MEASURES OF PHYSICAL FUNCTION AS RISK FACTORS FOR DIABETES MELLITUS AND INSULIN RESISTANCE AMONG HIV-UNINFECTED AND HIV-INFECTED MEN

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Physical activity is an accepted intervention for the prevention of diabetes mellitus (DM) and insulin resistance (IR) in the general population. Few studies in HIV-infected persons assessed the role of physical function or physical activity as a contributing factor to glucose disorders. The relationship between self-reported and performance-based measures of physical function in HIV-infected individuals has not been assessed. This dissertation examined associations between self-reported and performance-based measures of physical function, DM, and IR in HIV-uninfected and HIV-infected men.

Data from 658 men from the Pitt Men's Study were analyzed to assess the contribution of self-reported physical function to prevalent DM and IR. Physical function score (AOR 1.5 per 25 unit decrease, p=0.02) was significantly associated with diabetes, but not IR, after adjustment for covariates.

Data from 1790 men from the Multicenter AIDS Cohort Study (MACS) were used to assess physical function as a risk factor for incident DM and IR. Cumulative DM incidence was highest among HIV-uninfected and HIV-infected men with low physical function. Low physical function was a risk factor for incident DM in HIV-uninfected men using more stringent (HR

1.31; 95% CI 1.02-1.66) and less stringent (HR 1.29; 95% CI 1.11-1.50) diabetes definitions adjusting for BMI, family history of diabetes and race. Among HIV-infected men, physical function was a risk factor for incident DM using the less stringent diabetes definition.

To assess the relationship between self-reported and performance-based measures of physical function, DM and IR, a cross-sectional study of 2079 men from the MACS was conducted. Self-reported physical function and performance-based measures correlated weakly. (HIV-uninfected: ρ=0.12-0.23, $p<0.01$; HIV-infected ρ=0.16-0.24, $p<0.01$). Self-reported physical function had a stronger association with DM and IR than performance-based measures in HIV-uninfected but not HIV-infected men.

There are important public health implications of this dissertation. Low physical function is a risk factor for DM in two cohorts of HIV uninfected and HIV-infected men; therefore interventions to increase physical function may decrease DM risk while simultaneously reducing the risk of further disability and chronic sequelae among HIV-infected individuals already diagnosed with diabetes. This is essential given the national burden of HIV infection and DM.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

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1.0 INTRODUCTION

1.1 SPECIFIC AIMS

Physical activity is an accepted intervention for the prevention and management of diabetes mellitus (DM) and insulin resistance (IR) in the general population[1-9]. However, its role in the prevention of DM has not been addressed in most studies of HIV-infected populations[10-14].

Numerous studies in HIV-uninfected populations have established that physical activity levels are correlated with physical function [15-20]. Among HIV-infected persons, resistance training has been shown to improve self-reported physical function in patients with HIV wasting[21]. Therefore, physical function is likely to reflect physical activity. To date, no studies have assessed the association between self-reported and performance-based measures of physical function, diabetes mellitus, and insulin resistance in HIV-infected men. The goal of the proposed research is assess the association of physical function, a correlate of physical activity, with diabetes mellitus and insulin resistance and, further, to compare self-reported physical function with performance-based measures of physical function in HIV-infected and HIV-uninfected men.

The following research aims and hypotheses will be used to achieve this goal:

1. To investigate the association between self-reported low physical function and prevalent and incident diabetes mellitus among HIV-infected and HIV-uninfected

men. *We hypothesize that low physical function will be independently associated with both prevalent and incident diabetes mellitus in HIV-infected and HIV-uninfected men.*

2. To investigate the association between low physical function and prevalent and incident insulin resistance among HIV-infected and HIV-uninfected men. *We hypothesize that low physical function will be independently associated with both prevalent and incident insulin resistance in HIV-infected and HIV-uninfected men.*
3. To compare incidence rates of diabetes in HIV-infected and HIV-uninfected men with low physical function to HIV-infected and HIV-uninfected men with high physical function. *We hypothesize that HIV-infected and HIV-uninfected men with low physical function will have higher cumulative incidences of diabetes than HIV-infected and HIV-uninfected men with high physical function.*
4. To assess the relationship between self-reported and performance-based measures of physical function in HIV-infected and HIV-uninfected men. *We hypothesize that performance-based measures of physical function will be significantly correlated with self-report physical function in both HIV-infected and HIV-uninfected men.*

5. To determine whether self-report or performance-based measures of physical function are more strongly associated with prevalent diabetes mellitus and insulin resistance in HIV-infected and HIV-uninfected men. *We hypothesize that the performance-based measures of physical function will have a stronger association with prevalent diabetes and insulin resistance than self-reported physical function.*

1.2 BACKGROUND

1.2.1 Introduction

The introduction of highly active antiretroviral therapy (HAART) dramatically changed the course of HIV infection. Individuals living with HIV infection are now faced with co-morbidities that are common in the general population. Type 2 diabetes mellitus (DM) and insulin resistance (IR) are two such conditions. To date, the etiology of DM and IR in HIV-infection remains unclear. Traditional risk factors such as advancing age and higher body mass index (BMI) have consistently been reported and HIV-specific risk factors such as HAART use are thought to play a role. Physical activity is a well accepted intervention for the prevention of DM in the general population, yet its role has been overlooked in the majority of studies of DM in HIV-infected persons. The purpose of this literature review is to evaluate what is currently known about glucose disorders in the HIV-infected population as well as to underscore the paucity of physical activity literature in this specific population. In addition, the correlation between physical activity and physical function will be addressed.

1.2.2 Glucose disorders

1.2.2.1 Diabetes

Diabetes mellitus is a disease in which the body does not either produce or properly use insulin[22, 23]. Insulin helps to maintain normal blood glucose levels in the body by improving the glucose uptake from the blood across cell membranes using the glucose transporter GLUT4[24]. Diabetes is a complex chronic disorder of carbohydrate, fat, and protein metabolism that is typically the result of a relative or a complete lack of insulin secretion by the beta cells of the pancreas or due to defects of the insulin receptors[25]. In diabetes, the pancreas does not make enough insulin

(Type 1) or can't respond normally to the insulin that is made (Type 2). This leads to an increase in blood glucose levels which can cause acute complications (diabetic ketoacidosis) as well as long term complications (cardiovascular disease, nephropathy, retinopathy, neuropathy) typically requiring continued medical care and patient self management[22, 25]. Currently, the American Diabetes Association (ADA) recognizes 4 classes of diabetes: 1) type 1 diabetes resulting from Beta cell destruction typically resulting in absolute insulin deficiency; 2) type 2 diabetes typically resulting from insulin resistance combined with relative insulin deficiency; 3) other specific types of diabetes due to causes such as genetic defects in Beta cell function, genetic defects in insulin action, diseases of the exocrine pancreas and drug or chemical induced; and 4) gestational diabetes mellitus which is diagnosed during pregnancy[22].

Type 2 diabetes occurs most frequently in older adults and is often not diagnosed until symptoms occur. It is estimated that one-third of all individuals with diabetes are undiagnosed[22]. Over the past 50 years, the prevalence and incidence of obesity, insulin resistance and type 2 DM have been increasing throughout the world at alarming rates[26]. Individuals with Type 2 DM comprise 90-95% of all cases of DM worldwide[24]. It is estimated that the number of type 2 diabetes cases will double from 171 million in 2000 to 366 million in 2030 with incidence rates increasing faster in developing countries[24, 27]. The worldwide prevalence in adults was 4.0% in 1995 and may rise to as high as 5.4% by 2025[28]. In the United States, a six fold increase in the prevalence of type 2 DM was reported between 1958 and 1993 with current estimates suggesting that 6-8% of adults have diabetes[4, 5, 26, 29]; however the true prevalence may be closer to 10% after considering undiagnosed cases[4, 5, 29]. This has lead to an estimated national burden in excess of $174 billion ($116 billion in excess medical expenditures and $58 billion in decreased national productivity from premature disability, premature death, missed work days, restricted

activity, and sick leave) [7, 24]. While the specific etiologies of type 2 DM remain unknown, certain risk factors are well documented[24]. These include family history of DM, age, race/ethnicity, obesity, and physical inactivity.

The risk of developing diabetes for an individual with a positive family history varies depending upon the family member's age, the age at diagnosis and the type of diabetes mellitus. The risk of a child developing type 2 diabetes is approximately 14% if the parent with DM was diagnosed before age 50 and 8% if diagnosed after age 50. The risk increases to 50% if both parents have type 2 DM[24]. Older age can also lead to an increased risk of developing type 2 DM, with the greatest risk occurring in persons aged 45 years and older[24]. This is likely due to a combination of loss of muscle mass with subsequent increases in body fat (especially in the abdomen) as well as defects in fatty acid oxidation in muscle with aging (which enhances insulin resistance) [24, 30]. In addition, racial/ethnic minorities including African, Hispanic, Indian, Asian Americans, and Pacific Islanders have a greater risk of developing type 2 DM. This is likely due to a combination of environmental, genetic, and metabolic differences[24]. Individuals with a body mass index (BMI) of > 25 kg/m^2 (normal BMI = 18-25 kg/m^2) are considered to be at an increased risk for type 2 DM[8, 31]. Large waist circumference is also associated with an increased risk of type 2 DM, likely due to its use as surrogate for abdominal fat distribution[24].

Physical inactivity can lead to the development of obesity and modifies muscle insulin sensitivity, both of which increase risk of type 2 DM development[2, 24]. Other factors such as dyslipidemia, hypertension, prior gestational diabetes, polycystic ovary syndrome (PCOS), inflammation, and prothrombotic factors are also thought to increase the risk of developing DM.

Early diagnosis is critical for diabetes management. According to ADA criteria, there are 3 ways to diagnose diabetes, each of which must be confirmed on a subsequent day[22]: 1)

symptoms of diabetes such as excessive urination, excessive thirst, unexplained weight loss and a casual plasma glucose of > 200 mg/dL (casual is defined as "any time of day without regard to time since last meal") or 2) fasting plasma glucose (FPG) $\geq$ 126 mg/dl where fasting is defined as no caloric intake for at least 8 hours or 3) 2-h plasma glucose $\geq$ 200 mg/dl during a 75-g oral glucose tolerance test (OGTT) as described by the World Health Organization. Hyperglycemia that does not meet the aforementioned criteria is classified as either impaired fasting glucose or impaired glucose tolerance depending upon the diagnostic test used. IFG is defined as an FPG of 100 mg/dl to 125 mg/dl while IGT is defined as a 2 hour OGTT of 140 mg/dl to 199 mg/dl. People with IFG and IGT, who are at risk for DM, have recently been officially designated as having "pre-diabetes[22]." Normal glucose tolerance is defined as an FPG < 100 mg/dl. Impaired glucose tolerance and impaired fasting glucose can increase the risk of DM development. Individuals diagnosed with IFG or IGT have a 40% risk of developing type 2 DM over the next 5 years [24].

1.2.2.2 Insulin Resistance

In the U.S. alone, it is estimated that 70-80 million people have insulin resistance syndrome[3]. Insulin resistance is defined as the diminished ability of cells to respond to the action of insulin in transporting glucose from the blood stream into the muscle or other tissues[24]. The pancreas overproduces insulin in response to this resistance. If the body can produce enough insulin to overcome this resistance, blood glucose levels remain normal. The overproduction of insulin (hyperinsulinemia) can lead to an excess of glucose and insulin in the bloodstream as cells become resistant to insulin. Insulin resistance, in turn, may ultimately progress to DM. IR is likely caused by a combination of genetic and environmental factors (such as physical inactivity and diet) [6, 24]. IR can include both elevated blood glucose levels and elevated levels of

circulating insulin[24]. Several mechanisms are thought to lead to IR including reduced binding of insulin to the insulin receptor, changes in intracellular signaling pathways, and defective cellular uptake of glucose[32]. IR, in combination with insulin deficiency, likely plays a key role in the pathophysiology of type 2 DM. Defects in insulin secretion, abnormalities in glucose uptake and insulin resistance are uniform findings in type 2 DM[3]. The body's ability to maintain glucose homeostasis depends upon the normal insulin secretory response by the pancreatic beta cells as well as normal tissue sensitivity[3, 6, 24]. Risk factors for IR are similar to those of DM and include obesity, physical inactivity, family history of DM, PCOS, hypertension, hyperlipidemia, and an increased waist circumference.

The current "gold standard" for measuring IR is the hyperinsulinemic euglycemic clamp[33]; however the technique is complicated to administer[34]. Alternatives such as the Quantitative Insulin Sensitivity Index Check (QUICKI) and the homeostasis model assessment (HOMA) utilize fasting insulin and glucose levels to calculate IR and were developed to offset the complicated nature of the clamp technique. Both the HOMA ($r = -0.820$, $P < 0.0001$)[35] and the QUICKI ($r=0.77$, $P< 0.0001$)[36] have been found to correlate well with clamp technique and are acceptable for use as a measures of insulin sensitivity and insulin resistance in studies in which only a fasting blood sample is available[34-38].

1.2.3 Diabetes and physical activity in HIV-uninfected populations

1.2.3.1 Physical activity and exercise

According to the 1996 "Physical Activity and Health" Surgeon General report, physical activity (PA) is defined as bodily movement produced by the contraction of skeletal muscle that requires energy expenditure in excess of resting energy expenditure[39]. Exercise is a subset of PA that

consists of planned, structured, and repetitive bodily movements that are performed to either improve or maintain one or more components of physical fitness including cardiorespiratory fitness, muscular fitness, and flexibility. While exercise is a type of physical activity, it is important to note that not all physical activity is considered exercise[16]. An individual may be physically active during the day, walking at an occupation, doing housework, etc without actually doing structured exercise. Despite these differences, the terms are often used interchangeably.

The Surgeon General's Report recommends 30 minutes of moderate intensity physical activity, similar in intensity to brisk walking, on most days of the week, although it is not necessary to complete all 30 minutes in one continuous session. Short bouts of 10 minutes or longer completed during a single day are acceptable. However, 1998 data from the Behavioral Risk Factor Surveillance System suggest that a mere 25.4% of individuals participate in the recommended level of physical activity while 45.9% and 28.7% report insufficient activity or no activity respectively[40]. Findings from the Third National Health and Nutrition Examination Survey (NHANES III) indicate that 31% of individuals with type 2 DM reported that they do not partake in physical activity while an additional 38% reported that they participated in less than the recommended levels of physical activity[41].

1.2.3.2 Prevention of diabetes

Throughout the years, the role of physical activity in preventing type 2 DM in HIV-uninfected individuals has become well established. Four major clinical trials (three of which were randomized) and numerous large cohort studies provide strong evidence to suggest that physical activity can reduce the incidence of DM[42-50]. The Swedish Malmo Feasibility study was the earliest clinical trial aimed at preventing diabetes[42]. This six year non-randomized trial enrolled

161 men with impaired glucose tolerance (IGT) in a diet-plus-physical activity intervention and compared these men to 56 men with IGT who declined the same intervention. After 6 years, the cumulative incidence of type 2 DM was 11% in the diet-plus-PA group compared with 21% in the control group (relative risk (RR) 0.37, 95% CI 0.20-0.68)[42]. In addition, after 12 years of follow-up, the mortality among men with IGT in the intervention group was 6.5 per 1,000 person years versus 14.0 per 1000 person-years in the control group[43]. Despite these encouraging results, the study had an important limitation. As previously mentioned, this trial was non-randomized therefore baseline differences between groups (the 2 arms differed by medical conditions) affected the study's internal validity.

The first randomized trial, the Da Qing IGT and Diabetes Study, addressed life style interventions with the goal of preventing type 2 DM[48, 49]. This study randomized, by clinic site, 577 Chinese men and women aged 25 years and older with IGT to one of four interventions: diet-only, exercise-only, diet-plus-exercise, and a control group. Subjects were followed for six years and the cumulative incidence of DM was calculated. The cumulative incidence of type 2 DM was highest in the control group (68%), followed by the diet group (44%), the exercise group (41%) and the diet plus exercise group (46%) respectively. Each intervention group differed significantly from the control group ($p<0.05$). In a proportional hazards model comparing the intervention groups to the control group after adjustment for body mass index and fasting glucose, there was an overall lower incidence of DM by 31% in the diet-only group ($p<0.03$); 46% in the exercise-only group ($p<0.0005$) and 42% in the diet-plus-exercise group ($p<0.005$)[48]. This study provides evidence to suggest that both diet and exercise can be important interventions in preventing DM. This study did however have two major limitations: 1) randomization occurred at the clinic level rather than at the participant level and 2) the

baseline exercise units for the two PA groups were significantly higher than the control or diet-only group. Generalizability of results is also limited as this study restricted participating clinics to a single city in China (Da Qing). Therefore results may not extend to other ethnic groups especially given the leanness of the Da Qing cohort (mean BMI ~ 23 kg/m^2).

Results from subsequent clinical trials completed in Finland and the United States produced similar results but differed from the Da Qing study by randomizing individual participants rather than clinics. In the Finnish Diabetes Prevention Project 522 overweight participants with IGT ranging in age from 40-65 years were randomized to a lifestyle intervention (with both a dietary and a PA component) or a control group[44, 45, 47]. The cumulative incidence of DM after 4 years was 11% in the intervention group compared with 23% in the control group. In Cox regression models, the cumulative incidence in the intervention group was 58% lower (hazard ratio (HR) 0.4; $p<0.01$) than in the control group. The incidence of DM was reduced by 63% in men ($p=0.01$) and by 54% in women ($p=0.008$). A post-intervention follow-up study by the same group produced similar results. The incidence rates were 4.3 per 100 person years in the intervention group and 7.4 per 100 years in the control group ($p=0.0001$) with a corresponding HR of 0.57. The 6-year cumulative incidence for DM was 23% in the intervention group and 38% in the control group[46].

The Diabetes Prevention Program (DPP) was a large, randomized clinical trial conducted in the U.S. which included 3234 overweight men and women 25 years and older with impaired glucose tolerance[50]. The study's objective was to determine whether a lifestyle intervention or treatment with metformin would prevent or delay the onset of type 2 DM. Participants were randomized to one of three interventions: standard lifestyle recommendations plus metformin, standard lifestyle recommendations plus placebo, or an intensive lifestyle modification program

and were followed for a mean of 3.2 years. The crude incidence of diabetes was 11.0, 7.8, and 4.0 cases per 100 person years in the placebo, metformin, and lifestyle intervention groups respectively after a mean of 2.8 years of follow-up. The risk reduction was 58% in the lifestyle group and 31% in the metformin group compared to the placebo group. In addition, the incidence of diabetes was 39% lower in the lifestyle group than the metformin group. The estimated cumulative incidence of DM at three years was 28.9% in the placebo group, 21.7% in the metformin group and 14.4% in the lifestyle intervention group. These results were similar in both men and women as well as in all racial and ethnic groups[50].

In addition to these 4 well known clinical trials, a number of large cohort studies[51-60] and smaller clinical trials[61, 62] also found that higher levels of exercise and/or cardiorespiratory fitness were associated with a decreased risk of developing type 2 DM. The independent effect of exercise remained, when accounting for known diabetes risk factors including hypertension, familial history of DM, and obesity.

Despite the consistent findings from these clinical trials, it is important to note that a few questions regarding physical activity and diabetes are not yet answered[63]. The aforementioned clinical trials provide strong evidence for the promotion of lifestyle interventions in the prevention of type 2 DM; however in 3 of the 4 trials the independent effect of activity alone was not tested. All of the trials, except the Da Qing Study, used a combined lifestyle intervention including physical activity, diet, and weight loss. Therefore, in order to truly understand the role that PA plays in preventing type 2 DM, the physiological effect of this relationship needs to be better defined.

Given the results of the aforementioned studies, the American Diabetes Association (ADA) maintains that “the importance of promoting physical activity as a vital component of the

prevention as well as management of type 2 diabetes must be viewed as a high priority[64]." In addition, the ADA suggests that the exercise benefits of improved metabolic abnormalities in type 2 DM are greatest when exercise is introduced early in the progression of the disease[64].

1.2.3.3 Metabolic effects of physical activity in diabetes management

Although physical activity has been used for decades as an important facet of diabetes management, it has only been in the past few years that good quality evidence strengthened the importance of its use[65]. Numerous cross-sectional and cohort studies provide evidence that physical inactivity is associated with impaired glucose tolerance[66-71]. Physical activity can lower blood glucose by its synergistic action with insulin in tissues that are insulin-sensitive[72]. The specific metabolic effects of physical activity on type 2 diabetes and insulin resistance follow.

Boulé et al conducted a meta-analysis of controlled clinic trials (through December 2000) on the effect of physical activity interventions ($\geq$ 8 weeks duration) on glycemic control in type 2 diabetics using glycosylated hemoglobin (HbA_{1c})[73]. In pooled post intervention results, HbA_{1c} was significantly lower in the intervention groups as compared to the control groups (7.65% versus 8.31%, weighted mean difference -0.66%; $p<0.001$). Boulé et all suggested that a reduction in HbA_{1c} by 0.66% was significant enough to reduce the risk of diabetes complications and was similar in effect to differences between conventional and intensive glucose-lowering therapy in the United Kingdom Prospective Diabetes Study[74, 75]. In addition, the data from the meta-analysis was taken from a number of different ethnic populations, ages, dietary interventions and medication interventions, and can thus be generalized to middle aged individuals with type 2 DM. Post intervention body weights did not significantly differ between the intervention and control groups (weighted mean difference 0.06, $p=0.60$). Meta-regression analysis indicated that the HbA_{1c} difference were independent of body weight (weight loss),

exercise intensity, or exercise volume. This finding suggests that even without weight loss, exercise can beneficially impact glycemic control. Exercise affects a number of mechanisms, not necessarily involved with weight loss, that decrease hepatic and muscle insulin resistance while increasing glucose disposal. These mechanisms include increased post receptor insulin signaling, increased glucose transporter and messenger RNA, increased glycogen synthase and hexokinase activity, decreased release and clearance of free fatty acids, increased muscle glucose delivery (due to an increased muscle capillary density), and changes in muscle composition which help to increase glucose disposal[76-83].

In their randomized trial of 251 adults ages 39 to 70 years with type 2 DM, Sigal et al also reported improvements in HbA_{1c} with aerobic and resistance training[84]. The absolute change in HbA_{1c} value in the aerobic training group was -0.51 percentage point compared to the control group (95% CI, -0.87 to -0.14). Similarly, a change of -0.38 was observed in the resistance training group compared with the controls (95% CI -0.72 to -0.22). The control group had an increase in HbA_{1c} of 0.07 percentage point whereas the aerobic group and resistance group had decreases of 0.43 and 0.30 percentage points respectively.

During physical activity, a 20-fold increase in whole-body oxygen consumption can occur in the working muscles. Skeletal muscle will use its own stores of glycogen, triglycerides, and free fatty acids from the breakdown of adipose tissue triglycerides and glucose released from the liver to meet the body's energy needs during exercise[64].

Skeletal muscle IR is the characteristic feature of patients with type 2 DM[26]. Although the primary cause of whole-body insulin resistance remains unclear, recent studies have improved our understanding of the molecular basis that leads to the beneficial role of exercise in stimulating the entry of glucose into insulin-sensitive tissues. These mechanisms include defects

in early and intermediate insulin signal transduction in skeletal muscle, gene expression, enzyme regulation, and lipid dynamics breakdown[26]. Insulin-mediated glucose uptake takes place mostly in skeletal muscle and is directly related to the amount of muscle mass while inversely associated with fat mass.

It has become well accepted that regular exercise is an effective therapy to improve insulin action in the skeletal muscle of insulin resistant individuals[3, 72, 85, 86]. Studies suggest that exercise increases both peripheral and visceral insulin sensitivity for 12 to 24 hours post exercise among individuals with type 2 DM[72, 87-89]. Exercise training studies have also established that PA can improve insulin sensitivity independent of its effect on weight loss and fat distribution[81, 90].

1.2.4 HIV Epidemiology

More than twenty-five years have passed since the first cases of the human immunodeficiency virus (HIV) emerged yet today the disease remains one of considerable public health significance. According to 2006 UNAIDS data, an estimated 38.6 million individuals live with HIV worldwide; 1.1 million of these reside within in the United States[91, 92]. The majority of individuals living with HIV in the US at the end of 2006 were nonwhite (65.4%) and almost half were men who have sex with men (MSM) (48.1%)[92]. Of the prevalent cases 74.8% were males and 70% of persons living with HIV in the US were between the ages of 25-49. In August 2008 the Centers for Disease Control and Prevention (CDC) estimated that approximately 56,300 people were newly infected with HIV in the United States in 2006 (95% CI: 48,200–64,500)[93]. This is higher than the previous estimate of 40,000. The new estimate also confirmed that gay and bisexual men of all races, African Americans, and Hispanics/Latinos were most affected[94].

HIV infects CD4 cells by integrating into host DNA. The virus converts its RNA into DNA through the use of a reverse transcriptase enzyme[95]. If left untreated HIV infection results in a chronic, progressive, and eventually fatal disease characterized by depletion of CD4 lymphocytes[96]. Although HIV and the acquired immunodeficiency syndrome (AIDS) claimed 545,805 lives in the United States since 1981, the effective use of highly active antiretroviral therapy (HAART) throughout the past decade significantly reduced morbidity and mortality among those affected with HIV[97-99].

Currently, there are 3 main classes of antiretroviral agents (ARV) in use, the reverse transcriptase inhibitors (RTI) [nucleosides (NRTI); non-nucleosides (NNRTI) and nucleotides], protease inhibitors (PI), and entry inhibitors[100]. NRTIs were the first type of drug available to treat HIV infection[95]. They contain faulty versions of the nucleotides used by reverse transcriptase to convert RNA into DNA. Due to the faulty nucleotides, new DNA cannot be correctly built and HIV's genetic material is not incorporated into the cell. Thus replication of new virus is prevented. NNRTIs attach directly to the reverse transcriptase enzyme, change its shape, and prevent the enzyme from converting RNA into DNA. Protease inhibitors block the ability of the protease enzymes to cut the long strands of amino acids into working proteins for HIV[95]. Therefore, the virus is unable to make copies to infect new cells. When used in combination with RTIs, PIs are the most effective HIV treatment to date[95]. Entry inhibitors are the newest antiviral drugs available to treat HIV infection and work by blocking the attachment of HIV to the CD4 T receptor or the CCR5/CXCR4 co-receptors[101].

1.2.5 Glucose disorders in HIV-infected populations

The wide spread usage of highly active antiretroviral therapy (HAART) presented unforeseen clinical challenges within the dynamic HIV epidemic[99]. As the paradigm of HIV treatment shifted from palliative care to chronic disease management, unexpected metabolic complications surfaced[102, 103]. Syndromes such as lipoatrophy, visceral fat redistribution and accumulation, hyperlipidemia, diabetes mellitus, impaired glucose tolerance, and insulin resistance began to occur in both individuals receiving HAART[102-106] as well as in HIV-infected patients not using ARV agents[100]. Patients with chronic HIV disease can have an abnormal metabolic profile including elevated lipids and insulin resistance. A full understanding of these complications remains elusive, but may involve a combination of antiretroviral therapy and duration of HIV infection (likely due to the pro-inflammatory effects of HIV itself[103]) as well as traditional risk factors such as lifestyle, body mass index (BMI)[11, 107-110], age, sex, and genetic predisposition[111, 112]. Adiponectin and a high level of free fatty acids have also been implicated with IR among individuals with HIV infection. Similarly, increased fatty acids in HIV patients with fat redistribution correlate with IR[113, 114].

1.2.5.1 Diabetes Mellitus

Prior to HAART introduction, cases of DM and IR rarely occurred in HIV-infected individuals[115]. Beginning as early as 1998, cross sectional and cohort studies reported an increase in glucose disorders among HIV-infected individuals[14, 103, 108, 109, 114, 116-120]. Prevalence estimates of DM among HIV-infected persons have been found to vary greatly and range from 1% to 16%[107-109, 118, 119, 121]. This range likely occurs for a number of reasons, including differing study designs and populations as well as the specificity and sensitivity of the diabetes definition

used. In one of the first studies, Carr et al reported a 7% DM prevalence among HIV-infected participants receiving protease inhibitors[116]. However, it is important to note that this study lacked an HIV-uninfected control group, had a small size and did not confirm glucose levels by subsequent testing. The majority of studies have documented prevalence rates between 6-10%,[118, 120, 122, 123] however a larger, prospective cohort study in 1278 HIV-uninfected and HIV-infected men by Brown et al found that prevalent DM was more common in HIV-infected men receiving HAART compared to HIV-uninfected men (14% versus 5%)[121]. HIV-infected men not on HAART were also found to have an increased risk of prevalent DM (PR 2.21; 95% CI 1.12-4.38) compared to HIV-uninfected men. However, it is important to note that FG levels were not confirmed by a subsequent test, which may have affected prevalence estimates. Regardless, the DM prevalence differences in HIV-infected versus HIV-uninfected participants deserve attention.

Extremes in prevalence estimates are noted. Brar et al, used a cohort of ART naïve participants which may account for their lower prevalence estimates (3.3%) given results from studies which suggest that ARVs may play a role in diabetes development[107]. They excluded participants over the age of 59 years (mean age 38 years) which may partially explain their lower estimates[107]. In addition, their DM definition was based on historic self-report rather than on glucose testing. In contrast, Howard et al reported much higher DM prevalence in their cross-sectional studies of HIV-infected and HIV-uninfected men and women[108, 109]. The first of these studies assessed the associations of HIV, HAART, and other factors with prevalent diabetes in a cohort of 288 HIV-uninfected and 332 HIV-infected middle-aged (ages 35-71) women[108]. Of these women, over 80% were black or Hispanic, 74% were overweight and 75% were not physically active. Diabetes was defined by self-report of a DM diagnosis. Of the entire cohort,

13% reported being told by a health care provider that they had DM and no differences were noted by HIV status (12% for HIV-infected and 13% for HIV-uninfected, p = 0.75) or by PI use (15% for PI experienced versus 8% for PI-naïve, p=0.06). A similar study by the same authors was conducted in a cohort of 643 HIV-uninfected and HIV-infected men ≥ 49 years. Of these men, over 75% were black or Hispanic, 58% were overweight and 70% were not physically active[109]. The definition for DM was analogous to their study in women. Of the entire cohort, 18% reported being told by a health care provider that they had DM and no differences were noted by HIV status (16% for HIV-infected and 20% for HIV-uninfected, p = 0.25) or by PI use (18% for PI experienced versus 12% for PI-naïve, p=0.13). The high prevalence rates in these two studies can likely be attributed to the high risk profiles in the study populations. The prevalence of DM in HIV-uninfected subjects (20% for men and 13% for women) was much higher than the prevalence in the general population (6-8%)[4, 5, 26, 29, 103]. A second study in women with similar demographics to the Howard study reported a 10.2% prevalence in HIV-uninfected women, 8.1% in HAART naïve women, and 4.2% of women on HAART (although these differences were not significant)[120]. These somewhat surprising results may be due to BMI and minority differences between the groups.

A number of studies have also assessed the incidence of DM in HIV-infected populations. Brown et al[121] (n=680 for incidence analysis) reported a 4-fold increase the incidence rate of DM in HIV-infected men on HAART compared to HIV-uninfected men (47 per 1000 person-years [PY] versus 14 per 1000 PY; age and BMI adjusted RR 4.11, 95% CI 1.85-9.16); however no differences in incidence rates were observed between HIV-infected men not using HAART (17 per 1000 PY) and HIV-uninfected men (demographics similar for men on HAART and men not on HAART). Because fasting glucose levels were not confirmed, it is

possible that the observed incidence rate in this study is overestimated. In addition, other factors such as physical activity and family history of DM were not assessed and may confound RR results. Ledergerber et al[14], in their cohort of 6513 HIV-infected participants from the Swiss HIV Cohort Study, reported a much lower incidence of DM (4.42 cases per 1000 person-years, 95% CI 3.7-5.3) while De Wit et al reported a similar low incidence of new onset DM (5.72 per 1000 person years, 95% CI 5.31-6.13) in a cohort of 32,437 HIV-infected men and women in Europe, the US, Argentina, and Australia. Explanations for these discrepancies include a lower population background DM incidence in Europe compared with the US[124], differing study demographics (lower mean age and BMI compared with the Brown study) and a confirmatory fasting glucose. However, neither of these studies had an HIV-uninfected control group.

Results from a multicenter (6 inner city US sites) prospective cohort study of 1435 HIV-infected and 350 HIV-uninfected women reported an incidence of 14 cases per 1000 person-years in HIV-uninfected women, 12 per 1000 person-years, 12 per 1000 person-years and 28 per 1000 person-years in the NRTI, no HAART, and PI groups respectively[13]. However, DM cases were based on self-report so misclassification was possible. Tien at el reported incidence rate results from the same cohort using fasting glucose levels or initiation of diabetes medications[125]. They reported a DM incidence rate of 19.6 per 1000 person-years in HIV-uninfected women, 15.3 per 1000 person-years in HIV-infected women not on HAART, 25 per 1000 person-years in HIV-infected women on HAART in combination with a PI and 28.9 per 1000 person-years in women on non-PI HAART; however none of the relative hazards significantly differed from one another. Therefore, chance cannot be ruled out. Regardless, these studies are important because they provided some insight into the incidence of DM in women, a less studied HIV-infected population.

This current literature has several limitations including differing DM definitions (making prevalence and incidence comparisons difficult), sample size differences and few studies in HIV-infected women and populations at lower risk for DM. In addition, it is important to note that the differences in DM and IR prevalence and incidence in the post-HAART era compared with the pre-HAART era could also be attributed to longer life expectancies (and thus more time to develop DM), increased testing and screening, and the 1997 change in diagnostic criteria which implemented a lower cutoff for DM (126 mg/dL)[126].

1.2.5.2 Insulin resistance

Walli et al[32, 127] and Carr et al[103, 116] were among the first to document the development of insulin resistance in HIV-infected individuals in epidemiological studies. Walli et al[32] reported a 61% prevalence of IR among patients treated with protease inhibitors as well as significantly lower insulin sensitivity (75 μmol/l/min) compared with therapy naive patients (156 μmol/l/min, $p<0.001$). Cross-sectional studies by Carr found that men on PI therapy had significantly higher insulin levels than both HIV-infected men not on PIs and HIV-uninfected men (9.1 versus 7.2 versus 5.1 mlU/l respectively) and reported a 16% prevalence of impaired glucose tolerance among the men on protease inhibitors[103, 116]. Conversely, Danoff et al, did not find significant differences in the HOMA score between 88 HIV-uninfected and 179 HIV-infected women ($p=0.4$) or by HIV-treatment group[120]. However, sample sizes were small in these studies and power may have been limited. Howard et al, did not find any difference in the prevalence of impaired glucose tolerance according to PI or HAART use in their cross-sectional studies of HIV-uninfected and HIV-infected men[109]. In addition, prevalence of IGT did not vary by HIV serostatus in men. Conversely, women receiving non-PI HAART were more likely to

have IGT when compared with HIV-uninfected women (25% versus 9%, P=0.02) [108]. Due to the cross-sectional design of these initial studies, a temporal relationship between PI use and IR could not be determined. In addition, subjects in these studies were not randomized to treatment group; therefore it is possible that other factors (such as PA and other unmeasured variables) confounded this relationship. In a case-control study, Hadigan et al matched 213 healthy HIV-uninfected control subjects (from the Framingham Offspring Study) to 71 HIV-infected patients with lipodystrophy[128]. Thirty HIV-infected participants without lipodystrophy were separately matched to 90 HIV-uninfected controls. Participants were matched on age and BMI. The study found that 35% of patients with lipodystrophy had impaired glucose tolerance. HIV-infected cases with lipodystrophy were more likely to have impaired glucose tolerance than their matched HIV-uninfected controls (OR 6.5 adjusted for waist-to-hip ratio, 95% CI 2.9-14.7). In addition, HIV-infected cases with lipodystrophy were more likely to have hyperinsulinemia (adjusted OR 3.2, 95% CI 1.7-7.2). Insulin levels and glucose levels did not significantly differ between HIV-infected patients without lipodystrophy and their HIV-uninfected controls. Selection bias may have affected results, as HIV-infected cases were responders to community-based advertisements or due to physician referrals and thus may differ from HIV-infected individuals who chose not to participate. Likewise, controls were not chosen in a similar manner but, instead, were taken from a large population based study. The varying results of the aforementioned studies underscore the difficulty in determining the exact prevalence and incidence rates of IR and IGT in HIV-infected populations.

While the exact mechanism is not known, a number of theories have been proposed to help explain the cause of IR in HIV-infected populations[102]. These mechanisms include direct metabolic effects from antiretroviral therapies[129, 130], metabolic dysfunction due to HIV infection

itself secondary to cytokine and hormonal abnormalities, and an interaction between HIV disease and antiretroviral therapies[128].

Numerous studies found an association between protease inhibitor use (specifically indinavir, amprenavir, nelfinavir, and ritonavir) and the development of IR[116, 131-135]. These results have been strengthened by studies showing that switching patients to other regimens improved the hyperglycemia[136, 137]. The use of PIs has been shown to lead to abnormal lipids and glucose metabolism even in the absence of HIV[132, 138]. For example, Noor et al found that indinavir reduced insulin sensitivity by 38% after a single dose in healthy, HIV-uninfected individuals[132]. Although the mechanism is not fully understood, current literature suggests that PIs may lead to insulin resistance by interfering with glucose transport and phosphorylation[130]. Others propose that PI regimens cause peripheral IR in skeletal muscle and adipose tissue as well as impair the ability of the beta cells to deal with these changes by reducing pancreatic beta cell insulin secretion[134, 135, 139]. In addition, PIs have been shown to inhibit GLUT4, a necessary rate-limiting step in the transport of glucose across cell membranes, thus decreasing the glucose regulating ability of GLUT4 with subsequent increases in cellular glucose uptake[100]. Other drug regimens such as nucleoside analogues may not directly affect glucose metabolism but still may contribute to IR through body fat distribution changes[135].

While the majority of literature does indicate that a relationship exists between PIs and IR[133, 134, 140], a number of studies found contradictory results suggesting that other medications, factors related to HIV, and traditional IR risk factors may be of importance[141]. Hadigan et al reported similar increases in fasting and 2-h insulin levels among PI-naïve patients as well as in both current and past recipients of PI therapy[128]. They also found that the duration of NRTI exposure but not duration of PI exposure predicted fasting hyperinsulinemia in multivariate

regression analysis and proposed that a more complex pathophysiologic mechanism for metabolic abnormalities exists. Howard et al, also did not find a significant association between PI use and IR likely due to the lower number of men on indinavir (13%) compared with other PIs that have a weaker effect on the development of IR[109, 131, 132, 142-146]. A larger, prospective cohort study by Brown et al assessed IR and its relationship to HAART in a cohort of HIV-infected and uninfected men and found that of the 3 major drug classes, only cumulative exposure to NRTI was independently associated with fasting hyperinsulinemia (OR 1.08; 95% CI 1.02-1.13) although cumulative exposure to PIs had a similar, but non-significant relationship (OR 1.06; 95% CI 0.99-1.14) [141]. It is possible that the lack of association with PIs in the above studies is due to the heterogeneous effect of protease inhibitors on IR. Grouping PIs together as class rather than assessing the effect of the individual PI may dilute any effect of the individual medication[141]. It is also important to recognize that studies focusing on cumulative or long-term drug effects may report conflicting results compared with those focused on recent drug exposure as PIs (specifically indinavir) typically lead to an acute onset of IR which is reversible after drug discontinuation[11].

1.2.5.3 Risk factors for glucose disorders in HIV-infected populations

While the mechanism for DM onset in HIV-infected populations is unknown, many authors speculate that protease inhibitor use plays a role due to insulin resistance[32, 100, 110, 129, 133, 134, 147, 148]. The rate at which IR and IGT progress to DM in HIV-infected individuals is not fully known and because insulin resistance from PIs is reversible, other risk factors for DM should be considered[11, 137]. Limited data is available on the association of DM with NRTI use although studies do suggest that cumulative exposure to this drug class may be associated with glucose disorders[11, 14, 125, 128, 141, 149]. The mechanism for this association is under investigation and may

involve inhibition of mitochondrial DNA polymerase-gamma[150]. It is possible that chronic HIV infection (due to prolonged inflammation and cytokine over expression)[103, 151, 152], and risk factors that are more specific to HIV-infected populations including hepatitis C virus infection (HCV)[122, 123, 153], drug-drug interactions[12, 110, 152], lipoatrophy and body fat redistribution[110, 128, 149, 154, 155], and a history of an AIDS defining illness[14, 107, 123, 153] may play a role in DM and IR development. However, it is important to note that risk factors vary from study to study depending on population, sample size and study design. For example, Mehta et al found that HCV infection was associated with hyperglycemia and DM[123] whereas Hughes et al[12] did not find an association and results from Ledergerber et al were inconclusive[14]. Further, Brar et al did not find an association between HCV coinfection and DM in HAART naive individuals[107]. Differences in HCV study populations such as younger age in the Hughes study and a larger percentage of minority participants in the Mehta study may explain these discrepancies as well as power differences based on sample sizes and variations in drug therapy. This example illustrates the difficulty of defining the risk factors associated with new onset DM and IR in HIV-infected populations.

Regardless of these discrepancies, findings from numerous studies underscore the importance of traditional risk factors in the development of DM in HIV infected populations[107-109]. Factors such as older age[11, 12, 14, 107, 109, 123, 148, 153], higher BMI[11, 107-110, 156, 157], black or Hispanic race[11, 12, 14, 107-109, 153], family history of DM[108, 109, 156] and male sex[11, 14] were consistently associated with DM in HIV-infected populations regardless of study design, population, or sample size.

1.2.6 Physical activity in HV-infected populations

1.2.6.1 Prevalence

In the general population, it is well accepted that a physically active lifestyle helps prevent many chronic diseases and conditions. Less is known about the risks and benefits of physical activity participation in HIV-infected individuals[158]. In fact, most of the studies have focused on exercise, a subset of PA[159]. Early studies suggest that physical activity can be implemented safely in HIV-infected populations, however results should be interpreted cautiously due to small sample sizes[160-169], high dropout rates[160, 165, 166, 168-170], and lack of an HIV-uninfected control group[160, 164, 165, 167-169] or a non-exercising control group[165, 169]. A 2004 meta-analysis by O'Brien et al was not able to confirm an overall effect of aerobic exercise on CD4, viral load, or $VO_{2max,}$ however they reported the possibility of clinically important improvements in VO_{2max} in exercisers compared with non-exercisers[171]. They attributed the lack of statistical significance to small sample sizes and concluded that aerobic exercise for HIV-infected adults appears to be safe due to the stability of immunological and virological measures as well as the absence of adverse event reports among exercisers in the included studies[171]. Mustafa et al reported that exercise was associated with slower progression to AIDS at 1 year (HR= 0.68, 90% CI 0.4-1.17). An increase in CD4 count by 107% during the year was also reported compared with non-exercisers[172]. The authors did not adjust for other factors in their models; therefore it is possible that improvements in CD4 count were due to factors such as medication adherence or better medical care. Despite these limitations, the fact that exercise appeared beneficial rather than harmful to CD4 count deserves attention. Bopp et al were the first to assess the effect of daily physical activity on CD4 cell counts and viral load in HIV-infected individuals and reported a significant, inverse association between PA levels (measured by wrist actigraph) and viral load

($r = -0.425$, $p=0.0061$)[173]. Although the cross-sectional design limited the ability to make causal inferences, the results do provide some evidence that HIV-infected persons who partake in regular physical activity may incur health benefits compared with their more sedentary counterparts. Current exercise recommendations for HIV-infected persons support the safety and efficacy of moderate to high intensity aerobic and resistance training if prescribed by a trained professional[174].

A few studies have assessed the prevalence of overall physical activity participation in HIV-infected populations[159, 175-180] and results varied greatly based on study population (Table 1). None of the studies were population based, making comparisons with the general population as well as the overall HIV-infected population difficult.

Arendt et al, reported a higher prevalence of activity in HIV-infected men than in Canada's general population (84.5% versus 56%)[175]. However, comparability is limited as participants in this study may not be representative of the general HIV-infected population (study consisted of white homosexual or bisexual men).

Filipas et al reported that nearly three quarters (73.8%) of their HIV-infected population met CDC and American College of Sports Medicine Guidelines (ACSM) for PA while 65.8% of their HIV-uninfected population met the guidelines[177]. However, this study had several limitations including a small sample size, limited demographic data, possible misclassification of HIV-uninfected participants (based on self-report only) and use of the International Physical Activity Questionnaire (IPAQ) which tends to overestimate physical activity levels[179, 181]. In an IPAQ validation study, Ramirez-Marrero et al[179] compared self-reported PA levels from the IPAQ with objective PA measures including accelerometer use and found that the IPAQ significantly overestimated moderate and vigorous PA compared with the Actigraph (mean

difference -268.6 $\pm$ 314.0 min/wk IPAQ > Actigraph, t = - 6.16, p< 0.01) in a sample of HIV-infected Hispanic adults. The proportion of participants who were classified as physically active (defined as $\geq$ 150 min/wk of moderate to vigorous PA) was 81% when using the IPAQ compared with 54% based on Actigraph data. Overestimations of PA were more frequent in men (72%) than in women (43%). This is the only study using an objective physical activity measure; therefore prevalence estimates are likely more accurate than estimates based on self-report. Unfortunately, the sample size was small and subjects from the parent study were not randomly chosen for participation. Larger, randomized studies are needed to verify their results. A cross-sectional study by the same authors found that HIV-infected participants reported participation in 1.5 hours/day of physical activity with 59% meeting the minimum PA recommendations of 30 minutes daily; however over reporting in this study was possible due to inconsistencies with reported amounts of hours spent watching television (up to 5.9 hours/day) as well as reports of minimal daily exertion (based on the Leisure Activity Inventory)[182].

Smit et al reported lower levels of vigorous PA in HIV-infected participants using HAART compared with HIV-uninfected participants and HIV-infected participants not using HAART suggesting a possible lower intensity PA tolerance among HAART users; however no significant differences in overall PA levels were found (p=0.26)[180]. Due to the cross-sectional design of the study, temporal inferences regarding HAART use and activity levels cannot be made. In addition, a greater proportion of HAART users had clinical AIDS (21.64% non HAART versus 15.19% HAART) and were less likely to be employed (25.32% non HAART versus 18.94% HAART) therefore it is possible that HAART users were more limited in PA due to illness. Muhammed et al also found that HIV-infected participants reported higher levels of PA than HIV-uninfected counterparts, however these results were not representative of the

general population as all participants had Nonalcoholic Fatty Liver Disease[178]. In addition, sample sizes were very small and HIV-infected participants were generally healthier with lower proportions of DM, hypertension and cardiovascular disease, which may partially explain the higher PA levels. Clingerman found that, while the majority of her Canadian HIV-infected population participated in some form of PA, only 28% met the *Healthy People 2010* recommendations for moderate activity (at least 30 min 5 or more days per week) and even less (19.2%) met the vigorous activity recommendations (at least 20 min 3 or more days per week)[176]. 39.7% did not meet any of the recommendations. This study also had a small sample size and did not have an HIV-uninfected control group making interpretation of results limited.

Florindo et al reported that 65% of HIV-infected men and women participated in "adequate" locomotion physical activity while 47.3% participated in leisure physical activity. Unfortunately, the authors do not define "adequate" so estimates may not be comparable to other studies[183]. Using the Minnesota Leisure Time Physical Activity Questionnaire, Domingo et al reported a physical activity prevalence of approximately 30% in HIV-infected participants living in Barcelona, Spain[184]. Again, small sample sizes and a lack of an HIV-uninfected group limit interpretation of results.

Finally, the Howard studies[108, 109] also found much lower prevalence estimates (> 70% classified as inactive) as did Danoff et al[120] and Mustafa et al[172]; however it is important to note that the definitions of physical activity were limited to exercise and may not capture other forms of activity done throughout the day such as walking at an occupation or for transportation. Their estimates likely underestimate the true PA prevalence based on this definition.

In general, the studies indicate that a significant number of HIV-infected persons do participate in some form of regular physical activity, although larger population studies are

needed to get more accurate prevalence estimates. The cultural diversity of the studies indicates that participation is occurring on a somewhat global scale, although estimates from developing nations are not available. The current studies have limitations such as small sample sizes, selection bias, reporting bias, mostly male participants, and lack of an HIV control group which make comparisons with the general HIV-infected population difficult. Given the clinic-based populations used in the aforementioned studies, it is possible that the HIV-infected participants in these studies represent a healthier and thus more active subset compared with the general HIV-infected population. In addition, all but one of the studies used self-reported PA measures possibly resulting in a reporting bias and a potential overestimation of PA prevalence. Studies using objective PA measures such as an Actigraph accelerometer are necessary to better understand the PA prevalence among HIV-infected individuals.

Table 1. Physical activity prevalence studies in HIV-infected populations

Author, year	*Study design*	*Study population*	*PA Measurement*	*Results*
Arendt (2008)	Cross-sectional	65 HIV-infected men from the University Health Network, Toronto, Canada with at least one feature of metabolic syndrome (mean age 47)	7 day PA log	84.5% met Canada's PA Guide (60 min of mild or 30-60 min of moderate activity per day) 41.4% sedentary using the classification of the Institute of Medicine More active than general Canadian Population (44.1% physically inactive)
Fillipas (2008)	Cross-sectional	191 HIV-infected patients and 70 HIV-uninfected patients (with non HIV infectious disease) from Infectious Disease Clinic of The Alfred hospital, Melbourne Australia, age range 18-81 years	International Physical Activity Questionnaire (IPAQ)	73.8% of HIV infected and 65.8% of HIV-uninfected participants met Centers for Disease Control and American College of Sports Medicine Guidelines
Ramirez-Marrero (2008)	Descriptive/ correlational	58 HIV-infected Hispanic adults from the AIDS Clinical Trials Unit in Puerto Rico; (mean age 46.5)	IPAQ; Actigraph accelerometer; pedometer	IPAQ: 81% classified as physically active ($\geq$ 150 min/wk of moderate to vigorous PA) Actigraph: 54% classified as physically active ($\geq$ 150 min/wk of moderate to vigorous PA) Pedometer: 17% classified as physically active ($\geq$ 10,000 steps/day)
Mohammed (2007)	Cross-sectional	26 HIV-infected (age 46.2) and 25 HIV-uninfected men (age 43.1) with Nonalcoholic Fatty Liver Disease from University Health Network clinics	7 day PA log	Physical activity was significantly higher in the HIV-infected group (8 units per day) compared with the HIV-uninfected group (4 units per day) (p=0.029)
Florindo (2007)	Cross-sectional	220 HIV-infected men and women from the AIDS Clinic of the Infectious and Parasitic Diseases Division, San Paolo, Brazil (Ages 18-59)	Baecke questionnaire	65% of participants reported adequate locomotion physical activity (70.6% women and 63.3% men) 47.3% participate in leisure physical exercise

Table 1. (continued)

Author, year	*Study design*	*Study population*	*PA Measurement*	*Results*
Smit (2006)	Cross-sectional	324 subjects (213 HIV- infected with mean age 42 and 99 HIV-uninfected with mean age 46) from the AIDS Linked to Intravenous Experiences (ALIVE) cohort (mostly African American cohort of inner city intravenous drug users)	Modified Paffenbarger questionnaire	Vigorous activity expenditure was lower among participants on HAART (267 kcal/day) than both HIV-uninfected (438 kcal/day) and HIV-infected participants not on treatment (623 kcal/day) however total energy expenditure did not significantly differ between groups (p=0.26)
Howard (2006)	Cross-sectional	279 HIV-uninfected men and 364 HIV-infected men (mean ages 54) (N=643) Inner city U.S (Bronx, NY)	Self-reported physical activity defined as moderate or strenuous for > 20 minutes on > 1day per week	29% of HIV-uninfected men were classified as physically active while 30% of HIV-infected men were physically active (difference not significant)
Howard (2005)	Cross-sectional	288 HIV-uninfected women (mean age 45) and 332 HIV-infected women (mean age 44) (N=620) Inner city U.S (Bronx, NY)	Self-reported physical activity defined as moderate or strenuous for > 20 minutes on > 1day per week	23% of HIV-uninfected women were classified as physically active while 20% of HIV-infected women were physically active (difference not significant)
Danoff (2005)	Cross-sectional	258 women: 88 HIV-uninfected (mean age 37.6), 74 HIV-infected not on HAART (mean age 37.6), 96 HIV-infected on HAART (mean age 37.6), Women's Interagency HIV Study Urban U.S.	Self-reported physical activity defined as > or < 6 hours per week	54% of HIV-uninfected women participated in > 6 hours compared with 56.2% of HIV-infected women not on HAART and 46.3% on HAART.

Table 1. (continued)

Author, year	*Study design*	*Study population*	*PA Measurement*	*Results*
Ramirez-Marrero (2004)	Cross-sectional	68 HIV-infected men (n=43) and women (n=25) recruited from the AIDS Clinical Trial Unit (mean age 40.4) Puerto Rico	Seven-Day Physical Activity Recall	41% of HIV-infected adults did not meet the minimal PA recommendation Time spent in daily physical activity was an average of 1.2 hours per day with most of the reported activities occupational 32% reported participating in leisure PA (walking, jogging, etc)
Clingerman (2003)	Cross-sectional	78 HIV-infected men (n=70) and women (n=8) ages 23-70 years who received primary care at an infectious disease clinic or community support at a local agency (Northern Great Lakes Region of U.S.)	Physical Activity Questionnaire (PAQ)	73.08% of participants engaged in moderate PA while 19.2% engaged in vigorous PA 51.7% participated in PA for recommended weekly frequency. 28.2% met *Healthy People 2010* recommendations for moderate PA and 7.7% met recommendations for vigorous PA 39.7% did not meet any of *Healthy People 2010* recommendations
Domingo (2003)	Cross-sectional	120 HIV-infected men and women (mean age 39) recruited from participants in a cross-sectional study of metabolic disturbances Barcelona, Spain	Minnesota Leisure Time Physical Activity Questionnaire	28.0% of participants physically active (>143 kcal/day) using stavudine and 25.3% physically active using zidovudine
Mustafa (1999)	Prospective cohort	156 HIV-infected (mean age 35) and 259 HIV-uninfected (mean age 37) men participating in The Longitudinal AIDS Impact Project (New York City)	Self-report "How many times a week do you engage in physical exercise?"	29% of HIV-infected and 28% of HIV-uninfected men were non-exercisers 35% of HIV-infected and 31% of HIV-uninfected men exercised daily 36% of HIV-infected and 41% of HIV-uninfected men exercised 3-4 times/wk

1.2.6.2 Prevention of diabetes in HIV-infected populations

Because PA and exercise are cost-effective health promotion interventions that could decrease the need for health care resources, slow HIV disease progression, and prevent or delay the onset of chronic conditions, the role of physical inactivity as risk factor for DM in HIV-infected persons deserves attention given the prevalence of HIV-infected populations already participating in regular physical activity[32, 100, 129, 133, 134, 147, 175-177, 180]. Unfortunately, the majority of the studies assessing risk factors for DM in HIV-infected populations did not account for levels of physical activity, an important risk factor for DM in HIV-uninfected populations[11-14, 107]. Therefore, the results of previous studies that observed an association between HAART use as well as other non-traditional risk factors and DM/IR might have been confounded by PA levels. Brar et al clearly state in their manuscript introduction that studies aimed at understanding the risk factors associated with DM in HIV-infected populations discount traditional "classic risk factors" yet in their study assessing risk factors for DM among ART naïve participants, they do not account for physical activity levels (although the authors do recognize this limitation)[107]. Similarly, Hughes et al and Palacios et al emphasize the importance of traditional risk factors in the development of DM in HIV-infected populations, yet did not assess physical activity[12, 110]. Further, the newly released European AIDS Clinical Society guidelines on the prevention and management of metabolic diseases in HIV acknowledged the limited amount of available literature with respect to PA and DM and base their physical activity recommendations for the prevention of DM on "extrapolations from general medical guidelines[185]."

Only 4 studies have addressed associations between physical activity with DM and IR in HIV-infected populations (Table 2). Howard et al define "physical activity" as moderate or

strenuous exercise for $\geq$ 20 min on > 1 day/week[108, 109]. Among their participants, 70% of both HIV- uninfected and HIV-infected men were inactive while 79% of women were inactive. They found that physical inactivity was associated with previously diagnosed diabetes in HIV-uninfected and HIV-infected women (OR 0.4, 95% CI 0.2-0.96); however this result was not replicated in their study of HIV-infected men (OR 0.6, 95% CI (0.3-1.4). The discrepancy in findings may be attributed to the demographic differences between the two cohorts given the comparable study designs and sample sizes. Risk factors such as black or Hispanic race/ethnicity and older age could potentially have overridden any PA effect among the male cohort. In comparison, the female cohort had younger mean age (by 10 years) as well as a lower percentage of individuals of black or Hispanic race/ethnicity potentially allowing for an increased PA effect. Conversely, Danoff et al did not find an association between PA and DM in their cross-sectional study of 258 HIV-infected and HIV-uninfected women[120]. However, the sample size was small and power may have been limited. Further, PA was defined differently (< or > 6 hours of exercise per week) than in the Howard study, making comparisons difficult. The smallest of the 4 cross-sectional studies evaluated the association between IR and habitual exercise in a cohort of 120 HIV-infected individuals[186]. The authors report a significant independent and inverse relationship between total exercise (defined as number of sessions per week x duration per session x intensity) and IR (std β = -.20, P=0.03). In contrast to the 3 other studies, their cohort consisted of mostly white individuals with a lower than average BMI, a large proportion of whom participated in some form of exercise. Therefore, participants may have started with a lower background DM risk profile. Despite a paucity of literature, regular PA is recommended for HIV-infected individuals with IR and DM; therefore it is possible that individuals with IR in that study were encouraged to exercise potentially leading to their

observed results[187]. Finally, they lacked an HIV-uninfected control group and were thus unable to control for HIV status in their multivariate analysis.

Limitations do exist in the current literature. All 4 of the studies were cross-sectional and therefore were unable to assess any causal relationship between physical activity and the development of DM and IR. It is possible that low physical activity is a result of the diabetes, rather than a precursor to its onset or that that PA activity was started based on doctor recommendations to manage IR and DM[187]. Recent literature implies that the presence of diabetes may independently contribute to impaired exercise capacity[188]. Left ventricular dysfunction [188], aging, female sex, poor diabetes control, reduced heart rate recovery, obesity[189, 190], race[190], impaired femoral arterial blood flow[191], and impaired exercise stroke volumes[192], as well as microvascular diabetic complications including neuropathy and retinopathy[193] may be associated with impaired exercise capacity in individuals with type 2 diabetes. Regensteiner et al, also observed a reduced rate of oxygen consumption increases during treadmill testing of healthy patients with non-insulin dependent diabetes, indicating that oxygen delivery limitations may lead to impaired exercise performance[194].

Secondly, three of the studies used cohorts that included a majority of individuals at very high risk for DM due to older age, higher BMI, black/Hispanic ethnicity, and lower levels of PA[108, 109, 120]. In addition, all 4 studies were conducted in urban or inner city sites in the United States. Thus results may not generalize to HIV-infected populations at lower risk for DM. Two of the studies used self-reported DM as their outcome rather than measuring glucose levels for all participants while the other studies did not confirm glucose levels on a subsequent visit[108, 109]. Finally, it is important to note that none of the 4 studies measured physical activity in its entirety but rather focused exclusively on exercise, a subset of PA. This is important because it is

possible that an individual was physically active throughout the day (i.e. at an occupation, completing housework, walking for transportation, etc) without actually participating in structured exercise[16]. Therefore, results may actually underestimate a true PA effect. Conversely, a reporting bias due to the use of self-report exercise may have lead to an overestimation, especially in the Gavrila study, which had a large proportion of individuals who reported exercise participation[186].

Due to the paucity of literature as well as limitations in the current literature, large prospective cohort studies or randomized trials, similar to those completed in HIV-uninfected populations are necessary to assess the role of PA in the prevention of DM and IR in HIV-infected populations. Further, these studies must use validated physical activity questionnaires or objective PA measures to accurately assess the PA levels (including exercise) of the study populations.

Table 2. Studies assessing physical activity as a risk factor for diabetes and insulin resistance in HIV-infected populations

Author (year)	Study design	Sample	Measurement of IR/DM	Physical activity assessment	Results
Howard (2006)	Cross-sectional	279 HIV-uninfected men and 364 HIV-infected men (mean ages 54) (N=643) 54 HIV-uninfected men and 126 HIV-infected men for metabolic substudy (mean ages 54) (N=216) Inner city U.S (Bronx, NY))	Self-report Fasting glucose and OGTT for metabolic substudy	Defined as moderate or strenuous for > 20 minutes on > 1day per week	DM risk factors: use of non-PI HAART (OR 1.8, 95% CI 1.03-3.0), current methadone treatment (OR 6.7, 95% CI 3.8-11.9), alcoholism (OR 1.7 95% CI 1.1-2.7), high BMI (OR 1.4, 95% CI 1.8-6.2), and family history of DM (OR 3.5, 95% CI 2.2-5.6) Metabolic substudy IR risk factors: waist circumference ($p<0.0001$) and history of heroin use ($p=0.005$) Abnormal OGTT risk factors: age > 55 (OR 2.0 95% CI 1.03-3.9), Hispanic ethnicity (OR 3.8, 95% CI 1.05-14.0) *Physical activity not associated with DM or IR
Danoff, (2005)	Cross-sectional	258 women: 88 HIV-uninfected (mean age 37.6), 74 HIV-infected not on HAART (mean age 37.6), 96 HIV-infected on HAART (mean age 37.6), participating in Women's Interagency HIV Study Urban U.S. (Bronx/Manhattan, NY and San Francisco, CA)	DM: Fasting glucose, self-report, use of hypoglycemic medications, OGTT IR: HOMA	> or < 6 hours per week of exercise	DM risk factors: BMI (per kg/m^2) (OR 1.104, $p < 0.0002$) *Exercise not associated with DM or IR

Table 2. (continued)

Author (year)	Study design	Sample	Measurement of IR/DM	Physical activity assessment	Results
Howard (2005)	Cross-sectional	288 HIV-uninfected women (mean age 45) and 332 HIV-infected women (mean age 44) (N=620) 88 HIV-uninfected women and 133 HIV-infected women for metabolic substudy (mean ages 44 and 45 respectively) (N=216) Inner city U.S. (Bronx, NY)	Self-report Fasting glucose and OGTT for metabolic substudy	Defined as moderate or strenuous for > 20 min on > 1day per week	DM risk factors: current methadone treatment (OR 1.8, 95% CI 1.01-3.3), high BMI (OR 2.6, 95% CI 1.04-6.7), family history of DM (OR 2.7, 95% CI 1.6-4.7), and physical activity (OR 0.4, 95% CI 0.2-0.96) Metabolic substudy IR risk factors: waist circumference ($p<0.0001$), Hispanic ethnicity ($p=0.01$), and PA ($p=0.03$) Abnormal OGTT risk factors: age > 50 (OR 3.8 95% CI 1.3-11.2), family history of DM (OR 2.7, 95% CI 0.1-0.6), PA (OR 0.2, 95% CI 0.1-0.6), and smoking (OR 1.5 per 10 pack-years, 95% CI 1.3-1.8)
Gavrila (2003)	Cross-sectional	120 HIV-infected men and women Urban U.S. (Boston)	DM: Fasting glucose IR: HOMA	Self-report Cumulative index= number of sessions per week x duration per session x exercise intensity	*significant inverse association between total exercise and IR (std β= -.20, P=0.03)

1.2.6.3 Management of glucose disorders

A few small prospective studies and clinical trials have investigated the role of exercise on glucose and insulin reduction in HIV-infected populations with varying results[111, 195, 196]. Driscoll et al randomized 42 HIV-infected participants to one of two treatment groups (metformin alone and metformin + exercise). Participants in the exercise arm completed 3 months of an aerobic and resistance training program. Significant differences for fasting insulin ($p=0.03$) were reported between the two treatment groups[196]. The metformin + exercise group had a greater decrease in insulin levels from baseline compared with the metformin alone group. Conversely, in their randomized trials of 40 HIV-infected women and 42 HIV-infected men and women, Dolan et al and Terry el al did not find significant reductions in fasting glucose levels between an exercise group and the control group[169, 197, 198]. Similarly, Thoni et al did not find significant differences from baseline in fasting insulin, fasting glucose, or insulin resistance levels after completion of a 16 week aerobic training program in 19 HIV-infected adults (p-values not reported)[199]. In a prospective study of 18 men with HIV-infection no significant reductions in insulin were noted after completion of a 16 week resistance training program[200]. Finally, Fitch et al randomized 34 men and women with HIV-infection and metabolic syndrome to a lifestyle intervention, modeled after the Diabetes Prevention Project intervention, and to a control group[111]. Fasting glucose levels and hemoglobin A1C percentage did not significantly change in the lifestyle group when compared with the control group. Insulin levels and IR (HOMA) improved in the subjects in the intervention group compared to the control group; however the results were not significant due to small sample sizes.

Significant limitations in this literature restrict the interpretation of results. None of the studies utilized an HIV-uninfected control group; therefore the effect of HIV cannot be

examined. Sample sizes were very small in all studies and power to detect differences was limited. All of the studies recruited participants from clinics so results cannot be generalized to the general HIV-infected population. Measures such as HbA_{1c} were not assessed in 3 of the studies therefore the effect of the activity on direct glycemic control is not fully known. None of the studies used participants with diagnosed type 2 DM, so the effect of exercise on potentially higher baseline fasting glucose and insulin levels in HIV-infected populations is also unknown. In addition, the studies were all very short (6 months or less) compared to those completed in the general population. Larger and longer population based intervention trials are necessary to fully understand the effect of exercise and physical activity on the management of DM and IR in HIV-infected populations.

1.2.7 Physical activity and physical function correlation

1.2.7.1 HIV-uninfected populations

Although related, physical activity and physical function have differences. Physical activity is defined as any voluntary movement produced by the skeletal muscles that results in increased energy expenditure[201], whereas physical function is defined as one's ability to carry out various activities that require physical capability, ranging from self-care (activities of daily living) to more vigorous activities that require increasing degrees of mobility, strength, or endurance[202]. Physical activity is associated with reduced risk of mortality, onset of diseases, and incident disability while maintaining physical function is of great importance to successful aging[18, 203, 204]. Despite these differences, numerous cross-sectional and prospective studies in HIV-uninfected populations established that physical activity levels are correlated with physical function

performance and that low physical activity is a risk factor for declines in physical function[15-18, 201, 203-210].

While prior studies in aging populations utilized self-report measures only[206-211], Brach et al observed a correlation between objective physical activity measures (pedometer) with the Functional Status Questionnaire (FSQ) (a self-report measure of physical function) ($r=0.34$, $p<0.01$) and the Physical Performance Test (PPT) (a comprehensive performance-based measure of function) ($r=0.41$, $p< 0.01$) in a cohort of 290 community dwelling older women[15]. Correlations for the aforementioned physical function measures with a self-report physical activity questionnaire (Modified Paffenbarger) were also reported ($r=0.34$, $p < 0.01$ for the FSQ; $r=0.16$, $p <0.05$ for the PPT; $r=0.24$). It is important to note that this study excluded women with physical limitations that might have prevented walking and thus the women participating in this study were functioning better than 90% of the community-dwelling older adults. In addition, the majority of women was of upper social and economic class and was Caucasian. Therefore, results may not generalize to more disadvantaged populations.

Studies are not limited to geriatric populations. A recent study of 8,702 U.S. and 1,507 British middle-aged adults (aged 50 to 69), found that physical activity was protective against impaired physical function (self-report and measured) independent of BMI[205]. Participants who reported $\geq$ 3 days of activity per week had a lower incidence of physical impairment than individuals who reported less activity in each BMI category (recommended weight, overweight, obese). Hillsdon et al also showed that regular physical activity (defined as 2.5 hours per week of moderate PA or $\geq$ 1 hour of vigorous activity per week) was associated with higher self-reported physical function (OR 1.6, 95% CI 1.3-1.98 adjusted for age, gender, chronic illness, baseline PF, BMI, smoking, and SES) in a cohort of 6,398 middle aged men and women (aged 39 to 63

years) [18]. Despite the lack of objectively measured physical activity, these studies are important because they extend the protective effect of physical activity on physical function to slightly younger populations.

Although less common, studies have also shown that individuals with impaired physical function and lower perceived physical function are less likely to participate in regular physical activity. According to the U.S. Department of Health and Human Services national survey data, people with physical disabilities and chronic illness were less likely to report participation in moderate physical activity than their healthy counterparts (27.2% versus 34.4% participation) as well as vigorous physical activity (9.6% versus 14.2% participation)[39]. Similarly, according to *Healthy People 2010*[212], 56% of individuals with disabilities reported no leisure-time PA compared to 36% without disabilities. Only 12% of persons with disabilities reported 30 min of moderate PA 5 or more days per week[212].

In a study of 2311 men and women with diabetes, Plotnikoff et al found that higher levels of physical activity were independently associated with lower levels of perceived disability among individuals with type 1 ($\beta = -0.22$, $P<0.001$) and type 2 diabetes ($\beta = -0.18$, $P<0.001$) [213]. Due to the cross-sectional study design, causal inferences between impaired physical function and physical activity could not be addressed. In addition, the study did not use an objective measure for physical function or physical activity, instead relying on self-report. The potential for reporting bias exists. A stronger, longitudinal study by the same authors produced similar results[214]. Participants with diabetes who reported less difficulty in completing tasks of daily living were more likely to participate in higher levels of physical activity ($\beta = -0.08$, $P<0.001$ in type 2 diabetes and $\beta = -0.12$, $P<0.001$ in type 1 diabetes).

These findings demonstrate that, although different, physical function and physical activity are associated with one another. The data suggest that physical activity participation not only predicts physical function but is also lower among individual with functional limitations and disability.

1.2.7.2 HIV-infected populations

Similar studies have not yet been completed in HIV-infected cohorts in the post-HAART era; therefore the relationship between physical activity and physical function in this population is unknown. A pre-HAART randomized trial assessed the effectiveness of a 15-week home based aerobic exercise program on health related quality of life measures, including physical function[160]. One hundred twenty three HIV-infected subjects were randomized to a control group or an exercise group. Physical function was measured using the Medical Outcomes Study HIV Health Survey. Following the 15-week exercise program, no significant difference in physical function was reported between the control group and the exercise group ($p=0.47$). Of note, non-exercisers tended to report lower physical functioning (89.6% versus 86.5% in the exercise and control group respectively). These results, however, are limited to aerobic exercise only and do not encapsulate physical activity as a whole. Results must be interpreted with caution because occupational physical activity levels were not assessed and may have confounded results if differences between groups existed.

In a small prospective study of 6 men with AIDS wasting and 19 men and women with HIV infection but without wasting, Roubenoff and Wilson, reported an increase in physical function status in patients with HIV wasting who completed a resistance training program[21]. Of note, this study did not assess overall physical activity, but rather a progressive resistive training program. Further, an HIV-uninfected control group was not included and sample size was small.

Clinical predictors for current levels of function and declines in physical functioning among individuals with AIDS were evaluated in studies by Wilson et al; however physical activity was not one of the variables that was assessed[215, 216]. In addition, these studies were completed prior to HAART introduction. In light of the longer life expectancy and decreased morbidity due to HAART use[99], factors need to be re-examined.

Despite the lack of literature in HIV-infected populations, studies of the relationship between PA and physical functioning in cohorts with other chronic conditions have been completed. Seeman et al reported that regular physical activity protected against declines in physical function in older adults (ages 70-79 years) with histories of hypertension, cancer, and cardiovascular disease[217]. Similarly, Stewart et al reported that higher baseline levels of exercise were associated with better physical function both at baseline and after 2 years for individuals with chronic diseases[218]. These findings underscore the importance of using PA to promote higher levels of physical functioning, even among those with chronic conditions[217, 218]. In light of these promising results, studies in individuals with chronic HIV-infection are warranted and similar effects should be possible.

Older adults now comprise a greater proportion of HIV-infected individuals due to the success of highly active antiretroviral therapy as well as an increase in new infections among adults older than age 50[99, 219]. It has become necessary to address not only HIV infection but also co- morbidities associated with the normal aging process. In fact, Oursler et al demonstrated that co- morbid conditions were associated with impaired physical function independent of HIV status[220]. Although the impact of HIV infection and aging on physical function is documented, the association of physical function with physical activity levels has not been assessed[220]. Maintaining physical function has been shown to be a key aspect of healthy

aging in the general population[221] and will likely become more of a focus in HIV-infected individuals as HAART use continues to slow disease progression[220]. Therefore, it is imperative to identify factors, such as physical activity, that promote independent and disability free functioning in persons aging with HIV.

1.2.8 Relationship between self-report and performance-based measures of physical function

1.2.8.1 HIV-uninfected populations

Physical function can be measured using either self-report or performance-based measures. Self-report questionnaires are often used due to their low cost and ease of administration[222]. However, discrepancies between an individual's perception of ability and actual ability do exist and self-report measures may be influenced by psychosocial factors including mood, expectations, attitudes, and psychological distress[222, 223]. Performance-based measures have face validity and are sensitive to change over time yet likely depend on a participant's motivation to perform the task and may not accurately reflect performance in daily life[222].

A number of studies have assessed the association between these two types of measurements among differing populations. In general, the results across studies are comparable and suggest that, at most, performance-based measures are only moderately correlated with measures of self-report[222, 224-227]. Correlation coefficients in studies among older adults, patients with low back pain, and patients with fibromyalgia were similar and generally ranged from 0.1 to 0.6 depending on task and self-report survey used[222, 223, 226, 228, 229]. The lack of a stronger correlation is likely due to the fact that performance-based and self-report measures assess different aspects of the physical function construct[226]. While performance-based measures

examine an individual's actual ability to complete a task through performance observation, measures of self-report rely on an individual's perception of his or her ability to complete the task[226]. Given these results, it is reasonable to suggest that the most accurate measure of physical function may be a complementary approach using both self-report and performance-based measures as subjective measures may provide useful information beyond that obtained solely on observation[226].

1.2.8.2 HIV-infected populations

To date, similar studies have not yet been conducted in HIV-infected cohorts, therefore the relationship between performance-based and self-report measures in this population is not known. Clarifying this relationship may help to provide insight into the possible overlap between differing measures of physical function. This is important to gain a comprehensive understanding of physical function among individuals with HIV infection and to establish whether both types of measurements are beneficial to fully explain an individual's functional capacity.

Studies have been conducted which characterize levels of physical function among HIV-infected populations. Simmonds et al utilize both performance-based and self-report measures in their study of 100 HIV-infected men and women on the differential influence of pain and fatigue on physical performance. Yet, they do not assess associations between the two types of physical function measurements[230]. Their study suggests that, as a group, physical performance among HIV-infected individuals was much lower than "age-equivalent healthy patients." They report that their population took up to 4 times as long to complete a sit-to-stand task and walked 180 meters slower than healthy individuals. However, these results should be interpreted with caution as their study did not have an HIV-uninfected group and the authors do not describe

where they obtained the data from the "healthy patients" used in the aforementioned comparisons. In addition, a large percentage of their population (48%) were classified as having AIDS and may represent a sicker and thus more functionally impaired cohort of HIV-infected individuals. O'dell et al, in their cross-sectional analysis of 546 HIV-infected men with AIDS, found that 10% to 50% of men reported some degree of physical disability (based on self-report physical function using the HIV Health Assessment Questionnaire)[231]. The disability scores were more severe with the completion of higher level instrumental activities of daily living. It is important to note that this study was conducted in the pre-HAART era therefore these estimates may no longer be applicable. In addition, because all participants had AIDS, results may not generalize to more healthy HIV-infected populations. Finally, an HIV-uninfected group was not utilized so it is not known how these results compare to the general population. Population based studies have also been conducted. Crystal et al assessed self-reported physical functioning in 2836 participants in the HIV Cost and Services Utilization Survey (United States) using a 9-item scale[232]. They found that physical limitations were more prevalent in tasks which required higher levels of energy expenditure such as stair climbing (43% limitation) and walking greater than 1 block (26% limitation) compared with self care tasks such as bathing or dressing (14% limitation). Protease inhibitor use was found to be associated with significantly less physical limitation ($p< 0.05$). A similar study was conducted by Rusch et al among 762 HIV-infected members of the British Columbia Persons with AIDS Society[233]. A fifteen-item questionnaire was used to assess how well individuals were able to manage typical daily tasks such as eating and walking one block. Activity limitations were reported in the majority of respondents (80.6%). A median of 3 limitations was reported. A significant difference in the percentage of activity limitations was observed after stratification by CD4 count ($p=0.041$). Limitations in

these studies do exist. Both studies utilized measures of self-report physical function which may not accurately reflect an individual's actual functional ability. Self-reported measures are often influenced by psychosocial factors such as mood, cognition, expectations, reporting bias, attitudes, and emotional distress[223, 230]. In addition, HIV-uninfected comparison groups were not used and a potential for selection bias existed, especially in the Rusch study which mailed questionnaires to potential participants.

Two recent studies by Oursler et al found similar levels of physical functioning among HIV-infected and HIV-uninfected participants. Their study of 889 HIV-infected and 647 HIV-uninfected participants in the Veterans Aging Cohort 5-Site Study found no significant difference in the unadjusted mean physical disability score when stratified by HIV serostatus ($p=0.4$)[220]. In addition, the proportion of participants who reported difficulties with basic ADLs, mobility, and vigorous activities was similar in HIV-infected and HIV-uninfected participants ($p>0.05$ for all activities). Regardless of HIV status, a higher percentage of individuals reported difficulty in more physically demanding tasks such as heavy work or active sports (>50%) compared with basic ADLs such as dressing (<9%). It is important to note that these results were unadjusted and that the HIV-infected population in this study was younger than the HIV-uninfected population. In addition, the physical function measure was based on self-report and thus may not reflect actual abilities. However, a second study by Oursler utilized functional performance testing[234]. A total of 32 HIV-infected and 47 HIV-uninfected men from the Baltimore VA participated. Functional performance measures included grip strength, the 6-min walk test, and graded exercise testing on a treadmill. HIV-infected men aged 40 years and older were found to have a 41% reduced VO2 peak compared to age and gender-matched controls; however the mean 6-min walk distance was reduced only 8% compared to expected values for

healthy adults (adjusted for age, gender, and BMI). After stratification by age, only the middle-aged HIV-infected subjects (50-59 years) had significantly reduced grip strength as compared to published values for healthy men of similar age ($p=0.02$). No significant differences were observed in the younger (40-49 years) or older men (60-69 years) when compared with healthy men by age group. Grip strength was reduced by 10% (41.3 kg vs 46.2 kg) in HIV-infected adults using a weighted average. This study was limited by small sample sizes and a potential for selection bias as all participants were volunteers. Thus, results may not be representative of all patients with HIV. Finally, HIV-uninfected controls were selected to be free of co-morbid conditions as compared with the HIV-infected men who were not necessarily excluded based on the presence of conditions such as diabetes and coronary artery disease. Therefore, it is possible that any observed differences are not solely due to HIV disease and results should be interpreted with caution.

Finally, a study by Bauer et al compared measures of balance and gait between 78 HIV-uninfected volunteers to 28 HIV-infected participants receiving no ARV therapy, 25 receiving only nucleoside analogue therapy, and 37 participants receiving HAART[235]. They found no significant differences in measures of proximal strength (360 degree turn, time to complete 5 chair rises) and gait speed and cadence between any of the groups. This study differs from the Oursler studies in that the majority of participants were female. A potential selection bias towards a healthier HIV-infected subset is possible as participants were chosen on a volunteer basis from an outpatient clinic. Therefore, results may not be representative of the entire HIV-infected population.

1.2.8.3 Physical function and glucose disorders

Numerous studies suggest that glucose disorders such as diabetes are associated with functional impairment[236-244]. Yet, few studies have assessed measures of physical function as risk factors for glucose disorders despite recent literature showing that the loss of muscle mass and strength with age is associated with type 2 DM[238, 242]. None of these studies were conducted in HIV-infected populations. Lazarus et al examined the cross-sectional and prospective relationships between handgrip strength and fasting insulin levels in 655 men from the Normative Aging Study cohort[245]. Although handgrip strength was not found to be significantly correlated with unadjusted fasting insulin levels (r=-0.06), a negative cross-sectional association was observed after adjustment for confounders (p=0.013). Similarly, in their prospective analysis, higher baseline handgrip values predicted lower fasting insulin levels after twenty years (p=0.017). The authors suggested that skeletal muscle weakness may serve as a marker for an increased risk of hyperinsulinemia and may ultimately predict the development of insulin resistance. Generalizability in this study is limited to males and it is important to note that markers of insulin resistance (i.e. HOMA or QUICKI) were not assessed. A cross-sectional study by Sayer et al assessed the relationship between grip strength and metabolic syndrome in 1684 men and women born in Hertfordshire United Kingdom. The HOMA formula was used a marker of IR while DM and IGT were classified using a 2 hour glucose concentration. They reported a significant association between lower handgrip strength and a higher 2 hour glucose (0.07 standard deviation increase, p=0.001) and with an increased HOMA (0.05 standard deviation increase, p=0.008) independent of weight, levels of PA, and age. Despite these results, it is important to note that a temporal relationship could not be established as this study was cross-

sectional in design. Larger prospective studies are necessary elucidate the role of physical function as a risk factor for IR and DM in both HIV-uninfected and HIV-infected populations.

1.2.9 Summary

It is well established that metabolic disorders including insulin resistance and diabetes mellitus are prevalent in HIV-infected adults. Although the current dogma implicates HAART use, the true cause of these disorders remains unclear. The effect of physical activity and physical function is glaringly absent from the majority of studies that assess risk factors for DM and IR in HIV-infected populations despite its known importance in HIV-uninfected populations. Therefore, previous studies may have been affected by uncontrolled confounding. In addition, the relationship between self-report and performance-based measures of physical function in HIV-infected populations has not been defined. As individuals age with chronic HIV infection, it is imperative to identify early predictors of glucose disorders in order to help prevent the chronic complications associated with their progression[22]. This is especially important for individuals with HIV-infection who may already be at risk for physical disability due to HIV associated symptoms[220].

The objective of this dissertation is to define the role of measures of physical function, a correlate of physical activity, as risk factors for diabetes mellitus and insulin resistance among HIV-uninfected and HIV-infected men in the Mutlicenter AIDS Cohort Study and, further, to describe the association between self-report and performance-measures of physical function in order to gain a comprehensive understanding of physical function among individuals with HIV-infection.

2.0 MANUSCRIPT 1: SELF-REPORTED LOW PHYSICAL FUNCTION IS ASSOCIATED WITH DIABETES MELLITUS AND INSULIN RESISTANCE IN HIV-INFECTED AND HIV-NEGATIVE MEN

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2.1 ABSTRACT

Aims: This study investigated the association between self-reported physical function (as a surrogate for physical activity) and diabetes mellitus (DM) and insulin resistance (IR) among HIV-infected and negative men.

Patients and Methods: 384 HIV-negative and 274 HIV-infected men from the Pitt Men's Study contributed data. DM was defined by fasting serum glucose levels. IR was calculated using the homeostasis model assessment. The Physical Functioning Ten Scale from the Short Form-36 Health Survey measured physical function. Multivariate logistic regression assessed the independent association between physical function and DM and IR.

Results: Physical function, older age, and black race were associated with DM in multivariate analysis. Physical function/HIV interaction, older age, higher BMI, HIV infection, and black race were associated with IR in multivariate analysis.

Conclusions: This study suggests that self-reported low physical function is associated with DM and IR in HIV-negative and HIV-infected men.

2.2 INTRODUCTION

The wide spread usage of highly active antiretroviral therapy (HAART) presented unforeseen clinical challenges within the dynamic HIV epidemic. As the paradigm of HIV treatment shifted from palliative care to chronic disease management, new metabolic complications surfaced including insulin resistance (IR) and diabetes mellitus (DM)[102, 103]. A full understanding of these complications remains elusive, but may involve a combination of antiretroviral therapy and duration of HIV infection as well as lifestyle, body mass index (BMI), age, sex, and genetic predisposition[111, 112]. Prospective studies in HIV negative individuals suggest that participation in physical activity plays a significant role in the prevention of type 2 DM and insulin resistance[71, 246]. However, the role of physical inactivity as a contributing factor to the development of DM has been overlooked in most studies of HIV-positive populations. The few studies that have assessed physical inactivity as a risk factor for DM yielded conflicting results[108, 109]. Physical inactivity was found to be associated with previously diagnosed diabetes among HIV-positive women; however despite similar methods and sample sizes, this observation was not replicated in HIV-positive men[108, 109]. These studies by Howard, et al used a high risk cohort of mostly older black and Hispanic individuals without a standardized assessment of physical activity. Therefore results may not generalize to other ethnic populations[108, 109].

Although related, physical activity and physical function have differences. Physical activity is defined as any voluntary movement produced by the skeletal muscles that results in

increased energy expenditure[201], whereas physical function is defined as one's ability to carry out various activities that require physical capability, ranging from self-care (activities of daily living) to more vigorous activities that require increasing degrees of mobility, strength, or endurance. Despite these differences, numerous studies in HIV-negative populations established that physical activity levels are correlated with physical function performance. Both cross-sectional and prospective studies suggest that low physical activity levels are an independent predictor of low physical function[15-20]. Among HIV-positive populations, resistance training has been shown to improve self-reported physical function in patients with HIV wasting[21]. Therefore, the use of physical function as a surrogate for physical activity is justified.

Current studies document a substantial prevalence and incidence of DM in HIV-positive men. Data from the Multicenter AIDS Cohort Study (MACS) reported a 14% prevalence of diabetes mellitus (DM) among HIV-positive men compared to 5% among HIV-negative men and an incidence rate of 4.7 cases per 100 person-years compared with an incidence rate of 1.4 cases per 100 person years among HIV negative men[106]. There is also a greater reported prevalence of insulin resistance in HIV-positive patients with lipodystrophy (35%) compared to matched controls without HIV (5%)[128]. This trend is also noted in HIV-positive patients without lipodystrophy (5.6% IR prevalence) as compared to controls (3.3 IR prevalence)[128].

Given the strong association between low physical activity and DM among HIV negative individuals as well as the known risk for DM and IR development in HIV-positive men, the role of low physical activity in the HIV-positive population warrants further investigation. Therefore, the objective of this study was to investigate the role of self-reported low physical function as a surrogate for low physical activity as a potential contributor to diabetes mellitus and insulin resistance among HIV-positive and HIV negative men.

2.3 METHODS

2.3.1 Study participants

All study participants were from the Pitt Men's Study in Pittsburgh, PA, one of four clinical centers which contribute data to the MACS. The MACS is an ongoing multicenter prospective cohort study of HIV infection in homosexual and bisexual men. Briefly the MACS follows a 6-month visit schedule and involves detailed data collection regarding medical history, physical examination, and collection of biological specimens. Institutional review boards at each site approved the MACS protocol, and each participant provided informed consent. Further detail can be found in Kaslow et al[247]. The MACS is currently in the 47th consecutive 6-month follow-up period of the original cohort.

The current study includes data taken after implementation of the MACS Metabolic Study in April 1999 (Visit 31) at which time fasting serum samples (fasting $\geq$ 8 hours) were added to measure glucose and insulin levels and for use in diagnosing diabetes. 772 men from the Pitt Men's Study were eligible for inclusion in this study. Of these, 658 (384 HIV negative and 274 HIV-positive) participants had a fasting serum sample from which insulin and glucose concentrations were obtained.

2.3.2 Outcome Ascertainment-Diabetes Mellitus and Insulin Resistance

For the purpose of this study, a diabetes outcome was defined by fasting serum glucose levels drawn at each bi-annual visit from April 1, 1999 through March 31, 2006. The first visit at which a participant underwent a fasting serum determination was defined as the baseline visit. Participants with a fasting glucose of less than 100 mg/dl for all visits were classified as "normoglycemic"; participants with at least one fasting glucose level between 100 and 126 mg/dl were classified as "pre-diabetic"; and participants with at least one fasting glucose level of 126 mg/dl and above were classified as having "diabetes." This diabetes definition was chosen based upon a similar definition used by recently published literature in HIV-positive cohorts[106, 120]. Using this definition, 86 men were classified as "diabetic." Of these 86, 38 had confirmed glucose levels of $\geq$ 126 mg/dl at their next visit; an additional 8 were placed on diabetes medications and 9 had a second non-consecutive visit with a glucose measurement of $\geq$ 126 mg/dl. Participants with glucose levels consistent with diabetes ($\geq$ 126 mg/dl) at baseline were not excluded from analysis (n=10).

Insulin concentrations were also obtained from the fasting serum samples with normal insulin defined as $\leq$ 15 μU/ml and high insulin defined as >15 μU/ml based on the published normal range for the insulin assay used. Insulin resistance was calculated using the homeostasis model assessment (HOMA): [fasting insulin (μU/ml) x fasting glucose (mmol/L)]/22.5[248]. HOMA-IR levels were further classified into a dichotomous variable for use in logistic regression based on the median level of 3 μU/ml x mmol/L. Glucose levels were converted to mmol/L by dividing mg/dl by 18.

2.3.3 Exposure-Self-Reported Physical Function

The Physical Functioning Ten (PF 10) Scale from the Medical Outcomes Study (MOS) Short Form-36 (SF-36) Health Survey served as a surrogate for a measure of physical activity. The SF-36 is one of the most widely used Health Related Quality of Life Instruments and consistently demonstrates high levels of both reliability (>0.70) and validity[249]. Specifically, for the PF 10, Jenkinson et al report a Cronbach's alpha of 0.93[250] while relative validity has been reported at 1.00[251].

This study includes data from PF 10 questionnaires administered at each bi-annual visit from April 1, 1999 through March 31, 2006 (except visit 43: April 1, 2005 through September 30, 2005). During the administration of the PF-10, participants were asked the following question regarding physical activities that might be done in a typical day: "Does you health now limit you in these activities? If so, how much?" Participants chose between "Yes, limited a lot", "Yes, limited a little", or "No, not limited at all" for vigorous activities (running, lifting heavy objects); moderate activities (vacuuming, golf); lifting or carrying groceries; climbing several flights of stairs; climbing one flight of stairs; bending, kneeling, or stooping; walking more than a mile; walking several blocks; walking one block; bathing or dressing (Table 3). Each item was scored on a 0 to 100 range as follows: 100= not limited at all; 50= limited a little; and 0= limited a lot, based on the RAND scoring method.[252] A mean of the 10 activities was then calculated to determine an overall score for the PF 10 ranging from 0 to 100 with a score of 100 indicating that a participant's health did not limit his ability to complete physical activity. Thus, a lower score indicates lower physical function. The first visit at which a participant has a PF score was defined as the baseline visit. Given the strong correlation between an individual's baseline

physical function score and his overall mean physical function score (r=0.82; p <0.0001), the baseline score was used in the analysis.

2.3.4 Covariates

Covariates of interest included age, race, HIV status, AIDS status, body mass index (BMI), and CD4 count and were obtained for all individuals from the baseline visit, defined as the visit at which a participant had an initial recording of the covariate during visit 31-visit 44. These covariates were chosen because of their association with physical function and/or diabetes development[253, 254].

2.3.5 Statistical Methods

SAS Version 9.1 was used for all statistical analysis. The Fisher exact, Wilcoxon, and Kruskal-Wallis nonparametric tests, as appropriate, were used to test for differences in proportions and distributions for both HIV serostatus and diabetes status groups. Differences in physical function scores between glycemic groups (normal, pre-diabetes, and diabetes) were assessed using the Kruskal-Wallis Test. These differences were also tested after stratification by HIV status as well as AIDS status. Chi-square and Wilcoxon Rank Sum tests were used to assess associations between physical function scores for insulin levels and HOMA scores stratified by HIV serostatus. Statistical significance was determined using two tailed tests with an alpha of 0.05. Univariate logistic regression analysis was performed to assess unadjusted associations between predictors and the binary outcome of interest, diabetes status. We compared individuals with

diabetes to those with normoglycemia; individuals with pre-diabetes were excluded from the regression analysis thus reducing the sample size to 289 for this analysis only. Multivariate logistic regression using a forward stepwise methodology for the addition of significant variables was used to assess the association between DM and baseline physical function score as well as to assess the association between IR and baseline physical function using a p-value cut-off of <0.05 for inclusion in the model. Predictors that were not significant in the multivariate analysis were not retained in the model regardless of statistical significance in univariate analysis. Regression analysis was also completed separately for HIV-negative and HIV-positive men to determine whether or not risk factors for elevated glucose and insulin resistance differed by HIV status.

2.4 RESULTS

The baseline characteristics of the 658 men stratified by glucose level and HIV serostatus are displayed in Table 4. Seventy five percent of men were white. Overall, HIV negative men were older than HIV-positive men. BMIs were significantly lower among HIV-positive in those with pre-diabetes and diabetes and among HIV-positive men with normoglycemia although the difference was not significant. CD4 counts, as expected, were significantly lower in HIV-positive men independent of diabetes status. Fasting insulin levels and HOMA scores were higher among the HIV-positive men across all glucose levels, although the differences were not statistically significant.

Men with diabetes mellitus were older and had higher BMIs than men with normoglycemia and pre-diabetes. A higher proportion of black men as well as HIV-positive men

with AIDS had fasting glucose levels consistent with diabetes. In both HIV-positive and HIV negative men, IR and hyperinsulinemia increased progressively from those with normoglycemia to pre-diabetes and diabetes.

Table 5 shows the individual mean self-reported physical function scores by diabetes status for thirteen six-month periods commencing April 1, 1999. Men with diabetes consistently had the lowest physical function scores while men with normoglycemia and pre-diabetes had relatively similar scores. Significant differences between the three glucose levels occurred in later visits likely due to larger sample sizes (accounting for a second MACS recruitment).

In both HIV-negative and HIV-positive men, baseline physical function scores were lower for men with hyperinsulinemia. In addition, physical function scores were lower in HIV-positive men compared to HIV-negative men for both insulin levels. Similarly, baseline physical function scores were lower in men with HOMA levels > 3 in both HIV negative and HIV-positive men. Physical function scores were lower for both HOMA levels in HIV-positive men as compared to men without HIV (Tables 6 and 7).

The relationship between DM status and baseline physical function by HIV serostatus and men with AIDS is illustrated in Figure 1. Overall, the best physical function scores were observed among HIV-negative men with normoglycemia. HIV-negative males had better physical function scores compared with HIV-positive males in each of glucose levels. Among HIV-negative males, mean physical function scores decreased as glucose levels increased ($p<0.0001$). The men with normoglycemia had the highest physical function scores while the men the diabetes had the lowest scores in HIV-negative men, HIV-positive men and men with AIDS; however significant differences were only observed in the HIV-negative group, likely due to the small number of men with HIV-infection and AIDS. In addition, the mean physical

function scores for men with AIDS were lower than both the HIV negative men and the HIV-positive men in all three of the glucose levels. Men with both diabetes and AIDS had the lowest mean physical function score among all groups.

In the univariate analysis (Table 8), lower physical function score (OR 1.9 per 25 unit decrease, p <0.0001); higher BMI (OR=1.6 per 5 units, p=0.0012) and older age (OR 1.5 per 5 years, p<0.0001) were found to be independently associated with diabetes. Baseline CD4 counts, AIDS status, HIV status and race were not significantly associated with diabetes in the univariate analysis. However, in the multivariate analysis, lower physical function score (OR=1.5 per 25 unit decrease, p=0.02), older age (OR = 1.5 per 5 years, p<0.0001), and black race (OR=2.8, p=0.002) were found to be significantly associated with diabetes. BMI and AIDS were not found to be significant at p=0.05 and thus were not included in the final model. However, given the known relationship between BMI and DM in HIV-negative populations[255] a sensitivity analysis was completed to determine if results changed with BMI forced into the model (data not shown). All three variables, physical function, age and race, remained significant with BMI in the model, suggesting that BMI did not influence DM in this study therefore BMI was removed from the model for parsimony. Given the observation that physical function scores were slightly lower among HIV-positive men compared with negative men, an interaction between HIV serostatus and mean physical function scores was tested in both univariate and multivariate analysis. This interaction was not statistically significant (p=0.9; data not shown). After stratification by HIV infection, age and race remained significantly associated with DM status regardless of HIV status, however BMI was associated with diabetes in the HIV-negative men. Physical function was not associated with diabetes in either HIV group after stratification.

Table 8 also shows univariate and multivariate associations with IR. In the univariate analysis, physical function score (OR=2.4 per 25 unit decrease, $p<0.0001$); older age (OR=1.3 per 5 years, $p<0.0001$); higher BMI (OR=2.6 per 5 units, $p<0.0001$) and HIV infection (OR=1.5, $p=0.01$); and black race (OR=2.0, $p=0.006$) were associated with IR. However in the multivariate analysis, the HIV/physical function interaction became significant (OR 2.1, $p=0.0003$) while older age (OR=1.3 per 5 years, $p<0.0001$); higher BMI (OR=2.8 per 5 units, $p<0.0001$); HIV infection (OR=11.3, $p=0.0002$); and black race (OR=2.0, $p=0.002$) remained associated with IR. Neither CD4 count nor AIDS status were associated with IR in either univariate or multivariate analysis. After stratification by HIV infection, BMI, age, and race were associated with IR in HIV-negative men and age, BMI, and physical function were associated with IR in HIV-positive men.

2.5 DISCUSSION

Our data suggest that self-reported low physical function as a surrogate for low physical activity is associated with DM, independent of HIV status. After adjustment for age and race, physical function remained significantly associated with DM such that for every 25 unit decrease in physical function score, the odds of having DM increased by 50% ($p<0.05$). This result is strengthened by our observation that insulin levels and insulin resistance were also associated with lower physical function scores especially among HIV-positive men (Tables 6 and 7). While the main effect of physical function score was not associated with IR in multivariate analysis, the significance of the physical function/HIV status interaction deserves attention. This indicates that the effect of low physical function on insulin resistance depended upon HIV status such that

the odds of having insulin resistance were greater for men with both low physical function scores and HIV infection (OR 2.1, p=0.0003). Alternatively, the association between HIV infection and IR, but not DM, may simply indicate that IR precedes DM and we had greater statistical power to detect this. While this association needs to be replicated in other cohort studies, it is important to encourage physical activity among individuals with HIV. Using previously published studies that support the use of physical function as a surrogate for physical activity[15-20], it is plausible to suggest that low physical activity levels may be associated with the onset of insulin resistance and DM in HIV-positive men.

In addition, our finding that physical function scores were lowest among persons with AIDS provides important information regarding DM in our population despite the lack of statistical significance. As shown in Figure 1, persons with AIDS contributed strongly to lower physical function scores among those with diabetes. This association is highly plausible as persons with late stage HIV infection and AIDS have likely experienced multiple events which contributed to lower physical function over a long history of HIV infection. It is possible that the lack of statistical significance was due to the limited sample of persons with AIDS (n=28). Studies with larger samples of individuals with AIDS should be completed to further clarify the contribution of AIDS to the complex relationship between physical function and DM in the HIV positive population.

BMI was not found to be associated with diabetes mellitus in the multivariate analysis in this study. While higher BMI is a known risk factor for DM, BMIs among HIV-positive individuals tend to be lower with subsequent loss of subcutaneous adipose tissue (without increases in visceral adipose tissue) compared with the HIV-negative population [256-258]. This was true in our study in which 40.3% of HIV negative men were overweight compared with

36.5% in the HIV-positive group. The HIV-negative men also had higher frequencies of obesity compared to the HIV-positive men. Therefore, the lack of association between BMI and DM after adjustment for HIV status and the other covariates is not surprising. Our result was strengthened by the observation that BMI was associated with DM in the HIV-negative men but not in the HIV-positive men. This seemingly contradictory finding highlights the difficulty in assessing the role of BMI as a risk factor for most metabolic disturbances common to those with HIV infection. We were unable to measure visceral fat as a component of BMI in this study and therefore our inferences are limited to BMI.

Our findings using physical function as a surrogate for physical activity support a previous observation by Howard et al that physical activity may be independently associated with diabetes mellitus in HIV-positive women[108]. However, this result was not replicated in their similarly designed study in a sample of HIV-positive men[109]. Likewise, Danoff et al[120] failed to find an association with physical activity and diabetes among HIV-positive women. The current study differs from these three previous studies as it is composed primarily of Caucasians (75%) rather than African American and Hispanic cohorts. Compared to the Howard men's study[109], the HIV-positive men in our cohort have a younger median age (42 years) but similar BMI compositions (45% with normal BMI). The differing demographics between studies may partially explain the discrepancy between our findings and those in the Howard study. Because both older age and African American race are known risk factors for diabetes mellitus[253], our cohort of younger, Caucasian men may allow for an increased association of low physical function and diabetes mellitus compared to the older, African American cohort in the Howard study. However, comparisons between our study and the Howard studies are difficult given our use of physical function data as a surrogate for physical activity level.

The present study had several limitations. First, given the design of this study, a temporal relationship between impaired physical function and diabetes development was not determined. Therefore, it is possible that the lower physical function scores are a result of the diabetes, rather than a precursor to its onset. Recent literature implies that the presence of diabetes may independently contribute to impaired exercise capacity[188]. Left ventricular dysfunction [188], aging, female sex, poor diabetes control, reduced heart rate recovery, obesity[189, 190], race[190], impaired femoral arterial blood flow[191], and impaired exercise stroke volumes[192], as well as microvascular diabetic complications including neuropathy and retinopathy[193] may be associated with impaired exercise capacity in type 2 diabetes. Regensteiner et al, also observed a reduced rate of increase in oxygen consumption during treadmill testing of healthy patients with non-insulin dependent diabetes, indicating that oxygen delivery limitations may lead to impaired exercise performance[194]. However, given the noted correlation between the baseline and overall mean physical function scores in our study, it is reasonable to suggest that physical function scores did not drastically decrease following the onset of diabetes. It is also important to note that other factors such as ongoing substance abuse, depression, and chronic physical and mental health issues may also affect physical function. Future research using larger cohort studies to establish incident diabetes cases are necessary to establish a temporal association and to verify the results of this analysis while simultaneously assessing the contribution of additional factors to low physical activity. Secondly, the physical function measure used in this study does not objectively measure physical activity but rather serves as a surrogate by assessing how a person's health status limits his ability to complete physical function tasks. As previously discussed, numerous studies in HIV-negative populations established that physical activity levels are correlated with physical function performance. Brach et al observed a correlation between

pedometer readings as a measure of physical activity with the Functional Status Questionnaire (r=0.34); the Physical Performance Test (r=0.41); and gait speed (r=0.52)[15]. Both cross-sectional and prospective studies suggest that low physical activity levels are an independent predictor of both measured and self-reported low physical function[15-20]. A recent study in 8,702 U.S. and 1,507 British middle-aged adults (aged 50 to 69), found that physical activity was protective against impaired incident physical function (self-report and measured) independent of BMI.[205] Participants who reported $\geq$ 3 days of activity per week had a lower incidence of physical impairment than individuals who reported less activity in each BMI category (recommended weight, overweight, obese). Hillsdon et al also show that regular physical activity (defined as 2.5 hours per week of moderate PA or $\geq$ 1 hour of vigorous activity per week) is associated with high self-reported physical function (OR 1.6, 95% CI 1.3-1.98 adjusted for age, gender, chronic illness, baseline PF, BMI, smoking, and SES) in a cohort of 6,398 middle aged men and women (aged 39 to 63 years)[18]. Despite the lack of objectively measured physical activity, these studies are important because they extend the protective effect of physical activity to slightly younger populations. While similar studies have not yet been conducted in HIV-positive cohorts, Roubenoff and Wilson, reported an increase in physical function status in patients with HIV wasting who completed a resistance training program[21]. Therefore, the use of physical function as a surrogate for physical activity, although not ideal, was justified. Studies that objectively measure physical activity levels will need to be completed to verify and strengthen our results. Finally, this study was unable to assess the impact of antiretroviral therapy on diabetes mellitus as over 90% of the HIV-positive men utilized HAART at some point during the study period and there was little variation in the duration of HAART usage. However, this inability to assess the association of HAART and DM does not detract from our inference that impaired physical

function is associated with DM given that physical function scores were significantly lower in the both the HIV-negative and HIV-positive men with diabetes.

2.6 CONCLUSIONS

Despite evidence that physical inactivity may play a role in the development of DM among HIV-negative individuals[63, 71, 246], the majority of studies of DM and IR in HIV-positive populations have not accounted for physical activity, potentially over-estimating the role of anti-retroviral therapy as a cause of diabetes in this population[10, 123, 259]. This study found that self-reported low physical function as a surrogate for physical activity was associated with DM and IR in both HIV-positive and HIV-negative men. Given these results, future research using objective physical activity measures is warranted to further understand the contribution of low physical activity to DM and IR among HIV-positive populations. Ongoing HIV cohort studies addressing the issues of glucose metabolism in HIV-positive populations should address the role of physical activity.

2.7 SUMMARY POINTS

- HIV-positive men had lower physical function scores than HIV-negative men.
- HIV-positive men had lower physical function scores than HIV-negative men regardless of insulin level and HOMA score.

- Men with diabetes had consistently lower mean physical function scores than both the pre-diabetic men and the normoglycemic men.
- Baseline physical function scores were lower for men with hyperinsulinemia and men with HOMA levels > 3 among HIV-negative and HIV-positive participants.
- Men with both diabetes and AIDS had the lowest mean physical function score among all men.
- In multivariate analysis, lower physical function score (OR=1.5 per 25 unit decrease, p=0.02), older age (OR = 1.5 per 5 years, p<0.0001), and black race (OR=2.8, p=0.002) were found to be significantly associated with diabetes.
- In multivariate analysis, older age (OR=1.3 per 5 years, p<0.0001); higher BMI (OR=2.8 per 5 units, p<0.0001); HIV infection (OR=11.3, p=0.01); black race (OR=2.0, p=0.004); and the interaction between HIV and physical function (OR=2.1, p=0.0003) were associated with IR.
- This study concluded that low physical function (as a surrogate for physical activity) was associated with DM and IR in both HIV-positive and HIV-negative men.
- Future research using objective physical activity measures is warranted to further understand the contribution of low physical activity to DM and IR among HIV-positive populations.

2.8 FUTURE PERSPECTIVE

Over the next decade, clinical trials among HIV-positive populations similar to those completed in HIV-negative populations would be required in order to establish a casual

association between low physical activity and the onset of DM and IR. This will take time. At present, researchers and clinicians alike are encouraged to consider the potential for a similar benefit to HIV-positive individuals as demonstrated in the general population. As this relationship becomes more clearly recognized, increased physical activity will become an integral part of diabetes prevention and management in HIV-positive individuals.

2.9 TABLES

Table 3. Physical Function 10 (PF 10) questions from the Medical Outcomes Study (MOS) 36-Item Short Form Health Survey (SF 36)

"The following items are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much"	Yes, Limited A Lot	Yes, Limited a Little	No, Not Limited at all
Vigorous activities, such as running, lifting heavy objects, participating in strenuous sports			
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf			
Lifting or carrying groceries			
Climbing several flights of stairs			
Climbing one flight of stairs			
Bending, kneeling, or stooping			
Walking more than a mile			
Walking several blocks			
Walking one block			
Bathing or dressing yourself			

Table 4. Baseline demographics by HIV serostatus and glucose levels

	Normal n=203		Pre-Diabetes n=369		Diabetes n=86		Overall P-value[+]
Baseline Characteristic	HIV-Negative n=125	HIV-Positive n=78	HIV-Negative n=209	HIV-Positive n= 160	HIV-Negative n=50	HIV-Positive n =36	
Age (median)	41.5	39.0	45.5	42.6	52.9	48.0***	<0.0001
(range)	18.7-76.9	22.7-57.2	18.6-70.9	21.8-64.2	30.7-79.1	24.0-68.4	
Race n (%)							0.05
White	95 (76.6)	65 (83.3)	176 (84.2)	133 (83.1)	34 (69.4)	26 (72.2)	
Black	27 (21.8)	13 (16.7)	30 (14.4)	24 (15.0)	15 (30.6)	8 (22.2)	
Other	2 (1.6)	0 (0)	3 (1.4)	3 (1.9)	0 (0)	2 (5.6)	
BMI (median)	25.3	23.8	26.3	25.4**	28.2	25.2***	0.0008
AIDS n (%)	N/A	10 (4.9)	N/A	11 (3)	N/A	8 (9.30)	
CD4 (median)	851.0	548.0*	942.0	496.0**	927.5	471.5***	0.7
Insulin n (%)							<0.0001
≤ 15 μU/ml	92 (73.6)	50 (64.1)	91 (43.5)	57 (35.6)	8 (16)	1 (2.78)	
> 15 μU/ml	33 (26.4)	28 (35.9)	118 (56.5)	103 (64.4)	42 (84)	35 (97.2)	
HOMA-IR, median μU/ml x mmol/L	2.2	2.4	3.0	3.3	6.5	6.7	<0.0001

Wilcoxon Rank Sum for continuous variables and Fisher's Exact for categorical variables for serostatus comparisons

Kruskal-Wallis for continuous variables or Fisher's Exact for categorical variables for overall glucose comparisons

BMI: Body mass index; HOMA-IR: homeostasis model assessment insulin resistance

* p <0.05 between HIV negative and HIV-positive men with normoglycemia

** p <0.05 between HIV negative and HIV-positive with pre-diabetes

*** p <0.05 between HIV negative and HIV-positive with diabetes

+exact p-value for comparisons between the three glucose groups with HIV negative and HIV-positive combined

Table 5. Mean cross-sectional Physical Function 10 scores from the Short Form-36 by diabetes status at each visit date (HIV-negative and HIV-positive men)

Visit Date	*Normo-glycemic*	*Pre-Diabetes*	*Diabetes*	*p-value*
4/1/1999-9/30/1999 (n=27)	90.7	97.3	89.0	0.89
10/1/1999-3/31/2000 (n=114)	85.5	89.1	86.1	0.96
4/1/2000-9/30/2000 (n=106)	96.9	88.9	78.8	0.23
10/1/2000-3/31/2001 (n=119)	89.0	92.4	84.4	0.42
4/1/2001-9/30/2001 (n=101)	90.0	91.3	86.3	0.79
10/1/2001- 3/31/2002 (n=190)	86.9	91.4	89.5	0.35
4/1/2002- 9/30/2002 (n=202)	89.6	90.6	82.8	0.01*
10/1/2002- 3/31/2003 (n=245)	93.5	91.1	87.6	0.09
4/1/2003- 9/30/2003 (n=340)	91.4	90.7	77.9	<0.0001*
10/1/2003- 3/31/2004 (n=337)	93.6	89.4	79.0	0.008*
4/1/2004- 9/30/2004 (n=370)	90.7	90.8	80.8	0.009*
10/1/2004- 3/31/2005 (n=375)	91.5	88.6	78.2	0.003*
10/1/2005- 3/31/2006 (n=388)	92.2	88.1	77.5	<0.0001*

Kruskal-Wallis Test for all comparisons
*indicates significant at p <0.05

Table 6. Baseline characteristics of study populations by HIV serostatus and insulin levels

	HIV-negative (n=366)			HIV-positive (n=239)		
	Insulin ≤ 15 μU/ml	Insulin >15 μU/ml	P-value	Insulin ≤ 15 μU/ml	Insulin >15 μU/ml	P-value
Physical function score (mean)	93.4	87.1	0.0008	90.9	82.1	0.05
Age (median)	42.4	50.4	<0.0001	41.2	42.7	0.05
BMI (median)	25.5	27.5	<0.0001	25.4	24.3	0.13
Race, n (%)			0.02			0.15
White	221 (59.6)	77 (20.8)		136 (54)	61(27)	
Black	39 (10.5)	29 (7.8)		22 (8.7)	20 (8.3)	

Note: Wilcoxon Rank Sum for continuous variables and Chi square test for categorical variables; BMI: Body mass index

Table 7. Baseline physical function score by HIV serostatus and HOMA score

	HIV-negative (n=366)			HIV-positive(n=239)		
	HOMA-IR ≤ 3 μU/ml x mmol/L	HOMA-IR > 3μU/ml x mmol/L	P-value	HOMA-IR ≤ 3 μU/ml x mmol/L	HOMA-IR > 3μU/ml x mmol/L	P-value
Physical function score (mean)	93.4	86.5	<0.0001	91.4	80.8	0.008

Note: Wilcoxon Rank Sum for continuous variables and Chi square test for categorical variables. HOMA-IR: homeostasis model assessment - insulin resistance; BMI: Body mass index

Table 8. Multivariate logistic regression analysis of baseline factors associated with diabetes and insulin resistance among HIV-positive and -negative men

Risk Factor	Unadjusted OR	p-value	Adjusted OR	p-value	Unadjusted OR	p-value	Adjusted OR	p-value
	Diabetes (n=262)				Insulin resistance (HOMA-IR) (n=239)			
Physical function score (Per 25 unit decrease)	1.9	<.0001	1.5	0.02	2.4[+]	<.0001	1.2	0.26
Age (Per 5 year increase)	1.5	<.0001	1.5	<.0001	1.3	<.0001	1.3	<0.0001
BMI (Per 5 unit increase)	1.6*	0.0012			2.6	<.0001	2.8	<0.0001
AIDS Status[a]	2.0*	0.2			1.5**	0.3		
HIV Status[b]	1.2*	0.6			1.5	0.01	11.3	0.01
Race[c]	1.6	0.1	2.8	0.002	2.0	0.006	2.0	0.004
CD4	1.0*	0.9			1.0**	0.4		
Physical function/HIV interaction							2.1	0.0003

2.10 FIGURES

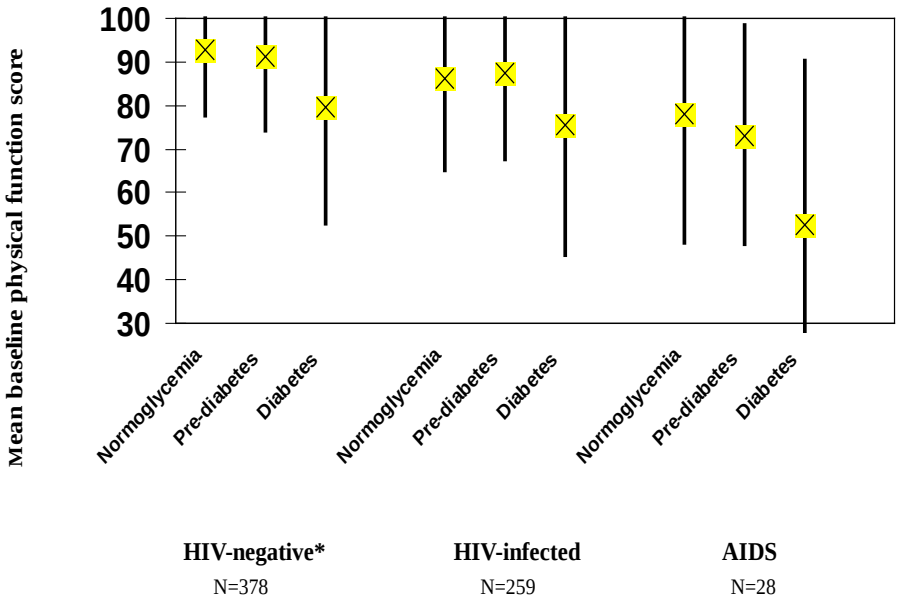

Figure 1. Mean baseline physical function scores by diabetes status for HIV-negative men, HIV-positive men, and men with AIDS (Mean + 1 standard deviation)

3.0 MANUSCRIPT 2: LOW PHYSICAL FUNCTION AS A RISK FACTOR FOR INCIDENT DIABETES MELLITUS AND INSULIN RESISTANCE IN THE MULTICENTER AIDS COHORT STUDY

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3.1 ABSTRACT

Aims: To evaluate relationships between physical function, incident diabetes mellitus (DM) and insulin resistance (IR) among HIV-infected and uninfected men.

Methods: We analyzed data from 1790 HIV-infected and uninfected men in the Multicenter AIDS Cohort Study. DM was defined in two ways using less stringent and more stringent criteria. The Physical Functioning Ten Scale from the Short Form-36 Health Survey measured baseline physical function. Cox regression assessed associations between physical function and DM and IR.

Results: 73 men developed diabetes using the more stringent definition compared to 238 using the less stringent definition. Cumulative DM incidence was highest among HIV-uninfected and HIV-infected men with low physical function. Physical function was a risk factor for DM in HIV-uninfected men and remained so after controlling for BMI, DM family history, and race using both the more stringent (hazard ratio (HR) 1.31; 95% CI 1.02-1.66) and less stringent (HR 1.29; 95% CI 1.11-1.50) diabetes definitions. Among HIV-infected men, physical function was an independent risk factor for DM using the less stringent diabetes definition.

Conclusions: This study supports our previous findings that low physical function is an important risk factor for DM in the MACS cohort.

3.2 INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) dramatically changed the course of HIV infection[99]. Individuals living with HIV infection have a longer life expectancy, albeit faced with co-morbidities common in the general population that may be accelerated due to infection with HIV[260]. Diabetes mellitus (DM) and insulin resistance (IR) are two such conditions. Current studies document a high prevalence and incidence of Type 2 DM in HIV-infected men. The Multicenter AIDS Cohort Study (MACS) reported a 14% prevalence of diabetes mellitus (DM) among HIV-infected men compared to 5% among HIV-uninfected men and an incidence rate of 4.7 cases per 100 person-years compared with an incidence rate of 1.4 cases per 100 person years among HIV negative men[106]. There is also a greater prevalence of insulin resistance reported in HIV-infected patients with lipodystrophy (35%) compared to matched controls without HIV (5%)[128]. This trend has also been noted in HIV-infected patients without lipodystrophy (5.6% IR prevalence) when compared to controls (3.3% IR prevalence)[128].

To date, the etiology of DM and IR in HIV infection remains unclear. Traditional risk factors such as advancing age[10, 109] and higher BMI[10, 109] have consistently been reported and HIV specific risk factors such as HAART use[100, 110] are thought to play a role.

Physical activity is an accepted intervention for the prevention of DM in the general population[42-50] and low physical activity helps to predict the incidence of new-onset DM[48, 261]. However, physical activity's role as a contributing factor to the incidence and prevention of DM has not been described in most studies of HIV-infected populations[10-14].

We previously demonstrated that low physical function was associated with DM and IR in a cohort of HIV-infected and uninfected men from the Pittsburgh component of the MACS[262]. This result was strengthened by our observation that insulin levels and markers of insulin resistance were also associated with lower physical function scores among HIV-infected men. However, sample size did not permit the exclusion of prevalent diabetes and a temporal relationship could not be established. In addition, we were unable to assess the impact of antiretroviral therapy on DM incidence.

Physical activity and physical function are related, yet, distinct. Physical activity is defined as any voluntary movement produced by the skeletal muscles that results in increased energy expenditure[201], whereas physical function is defined as one's ability to carry out various activities that require physical capability, ranging from self-care to more vigorous activities that require increasing degrees of mobility, strength, or endurance[202]. Despite these differences, numerous studies in HIV-uninfected populations have established that physical activity levels are correlated with physical function[15-20]. Among HIV-infected persons, resistance training has been shown to improve self-reported physical function in patients with HIV wasting[21]. Therefore, physical function is likely to reflect physical activity.

The current study addresses important limitations of our prior study[262] by using incident diabetes cases from the MACS cohort to assess the independent contribution of physical function to the onset of DM and IR in HIV-infected and uninfected men. The effect of highly active antiretroviral therapy (HAART) on this relationship was assessed. Finally, we compared the incidence rates of diabetes among HIV-infected and uninfected men with low physical function to men with high physical function.

3.3 METHODS

3.3.1 Study Participants

All participants were from the Multicenter AIDS Cohort Study (MACS). The MACS is an ongoing NIH-supported (Baltimore, MD; Chicago, IL; Los Angeles, CA; and Pittsburgh, PA) prospective cohort study of the natural history of HIV infection. It was designed to gather information on the epidemiology, virology, immunology, and pathogenesis of HIV. Homosexual and bisexual men aged $\geq$ 18 years without AIDS were recruited from local communities in three recruitment cycles (April 1984-March 1985; April 1987-September 1991; October 2001-August 2003). Briefly, the MACS follows a 6-month visit schedule and involves detailed data collection regarding medical history, physical examination results, and specimen collection. Institutional review boards at each site approved the protocol, and each participant provided informed consent. Further detail can be found elsewhere [247, 263].

Our analysis includes data collected after implementation of the MACS Metabolic Study in April 1999 when serum samples ($\geq$ 8 hours fasting) were added to measure glucose and insulin levels. The first visit at which a participant had such testing was defined as his baseline visit. Of 2,800 eligible men, 193 (6.9%) had prevalent diabetes at baseline and were excluded. Prevalent diabetes was defined as a fasting glucose concentration of $\geq$126 mg/dL, self-reported DM, or use of an antidiabetic medication at baseline. An additional 817 participants did not have any fasting serum samples and were excluded. Therefore, the final sample includes 1790 men (1023 HIV-uninfected and 767 HIV-infected) without baseline diabetes.

3.3.2 End Point Ascertainment-Diabetes Mellitus and Insulin Resistance

Diabetes was defined at each bi-annual visit from April 1, 1999 through April 2, 2008. The date of incident DM was defined as the mid-point between the last visit with a fasting glucose concentration <126 mg/dL and the date of the first visit with a fasting glucose concentration of ≥126 mg/dL. Incident DM was defined in two ways. The first definition, consistent with our previous work[3], was a single fasting glucose of ≥126 mg/dL, self-reported DM, or use of an antidiabetic medication. The second, more stringent definition, required two consecutive 6-month visits with a fasting glucose of ≥ 126 mg/dL, 1 visit with a glucose of ≥ 126 mg/dL and self-reported initiation of antidiabetics medication or self-reported DM.

Insulin concentrations were also obtained from fasting serum samples. IR was estimated using the homeostasis model assessment (HOMA): (fasting insulin [(μU/ml] x fasting glucose [mmol/L)]/22.5.[248] IR was defined by the highest HOMA quintile (≥4.3 μU/ml x mmol/L). Men with prevalent IR were excluded from incident IR analysis.

3.3.3 Exposure-Self-reported Physical Function

The Physical Functioning Ten Scale from the Medical Outcomes Study Short Form-36 Health Survey served as the physical function measure. The SF-36 is one of the most widely used Health Related Quality of Life Instruments and consistently demonstrates high levels of reliability and validity [(249-251)]. In the MACS cohort, internal consistency estimates ranged from 0.85 to 0.86 depending on the SF-36 scale used[264].

This study includes data from PF 10 questionnaires administered at each bi-annual visit from April 1, 1999 through March 31, 2005 and then annually on even visit dates. Participants were asked the following question regarding physical activities that might be done in a typical day: "Does your health now limit you in these activities? If so, how much?" Participants chose between "Yes, limited a lot", "Yes, limited a little", or "No, not limited at all" for vigorous activities (running, lifting heavy objects); moderate activities (vacuuming, golf); lifting or carrying groceries; climbing several flights of stairs; climbing one flight of stairs; bending, kneeling, or stooping; walking more than a mile; walking several blocks; walking one block; bathing or dressing. Each item was scored on a 0 to 100 scale as follows: 100= not limited at all; 50= limited a little; and 0= limited a lot, based on the RAND scoring method[252]. A mean of the 10 activities was calculated to determine an overall score ranging from 0 to 100 with a score of 100 indicating that a participant's health did not limit his ability to complete physical activity. A lower score indicated lower physical function. For use in Kaplan-Meier plots, baseline physical function scores were categorized as high physical function (> than 80) and low physical function ($\leq$ to 80). A score of 80 was chosen based on the lowest quintile of physical function in the current study population. Baseline physical function score was used in multivariate models as a continuous variable.

3.3.4 Assessment of Exposure to Antiretroviral Therapy

Each visit includes detailed questions regarding the use of specific antiretroviral therapies. The definition of HAART followed the DHHS/Kaiser Panel Guidelines and has been described elsewhere[265, 266].

Men were classified into the following 3 groups: 1) HIV-uninfected; 2) HIV-infected not using HAART; and 3) HIV-infected using HAART. The "HIV-infected not using HAART group" combined men who were antiretroviral free (n=254), men using monotherapy (n=3), and men using less-than-HAART combination therapy (n=22) at the baseline visit. This classification was chosen because of the small numbers of men using either monotherapy or less-than-HAART combination therapy.

3.3.5 Statistical Analysis

SAS Version 9.2 was used for all statistical analyses. Chi-square test and the Student's t-test were used to test for differences in proportions and distributions between HIV serostatus groups and physical function groups. Statistical significance was determined using two-tailed tests with an alpha of 0.05.

In order to analyze incident DM/IR, person-time for each participant was calculated from the date of the baseline visit to the date of the onset of DM/IR or to the date of censoring at the last visit free of DM/IR (either due to loss to follow-up or to the study end date of April 2, 2008). Incidence rates per 100 person-years were calculated by dividing the number of DM/IR endpoints by person-years and multiplied by 100.

The association between baseline physical function and incident DM was examined using unadjusted and adjusted hazard ratios (HR) from Cox proportional hazards regression models. Univariate Cox regression for each variable was used to determine the association between the variable of interest and incident DM. Baseline physical function, used as a continuous variable, was forced into all models followed by the addition of each significant variable from the univariate analyses, from lowest to highest p-value. Models were run separately for all men

combined, HIV-uninfected men and HIV-infected men. An identical model-building strategy was used to examine the association between physical function and incident IR. The proportional hazard assumption was met based on visual inspection of Kaplan-Meier survival curves.

3.4 RESULTS

The baseline characteristics of the 1790 men, of whom 43% were HIV-infected, are displayed in Table 9. The mean age of the study population was 43.1 years, 58.2% were white, 31.1% had a family history of diabetes and 66% had a history of smoking. The mean BMI was 25.9 kg/m^2 and the mean physical function score was 86.0 (SD 22.1).

The HIV-infected men were younger, had a lower mean BMI, and lower CD4 counts. The mean baseline physical function score was significantly lower ($p<0.001$) in HIV-infected men (mean 83.0; SD 23.3) compared with HIV-uninfected men (mean 88.2, SD 20.8). A greater proportion of HIV-infected men was non-white and had a history of smoking. Mean glucose levels and family history of DM did not differ between HIV serostatus groups; however mean insulin ($p=0.0007$) and HOMA levels ($p=0.0006$) were significantly higher in HIV-infected men.

Table 10 compares men with high and low physical function, stratified by HIV serostatus. Characteristics tended to differ more in HIV-uninfected men compared with the HIV-infected men. Among the HIV-uninfected men, those with low physical function were older and had higher insulin and HOMA levels. In addition, a greater proportion of men with low physical function were non-white while a higher proportion of men had a history of smoking. BMI, fasting glucose concentrations, and family history of DM did not differ.

In the HIV-infected men, race, CD4 count, and proportion with AIDS differed by physical function level. A greater proportion of men with low physical function were non-white. HIV-infected men with low physical function had lower CD4 counts and a higher proportion had AIDS. None of the other characteristics differed significantly between men with high and low physical function in the HIV-infected group.

Incident DM varied substantially depending on the diabetes definition used. Of the 1790 men, 73 developed diabetes (41 HIV-uninfected and 32 HIV-infected) using the more stringent definition. Forty-three incident cases were due to two consecutive glucose concentrations of $\geq$126 mg/dl, or 1 elevated glucose ($\geq$ 126 mg/dl) with the initiation of antidiabetic medications, 22 were due to a self-reported diagnosis of DM and 8 were due only to self-reported use of antidiabetic medications. When using the less stringent definition, 238 (126 HIV-uninfected and 112 HIV-infected) incident cases of diabetes were observed. One hundred ninety two of these were due to a single elevated fasting glucose ($\geq$ 126 mg/dl), 27 were due to a self-reported diagnosis of DM and 19 were due only to self-reported use of antidiabetic medications. A total of 520 (30%) were lost to follow-up. The median follow-up was 5.0 years.

The incidence rate for DM among all men was 0.943 per 100 person-years (PY) using the more stringent definition and 3.24 per 100 PY using the less stringent definition. Among HIV-uninfected men the rate was 0.896 per 100 PY using the more stringent definition and 2.89 per 100 PY with the less stringent definition. Finally, among HIV-infected men, use of the more stringent definition yielded a rate of 1.04 per 100 PY compared with 3.75 per 100 PY using the less stringent definition. Similarly, the DM definition used strongly influenced the incidence rates for HIV-infected men based on HAART status. HIV-infected men using HAART had an incidence rate range of 1.0 per 100 PY using the more stringent definition compared to 3.97 per

100 PY using the less stringent definition. The HIV-infected men not using HAART had a rate of 1.1 per 100 PY with the more stringent definition and 2.48 per 100 PY.

Figure 2 presents the percentage of men free of DM stratified by HIV status and physical function for both definitions of DM. The cumulative incidence of DM was higher (smaller percentage of participants free of diabetes) in all four groups when the less stringent definition was used. Regardless of definition used, the cumulative DM incidence was highest among HIV-uninfected men with low physical function and next highest in HIV-infected men with low physical function. The log-rank test across the 4 strata was not significant (p=.15) when using the more stringent definition. When the less stringent DM definition was used, the 4 strata differ significantly from one another ($p<0.001$).

In the univariate analysis (data not shown), lower physical function score (HR 1.34 per 20 point decrease, $p < 0.001$); higher BMI (HR=1.13, $p < 0.001$); older age (HR 1.17 per 5 year increase, p=0.006); non-white race (HR 1.77, p=0.02); and family history of DM (HR 1.68, p=0.004) were found to be individually associated with diabetes when using the more stringent definition. Baseline CD4 cell counts and HIV serostatus were not significantly associated with diabetes in the univariate analysis. The same covariates were found to be significant when using the less stringent definition. Among HIV-uninfected men, lower physical function, BMI and family history of DM were associated with DM when the more stringent definition was used. When using the less stringent definition age, race, and CD4 cell count were also associated with DM. Among HIV-infected men only age and BMI were significant risk factors. Neither physical function nor HAART use was significantly associated with DM in HIV-infected men using the more stringent definition; however using the less stringent definition, physical function, race, and family history of DM were significantly associated with DM.

To determine the independent effect of physical function on DM after adjustment for covariates, a series of multivariate Cox models were used for both diabetes definitions (Table 11). When using the more stringent definition, the physical function HR was somewhat diminished after adjustment for BMI, family history of DM and age but remained a significant risk factor for incident DM (HR 1.24; 95% CI 1.04-1.49) in all men. The effect of physical function was no longer significant with the addition of race into the model (HR 1.14; 95% CI 0.94-1.38). While the use of the less stringent definition had little effect on the HR for DM when compared with the more stringent definition, it is important to note that physical function remained significant after adjustment for all covariates, including the addition of race to the model (HR 1.21, 95% CI 1.08-1.35). The first order interaction between HIV and physical function was not significant using either definition.

For HIV-uninfected men, adjustment for BMI, family history of DM, and race had little effect on the independent effect of physical function on incident DM (HR 1.31; 95% CI 1.02-1.66) using the more stringent definition. After the addition of age, physical function was no longer a significant risk factor; however the HR was only slightly attenuated (HR 1.24; 95% CI 0.96-1.60). Use of the less stringent definition did not change the HR for DM among HIV-uninfected men, yet physical function remained significantly associated with DM in the model with all covariates entered (HR 1.20, 95% CI 1.02-1.41).

The choice of DM definition had the greatest impact in the HIV-infected men. Using the more stringent definition, physical function was not an independent risk factor for incident DM and adjustment for BMI, age, and race had little effect on the HR. When the less stringent definition was used, the HR ratio increased and physical function was independently associated with DM even after adjustment for BMI and age (HR 1.23, 95% CI 1.06-1.44). Although the

addition of race to the model did not change the HR only borderline significance was achieved (HR 1.16, 95% CI 1.00-1.38).

Lower physical function (HR 1.15, p=0.002); higher BMI (HR 1.14, p<0.001), black race (HR 1.25, p=0.03); and HIV status (HR 1.24, p=0.005) were significantly associated with incident insulin resistance among all men in univariate analysis. Among HIV-uninfected men, only physical function (HR 1.20, p=0.02) and BMI (HR 1.17, p<0.001), were associated with IR. As with the DM outcome, physical function was not an independent risk factor for IR in HIV-infected men (HR 1.08, p=0.1) while older age (HR 1.20, p=0.01), higher BMI (HR 1.10, p=0.04) and HAART use (HR 1.7, p=0.05) were associated with incident IR.

Adjustment for covariates only minimally decreased the HR for low physical function among all men with incident IR (Table 12). Physical function was associated with insulin resistance in univariate analysis (HR 1.15; 95% CI 1.04-1.27) but was not significantly associated with IR after adjusting for covariates (although the HR remained unchanged). Similarly, among HIV-uninfected men, physical function was associated with IR in univariate analysis (HR 1.20; 95% CI 1.04-1.38) but the addition of BMI, CD4 count, and family history of DM attenuated the physical function HR (HR 1.01; 95% CI 0.84-1.22). Finally, physical function was not an independent risk factor for incident IR in HIV-infected men (HR 1.08; 95% CI 0.94-1.25). Adjustment for covariates had no effect on the HR.

3.5 DISCUSSION

Our finding that lower physical function is a risk factor for incident DM in a large cohort of HIV-uninfected and infected men is biologically plausible and supports our previous findings[262].

Men with low physical function were more likely to develop diabetes than men with higher physical function, even after adjustment for risk factors such as BMI, family history of DM, and age. We observed similar associations between physical function and DM in HIV-uninfected men but the association was weaker among HIV-infected men regardless of the DM definition used. The current study expands our previous research[262] by suggesting a temporal relationship between physical function and incident DM, as men with prevalent DM were excluded. Additionally, we assessed the effect of HAART use on incident DM and utilized a second, more stringent DM definition. Given the strength of previous studies that support the strong correlation of physical function with physical activity[15-20], our results are consistent with the notion that low physical activity is a risk factor for incident DM in HIV-uninfected and infected men.

Although the majority of prior studies did not assess the role of physical function or physical activity as a contributing factor to DM among HIV-infected persons, our results support the Howard et al[108] and Gavrila et al[186] studies, in which physical inactivity was associated with DM and IR in HIV-infected persons. Our analysis is unique in that we used a prospective design with incident DM cases, in contrast to the cross-sectional designs used in prior studies. We also included HIV-uninfected as well as HIV-infected men, allowing us to assess and control for HIV-infection. Finally, we used a definition of DM consistent with ADA criteria[22], while prior studies either used only self-reported DM or did not confirm glucose concentrations.

HIV infection was not found to be a significant risk factor for DM in our study but was shown to be associated with incident IR in univariate analysis, consistent with our previous study[262]. These findings suggest that HIV disease may be associated with mild, perhaps transient, glucose disorders but that traditional DM risk factors play a stronger role in the

progression to DM than HIV itself or the inflammatory processes to which it gives rise[103]. Alternatively, the association between HIV infection and IR, but not with DM, may simply indicate that IR precedes DM and that we had greater statistical power to detect this difference. Finally, because HAART use itself has been identified as a risk for IR among HIV-infected individuals[100], it is plausible that the association between HIV and IR is confounded by HAART use and IR is not merely a direct result of HIV-infection.

HAART use was not a significant risk factor for DM in our study but was found to be associated with incident IR. Several explanations are possible for this finding. HAART use, specifically protease inhibitors[116, 131, 133, 134, 146, 267] as well as cumulative exposure to nucleoside reverse transcriptase inhibitors[141], has been associated with elevated IR markers among HIV-infected individuals. It is also possible that our median follow-up time of 5 years was not long enough for IR to progress to DM, thus diminishing our ability to observe an association between DM and HAART use. Likewise, simultaneous stratification by HIV and by HAART use reduced the sample size and limited the power to detect differences. Finally, individual HAART regimens are heterogeneous with respect to effects on glucose metabolism[100]; therefore, using HAART as a drug exposure class may have reduced the effect of any individual medication or specific medication combinations.

This study underscores the impact of diabetes definition on the incidence rates of DM, regardless of HIV infection. The DM incidence rate in our study is lower than that initially published for the MACS [106] when using the more stringent diabetes definition; however when using the less stringent definition employed in our previous work[106], the incidence rates were similar. We previously reported a rate of 1.4 per 100 PY among HIV-uninfected men compared with our current findings of 0.9-2.9 per 100 PY depending on the definition used. Similarly, for

HIV-infected men, the incidence rate of DM using the less stringent definition was comparable to our prior work (1.7 versus 2.5 per 100 PY in HAART naïve men[106] and 4.7 versus 4.0 per 100 PY in HAART users[106]). The additional requirement of a confirmatory fasting glucose substantially reduced these incidence rates (1.1 and 1.0 per 100 PY, respectively). Other studies using confirmatory glucose concentrations also report low DM incidence rates. Ledergerber et al.[18] in their analysis of 6513 HIV-infected participants from the Swiss HIV Cohort Study, found a rate of 0.442 cases per 100 PY, while De Wit et al[11] report a similar low incidence (0.572 per 100 PY, 95% CI 5.31-6.13) in a cohort of 32,437 HIV-infected men and women in Europe, the US, Argentina, and Australia.

The current study had two main limitations. The number of persons developing DM was smaller than expected because of the stringent case definition that we used. Thus, our power to detect differences may have been reduced, especially in analytic models stratified by HIV status. The secondary analyses using the less stringent definition increased the number of DM events; therefore our power to detect differences with this more sensitive and less specific definition was increased. We also did not have the power to limit our analysis to men with normoglycemia at baseline; however mean physical function scores did not significantly differ between men with normoglycemia and men with pre-diabetes at baseline.

Secondly, because the MACS never collected physical activity data, we were limited to the use of physical function. Future studies with objective measures of physical activity are required to confirm our results. As previously discussed, numerous studies conducted among HIV-uninfected populations have established that physical activity levels are correlated with physical function performance. Brach et al observed a correlation between pedometer readings and the Functional Status Questionnaire (r=0.34); the Physical Performance Test (r=0.41); and

gait speed (r=0.52) [15]. Cross-sectional and prospective studies suggest that low physical activity is an independent predictor of both measured and self-reported low physical function[15-20]. While similar studies have not yet been conducted in HIV-infected cohorts, Roubenoff and Wilson reported an increase in physical function in HIV-infected patients with wasting who completed a resistance training program[21]. Given these results, it is plausible to suggest that the men in our study with low physical function also had lower physical activity levels compared to men with higher physical function.

To our knowledge, this is the first prospective study to assess the contribution of physical function to incident DM and IR in a cohort that included both HIV-uninfected and HIV-infected men. This study supports our previous findings that self-reported low physical function is an important risk factor DM in the MACS cohort. These results underscore the clinical relevance of the association between physical function, BMI and DM. Improved physical function in this population would likely result from an increase in physical activity and a decrease in BMI, two important factors known to reduce the incidence of DM. Although future research using objective physical activity measures is necessary to further elucidate the contribution of low physical activity to DM and IR development in HIV-infected persons, ongoing studies addressing the issues of glucose metabolism in HIV-infected populations should include assessments of physical activity levels.

3.6 TABLES

Table 9. Characteristics of 1790 men at the index visit

Characteristic	Current Study Population (N=1790)	HIV-uninfected (N=1023)	HIV-infected (N=767)	*P*-value
Age, mean (range)	43.1 (18.2-82.6)	44.9 (18.2-82.6)	40.6 (19.6-68.9)	<0.001*
White subjects, No (%)	1042 (58.2)	710 (69.4)	332 (43.3)	<0.001*
Body mass index, mean ++	25.9	26.3	25.4	<0.001*
Glucose level, mg/dL (mean)	89.5	89.3	89.9	0.3
Insulin, μU/ml (mean)	13.5	12.7	14.4	<0.001*
HOMA, μU/ml x mmol/L (mean)	3.1	2.9	3.3	<0.001*
CD4 count, cells/mm^3	764.1	930.8	540.7	<0.001*
Physical function, mean	86.0	88.2	83.0	<0.001*
Family history of DM, No (%)	555 (31.1)	300 (29.5)	255 (33.3)	0.2
History of smoking, No (%)	1163 (66.0)	628 (62.0)	535 (71.4)	<0.001*

Abbreviations: HIV: human immunodeficiency virus; DM: diabetes mellitus; HOMA: homeostasis model assessment

* $P < 0.05$ comparing the HIV-uninfected men with the HIV-infected men using the Chi-square test or the Student's t-test, as appropriate

++Calculated as weight in kilograms divided by the square of the height in meters.

Table 10. Baseline characteristics of men with high and low physical function stratified by HIV serostatus

	HIV-uninfected			HIV-infected		
Characteristic	High physical function (N=775)	Low physical function (N=248)	P-value	High physical function (N=461)	Low physical function (N=286)	P-value
Age, mean	44.0	47.7	<0.001*	40.4	41.0	0.3
White subjects, No (%)	570 (73.5)	140 (56.5)	<0.001*	253 (52.6)	79 (27.6)	<0.001*
Body mass index, mean [++]	26.2	26.6	0.2	25.3	25.4	0.9
Glucose level, mg/dL (mean)	89.1	89.9	0.4	90.5	88.7	0.07
Insulin, μU/ml (mean)	12.1	14.6	0.002*	14.3	14.7	0.7
HOMA, μU/ml x mmol/L (mean)	2.7	3.3	0.003*	3.3	3.3	0.9
CD4 count, cells/mm^3	913.2	985.6	0.002*	565.3	499.4	0.003*
Family history of DM, No (%)	232 (30.1)	68 (27.6)	0.4	158 (32.9)	97 (33.9)	0.9
History of smoking, No (%)	446 (57.6)	182 (76.5)	<0.001*	338 (70.2)	197 (73.5)	0.3
AIDS, No (%)	N/A	N/A	N/A	25 (5.2)	43 (15.0)	<0.001*
HAART use, No (%)	N/A	N/A	N/A	406 (84.5)	237 (82.9)	0.6

Abbreviations: HIV: human immunodeficiency virus; HOMA: homeostasis model assessment; AIDS: acquired immunodeficiency syndrome; HAART: highly active antiretroviral therapy

High physical function > 80; Low physical function $\leq$ 80

* $P < 0.05$ using the Chi-square test or the Student's t-test, as appropriate

[++]Calculated as weight in kilograms divided by the square of the height in meters

Table 11. Cox regression for incident diabetes mellitus

All men	Stringent diabetes definition[a]		Less stringent diabetes definition[b]	
	Physical Function HR	95% Confidence Interval	Physical Function HR	95% Confidence Interval
Model 1 (physical function)	1.34	1.13-1.59	1.34	1.22-1.50
Model 2 (physical function, BMI)	1.24	1.04-1.49	1.30	1.17-1.44
Model 3 (physical function, BMI, DM family history)	1.25	1.04-1.49	1.30	1.17-1.44
Model 4 (physical function, BMI, DM family history, age)	1.24	1.04-1.49	1.30	1.17-1.44
Model 5 (physical function, BMI, DM family history, age, race)	1.14	0.94-1.38	1.21	1.08-1.35
HIV-uninfected men				
Model 1 (physical function)	1.50	1.22-1.83	1.43	1.25-1.63
Model 2 (physical function, BMI)	1.36	1.08-1.73	1.33	1.15-1.56
Model 3 (physical function, BMI, DM family history)	1.36	1.06-1.73	1.33	1.15-1.56
Model 4 (physical function, BMI, DM family history, race)	1.31	1.02-1.66	1.29	1.11-1.50
Model 5 (physical function, BMI, DM family history, race, age)	1.24	0.96-1.60	1.22	1.04-1.44
Model 6 (physical function, BMI, DM family history, race, age, CD4)	1.23	0.94-1.63	1.20	1.02-1.41
HIV-infected men				
Model 1 (physical function)	1.12	0.85-1.50	1.23	1.06-1.44
Model 2 (physical function, BMI)	1.08	0.80-1.47	1.22	1.06-1.41
Model 3 (physical function, BMI, age)	1.10	0.82-1.50	1.23	1.06-1.44
Model 4 (physical function, BMI, age, race)	1.02	0.76-1.38	1.16	1.00-1.38

Abbreviations: HR: hazard ratio; BMI: body mass index; DM: diabetes mellitus

[a] DM defined using a confirmatory fasting glucose $\geq$ 126 mg/dl

[b] DM defined using a single fasting glucose $\geq$ 126 mg/dl

Note: physical function HR per 20 point decrease

Table 12. Cox regression for incident insulin resistance

All men		
	Physical Function HR	95% Confidence Interval
Model 1 (physical function)	1.15	1.04-1.27
Model 2 (physical function, BMI)	1.09	0.96-1.22
Model 3 (physical function, BMI, age)	1.07	1.00-1.20
Model 4 (physical function, BMI, age, DM family history)	1.15	1.02-1.30
Model 5 (physical function, BMI, age, DM family history, HIV)	1.14	1.00-1.30
HIV-uninfected men		
Model 1 (physical function)	1.20	1.04-1.38
Model 2 (physical function, BMI)	1.00	0.84-1.17
Model 3 (physical function, BMI, CD4)	1.01	0.84-1.17
Model 4 (physical function, BMI, CD4, DM family history)	1.01	0.84-1.22
HIV-infected men		
Model 1 (physical function)	1.08	0.94-1.25
Model 2 (physical function, age)	1.07	0.94-1.25
Model 3 (physical function, age, BMI)	1.11	0.96-1.30
Model 4 (physical function, age, BMI, HAART)	1.10	0.94-1.27

Abbreviations: HR: hazard ratio; BMI: body mass index; HAART: highly active antiretroviral therapy
Insulin resistance was defined as the highest homeostasis model assessment (HOMA) quintile in our data ($\geq$4.3 μU/ml x mmol/L)
Note: physical function HR per 20 point decrease

3.7 FIGURES

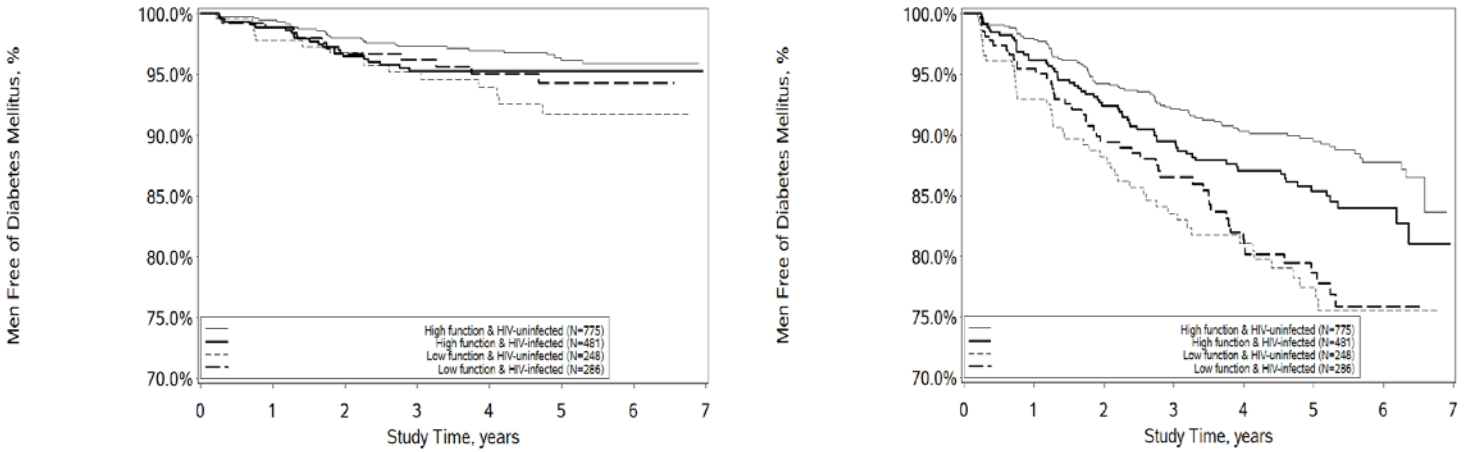

Figure 2. Kaplan-Meier survival curve for incident DM among HIV-uninfected and HIV-infected men with high and low physical function at baseline using the more stringent definition of diabetes and less stringent definition of diabetes, respectively

4.0 MANUSCRIPT 3: ASSOCIATIONS BETWEEN SELF-REPORTED AND PERFORMANCE-BASED MEASURES OF PHYSICAL FUNCTION, DIABETES MELLITUS AND INSULIN RESISTANCE IN THE MULTICENTER AIDS COHORT STUDY

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4.1 ABSTRACT

Aims: To assess associations between self-reported physical function and performance-based measures of physical function, diabetes mellitus (DM), and insulin resistance (IR).

Methods: We analyzed cross-sectional data from 2079 HIV-infected and uninfected men in the Multicenter AIDS Cohort Study (MACS). DM was defined as a fasting glucose of $\geq$126 mg/dl or self-reported diagnosis of diabetes and use of diabetes medication. IR was calculated using the homeostasis model assessment. The Physical Functioning Ten Scale measured self-reported physical function. Handgrip strength and gait speed were used as performance-based measures. Spearman rank order correlation coefficients and logistic regression models assessed relationships between measures of physical function, DM and IR.

Results: Self-reported physical function and performance-based measures were weakly correlated. (HIV-uninfected: ρ=0.12-0.23, $p<0.01$; HIV-infected ρ=0.16-0.24, $p<0.01$). Among HIV-uninfected men, self-reported physical function was more strongly associated with DM than grip strength or gait speed. This trend remained after adjustment for covariates (physical function AOR 1.22, p=0.14 vs grip strength AOR 1.13, p=0.14 in men with DM). Among HIV-infected men, handgrip strength was the only physical function measure associated with DM (AOR 1.16, p=0.06). Self-reported physical function was significantly associated with IR in HIV-uninfected men in multivariate analysis (AOR=1.43, $p<0.001$). None of the physical function measures were significantly associated in HIV-infected men with IR.

Conclusions: Our results suggest that both self-report and performance-based measures of physical function should be used in a complementary manner in order to gain a comprehensive

understanding of physical function among individuals with HIV-infection. The associations between self-reported physical function and grip strength with DM and IR in the MACS support the need for prospective studies assessing these measures as markers for glucose disorders in HIV-infected populations.

4.2 INTRODUCTION

Older adults now comprise a greater proportion of HIV-infected individuals due to the success of highly active antiretroviral therapy (HAART) as well as an increase in new infections among adults older than age 50[99, 219]. It is necessary for researchers and clinicians to address not only HIV infection but also co morbidities associated with the normal aging process, which may be accelerated in HIV-infected individuals.[260] In fact, Oursler et al demonstrated that co morbid conditions were associated with impaired physical function independent of HIV status[220]. Maintaining physical function has been shown to be a key aspect of healthy aging in the general population[221] and will become more of a focus in HIV-infected individuals as HAART use continues to slow disease progression[220]. Lower self-reported physical function has been observed among individuals with HIV infection and AIDS compared to HIV-uninfected counterparts[231, 262].

Self-report questionnaires provide insight into an individual's perception of ability but are often influenced by psychosocial factors including mood, cognition, expectations, reporting bias, attitudes, and emotional distress[223, 230]. Therefore, measures of self-report among HIV-infected individuals may not accurately reflect an individual's actual functional ability. Simmonds et al suggest that measured physical performance was worse among HIV-infected men and women compared with healthy individuals; however this study did not compare these results to self-reported function[230].

Studies of patients with fibromyalgia, low back pain, and rheumatoid arthritis have demonstrated that the relationship between self-report and performance-based physical function

measures ranges from fair to good[223, 228, 268]. Similar studies have not yet been conducted in HIV-infected participants. Clarifying this relationship may provide insight into the overlap between self-report and performance-based measures in this population. This is important to gain a comprehensive understanding of physical function among individuals with HIV infection.

Individuals living with HIV infection are faced with co-morbidities that are common in the general population. Diabetes mellitus (DM) and insulin resistance (IR) are two such conditions. To date, the etiology of DM and IR in HIV-infection remains unclear. Traditional risk factors such as advancing age[10, 269] and higher BMI[10, 269] have consistently been reported and HIV specific risk factors such as HAART use[100, 110] are thought to play a role. We have shown that self-report physical function is associated with DM and IR in the Pittsburgh component of the Multicenter AIDS Cohort Study (MACS)[262]; however the role of performance-based functional measures has not been assessed in HIV-infected populations.

Handgrip strength was negatively associated with fasting insulin levels ($p=0.013$) in a cohort of community-dwelling HIV-uninfected men and women[245, 270]. In addition, the prospective analysis found that handgrip strength was predictive of fasting insulin 23 years after baseline adjusting for age, BMI, and ratio of abdominal girth to hip breadth[245]. The authors suggest that skeletal muscle weakness may predict the development of IR and subsequent DM. Given our observation that self-reported low physical function in HIV-infected men is associated with DM and IR, it is plausible to suggest that markers of function such as grip strength and gait speed may also be associated with IR and DM in HIV-infected individuals. It is imperative to identify early predictors of glucose disorders to help prevent the chronic complications associated with their progression[22, 25]. This is especially important for individuals with HIV-infection who are already at risk for physical disability due to HIV associated symptoms[220].

This cross-sectional study uses data from the Multicenter AIDS Cohort Study (MACS) to assess the correlation between self-reported physical function and performance-based measures of physical function including gait speed and grip strength. It also compares multivariate models to determine if performance-based measures of physical function are more strongly associated with diabetes mellitus and insulin resistance than are self-reported measures.

4.3 METHODS

4.3.1 Study Participants

All study participants were from the Multicenter AIDS Cohort Study (MACS). The MACS is an ongoing multicenter (Baltimore, MD; Chicago, IL; Los Angeles, CA; and Pittsburgh, PA) natural history prospective cohort study of HIV infection. It was designed to gather information on the epidemiology, virology, immunology, and pathology of HIV. Homosexual and bisexual men aged $\geq$ 18 years without AIDS were recruited from the local communities in three recruitment cycles (April 1984-March 1985; April 1987-September 1991; October 2001-August 2003). The second and third cycles focused on increasing the proportion of minority participants. Briefly, the MACS follows a 6-month visit schedule and involves detailed data collection regarding medical history, physical examination, and collection of biological specimens. Institutional review boards at each site approved the MACS protocol, and each participant provided informed consent. Further detail can be found in Kaslow et al and Silvestre et al [263, 271].

The current study includes subjects in the MACS cohort during visit 48 (October 1, 2007-March 31, 2008). This date was chosen for three reasons: 1) to ensure the completion of the third recruitment wave (October 2001-August 2003); 2) to ensure the inclusion of grip strength and gait speed data which was added during visit 44; 3) to ensure the inclusion of the self-report physical function questionnaire which is administered every other visit (even visits). Two thousand seventy nine men from the MACS were eligible for inclusion in this analysis.

4.3.2 Exposure: Measures of Physical Function

4.3.2.1 Self-Report

The Physical Functioning Ten (PF 10) Scale from the Medical Outcomes Study (MOS) Short Form-36 (SF-36) Health Survey measured self-reported physical function. The SF-36 is one of the most widely used Health Related Quality of Life Instruments and consistently demonstrates high levels of both reliability and validity in HIV-uninfected[249-251] and HIV-infected populations[272-276]. Specifically, in the MACS cohort[264], internal consistency estimates ranged from 0.85 to 0.86 depending on the SF-36 scale while the factor structure was found to be similar to previously documented factor structures in both the general population and in other diseases.

This study includes data from PF 10 questionnaires administered at visit 48. During the administration of the PF 10, participants were asked the following question regarding physical activities that might be done in a typical day: “Does you health now limit you in these activities? If so, how much?” Participants chose between “Yes, limited a lot”, “Yes, limited a little”, or “No, not limited at all” for vigorous activities (running, lifting heavy objects); moderate activities (vacuuming, golf); lifting or carrying groceries; climbing several flights of stairs; climbing one flight of stairs; bending, kneeling, or stooping; walking more than a mile; walking

several blocks; walking one block; bathing or dressing (Table 1). Each item was scored on a 0 to 100 range as follows: 100= not limited at all; 50= limited a little; and 0= limited a lot, based on the RAND scoring method[252]. A mean score for the 10 activities was then calculated to determine an overall score for the PF 10 ranging from 0 to 100 with a score of 100 indicating that a participant's health did not limit his ability to complete the physical activity tasks. Thus, a lower score indicates lower physical function.

4.3.2.2 Performance-based

Handgrip strength and gait speed were used as performance-based measures of physical function and strength. Grip strength was measured using a calibrated, Jamar dynamometer. Each participant was asked to place his dominant arm on a table at a 90 degree angle to his body and to squeeze the dynamometer as hard as possible. Three measurements of grip strength were taken with the dynamometer reset to zero prior to each reading. A mean of the three measurements was calculated for each participant to obtain his overall grip strength (in kilograms). Normal grip strength for adult males aged 40-75+ ranges from 29.8-53.0 kg depending upon age[277].

Gait speed was measured using a 4-meter walking course. Participants were instructed to place their feet with their toes behind, but touching, the start line and to walk at their usual pace from a standing start. Participants completed the walk twice. Gait speed was determined by dividing the distance walked in meters by the time in seconds. A mean of the 2 gait speeds was calculated for use in the analysis. Normal gait speed for adults ranges from 1.2-1.3 m/s[278, 279].

4.3.3 Outcome: Diabetes Mellitus and Insulin Resistance

Diabetes was defined as either a fasting glucose concentration of $\geq$126 mg/dl or self-reported diagnosis of diabetes and use of diabetes medications; consistent with the Center for the Analysis and Management of the MACS Data (CAMACS) algorithm for prevalent DM. Self-reported DM was determined using the following questions: "Since your last visit have you been told by a practitioner that you have diabetes?"; "Have you ever been told that you have high blood sugar or diabetes?"; "Have you seen a doctor or other medical practitioner for any condition since your last visit? If yes, was there a diagnosis for your condition?" Men who listed a diagnosis of diabetes were included. Antidiabetic medication use was obtained from a report of medications used since the previous visit. A fasting glucose concentration of $\geq$ 126 mg/dl is consistent with American Diabetes Association Guidelines[22].

Insulin concentrations were also obtained from the fasting serum samples. Insulin resistance was estimated using the homeostasis model assessment (HOMA): (fasting insulin [(μU/ml] x fasting glucose [mmol/L)]/22.5[248]. Glucose levels were converted to mmol/L by dividing mg/dl by 18. Insulin resistance was defined by the highest HOMA quintile in our data ($\geq$ 4.29 μU/ml x mmol/L).

4.3.4 Covariates

Covariates of interest, taken from visit 48, included age, race (white/non-white), HIV status, AIDS status, HAART status (yes/no), lipoatrophy[257], CD4 count, body mass index (BMI), and family history of DM. Lipoatrophy was defined as examiner observed moderate or severe

atrophy in at least one of the following four sites: face, arm, leg, buttocks. These covariates were chosen because of their association with physical function or diabetes development[253, 254].

4.3.5 Data Analysis

SAS Version 9.2 was used for all statistical analyses. Chi-square tests and the Student's t-test were used to test for differences in proportions and distributions of physical function measures, covariates and disease status between HIV serostatus groups. The relationship between self-reported and performance-based measures of physical function was examined using Spearman rank order correlation coefficients.

Univariate logistic regression analysis was performed to assess unadjusted associations between covariates and the outcomes of interest, DM and IR. Multivariate logistic regression models using a stepwise methodology were constructed to assess the independent association between self-report physical function, gait speed and handgrip strength with diabetes and insulin resistance after adjusting for important covariates. Covariates with a p-value of $\leq$ 0.3 in univariate analysis were chosen for the multivariate models. Among the chosen covariates from univariate analysis, those with a p-value $\leq$ 0.25 initially entered the model while covariates with p-values of $\leq$ 0.15 remained in the final model.

4.4 RESULTS

The characteristics of the 2079 men at visit 48, stratified by HIV serostatus, are presented in Table 13. Of these men, 1082 were HIV-uninfected and 997 were HIV-infected. The HIV-

infected men were younger, had a lower mean BMI, a higher percentage of non-white participants, and lower CD4 counts compared with their HIV-uninfected counterparts. Family history of DM was similar between the 2 groups. Glucose levels did not differ significantly between HIV-serostatus groups; however both fasting insulin levels and mean HOMA were higher in HIV-infected men. The proportion of men with DM and IR did not differ by HIV serostatus. Although mean self-reported physical function scores were lower in the HIV-infected men compared with the HIV-uninfected men (84.6 and 87.5 respectively, p=0.004), grip strength was higher men with HIV infection (39.4 kg versus 38.4 kg, p=0.03). Mean gait speed was identical in both groups (1.1 m/sec). Of the HIV-infected men, 14.7% had AIDS, 16.1% had lipoatrophy, and 89.9% were using HAART at visit 48.

The correlations between self-report physical function and the performance-based measures, although significant, were weak regardless of HIV serostatus (Table 14). The weakest of these associations was the correlation between gait speed and handgrip strength (ρ=0.07, p<0.01, all men). The correlations between PF-10 score and handgrip strength were higher (ρ=0.14, p<0.01, all men). This association was somewhat stronger in HIV-infected men than in HIV-uninfected men (ρ=0.16 and ρ=0.12 respectively). The strongest of the associations was observed between PF-10 score and gait speed (ρ=0.23, p<0.01, all men). The correlations were similar in HIV-infected versus HIV-uninfected men (ρ=0.24 and ρ=0.23 respectively).

Table 15 shows mean PF-10 scores for men with the slowest gait speed and weakest handgrip (Quartile 0-25%), men with intermediate gait speed and intermediate grip handgrip (Quartiles 25-75%), and men with the fastest gait speed and strongest handgrip (Quartile (75-100%) stratified by HIV serostatus. Men who did not fall into one of these categories were not included. Self-report physical function did not differ by HIV-status in any of the quartiles. The

scores were higher among the men with the fastest gait speed and strongest grip strength compared to the men with the slowest gait and weakest grip. This trend was most pronounced in the HIV-infected men with a difference of 15 between the highest and lowest quartiles (93.20 versus 78.46). HIV-infected men had lower self-reported physical function scores in each of the quartiles, although these differences were not significant.

In univariate analysis (Table 16), lower physical function score (odds ratio (OR): 1.40 per 20 unit decrease, 95% CI 1.22-1.50), weaker grip strength (OR: 1.19 per 5 unit decrease, 95% CI 1.05-1.29), older age (OR: 1.21 per 5 year increase, 95% CI 1.10-1.34), higher BMI (OR: 1.10 per unit increase, 95% CI 1.06-1.13), and non-white race (OR: 1.68, 95% CI 1.21-2.33) were associated with DM among all men. Family history of DM, HIV serostatus, CD4 count, gait speed (per unit decrease) and the first-order interaction between HIV serostatus and physical function score were not associated with DM in univariate analysis. However, in multivariate analysis, HIV serostatus (adjusted odds ratio (AOR): 2.05, 95% CI 1.27-3.33) became significantly associated with DM in addition to weaker grip strength (AOR: 1.13 per 5 unit decrease, 95% CI 1.05-1.29), older age (AOR: 1.30 per 5 year increase, 95% CI 1.16-1.47), higher BMI (AOR: 1.10 per unit increase, 95% CI 1.06-1.15), and non-white race (AOR: 1.98, 95% CI 1.24-3.18). Self-reported physical function (AOR: 1.19 per 20 unit decrease, 1.00-1.50) and CD4 count (AOR 1.04 per 100 unit increase, 95% CI 1.00-2.70) were of borderline significance.

Similar covariates were also significantly associated with DM in univariate and multivariate analysis among HIV-uninfected men. Lower physical function score (OR: 1.55 per 20 unit decrease, 95% CI 1.22-1.84), weaker grip strength (OR: 1.20 per 5 unit decrease, 95% CI 1.05-1.36), older age (OR: 1.19 per 5 year increase, 95% CI 1.05-1.34), higher BMI (OR: 1.14

per unit increase, 95% CI 1.09-1.20), non-white race (OR: 2.05, 95% CI 1.27-3.32), and CD4 count (OR: 1.11 per 100 unit increase, 95% CI 1.00-2.70) were associated with DM in univariate analysis. In multivariate analysis, there were borderline significant trends towards associations between DM and lower physical function score (AOR: 1.22 per 20 unit decrease, 95% CI 1.00-1.50) and weaker grip strength (AOR: 1.13 per 5 unit decrease, 95% CI 0.95-1.36). Older age, higher BMI, non-white race and CD4 count all remained significantly associated with DM in multivariate analysis.

Among HIV-infected men, only lower physical function score (OR: 1.25 per 20 unit decrease, 95% CI 1.00-1.50), weaker grip strength (OR: 1.20 per 5 unit decrease, 95% CI 1.05-1.36), and older age (OR: 1.32 per 5 year increase, 1.16-1.54) were associated with DM in univariate analysis. Lipoatrophy was not associated with DM in univariate analysis. In multivariate analysis, older age (AOR: 1.37 per 5 year increase, 95% CI 1.16-1.69) was the only covariate to remain significantly associated with DM. Self-reported physical function did not remain in the model while non-white race (AOR: 1.87, 95% CI 1.00-3.48) and weaker grip strength (AOR: 1.17 per 5 unit decrease, p=0.06) and BMI (AOR: 1.06 per unit increase, 95% CI 0.99-1.13) were of borderline significance.

Table 16 also shows univariate and multivariate associations with IR. Among all men, physical function score (AOR: 1.24 per 20 unit decrease, 95% CI 1.22-1.50), BMI (AOR: 1.23 per unit increase, 95% CI 1.19-1.27), older age (AOR: 1.09 per 5 year increase, 95% CI 1.00-1.16) and HIV serostatus (AOR: 1.88, 95% CI 1.37-2.58) were significantly associated with IR in multivariate analysis.

In HIV-uninfected men, physical function score (AOR: 1.45 per 20 unit decrease, 95% CI 1.22-1.84), BMI (AOR: 1.27 per unit increase, 95% CI 1.20-1.33), and CD4 count (AOR: 1.00

per 100 unit increase, 95% CI 1.00-2.70) were all associated with IR in the multivariate model. Finally, among HIV-infected men, BMI (AOR: 1.17 per unit increase, 95% CI 1.11-1.22) was the only variable significantly associated with IR in multivariate analysis; however there were also non-significant trends towards associations with IR and older age (AOR: 1.12 per 5 year increase, 95% CI 0.95-1.28) and non-white race (AOR 1.08, 95% CI 0.97-1.21).

4.5 DISCUSSION

This study is one of the first to assess the association between self-reported and performance-based measures of physical function in HIV-infected men and to assess these measures as risk factors for DM and IR. Significant but weak associations were found between gait speed and grip strength with the SF-36 PF-10 scale. Correlations were slightly higher among HIV-infected men. The weak correlations observed in our study suggest that self-reporting of physical abilities may not accurately reflect an individual's actual functional ability, regardless of HIV serostatus, but that other psychosocial factors such as mood, cognition, expectations, attitudes, and emotional distress may also play an important role in an individual's perception of function[223].

The strongest association was observed between gait speed and the PF-10, regardless of HIV serostatus. This was not surprising given the nature of the PF-10 questionnaire. The majority of items (6 of the 10) on the PF-10 scale focus on the lower extremities, specifically on walking distances and stair climbing; therefore a stronger correlation with gait speed was expected.

Numerous studies have assessed the association between self-report and performance-based measures of physical function in HIV-uninfected populations. The results across studies

are comparable to our findings and suggest that performance-based measures are low to moderately correlated with measures of self-report[222-227]. Correlation coefficients in studies among older adults, patients with low back pain, and patients with fibromyalgia were similar and ranged from 0.1 to 0.6 depending on the task and self-report questionnaire used[222, 223, 226, 228, 229]. Lee et al, in their cross-sectional analysis of men and women with low back pain, reported correlations ranging from -0.09 to -0.41 between the Roland-Morris Disability Questionnaire and a physical performance test battery[223]. Mannerkorpi et al found slightly higher correlations in their study of women with fibromyalgia[228]. Their six-minute walk test and measure of handgrip strength showed fair to good correlations with the SF-36 PF-10 scale (ρ=0.48 and ρ=0.52, respectively). It is important to note that this study was conducted entirely in women, making comparisons with our study limited.

The lack of a stronger correlation is likely due to the fact that performance-based and self-report measures assess different aspects of the physical function construct[226]. While performance-based measures examine an individual's actual ability to complete a task through performance observation, measures of self-report rely on an individual's perception of his or her ability to complete the task[226]. Given these results, it is reasonable to suggest that the most accurate method of measuring physical function in HIV-infected populations may be a complementary approach using both self-report and performance-based measures as subjective measures may provide useful information beyond that obtained solely on observation[226]. The relatively weak correlations reported in our study coupled with no better than moderate-to-good correlations in the above studies support the notion that psychosocial factors may be involved in self-reported physical function among HIV-infected individuals[223].

Interestingly, the results of our study indicate that the performance-based measures of physical function were similar in HIV-infected and HIV-uninfected men despite significantly lower self-reported scores in the HIV-infected men. Our study suggests that, in the MACS cohort, HIV serostatus did not have an effect on actual physical performance but did impact a participant's perception of his functional abilities. A few explanations for this finding are possible. Firstly, individuals living with a chronic disease, specifically one that is present for a prolonged period of time and that is influenced by waxing and waning symptoms may make it difficult for an individual to judge functional declines[230]. Secondly, the psychosocial impact of living with a chronic disease on mood, cognition, expectations, reporting bias, attitudes, and emotional distress may influence an individual's perception of his functional ability[227]. Finally, the potential side effects of HAART such as nausea, diarrhea, and vomiting[280] may influence self-reported physical function without impacting actual physical performance. Regardless, the similarity in physical function between the HIV-uninfected and infected men is encouraging and indicates that men infected with HIV are capable of functioning at levels that comparable with their HIV-uninfected peers.

Previous studies report conflicting results when comparing physical function in HIV-infected and uninfected populations. Simmonds et al utilize both performance-based and self-reported measures in their study of the differential influence of pain and fatigue on physical performance in HIV-infected men and women[230]. Their study suggests that physical performance among HIV-infected individuals was much lower than "age-equivalent healthy patients." However, a large percentage of their population (48%) were classified as having AIDS and may represent a sicker, thus more functionally impaired cohort of HIV-infected individuals compared with the men in the MACS cohort. In contrast, two studies by Oursler et al

found similar levels of physical functioning among HIV-infected and HIV-uninfected participants. Their found no significant difference in the unadjusted mean physical disability score when stratified by HIV serostatus ($p=0.4$)[220]. In addition, the proportion of participants who reported difficulties with basic activities of daily living (ADLs), mobility, and vigorous activities was similar in HIV-infected and uninfected participants ($p>0.05$ for all activities). A second study by Oursler utilized functional performance testing[234]. They found that the mean 6-min walk distance was reduced only 8% in HIV-infected men compared to expected values for healthy adults (adjusted for age, gender, and BMI). After stratification by age, only the middle-aged (50-59 years) HIV-infected men had significantly reduced grip strength as compared to published values for healthy men of similar age ($p=0.02$). Grip strength was reduced by 10% (41.3 kg vs. 46.2 kg) in HIV-infected adults using a weighted average. Finally, a study by Bauer et al compared measures of balance and gait between 78 HIV-uninfected volunteers to 28 HIV-infected participants receiving no antiretroviral therapy, 25 receiving only nucleoside analogue therapy, and 37 participants receiving HAART[235]. They found no significant differences in measures of proximal strength, gait speed and cadence between any of the groups.

The results of our logistic regression analysis indicate that, in the MACS cohort, self-report physical function appears to be more strongly associated with DM and IR than either grip strength or gait speed. These results are consistent with our previously published findings that self-report physical function is associated with DM and IR in HIV-infected and uninfected men[262]. The unadjusted OR was higher for the self-report physical function measure compared with grip strength regardless of HIV serostatus. This trend remained after adjustment for covariates; however grip strength among all men was the only physical function covariate significantly associated with DM in the multivariate model. Conversely, self-report physical

function score the only measure of physical function significantly associated with IR in all men and HIV-uninfected men. None of the physical function measures where associated with IR in the HIV-infected men. Gait speed was not associated with either IR or DM, likely due to the small standard deviation range in both HIV-infected (1.1 m/sec $\pm$ 0.19) and HIV-uninfected (1.1 m/sec $\pm$ 0.18) men. A recent study by Brach et al found an association between gait speed and diabetes; however comparisons with our study are difficult given their much older population (mean age 79 years).

One possible explanation for our findings that self-reported physical function was more strongly associated with DM is that individuals living with a chronic disease such as DM may perceive their functional abilities to be lower than actual performance. The weak correlations between self-report measures and grip strength in our study support this notion. Interestingly, self-reported physical function was not associated with having the combination of both DM and HIV in multivariate analysis; however it is possible that, due to limited power, the strength of traditional risk factors such as age, BMI, and race outweighed any association with self-report physical function. Finally, it is possible that the questions on the PF-10 that addressed the difficult physical function tasks (i.e. ability to walk 1 mile) were able to capture participants with more severe functional limitations as compared with the simpler gait speed and grip strength measures.

Despite its slightly weaker association with DM, the inclusion of grip strength in all DM models deserves attention. The borderline significant association among HIV-infected men is of particular interest. This suggests that lower skeletal muscle strength among these men may serve as a marker for DM. Insulin-mediated glucose uptake takes place mostly in skeletal muscle and is directly related to the amount of muscle mass while inversely associated with fat mass.

Skeletal muscle is an important site for the disposal of glucose during carbohydrate loading which appears to be assisted by insulin. Therefore, it is biologically plausible that changes in the physiology of skeletal muscle may result in lower levels of muscle strength, peripheral sensitivity to insulin with decreased tolerance to carbohydrate loading and thus eventual DM[3, 6, 245].

Although prospective studies are necessary to verify associations between low grip strength and the development of diabetes, our result is encouraging because identifying early functional markers of glucose disorders may help prevent further functional declines and chronic complications associated with their progression[22, 25]. This is essential for individuals with HIV-infection who are already at risk for physical disability due to HIV associated symptoms[220]. However, it is important to note that the lack of association between grip strength and IR may indicate that the decreased strength observed in men with DM is a result of complications associated with diabetes itself or that the decrease in strength occurs somewhere in the continuum between IR and DM.

Few studies have assessed measures of physical function as risk factors for glucose disorders despite recent literature showing that the loss of muscle mass and strength with age is associated with type 2 DM[238, 242]. None of these studies were conducted in HIV-infected populations. Lazarus et al examined the cross-sectional and prospective relationships between handgrip strength and fasting insulin levels in 655 men from the Normative Aging Study cohort[245]. Although handgrip strength was not significantly correlated with unadjusted fasting insulin levels (r=-0.06), a negative cross-sectional association was observed after adjustment for confounders (p=0.013). In their prospective analysis, higher baseline handgrip values predicted lower fasting insulin levels twenty years later (p=0.017). The authors suggest that skeletal

muscle weakness serves as a marker for an increased risk of hyperinsulinemia and may ultimately predict the development of insulin resistance. A cross-sectional study by Sayer et al assessed the relationship between grip strength and metabolic syndrome in 1684 men and women born in Hertfordshire United Kingdom. The HOMA formula was used a marker of IR while DM and IGT were classified using a 2 hour glucose concentration. They reported a significant association between lower handgrip strength and a higher 2 hour glucose (0.07 standard deviation increase, p=0.001) and with an increased HOMA.

When interpreting our findings, the limitations of the study must be considered. Given the cross-sectional design, the direction of the association between measures of physical function and DM and IR cannot be determined. Therefore, it is possible that the lower physical function scores and handgrip values are a result of the diabetes, rather than a precursor to its onset. Current literature does imply that complications associated with DM and IR may lead to functional impairments and reduced muscular strength[236, 237, 239, 240, 242]. However, Lazarus et al, report a prospective association between grip strength and elevated fasting insulin levels and suggest a biologically plausible link between lower muscular strength and the development of IR[245]. In addition, the fasting glucose measurements used to define a diabetes case were taken from visit 48 only and were not confirmed at a subsequent visit. Therefore, it is possible that misclassification of DM cases occurred, potentially over-inflating relationships between covariates and the DM outcome. We were unable to complete a prospective analysis which would have allowed us to confirm glucose concentrations because gait speed and grip strength were not added until visit 44 (October 1, 2005-March 31, 2006). The short period of follow-up substantially limited our power; therefore, a cross-sectional analysis was necessary. Future

research using prospective studies is essential to further assess the role of performance-based measures of physical function as risk factors for DM and IR in HIV-infected populations.

Our findings show that among HIV-infected men, self-report physical function and performance-based measures correlate weakly. Therefore, each component may provide independent information with respect to the physical function construct indicating that both types of measures should be used in a complementary manner in order to gain a comprehensive understanding of physical function among individuals with HIV-infection.

In addition, self-report physical function and upper limb weakness were found to be associated with DM in the MACS men indicating that early interventions aimed at increasing function and strength may help to attenuate DM risk. Our results support the need for prospective studies assessing these measures as markers for glucose disorders in HIV-infected populations

4.6 TABLES

Table 13. Characteristics of 2079 men at visit 48

Characteristic	HIV-uninfected (N=1082)	HIV-infected (N=997)	*P*-value
Age, mean (range)	52.8 (22.7-82.8)	49.5 (22.7-79.5)	<0.0001+
White subjects, No (%)	836 (77.3)	632 (63.4)	<0.0001+
Body mass index, mean ++	27.1	25.5	<0.0001+
Glucose level, mg/dL (mean)	101.4	101.0	0.8
Prevalent diabetes, No (%)	88 (11.7)	87 (14.1)	0.18
Insulin, μU/ml (mean)	13.4	15.4	0.006+
HOMA, μU/ml x mmol/L (mean)	3.5	4.0	0.05+
Insulin resistance*, No (%)	167 (22.2)	166 (26.2)	0.08
CD4 count, cells/mm^3	937.2	563.0	<0.0001+
Physical function, mean ± SD	87.5 ± 21.2	84.6 ± 22.6	0.004+
Grip strength, kg mean ± SD	38.4 ± 8.62	39.4 ± 8.99	0.03+
Gait speed, m/sec mean ± SD	1.1 ± 0.18	1.1 ± 0.19	0.6
Family history of DM, No (%)	29 (3.2)	19 (2.2)	0.4
History of smoking, No (%)	595 (57.5)	582 (62.3)	0.03+
AIDS, No (%)	N/A	146 (14.7)	N/A
Lipoatrophy, No (%)	N/A	132 (16.1)	N/A
HAART, No (%)	N/A	896 (89.9)	N/A

Abbreviations: HIV: human immunodeficiency virus; HOMA: homeostasis model assessment; DM: diabetes mellitus; AIDS: acquired immunodeficiency syndrome; HAART: highly active antiretroviral therapy: SD; standard deviation

*Insulin resistance defined as the highest HOMA quintile in our data (≥ 4.29 μU/ml x mmol/L).

+ $P < 0.05$ comparing the HIV-uninfected men with the HIV-infected men using the Chi-square test or the Student's t-test, as appropriate

++Calculated as weight in kilograms divided by the square of the height in meters.

Table 14. Relationships between self-report and performance-based measures of physical function by Spearman rank order correlations stratified by HIV serostatus

	All men			HIV-uninfected men			HIV-infected men		
	PF-10 score	Gait Speed	Handgrip Strength	PF-10 score	Gait Speed	Handgrip Strength	PF-10 score	Gait Speed	Handgrip Strength
PF-10 scale	-	0.23*	0.14*	-	0.23*	0.12*	-	0.24*	0.16*
Gait Speed		-	0.07*		-	0.04		-	0.09+

Abbreviations: PF-10: Physical Functioning Ten; HIV: human immunodeficiency virus
*P<0.01
+P<0.05

Table 15. Mean self-reported physical function ten scores by gait speed and handgrip strength quartile, stratified by HIV serostatus

	All men	HIV-uninfected	HIV-infected	P-value++
	Mean physical function ten score			
Slowest gait speed and weakest handgrip (Quartile 0-25%), N=596	80.78	82.75	78.46	0.08
Intermediate gait speed and intermediate handgrip (Quartiles 25-75%), N=377	88.80	89.78	87.77	0.29
Fastest gait speed and strongest handgrip (Quartile 75-100%), N=91	93.68	94.27	93.20	0.71

Abbreviations: HIV: human immunodeficiency virus
++ P value comparing the HIV-uninfected men with the HIV-infected men

Table 16. Logistic regression analysis of factors associated with diabetes and insulin resistance among HIV-uninfected and HIV-infected men at visit 48

Risk Factor	Unadjusted OR	95% CI	AOR	95% CI	Unadjusted OR	95% CI	AOR	95% CI
	Diabetes				Insulin resistance (HOMA-IR)			
All men								
Physical function-10 score^{+}	1.40	1.22-1.50	1.19	1.00-1.50	1.31	1.22-1.50	1.24	1.22-1.50
Handgrip strength^{++}	1.19	1.05-1.29	1.13	1.05-1.29	1.00**	0.91-1.11		
Gait speed	1.01*	0.43-3.09			1.97**	0.91-4.26		
Age^{+++}	1.21	1.10-1.34	1.30	1.16-1.47	1.04	0.95-1.10	1.09	1.00-1.16
BMI	1.10	1.06-1.13	1.10	1.06-1.15	1.21	1.18-1.25	1.23	1.19-1.27
HIV Status	1.24	0.90-1.71	2.05	1.27-3.33	1.25	0.98-1.60	1.88	1.37-2.58
Race (reference: white)	1.68	1.21-2.33	1.98	1.24-3.18	1.42**	1.09-1.85		
Family DM	1.12*	0.81-1.56			1.12**	0.86-1.44		
CD4^{++++}	1.04	1.00-2.70	1.07	1.00-2.70	1.03**	1.00-2.70		
HIV-uninfected men								
Physical function-10 score^{+}	1.55	1.22-1.84	1.22	1.00-1.50	1.54	1.22-1.84	1.43	1.22-1.84
Handgrip strength^{++}	1.20	1.05-1.36	1.13	0.95-1.36	1.03**	0.91-1.16		
Gait speed	0.54*	0.14-2.11			2.81**	0.94-8.40		
Age^{+++}	1.19	1.05-1.34	1.26	1.05-1.47	1.05**	0.95-1.16		
BMI	1.14	1.09-1.20	1.13	1.07-1.19	1.30	1.23-1.36	1.27	1.20-1.33
Race (reference: white)	2.05	1.27-3.32	2.27	1.13-4.55	1.55**	1.04-2.31		
Family DM	0.57*	0.70-1.74			1.07**	0.75-1.52		
CD4^{++++}	1.11	1.00-2.70	1.09	1.00-2.70	1.10	1.00-2.70	1.00	1.00-2.70
HIV-infected men								
Physical function-10 score^{+}	1.25*	1.00-1.50			1.10**	1.00-1.22		
Handgrip strength^{++}	1.20	1.05-1.36	1.17	1.00-1.50	1.00**	0.86-1.11		
Gait speed	2.60*	0.62-10.87			1.39**	0.47-4.10		
Age^{+++}	1.32	1.16-1.54	1.37	1.16-1.69	1.07	0.95-1.16	1.12	0.95-1.28
BMI	1.04	0.98-1.11	1.06	0.99-1.13	1.16	1.11-1.22	1.17	1.11-1.22
Race (reference: white)	1.33	0.84-2.12	1.87	1.00-3.48	1.24	0.86-1.79	1.08	0.97-1.21
Family DM	1.15*	0.72-1.85			1.19**	0.82-1.72		
CD4^{++++}	1.02*	0.36-2.70			1.01**	0.36-1.00		
AIDS	1.24*	0.66-2.31			1.14**	0.69-1.88		
Lipoatrophy	1.03*	0.54-1.97			1.07**	0.64-1.78		
HAART	1.53*	0.64-3.68			1.37**	0.70-2.66		

OR: odds ratio; AOR: adjusted odds ratio; BMI: Body mass index; HOMA-IR: homeostasis model assessment insulin resistance, CI: confidence interval
+ per 20 unit decrease; ++ per 5 kg decrease, +++ per 5 year increase, $^{++++}$ per 100 unit increase
*Variable did not remain in the final diabetes multivariate model, **Variable did not remain in the final insulin resistance multivariate model.

5.0 CONCLUSION

In these studies, we used data from the Pitt Men's Study and the Multicenter AIDS Cohort Study to investigate the associations of measures of physical function, as a correlate of physical activity, with diabetes mellitus and insulin resistance in both HIV-uninfected and HIV-infected men by addressing five aims. This work is important because, to date, the published literature assessing the risk factors for glucose disorders in HIV-infected populations has not accounted for physical function or physical activity level, despite the known association in the general population.

Our first goal was to investigate the role of self-reported low physical function as a risk factor for prevalent and incident diabetes mellitus among HIV-infected and HIV-uninfected men. Our results suggest that self-reported low physical function was associated with prevalent DM, independent of HIV status. After adjustment for age and race, physical function remained significantly associated with DM prevalence such that for every 25 unit decrease in physical function score, the odds of having DM increased by 50% ($p<0.05$). Similar findings were observed for incident diabetes; however stratification by HIV status and adjustment for covariates attenuated these results such that the physical function HR was reduced in HIV-uninfected men (adjusted HR 1.23, 95% CI 0.94-1.23) and in HIV-infected men (unadjusted HR 1.12, 95% CI 0.85-1.50) Further, the choice of diabetes definition impacted our findings such that physical function was not associated with incident DM in HIV-infected men using a more

stringent definition, but was a significant risk factor when less stringent criteria were employed. This finding highlights the importance of careful consideration when choosing case definitions as well as the importance of proper interpretation of findings. Interestingly, unlike previously published literature[102-106], our research did not find a link between HAART use and incident diabetes among our study cohort, but instead found that, similar to the general population, the risks for diabetes included older age, non-white race, higher BMI and lower physical function level regardless of HAART use. Our lack of an association with HAART is likely due to our use of HAART as a drug exposure class which may have reduced the effect of any individual medication or specific medication combinations.

The second aim was to investigate the role of self-reported low physical function as a risk factor for prevalent and incident insulin resistance among HIV-infected and HIV-uninfected men; however results were contrary to our hypothesis. Physical function was significantly associated with prevalent IR in univariate analysis in the Pitt Men's Study Cohort; however it did not remain a significant risk factor after adjustment for covariates. This result was replicated using MACS population. Physical function was associated with IR among all men and among HIV-uninfected men in univariate, but not multivariate, analysis. However, among HIV-infected men, physical function not significantly associated with IR even in univariate analysis. The strength of the more traditional as well as HIV-specific risk factors in multivariate analysis may partially explain these findings.

Our third aim was to compare incidence rates of diabetes in HIV-infected and HIV-uninfected men with low physical function to rates in HIV-infected and HIV-uninfected men with high physical function. Our results were consistent with the stated hypothesis. The cumulative incidence of DM was highest among HIV-uninfected men with low physical function

and next highest in HIV-infected men with low physical function and lowest HIV-infected and uninfected men with high physical function, regardless of the stringency of the diabetes definition employed. This finding is important because it shows that both HIV-infected and HIV-negative men with high physical function were more likely to remain diabetes free for a longer period of time. Therefore, interventions aimed at increasing and maintaining high levels of physical function may reduce the number of new diabetes cases and limit the disabling effects of chronic diabetes.

The goal of aim four was to assess the relationship between self-reported and performance-based measures of physical function in HIV-infected and HIV-uninfected men. Based on published literature in HIV-uninfected populations with chronic diseases[222-228], we expected moderate correlations (ρ=0.25-0.5); however we found a slightly weaker correlation in our cohort for both HIV-uninfected (ρ=0.12-0.23) and HIV-infected men (ρ=0.16-0.24). Our relatively heterogeneous sample of men may partially explain these findings. In addition, comparisons with other studies are difficult due to the utilization of differing self-report questionnaires and performance-based measures from the comparison studies. The relatively weak correlations reported in our study support the notion that psychosocial factors are important in self-reported physical function among HIV-infected individuals[223] Therefore, it is likely that the most accurate measure of physical function in HIV-infected populations is a complementary approach that uses both self-report and performance-based measures.

Finally, in aim five, our goal was to construct multivariate models to determine whether self-report or performance-based measures of physical function are more strongly associated with prevalent diabetes mellitus and insulin resistance in HIV-infected and HIV-uninfected men. Contrary to our hypothesis, we found that self-reported physical function, rather than the

performance-based measures, was more strongly associated with DM and IR. The unadjusted OR was higher for self-report physical function compared with grip strength regardless of HIV serostatus. This trend remained after adjustment for covariates. Gait speed was not associated with diabetes or insulin resistance in either HIV-infected or uninfected men. The perception of physical function compared with actual performance due to living with a chronic disease may partially explain these findings. While the cross-sectional design of our study limited the directionality of our findings, the inclusion of both self-reported physical function and grip strength in the DM models supports the need for future prospective studies.

5.1 FUTURE RESEARCH

These studies suggest that low physical function, a correlate for low physical activity, is a risk factor for diabetes mellitus and insulin resistance in the Pitt Men's Study and the Multicenter AIDS Cohort Study. Given the strength of previous studies that support the strong correlation of physical function with physical activity in HIV-uninfected populations[15-20], our results are consistent with the notion that low physical activity is a risk factor for incident DM in HIV-uninfected and HIV-infected men. However, because the MACS never collected physical activity data, we were limited to the use of physical function. The correlation between physical activity levels and physical function abilities in HIV-infected populations is currently unknown. Given the study population, we were also unable to assess these associations in HIV-infected women. Therefore, important questions remain regarding the role of objectively measured physical activity as a risk factor for DM and IR in the general HIV-infected population. Finally, the role of physical activity interventions in the prevention of DM in HIV-infected men and

women has yet to be addressed in large controlled trials. That is, do physical activity interventions prevent the development of DM in HIV-infected populations similar to the in general population? In order to address these unanswered questions, future prospective studies and randomized controlled trials using objective physical activity measures and interventions are necessary. Such studies should further explore: 1) the association between objectively measured levels of physical activity and actual physical function performance in HIV-infected populations; 2) the role of objective measures of physical activity (i.e. using pedometer/accelerometer) with the onset of incident DM and IR in both HIV-infected men and HIV-infected women; 3) physical activity interventions, including exercise, to prevent DM among HIV-infected populations with normoglycemia and with those IGT. These studies are essential in order to better understand the etiology and prevention of DM in HIV-infected populations.

Further, the associations between performance-based measures of physical function, DM, and IR in this study were assessed in a cross-sectional analysis, thus the question of directionality between these associations remains unanswered. A prospective study conducted in HIV-uninfected individuals supports a relationship between grip strength and elevated fasting insulin levels, suggesting a biologically plausible link between lower muscular strength and the development of IR[245]. However, the prospective association has yet to be studied in HIV-infected populations. Larger, prospective studies are necessary to determine whether or not performance-based measures of physical function can be used as markers of future IR and DM in HIV-infected cohorts. This research is clinically important because identifying early functional markers of glucose disorders may help prevent further functional declines and chronic complications[22, 25], especially among individuals with HIV-infection who may already be at risk for physical disability due to HIV associated symptoms[220].

5.2 PUBLIC HEALTH RELEVANCE

Type 2 diabetes mellitus and insulin resistance are prevalent and serious conditions among HIV-uninfected and HIV-infected individuals. These glucose disorders are a huge burden to the national health care system, costing an estimated $174 billion annually, with an additional $36.4 billion required for new HIV infections[7, 281]. Prior to the introduction of HAART, cases of diabetes mellitus and insulin resistance were rarely documented among HIV-infected individuals[115]. Beginning as early as 1998, cross-sectional and cohort studies reported an increase in glucose disorders among HIV-infected individuals, often with higher prevalence rates than in their HIV-uninfected counterparts [14, 103, 108, 109, 114, 116-120]. This raised the spectra of an association between HIV, HAART, and diabetes mellitus. However, a full understanding of these complications remains elusive, and likely involves a combination of antiretroviral therapy and duration of HIV infection (likely due to the pro-inflammatory effects of HIV itself[103]) as well as traditional risk factors such as lifestyle, body mass index (BMI)[11, 107-110], age, sex, and genetic predisposition[111, 112]. Given the burden of these diseases as well as the uncertainty regarding their cause, it has become essential to identify modifiable risk factors to help prevent the development of these glucose disorders, especially among individuals already living with chronic HIV infection.

Physical activity is one such risk factor. Because physical activity and exercise are cost-effective health promotion interventions that could decrease the need for health care resources, slow HIV disease progression, and prevent or delay the onset of chronic conditions, the role of physical activity as risk factor for diabetes in persons infected with HIV deserves attention. Unfortunately, it had been overlooked in the majority of studies of glucose disorders in HIV-infected person, despite its acceptance as a known risk factor in the general population. Thus, it

is important to recognize that the results of previous studies that observed an association between HAART use as well as other non-traditional risk factors, diabetes mellitus and insulin resistance might have been confounded by physical activity levels.

The results of our work indicate that individuals with low self-reported physical function and grip strength, and thus likely low physical activity, have an increased risk of diabetes mellitus. This trend, although present, was weaker among the HIV-infected men. Regardless, the association deserves attention. Given the known correlation between physical function and physical activity, it is biologically plausible to suggest that interventions aimed at increasing physical function and strength in HIV-infected populations will increase physical activity levels while reducing the incidence of DM. However, it is also possible that the weaker association in HIV-infected men suggests that, at the very least, physical function and potentially physical activity interventions may not work as well to prevent DM in HIV-infected populations and that interventions deemed appropriate in the general population may not apply to all diseased subgroups. Future studies that actually assess physical activity rather than physical function are essential in order to evaluate the effectiveness of physical activity as a modifiable risk factor for DM in HIV-infected populations.

In order to design appropriate interventions, it is essential to understand the entire physical function construct among individuals living with HIV. Our work was the first to assess the relationship between self-report and performance-based measures of physical function in an HIV-infected cohort and demonstrated that both are essential to gain a full understanding of physical function in HIV-infected individuals. The use of appropriately designed interventions could significantly reduce the number of incident diabetes cases in HIV-infected populations, while simultaneously decreasing the risk of further disability and chronic sequelae among HIV-

infected individuals already diagnosed with diabetes. This is of great public health significance given the national burden of both HIV infection and diabetes mellitus.

Over the next decade, clinical trials among HIV-infected populations similar to those completed in HIV-uninfected populations are necessary in order to establish a casual association between low physical activity and the onset of DM and IR. At present, researchers and clinicians alike are encouraged to consider the potential for a similar benefit to HIV-infected individuals as demonstrated in the general population. As this relationship becomes more clearly recognized, increased physical activity will become an integral part of diabetes prevention and management in HIV-positive individuals. Therefore, ongoing cohort studies addressing the issues of glucose metabolism in HIV-infected populations should address the role of physical activity and physical function in order to further clarify this relationship.

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