group. Despite a plethora of physical activity questionnaires being available, very few have been validated in the context of chronic HIV infection. Current physical activity data collected in HIV-infected populations worldwide have relied on generic questionnaires whose measurement properties have not been examined in people living with HIV.

The International Physical Activity Questionnaire was developed by an international working party as a common instrument for epidemiological research[38]. The main evaluation study of the IPAQ tested its clinical utility in 14 centres from 12 countries and found it to have acceptable measurement properties[38]. Many other validity and reliability studies of the IPAQ in a diverse range of populations have also been published[123-127]. Today, the IPAQ remains the instrument of choice for many researchers undertaking physical activity epidemiological research[44, 128-131], including studies of chronic disease populations[45, 132]. Its use in HIV–infected populations is in its infancy, however the Spanish IPAQ short version has been used and tested in a HIV-infected population[47].

The paper presented within this Chapter therefore describes the validity of the last-7-day, self-administered long version of the IPAQ in HIV-infected adult males.

3.2 **Fillipas S**, Cicuttini FM, Holland AE and Cherry CL. The International Physical Activity Questionnaire overestimates moderate and vigorous physical activity in HIV. **Journal of Nurses in AIDS Care.** 21(2):173-181, 2010.

We found that the long version of the IPAQ correlated with the objective criterion (accelerometry). Self reported total number of metabolic equivalents minutes per week correlated moderately with accelerometer total activity counts (r=0.41, p=0.02). However, mean differences revealed over-reporting with the IPAQ; 546.63 min/wk (95% confidence interval: 217.1-871.2 minutes) for moderate and 295.3 min/wk (95% confidence interval: 88.08-502.6 minutes) for vigorous activity. The sensitivity of the IPAQ to detect individuals with insufficient physical activity to derive a health benefit was low (9.5%), however the tool's specificity was high (100%).

There was significant correlation between physical activity measured by the IPAQ and accelerometry, however problems of overestimation and its poor ability to identify inactive individuals are of concern. These data suggest that this tool could be used in screening physical activity behaviours but should not be used when precise measurements of physical activity are required. Clinicians seeking precise measurements of physical activity should use objective instruments, such as an accelerometer or pedometer. The reliability properties of this tool need further evaluation.

Declaration for Thesis Chapter 3

Monash University

Declaration for Thesis Chapter 3: The International Physical Activity Questionnaire Overestimates Moderate and Vigorous Physical Activity in Individuals with Human Immunodeficiency Virus

Declaration by candidate

In the case of Chapter 3 the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Consent, data collection, data synthesis and analysis, writing the manuscript	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Flavia Cicuttini	Study concept and design ,revision of manuscript	
Anne Holland	Study concept and design , revision of manuscript	
Catherine Cherry	Revision of manuscript	

Candidate's Signature	███████████████	Date 17·4·2011
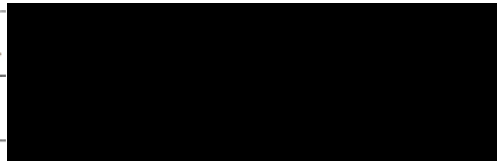
Declaration by co-authors

The undersigned hereby certify that:

(7) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(8) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(9) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(10) there are no other authors of the publication according to these criteria;

(11) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(12) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	The Alfred Hospital, Melbourne

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	███████████	Date 3/4/11
Signature 2	████████████████████	15/4/11
Signature 3	████████████████████	15/4/11

The International Physical Activity Questionnaire Overestimates Moderate and Vigorous Physical Activity in HIV-Infected Individuals Compared With Accelerometry

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This study evaluates the validity of the last-7-day, self-administered version of the International Physical Activity Questionnaire (IPAQ) long form in HIV-infected people, using accelerometry as the objective criterion. The ActiGraph GT1M accelerometer was worn during all waking hours for 7 days, and the IPAQ was completed on day 7. A total of 30 men were recruited as participants from the Alfred Infectious Disease Clinic, Melbourne, Australia. Self-reported total number of metabolic equivalents minutes per week correlated moderately with accelerometer total activity counts ($r = .41$, $p = .02$). However, mean differences showed overreporting with the questionnaire; 546.63 min/wk (95% confidence interval: 217.1-871.2 minutes) for moderate and 295.33 min/wk (95% confidence interval: 88.08-502.6 minutes) for vigorous activity. The IPAQ correlated with accelerometry, but substantial overreporting occurred. The tool may be useful in screening physical activity but should not be used to determine precise levels.

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Key words: *HIV, international physical activity questionnaire, validity*

Physical activity is an important health-related behavior for people living with HIV (PLWH). Growing evidence has suggested that physical activity has multiple health benefits for PLWH including improved aerobic fitness (MacArthur, Levine, & Birk, 1993; Stringer, Berezovskaya, O'Brien, Beck, & Casaburi, 1998), strength (Grinspoon et al., 2000; Roubenoff & Wilson, 2001), quality of life (Fillipas, Oldmeadow, Bailey, & Cherry, 2006; Wagner, Rabkin, & Rabkin, 1998), self-efficacy

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(Fillipas et al., 2006), and a reduction in cardiovascular disease risk (Malita, Karelis, Toma, & Rabasa-Lhoret, 2005; Terry et al., 2006). Despite the well-established benefits, knowledge about levels and patterns of physical activity is limited, in part because of the difficulty of accurately measuring this complex behavior. The availability of measuring tools validated in this context would allow more precise estimates of the prevalence of physical activity in PLWH and facilitate the identification of individuals who are insufficiently active to derive a health benefit. It would also allow assessment of the efficacy of physical activity on managing side effects and complications.

Questionnaires are used to measure physical activity in most epidemiological studies (Kriska & Casperson, 1997). Multiple questionnaires have been developed; however, few have been validated in PLWH. The International Physical Activity Questionnaire (IPAQ), recently developed specifically to address the need for an international, standardized, valid, and reliable tool, measures total habitual physical activity across multiple domains. Both the long and short versions have been used in healthy (Craig et al., 2003; Rutten et al., 2003), disease-specific (Faulkner, Cohn, & Remington, 2006; Tehard et al., 2005), and recently in an HIV-infected population (Fillipas et al., 2008). Evaluation of the reliability and validity of IPAQ has been performed in several studies (Craig et al., 2003; Ekelund et al., 2006; Hagstromer, Oja, & Sjostrom, 2006). The largest study performed to date involved 14 centers in 12 countries (Craig et al., 2003). The IPAQ produced repeatable data (Spearman ρ, approximately .8) and showed reasonable criterion validity (approximately $\rho = .30$). These results compare favorably to a review conducted on seven well-established physical activity questionnaires, including the Baecke Questionnaire of Habitual Physical Activity and the Paffenbarger Physical Activity Questionnaire (Sallis & Saelens, 2000). However, little has been done in the context of HIV infection. The Spanish version of the IPAQ short form has been reported to overestimate physical activity in Hispanics with HIV, showing reasonably poor validity correlation coefficients (ρ: $-.3$ to .28) but better test-retest reliability (ρ: .32-.75; Ramirez-Marrero et al., 2008). The measurement properties of the more detailed IPAQ long form in HIV-infected subjects have not been explored. The aim of this preliminary study was to evaluate the criterion and absolute validity of the last-7-day, long form, self-administered version of the IPAQ in an HIV-infected population, using accelerometry as the objective criterion.

Methods

Participants

The participants were recruited from an observational cohort study simultaneously being conducted at the Infectious Diseases Clinic of the Alfred Hospital, Melbourne, Australia. The first 30 participants enrolled in the observational study were asked to participate in the current study. Written informed consent was obtained from all participants, and the Alfred Hospital Human Ethics Committee approved the study.

Measurements of Physical Activity

The IPAQ instrument. The last-7-day, long form, self-administered version of the IPAQ, which is detailed elsewhere (Craig et al., 2003; IPAQ, n.d.), was used to collect self-reported physical activity data. The data were prepared following the IPAQ guidelines for data processing (IPAQ, n.d.). The IPAQ long form evaluates habitual physical activity performed in everyday life in the four domains, namely leisure, work, transport, and domestic/gardening, during the previous 7 days. Participants were asked to report frequency and duration of vigorous, moderate intensity and walking activities lasting for at least 10 minutes.

The data were converted to metabolic equivalent (MET) scores, an indicator of energy expenditure (EE), by weighting the reported minutes per week in moderate and vigorous activities by a MET energy estimate (Craig et al., 2003). MET energy estimates that were included were between 3 and 6 METS for moderate and greater than 6 METS for vigorous intensity activities. Total weekly EE was also calculated (MET-min/wk) by multiplying the time spent in vigorous, moderate intensity and walking activities by an average MET score (IPAQ, n.d.).

Activity monitoring. The ActiGraph GT1 M activity monitor (ActiGraph, LLC, Pensacola, FL) is a uniaxial accelerometer that records accelerations in the vertical plane per selected time interval (epoch) as activity counts. Activity counts are the summation of accelerations measured during an epoch. The term *acceleration* is defined as a change in velocity with respect to time, often expressed as a gravitational unit (g) and changes in body accelerations, which reflect changes in EE. One activity count is equal to 4 ml Gs/sec. Monitors were initialized as described by the manufacturer, and the epoch was set at 60 seconds. Activity monitor data were included in the analyses if at least 600 minutes of registered time per day were recorded for at least 5 days, one of which had to be on a weekend (Craig et al., 2003).

Activity counts were categorized into one of the three activity levels, and time spent in each level was calculated (Actigraph, n.d.). The three levels were: (a) light, < 1,953 counts (< 3 METS); (b) moderate, between 1,953 and 5,724 counts (3-6 METS); and (c) vigorous, > 5,725 counts (> 6 METS). Activity counts were converted into total EE per week, expressed as kilocalories per week using the accompanying Actilife Software (Actigraph, n.d.). A total weekly step count was also obtained.

Time spent (minutes/week) in each activity level was compared with the self-reported time at these activity levels from the IPAQ long form. Total weekly activity counts as measured by the activity monitor were compared with the self-reported total weekly MET-min/wk calculated from the IPAQ long form. EE, calculated using the activity monitor data, was compared with EE calculated from the IPAQ data. The latter was calculated using the formula MET-min/wk × weight (kg)/60 (Actigraph, n.d.).

Participant physical activity levels were classified according to the Centers for Disease Control and Prevention and American College of Sports Medicine physical activity guidelines (Pate et al., 1995). Participants were classified as sufficiently active provided they performed at least 30 minutes of moderate intensity activity on at least 5 days per week or at least 20 minutes of vigorous intensity activity on at least 3 days per week. Participants who did not meet these criteria were classified as inactive.

Procedure

During the initial assessment (Day 1), participants were issued an activity monitor and provided with detailed verbal and written instructions on its use. On that day, the activity monitor was placed on the right hip and was worn for 7 consecutive days during all waking hours except during water-based activities. Adherence with the monitor was strongly encouraged and documented by the participants. All activities performed while the monitor was not worn were recorded in a diary.

Basic anthropometric measures, body weight (kg) and height (m), were measured, and body mass index was then calculated (kg/m^2). Waist-to-hip ratio was measured at the waist (midway between the 10th rib and iliac crest) and hips (widest point of buttocks; Gibson, 2005), and self-reported demographic data were also collected during the initial assessment. On Day 8, participants returned the activity monitor and diary and completed the IPAQ long form.

Statistical Analyses

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 16, and the level of significance was set at $p < .05$. Characteristics of participants were described as means, standard deviations, and ranges.

The total amount of physical activity recorded by the activity monitor, expressed as total weekly activity counts, was used as the main criterion measure in the validity evaluation. IPAQ long form data were compared with the activity monitor measures of physical activity over 7 days. The self-report data were not of normal distribution, hence nonparametric Spearman rank correlation coefficients (ρ) were calculated to assess the relationship between data obtained from the IPAQ long form and activity monitor counts.

The absolute validity of the IPAQ long form (the ability of this tool to assess the absolute levels of physical activity) was examined using a modified Bland Altman technique (Bland & Altman, 1986). Agreement between self-reported time in physical activity and objectively measured time by the activity monitor was evaluated. The difference between objectively measured time by the activity monitor (criterion measure) and self-reported time

as measured by the IPAQ long form at the same intensity levels was plotted against the criterion. Sensitivity (the probability of correctly identifying inactive individuals using the IPAQ long form) and specificity (the probability that an individual identified as inadequately active using the IPAQ long form is truly inactive using objective criteria) were then determined.

Results

Participant Characteristics

A total of 30 HIV-infected men participated in the study. Demographic characteristics are in Table 1. The cohort was typical of PLWH seen at this center, being largely White (90%), men who had sex with men (97%), and who were currently on antiretroviral treatment (100%). Most had completed at least 11 years of formal education. Approximately one fourth of participants reported current depression; however, there was a very low prevalence of other major comorbidities such as heart disease, diabetes, and current illicit drug use. More than half (53%) were smokers. All participants wore the activity monitor for the time required.

Physical Activity Described by the IPAQ Long Form and Activity Monitor

Self-reported time spent in weekly physical activity and EE are depicted in Table 2. Participants reported that they spent the most time and expended the most energy in moderate activity (557 minutes and 1,997.5 MET-minutes, respectively). The least amount of time was spent in vigorous activity (120 minutes). Table 2 also shows objectively measured weekly activity monitor data. Results obtained using the monitor confirmed that more time was spent in moderate activity (237 minutes) than vigorous activity (8 minutes) but showed that overall, substantially less time was spent in moderate or vigorous activity than participants reported. The median IPAQ long form estimate and the mean activity monitor estimate of total kilocalories per week were 6,852.5 (2,815.9-11,617) and 2,497.1 (1,146.3), respectively.

Table 1. Characteristics of Participants ($n = 30$)[a]

	M (SD)	Median (Range)
Age (years)	53.2 (10.2)	
Years on ART		6 (.25-21)
Years living with HIV	13.4 (7.4)	
CD4+ T-cell count		403.5 (95-1,145)
Viral load		50 (50-100,000)
Height (m)	1.77 (.097)	
Weight (kg)	81.04 (16.3)	
BMI	25.6 (4.04)	
WHR	.98 (.57)	

NOTE: ART = antiretroviral therapy, BMI = body mass index, WHR = waist to hip ratio.

a. Normally distributed variables are described using mean (standard deviation) and nonnormally distributed variables as median (range).

Validity

The total number of MET-minutes/week reported on the IPAQ long form showed a moderate correlation with the main criterion measure of total weekly activity counts measured by the activity monitor ($r = .41$, $p = .02$; see Table 3). A moderate correlation was also observed between time spent in vigorous activities as measured by the IPAQ long form and the registered time in vigorous activities measured by the activity monitor ($r = .38$, $p = .04$).

The modified Bland Altman plots (Figure 1) illustrate the difference between objectively measured time spent in moderate and vigorous intensity physical activity, respectively, and self-reported time plotted against activity monitor estimates. Time spent was overreported on the IPAQ long form (mean difference compared with activity monitor 546.63 min/wk, 95% confidence interval [CI] 217.1-871.2 minutes). Over-reporting of vigorous physical activity was also evident (mean difference 295.33 min/wk, 95% CI: 88.08-502.6 minutes).

Sensitivity and Specificity

Two participants reported insufficient physical activity on the IPAQ long form and both were classified similarly on the activity monitor. Of those participants who reported sufficient physical activity to gain a health benefit on the IPAQ long form ($n = 28$), only 2 were classified as sufficiently active by the activity monitor (Table 4). The sensitivity of the IPAQ long

Table 2. Descriptive Data From the IPAQ Long Form and From the Activity Monitor

	IPAQ		Activity Monitor	
	Median Duration (min/wk) (Interquartile Range)	Median Intensity (MET-min/wk) (Interquartile Range)	Activity Monitor Objective Physical Activity Variables	M (SD)
Vigorous activity	120 (0-367.5)	960 (0-2,940)	Vigorous activity > 5,724 counts (min/wk)	8.17 (15.99)
Moderate activity	557 (105-1,207.5)	1,997.5 (420-4,650)	Moderate activity 1,952-5,724 counts (min/wk)	237.2 (165.60)
Leisure	2,02.5 (95-436.3)	1,174.5 (396-2,225.3)		
Transport	210 (68.8-500)	805.5 (226.9-1,650)		
Domestic and garden	240 (15-650)	937.5 (60-2,596.3)		
Work	0 (0-585)	0 (0-2,532)		
Total	4,165 (3,260-4,880)	5,993.8 (1,995.4-9,596.8)	Total activity counts per week	176,7400 (796,028)
			Total step counts per week	47,608.9 (19,839.6)

NOTE: IPAQ = International Physical Activity Questionnaire, MET = metabolic equivalent.

Table 3. Spearman Rank Correlation Coefficients for Physical Activity From the IPAQ Long Form and the Activity Monitor

IPAQ Long Form Self-Reported Variables	Activity Monitor Variables	Spearman r (p)
Total MET, min/wk	Total activity counts	.41 ($p = .02$*)
Total MET, min/wk	Total step count	.34 ($p = .07$)
Total MET, min/wk	Total kcals	.30 ($p = .13$)
Walk MET, min/wk	Total step count	.23 ($p = .23$)
Total kcals	Total kcals	.35 ($p = .06$)
Moderate activity duration	Moderate activity duration	.19 ($p = .33$)
Vigorous activity duration	Vigorous activity duration	.38 ($p = .04$*)

NOTE: IPAQ = International Physical Activity Questionnaire, kcal = kilocalories, MET = metabolic equivalent.
* $p < .05$.

form to detect individuals with insufficient physical activity to derive a health benefit was low (9.5%); however, this tool showed high specificity (100%).

Discussion

This small preliminary study is the first to evaluate the validity of the IPAQ long form in a group of PLWH. There was a significant correlation between physical activity measured by the two methods; however, the presence of overreporting of the IPAQ long form and its poor ability to identify inactive individuals is of concern. These results suggest that the IPAQ long form may be useful as an initial physical activity screening of HIV-infected individuals, but it cannot be used to determine precise amounts of physical activity.

The criterion validity results obtained in this study are comparable to other published correlation coefficients. The correlation coefficient of .41 is consistent with accepted criterion correlations for physical activity questionnaires in the general population (Kriska & Casperson, 1997; Sallis & Saelens, 2000). Importantly, these results compared favorably with those published in the international reliability and validity study of the IPAQ (pooled $r = .33$, 95% CI: .26-.39; Craig et al., 2003). This suggests that the IPAQ long form exhibited reasonable measurement properties in the HIV context that were comparable to those in the general population.
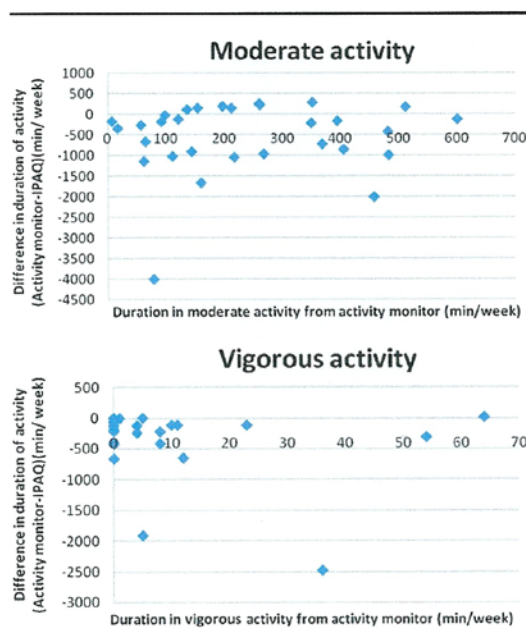
Figure 1. Differences between objectively measured and self-reported time spent in moderate and vigorous activity (min/wk). Self-reported activity using the IPAQ was plotted against activity from activity monitor. Moderate activity: Mean difference, -546.6 min/wk; limits of agreement, 876.2 to -217.1 min/wk. Vigorous activity: mean difference, -295.3 min/wk; limits of agreement, -502.6 to -88.1 min/wk. NOTE: IPAQ = International Physical Activity Questionnaire.

Table 4. Number of Participants Classified as Being Sufficiently Active According to CDC/ACSM Physical Activity Guidelines by the IPAQ Long Form and by the Activity Monitor ($n = 30$)

Meeting PA Guidelines, IPAQ Long Form	Meeting PA Guidelines, Activity Monitor		
	No	Yes	Total
No	2	0	2
Yes	19	9	28
Total	21	9	30

NOTE: ACSM = American College of Sports Medicine, CDC = Centers for Disease Control and Prevention, IPAQ = International Physical Activity Questionnaire, PA = physical activity.

sensitivity (23%) and a high specificity (87%). This suggests that individuals identified as inactive by either the short or long form of the IPAQ are almost certainly inactive, but it is not possible to be confident that those individuals identified as active are truly engaging in sufficient physical activity.

The IPAQ long form, like all self-report measures of physical activity, has the potential for overestimation. The authors evaluated the absolute difference in self-reported time in physical activity measured by the IPAQ long form and objectively measured time as measured by the activity monitor. The IPAQ long form was reported to significantly overestimate time spent in both moderate and vigorous activity. The issue of overestimation with the IPAQ was also observed in other studies conducted in both healthy and diseased populations (Ekelund et al., 2006; Ramirez-Marrero et al., 2008; Rzewnicki, Vanden Auweele, & De Bourdeaudhuij, 2003). Overestimation because of other factors may have also influenced this study. A social desirability bias may have contributed to the problem. This phenomenon, also reported elsewhere in PLWH (Ramirez-Marrero et al., 2008), may have occurred because the participants were well known to the investigators and may have felt a degree of pressure to report better activity levels.

The IPAQ long form's ability to correctly identify inactive PLWH was very poor. Other accelerometer-based validation studies have also shown poor classification of physical activity, using both the long and short forms of the IPAQ. High sensitivity (77%) and reasonably poor specificity (45%) were shown in

The availability of validated questionnaires for PLWH is limited. To date, studies evaluating physical activity in this population have used other known questionnaires such as the Behavioral Risk Factor Surveillance Survey (Clingerman, 2003) and the Paffenbarger Survey (Smit et al., 2006); however, these tools have not been validated. The Baecke's questionnaire, evaluating habitual activity over the previous year, has been tested and reported to be valid (Florindo et al., 2006). As far as the authors know, only one study has evaluated both the validity and reliability of the IPAQ in PLWH. This study included Hispanic adults, both men and women, and evaluated the IPAQ short form Spanish version (Ramirez-Marrero et al., 2008). Similar to this study, that study reported a low

a healthy population using the IPAQ short form (Eke-lund et al., 2006), and in PLWH, as previously mentioned (Ramirez-Marrero et al., 2008). Poor specificity (59%) of the IPAQ long form was also shown in a study of women with breast cancer (John-son-Kozlow, Sallis, Gilpin, Rock, & Pierce, 2006). Also, the use of previously published accelerometer cut points to determine physical activity levels may not be relevant because they were derived in healthy and not chronically ill populations. Low sensitivity may also be because of PLWH reporting perceived exertion in lighter activities as higher intensities because of the difficulties of living with a chronic illness (Ramirez-Marrero et al., 2008).

Time spent in vigorous but not moderate activity as measured by the IPAQ long form was significantly correlated with objective (activity monitor) measures. Other studies have also shown this result (Hagstromer et al., 2006; Welk, 2002). This can be explained because higher intensity activities, often involving structured exercise, can result in better recall compared with lower intensity activities accumulated gradually over the course of a day.

The selection of an appropriate criterion in physical activity validation studies is challenging because the accepted gold standard for estimating EE, the doubly labeled water method (Schoeller, 1988), is expensive and cannot provide data on physical activity intensity, frequency, and duration. The present study, like other previously published validation studies of the IPAQ (Craig et al., 2003; Ekelund et al., 2006), used acceler-ometry to assess validity. Activity monitors are considered highly appropriate when validating phys-ical activity questionnaires (Welk, Blair, Wood, Jones, & Thompson, 2000). Although considered very acceptable, accelerometry still has some limitations that may have affected the results. Studies suggest that accelerometers may underestimate EE (Bouten, Verboeket-van de Venne, Westerterp, Verduin, & Jans-sen, 1996; Bouten, Westerterp, Verduin, & Janssen, 1994) because they cannot accurately measure all types of activities. Bicycling, weight training, uphill walking, and water-based activities cannot be measured accurately. Apart from swimming, which was not largely reported by this group in their diaries, the other listed activities might not have been objec-tively measured with accuracy in this study, poten-tially underestimating the activity monitor's EE.

The limitations of this study include its relatively moderate sample size and the fact that it included a small number of participants who self-reported a low level of physical activity. The results of this study may not be generalizable to all PLWH. All of the patients were recruited from a clinic that promotes a healthy lifestyle. The authors know that most of their patients participate in regular physical activity (Fillipas et al., 2008); however, the clinic has a high smoking rate despite smoking cessation programs, which may have influenced the self-report of physical activity. The authors also included only men in the study. Reliability of the questionnaire and sensitivity to change were not examined and should be addressed at a later point.

The preliminary data presented in this study show that the validity of the IPAQ long form in PLWH shows promise; however, issues with over-estimation are of concern. The IPAQ long form is useful in screening physical activity levels of indi-viduals but should not be used as a precise measurement tool. It is recommended that clini-cians seeking precise measurements of physical activity also use an objective instrument, like an accelerometer. To optimize the evaluation of this tool for use in this population, further research is needed to determine reliability and improve under-standing of sensitivity.

Clinical Considerations

- Self-reported physical activity measured by the IPAQ long form correlates with the objective criterion of accelerometry, but substantial over-reporting occurs.
- It is recommended that clinicians use the IPAQ long form to screen physical activity levels but should not use it to determine precise amounts of activity.
- Clinicians seeking precise measurements of physical activity should use an objective instru-ment, such as an accelerometer.

Disclosures

Acknowledgments

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Chapter 4 The Effects of Exercise Training on Metabolic and Morphological Outcomes for People Living With HIV: A Systematic Review of Randomised Controlled Trials

Chronic HIV infection and HAART are associated with the development of several metabolic and morphological complications[133]. These include increased central adiposity, peripheral lipoatrophy, peripheral insulin resistance, dyslipidaemia and osteopenia[59]. These complications may increase the risk of CVD, diabetes, and osteoporosis. There is a need for evidence-based use of non-pharmacological interventions, such as exercise training, to manage these common clinical problems in the context of HIV.

Systematic reviews of published trials of exercise training in HIV-infected individuals are available[28-29], however a profound lack of metabolic and morphological outcomes is a major limitation. Despite exercise training and its effect on metabolic and morphological complications in HIV-infected individuals being the subject of several published papers, the evidence has yet to be systematically evaluated. Furthermore, the wide use and acceptance of exercise training as an intervention to manage common complications observed in today's clinical practice, warrants a systematic evaluation of current evidence.

The paper presented within this Chapter aims to evaluate systematically the available evidence from published RCTs on the effects of exercise training on metabolic and morphological outcomes among individuals living with HIV.

4.1 **Fillipas S,** Cherry CL, Cicuttini FM, Smirneos L, Holland AE. The effects of exercise training on metabolic and morphological outcomes for people living with HIV: a systematic review of randomised controlled trials. **HIV Clinical Trials** 11 (5): 270-82, 2010.

Nine randomised controlled trials were included in this systematic review. Four hundred and ninety four participants (41%females) at various stages of HIV disease were included (CD4 counts ranging <100 to >1000 cells/mm^3). Basic anthropometric outcomes were evaluated in all included studies, however only two studies utilised imaging to assess body composition and none evaluated bone health. We found both aerobic exercise and progressive resistive exercise can improve body composition. Specifically, aerobic exercise can improve body composition where central adiposity and overweight/obesity are of concern in patients, while progressive resistive exercise can increase body weight and limb girth where reversal of muscular atrophy and weight gain are of priority. Combining aerobic exercise and progressive resistive exercise demonstrated no additional benefits. Data on the effects of exercise training are less convincing, however there is some evidence that aerobic exercise maybe more efficacious than progressive resistive exercise on certain lipid subsets.

These data suggest that exercise training shows promise in managing some morphological complications, however the effects on metabolic outcomes remain largely unknown. Larger studies evaluating exercise training and metabolic parameters such as blood lipids, glucose, and bone density are warranted.

Declaration for Thesis Chapter 4

Monash University

Declaration for Thesis Chapter 4: The Effects of Exercise Training on Metabolic and Morphological Outcomes for People Living With HIV: A Systematic Review of Randomised Controlled Trials

Declaration by candidate

In the case of Chapter 4 the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Consent, data collection, data synthesis and analysis, writing the manuscript	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Catherine Cherry	Revision of manuscript	
Flavia Cicuttini	Revision of manuscript	
Lorena Smirneos	Search strategy	
Anne Holland	Study concept and design ,revision of manuscript	

		Date
Candidate's Signature	████████████	17. 4 · 2011

Declaration by co-authors

The undersigned hereby certify that:

(13)   the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(14)   they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(15)   they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(16)   there are no other authors of the publication according to these criteria;

(17)   potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(18)   the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	The Alfred Hospital, Melbourne

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

		Date
Signature 1	███████████████	15/4/11
Signature 2	███████████████	3/4/11
Signature 3	████████	8/4/11

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Signature 4 | ████████████ | | 15/4/11 |

The Effects of Exercise Training on Metabolic and Morphological Outcomes for People Living With HIV: A Systematic Review of Randomised Controlled Trials
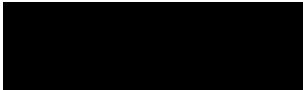
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Purpose: To determine the effects of exercise on metabolic and morphological outcomes among people with HIV using a systematic search strategy of randomized, controlled trials (RCTs). **Methods:** Two independent reviewers assessed studies using a predetermined protocol. **Results:** Nine RCTs (469 participants, 41% females) of moderate quality were included. Compared to nonexercising controls, aerobic exercise (AE) resulted in decreased body mass index (weighted mean difference [WMD] −1.31; 95% CI, −2.59, −0.03; n=186), triceps skinfold thickness of subcutaneous fat (WMD −1.83 mm; 95% CI, −2.36, −1.30; n=144), total body fat (%) (standardised mean difference [SMD], −0.37; 95% CI, −0.74, −0.01; n=118), waist circumference (SMD −0.74 mm, 95% CI, −1.08, −0.39; n=142), and waist:hip ratio (SMD −0.94; 95% CI, −1.30, −0.58; n=142). Progressive resistive exercise (PRE) resulted in increased body weight (5.09 kg; 95% CI, 2.13, 8.05; n=46) and arm and thigh girth (SMD 1.08 cm; 95% CI, 0.35, 1.82; n=46). Few studies examined blood lipids, glucose, and bone density. **Conclusions:** Few RCTs exist and their quality varies. AE decreases adiposity and may improve certain lipid subsets. PRE increases body weight and limb girth. No additional effects of combining AE and PRE are evident. Larger, higher quality trials are needed to understand the effects of exercise on metabolic outcomes (eg, lipids, glucose, bone density) relevant to persons with chronic, treated HIV. **Key words:** aerobic exercise, HIV, progressive resistive exercise, randomised controlled trial

The introduction of highly active antiretroviral therapy (HAART) has reduced the morbidity and mortality associated with human immunodeficiency virus (HIV).[1,2] Even among patients with access to HAART, however, HIV remains a serious illness. In particular, both HIV infection and HAART can be associated with metabolic and morphologic complications.[3] Abnormal lipid and glucose metabolism and fat redistribution (central lipohypertrophy and peripheral lipoatrophy) are common amongst HAART-treated patients.[4,5] Osteoporosis and osteopenia are also increased.[6] These problems may predispose patients to premature cardiovascular disease, diabetes, and fractures and may increase psychological distress.

Medications may ameliorate some HAART-related problems, but their use is associated with financial costs and potential toxicities. HAART modification may improve lipoatrophy, however no drug is proven to prevent or reverse visceral lipohypertrophy.[7,8] Safe, effective, nonpharmacological interventions are needed to prevent and manage the metabolic and morphologic abnormalities seen in HIV-infected patients. Exercise training improves and maintains health and reduces chronic disease risk in healthy adults.[9] Current guidelines generally recommend nondrug therapies, including exercise and diet, as a first-line treatment for dyslipidemia in HIV,[10] based largely on the known cardiovascular benefits of exercise in other contexts. However,

although systematic reviews have concluded aerobic exercise (AE) and progressive resistive exercise (PRE) interventions are beneficial and safe for individuals living with HIV, evaluation of morphologic endpoints was limited and metabolic parameters were not examined.[11,12]

This review was undertaken to examine the quality and content of existing clinical trial evidence of the effects of exercise training on metabolic and morphological endpoints in HIV-infected adults.

METHODS

Criteria for Considering Studies for Review

Study designs

A systematic review of the published literature was conducted on the effects of exercise training on metabolic and morphological complications in HIV-infected patients. Only randomised trials where a prescribed AE, PRE, or a combined AE and PRE intervention was compared with no exercise or with another exercise intervention at least twice weekly, over at least 4 weeks, were included. Trials combining exercise with nonexercise intervention (eg, anabolic steroids), non-English language publications, unpublished studies, abstracts, and conference proceedings were excluded.

Types of participants

Studies of HIV-infected adults (aged ≥18 years) were included.

Types of intervention

Exercise training including AE, PRE, or a combination of both, either supervised or unsupervised, were included. AE was defined as an intervention containing AE (eg, walking, jogging, running, rowing, or cycling). PRE was defined as resistive exercise intervention (eg, weight training, isotonic, or isometric exercises). Comparisons examined were exercise training versus no exercise training (control) and exercise training versus another form of exercise training.

Outcome Measures

Metabolic outcomes considered were blood lipids (total cholesterol [TC], high-density lipoprotein cholesterol [HDL], low-density lipoprotein cholesterol [LDL] and triglycerides [TG]) and blood glucose.

Morphological outcomes considered were body weight, body mass index (BMI), waist circumference, waist to hip ratio (WHR), bone mineral density (BMD), skinfold thickness of subcutaneous fat (SFT), girth circumference (chest, arm, leg), and magnetic resonance imaging (MRI) or computed tomography (CT) measured subcutaneous abdominal adipose tissue (SAT) and visceral abdominal adipose tissue (VAT).

Search Methods for Identification of Studies

Electronic searches were conducted from 1980 to November 2009 using MEDLINE, CINAHL, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews, Physiotherapy Evidence Database (PEDro), SportDiscus, and Informit. The search combined 3 subject groups: HIV, exercise, and study design. The HIV group included the terms HIV, HIV infections, HIV long-term survivors, AIDS, human immunodeficiency virus, or acquired immunodeficiency syndrome. The exercise group included the terms exercise, physical fitness, exertion, sports, physical education and training, aerobic, anaerobic, progressive resistive/resistance, exercise therapy, or physical training.

The study design group included the terms "randomized controlled trials," "double blind," "single blind," or "clinical trials." For some databases, the search strategy was slightly modified.

The reference lists of identified manuscripts were hand-searched for additional studies that met the inclusion criteria.

Assessment of Quality

The quality of included studies was assessed using the PEDro scale, designed to assess trials of physiotherapy interventions. Criteria and scoring of the PEDro scale are described elsewhere.[13]

Data Extraction and Analyses

Two reviewers (S.F. and A.H.) independently assessed all titles and abstracts of identified studies. Full-text versions were obtained of studies where:

- participants were HIV-infected adults, and
- the intervention was AE, PRE, or combined AE and PRE performed at least twice weekly for at least 4 weeks, and
- the study was a randomised controlled trial, and
- the comparison group was either a no-exercise or another type of exercise group.

For any study where it was unclear whether these criteria were met, a discussion between the reviewers occurred to reach consensus.

Data were independently extracted from all included studies using a prepared checklist before entering into Review Manager (RevMan [Computer program], Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008), with random checks for accuracy. Disagreements were resolved by discussion to reach consensus. Corresponding authors of included studies with missing data were contacted to obtain missing data where possible.

For continuous variables, the mean change from baseline or the postintervention mean and standard deviation (*SD*) for each group was recorded. The mean difference (MD) for outcomes measured with the same metric units or standardised mean difference (SMD) for outcomes measured with different metric units with 95% confidence intervals (95% CI) was calculated where possible using RevMan 5. Effect sizes and 95% confidence intervals were calculated where possible using Web-based software (www. cemcentre.org/renderpage.asp?linkid=30325017).

RESULTS

The initial search identified 2,202 citations (**Figure 1**). This was reduced to 23 studies after elimination of duplicates and application of the inclusion and exclusion criteria by 2 independent reviewers screening the title and abstracts. A further 11 studies were excluded after retrieving the full text. Of these, 8 were RCTs that did not examine outcomes of interest to this review[14-21] and 4 studies were not RCTs.[22-25] Three additional papers were excluded as they were deemed duplicate studies of included papers.[26-28] The final yield included 9 studies (**Table 1**).[29-37]

Methodological Quality

Quality of included trials as assessed by the PEDro score was a median 5 (range, 3 to 8) out of a possible score of 10. Only 1 study had concealed
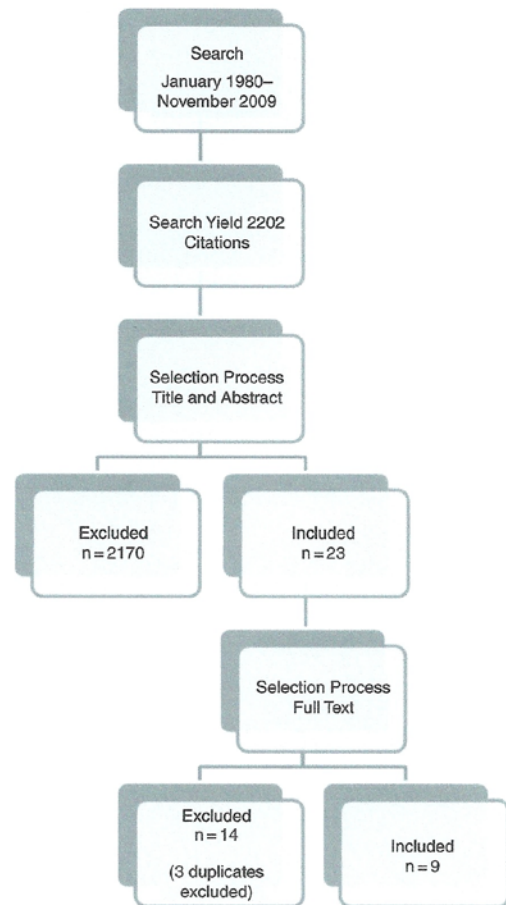
Figure 1. Search yield.

allocation[29] and only 2 presented an intention-to-treat analysis.[29-30] Lack of blinding was common, with only 2 studies blinding assessors.[29,31] Blinding of therapists providing the exercise intervention was not possible in any study.

Participants of Included Studies

Overall, 494 participants (41% female) were included (**Table 1**). Adults at various stages of HIV disease were included with CD4 counts ranging from <100 to >1000 cells/mm^3. The mean age of participants in individual studies ranged from 18 to 71 years. Five studies included participants who were all on HAART (at least 3 antiretrovirals),[29-33] and one did not describe antiretroviral use.[37]

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The remainder recruited participants using non-HAART regimens.[34-36]

imaging to assess body fat distribution[30,32] and none collected bone outcomes.

Outcomes of Included Studies

Basic anthropometric outcomes were evaluated in all included studies, however only 2 utilized

Effects of AE on Metabolic Outcomes

Two studies examined the effects of AE on blood lipids and glucose,[33,37] however insufficient data

Table 1. Characteristics of included studies in the systematic review.

Author/year/country	Number/males %	Trial design	Type of exercise	Exercise dosage: frequency, intensity, duration	Setting/supervision	Withdrawal rates
Spence et al/1990/USA	N=24/100%	2 groups: PRE and controls	Hydraulic strength training	PRE: Begin at 1 set of 15 reps at min resistance to 3 sets of 10 reps at max resistance (levels 1–6). 3/wk for 6 wks Controls: usual activity	NR/yes	0% (0/24)
Terry/1999/USA	N=31/66.7%	2 groups: moderate and high intensity interval AE	Walking/running	Moderate: 55–60% HR max 30 min (5 min target intensity, 1 min recovery) High: 75–85% HR max 30 min (5 min target intensity, 1 min recovery) Both groups: 3/wk for 12 wks and 15 min stretch pre/post	NR/yes	32% (10/31)
Perna et al/1999/USA	N=43/86%	2 groups: AE interval and control	Stationary bike	AE: 70–80% HR max; 10 min stretch pre/post; 3/wk for 12 wks Control: wait-listed control	Laboratory/yes	51% (22/43)
Smith et al/2001/USA	N=60/87%	2 groups: AE and control	Walk/jog/run treadmill or track	AE: Initial 20 min 60–80% VO$_2$max; warm/cool down; 3/wk for 12 wks Control: wait-listed control	Medical centre/yes	18% (11/60)
Lox et al/1996, 1995/USA	N=34/100%	3 groups: AE, PRE and control	Stationary bike, variable isotonic equipment	AE: 24 min target HR (50%–80% of HR reserve) RE: 3 × 10 reps; beginning @ 60% 1-RM Both groups: 3/wk for 12 wks	Fitness club/yes	3% (1/34)

(Continued)

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Table 1. Continued

Author/year/ country	Number/ males %	Trial design	Type of exercise	Exercise dosage: frequency, intensity, duration	Setting/ supervision	Withdrawal rates
Dolan et al/ 2006/USA	N=40/0%	2 groups: combined AE/PRE and control	Stationary cycling, flexion-extension bench, squat stand, free weight sets	AE: 1–2 wks 20 min 60% max HR, then 30 min 75% max HR RE: 1–2 wks 60% 1RM, 2–4 wks 70% 1-RM, 5–16 wks 80% 1-RM. Warm up/cool down. 3/wk for 16 wks Control: Usual activity	Domiciliary/ yes	5% (2/40)
Fillipas et al/ 2006/ Australia	N=40/100%	2 groups: combined AE/PRE and control	Cycling, treadmill stepper or cross trainer; free weights; isotonic machines	AE: 60%–75% max HR RE: 3 sets of 10 60%–80% 1-RM; 2/wk for 24 wks Control: Walking 2/wk, 20 min and monthly group forum	Fitness club or hospital physiotherapy department/ yes	13% (5/40)
Mutimura et al/2008/ Africa	N=100/ HIV+ with LDS n=50; HIV+ without LDS n=50; HIV-40%	4 groups: AE and 3 comparison groups a. HIV+/LDS no exercise b. HIV +/no LDS no exercise c. HIV- no exercise	Walking, jogging, running, stair climbing, low back/ abdominal	AE: 1–3 wks 45–60 min 45% max HR, 4–9 wks 60% max HR, 10–24 wks 75% max HR; stretching; 15 min brisk walk 3/wk for 24 wks Control: Usual activity	Fitness club/yes	7% (13/200)
Lindegaard et al/2008/ Denmark	N=35 (20 HIV+ and 15 age- matched controls)/100%	2 groups: AE and PRE	Isotonic machines	AE: First 8 wks, mean intensity 65% VO_2max and last 8 wks, 75% VO_2max PRE: Resistance progressed gradually Both groups: 3/wk for 16 wks; 5 min warm up	Fitness club/yes	10% (2/20)

Note: NR = not reported; VO_{2max} = maximum oxygen uptake; HR_{max} = heart rate maximum; $HR_{reserve}$ = heart rate reserve; 1-RM = 1 repetition maximum.

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Table 2. Effects of aerobic exercise versus no exercise controls

Outcomes	Study	Treatment group	Control group	Effect size (95% CI)
Body weight, kg	Smith et al, 2001	82.40±12.90	85.1±12.40	0.21 (−0.80, 0.38)
BMI, kg/m²	Smith et al, 2001	26.00±4.40	27.7±4	−0.41 (−1.00, 0.19)
	Perna et al, 1999	23.5±3.2	26.9±5.9	−0.73 (−1.58, 0.18)
	Mutimura et al, 2008	−0.53±1.20	0.06±0.60	−0.62 (−1.03, −0.21)[a]
Triceps SFT, mm	Smith et al, 2001	−2.20±2.10	1.20±0.70	−2.42 (−3.14, −1.62)[a]
	Mutimura et al, 2008	−1.42±2.10	−0.20±0.70	−0.78 (−1.19, −0.36)[a]
Biceps SFT, mm	Mutimura et al, 2008	−0.63±1.6	−0.06±0.3	−0.50 (−0.90, −0.09)[a]
Central SFT, mm	Smith et al, 2001	29.8±19.0	54.1±33.4	−0.86 (−1.47, −0.22)
Peripheral SFT, mm	Smith et al, 2001	49.2±24.70	74.9±29.1	−0.94 (−1.55, −0.29)
Subscapular SFT, mm	Mutimura et al, 2008	−1.9±3.2	−0.55±1.7	−0.53 (−0.93, −0.12)[a]
Suprascapular SFT, mm	Mutimura et al, 2008	−2.1±3.5	−0.43±1.4	−0.63 (1.03, −0.22)[a]
SSF, mm	Mutimura et al, 2008	−6.15±8.2	−0.43±−1.4	−0.78 (−1.19, −0.36)[a]
Body fat, %	Mutimura et al, 2008	−1.5±3.3	−0.16±0.70	−0.56 (−0.97, −0.15)[a]
WHR	Smith et al, 2001	0.96±0.06	0.97±0.07	−0.15 (−0.74, 0.44)
	Mutimura et al 2008	−0.10±0.1	0.00±0.1	−1.00 (−1.41, −0.57)
Waist, cm	Smith et al, 2001	−2.60±2.62	0.30±4.36	−0.76 (−1.36, −0.14)
Body weight, kg	Mutimura et al, 2008	−7.13±4.4	0.03±0.7	−0.87 (−1.28, −0.45)
TC, mmol/L	Mutimura et al, 2008	−0.03±1.11	0.066±1.28	−0.08 (−0.48, 0.32)[a]
HDL, mmol/L	Mutimura et al, 2008	0.03±0.21	0.07±0.14	−0.22 (−0.62, 0.18)[a]
LDL, mmol/L	Mutimura et al, 2008	0.14±0.89	0.19±0.98	−0.05 (−0.45, 0.35)[a]
TG, mmol/L	Mutimura et al, 2008	−0.22±0.48	0.07±0.49	−0.60 (−1.00, −0.19)[a]
Glucose, mmol/L	Mutimura et al 2008	−0.21±0.71	0.39±1.25	−0.59 (−0.99, −0.18)[a]
Insulin, ρmol/L	Mutimura et al 2008	−1±18	0±0.1	−0.19 (−0.59, 0.21)

Note: Postintervention data or change score data (indicated with a superscript a) used to calculate effect sizes. Data expressed as mean ± SD. BMI = body mass index; SFT = skin-fold thickness of subcutaneous fat; SSF = sum of SFT; WHR =waist to hip ratio; TC = total cholesterol; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol; TG = triglycerides.

and major differences in exercise interventions prevented meta-analysis. One showed reductions in TC and insulin following AE with small effect sizes, whilst reductions in glucose and TG with moderate effect sizes were reported[33] (**Table 2**). The other found no effect on any metabolic parameter with AE.[37]

Effects of AE on Morphological Outcomes

Body weight

Two studies compared the effects of AE versus no exercise on body weight.[31,35] No difference was found (weighted mean difference [WMD], 4.20 kg; 95% CI, −10.98, 19.39; n=68) (**Figure 2**).[31,35]

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Lox 1996	85.2	15.35	11	72.3	14.51	10	44.3%	12.90 [0.13, 25.67]
Smith 2001	82.4	12.9	18	85.1	12.4	29	55.7%	−2.70 [−10.18, 4.78]
Total (95% CI)			29			39	100.0%	4.20 [−10.98, 19.39]

Heterogeneity: Tau² = 93.17; Chi² = 4.27, df = 1 (P = 0.04); I² = 77%
Test for overall effect: Z = 0.54 (P = 0.59)
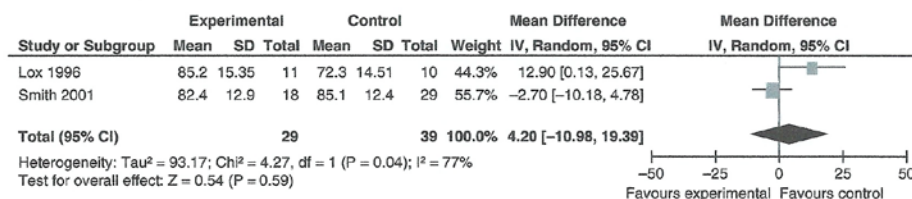
Figure 2. Aerobic exercise (AE) versus controls: body weight.

BMI

Four studies compared the effects of AE versus no exercise on BMI (**Table 4**).[31,33,35,36] Meta-analysis demonstrated a decrease in BMI with AE intervention compared with no exercise (WMD -1.31 kg.m^{-2}; 95% CI, -2.59, -0.03; n=186) (**Figure 3**).[31,33,35,36]

Triceps skinfold thickness of subcutaneous fat, waist to hip ratio, and waist circumference

Meta-analyses of 2 studies[31,33] found exercise training to be effective for all outcomes, with AE (compared with nonexercising controls) associated with a decrease in triceps SFT (WMD -1.83 mm;

95% CI, -2.36, -1.30; n=144) (**Figure 4**), WHR (standardised mean difference [SMD] -0.94; 95% CI, -1.30, -0.58; n=142) (**Figure 5**), and waist circumference (SMD -0.74 mm; 95% CI, -1.08, -0.39; n=142) (**Figure 6**).

Body fat mass (%)

Two studies evaluated the effects of AE on body fat mass (%), as calculated using SFT measures.[33,35] Meta-analyses found AE to decrease body fat mass (%) compared with nonexercising controls (SMD -0.37; 95% CI, -0.74, -0.01; n=118) (**Figure 7**).
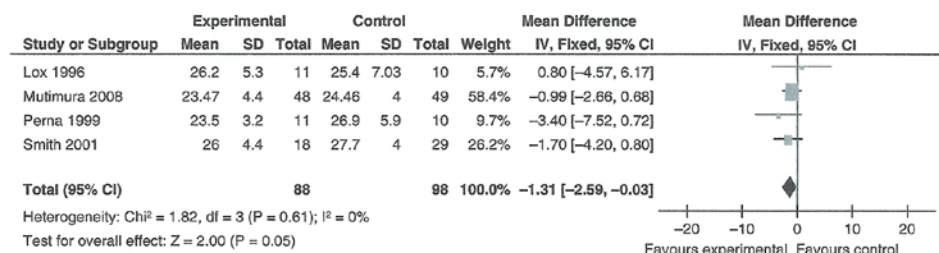
Figure 3. Aerobic exercise (AE) versus controls: body mass index (BMI).
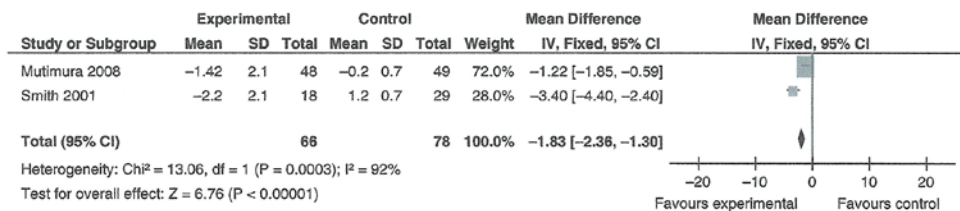
Figure 4. Aerobic exercise (AE) versus controls: triceps skinfold thickness of subcutaneous fat (SFT).
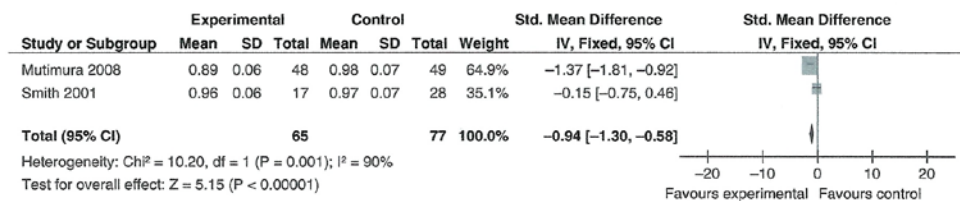
Figure 5. Aerobic exercise (AE) versus controls: waist to hip ration (WHR).

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| Study or Subgroup | Experimental | | | Control | | | Weight | Std. Mean Difference | Std. Mean Difference |
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI	IV, Fixed, 95% CI
Mutimura 2008	83	10.9	48	92.33	10.3	49	68.1%	−0.87 [−1.29, −0.46]	
Smith 2001	89.7	10.9	17	94.5	10.3	28	31.9%	−0.45 [−1.06, 0.16]	
Total (95% CI)			65			77	100.0%	−0.74 [−1.08, −0.39]	

Heterogeneity: Chi² = 1.27, df = 1 (P = 0.26); I² = 21%
Test for overall effect: Z = 4.20 (P < 0.0001)

Favours experimental Favours control

Figure 6. Aerobic exercise (AE) versus controls: waist circumference.

| Study or Subgroup | Experimental | | | Control | | | Weight | Std. Mean Difference | Std. Mean Difference |
	Mean	SD	Total	Mean	SD	Total		IV, Fixed, 95% CI	IV, Fixed, 95% CI
Lox 1996	18.66	5.91	11	15.03	8.57	10	17.8%	0.48 [−0.39, 1.35]	
Mutimura 2008	−1.5	3.3	48	−0.16	0.7	49	82.2%	−0.56 [−0.97, −0.15]	
Total (95% CI)			59			59	100.0%	−0.37 [−0.74, −0.01]	

Heterogeneity: Chi² = 4.48, df = 1 (P = 0.03); I² = 78%
Test for overall effect: Z = 2.00 (P = 0.05)

Favours experimental Favours control

Figure 7. Aerobic exercise (AE) versus controls: body fat mass (%).

Effects of PRE on Metabolic and Morphologic Outcomes

BMI

One study demonstrated a small increase in BMI with PRE compared to nonexercising controls.[35]

Body weight

Meta-analysis of 2 studies[34,35] demonstrated increased body weight for participants in PRE groups compared with nonexercise controls (WMD 5.09 kg; 95% CI, 2.13, 8.05; n=46) (**Figure 8**).

Girth

Girth measurements were performed in 2 studies,[34,35] but measurement methods varied. Meta-analyses demonstrated an increase in the sum of arm and thigh girth in PRE groups compared with nonexercise controls (SMD 1.08 cm; 95% CI, 0.35, 1.82; n=46) (**Figure 9**).

Effects of Combined AE and PRE on Metabolic and Morphologic Outcomes

Two studies examined the effects of combined training (**Table 3**). One study found no effect on blood lipids or glucose nor on dual energy x-ray absorptiometry (DEXA) or CT measures of fat.[30] The other study demonstrated no effect on body weight.[29]

Comparison of Effects of AE and PRE on Metabolic and Morphologic Outcomes

One study compared the independent effects of AE and PRE.[32] Both exercise modalities improved insulin-mediated glucose uptake with no differences between groups. Decreases in TC and LDL and increases in HDL were greater with AE than with PRE, with large effect sizes (**Table 4**). However, PRE increased lean body mass compared to baseline [mean 2.06 kg (95% CI, 0.8, 3.3 kg)], decreased total fat [−3.3 kg (−4.6, −2.0)], trunk fat [−2.50 kg (3.5, −1.5)], and limb fat mass [−0.75 kg (−1.1, −0.4)], whereas AE did not change these measures (data not reported).

DISCUSSION

The available evidence suggests AE and PRE are effective for improving some morphological complications of chronic, treated HIV infection. AE results in decreased BMI, waist circumference, body fat mass (%), WHR, and triceps SFT. Similarly,

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Lox 1996	2.12	2.1	12	−4.5	2.9	10	46.9%	6.62 [4.47, 8.77]
Spence 1990	1.7	2.1	12	−1.9	2.9	12	53.1%	3.60 [1.57, 5.63]
Total (95% CI)			24			22	100.0%	5.02 [3.54, 6.49]

Heterogeneity: Chi² = 4.01, df = 1 (P = 0.05); I² = 75%
Test for overall effect: Z = 6.66 (P < 0.00001)

Figure 8. Progressive resistive exercise (PRE) versus controls: body weight.

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Lox 1996	173.59	11.73	12	171.17	22.52	10	76.4%	0.13 [−0.71, 0.97]
Spence 1990	83.7	1.66	12	76.3	1.78	12	23.6%	4.15 [2.64, 5.66]
Total (95% CI)			24			22	100.0%	1.08 [0.35, 1.82]

Heterogeneity: Chi² = 20.69, df = 1 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.88 (P = 0.004)
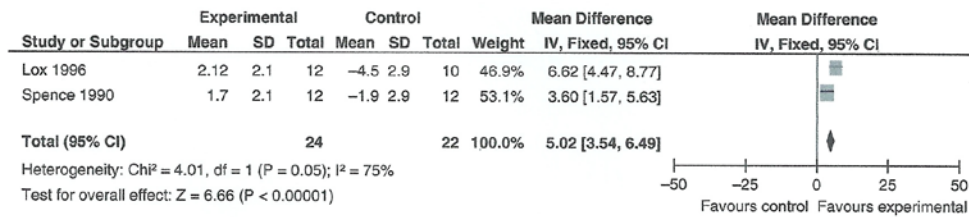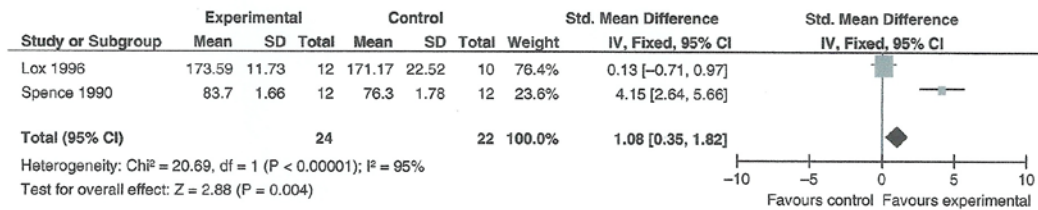
Figure 9. Progressive resistive exercise (PRE) versus controls: girth.

Table 3. Combined aerobic and progressive resistive exercise versus controls

Outcomes	Study	Treatment group	Control group	Effect size (95% CI)
Body weight, kg	Fillipas et al, 2006	1.97±3.53	−0.12±2.92	0.65 (−0.05, 1.31)
HDL, mmol/L	Dolan et al, 2006	0.026±0.225	0.078±0.236	−0.23 (−0.86, 0.42)
LDL, mmol/L	Dolan et al, 2006	0.08±0.56	0.026±0.564	0.09 (−0.55, 0.73)
Waist circumference, cm	Dolan et al, 2006	1.00±2.62	1.50±4.36	−0.14 (−0.77, 0.50)
DEXA total fat, kg	Dolan et al, 2006	−0.20±1.74	−0.70±3.05	0.20 (−0.44, 0.83)
CT SAT, cm²	Dolan et al, 2006	3.00±34.87	−14.00±56.67	0.36 (−0.29, 0.99)
CT VAT, cm²	Dolan et al, 2006	−2.00±30.50	8.00±30.51	−0.33 (−0.96, 0.32)

Note: Data expressed as mean ± SD. Change score data used to calculate effect sizes. HDL = high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; DEXA, dual-energy X-ray absorptiometry; CT SAT, computed tomography subcutaneous abdominal adipose tissue; CT VAT = computed tomography visceral abdominal adipose tissue.

Table 4. Comparison of progressive resistive exercise and aerobic exercise

Outcomes	Study	PRE group	AE group	Effect size (95%CI)
HDL, mmol/L	Lindegaard et al, 2008	0.05±0.018	0.09±0.04	−1.35 (−2.30, −0.26)
LDL, mmol/L	Lindegaard et al, 2008	0.16±0.15	−0.18±0.13	2.40 (1.09, 3.48)
TG, mmol/L	Lindegaard et al, 2008	−0.38±0.31	0.01±0.12	−1.57 (−2.54, −0.44)
TC, mmol/L	Lindegaard et al, 2008	−0.02±0.22	−0.16±0.14	0.74 (−0.25, 1.66)
Glucose, mmol/L	Lindegaard et al, 2008	−0.07±0.47	0.004±0.14	0.49 (−1.67, 0.25)

Note: Data are change from baseline expressed as mean ± SD. Change score data used to calculate effect sizes. HDL = high-density lipoprotein cholesterol; LDL = low-density cholesterol lipoprotein; TG = triglycerides; TC = total cholesterol.

PRE has been associated with increased body weight and arm and thigh girth. Studies examining combined AE and PRE in the context of HIV are inconclusive. Limited available evidence suggests AE may be more effective than PRE in improving TC and LDL, whilst PRE is more effective than AE for improving lean muscle mass and reducing fat mass. Data are limited regarding possible benefits of any type of exercise training on metabolic outcomes in this population. We found few studies where blood lipids and glucose were examined and none that included measures of bone health. Further work is needed to understand the effects of exercise intervention on these clinically important parameters in HAART-treated HIV patients.

This is the first review to evaluate systematically the published RCT evidence for exercise training alone on metabolic and morphological outcomes in HIV-infected individuals. Previous systematic[11,12] and narrative reviews[38] on the effects of exercise training in HIV-infected patients included studies combining physical training with another treatment/pharmacological modality, making effects attributable to exercise difficult to distinguish. The current systematic review aimed to delineate the effects of exercise alone on a broader range of morphological (including imaging) and metabolic (including blood lipids and glucose) outcomes using all available RCTs in HIV-infected adults.

AE Intervention

Aerobic exercise improves blood lipids in the general population[39] and is an essential part of any exercise regimen aiming to improve blood lipids. This review found only one study evaluating blood lipid and glucose parameters with AE compared to controls and found reductions in TG and glucose with moderate effect sizes.[33] Similar lipid changes were reported in a 4-month, nonrandomised trial of AE in HIV-infected adults,[40] but further, high-quality study in this area is needed before evidence-based, population-specific recommendations can be made.

AE improves body composition and fat distribution in healthy adults by reducing total body fatness and abdominal obesity.[41] We found similar anthropomorphic improvements on meta-analyses of studies performed in HIV-infected adults, including decreased BMI, triceps SFT, body fat mass (%), waist circumference, and WHR.

PRE Intervention

PRE improves lean muscle mass, strength, and overall metabolic state and reduces adiposity in the general population.[42] This suggests PRE could improve the body composition changes associated with HIV and HIV treatments. Meta-analyses performed here found body weight and girth measures to increase with PRE in HIV-infected adults. The included studies were conducted in the pre-HAART era. Nonetheless, the results demonstrate the utility of PRE for increasing body weight and muscle mass in the context of HIV-infection – outcomes that remain desirable in many HAART-treated patients today.

PRE can improve bone mineral density and overall skeletal health.[43,44] Increased prevalence of bone disorders (eg, osteoporosis and osteopenia) are reported in HAART-treated individuals.[45] A recent longitudinal study found PRE may protect against bone loss and improve bone mineral density in HIV-infected adults.[46] Unfortunately, despite the rising prevalence of bone disease among adults with HIV infection, no included study evaluated the impact of exercise training on bone structure or function.

Combined AE and PRE Intervention

Participation in combined AE and PRE training has recently been recommended for healthy adults and those living with chronic medical conditions.[9] Despite this, little information is available from randomised trials on the effects of combined training in HIV-infected populations. Only 2 studies met our inclusion criteria, and neither found any effect on metabolic nor morphological parameters.[29,30] Similarly, the DEXA and CT data available in 1 study did not find evidence of body composition change with combined training.[30] These findings are inconsistent with other published work. Both body and trunk fat decreased with 16 weeks of thrice weekly combined training in an open-label pilot study involving HIV-infected males with lipodystrophy,[47] and blood lipids and body adiposity decreased with 10 weeks of training.[22] Further study is needed to clarify the role of combined exercise training in managing the metabolic and morphologic abnormalities associated with HIV and HIV treatments.

Comparison of Effects of AE and PRE Interventions

One study compared the effect of AE to PRE in HIV-infected adults.[32] These modes of exercise training influenced blood lipid parameters differently. No body composition changes were observed on DEXA with 16 weeks of AE,[32] however increased muscle mass and a decrease in specific fat outcomes were observed with PRE. Although this is supported by similar findings in a nonrandomised trial of an 8-week PRE program in 25 HIV-infected adults,[48] more work is needed to understand the comparative effects of AE and PRE on blood lipid and body composition.

Limitations

This review only included 9 trials, with fewer than 500 participants overall. Meta-analyses were limited by differences in exercise interventions, outcome measures, and participants. No more than 4 studies could be included in any meta-analysis, with sample sizes ranging from 46 to 186 participants. Large withdrawal rates in some studies and lack of female participants may also reduce the generalisability of findings.

This review was also limited by the quality of the available studies. Trials were of short duration, limiting knowledge on the long-term effects of exercise training which is important in the management of chronic disease. All included studies provided simplistic exercise protocol descriptions. More precise information would allow a better understanding of the effects of each program on specific outcomes. No adverse events attributable to training interventions were seen in any trial. This suggests that the dosage, intensity, frequency, and type of exercise training were safe. However, as individuals living with HIV are becoming more complex, more detailed descriptions are warranted to enhance exercise prescription for this population.

Due to the small number of RCTs available, we included trials involving both HAART-treated and non–HAART-treated patients. Although some exercise training goals are universally applicable (eg, increasing endurance), patient treatment status may result in unique exercise training objectives. For example, in patients with untreated HIV, it is typically desirable to increase body weight. However reducing body weight and central fat may be the key aim in HAART-treated individuals.

We have taken care to perform and interpret meta-analyses taking this important point into consideration, with the aim of making the results relevant to current practice.

Although CT or MRI scanning are considered the gold standard for measuring central adiposity,[49] few trials used imaging to evaluate the impact of exercise on body composition. It was disappointing to find that no included studies evaluated effects of exercise training on bone health. Urgent attention is needed to address this data gap. Exercise training improves osteoporosis and osteopenia in the general population,[50] and impaired bone health is an emerging complication of chronic, treated HIV.[6]

CONCLUSION

Both AE and PRE can improve some morphological outcomes in HIV-infected individuals. Specifically, AE can improve body composition where overweight or central adiposity are of concern in HAART-treated individuals, while PRE can increase body weight and peripheral girths where reversal of muscular atrophy and weight gain are of priority. There is less available evidence for metabolic outcomes, however AE may be more efficacious than PRE on certain lipid subsets. No additional effects of combining AE and PRE on metabolic or morphologic outcomes are evident from the limited available literature. These preliminary findings need confirmation in larger, high-quality studies before evidence-based, population-specific guidelines can be developed. More emphasis is needed on improving trial quality, particularly performing intention-to-treat analyses and recruiting more participants to increase statistical power. Reporting of trials should follow the CONSORT statement.[51] With HIV management guidelines recommending earlier HAART initiation,[52] individuals on HAART are most likely to be included in future trials. Urgent work is needed to evaluate and quantify the effects of exercise training on metabolic outcomes such as blood lipids, glucose, and bone density.

ACKNOWLEDGMENTS

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Chapter 5 Physical Activity Participation and Cardiovascular Fitness in People Living with HIV: A One-Year Longitudinal Study

Despite increased longevity amongst those living with HIV infection since effective treatments became available, longitudinal data on the potential health benefits and risks associated with physical activity are lacking. Evidence-based health recommendations and interventions require knowledge of the effects of sustained, habitual physical activity. An increased understanding of the determinants of and barriers to participation in physical activity is also needed.

The paper presented within this Chapter aims to evaluate the relationships between physical activity/ cardiovascular fitness and body composition, body image and CVD risk, over a 12-month period. A secondary aim was to explore determinants associated with physical activity in HIV-infected individuals.

5.1 **Fillipas S**, Cicuttini FM, Holland AE and Cherry CL. Physical activity participation and cardiovascular fitness in people living with HIV: a one- year longitudinal study. Submitted to **HIV Medicine** May 2011.

As far as we know, this is the first study to document long term physical activity and cardiovascular fitness in a population with HIV. We observed a suboptimal level of participation in physical activity, with 19-27% of our cohort classified as "inactive". In this medically stable, HAART-treated cohort, both physical activity levels and cardiovascular fitness were relatively stable over the twelve months of study. Long term physical activity and cardiovascular fitness were found to have different relationships to body composition, and body image. Cardiovascular fitness was associated with improved body composition suggesting that HIV-infected individuals should be encouraged to improve and maintain cardiovascular fitness, whilst improving physical activity levels were associated with improved perceived body image, supporting the

uptake of physical activity to improve this aspect of psychological well being. We did not find an obvious association between CVD risk and either physical activity or cardiovascular fitness in this medically stable cohort, however this does not preclude the possibility that an exercise intervention may be useful as part of an overall strategy aiming to improve CVD risk in an inactive cohort. Finally, our finding that being in a permanent relationship was associated with higher levels of physical activity suggests that HIV-infected individuals who are socially isolated may be at risk of inactivity. Interventions may need to be targeted to this group to prevent adverse health consequences of inactivity. Future studies should involve larger intervention studies and studies of longer duration to reveal potential effects of both long term physical activity and cardiovascular fitness amongst those with chronic HIV infection.

Declaration for Thesis Chapter 5

Monash University

Declaration for Thesis Chapter 5: Physical Activity Participation and Cardiovascular Fitness in People Living with HIV: A One- Year Longitudinal Study

Declaration by candidate

In the case of Chapter 5 the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Consent, data collection, data synthesis and analysis, writing the manuscript	70%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Flavia Cicuttini	Study concept and design, revision of manuscript	
Catherine Cherry	Study concept and design ,Revision of manuscript	
Anne Holland	Revision of manuscript	

Candidate's Signature	[signature redacted]	Date 17·4·20 11
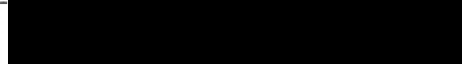
Declaration by co-authors

The undersigned hereby certify that:

(19)   the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(20)   they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(21)   they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(22)   there are no other authors of the publication according to these criteria;

(23)   potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(24)   the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	The Alfred Hospital, Melbourne

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

Signature 1	[signature redacted]	Date 3/4/11
Signature 2	[signature redacted]	15/4/11
Signature 3	[signature redacted]	15/4/11

Physical activity participation and cardiovascular fitness in people living with HIV: a one- year longitudinal study

Short title: Physical activity and HIV

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Abstract

Objective: Physical activity and cardiovascular fitness are beneficial for HIV-infected individuals, however long-term effects are unknown. This 12 month study aimed to document long-term habitual physical activity and cardiovascular fitness in stable, HAART-treated individuals with HIV, explore relationships to body composition, body image and cardiovascular disease (CVD) risk and evaluate physical activity determinants.

Methods: Eighty adults participated. Physical activity was reported using the International Physical Activity Questionnaire and cardiovascular fitness assessed using the Kasch Pulse Recovery Test.

Results: 19-37% participants reported suboptimal physical activity levels at each study visit, while physical activity and cardiovascular fitness were largely stable over the study period. Higher cardiovascular fitness was associated with better body composition and this association persisted over time (p<0.03 for all). Greater total energy expenditure was associated with improved body image (r=-0.325, p=0.027) but not CVD risk. Being in a permanent relationship was independently associated with higher levels of physical activity.

Conclusions: This study found benefits for both long-term physical activity and cardiovascular fitness for chronic HIV-infection.

Introduction

The introduction of highly active antiretroviral therapy (HAART) has reduced the morbidity and mortality associated with human immunodeficiency virus (HIV)(1). However, patients still suffer a serious chronic disease, with a range of physical and psychological complications. Increased cardiovascular disease (CVD) risk and emerging metabolic and morphological complications associated with the virus and its treatment are of particular significance(2). People living with HIV are also susceptible to a range of psychological problems, particularly related to the profound body composition changes commonly observed(3).

Pharmacological interventions may mitigate some HIV and HAART-related problems, but are associated with financial costs and potential toxicities. Optimizing physical activity and cardiovascular fitness are non-pharmacological strategies that can improve many physical and psychological outcomes in the general population(4) and the available data suggest likely benefits for those with HIV(5-6). Physical activity is defined as "any bodily movement produced by skeletal muscles that results in energy expenditure"(7) whilst cardiovascular fitness is "a set of attributes that people have or achieve that relates to the ability to perform physical activity"(7). These concepts are closely related, but may result in different health outcomes.

Data are lacking on relationships between longer-term patterns of physical activity and cardiovascular fitness and clinically relevant outcomes for the HAART-treated HIV patient. Truly evidence-based health recommendations/interventions require knowledge of the effects of sustained, habitual physical activity and an understanding of the determinants of and barriers to participation in physical activity in the relevant patient population.

This study aimed to document habitual physical activity participation and cardiovascular fitness over 12 months in a cohort of medically stable, HAART-treated, HIV-infected adults and explore relationships between physical activity and cardiovascular fitness and body composition, perceived body image and CVD 10-year risk, in this population. Determinants associated with physical activity in HIV-infected individuals were also explored.

Methods

This was a 12 month prospective, longitudinal cohort study. Ambulant HIV-infected adults (aged $\geq$18 years) on HAART were recruited from The Alfred Hospital Infectious Diseases clinic and local HIV community clinics in March-October 2007. Exclusion criteria were contraindications to submaximal exercise testing/training(8). The study was approved by the local Human Ethics Committee and all participants gave written, informed consent to participate.

Variables measured

All questionnaires and cardiovascular fitness testing were administered by a physiotherapist at baseline, six and 12 months.

Physical activity: The International Physical Activity Questionnaire- long form (IPAQ) was used to estimate physical activity(9). Participants were classified as 'active' when their energy expenditure met the moderate and highly active IPAQ category definitions and 'inactive' if energy expenditure was in the low category(9).

Cardiovascular fitness: The Kasch Three Minute Step Test(10) was used as an estimate of cardiovascular fitness . The score of the test was the one-minute post recovery heart rate, measured in beats per minute (bpm).

Body composition: Height, weight, waist to hip ratio (WHR) and waist circumference (cm) were measured with subjects standing wearing light clothing and no shoes(11). Height and weight were measured to the nearest 0.1cm and 0.1kg, respectively. Body Mass Index (BMI) was calculated (weight/height^2) (kg/m^2).

Body image: The Body Image Scale (BIS) is a 12-item, disease-specific, valid and reliable tool that measures perceived body image along five dimensions (comfort, competence, appearance, predictability, existential self). Each item utilises a five point visual analogue scale and scores range from 12 to 60 (higher scores reflect poorer body image)(12).

Cardiovascular Disease Risk: CVD 10-year risk score was estimated using the Framingham equation (13) incorporating age, gender, systolic blood pressure (mm/Hg), total cholesterol (TC) (mg/dL) and high–density lipoprotein cholesterol (HDL-chol) (mg/dL), treatment for hypertension (yes/no) and current smoking status (yes/no). The Framingham score estimates 10–year risk for cardiac events and has been widely used in HIV-infected populations(14).

Demographic: Clinical and laboratory details were collected by patient questionnaire and medical record review. Self-report data included education level (<11th grade versus ≥high school graduate), race/ethnicity (Caucasian or other), CVD (past history of CVD event), diabetes, current relationship status (stable relationship versus single), current depression, current smoking status, current recreational drug use and employment (full-time/ part-time or unemployed). Data collected form the medical record included CD4 cell count (cells/mm^3), HIV RNA viral load (copies/mL), time living with HIV(years), HIV acquisition risk [males who have sex with males (MSM), heterosexual, unknown and other] and current HAART use (yes/no).

Statistics:

Outcome variables were assessed for normality and active and inactive participants compared with Mann-Whitney U or chi-square tests as appropriate. Relationships between physical activity and cardiovascular fitness and dependent variables were assessed using Spearman's correlations, adjusting for age where appropriate. Multivariate analyses used generalised

linear modelling and repeated measures (Friedman's Test was used with non parametric data). A two-sided p-value of 0.05 was considered statistically significant. Analyses were performed using SPSS (standard version 18.0, SPSS, Chicago, IL, USA).

Results

Eighty individuals participated. At six months, five participants (four males, one female) withdrew from study. One subject died before his 12 month assessment, so 74 individuals completed all study visits. Demographics are shown in Table 1. Participants who completed the study were demographically similar to those who withdrew (data not shown).

Almost one fifth of participants were classified as inactive at baseline (low levels of physical activity reported on the IPAQ) with a greater proportion of inactive participants at both six and 12 months (37% and 27% respectively) (Table 2).

Both physical activity levels and cardiovascular fitness (post step test heart rate) were relatively stable over the 12 months of study (Table 3). Reported levels of physical activity (total energy expenditure) were somewhat lower at six month visits, most of which occurred at the hottest time of year in Melbourne, than at baseline and 12 month visits, which were generally during cooler months (p=0.017) (Table 3).

Greater cardiovascular fitness was associated with better body composition measures at baseline. These relationships persisted at 12 months (Table 4) and were independent of patient age.

No association between cardiovascular fitness and body image was observed, however the longitudinal study design demonstrated an inverse correlation between change in total energy expenditure and change in body image (r=-0.325, p=0.027). Increases in physical activity were associated with improvements (lower numbers) in body image.

We found no association between any self-reported physical activity variable or cardiovascular fitness and calculated CVD 10-year risk (p>0.05 for all).

Neither HIV disease markers (CD4 cell count and HIV RNA viral load) nor known determinants of physical activity in the general population (education, age, smoking and depression(15)) were associated with self-reported physical activity level in this cohort. At baseline, the proportion of subjects in a permanent relationship was higher among active versus inactive participants [47.7% versus 13.3% (p=0.032)]. A similar trend was seen at six and 12 months.

Discussion

This is the first study to describe longer-term physical activity participation and cardiovascular fitness in a medically stable cohort of HAART-treated HIV–infected adults. It identifies benefits for both long-term physical activity and cardiovascular fitness for those with HIV. We found a concerning sub-set of patients who persistently reported inactivity, while habitual physical activity participation and cardiovascular fitness were generally stable over 12 months. Higher levels of cardiovascular fitness were associated with better body composition. Moreover, we demonstrated that increasing total energy expenditure was associated with improving body image. Conversely, we found no association between either physical activity and cardiovascular fitness and 10-year CVD risk. Exploration of physical activity determinants was limited due to most participants being active, nonetheless being in a permanent relationship was associated with higher levels of physical activity.

Habitual physical activity participation levels changed little over 12 months in this medically-stable cohort of HIV-infected patients. Energy expenditure compared favourably to that reported in healthy adults in a previous study of IPAQ validity/reliability (2514METmins/wk)(9). Nonetheless, a concerning 19-37% of participants were inactive at each study visit, consistent with rates of physical inactivity we and others have previously reported in cohorts with HIV(16-18). This inactive subset could benefit most from physical activity interventions aiming to prevent or ameliorate a range of HIV-associated morbidities.

Cardiovascular fitness was associated with improved body composition measures, a finding that persisted over time. This is consistent with short-duration intervention studies demonstrating positive effects on body composition from improved cardiovascular fitness in

HIV(6). Our finding implies that improving cardiovascular fitness, not just increasing energy expenditure, may be a useful long-term strategy to improve body composition in HIV.

We demonstrated an association between increasing energy expenditure and improved body image in HIV-infected individuals. This is consistent with the limited findings available from HIV-negative cohorts,(19) and the only previously published trial evaluating effects of exercise training on body image in HIV-infected adults(20). Morphological changes associated with HIV and HAART profoundly affect body image and influence health-related quality of life(3, 21). Further exploration of the role of physical activity in improving body image in HIV is warranted.

Physical activity and cardiovascular fitness are beneficial in the general population, reducing CVD risk through their effect on several modifiable risk factors(22). Similar benefits for those with HIV have also been proposed (23-24), however relationships between physical activity and estimated CVD 10-year risk per se have not been investigated. Physical activity is not included in the Framingham Equation. Nonetheless, we hypothesized that overall physical activity and cardiovascular fitness may be associated with estimated CVD risk through their expected influence on included variables, notably blood lipids and blood pressure(22). In this study, no clear association between physical activity and cardiovascular fitness and CVD risk was observed in a medically-stable cohort. However, this does not preclude possible benefits from an exercise intervention as part of an overall strategy to improve CVD risk among inactive individuals.

Being in a permanent relationship was the only determinant of higher physical activity levels observed in this study. Few studies have evaluated factors associated with physical activity

behaviours in people with HIV(25-26),but social support is known to help sustain physical activity participation in other chronic diseases(27). Targeting HIV patients with inadequate social support may be useful to identify those at risk of inactivity. We did not observe associations between physical activity and known general population physical activity determinants (age, education, smoking)(15, 28) or HIV disease markers (CD4 count, HIV viral load, years living with HIV). This relative lack of variation in physical activity patterns in our cohort may have limited our power to observe such relationships, if they exist.

Limitations of this study include the modest sample size and observational design (precluding assessment of causality). Although we had a high follow-up rate, our results may have suffered from a type II error. Even a small number of withdrawals may have reduced power to detect changes in our main outcome measures. Some measurement error may have occurred due to use of self report methods of physical activity and submaximal exercise testing of cardiovascular fitness. The generalizability of results is limited by low numbers of female participants. Additionally, longer follow up may be required to detect changes in a medically-stable population

In this stable, HAART–treated HIV–infected cohort a sub-optimal level of physical activity participation was observed in more than one-fifth of participants. Cardiovascular fitness was associated with improved body composition, suggesting HIV- infected individuals should be encouraged to improve and maintain cardiovascular fitness. Similarly, increasing physical activity levels were associated with improved perceived body image, supporting use of physical activity to improve this aspect of psychological well being. Despite convincing evidence that physical activity and cardiovascular fitness are associated with reduced CVD risk in the general population, we did not confirm this in medically-stable HIV patients over

12 months. Finally, our finding that being in a permanent relationship was associated with higher physical activity levels suggests social isolation may be risk factor for inactivity in those with HIV. Further work, including larger cohorts and longer follow up is needed to explore factors that influence physical activity and cardiovascular fitness in HIV. Intervention studies are required to define the benefits obtainable for improving long-term physical activity uptake and cardiovascular fitness in this population.

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Table 1 Baseline characteristics of participants [a]

Characteristic	n=80
Age years	49.3 (9.8)
Gender males n (%)	75(93.8)
Height m	1.76 (0.09)
HIV years	13.75(0.6-25)
CD4 count (cells/mm^3)	429(7-1145)
Undetectable HIV RNA viral load (less than 50 copies/ml) n (%)	58(71.6)
Race n (%) Caucasian Other [b]	 73 (91.3) 7 (8.8)
HIV risk group n (%) Males who have sex with males Other [c]	 69(86.3) 11(13.5)
Depression n (%)	30 (37.5)
Diabetes n (%)	7(8.8)
Cardiovascular disease n (%)	4(5)
Recreational drug use n (%)	30(37.5)
Employment n (%)	29(36.3)
Relationship n (%)	33(41.3)
Education n (%) 11th grade or less High school graduate or above	 34/80(42.5) 46/80(57.5)
Smoker n (%)	40 (50)

[a] Normally distributed variables are shown as mean (standard deviation) and non normally distributed variables as median (range); [b] other racial groups were Aboriginal, Asian and other; [c] other HIV transmission groups were heterosexual, unknown and other

Table 2 IPAQ physical activity categories

IPAQ CATEGORY	BASELINE %	6 MONTHS[1] %	12 MONTHS[2] %
LOW	19	37	27
MODERATE	31	34	21
HIGH	50	28	51
ACTIVE[3]	81	63	73

[1]75 participants remaining in study, IPAQ data available in 67(participants left in study did not differ from those who withdrew or who did not provide data);

[2]74 participants remaining in study, IPAQ data available in 70(participants left in study did not differ from those who withdrew or who did not provide data);

[3]Active =moderate or high levels of PA reported by the IPAQ

Table 3 IPAQ (continuous data) and cardiovascular fitness post test heart rate
[1]

IPAQ VARIABLE	BASELINE median (range)	6 MONTHS median (range)	12 MONTHS median (range)
Total PA METmins/week	3000.7 (0-39,408)	1937(0-27,888)	3125.25(0-39,408)
Vigorous METmins/week	0 (0-14,400)	0(0-20,160)	0(0-22,320)
Moderate METmins/week	1470 (0-14,160)	750(0-15120)	1320(0-16,080)
Leisure METmin/week	918(0-5508)	462(0-4794)	565.5(0-5508)
Walk METmins/week	717.5(0-13,860)	528(0-5544)	750.75(0-13,860)
Sitting weekly duration (minutes)	2280 (70-7560)	2520(0-5880)	2400(70-7140)
Post test heart rate (bpm)	113.1 (21.6)	113.3 (20.4)	109.6(17.9)

[1] IPAQ data show median (range) and cardiovascular fitness post test heart rates show mean (SD)

Table 4 Relationship between baseline physical activity/cardiovascular fitness (post test heart rate) and body composition measures at baseline and 12 months[1]

	Baseline				12 months			
	Weight (kg)	BMI (kg/m^2)	Waist (cm)	WHR	Weight (kg)	BMI (kg/m^2)	Waist (cm)	WHR
Total PA METmins/week	0.144 P=0.213	0.163 P=0.157	0.024 P=0.836	-0.031 P=0.791	0.141 P=0.287	0.118 P=0.373	-0.034 P=0.799	-0.061 P=0.648
Post-test HR (bpm)	0.324 p=0.005[2]	0.354 p=0.002[2]	0.046 P=0.000[2]	0.416 p=0.000[2]	0.306 P=0.012[2]	0.270 p=0.027[2]	0.316 p=0.015[2]	0.553 p=0.000[2]

[1] Partial correlations performed adjusting for age ; [2]CVF (post-test HR) but not reported level of PA was associated with improved body composition, a relationship that was stable over time

Chapter 6 Body Composition and Knee Structure in Human Immunodeficiency Virus

Central obesity, also referred to as android obesity, is a common and concerning body composition abnormality observed in patients with HIV infection[5]. Central adiposity is associated with metabolic and cardiovascular complications in the HIV-infected population, including increased risks of diabetes, ischemic heart disease and stroke[8]. Obesity is also a major risk factor for OA in the general population[134-135] and it is possible that the body composition changes, seen in HIV infection, including central obesity, could be having an adverse effect on joints in this population.

Osteoarthritis is strongly associated with various body composition changes, including obesity [134-135] however this relationship has not been explored in HIV infection. To date, most musculoskeletal research in patients with HIV has been on opportunistic bone infections, osteonecrosis and more recently osteopenia and the risk of osteoporosis[14]. Given that anthropometric abnormalities including central adiposity, overweight and obesity are common among HAART-treated, HIV-infected individuals, it is plausible that they may be at an increased risk of knee OA. This relationship has not previously been examined.

The paper presented within this Chapter aims to examine relationships between body composition and knee cartilage volume, as assessed by magnetic resonance imaging (MRI) in HIV infection.

6.1 **Fillipas S**, Tanamas S, Davies-Tuck ML, Wluka AE, Wang Y, Cherry CL, Holland AE, Cicuttini FM .The relationship between body composition and knee structure in patients with Human Immunodeficiency Virus. Submitted to **J Rheumatology** May 2011.

Thirty five asymptomatic HIV-infected adult men and 18 healthy male controls matched for age and BMI were studied. We found body composition differences between those with stable HAART-treated HIV infection and controls. Specifically, HIV-infected males has less total body and gynoid fat (kg) and more percent android fat mass and percent trunk fat mass than controls. In HIV-infected males, total body fat mass was inversely associated with average tibial cartilage volume (R=-8.01, 95% Confidence interval -15.66, -0.36). Additionally, android fat mass was inversely associated with average tibial cartilage volume (R=-90.91, 95% confidence interval -158.66, -23.16). This finding is an early feature of early knee OA and this may be of future significance in the management of HIV-infected individuals. This patient group may be predisposed to OA and strategies aimed at avoiding or reducing abdominal obesity, such as physical activity should be encouraged. Further work is warranted to clarify this.

Declaration for Thesis Chapter 6

Monash University

Declaration for Thesis Chapter 6: Body Composition and Knee Structure in Human Immunodeficiency Virus

Declaration by candidate

In the case of Chapter 5 the nature and extent of my contribution to the work was the following:

Nature of contribution	Extent of contribution (%)
Consent, data collection, data synthesis and analysis, writing the manuscript	50%

The following co-authors contributed to the work. Co-authors who are students at Monash University must also indicate the extent of their contribution in percentage terms:

Name	Nature of contribution	Extent of contribution (%) for student co-authors only
Stephanie Tanamas	Data analyses, revision of manuscript	20%
Miranda Davies-Tuck	Data collection, revision of manuscript	2.5%
Anita Wluka	Revision of manuscript	
Yuanyuan Wang	Data analyses , revision of manuscript	

Catherine Cherry	Revision of manuscript	
Anne Holland	Revision of manuscript	
Flavia Cicuttini	Study concept and design, revision of manuscript	

Candidate's Signature	██████████	**Date**	17. 4. 2011

Declaration by co-authors

The undersigned hereby certify that:

(25) the above declaration correctly reflects the nature and extent of the candidate's contribution to this work, and the nature of the contribution of each of the co-authors.

(26) they meet the criteria for authorship in that they have participated in the conception, execution, or interpretation, of at least that part of the publication in their field of expertise;

(27) they take public responsibility for their part of the publication, except for the responsible author who accepts overall responsibility for the publication;

(28) there are no other authors of the publication according to these criteria;

(29) potential conflicts of interest have been disclosed to (a) granting bodies, (b) the editor or publisher of journals or other publications, and (c) the head of the responsible academic unit; and

(30) the original data are stored at the following location(s) and will be held for at least five years from the date indicated below:

Location(s)	The Alfred Hospital, Melbourne

[Please note that the location(s) must be institutional in nature, and should be indicated here as a department, centre or institute, with specific campus identification where relevant.]

		Date
Signature 1	██████████	13/4/11
Signature 2	██████████	5/4/11
Signature 3	████████	4/4/11
Signature 4	████	4.4.11
Signature 5	████████████	15/4/11
Signature 6	███████████	15/4/11
Signature 7	██████	3/4/11

The relationship between body composition and knee structure in patients with human immunodeficiency virus

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Abstract

Objective: Obesity is a risk factor for osteoarthritis (OA). Highly active antiretroviral therapy (HAART) treated HIV- infected patients are frequently affected by overweight and obesity, and may be at increased risk of OA. BMI, however is a measure which does not discriminate adipose from non-adipose body mass, or fat distribution, which may have different effects. This study aimed to examine relationships between body composition and knee cartilage volume, as assessed by magnetic resonance imaging (MRI) in HIV infection.

Methods: 35 HAART-treated HIV-infected males aged 35-65 years and 18 healthy males aged 35-63 years participated. Cartilage volume was measured on MRI of the dominant knee using validated methods. Body composition was measured using dual x-ray absorptiometry.

Results: HIV-infected participants had less total body and gynoid fat (kg) ($p=0.04$ and $p=0.007$ respectively) and more percent android fat mass and percent trunk fat mass ($p=0.001$ and $p<0.001$ respectively) than controls. In HIV-infected participants there was an inverse association between total body fat mass and average tibial cartilage volume (R= -8.01, 95% CI -15.66, -0.36). Also, in HIV–infected participants there was an inverse association between android fat mass and average cartilage volume (R=-90.91, 95% CI -158.66,-23.16).

Conclusion: This preliminary study found that both total body and android fat mass were inversely related to average knee cartilage volume in ambulant, HAART- treated HIV-infected adults. These findings are features of early knee OA and this may be of future significance in HIV.

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Introduction

HIV (human immunodeficiency virus) infection has become a chronic, manageable illness since the introduction of highly active antiretroviral therapy (HAART) (1). With increased survival, patients continue to experience the common chronic diseases. Central obesity, also referred to as central fat accumulation, android, abdominal or truncal obesity, is commonly seen in patients with HIV-infection and is a recognised feature of the anthropometric changes observed in the metabolic syndrome referred to as HIV lipodystrophy (2) . Consistent with findings in the general population, android obesity is associated with metabolic and cardiovascular complications in the HIV-infected population, including increased risks of diabetes, ischemic heart disease and stroke (3).

People living with chronic HIV-infection are also susceptible to a range of musculoskeletal diseases. Whilst the focus of most musculoskeletal work in patients with HIV has been on opportunistic bone infections, osteonecrosis and more recently osteopenia and the risk of osteoporosis (4), there has been no work examining the risk of osteoarthritis (OA). However, with the advent of very effective treatment of HIV and the improved clinical outcomes in patients with HIV, the impact of chronic diseases is becoming a major issue. This is particularly evident in the case of cardiovascular disease and diabetes that are associated with the HIV lipodystrophy syndrome and the related problems of central fat accumulation. Osteoarthritis is the most common form of arthritis, and is often accompanied by other components of the metabolic syndrome.

Although obesity is a risk factor for OA, the emerging evidence suggests the mechanism by which obesity increases OA risk is not simply an effect of increased loading on the joints but may also be associated with metabolic factors (5). For example, obesity is associated with the

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development of OA in non-weight bearing joints in the hand (5) and central adiposity has been shown to be a risk factor for knee and hip replacements (6). Given that HAART-treated HIV- infected patients are frequently affected by morphologic problems including central adiposity, overweight and obesity (7), they may be at increased risk of OA. Using magnetic resonance imaging (MRI), it is possible to identify early cartilage changes associated with knee OA even prior to the onset of clinical disease. Thus the aim of this study was to examine the relationship between body composition and knee cartilage volume (using MRI as a sensitive, non-invasive measure) in ambulant, HAART-treated HIV-infected adults and controls.

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Materials and Methods

Subjects

Thirty five asymptomatic HIV-infected adult men and 18 healthy male controls matched for age and BMI were studied. HIV–infected participants were recruited through the Alfred Hospital and local HIV specialist clinics between March and October 2007. HIV- infected males had stable, HAART-treated HIV infection. Controls were initially recruited for a study of the relationship between obesity and musculoskeletal diseases by advertising in the local press, at the hospitals in the waiting rooms of private weight loss/obesity clinics, and through community weight loss organisations. Exclusion criteria for both patient groups included physician diagnosed arthritis, prior surgical intervention to the knee, previous significant knee injury requiring non weight bearing therapy, knee pain precluding weight-bearing activity for >24 hours or prescribed analgesia, malignancy, inability to complete the study or contraindication to MRI. The study was approved by the Alfred Human Research and Ethics Committee, the Monash Standing Research Ethics Committee and Austin Health Human Research and Ethics Committee. All participants gave written, informed consent.

Anthropometric data

Weight was measured to the nearest 0.1 kg using a single pair of electronic scales. Height was measured to the nearest 0.1 cm using a stadiometer. BMI (weight/height^2 kgm^{-2}) was calculated.

Body composition

Body composition was measured using dual x-ray absorptiometry (GE Lunar Prodigy, using operating system version 9). The machine has a weight limit of approximately 130 kg. Standard regional analyses were used to measure total body, trunk, android and gynoid fat

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mass. Android fat mass refers to adipose tissue that accumulates in the abdomen region (8). Gynoid fat mass refers to adipose tissue accumulation around the hips (9). Total limb lean tissue mass was calculated as the sum of upper-limb lean tissue mass and lower-limb lean tissue mass. Short-term coefficients of variation, assessed in 15 normal young adults, were 1.2% for total body fat mass, 0.4% for total body lean tissue mass (10).

Magnetic resonance imaging (MRI)

For the HIV-infected participants, an MRI of the dominant knee of each participant was performed on a 1.5-T whole body MRI unit (Phillips, Medical Systems, Eindhoven, the Netherlands). The following sequence and parameters were used: a T1-weighted fat suppressed 3D gradient recall acquisition in the steady state; flip angle 55 degrees; repetition time 58 msec; echo time 12 msec; field of view 16 cm; 60 partitions; 512 x 512 matrix; one acquisition time 11 min 56 sec. Sagittal images were obtain at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 x 0.31 mm (512 x 512 pixels). For the controls, an MRI of the dominant knee was performed in the sagittal plane on a 1.5-T whole body magnetic resonance unit (Signa Advantage GE Medical Systems Milwaukee, WIS) with use of a commercial transmit-receive extremity coil as previously described (11). The following image sequence was used: a T1-weighted fat saturation 3D gradient recall acquisition in the steady state; flip angle 55 degrees; repetition time 58 msecs; echo time 12 msec; field of view 16 cm; 60 partitions; 512 x 512 matrix; acquisition time 11 min 56 sec; one acquisition. Sagittal images were obtained at a partition thickness of 1.5 mm and an in-plane resolution of 0.31 x 0.31 (512 x 512 pixels).

Cartilage volume was determined by manually drawing disarticulation contours around the cartilage boundary, using independent workstation software Osiris. Measurement was done by one trained observer with random cross checks blindly performed by an independent

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trained observer. The coefficient of variation (CV) was 2.1% (12). Tibial bone plateau area was determined using the independent workstation Osiris, by creating an isotropic volume from the input images, which were reformatted in the axial plane. One trained observer performed the measurements, with random cross checks blindly performed by an independent trained observer. The CV was 2.3% (12).

Statistical Analysis

The characteristics of the study population were tabulated. Difference between cases and controls were calculated using the independent samples t-test. Average cartilage volume was calculated by dividing total tibial cartilage volume by tibial plateau bone area, which allows adjustment of cartilage volume for bone size. Linear regression was used to assess relationships between body composition measurements and average cartilage volume. The multivariate model was adjusted for age and BMI. A p value of less than 0.05 (two-tailed) was considered statistically significant. All analyses were performed using the SPSS statistical package (standard version 18.0, SPSS, Chicago, IL, USA).

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Results

Thirty five HAART-treated HIV-infected males and 18 controls took part. Characteristics of study participants are presented in Table 1. HIV- infected participants had a recent plasma viral load below detection and the median CD4 T-cell count was 538 cells/mm^3 (IQR 405-797cells/mm^3). Median duration of known HIV infection was 15 years.

Controls and patients were similar with regards to age, average BMI and tibial cartilage volume (Table 1). Despite these similarities, body composition differed substantially between groups. HIV-infected participants had less total body fat and gynoid fat (kg) (Table 1). Additionally, HIV-infected participants had a higher percentage of android fat (mean 12.85 versus 10.57; p=0.001 for difference) and percentage trunk fat (mean 68.29 versus 60.10; p<0.001 for difference) compared with controls.

We analysed the relationship between fat and lean tissue mass and average tibial cartilage volume (Table 2). When adjusted for age and BMI, average tibial cartilage volume was decreased with increasing total body fat mass (Regression coefficient -8.01, 95% CI -15.66, -0.36) in the HIV-infected participants. This remained significant when further adjusted for total body lean tissue mass (Regression coefficient -8.40, 95% CI -16.33, -0.47).

Moreover in HIV–infected participants, there was also an inverse association between android fat mass and cartilage volume, independent of age and BMI. No significant relationships were found for controls.

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Discussion

We found significant body composition differences between adult men with stable HAART-treated HIV infection and controls. Despite BMI being similar in both groups, HIV –infected males had lower total body and gynoid fat mass (kg) but higher percent android and percent trunk fat mass. Total knee cartilage volume was similar in both groups but the relationships between body composition and knee structure were different. We found both total body fat and android fat were inversely associated with knee cartilage volume in HIV-infected individuals but not controls.

In this study of stable, HAART-treated HIV-infected males, we found body composition abnormalities of adipose tissue, similar to those described by others (2). We demonstrated android fat mass, measured using DEXA, to be inversely associated with knee cartilage volume, suggesting that central fat accumulation associated with HAART may predispose HIV-infected patients to reduced knee cartilage volume, which has been associated with the onset of knee OA in other populations (13). Importantly, these relationships between body composition and knee structure were independent of body size. In contrast, no similar relationship was seen in controls. This may be likely due to the modest number of controls studied. Nonetheless, our results suggest that the health consequences of central adiposity in HIV- infected individuals may include an increased risk of OA. This is consistent with what has been observed for other chronic diseases, such as diabetes and ischemic heart disease where the relationship between risk factors and disease development is similar in both HIV-infected and non HIV- infected individuals. Given the well documented problem of fat redistribution in HIV- infected individuals, the present findings suggest that this population may be at increased risk of knee OA.

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The mechanism by which android obesity is associated with less cartilage volume in HIV – infected individuals warrants further investigation. It is well recognised that obesity is associated with early structural changes of the knee joint due to increased mechanical load, however there is growing evidence implicating systemic processes of adipose tissue. We found android obesity, despite similar BMI, to be associated with reduced cartilage volume, suggesting that other mechanisms, such as the systemic impact of adipose tissue, perhaps by adipokines, may play a role in joint damage. The anatomical distribution of adipose tissue in the visceral region is associated with multiple adverse health complications, including metabolic abnormalities (14). Indeed, the health risks associated with android adipocytes have been well documented, and may be attributable to the fact that they are prone to the release of free fatty acids (14). Of key importance, is our emerging understanding of adipose tissue as a metabolically active tissue, releasing hormones and cytokines and other important mediators of metabolism, known as adipokines (15). These metabolic processes contribute to OA, which is now considered a metabolic disease (15). Given the metabolic disturbances observed in HIV- infected individuals, it is plausible that such pathways may adversely affect joint structure in this patient group. The exact mechanism (increased load, metabolic or a combination of both) by which adipose tissue affects joint structure, in HIV- infected individuals requires further exploration.

This study has a number of limitations; notably the modest sample size and its cross-sectional nature. In addition, we limited our investigations to adult men with HAART-treated HIV, so findings may not be generalisable to other groups. Additional investigation is required to understand relationships between knee structure and HIV-related factors in women and in those not using HAART. However it is likely that the relationships we observed relate to the fat distribution which is related to combination antiretroviral therapy use rather than the

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individual medications per se. Our findings warrant confirmation in a larger cohort studies, also allowing exploration of the effects of specific HIV treatments on knee structure. Due to low numbers, we also had a limited ability to show relationships or variations in body fat distribution in controls. Finally, our ability to compare measures of cartilage volume between groups directly was limited because different MRI machines were used in the two groups studied, however, this should not affect the association between body composition and average cartilage volume within each separate group. Furthermore, the average cartilage volume was similar in both groups.

We found abdominal obesity, commonly observed in HIV- infected individuals, to be associated with reduced knee cartilage volume in adult men with HAART-treated HIV. These MRI findings suggested that common body composition abnormalities observed in HAART-treated cohorts may predispose people living with treated HIV to knee OA. These findings need confirmation in larger studies. Meanwhile, efforts to avoid abdominal obesity in people living with HIV may offer some protection against knee OA.

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Table 1. Comparison of characteristics between HIV- infected males and controls

	Cases (n=35)	Controls (n=18)	P-value
Age (years)	51.7 (7.9)	49.5 (6.4)	0.32
BMI (kg/m^2)	25.2 (4.1)	26.7 (3.8)	0.12
Total body fat mass (kg)	18.2 (9.9)	24.4 (10.3)	0.04
Trunk fat mass (kg)	12.1 (5.9)	14.8 (6.3)	0.14
Android fat mass (kg)	2.2 (1.1)	2.6 (1.2)	0.25
Gynoid fat mass (kg)	2.8 (1.8)	4.2 (1.6)	0.007
Total body lean tissue mass (kg)	58.6 (7.3)	60.0 (6.4)	0.50
Average tibial cartilage volume (μm)	1188 (182)	1147 (288)	0.59

Values presented as mean (SD)

P value for difference calculated using independent t-test

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Table 2. Relationship between fat and lean tissue mass and tibial cartilage volume

	Univariate regression coefficient (95% CI)	P value	Multivariate regression coefficient (95% CI)	P value
HIV- infected males				
Total body fat mass (kg)	1.51 (-5.09, 8.12)	0.64	-8.01 (-15.66, -0.36)	0.04
Trunk fat mass (kg)	3.14 (-7.82, 14.09)	0.56	-15.37 (-29.27, -1.47)	0.03
Android fat mass (kg)	6.69 (-52.53, 65.90)	0.82	-90.91 (-158.66, -23.16)	0.01
Gynoid fat mass (kg)	8.47 (-27.85, 44.79)	0.64	-30.16 (-68.50, 8.17)	0.12
Total body lean tissue mass (kg)	7.31 (-1.26, 15.89)	0.09	-0.24 (-10.25, 9.77)	0.96
Controls				
Total body fat mass (kg)	-0.22 (-15.04, 14.59)	0.98	-1.22 (-44.44, 42.01)	0.95
Trunk fat mass (kg)	-4.93 (-29.10, 19.23)	0.67	-26.44 (-92.47, 39.59)	0.41
Android fat mass (kg)	-36.21 (-162.18, 89.76)	0.55	-151.79 (-466.60, 163.03)	0.32
Gynoid fat mass (kg)	26.94 (-66.87, 120.75)	0.55	108.11 (-112.45, 328.67)	0.31
Total body lean tissue mass (kg)	17.21 (-4.92, 39.33)	0.12	14.55 (-13.68, 42.77)	0.29

Multivariate analyses adjusted for age and BMI

Chapter 7 General Discussion

The available evidence regarding the health benefits of physical activity and exercise training for HIV-infected individuals has focussed on short term structured exercise interventions. Short term exercise training in the context of HIV infection has been shown to improve conventional outcomes associated with exercise and health such as strength and endurance[28-29]. Importantly there are also limited data suggesting that short term exercise may improve some clinically important problems observed in HAART-treated, HIV–infected individuals including various metabolic and morphological complications. Importantly, despite the known benefits of exercise training, there is some epidemiological and anecdotal evidence to suggest that a proportion of HIV-infected individuals do not participate in enough physical activity to achieve a health benefit. The factors associated with this have not been well determined.

The aims of this Thesis were to document the prevalence of physical activity uptake among Australian adults living with HIV and to address the lack of data on the relationships between long term, habitual physical activity participation and clinically relevant endpoints important in the HAART era. This provided the opportunity to determine associations between long term physical activity/cardiovascular fitness and health outcomes including body composition, body image and CVD risk. The findings of this Thesis have the potential to further our understanding of the role, measurement and determinants of physical activity for individuals living with chronic, treated HIV infection.

7.1 Main Findings

This Thesis explored physical activity and cardiovascular fitness in the context of HAART-treated HIV. To achieve the aims set out in Chapter 1, a physical activity prevalence study was performed in a Melbourne Infectious Diseases outpatient clinic. Next, a widely used self-report questionnaire (the IPAQ long form) was validated against accelerometry for quantifying physical activity among Australian adults with HIV. A 12-month cohort study then allowed exploration of the determinants of physical activity among adults with HAART-treated HIV and the associations between physical

activity/cardiovascular fitness and body composition, body image and CVD risk. Within the cohort study, a sub-study was performed examining associations between knee structure and body composition in the context of HAART-treated HIV.

The results of this Thesis (summarized below) provide an improved understanding of the role of exercise training, physical activity and cardiovascular fitness in HIV-infected individuals with implications for increased awareness of physical activity, its determinants and measurement. In the absence of evidence-based physical activity guidelines for HIV-infected individuals, this Thesis can provide the basis for the future development of population specific recommendations.

7.1.1 Physical Activity Uptake in Patients with Human Immunodeficiency Virus

Both local and international physical activity prevalence data regarding how well HIV-infected individuals meet recommended physical activity guidelines are scarce. Current knowledge describes physical activity behaviours in predominantly HIV–infected African American males[39] and HIV-infected injecting drug users[41]. While existing data are important, they may not be relevant to other HIV-infected populations, including those seen in Australia. The first paper presented within this Thesis described the prevalence of physical activity in a local cohort of HIV-infected individuals and the proportion of participants who met well recognised physical activity guidelines.

In this study, we determined that a significant proportion of local, HAART-treated, HIV-infected individuals, who were predominantly males who have sex with males, were sufficiently active to gain a health benefit. However, almost one quarter of HIV-infected participants were classified as inactive. This latter finding may be of clinical significance given the well documented benefits of physical activity. This finding also provided the impetus to determine factors associated with physical activity which could then help identify patients at high risk of inactivity and avoid the adverse consequences associated with this.

7.1.2 The International Physical Activity Questionnaire Overestimates Moderate and Vigorous Physical Activity in Individuals with Human Immunodeficiency Virus

The surveillance of physical activity behaviours in HIV-infected populations is limited by the lack of validated, reliable and practical physical activity measurement instruments. The second paper presented within this Thesis described the validation of the IPAQ long form in HIV-infected individuals.

This study tested the performance of the IPAQ long form in a group of HAART-treated, HIV-infected men using accelerometry as the objective criterion. Consistent with previous studies evaluating the IPAQ's performance[47, 136], we also identified problems of over-reporting. However, given that some crucial aspects of the IPAQ did correlate with accelerometry, we recommend that this tool be used as a physical activity screening tool for clinicians. We also recommend that more objective methods, such as acclerometry or pedometry, are used when precise measurements are required. Questions that remain about the clinical utility of the IPAQ for use in the context of HIV infection are related to its reliability, application in female cohorts and other culturally diverse groups. The IPAQ provides extensive, comparable data on many aspects of physical activity behaviour and more work is needed to assess its suitability for use in chronic diseases including HIV infection.

7.1.3 The Effects of Exercise Training on Metabolic and Morphological Outcomes for People Living with HIV: A Systematic Review of Randomised Controlled Trials

The challenge faced by clinicians in managing commonly observed metabolic and morphological problems in HAART-treated, HIV-infected patients has prompted great interest in exercise training as a potential intervention. Changes to HAART regimes can improve lipoatrophy to some extent, however pharmacological interventions have been unsuccessful in preventing or reversing abdominal obesity[137]. The third paper presented within this Thesis was a systematic review of nine RCTs evaluating the effects of

aerobic exercise, progressive resistive exercise and combined aerobic exercise and progressive resistive exercise on metabolic and morphological complications in people living with HIV.

This review confirmed that exercise training may be useful in managing some morphological complications, however the effects on metabolic outcomes could not be elucidated due to a lack of published data. Of concern was the lack of imaging techniques used in the included studies to assess the effects of exercise training on body composition and also the limited evaluation of blood lipids and glucose. The absence of data regarding the effects of exercise training on bone health outcomes was also noted. Strong evidence exists that exercise training is effective in managing blood lipid abnormalities[138] and improving bone density in other populations[139 140], however this has yet to be shown in the context of HIV. Larger RCTs addressing the aforementioned issues are needed.

7.1.4 Physical Activity Participation and Cardiovascular Fitness in People Living with HIV: A One- Year Longitudinal Study

Chapter 5 aimed to document long term, habitual physical activity/ cardiovascular fitness patterns in people living with HIV. Despite increased longevity of patients and an urgent need to determine the long term effects of interventions, only cross sectional data are available describing physical activity in this chronic illness. To address this, the fourth paper presented within this Thesis described habitual physical activity patterns and cardiovascular fitness levels in a cohort of HAART-treated, HIV-infected individuals over a 12 month period. Relationships between long term physical activity participation/cardiovascular fitness and body composition, perceived body image and CVD risk were also explored.

The need to increase levels of physical activity participation among all HIV-infected is highlighted within Chapter 5. Suboptimal physical activity levels were identified in the studies presented in Chapters 2 and 5. Factors that affect physical activity participation

in this population were explored, however the data obtained was limited due to a relative lack of variation in physical activity patterns. Very few demographic and clinical factors were identified as determinants of physical activity in the HIV cohort studied and many factors accepted as determinants of physical activity in the general population were not relevant. Social support, in the form of being in a permanent relationship, was the only factor associated with physical activity participation. Further work involving larger number of participants and a wider spectrum of participant activity levels is necessary to fully explore potential determinants of physical activity in this complex chronic illness.

Long term benefits of physical activity and cardiovascular fitness were found. First, cardiovascular fitness was associated with improved body composition suggesting that HIV-infected individuals should be encouraged to improve and maintain cardiovascular fitness. Secondly, improving physical activity levels were associated with improved perceived body image, supporting the uptake of physical activity to improve this aspect of psychological well being.

No association was observed between physical activity/cardiovascular fitness and CVD risk in this study. The lack of inclusion of a direct physical activity variable in the estimated CVD risk may explain this finding, but we had hypothesized that CVD risk would be influenced by the indirect effects of activity and fitness on factors such as blood lipids and blood pressure. The lack of association found may also be attributable to the surrogate physical activity and cardiovascular measures used. Although the IPAQ short form has been validated in the context of HIV, both the IPAQ long form and the Kasch Test have not been validated in this setting. Given that patients are advised to improve physical activity levels to manage many HAART related complications and to reduce their CVD risk, future work is needed to better elucidate potential benefits. Longer duration observational and intervention studies are needed to understand fully the effects of physical activity/cardiovascular fitness on long term CVD risk.

The absence of current physical activity health recommendations for those with HIV infection needs to be addressed. It is unknown whether health recommendations should be prioritizing increased energy expenditure or increased cardiovascular fitness levels in this patient group. This study has demonstrated health benefits for both sustained habitual physical activity and cardiovascular fitness in patients with stable, HAART-

treated HIV infection. The preliminary evidence presented within this Chapter will assist in the development of physical activity recommendations for patient living with HIV, however more work is needed.

7.1.5 Body Composition and Knee Structure in HIV

Current research has suggested that metabolic factors may contribute to the development of osteoarthritis (OA). The fifth paper presented within this Thesis suggests that OA may indeed be another metabolic consequence faced by individuals living with HIV infection, adding to the list of metabolic complications already known to be associated with the virus and its treatment. Given the rising incidence of overweight, obesity and central adiposity in HIV-infected individuals and the established link between these body composition abnormalities and OA in the general population, the risk of OA in HIV infection needs exploration. The fifth paper presented within this Thesis explored the relationship between body composition and knee structure in HIV-infected individuals.

We found abdominal obesity to be associated with reduced knee cartilage volume in adult men with HAART-treated HIV. This novel finding suggests that HAART-treated individuals with altered fat distribution, notably abdominal obesity, may be predisposed to knee OA. Health care providers working with HIV patients need to consider monitoring for symptoms of knee OA and offering advice and strategies to patients to avoid abdominal obesity. Minimising the impact of abdominal obesity, through interventions such as physical activity may offer some protection against knee OA.

7.2 Potential Limitations of this Work

7.2.1 Populations Examined

The results of this Thesis are based on five papers (presented in Chapters 2 to 6) that have used different populations.

The population presented in Chapter 2 is comprised of HIV-infected and general infectious diseases male and female patients. A high study participation rate (75.2%) was achieved increasing the external validity of the results, however a degree of selection bias may have resulted as participants were all volunteers and may represent a relatively health conscious group. Despite both HAART treated- and non-treated HIV-infected participants being included, the proportion of non-treated participants was very low, hence the findings may not be generalisable to those with untreated HIV infection.

The results of Chapter 3 are based on a small cohort of participants recruited from the longitudinal study presented in Chapter 5. Again, patients discussed in Chapters 3 and 5, may represent a relatively health conscious group, as all were attending specialized clinics for HIV care and chose to participate in a clinical research study.

Chapter 4 presented a systematic review that synthesized data from nine studies, evaluating nine different HIV-infected populations. Pre-HAART to HAART-treated participants, with a diverse range of ages and stages of HIV infection were included. However, only one of the nine included studies were conducted in developing countries[112], hence results may not be generalisable to developing countries where HAART may not always be available and cultural and racial differences exist.

Finally, the study reported in Chapter 6 involved a population of HIV-infected males, recruited for the aforementioned longitudinal study and healthy male controls recruited for another study as described in the Methods section of the submitted paper. Both these groups may represent relatively health conscious groups as all were research volunteers.

Gender bias is a common problem in studies involving HIV-infected subjects and this limitation applied to most of the cohorts examined in this Thesis. The combined populations evaluated in the systematic review included 41% females, which is a comparatively high proportion, however this is due to the fact that one of the included studies involved only female participants.

The cohorts in Chapter 2, 3, 5 and 6 comprised of predominantly Caucasian males who have sex with males. This demographic is consistent with patients with HIV seen locally and in other parts of Australia, however it is distinct from populations seen in many other locations. Demographic variables of populations are an important consideration when exploring physical activity behavior and its uptake.

The cohorts in Chapters 2, 3, 4, and 6 also comprised predominantly HAART-treated, stable, chronic HIV-infected participants. Findings may not apply to newly diagnosed patients or those experiencing illness associated with the acute phases or later stages of HIV disease.

7.2.2 Study Design

7.2.2.1 Cross-sectional Studies

Findings resulting from cross-sectional studies presented in Chapters 2, 3 and 6 in this Thesis are unable to determine a temporal relationship between physical activity and outcome. Similarly, findings from Chapter 6 are unable to determine temporal relationships between body composition and knee structure. Longitudinal studies are warranted to confirm these results.

7.2.2.2 Longitudinal Studies

The study presented in Chapter 5 is observational in nature and thus we are unable to determine causation in the associations observed. Longitudinal studies are also prone to loss to follow up, however we experienced minimal withdrawal rates. Missing data can also be a problem for this type of study design and we experienced this with some of our endpoint data.

The one year follow up period used in the longitudinal study may not be long enough to determine the relationships between long term physical activity and chosen endpoints. Follow up of longer duration may be required.

7.2.3 The Measurement of Physical Activity

The measurement of physical activity, presented within Chapters 2 and 5, whilst undertaken using a well recognised and valid self report tool, was not based on gold standard methods of measurement. As discussed previously in Chapter 1, physical activity questionnaires are considered an acceptable method of quantifying physical activity, however the doubly labelled water method, indirect calorimetry or direct

observation, known to be costly and timely, are considered gold standard methods of measuring energy expenditure[33]. Ease of administration, convenience and economic constraints were the main reasons for the selection of the physical activity measurement methods employed in this research.

Recall bias has been identified as a potential limitation of using physical activity questionnaires, however we attempted to minimise this problem by asking participants about their activity patterns over a minimal duration (past week). Despite this, classifying participants' physical activity levels into the three IPAQ activity categories (low, moderate or high) on the basis of their self report responses and not from more objective methods, may have resulted in some misclassification of participants and possible information bias.

7.2.3.1. The Measurement of Cardiovascular Fitness

Cardiovascular fitness, discussed in Chapter 5, was estimated using a clinical submaximal exercise test. More direct measurements, such as VO2max were not used for participants involved in the relevant research within this Thesis as insufficient resources were available. The submaximal exercise testing used in Chapter 5 has been validated in other populations[141], and responsiveness to exercise training has been shown in an HIV infected population[56]. However its use in HIV-infected populations has not been formerly evaluated.

7.2.4 The Measurement of Endpoints

7.2.4.1 The Measurement of Body Composition

Waist circumference and waist to hip ratio (WHR) are the most widely used of anthropometric indirect measurements of visceral fat[142]. These measurement methods are subject to between-examiner and within-examiner variation and they cannot differentiate between visceral fat tissue and subcutaneous fat tissue. However, many studies have found good correlations between these anthropometric measures and

visceral fat and shown that, with training and the use of standardised procedures, they can produce valid and reliable results[142].

7.2.4.2 The Measurement of Cardiovascular Disease Risk

Current guidelines recommend that the risk of CVD in HIV-infected individuals be estimated from a conventional risk-prediction model, such as the Framingham score[143]. The Framingham score presented in Chapter 5 has been extensively used in both research[7] and widely adopted clinically for routine CVD risk factor screening of HIV-infected individuals. It has not been validated in the HIV-infected population but is considered an appropriate method of quantifying CVD risk in this patient group. Importantly, physical activity is not included in the Framingham equation, which may have contributed to the lack of any observed association between physical activity and CVD risk in this Thesis.

7.2.4.3 The Measurement of Knee Cartilage

Magnetic resonance imaging has been shown to be valid in the measurement of cartilage volume[144]. Cartilage volume measurements performed in the study presented in Chapter 6 used a trained observer and random checks by an independent observer were also employed.

7.2.5 Data Analysis and Interpretation

7.2.5.1 Sample Sizes

The validation study of the IPAQ presented in chapter 3 was based on a convenience sample of 30 males. While we did detect correlations between accelerometry and self reported physical activity data, we may have had insufficient power to detect other, weaker relationships.

The longitudinal study presented in Chapter 5 enrolled 80 participants. This number was calculated to allow detection of a clinically meaningful difference in CVD 10- year risk in those who adhere to moderate/high levels of physical activity over the study duration

(persistent exercisers) compared to those who did not (sub-optimal physically active). We anticipated that around 75% of patients would be exercising at study entry (based on our own prevalence study presented in Chapter 2) but that only half of these would maintain high levels of physical activity throughout the study period[145].Therefore, allowing for a 20% loss to follow up, we anticipated there would be 24 participants who were persistent exercisers and 40 who were sub-optimally active completing the study. With these numbers, we had 87% power to detect a mean difference in CVD 10-year risk of 2% in those who adhere to physical activity versus 6% in those who did not (SD=5%) with alpha=0.05. Allowing for the Bonferroni correction, this study therefore would be adequately (>80%) powered to detect clinically meaningful differences in the primary endpoint of 10 year CVD risk. However, although we only experienced a 9.3% loss to follow up, a Type II error may have occurred due to missing available data and this may have reduced the power to detect significant relationships. Also, levels of physical activity were stable throughout the study in the majority of participants, leading to fewer inactive participants over the study period than anticipated.

7.2.5.2 Determining Causation

The results presented within this Thesis (Chapters 2, 3, 5, 6) are from observational studies. To demonstrate whether the observed associations are causative will require properly conducted randomized trials.

7.3 Future Directions

There has been increasing pressure on clinicians to adapt to the changing demands of the HIV pandemic and to develop novel strategies to manage the complex manifestations observed in chronic HIV infection. All HAART-treated, HIV-infected individuals currently face long term disease and a healthy lifestyle, including the uptake of appropriate physical activity is likely to be an important part of optimized HIV management.

This Thesis highlights the need to address the measurement problems associated with quantifying physical activity in HIV-infected individuals. A measurement tool that can be applied in diverse HIV- infected populations, both locally and internationally, is needed. Such a tool would provide comparable data, allow trends in physical activity behaviours to be monitored and the associated effects on health determined. The continued use of self report tools to measure physical activity in future epidemiological studies will most likely be the method of choice. The work presented in this Thesis on the IPAQ supports further research into this tool. Given the noteworthy goal of the IPAQ, to produce internationally recognised comparable data, we recommend that more work is done to evaluate the IPAQ's performance in the context of HIV infection. In particular, strategies to adopt when administering the IPAQ to reduce the problem of over-reporting should be evaluated and further reliability testing should be conducted.

A secondary measurement issue identified as a result of this Thesis is the lack of valid and reliable submaximal exercise tests available for use in the context of HIV. The frequent clinical use of submaximal exercise testing in patients with HIV warrants further evaluation of their reliability and validity. Future work is needed to assess the clinical utility of an appropriate submaximal exercise test to be used with patients with HIV.

Current clinical recommendations advocating the use of exercise training to manage many HAART-related complications prompted the systematic review within this Thesis. The review highlighted the relative lack of high quality research conducted in this area. Future work must include larger randomised trials, the wider adoption of imaging to better assess body composition and the inclusion of metabolic and bone

health parameters. Although it was advantageous that participants with widely ranging stages of HIV infection were included, the effects of exercise at particular stages of immunosuppression could not be elucidated. Future studies should involve participants recruited at specific stages of HIV infection, as this would help identify the risks and benefits of exercise training at different stages of the disease. Furthermore, a lack of detailed information on exercise training protocols needs to be addressed in future research as this would allow an improved understanding of the effects of specific exercise programs. Additionally, the problem of the lack of female representation in HIV research studies needs to be addressed. This problem is not unique to physical activity based research involving HIV-infected populations, but is common amongst most research conducted in HIV-infected cohorts, particularly in developed countries. One female-only study was included in this review and few female participants in the other included studies could impact on the external validity of the review's results. Efforts to increase female participation in exercise training and physical activity research are necessary.

Despite extensive epidemiological evidence of the benefits of long term physical activity participation in the general population, no such data exist in populations with HIV infection. This Thesis was motivated by this knowledge gap. Future endeavours need to employ longer study periods and intervention study designs to better determine long term effects of physical activity. This vital information is needed to determine the type, intensity, frequency, and duration of activity required to maximize the benefits and minimize the hazards of physical activity in this population. This information, which is currently lacking in the literature, will be used by clinicians to improve exercise prescription and optimise health promotion advice offered to patients. Importantly, more evidence is needed to determine disease specific effects of physical activity and begin the much needed development of evidence based physical activity guidelines for this population.

This Thesis attempted an exploration of demographic and other factors that may influence physical activity participation in those living with HIV. Identifying barriers to physical activity in specific demographic groups of people living with HIV, in both developed and developing countries is warranted. Racial and cultural differences that

may influence this behaviour need to be better determined. These data are important for the identification of those at risk of physical inactivity and to target healthcare interventions aiming to prevent the complications associated with a sedentary lifestyle and better manage some HIV- and HAART-associated complications.

Finally, this Thesis discussed a novel finding relating to the commonly observed body composition changes in HIV-infected individuals. Chapter 6 is the first study to discuss a potential predisposition to osteoarthritis (OA) in HIV-infected individuals. OA may add to the already complex and diverse range of metabolic disturbances observed in chronic HAART-treated HIV infection. The possible link between body composition and OA supports the use of strategies to prevent and manage central fat accumulation, including the uptake of physical activity. Clinicians managing HAART-treated, HIV-infected patients are faced with many challenges, often complicated by disorders of aging. This Thesis purports that OA may be one of the next clinical challenges facing those with HIV infection. Larger studies are required to confirm whether this group of patients are indeed predisposed to OA, however until then, strategies such as physical activity should be recommended to help manage and prevent abdominal obesity.

Future research endeavours evaluating exercise training and physical activity need to be conducted in the most rigorous manner feasible. Observational study durations need to be of an optimal time frame to capture long term effects and intervention studies are greatly needed. The development of evidence based physical activity guidelines for HAART-treated, HIV–infected individual is a priority. The increasing advocacy for development of novel, non pharmacological strategies to improve HIV models of care further supports future research into the benefits of both physical activity and exercise training in this population.

Chapter 8 Conclusions

This Thesis evaluated the relationships between physical activity and clinically relevant health outcomes in HAART-treated, HIV-infected individuals. From these studies the following conclusions can be drawn:

1) The prevalence of physical activity behaviour in an HAART-treated HIV-infected population was determined. One in four HIV-infected individuals did not meet physical activity guidelines.

2) The IPAQ was evaluated for use in an HIV-infected population to measure physical activity. The IPAQ overestimates physical activity in comparison to accelerometry. Findings suggest that the IPAQ should not be used for precise measurements of physical activity; however it could be used as a screening physical activity tool.

3) Available evidence from RCTs suggest that exercise training can improve morphological complications observed in HIV-infected individuals, however there is a lack of data evaluating the effects of exercise on metabolic complications.

4) Long term physical activity patterns and cardiovascular fitness levels were documented in a stable, HAART-treated HIV- infected cohort. Important findings were:

a. 19-37% of participants reported suboptimal levels of physical activity participation at each study visit, while both physical activity and cardiovascular fitness were largely stable over one year.

b. Cardiovascular fitness was associated with improved body composition suggesting that HIV-infected individuals should be encouraged to improve and maintain cardiovascular fitness to manage morphological complications better.

c. Improving physical activity levels were associated with improved perceived body image, supporting the uptake of physical activity to improve this aspect of psychological well being.

d. Despite convincing evidence that physical activity and cardiovascular fitness are associated with reduced CVD risk in the general population, our findings are

inconclusive. Further research to elucidate the role of exercise in mitigating CVD risk for HIV-infected individuals is required.

e. Being in a permanent relationship was associated with higher levels of physical activity, suggesting that HIV-infected individuals who are socially isolated may be at risk of inactivity. Interventions may need to be targeted to this group to prevent adverse health consequences of inactivity.

5) A novel finding linking android obesity to early structural knee joint damage, suggesting that HIV-infected individuals may be pre-disposed to OA by the morphologic changes associated with the virus and its treatment. Further research evaluating the development and impact of OA in HIV-infected individuals is warranted.

The results of this Thesis provide a better understanding of the role of physical activity in HIV-infected individuals and will assist in the promotion of physical activity participation amongst those living with HIV infection. At the outset of this research there was little guidance in the literature regarding population specific physical activity guidelines, but it is anticipated that this Thesis has laid the foundations for such guidelines to be developed.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE SHORT VERSION

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. This is part of a large study being conducted in many countries around the world. Your answers will help us to understand how active we are compared with people in other countries.
The questions are about the time you spent being physically active in the last 7 days. They include questions about activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.
Your answers are important.

Please answer each question even if you do not consider yourself to be an active person.

THANK YOU FOR PARTICIPATING.

In answering the following questions,
♦ **vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder that normal.
♦ **moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder that normal.

1a. During the last 7 days, on how many days did you do **vigorous** physical activities like heavy lifting, digging, aerobics, or fast bicycling,?
Think about *only* those physical activities that you did for at least 10 minutes at a time.
_____ **days per week** ⇨
or
☐ **none**
2a. Again, think *only* about those physical activities that you did for at least 10 minutes at a time. During the last 7 days, on how many days did you do **moderate** physical activities like carrying light loads, bicycling at a regular pace, or doubles tennis? Do not include walking.
_____ **days per week** ⇨
or
☐ **none**
3a. During the last 7 days, on how many days did you **walk** for at least 10 minutes at a time? This includes walking at work and at home, walking to travel from place to place, and any other walking that you did solely for recreation, sport, exercise or leisure.
_____ **days per week** ⇨
or
☐ **none**
The last question is about the time you spent sitting on weekdays while at work, at home, while doing course work and during leisure time. This includes time spent sitting at a desk, visiting friends, reading traveling on a bus or sitting or lying down to watch television.
4. During the last 7 days, how much time in total did you usually spend *sitting* on a **week day?**
_____ **hours** _____ **minutes**
        This is the end of questionnaire, thank you for participating.

INTERNATIONAL PHYSICAL ACTIVITY QUESTIONNAIRE LONG VERSION

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the **last 7 days**. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the **vigorous** and **moderate** activities that you did in the **last 7 days**. **Vigorous** physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. **Moderate** activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1.   Do you currently have a job or do any unpaid work outside your home?

☐ Yes

☐ No ➝ *Skip to PART 2: TRANSPORTATION*

The next questions are about all the physical activity you did in the **last 7 days** as part of your paid or unpaid work. This does not include traveling to and from work.

2.   During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, digging, heavy construction, or climbing up stairs **as part of your work**? Think about only those physical activities that you did for at least 10 minutes at a time.

_____ **days per week**

☐ No vigorous job-related physical activity ➝ *Skip to question 4*

3.   How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

_____   **hours per day**

_____   **minutes per day**

4.   Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like carrying light loads **as part of your work**? Please do not include walking.

_____   **days per week**

☐   No moderate job-related physical activity   ➜   *Skip to question 6*

5.   How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____   **hours per day**

_____   **minutes per day**

6.   During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____   **days per week**

☐   No job-related walking   ➜   *Skip to PART 2: TRANSPORTATION*

7.   How much time did you usually spend on one of those days **walking** as part of your work?

_____   **hours per day**

_____   **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores,

movies, and so on.

8. During the **last 7 days**, on how many days did you **travel in a motor vehicle** like a train, bus, car, or tram?

    _____ **days per week**

    ☐ No traveling in a motor vehicle ➡ ***Skip to question 10***

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

    _____ **hours per day**

    _____ **minutes per day**

Now think only about the **bicycling** and **walking** you might have done to travel to and from work, to do errands, or to go from place to place.

10. During the **last 7 days**, on how many days did you **bicycle** for at least 10 minutes at a time to go **from place to place**?

    _____ **days per week**

    ☐ No bicycling from place to place ➡ ***Skip to question 12***

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

    _____ **hours per day**

    _____ **minutes per day**

12. During the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No walking from place to place ➡ ***Skip to PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY***

13. ***How much time did you usually spend on one of those days*** *walking* ***from place to place?***

_____ **hours per day**

_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the **last 7 days** in and around

your home, like housework, gardening, yard work, general maintenance work, and caring for your

family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ **days per week**

☐ No vigorous activity in garden or yard ➡ ***Skip to question 16***

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____   **hours per day**

_____   **minutes per day**

16.   Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____   **days per week**

☐   No moderate activity in garden or yard   ➡   *Skip to question 18*

17.   How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____   **hours per day**

_____   **minutes per day**

18.   Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____   **days per week**

☐   No moderate activity inside home   ➡   *Skip to PART 4: RECREATION, SPORT AND LEISURE-TIME PHYSICAL ACTIVITY*

19.   How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____   **hours per day**

_____   **minutes per day**

PART 4: RECREATION, SPORT, AND LEISURE-TIME PHYSICAL ACTIVITY

This section is about all the physical activities that you did in the **last 7 days** solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20.   Not counting any walking you have already mentioned, during the **last 7 days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ **days per week**

☐ No walking in leisure time ➡️ *Skip to question 22*

21.   How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**
_____ **minutes per day**

22.   Think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **vigorous** physical activities like aerobics, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

☐ No vigorous activity in leisure time ➡️ *Skip to question 24*

23.   How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**
_____ **minutes per day**

24.   Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last 7 days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and doubles tennis **in your leisure time**?

_____ **days per week**

☐ No moderate activity in leisure time ➡️ *Skip to PART 5: TIME SPENT SITTING*

25.   How much time did you usually spend on one of those days doing **moderate** physical activities in your leisure time?

_____ **hours per day**

_____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day**

_____ **minutes per day**

27. During the **last 7 days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ **hours per day**

_____ **minutes per day**

This is the end of the questionnaire, thank you for participating.

The Kasch Step Test Protocol

Equipment

- A 12 inch high step/bench
- A metronome set at 96 beats per minute[4 clicks of the metronome equal one step(up, up, down ,down at 24 steps per minute)]
- A timer for the 3 minutes and a timer for the recovery (these may be the same)
- A stethoscope to count recovery heart rate
- Testing forms to record data.

Procedure

- The physiotherapist demonstrates the stepping and explains the test.
- Explanation will provide the following details: test measures cardiovascular fitness, the patient will be informed of the time left during the test, the measurements taken during the test and the importance of sitting down quickly at the end of 3 minutes and remaining still for 1 minute so that heart rate can be measured accurately.
- The stepping is performed by facing the step and in time with the metronome, step one foot up on the bench (first beat), step up with the second foot(second beat), step down with the first foot(third beat) and step down with the second foot(fourth beat). The sequence is alternating feet. The patient may lead with any foot and may change feet during the course of the test.
- The patient must not practise, as this will affect the heart beat.
- Once the patient starts stepping, start the timer. The patient should be informed of each minute as it passes.
- When 20 seconds remain, inform the patient that he/she needs to sit down very quickly at the end of stepping and wait for the physiotherapist to take heart rate.
- When the patient sits down, immediately place the stethoscope on the chest and start counting for a full minute.
- Begin the count on a beat, counting that beat as zero. The recovery count must be started within 5 seconds or the heart rate will be significantly different. The 1 minute post exercise count reflects the heart's rate at the end of stepping as well as the rate of recovery.
- The total 1 minute post exercise heart rate is the score for the test and will be recorded on the assessment Form.

Score the total 1 minute post exercise heart rate in beats per minute.

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