DIET, PHYSICAL ACTIVITY, AND HEALTHY AGING IN PEOPLE LIVING WITH HIV

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ABSTRACT

As life expectancy for people living with human immunodeficiency virus (HIV) (PLWH) has increased, healthy aging in this community has become an emerging public health concern. Although the benefits of adopting healthy diets and regular physical activity (PA) are well-documented, implementing strategies for lifestyle modifications among older PLWH remains a challenge. The complex milieu of social, physiological, and economic burdens encountered by PLWH exposes this population to increased risk for adverse health outcomes, especially from preventable metabolic diseases. The interaction of diet, PA, and social determinants of health in persons who are HIV positive is an understudied area. The aim of this dissertation is to find answers that may potentially increase longevity and vitality during the midlife stage and effectively decrease the risk of developing chronic illness in PLWH. Specifically, this work attempts to answer the following: (i) What socioeconomic and psychological factors affect diet quality and dietary intake in older PLWH? (ii) Does high-dose vitamin D and calcium supplementation affect lipid and metabolic profiles in treatment-naïve patients beginning antiretroviral therapy (ART)? (iii) What are the general trends in PA patterns among PLWH in the U.S.? (iv) How does physical activity (PA) affect long-term risk for developing cardiometabolic disease in this population?

Our findings suggest that: 1) the Food Security Questionnaire (FSQ) measuring food insecurity is significantly associated with diet quality and micronutrient intake

in PLWH; 2) high-dose vitamin D3 (4,000 IU daily) and calcium supplementation (1,000 mg calcium carbonate daily) in HIV-infected participants initiating ART with efavirenz/emtricitabine/tenofovir (EFV/FTC/TDF) does not significantly affect lipid and metabolic profiles; 3) prevalence of self-reported Low/Very Low PA is especially high among PLWH; and 4) PLWH reporting Low and Very Low physical activity are at increased risk for developing diabetes, cardiovascular disease, hypertension, cerebrovascular disease, obesity, and multimorbidity. In conclusion, our results confirm interventions that facilitate practical lifestyle modification within the appropriate psychosocial and economic context are needed in this growing population.

Keywords: HIV, Aging, Diet Quality, Physical Activity, Supplementation, Vitamin D

DEDICATION

"And eat of the lawful and good (things) that Allah has given to you, and keep your duty to Allah, in Whom you believe."

Holy Qur'an, Surah 5: The Food, Ayat 88

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INTRODUCTION

PHYSICAL ACTIVITY TRENDS AND METABOLIC HEALTH OUTCOMES IN PEOPLE LIVING WITH HIV IN THE US, 2008–2015

LIST OF ABBREVIATIONS

aHEI	alternative Healthy Eating Index
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
BMI	body mass index
CMD	cardiometabolic disease
CR	caloric restriction
CVD	cardiovascular disease
DM	diabetes mellitus
DQ	diet quality
FFQ	Food Frequency Questionnaire
FSQ	Food Security Questionnaire
HIV	human immunodeficiency virus
IWL	intentional weight loss
LRC	Lipids Research Center
MDS	Mediterranean Diet Score
MSPSS	Multidimensional Scale of Perceived Social Support
NHANES	National Health and Nutrition Examination Survey

PA	physical activity
PHQ-8	Patient Health Questionnaire (eight questions)
PLWH	people living with HIV
PSS-10	Perceived Stress Scale (10 questions)
RFS	Recommended Food Score
VDD	vitamin D deficiency
VDR	vitamin D receptor

INTRODUCTION

Background

The human immunodeficiency virus (HIV) is a pathogenic agent that suppresses immune function and facilitates progression to acquired immunodeficiency syndrome (AIDS) [1]. Immunosuppression occurs gradually as the virus depletes CD4+ T-cells with continuous cycles of endocytosis, replication, and lysis of host immune cells [2]. When the number of CD4+ T-cells falls below a critical threshold (<200 cells/mm3), HIV has progressed to AIDS [3], an acute condition characterized by involuntary weight loss [4], malignancy [3, 5, 6], and increased susceptibility to opportunistic infections [3, 7]. If HIV is not treated, life expectancy is typically 10 years after infection. Previously, the short life expectancy of HIV/AIDS patients precluded investigations of long-term survival and quality of life. Consequently, healthy aging is understudied in people living with HIV (PLWH).

In 1981, physicians began diagnosing the first cases of HIV in the United States. Initially, there was little understanding of its etiology, virulence, and communicability, which led to widespread panic and misconceptions about risk factors [3, 8]. Unfortunately, HIV viremia, which is the presence of viruses in the blood, commonly progressed to full-blown AIDS in early patients [3, 7] and resulted in 450,000 HIV-related deaths between 1981 and 2000. This unusually high mortality rate fueled the demand for viable treatments [5].

A coalition of activists responded to the early crisis with intense advocacy efforts designed to increase public awareness and government support for prevention, treatment, and research initiatives [8]. These efforts resulted in the passage of the Ryan White Comprehensive AIDS Resources Emergency (CARE) Act and the development of medications that significantly diminished HIV replication in the body, anti-retroviral therapy (ART). Together, these watershed developments simultaneously expanded access to healthcare for disadvantaged patients [9] and increased the life expectancy of patients diagnosed with HIV [8, 10].

Today HIV is a manageable, chronic condition [10] because ART is more accessible, effective, and tolerable [4, 10] than in previous generations. Consequently, PLWH now survive significantly longer. In addition to an increase in long-term survivors, diagnoses among older adults have steadily increased [11, 12]. Half of the 1.2 million PLWH are aged 50 years or older and will be the first generation to experience aging with HIV [13]. Although ART can reduce HIV viral loads to undetectable levels [14-18], aging with HIV remains complex, multifactorial, and associated with poorer health outcomes [12, 18, 19] compared to the general population. Therefore, it is crucial to understand how well-controlled HIV viremia impacts health outcomes in this aging population [12, 13, 16, 20-27].

Aging is associated with an increased risk of developing cardiometabolic diseases such as diabetes, hypertension, and heart disease regardless of HIV serostatus. However, people aging with HIV face significantly higher risks for developing comorbidities and multimorbidity even when viral loads are suppressed with ART medication. The risk for developing metabolic comorbidities among those PLWH appears to be greater than

among uninfected individuals of similar age. Health outcomes are markedly worse for those who are infected and do not receive appropriate medical treatment. **Figure 1** shows the risk disparities between PLWH with poorly versus well-controlled HIV and the general population.

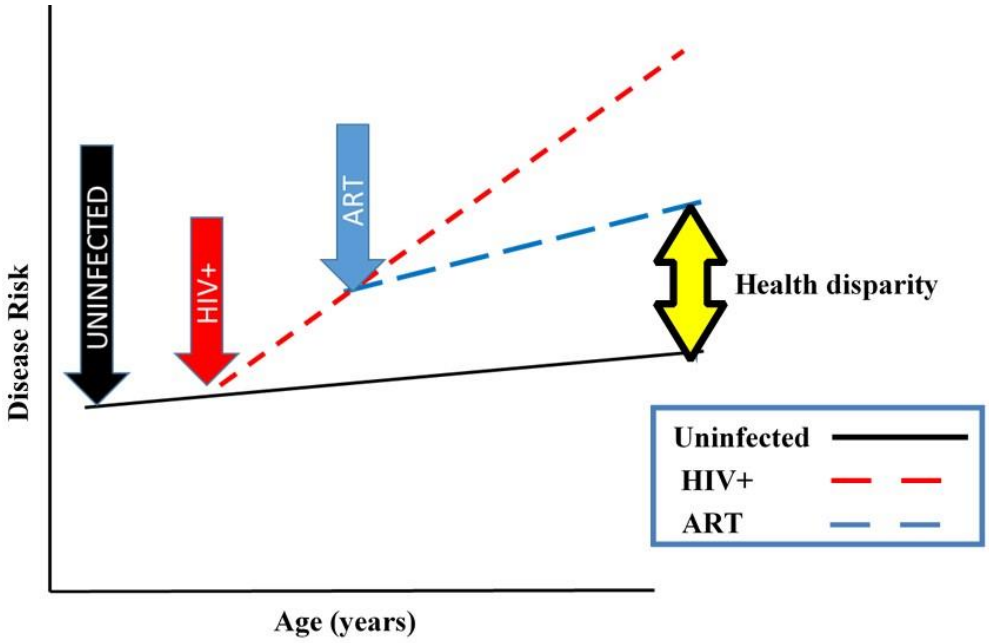

Figure 1. Pictorial representation of risk disparities in aging among PLWH with poorly controlled versus well-controlled HIV and non-infected persons. Aging (black solid line) increases the risk of developing one or more chronic diseases. HIV infection (red dotted line) significantly increases risks for comorbidities, even when it is well controlled with ART medication (blue dotted line).

Although the underlying reasons for disparities are not completely understood, it is believed chronic inflammation and metabolic dysfunction cause PLWH to experience aging differently than uninfected people [29, 30]. Physiological declines manifest across multiple organ systems in PLWH [12, 15, 17, 28], occurring earlier and more severely

than observed in their HIV-negative counterparts [18]. Thus, aging with HIV is typically complicated by one or more non-HIV related comorbidities which threatens the quality of life [31]. Furthermore, aging-dependent health in PLWH is affected by a complex milieu of physiological, social and psychological burdens that may affect perceptions of aging, self-efficacy, and health outcomes [32-34]. In the general population, high-quality diets and regular physical activity (PA) are prescribed to improve health outcomes in older adults [35-39]. Although PLWH are more likely to suffer disabilities and mortality [14, 16], the potential benefits of lifestyle modifications to affect healthy aging in this population have not been fully investigated. Therefore, developing interventions to facilitate healthy aging in older PLWH is necessary [19, 32].

The term "healthy aging" is poorly defined [32, 40-43] and can be interpreted subjectively. Our primary concern is the heightened risk of cardiometabolic dysfunction and other adverse health outcomes that are frequently observed in PLWH. In this dissertation, we define "healthy aging" as the process of aging with well-controlled HIV infection and minimized risk for cardio-metabolic disease in persons 50 years or older. In PLWH, aging is compounded by systemic and chronic inflammation, resulting in the onset of aging-associated health problems over a decade earlier in life than HIV-negative individuals [12, 17, 28]. The metabolic profiles of HIV-positive patients differ significantly from their HIV-negative counterparts, and PLWH have an increased risk compared to HIV-negative groups of developing metabolic dysfunction [52, 70]. Also, individual response to ART and abdominal obesity may further promote metabolic dysfunction within HIV-positive populations.

This dissertation is composed of three projects that investigate different strategies for preventing cardiometabolic disease, including improving diet quality, Vitamin D/calcium supplementation after ART initiation and increasing PA. In the general population, diet and PA have shown promise in preventing and enhancing adverse metabolic events [47, 72-77] but are understudied in PLWH. Thus, it is crucial to investigate lifestyle factors that can significantly impact the successful management of highly prevalent comorbid conditions such as type 2 diabetes mellitus (T2DM) in the study population [52].

We hypothesize age-related declines in diet quality, endogenous vitamin D production, and PA [18, 35, 36, 53, 72] may be exacerbated in the context of HIV infection [18, 62, 78], although this has not been determined. Currently, the interrelationships of lifestyle factors in the setting of well-controlled HIV are poorly understood. However, environmental, biological, and behavioral changes are believed to represent a collective insult to metabolic homeostasis and promote deleterious metabolic alterations [44, 79] that can manifest as insulin resistance, T2DM [15], and other comorbid conditions that jeopardize healthy aging and quality of life in PLWH. Significant metabolic dysfunction is evident in this "accelerated aging" syndrome among this population with prevalence of 66% overweight/obesity (body mass index $\geq$ 25) and 10.3% diabetes [4, 71, 80, 81]. Thus, the potential impact of lifestyle factors in mitigating non-HIV disease risk is of increasing investigative interest. However, it is important to first understand current lifestyle trends in PLWH before effective interventions can be implemented for this vulnerable community.

As persons with HIV live longer, the successful management of co-morbidities and multi-morbidities is becoming increasingly important. Studies consistently show aging in PLWH is complicated by a complex interplay among host, disease, and lifestyle factors.

Given the constellation of social burden experienced by PLWH, the risk of developing one or more chronic diseases is exacerbated. To date, there has not been a comprehensive examination of chief lifestyle behaviors that may enrich health outcomes in this population. Herein, several projects are presented in the context of healthy aging to answer the following questions: (i)What socioeconomic and psychological factors affect diet quality and dietary intake in older PLWH? (ii) Does high-dose vitamin D and calcium supplementation affect lipid and metabolic profiles in treatment-naïve patients beginning ART? (iii) What are the general trends in PA patterns among PLWH in the U.S.? (iv) How does PA affect the long-term risk of developing cardiometabolic disease in this population?

Diet Quality in PLWH

As HIV has transitioned to a manageable condition, the nutritional needs of PLWH have evolved accordingly [4, 80]. Today, greater emphasis is placed on reducing diet-related comorbidities in PLWH because healthy diets remain critical for healthy aging [4, 89]. PLWH may be impacted disproportionately by poor diet quality compared to uninfected individuals [78, 90, 91]. In fact, nutrition and weight management may be especially beneficial for aging PLWH because of the proliferation of diet-related diseases in

this population [90, 91]. In addition to addressing nutritional gaps, such as vitamin D deficiency [58, 63, 64], improved diet quality may be protective against physical decline, increase metabolic function [70], and improve quality of life for PLWH [18, 78, 92]. Conversely, published studies have yet to provide dietary recommendations specifically for this population. There is powerful evidence that definite diet patterns are protective against chronic disease risk in the general population [35, 36, 90, 93]. Further clarification is needed to understand factors that influence dietary behaviors in the context of aging with HIV.

Unfortunately, PLWH face a unique set of physical, social, and economic burdens that may affect their overall nutrition [94]. In addition to physiological changes and increased obesity risk [4, 18, 52, 80, 90, 95, 96], food insecurity [92, 97], perceived stress [98], depression [99], and perceived social support all contribute to social burden [100] and threaten healthful lifestyle habits [27, 101]. Currently, there is a shortage of studies evaluating the influence of psychological and socioeconomic factors on diet quality and how the interplay between social stressors shape patients' risk trajectory for chronic disease.

Vitamin D Deficiency in ART-Naïve Patients

Vitamin D deficiency (VDD) is a risk factor for deleterious lipid changes and other adverse health consequences in older PLWH [57, 61, 62], although causality has not been established. Dyslipidemia and VDD are usually found to coexist and are highly prevalent among people who are HIV positive. Therefore, the role of vitamin D in regulating lipid metabolism and inflammation for PLWH requires further investigation [54-61]. The prevalence of VDD and its concomitant issues persists for several reasons (see

Figure 2). Biological aging is independently associated with vitamin D insufficiency [72]. The conversion of serum 25(OH) (hydroxy vitamin D) to its active form 1, 25 (OH)2D (1, 25- dihydroxy vitamin D; calcitriol) is diminished by 50% due to age-related declines in renal function and calcium absorption [72, 105].

Aging-related declines in vitamin D production are complicated by HIV infection, which has been hypothesized to cause epigenetic alterations in the vitamin D receptor (VDR) [106] that attenuate production of calcitriol. Also, certain ART medications that suppress HIV viral load have previously contributed to vitamin D insufficiency, dyslipidemia, and insulin resistance [63-66, 108].

Vitamin D is partially obtained through dietary intake. Food consumption is dependent on various factors, including food insecurity [92, 109, 110], or the state of being without reliable access to a sufficient quantity of affordable, nutritious food [92]. Research has shown that psychosocial challenges [101, 112] such as perceived stress, one's perceptions of life stress [98, 99, 101, 113]; depression, feelings of severe despondency or dejection [99, 114]; and perceived social support, one's perception of support provided by others [115- 118] may disrupt or prevent regular consumption of foods rich in vitamin D, especially in persons with low socio-economic status (SES) [119].

An aspect of vitamin D that cannot be underestimated when discussing its health benefits is that vitamin D is obtained from sunlight exposure. Although PA has multiple health benefits in itself, PA may also be a useful proxy for estimating sunlight exposure in PLWH. Longitudinal patterns of PA in PLWH are not well characterized. However, there is evidence indicating PLWH are less physically fit to participate in traditional exercise programs [78, 120, 121] and consequently have self-reported levels of exercise that

are significantly lower than their HIV-negative counterparts [83, 84]. Therefore, lower levels of PA may further explain the consistently high prevalence of vitamin D insufficiency among older PLWH [87, 88].

Previous studies have shown vitamin D and calcium supplementation may be partially protective against adverse lipid changes in general and seropositive populations [31, 56, 62, 107, 122]. Therefore, dietary supplements may be a cost-effective, well-tolerated means to address nutritional deficiencies among geriatric adults [86]. A convenient, scalable supplement for patients would seem optimal, as vitamin D insufficiency and its connected issues remain prevalent among PLWH.

Physical activity. In the U.S., levels of PA among HIV-negative adults have been well characterized [75, 123-129]. Associations of PA with improved health outcomes [124, 128, 130] have also been well documented in the geriatric literature [39]. Consequently, recommendations for PA dosage in the general population have been established and standardized over time. Conversely, scientific understanding about trends and associations of PA with chronic disease in older PLWH is incomplete.

Even though PA is protective against age-related physiological declines in the general population, HIV infection has presented a unique set of challenges to those aging in the disease state, even with undetectable viral loads [39, 53, 131]. Therefore, the knowledge base concerning interrelationships of aging, HIV, and PA has evolved but remains disjointed. Subsequently, there are insufficient evidence-based guidelines for

PLWH concerning PA dosage beyond those previously prescribed for noninfected persons. Such recommendations may or may not be beneficial in the context of HIV infection, although this supposition has not been rigorously investigated [53].

As the scientific understanding of HIV-related aging continues to develop, people living with HIV will likely continue suffering adverse health outcomes that may be forestalled or prevented by increased PA. As the community of older adults living with HIV continues to expand, the complications of aging with well-controlled HIV viremia continue to manifest with adverse outcomes [41]. Disproportionate levels of non-HIV-related comorbidities in older PLWH persist despite significant advancements in HIV treatment [70]. In fact, ART medications that have increased the lifespan of PLWH may also contribute to age-related chronic disease [14, 26, 70]. Given the complex nature of existent relationships among illness, host, and treatment (see **Figure 2**), an increased understanding of the potential benefits of physical activity (PA) in this population is crucial. Therefore, an assessment of PA levels among adults with HIV may be a prudent first step in improving health disparities among PLWH.

It is also necessary to quantify chronic disease risk based on levels of PA. PA is highly recommended for the prevention of metabolic dysfunction in the general population [39]. Surprisingly, the potential benefits of PA in counteracting the deleterious effects of people aging with HIV remains understudied. While studies exploring PA in PLWH are sparse, there have been a few cross-sectional studies investigating PA patterns in this population. These studies consistently find PLWH report less physical activity and are less successful in completing exercise programs when compared to their counterparts in the general population [83, 84, 120, 121]. These findings suggest people with HIV

may face additional challenges with PA, are predisposed to a sedentary lifestyle, or both. Therefore, it is imperative to first describe the feasibility of PA in PLWH. Next, current levels of PS in PLWH should be investigated before additional resources are allocated to affect change through lifestyle interventions [83, 84, 90].

To this end, previous studies have shown PA is feasible in older PLWH. These studies have also shown PA may produce salutary effects in PLWH [39, 53]. Noted benefits include increased quality of life, ease of completing daily tasks, and mood enhancement. There is further evidence showing both aerobic and resistance training to be safe with beneficial effects [49-51, 120, 132] on morbidity and mortality risk in older PLWH. Given these results, an expanded role of PA in ameliorating adverse health outcomes in PLWH warrants further investigation.

Relationship among lifestyle factors. Associations among risk factors for chronic disease in the population are partially understood. It is evident diet quality, vitamin D sufficiency, and PA are preventive lifestyle aspects with the potential to reduce the risk of cardiometabolic disease among PLWH. Interestingly, research suggests that, at least in the general population, there may be an interrelationship through inflammation, a contributor to chronic disease [15]. Aging, HIV infection, some ART regimens, poor diet quality (DQ), vitamin D deficiency (VDD), and reduced PA are all associated with increased inflammation [15, 17, 18, 28, 53, 82]. Aging is also associated with decreased DQ, VDD, and reduced PA, which may further contribute to inflammation [11, 16, 40, 49, 54, 82]. HIV viremia and ART have each been observed to reduce physical fitness (and PA) and both are associated with VDD [54, 62, 63]. Poor diet quality may contribute to VDD

which, in turn, may reduce fitness to participate in more physical activities [83-88]. The multi-faceted, interrelationships of aging, HIV infection, and lifestyle behaviors and their respective contribution to cardiometabolic disease risk in PLWH are shown in **Figure 2**.

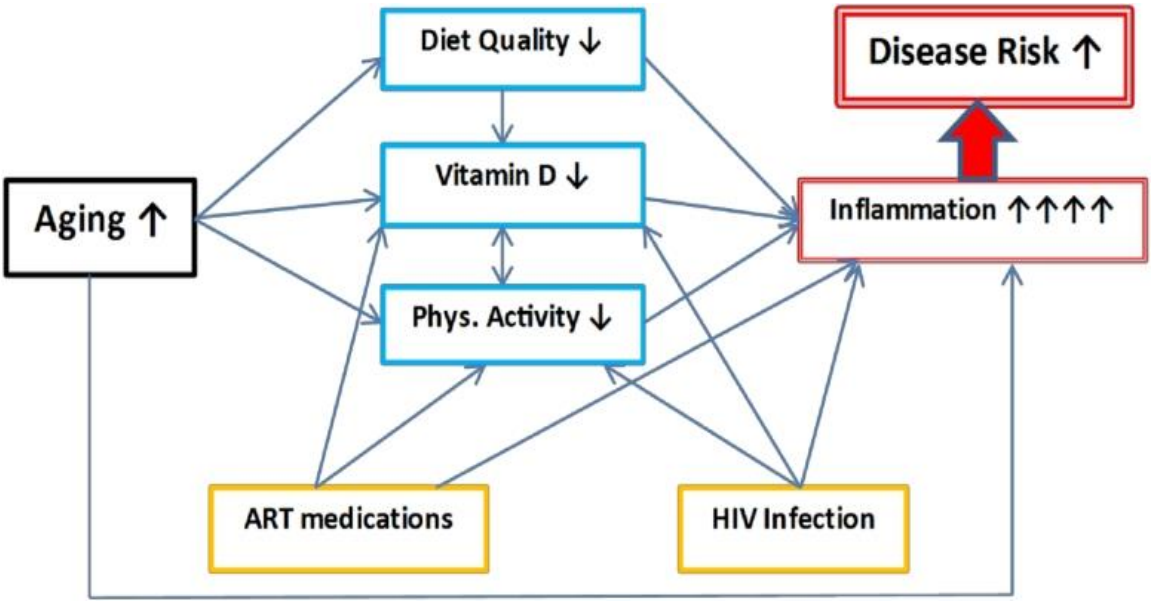

Figure 2. Relationships among factors contributing to age-related co-morbidities in PLWH. Increased inflammation contributes to chronic disease risk. There are direct, independent associations of aging, HIV infection, some ART regiments, poor DQ, VDD, and reduced PA with increased inflammation. Aging is also associated with decreased DQ, VDD, and reduced PA, which may further contribute to inflammation. HIV viremia and ART have each been observed to reduce physical fitness (and PA), and both are associated with VDD. Poor DQ may contribute to VDD, which, in turn, may reduce fitness to participate in more PAs.

Scope of This Dissertation. Given the state of limited information available to promote healthy aging in older PLWH, this dissertation investigates associations of diet quality, vitamin Dsupplementation, and PA [35, 39, 72, 86] with chronic disease risk to

better elucidate the potential impact of lifestyle modifications in our study population. This work represents a fundamental step in addressing health disparities in this vulnerable community. First, we investigate associations of psychosocial factors with nutrition using multiple measures of dietary intake and diet quality. Our purpose is to gain an understanding of social and psychological stressors potentially affecting diet quality in this population. Next, we examine the effects of vitamin D/calcium supplementation in a cohort initiating ART treatment to better understand how risk trajectory may be affected following entry into care. Finally, we describe longitudinal trends of PA in PLWH and their respective associations of physical activity with cardiometabolic disease risk. Ultimately, the goal is to design effective strategies for reducing morbidity and mortality in this community.

ASSOCIATIONS OF FOOD INSECURITY AND PSYCHOSOCIAL MEASURES WITH DIET QUALITY IN ADULTS AGING WITH HIV

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ABSTRACT

Objective: People aging with HIV face social stressors which may negatively affect their overall nutrition. Here, we assess relationships between self-reported measures of depression, perceived stress, social support, and food insecurity with diet quality in older adults with HIV.

Design: Retrospective analysis of self-reported data from parent study

Setting: The University of Alabama at Birmingham 1917 HIV Clinic

Participants: Sixty PLWH with controlled HIV infection (<50 copies/mL) aged 50 years or older participated in this cross-sectional study.

Measurements: Dietary intake was measured using the NHANES 12-month Food Frequency Questionnaire (FFQ) and three Automated Self-Administered (ASA) 24-hr diet recalls to calculate diet quality scores using the Mediterranean Diet Score (MDS); alternative Healthy Eating Index (aHEI); and the Recommended Food Score (RFS) indices. Food insecurity was measured with the Food Security Questionnaire (FSQ). Participants completed the following psychosocial scales: (1) depression – Patient Health Questionnaire-8 (PHQ-8); (2) perceived stress – Perceived Stress Scale (PSS-10); (3) social support – Multidimensional Scale of Perceived Social Support (MSPSS). Linear regression models were used to investigate relationships among variables controlling for gender and income.

Results: Mean age was 56±4.6 years, 80% African-American, and 32% women. Mean body mass index (BMI) was 28.4±7.2 with 55% reporting food insecurity. Most

participants reported having post-secondary education (53%), although 77% reported annual incomes <$20,000. Food insecurity was independently associated with measures of poor dietary intake: aHEI (β=-0.08, p=.02) and MDS (β=-0.23, p<0.01) and with low dietary intake of fiber (β=-0.27, p=.04), vitamin E (β=-0.35, p=.01), folate (β=-0.31, p=.02), magnesium (β=-0.34, p=.01), and copper (β=-0.36, p=.01). We failed to identify consistent associations between dietary assessments and psychosocial variables.

Conclusions: These data indicate food insecurity is associated with poor diet quality among PLWH. Clinical interventions are needed to improve food access for PLWH of low SES.

Keywords: HIV, diet quality; food insecurity; aging

Introduction

Nearly one-half of all people living with HIV (PLWH) in the United States are 50+ years of age [1, 2]. Although antiretroviral therapy (ART) has greatly increased life expectancy, psychosocial and economic stressors remain a threat to healthy aging [2-5]. The prevention of diet-related chronic diseases in this population has thus become a major public health concern [6-8].

We previously documented a rise in aging- and diet-related comorbidities among PLWH [9, 10]. Among HIV-negative adults, diet remains a key component to prevent chronic disease comorbidities in aging [11, 12]. Unfortunately, diet quality declines with aging and likely contributes to the increase and/or exacerbation of aging-related comorbidities [13, 14]. As HIV infection disproportionately affects persons of lower SES, older PLWH face significant challenges in meeting their nutritional needs. Unfortunately, few studies have investigated diet quality in the context of aging with HIV [15].

Several socioeconomic and psychosocial factors are associated with poor diet quality. Excess perceived stress adversely influences both aging [16, 17] and diet quality, although these findings have not been consistently demonstrated across demographic groups [18, 19]. Complicating these interactions, perceived stress in older PLWH is complex, multi-faceted, and interrelated with mood disorders and social support [20-22]. Depression has also been linked to dietary quality [23, 24]. Thus, for older PLWH, there are likely multiple complex factors affecting diet and its impact on health.

In order to develop clinical interventions to reduce morbidity and mortality among older PLWH, the interplay between psychosocial factors and dietary intake require further elucidation. In this analysis, we evaluate the associations between socioeconomic and psychosocial factors affecting PLWH and measures of dietary intake and diet quality. We hypothesized that psychosocial stressors are associated with poor nutrition quality among PLWH.

Methods

Study Population: PLWH were recruited for this cross-sectional study from the UAB 1917 HIV Clinic, which currently follows more than 3,500 HIV-infected persons, 40% of whom are ≥50 years of age. Enrolled participants were aged 50 and over, on ART for >1 year, with suppressed HIV viremia (<50 cp/mL) for >6 months. Participants were excluded if they used antibiotic therapy in the 30 days prior to their study visit or reported using proton pump inhibitors more than once per week. Due to limited representation of other racial groups in the clinic, we limited our recruitment to patients who self-identified as either African-American or white. Trained study staff assisted with completion of all measurements and questionnaires. The study was approved by the Institutional Review

Board (IRB) at the University of Alabama at Birmingham, and all participants provided written informed consent.

Diet-Related Measures

Dietary Intake: Two measures were used to characterize dietary intake. *Food Frequency Questionnaire (FFQ):* Participants completed the 2003–2004 National Health and Nutrition Examination Survey (NHANES) FFQ. The 139-item survey measures consumption of specific food items over 12 months. The questionnaire can accurately predict consumption of fruits, vegetables, whole grains, low-fat dairy, lean meats, and meat alternatives, especially when used in conjunction with multiple recalls. The NHANES FFQ was used to compute the Recommended Food Score (RFS) diet quality scores for this study sample [25].

Diet Recall*:* Three 24-hour dietary recalls (two in-person, one via phone) were conducted using the National Cancer Institute's Automated Self-Administered 24-Hour Recall tool (NCI ASA-24), Beta Version [26]. The NCI ASA-24 is a web-based tool for capturing 24-hour dietary intake drawn from the USDA's Automated Multiple-Pass Method. This tool uses the "gold standard" multiple-pass methodology [27-29]. Due to both reading and computer literacy issues within our targeted population, research staff performed the 24-hour recalls in a one-on-one interviewer format. The primary dietary outcome of interest was whether or not participants met the recommended daily intake for USDA recommended food groups: fruits, vegetables, whole grains, low-fat dairy, and lean meats. Secondary dietary outcomes of interest were overall energy, macronutrient, and micronutrient intake.

Diet Quality: Diet recall and FFQ data were used to calculate scores for the alternative Healthy Eating Index (aHEI) [30], Mediterranean Diet Score (MDS) [31], and Recommended Food Score (RFS). The diet quality concept has been validated in several studies to describing risk for cardiometabolic disease [14, 32-34].

Alternative Healthy Eating Index (aHEI): The validated aHEI measures adherence to U.S. Dietary Guidelines as proposed by the USDA Center for Nutrition Policy and Promotion. The aHEI scoring methodology is density based (per 1,000 calories) and uses least restrictive standards, taking into account demographic factors [30, 35]. A higher aHEI composite score represents higher overall diet quality. The 12-item index has a maximum value of 100 and measures intake of several food groups, including 1) total fruit; 2) whole fruit; 3) total vegetables; 4) greens and beans; 5) whole grains; 6) dairy; 7) total protein foods; 8) seafood and plant proteins; and 9) fatty acids, which are protective against chronic disease. Intake of 10) refined grains; 11) sodium; and 12) empty calories, which are recommended in moderation, are quantified.

Mediterranean Diet Score (MDS): Adherence to a Mediterranean diet may produce salutary effects [33, 34]. The MDS is a 14-item binary assessment measuring intake of the food groups listed above. The MDS score is calculated by awarding one point for each "YES" that corresponds to adherence to the recommended weekly consumption thresholds for each food item. A score at or near the maximum of 14 is considered compliant to the Mediterranean diet.

Recommended Food Score (RFS): The RFS measures variety within the NHANES FFQ and may be predictive of risk for chronic diseases [36]. The RFS is a 51-item inventory of food groups listed in the NHANES FFQ [37]. Scores are calculated by

awarding one point for weekly consumption of each food category listed in the inventory that have been associated with lower risk of chronic disease in the general population [13]. The maximum RFS score is 51, with higher scores representing a higher overall diet quality. To date, there are no published studies using the RFS to evaluate diet quality in PLWH.

Socioeconomic status. Food Security: Food Security was assessed at baseline using a validated two-item food security questionnaire (FSQ). Participants were categorized as either food secure (FSQ=0) or food insecure (FSQ >0). Participants reporting food insecurity without hunger (FSQ=1) or food insecurity with hunger (FSQ=2) were combined into the "food insecure" category [38].

Other SES Indicators: Participants were then asked to identify marital status, the highest grade or year of school completed (education), income category, and whether they currently receive food assistance (yes/no).

Psychological measures. Perceived Stress: The Perceived Stress Scale (PSS-10) was used to assess perceptions of life stress. The PSS-10 has adequate internal test-retest reliability (Cronbach's alpha = .88) and is positively correlated with a variety of self-report and behavioral indices of stress in adult populations [39-41]. The PSS-10 is not diagnostic and no cut-points have been established, although there are population norms for comparison [41]. Scores can be used to infer relative stress levels or within-group comparisons, with higher scores on the PSS-10 indicating greater perceived stress (possible range 0–40).

Depression: The Patient Health Questionnaire (PHQ-8) was used to assess depression. The PHQ-8 has adequate internal test-retest reliability (Cronbach's alpha = .88) and is positively correlated with a variety of self-report and behavioral indices of depression in the general and study populations [42, 43]. The PHQ-8 is diagnostic in nature with cut-points of 10 and 20 having been established to indicate moderate depression and severe depression, respectively. Scores can be used to infer relative depression levels or within-group comparisons, with higher scores on the PHQ-8 indicating greater level of depression (possible range 0–24).

Perceived Social Support: The Multidimensional Scale of Perceived Social Support (MSPSS) was used to assess perceptions of support from three sources: friends, family, and significant others. The MSPSS and its associated subscales have adequate internal test-retest reliability (Cronbach's alpha = .91; friends =.80; family =.86; significant other =.76) and are positively correlated with a variety of self-report and behavioral indices of perceived social support in the general and study populations [44, 45]. The MSPSS is not diagnostic in nature, and no cut-points have been established. Scores can be used to infer relative perceptions of support or within-group comparisons, with higher scores on the MSPSS indicating greater perceived support (possible range 0–4).

Anthropometric measures. Weight to the nearest 0.1 kg and height to the nearest 0.1 cm were measured by trained research staff according to a standardized protocol. Weight was measured in indoor clothing, without shoes, on a calibrated digital scale (Seca 847, Hanover, MD). Height was measured using a calibrated stadiometer (Seca 217, Hanover, MD). BMI was calculated as weight (kg)/height (m2).

Statistical Analysis: The respective values for education, income, and marital status were each reclassified and collapsed into tripartite categories for clarity. For continuous measures, we performed a median-split to categorize participants into categories relative to one another (example: lower stress versus higher stress). Comparisons of demographic variables and diet quality by perceived stress group were made using chi-square or fisher tests, *t*-tests, or Mann-Whitney analysis. Correlations of diet quality with perceived stress, depression, social support, and food security were assessed using Spearman correlation. Linear regression models were used to evaluate the relationship of diet quality with food security, perceived stress, depression, and social support after adjusting for covariates. Some values were log-transformed to approximate a normal distribution. Statistical analyses were performed using SAS version 9.4 with a significance level of $p < 0.05$.

Results. Demographics: We enrolled 60 PLWH with a mean age of 56±4.6 years, 32% women, and 80% black (**Table 1**). Mean CD4 count was 528.3±350.1 c/mm3, and all participants had plasma HIV viral load < 50 cp/mL. The majority (77%) reported household income <$20,000; 47% reported having a high school education or less; and only two (3%) participants were currently married. Mean body mass index (BMI) was 28.43 ±7.21 kg/m2 with 58% of participants classified as overweight or obese. When asked about food security, 55% reported being food insecure, and 60% received food assistance from one or more sources. Participants reported dietary intake of 2241.75 ± 905.28 kcals/day, with the following diet quality scores: 10.58 ± 6.83 (RFS); 4.08 ± 1.70 (MDS) and 46.78 ± 11.73 (aHEI) (**see Table 1**).

Psychosocial Measures: The mean values for psychosocial measures are also shown in Table 1. This study sample was characterized by a mean perceived stress score of 15.70 ± 7.63 and a mean depression score of 6.81 ± 5.75. The mean perceived social support score was 3.13 ± 0.58, with scores of 3.01 ± 0.69, 3.21 ± 0.73, and 3.16 ± 0.73 on the friends, significant other and family subscales, respectively. Among the psychosocial and economic measures, food insecurity was positively correlated with perceived stress ($r=0.31$, $p=.01$) and participation in food assistance programs ($r=0.27$, $p=0.04$, not shown in table), while it was inversely correlated with perceived social support and significantly correlated with the friends subscale ($r=-0.29$, $p=0.02$), indicating that persons with higher perceived stress and who required food assistance were more likely to be food insecure, while social support was protective from food insecurity. Perceived stress was observed to be inversely correlated with the MSPSS friends subscale ($r=-0.30$, $p<.02$) and positively associated with female gender ($r=0.32$, $p=.03$) and depression ($r=0.67$, $p<.01$).

Diet Quality: Associations between survey instruments and diet quality are shown in Table 3. Among the variables studied, only food insecurity was found to be correlated with diet quality on the aHEI ($r=-0.28$, $p=0.03$) and MDS ($r=-0.42$, $p<.01$) indices during univariate analysis. No significant correlations were found between diet quality and other parameters of interest. The association of food insecurity with both the aHEI ($\beta= - 0.08$, $p=.03$) and MDS ($\beta=-0.23$, $p<.01$) indices remained significant after multivariate analysis controlling for gender and income. After adjusting for covariates, none of the variables were associated with aHEI subscales.

Micronutrients: Associations between socioeconomic variables and micronutrient intake are shown in Table 4. In unadjusted models, food insecurity was significantly and

inversely correlated with dietary fiber (r= -0.27, p=.04), folate (r= -0.31, p=.02), magnesium (-0.34, p=.01), dietary copper (r= -0.36, p=.01), vitamin B6 (r=-0.28, p=.03), and vitamin E (r= -0.35, p=.01) intake, respectively. The PHQ-8 scale measuring depression was correlated with intakes of protein (r=-0.34, p=.01), vitamin B6 (r=-0.30, p=.03), and vitamin B12 (r=-0.31, p=.03), and the PSS scale measuring perceived stress was correlated with consumption of vitamin E (r=0.26, p=.04) and vitamin B6 (r=-0.29, p=.03). After multivariate analysis controlling for gender and income, only the FSQ scale measuring food insecurity remained significantly associated with the micronutrients listed in Table 4. Average daily intakes of nutrients stratified by food security status are shown in Table 5.

Discussion. This study evaluated associations of psychosocial and socioeconomic factors with dietary measures in a cross-section of older PLWH. Food insecurity was associated with lower diet quality irrespective of gender or income, while no significant associations were observed between diet quality and measures of psychosocial wellness in multivariate analyses. Our findings are consistent with previous studies in the general population investigating the relationship between food insecurity and diet quality [23, 46, 47]. More important, we provide preliminary evidence food security may be more closely associated with diet quality in older PLWH than depression, social support, or perceived stress, although these factors were commonly reported by our cohort. Furthermore, our findings support the evaluation of food insecurity as a screening tool during clinical evaluations or when designing interventions to reduce risk of chronic diseases through diet in this aging population.

The FSQ is a simple, validated survey that could be used to screen patients who may be food insecure [38]. Our findings suggest food security may be used as a preliminary predictor of general nutritional deficiencies, such fruit and vegetable intake. Similar to our findings, Leung et al. also reported lower-income food-insecure HIV-negative adults had diets low in fruits and vegetables with higher consumption of highly palatable, high-fat content foods [23]. Since fruit and vegetable intake is known to be associated with decreased risk for chronic disease in aging populations [13, 33], minimizing barriers to healthier foods in older PLWH may be a cost-effective preventive strategy for attenuating chronic disease risk. Our findings highlight the need for further explorations on the relationship between dietary intake and economic factors with health outcomes in this population. Whereas some people may consume foods with a certain sense of awareness of caloric intake and/or balance throughout the day, our population appears to consume foods based on accessibility, not knowing if there will be another meal during the day. Therefore, in the presence of limited resources, the dietary focus of individuals may be on the consumption of foods available for them at a specific time, rather than on the quantitative "balanced" diet approach.

We hypothesized that psychosocial pressures influenced diet quality in PLWH. Previous work by Hessol et al. provided evidence that food insecurity was associated with depressive symptoms in this population. While our findings confirmed food insecurity is correlated with both depression and perceived stress, neither depression nor perceived stress were independently associated with diet quality. Establishing the relationship between psychosocial wellness and diet quality has been a challenge in previous studies [4, 48-51]. A possible explanation may be that the beneficial effects of supportive

care provided by clinicians and healthcare professionals are not adequately measured by our survey instruments. There is extant literature suggesting engaging community resources can foster resiliency, or the ability to function under adverse conditions, in PLWH, which can attenuate stress-related behaviors [52-55]. Therefore, diet quality seen in this cohort may be more attributable to economic factors rather than psychological distress. Although we did not observe an association of diet quality with psychosocial measures, the importance of mental health in PLWH is well documented in the literature [56-58]. Previous studies have demonstrated perceived stress, depression, and perceived social support are all key factors driving longevity in this population [17, 57, 59-61]. Balbin et al. found that low perceived stress scores were associated with long-term survival in PLWH, while Lutgendorf et al. reported that perceived stress and social support mediates anxiety and depression and is associated with symptom frequency and disease progression in PLWH [62, 63]. Perceived stress scores in our sample were consistent with those observed in studies evaluating the effects of perceived stress in PLWH and the general population [64, 65]. Therefore, we have no evidence to conclude our cohort was atypical in that regard.

We further hypothesized gender would influence outcomes in diet quality. Previous studies have reported divergent responses to psychological stress reported in male and female PLWH; therefore, we expected similar results in our sample with respect to diet [60, 64]. While our results did confirm a significant correlation between gender and perceived stress, we found no significant associations of gender with diet quality in this population. This may be due to our small sample diminishing our ability to detect potential gender-specific associations of psychosocial factors with diet quality. Adams et al.

and Sirontin et al. both found in independent studies that food insecurity is associated with obesity in women [47, 66]. In our sample we found that women who were food insecure and reported higher perceived stress consumed more calories per day, while women who were food secure and reported less perceived stress had higher BMI. This suggests perceived stress may have an inverse relationship with both dietary intake and diet quality in women. Additionally, we found a significant correlation between gender and perceived stress. There was also a significant association of gender with food insecurity in our multivariate analysis. When considered in context with the extant literature suggesting potential interplay of perceived stress, food insecurity, and gender there may be underlying relationships that remain undefined.

Unexpectedly, we did not find significant associations of food security with the Recommended Food Score (RFS) diet quality index. The RFS is designed to measure dietary diversity within the NHANES FFQ, and there is evidence dietary diversity in food insecure settings can improve health outcomes in both the general and HIV positive and populations [15, 37, 50, 67]. While the RFS diet quality scores in our sample did confirm a general lack of dietary diversity, we also expected their diet quality would be associated with food insecurity, as had been the case with the MDS and aHEI indices. The lack of association may be attributed to self-report error and potential recall bias in reporting foods consumed over the past year. Although other studies have validated self-reported diet measures in the general population [68-72], we hypothesize the prevalence of food insecurity in our population may have further complicated some of the inherent limitations of self-report instruments. In the context of a food insecure sample, the RFS index may not accurately assess diet quality in a food insecure population in which available

foodstuffs may change from month to month. Given that nearly 77% of our participants earned < $20,000 per year, 60% reported having received food assistance, and 55% are food insecure, there may have been too much variation month to month for the RFS to accurately measure diet quality.

We also reported an inverse association of food insecurity with dietary intake of fiber, folate, magnesium, copper, and vitamin E. These micronutrients have important roles in healthy aging [73-79]. Although there is not currently a defined dietary pattern associated with food insecure PLWH, the micronutrients associated with food insecurity are found in common staple foods such as greens, beans, nuts, apples, breakfast cereals, and bread that would likely not be consumed by persons who are food insecure. In our study sample, we found participants reporting higher food insecurity did consume more cooked breakfast cereals and oatmeal but not the other foods (data not shown). This may be attributed to easier access to inexpensive, calorie-dense breakfast products. Our findings would likely be of interest to clinicians, social workers, and community outreach providers in assessing nutritional adequacy of food assistance programs. In the literature, food insecurity is associated with need-seeking behavior such as participating in food assistance programs [80]. In addition to providing nutritional support to persons in need, previous studies have shown structured food assistance programs may be associated with greater ART adherence and improved health outcomes in PLWH [81, 82]. These findings further reinforce the importance of food security as an essential component of HIV treatment programs.

There were limitations in our study. The study design was cross-sectional, which limited our ability to infer causality. Also, the sample size limited the number of covariates we controlled for, and was insufficient to test for possible mediating/moderating effects between diet quality and the psychosocial variables measured. Additionally, no corrections for multiple comparisons were done. In future studies, we would like to see more comprehensive measures of psychosocial wellness that include healthcare professionals. Our data collection was limited to measures of perceived support from close acquaintances and family members, not clinical caregivers [83-85]. The relationship between resilience and diet quality in aging PLWH is an area warranting further investigation. We believe our lack of evidence for a conclusive association of psychological measures with diet quality may be primarily attributed to homogeneity within our sample, which was 80% minority and 68% male, all within the same age group and geographic location [60]. The homogeneity within our sample may limit our ability to draw conclusions for the larger population of PLWH. However, this paper is one of the few to measure these variables among male African-Americans in the South, i.e., a high-risk population living in the epicenter of the current HIV epidemic. Also, the use of self-reported instruments for dietary intake was a limitation, as well, although surveys are a cost-effective data collection measure that have been validated in other studies [72]. Additionally, approximately 92% of the patient population at this clinic have an HIV viral load <200 copies/mL, and 100% of study participants presented with an undetectable viral load; thus, we cannot be certain that diet quality and psychosocial measures would be equivalent in PLWH with a detectable viral load [9].

In conclusion, older PLWH who experience food insecurity are likely to have poorer diet quality, compared to their food-secure counterparts. This population is at an increased risk for developing one or more comorbidities that can jeopardize healthy aging. Our findings suggest food insecurity as measured by the FSQ is more closely associated with diet quality than instruments measuring perceived stress, depression, and perceived social support. This information may be of interest to clinicians, dietitians, and social workers planning outreach interventions for reducing preventable diseases in this population. Further investigations are required to elucidate other associations among variables of interest.

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Table 1: Demographic Characteristics (Mean (SD) or (%)) of the Study Population

Characteristics	Study Sample (n=60)
Age, mean years (SD)	55.87 (4.63)
Anthropometrics	
BMI (kg/m2), mean (SD)	28.39 (7.21)
Women, %	31.67
Race, %	
White	20.00
African-American	80.00
Education, %	
< High School Diploma	20.00
High school diploma	26.67
> High School Diploma	53.33
Income, %	
<$10,000/year	41.67
= $10-$19,999/year	35.00
≥ $20,000/year	23.33
Food Security %	
Food Secure	45.00
Food Insecure without Hunger	18.33
Food Insecure with Hunger	36.67
Marital status, %	
Married	3.33
Never Married	51.67
Other	45.00
Mean CD4 Count (c/mm3) (SD)	528.30 (350.08)
Psychosocial Measures	
Perceived Stress Score, mean (SD)	15.70 (7.63)
Social Support Score, mean (SD)	3.13 (.582)
Friends	3.01 (0.58)
Significant Other	3.21 (0.73)
Family	3.16 (0.73)
Depression Score, mean (SD)	6.81 (5.75)
Diet Quality Scores	
Recommended Food Score (RFS), mean (SD)	10.58 (6.83)
Mediterranean Diet Score (MDS), mean	4.08 (1.70)
Alternative Healthy Eating Index (aHEI), mean (SD)	46.78 (11.73)

Table 2: €Correlation Matrix among Key Variables

Scale	PHQ8	PSS	MPSS	FSQ
	Correlation coefficient	Correlation coefficient	Correlation coefficient	Correlation coefficient
	p-value	p-value	p-value	p-value
PHQ8	1.00	**0.67**	-0.18	0.12
		<.01	0.19	0.40
PSS	**0.67**	1.00	-0.23	**0.31**
	<.01		0.07	**0.01**
MPSS	-0.18	-0.23	1.00	-0.11
	0.19	0.07		0.41
Friends	**-0.28**	**-0.30**	**0.79**	**-0.29**
	0.03	**0.02**	**<.01**	**0.02**
Significant Other	-0.16	-0.12	**0.85**	-0.08
	0.23	0.35	**<.01**	0.53
Family	-0.09	-0.04	**0.80**	-0.14
	0.50	0.74	**<.01**	0.30
FSQ	0.12	0.31	-0.11	1.00
	0.40	0.01	0.41	

€Unadjusted values

PHQ8: Patients Health Questionnaire (8 questions); PSS: Perceived Stress Scale; MPSS: Multidimensional Scale of Perceived Social Support; FSQ: Food Security Questionnaire;

Table 3: ¥Associations between Diet Quality and Psychosocial Survey Instruments

Diet Quality Index	PHQ8 Beta Estimate p-value	PSS Beta Estimate p-value	MPSS Beta Estimate p-value	FSQ Beta Estimate p-value
HEI	-0.02 0.67	0.01 0.04	-0.14 0.33	**-0.08** **0.03**
MDS	0.01 0.87	0.01 0.40	-0.24 0.37	**-0.23** **<0.01**
RFS	-0.19 0.46	-0.02 0.36	0.06 0.91	**0.09** **0.46**

¥Log adjusted values used in linear regression analysis controlling for gender and income
PHQ8: Patients Health Questionnaire (8 questions); PSS: Perceived Stress Scale; MPSS: Multidimensional Scale of Perceived Social Support; FSQ: Food Security Questionnaire; aHEI: alternative Healthy Eating Index; MDS: Mediterranean Diet Score; RFS: Recommended Food Score.

Table 4: κAssociations between Micronutrient Intake and Survey Instruments

Micronutrient	PHQ8	PSS	MPSS	FSQ
	Beta Estimate	Beta Estimate	Beta Estimate	Beta Estimate
	p-value	p-value	p-value	p-value
Fiber	-0.24	-0.23	0.17	**-0.14**
	0.41	0.07	0.19	**0.04**
Vitamin E	-0.41	-0.01	0.26	**-0.14**
	0.26	0.50	0.35	**0.04**
Folate	-0.19	<0.01	0.16	**-0.13**
	0.17	0.59	0.49	**0.02**
Copper	-0.23	<0.01	0.14	**-0.18**
	0.14	0.90	0.28	**0.01**
Magnesium	-0.11	<0.01	0.16	**-0.14**
	0.42	0.94	0.47	**0.01**

κAdjusted values

PHQ8: Patients Health Questionnaire (8 questions); PSS: Perceived Stress Scale; MPSS: Multidimensional Scale of Perceived Social Support; FSQ: Food Security Questionnaire

Table 5: £Average Daily Nutrient Intake in the Study Population Stratified by Food Security Status

Mean Nutrient Intake (SD)	Study Sample (n=60)	Food Secure Group (n-27)	Food Insecure Group (n=33)	p-value
Total (kcal/day)	2241.75 (905.28)	2391.35 (890.98)	2119.34 (911.97)	0.19
Fat (g/day)	91.23 (42.84)	100.48 (42.10)	83.67 (42.58)	0.10
Carbohydrate (g/day)	262.10 (105.59)	265.50 (81.43)	259.32 (123.09)	0.34
Protein (g/day)	**87.00 (32.93)**	**94.10 (34.01)**	**81.19 (31.35)**	**0.13**
Fiber (g/day)	16.90 (8.02)	18.66 (8.59)	**15.47 (7.34)**	0.14
Vitamin E (mg/day)	7.87 (4.14)	9.23 (5.04)	**6.76 (2.84)**	0.05
Folate (µg DFE/day)	413.61 (167.29)	466.62 (157.03)	370.23 (165.08)	0.02
Copper	1.33 (0.64)	1.55 (0.69)	1.15 (0.55)	0.001
Magnesium (mg/day)	274.44 (108.92)	307.61 (106.92)	247.30 (104.38)	0.02

£Unadjusted values

Wilcoxon Rank Sums Two-sided Test used to evaluate between-group differences in dietary intake.

VITAMIN D SUPPLEMENTATION DOES NOT AFFECT METABOLIC CHANGES SEEN WITH ART INITIATION

by

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ABSTRACT

Background: Insulin resistance and lipid changes are common after ART initiation. Observational studies suggest vitamin D supplementation reduces the risk of developing diabetes and improves lipid profiles.

Methods: This 48-week prospective, randomized, double-blind, placebo-controlled study evaluated high-dose vitamin D3 (4,000 IU daily) plus calcium supplementation (1,000 mg calcium carbonate daily) in HIV-infected participants initiating ART with efavirenz/emtricitabine/tenofovir (EFV/FTC/TDF). Changes in insulin resistance (as estimated by HOMA-IR), fasting lipid profile, and components of the metabolic syndrome were assessed at baseline and at 24 and 48 weeks. Stratified Wilcoxon rank sum tests and stratified normal score tests were used to evaluate differences between treatment arms, stratified by screening 25-OH vitamin D stratum (≤/> 20 ng/mL).

Results: 165 participants enrolled: 79 in vitamin Dcalcium (Vit D/Cal) arm and 86 in placebo arm. Only the placebo arm experienced a modest increase in insulin resistance at week 24 ($P<0.001$). While increases in total and HDL cholesterol were significant in both arms at weeks 24 and 48, increases in LDL cholesterol at week 24 were identified only in the placebo arm ($P=0.011$). BMI remained stable, whereas modest increases in waist circumference were observed in the placebo arm. Metabolic syndrome was present in 19 participants (12%) at baseline and 20 participants (14%) at week 48 without differences between arms.

Conclusions: Vit D/Cal supplementation over 48 weeks did not alter the lipid profile or glucose metabolism experienced with initiation of EFV/FTC/TDF in ART-naïve persons. Vitamin D supplementation is unlikely to be an effective strategy to attenuate metabolic dysregulations with ART initiation.

Introduction

Metabolic abnormalities, including insulin resistance and dyslipidemia, are common among HIV-infected persons and contribute to the increased risk of cardiovascular disease in this population [67, 182, 183]. The initiation of antiretroviral therapy (ART), even with modern ART regimens, increases visceral fat, worsens glycemia, and alters lipid profiles [184, 185]. For example, ART initiation with efavirenz (EFV) has been associated with less favorable lipid profile compared to other non-nucleoside reverse transcriptase inhibitors (NNRTIs) [185] and a modestly greater increase in fasting glycemia compared to atazanavir/ritonavir [186]. Notably, initiation of modern ART regimens, whether based on protease inhibitors (PIs), NNRTIs, or integrase strand transferase inhibitors (INSTI), induce similar increases in total cholesterol, total body weight, and fat mass [187-189]. Thus, even with modern ART, the metabolic dysregulations that occur with ART initiation require additional interventions.

Vitamin D deficiency has been associated with dyslipidemia and insulin resistance in both the general population and in HIV-infected patients, although whether the relationship between hypovitaminosis D and metabolic derangements is causal remains unclear [190, 191]. The expression of the vitamin D receptor on most nucleated cells in the body suggests that vitamin D serves some regulatory function beyond calcium

homeostasis. Potential non-calcitropic functions include lipid regulation or glucose metabolism [192]. Vitamin D supplementation trials examining glucose and lipid outcomes have had mixed results in the general population [56, 193-196], and data from HIV-infected populations are limited. In one study, vitamin D supplementation was associated with a decreased incidence of type 2 diabetes in an HIV-infected population [197]. In a small randomized 12-week supplementation trial among ART-treated virologically suppressed HIV-infected persons, vitamin D led to modest but significant decrease in total cholesterol with an increase in insulin resistance, estimated by HOMA-IR [198]. No study, to our knowledge, has examined the effect of vitamin D supplementation in HIV-infected persons on metabolic outcomes during the period of ART initiation.

We have previously shown in a randomized, placebo-controlled trial (ACTG A5280) that daily supplementation with vitamin D/calcium (4,000 IU/1,000 mg) given to HIV-infected individuals initiating ART with efavirenz/emtricitabine/tenofovir disoproxil fumarate (EFV/FTC/TDF) attenuated the loss in bone mineral density by approximately 50% over 48 weeks [69]. Here, we report the effects of vitamin D/calcium on metabolic outcomes in ACTG A5280. We hypothesized that vitamin D/calcium supplementation would be associated with salutary effects on glucose and lipid metabolism in HIV-infected persons initiating EFV/FTC/TDF.

Methods

ART-naïve, HIV-infected adults with baseline 25(OH) Vitamin D between 10-75 ng/mL (>25 and <188 nmol/L) were eligible to enroll [69]. Participants initiated ART with EFV/FTC/TDF and were randomized to 4,000 IU cholecalciferol (vitamin D3) daily

plus 500 mg calcium carbonate twice daily or identically matching placebo (Tishcon Corporation, Westbury, NY) for 48 weeks. The Institutional Review Boards of all participating sites approved the study; all participants provided written informed consent. (clinicalTrials.gov Identifier NCT01403051.)

Metabolic Assessments

Serum concentrations of glucose and insulin were measured using a Cobas Colorimetric Assay and Human-specific Insulin RIA, respectively, and serum concentration of 25(OH) D2 and D3 were measured by liquid chromatography tandem mass spectrometry at the Irving Institute Biomarkers Core at Columbia University Medical Center (New York, NY). Insulin resistance was assessed by Homeostatic Model Assessment (HOMA-IR) [199]. Fasting lipid profiles were performed at local laboratories in real time; low density lipoprotein cholesterol (LDL-c) was calculated using the Freidewald equation [200]. Daily calcium and vitamin D intake was determined by a 24-hour dietary recall performed at entry. Waist circumference was measured using a standardized protocol [201]. The metabolic syndrome was assessed using the ATPIII/NCEP criteria at each time point and was considered to be present if ≥ 3 of the following 5 criteria were observed: 1) waist circumference ≥ 102 cm (male), ≥ 88 cm (female); 2) triglyceride concentration: ≥ 150 mg/dL ;3) HDL-c concentration < 40 mg/dL (male), < 50 mg/dL (female) ; 4) systolic blood pressure (BP) ≥ 130 mmHg or diastolic BP ≥ 85 mmHg; 5) fasting glucose: ≥ 110 mg/dL [202].

Statistical analysis. All analyses were limited to participants with available data regardless of treatment change/discontinuation. Stratified Wilcoxon rank sum tests were used to evaluate differences between treatment arms for continuous outcomes, stratified by screening 25-OH vitamin D stratum (≤ or > 20 ng/mL). Wilcoxon signed rank tests were used to evaluate within treatment arm changes. Stratified normal score tests were used to evaluate differences between treatment arms in categorical responses, stratified by screening 25-OH vitamin D stratum. All statistical tests were two-sided and interpreted at the 5% nominal level of significance without adjustment for multiple comparisons. SAS version 9.4 and Cytel Proc StatXact package version 9 were used.

Results. The details and disposition of the study population have been previously described [69]. Of the 165 eligible participants included this analysis (79 in the VitD/Cal arm, 86 in the placebo arm), 148 (90%) completed 48 weeks of study treatment. Twenty-five (15%) participants discontinued EFV/FTC/TDF prematurely (13 in VitD/Cal and 12 in placebo arm).

Baseline demographics. Baseline characteristics are shown in Table 1. For the overall study population at baseline, the median age was 33 years, 90% male, 37% white non-Hispanic, and 33% black non-Hispanic, with a median BMI of 24.4 kg/m2 (Table 1).

25-OH Vitamin D. At baseline, 25(OH)D levels appear to be balanced between the treatment arms but differed over the 48-week study period (Tables 1-2). Increases in 25(OH)D levels were observed in the VitD/Cal arm at 24 and 48 weeks: median (Q1, Q3) concentrations increased 27.5 [15.0, 38.0] and 24.2 [14.6, 37.8]) ng/mL from baseline to

weeks 24 and 48, respectively; $p<0.001$ for both) in the VitD/Cal arm. No significant changes in the placebo arm were detected (-0.8 (-5.9, 4.9) and 0.6 (-6.1, 4.3) ng/mL, respectively).

Lipid profile. Baseline lipid parameters appear to be balanced between the treatment arms (Table 1). Fasting total and HDL cholesterol levels increased significantly by weeks 24 and 48 for both arms, with no significant differences between the two arms (Table 2). In the placebo arm, LDL cholesterol increased at week 24 from baseline but not at week 48. However, triglyceride changes from baseline to week 24 or 48 were not significant in either arm. None of the changes in lipid parameters appeared to differ by treatment arm.

Glucose metabolism and measures of insulin resistance. Baseline fasting glucose and insulin levels, as well as HOMA-IR values, appear to be balanced between arms (Table 1). Glucose levels were increased modestly at weeks 24 and 48 in both arms (Table 2). Insulin levels increased in the placebo arm but not in the VitD/Cal arm at week 24, while the week 48 changes were not statistically significant for either arm. HOMA-IR increases were modest for both arms only at week 24. Between arm differences were not significant for glucose, insulin, or HOMA-IR changes at either week 24 or 48 ($p>0.05$ for all).

Body composition and metabolic syndrome. Baseline waist circumference and BMI values appear to be balanced between the two arms (Table 1). Waist circumference increased in the placebo arm but not in the VitD/Cal arm at both weeks 24 and 48, but

differences between the two arms were not significant (Table 2). Changes in BMI were not significant over 48 weeks for either arm. Metabolic syndrome was identified in 19 participants (12%) at baseline and 20 participants (14%) at week 48 with no significant difference between arms. For specific parameters of the metabolic syndrome, low HDL prevalence decreased from a 45% overall prevalence at baseline to 26% at week 48, and elevated TG prevalence increased from a 14% overall prevalence at baseline to 22% at week 48.

Conclusions. Despite the marked increase in vitamin D levels from the time of ART initiation and benefits regarding bone health, high-dose vitamin D and calcium supplementation did not meaningfully improve relevant metabolic parameters, including glucose metabolism, insulin resistance, lipid profiles, body composition measures, or prevalence of the metabolic syndrome. While the observed modest increases in fasting glucose, insulin resistance, waist circumference, and total and HDL cholesterol observed in the placebo are consistent with previous trials in which participants initiated EFV/FTC/TDF, no consistent effect on these metabolic parameters was observed with supplementation. While the NNRTI class of HIV medications has been reported to have a more favorable effect on lipids and glucose metabolism than protease inhibitors and thymidine analog NRTIs and has not been associated with an increased risk for atherosclerotic cardiovascular disease, efavirenz has been previously reported to cause increases in cholesterol levels when compared to other NNRTIs [203-206]. One proposed explanation was the effect of efavirenz on vitamin D metabolism. Efavirenz has previously been demonstrated to decrease circulating 25(OH)D levels through induction of CYP3A4 (25- hydroxylase) and

CYP24 (24-hydroxylase) enzymes, which catabolize vitamin D3 to inactive metabolites [207]. While previous observational trials have identified an association between efavirenz and vitamin D deficiency, the current study failed to demonstrate a reduction in vitamin D with initiation of an efavirenz containing ART regimen [208-210]. A large proportion of the study population had 25(OH)D levels<30ng/mL at entry, yet the participants in the placebo arm had stable 25(OH)D levels throughout the trial. These findings from the placebo arm suggest that efavirenz does not significantly alter vitamin D metabolism. Furthermore, the demonstrable increase in 25(OH)D levels with vitamin D and calcium supplementation does not support earlier observations that efavirenz blunts the effect of vitamin D supplementation [198, 211, 212].

Despite having low vitamin D levels throughout the study, participants in the placebo arm had only modest changes in the metabolic parameters measured. Additionally, the VitD/Cal arm did not experience any metabolic benefits when compared to the placebo arm: changes in glucose, insulin, and HOMA-IR levels were similar to placebo. Parameters of the metabolic syndrome were also altered in similar fashion for both arms. These data did not affirm the hypothesis that vitamin D plays a crucial role in lipid metabolism or insulin sensitivity. While vitamin D deficiency has previously been associated with impaired pancreatic beta cell function and insulin resistance, as well as the metabolic syndrome in the general population and among persons with HIV [196, 197, 213], we did not identify these associations in a randomized clinical trial. It may be that metabolic changes related to ART initiation far outweigh the effects of vitamin D supplementation. Alternatively, vitamin D supplementation may be useful only in persons who de-

velop these metabolic derangements after some duration of exposure to the ART medications or that the level of 25(OH)D required to cause metabolic derangements is lower than that needed to maintain bone health. Alternatively, it is possible that the previous trials were confounded by some unmeasured variables.

The current analysis has several limitations. Karhapaa et al. showed the active form of vitamin D, 1,25-dihydroxyvitamin D (1,25-D) is more appropriate in assessing the link between vitamin D and lipids [107]. The duration of follow up was only one year, which may limit the ability to determine the long-term effect of vitamin D supplementation. Since we studied supplementation with only one ART regimen (EFV/FTC/TDF), we cannot assert whether vitamin D would have a different effect with other ART regimen. The study population was young and metabolically healthy. The effect of vitamin D supplementation may have beneficial effects on metabolic parameters for persons with diabetes or dyslipidemia but limited impact in persons with normal metabolic parameters. The low prevalence of the comorbidities of interest (i.e., diabetes, metabolic syndrome, dyslipidemia) in the cohort may have limited the effect of the intervention. Also, baseline data on physical activity, alcohol intake, and smoking status were not collected, which limited our ability to assess their effect on lipids and glucose metabolism in our sample. Previous studies have shown beneficial effects of vitamin D supplementation in women; however, the low number of women in our sample limits the generalizability of our findings.

In summary, vitamin D and calcium supplementation in HIV-infected persons initiating ART increased vitamin D levels and improved bone health but did not alter meta-

bolic parameters of relevance for cardiometabolic disease risk. Whether vitamin D supplementation would have different effects with other ART regimens or in patients with a higher prevalence of baseline metabolic abnormalities should be examined.

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Table 1. Baseline Demographic and Laboratory Parameters

Parameter	**Vitamin D/Calcium (n=79)**	**Placebo (n=86)**
Age (years)	36 (28, 47)	31 (25, 44)
Race/ethnicity White non-Hispanic Black non-Hispanic Hispanic	 28 (35%) 24 (30%) 23 (29%) 4 (6%)	 33 (38%) 30 (35%) 18 (21%) 5 (6%)
Male sex	72 (91%)	77 (90%)
BMI (kg/m2)	25.0 (22.5, 28.2)	24.0 (21.7, 27.2)
Presence of metabolic syndrome	7 (9%)	12 (14%)
Plasma HIV RNA (log10 cp/mL)	4.5 (4.1, 5.1)	4.5 (4.0, 5.1)
CD4 cell count	339 (230, 500)	342 (232, 454)
CD4 cell count ≤ 200 cells/mm3	17 (22%)	15 (17%)
Estimated daily Ca intake (mg)	813 (492, 1303)	811 (365, 1227)
Estimated daily Vit D intake	120 (62, 215)	137 (59, 279)
Laboratory Parameters		
25-OH Vitamin D	28.4 (20.9, 38.5)	26.4 (19.6, 33.0)
Insulin (ulU/ml)	5.0 (2.7, 9.8)	4.4 (1.9, 8.4)
Glucose(mg/dL)	85 (80, 91)	85 (79, 92)
HOMA-IR	0.97 (0.52, 2.12)	0.94 (0.46, 1.81)
Total Chol (mg/dL)	161 (138,182)	156 (135,184)
HDL-c (mg/dL)	43 (34,50)	42 (33,49)
LDL-c (mg/dL)	95 (80,112)	89 (72,115)
Triglycerides (mg/dL)	99 (65,127)	96 (73,116)

All values presented as median values with interquartile ranges (Q1, Q3) or number of participants with percentages.

Table 2. Changes in Metabolic Parameters at Weeks 24 and 48 by Treatment Arm

	Vitamin D/Calcium	Placebo	Pa	Vitamin D/Calcium	Placebo	Pa
Parameter	**Median (Q1, Q3) Change from**			**Median (Q1, Q3) Change from**		
25-OH Vitamin D	27.5* (15.0, 38.0)	-0.8 (-	<0.001	24.2* (14.3, 35.8)	0.6 (-6.1, 4.3)	<0.001
Insulin (ulU/ml)	0.4 (-1.5, 3.8)	1.4* (-1.1, 4.2)	0.24	0.5 (-1.5, 4.2)	0.9 (-1.8, 3.2)	0.78
Glucose (mg/dL)	5* (-4, 12)	5* (-3, 12)	0.91	4* (1, 8)	6* (-3, 12)	0.73
HOMA-IR	0.17* (-0.21, 0.91)	0.39* (-	0.21	0.13 (-0.26, 1.11)	0.26 (-1.09,2.73)	0.87
Total Chol (mg/dL)	11* (-4, 29)	18* (1, 31)	0.22	13* (-6, 28)	14* (-1, 37)	0.55
HDL-c (mg/dL)	8* (0, 15)	8* (2, 15)	0.72	8* (1, 14)	8* (1, 14)	0.44
LDL-c (mg/dL)	0 (-10, 17)	8* (-11, 20)	0.26	2 (-9, 14)	4 (-14, 27)	0.93
Triglycerides (mg/dL)	3 (-17, 45)	4 (-18, 28)	0.90	3 (-14, 31)	4 (-18, 39)	0.87
BMI (kg/m2)	0.0 (-0.5, 1.1)	0.1 (-0.6,0.9)	0.67	0.1 (-0.8, 1.1)	0.1 (-0.7, 1.0)	0.98
Waist Circ. (cm)	0.0 (-2.5, 3.0)	0.7* (-1.0,	0.17	0.3 (-2.5, 3.3)	0.9* (-2.0, 4.8)	0.38
	Number of partici-pants		**Pb**	**Number of partici-pants**		**Pb**
Presence of Meta-bolic Syn-	7/71 (10%)	11/78 (14%)	0.55	9/66 (14%)	11/75 (15%)	0.97
Central Obesity	19%	16%	-	21%	18%	-
Elevated triglycerides	22%	21%	-	24%	21%	-
Low HDL-c	27%	28%	-	24%	28%	-
Elevated BP	39%	42%	-	37%	41%	-
Elevated	6%	5%	-	6%	7%	-

*Wilcoxon signed rank p-value < 0.05 for within treatment arm change from baseline.
a Stratified Wilcoxon rank sum p-value evaluating the difference in changes from baseline between the two treatment arms, stratified by screening 25-OH vitamin D levels. b Stratified normal score p-value evaluating the difference between the two treatment arms, stratified by screening 25-OH vitamin D levels.
Statistical comparisons for the individual components of the metabolic syndrome were not performed.

PHYSICAL ACTIVITY TRENDS AND METABOLIC HEALTH OUTCOMES IN PEOPLE LIVING WITH HIV IN THE US, 2008–2015

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ABSTRACT

Background**.** Despite its potential to improve metabolic health outcomes, longitudinal physical activity (PA) patterns and their association with cardiometabolic diease among people living with HIV (PLWH) have not been well characterized.

Methods**.** We included PLWH with at least one PA self-report in the Centers for AIDS Research Network of Integrated Clinical Systems between 2008–2015. The 4-item Lipid Research Clinics PA instrument was used to categorize participants' activity levels as: Very Low, Low, Moderate, or High. We analyzed demographic differences in PA patterns. Multivariable generalized estimating equation regression models were fit to assess longitudinal associations of PA with blood pressure, lipid, and glucose levels. Logistic regression modeling was used to assess the odds of being diagnosed with obesity, cardiovascular disease (CVD), cerebrovascular disease, hypertension, diabetes, or multimorbidity.

Results**.** A total of 40,462 unique PA assessments were provided by 11,719 participants. Only 13% of PLWH reported High PA, while 68% reported Very Low/Low PA at baseline and did not increase PA levels during the study period. Those who had Very Low/Low PA had higher glucose and triglyceride levels, and lower HDL-c, compared to those with High PA. Compared to High PA participants, Very Low PA participants were more likely to have hypertension, obesity, CVD, multimorbidity, and cerebrovascular disease and 2.5 times more likely to have diabetes (all $P<0.01$).

Conclusions**.** The majority of participants reported low or very low PA, which was associated with worse metabolic health and increased cardiometabolic disease. PLWH may derive significant cardiometabolic benefit from simple PA interventions.
Keywords: HIV; exercise; physical activity; chronic disease; health outcomes

Introduction

An increasing burden of non-AIDS cardiometabolic diseases (CMD) is well documented among people living with HIV (PLWH).[214-216] We reported that while most PLWH gain weight during the first six months of antiretroviral therapy (ART) use, many continue to gain weight for up to two years after beginning treatment.[80] In the current United States (U.S.) epidemic, over 2/3 of PLWH are diagnosed as overweight/obese (25% obese), 40% with hypertension, 6% cardiovascular disease (CVD), and 10.3% with diabetes.[71, 80, 81] These alarming results highlight a need for interventions such as physical activity (PA) to prevent and treat CMD.

PA is associated with decreased mortality and improved health outcomes among the general population and PLWH.[217-219] Unfortunately, PLWH have lower physical fitness levels compared to other vulnerable populations,[220] and the amount of PA needed for meaningful improvement in CMD biomarkers and outcomes may be different for PLWH versus those without HIV.[221] Additionally, long-term data regarding PA habits of PLWH are lacking, while cross-sectional studies of PA levels that include smaller sample sizes from single sites reveal a wide disparity in self-reported activity levels.[221-223] To develop effective PA strategies, we require a greater understanding of

the longitudinal PA patterns reported by PLWH and the minimal amount of activity needed to reduce CMD risk.

To investigate patterns of PA and explore associations with CMD biomarkers and diagnoses, we analyzed PA and CMD data collected over 7.5 years from 11,719 PLWH in the multisite Centers for AIDS Research (CFAR) Network of Integrated Clinical Systems (CNICS) cohort of PLWH in the U.S. We hypothesized that higher self-reported PA would be associated with better lipid and glucose levels and lower prevalence of CMD diagnoses.

Methods

This retrospective analysis was conducted in the U.S. from CNICS. [224] CNICS is a nationally distributed clinical cohort that includes over 32,000 PLWH receiving routine clinical care. At regular intervals, CNICS sites provide comprehensive data on demographics, laboratory values, pharmaceutical history, HIV/AIDS clinical events, and comorbid conditions collected from electronic medical records and other data sources, including the CNICS clinical assessment of standardized Patient-Reported Outcomes (PROs) measured at four- to six-month intervals [225, 226] at seven CNICS sites. A rigorous, systematic quality assurance process is in place to maintain this centralized database.

Participants

This study includes all CNICS participants who completed a clinical assessment between January 2008 (first PA measures available) and mid-July 2015. Inclusion criteria

were: (1) at least one PA instrument completed, (2) ≥ 19years of age, and (3) height, weight available. Written, informed consent for CNICS was obtained from all study participants and documented at each site, and the protocol was approved by the Institutional Review Board (IRB) at each site. Ethical approval for this study was provided by the IRB at the University of Alabama at Birmingham. Procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2013.

Study measures. Physical activity (PA): Participants completed the 4-question, validated Lipid Research Clinics (LRC) instrument to provide an estimate of self-reported PA. [227] The LRC asks about respondents' perception, compared to peers, of exercise amount/intensity at work and outside of work. A 4-point scoring system is used to classify activity levels as (1) high PA (vigorous activity ≥ 3 times weekly), (2) moderate PA (active, but vigorous activity < 3 times weekly), (3) low PA (no vigorous activity but light activity perceived as equivalent to peers), or (4) very low PA (sedentary). The 4-point scoring identified physiologically relevant group differences in VO2max: High PA 41.9 ml/kg-1/min-1, Moderate 39.1 ml/kg-1/min-1, Low 33.2 ml/kg-1/min-1, and Very Low 32.9 ml/kg-1/min-1. [227]

Laboratory values: Vital signs and laboratory values closest to the date (± 90 days) of each PA assessment were included. Systolic (SBP) and diastolic (DBP) blood pressure were measured at the beginning of patient care encounters as part of routine clinical care. As participant lab draws occurred throughout the day, both fasting and non-

fasting glucose and lipid values (total cholesterol, LDL-c, HDL-c, triglycerides) were included.

Cardiometabolic diseases (CMD): We focused on five cardiometabolic outcomes: obesity, cardiovascular disease (CVD), cerebrovascular disease, hypertension, and diabetes as well as CMD multimorbidity. Participants were considered obese with a body mass index (weight [kg] / height [m2]) ≥ 30. CVD consisted of myocardial infarctions centrally adjudicated within CNICS [228] as well as diagnoses of chronic ischemic heart disease and congestive heart failure. Similarly, cerebrovascular diseases were based on diagnoses. Hypertension was based on the CNICS standard definition of a diagnosis of hypertension and the presence of any antihypertensive medication, or the average of at least two systolic blood pressure measurements ≥140 mmHg or diastolic blood pressure measurements ≥90 mmHg over 12 months. As we were unable to confirm whether all patients with hypertension or dyslipidemia were taking medications as prescribed, we included participants with both pharmaceutically treated and untreated conditions.

We defined diabetes based on the following criteria: a) hemoglobin A1c ≥6.5 OR b) use of a diabetes-specific medication such as insulin OR c) use of a diabetes-related medication frequently but not exclusively used to treat diabetes (e.g., biguanides) in the setting of also having a diabetes diagnosis. A diabetes diagnosis alone did not meet the definition. [229] Multimorbidity was computed as the presence of two or more of the above five CMD as well chronic kidney disease and cancer (HIV and non-HIV related). Presence of chronic kidney disease was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m2 for >3 months (2 values >90 days apart without an intervening normal value), or a charted diagnosis of stage 2, 3, 4, or 5 kidney disease.

Independent variables: We examined patient demographic and HIV-related laboratory information including age, sex, self-reported race/ethnicity, CD4+ T-cell count, viral load, HIV transmission risk factor (IV drug use, men having sex with men [MSM]), ART use (yes/no), insurance status (public, private, uninsured), and mortality (yes/no with confirmed date of death). The "d" drugs didanosine (DDI), stavudine (D4T), and zalcitabine (DDC) may contribute to mitochondrial toxicity and peripheral neuropathy that could impair PA ability; [230, 231] thus, we recorded whether a participant had ever been exposed to d-drugs. Since pharmaceutical therapy may impact the laboratory values evaluated, we documented each prescribed medicine that could affect results, with the list of medicines included for each laboratory value adjudicated by two clinical providers (GB and JW).

Statistical analyses. Descriptive characteristics were analyzed using chi-square tests, one-way analysis of variance (ANOVA), or Kruskal-Wallis ANOVA. Time of first PA assessment was considered the baseline for each participant. We computed prevalence, expressed as unadjusted percentages, for each cardiometabolic condition overall and by PA group. Because race/sex interactions were observed for cardiometabolic disease outcomes, a six- level race/sex variable was created (black men, black women, white men, white women, other men, other women) for subsequent analyses. The "other" racial category was approximately 40% self-reported Asian/Pacific Islander, 40% unidentified, 11% American Indian, and 9% multiracial.

For each continuous laboratory outcome, generalized estimating equations were fit to estimate the longitudinal effect of PA on laboratory variables after controlling for

covariates described under “independent variables.” We also controlled for outcome- specific non-ART medications – antihyperlipidemic agents, antihypertensives, oral hypoglycemic agents, insulin – prescribed. For CMD outcomes, multivariable logistic regression was used to compute odds ratio and 95% confidence intervals (CI) of the odds of developing each cardiometabolic condition controlling for the above covariates. Obesity was also a covariate in all models excluding those with multimorbidity and obesity as the dependent variable. For all analyses, site was included as a stratification factor and “High PA” was considered the referent group. With a multilevel modeling approach, adjustment for multiple comparisons was not performed [232]. All data were analyzed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) with a significance level of $P<0.05$.

Results: Demographics and physical activity patterns. Over 7.5 years, 40,462 unique PA assessments were provided by 11,719 CNICS participants, with 8,157 providing ≥ 2 reports, and 3029 completing ≥ 5 reports. There were no significant differences in demographic characteristics by those who had completed different numbers of PA assessments; thus, descriptive statistics for all 11,719 participants at their initial assessment are presented in **Table 1**. At time of first PA report, 26% reported being Very Low active, 42% Low active, 19% Moderate active, and 13% High active. Very Low and Low PA participants were younger, less likely to be male, more likely to report black race, and weighed more compared to other PA categories ($p <0.01$). Individuals identifying as transgender were more likely to report Very Low PA ($p = 0.04$). Approximately 54% of participants consistently reported Very Low/Low PA and 19% reported High PA at each

reporting period; thus, almost three quarters of respondents did not change PA levels during the observation period. There was no increase in Moderate/High PA over time. There was no difference in PA category frequency by year of first PA report and no difference by PA category in the percentage of participants prescribed ART (87-88%, p=0.50).

A slightly higher percentage of Very Low PA participants (23.7%) had been exposed to d-drugs compared to other groups (range 20.5-21.4%). Baseline CD4+ T-cell counts were significantly increased across PA categories ($p < 0.01$). Greater mortality was also observed in the Very Low PA group compared to all other groups.

Laboratory values. Laboratory values at time of first PA report are shown in **Table 1**. No significant differences were identified by PA group for DBP, total cholesterol, or LDL-c. Very Low PA participants had slightly lower SBP (125.2 mmHg) compared to other groups (range 126.0-126.4 mmHg). Those in the Very Low PA group presented with significantly lower HDL-c levels, higher triglycerides, and higher glucose compared to all other groups (all at $p < 0.01$).

These differences persisted in longitudinal adjusted analyses (**Figure 1; Supplemental Table 1**). When compared to the High PA category, a significant stepwise decrease in HDL-c was observed with Moderate (estimate -0.71; 95% CI -1.25, -0.17; $p = 0.009$), Low (-1.03; -1.54, -0.51; $p < 0.001$) and Very Low PA (-1.56; -2.17, -0.96; $p < 0.001$). An increase in triglyceride levels was also observed for each PA group: Moderate (7.78; 1.96, 13.59; $p = 0.009$), Low (16.12; 9.90, 22.34; $p < 0.001$), and Very Low (25.43; 15.64, 35.22; $p < 0.001$). When glucose was analyzed, the Low PA (1.35; 0.26,

2.45; p = 0.02) and Very Low PA (1.98; 0.47, 3.49; p = 0.01) groups had higher levels over time compared to the High PA group.

Cardiometabolic disease diagnosis. We observed significant differences in the prevalence of five cardiometabolic diseases and multimorbidity by PA group (**Figure 2**). Over one third of all participants were obese with significant group differences: High PA (27%); Moderate (31%), Low (35%,) and Very Low (41%). Similar differences were observed with hypertension, CVD, and cerebrovascular diagnoses (**Figure 2**). Finally, while 24% of the High PA group had cardiometabolic multimorbidity, greater prevalence was observed in other PA groups: Moderate (27%, P = 0.003), Low (31%, p < 0.001) and Very Low (40%, p < 0.001).

In adjusted models using High PA as the referent group (**Table 2**), only the Very Low PA group differed in prevalence of cerebrovascular disease (OR 1.76; 95% CI 1.13-2.74). Both Low and Very Low PA were associated with greater risk for hypertension, CVD, and diabetes, while a stepwise increase in risk of diagnosis was observed across all PA categories for obesity and multimorbidity. Participants with Very Low PA experienced 1.5-2 times greater risk of obesity, hypertension, CVD, and multimorbidity. In particular, the Very Low PA group had a 2.3 times greater risk of being diagnosed with diabetes.

Discussion. This is the first investigation to assess comprehensively and longitudinally PA patterns and associations with CMD in a large cohort of PLWH in the U.S. Despite nation-wide efforts to promote PA, the majority (68%) of PLWH reported Very

Low/Low PA at baseline (compared to 49.8% of the general population) and did not increase PA during the study period. Unfortunately, only 13% of PLWH reported High PA, versus 31.2% of the general population.[233] This is in contrast to recent reports of gradually increased leisure-time PA among the general population through 2014,[234, 235] and highlights the need to develop effective PA promotion strategies for PLWH.

We identified a consistent association of Very Low/Low PA with both CMD biomarkers and outcomes. The only differences in CMD risk for Moderate versus High PA were for obesity and multimorbidity, suggesting that even moderate PA may be sufficient to reduce risk for HTN, cerebrovascular disease, CVD, and diabetes. In particular, reporting Very Low PA was associated with higher glucose levels and almost 2.5 times increased diabetes risk. A recent meta-analysis in HIV-uninfected adults observed reductions in type 2 diabetes risk of 26% with Moderate PA and 53% with High PA.[236] Yarasheski et al. also reported that exercise augments the effects of pharmaceutical treatment in PLWH with diabetes.[237] However, due to HIV-related chronic inflammation, pharmaceutical and lifestyle interventions may be less effective in HIV-infected versus HIV–uninfected groups.[221, 238] Monroe and colleagues [221] reported that while low PA was associated with greater insulin resistance (e.g., higher HOMA-IR) regardless of HIV status, men with HIV still had higher HOMA-IR levels at equivalent levels of PA. Collectively, these results highlight uncertainty in exactly how much PA is required to achieve an equivalent benefit in diabetes prevention/treatment for this population.

While PA level did not correlate with clinic blood pressure measurements, PA level was associated with both hypertension and cerebrovascular disease. This association

may be attenuated by pharmaceutical interventions for blood pressure control. In the general population, exercise is associated with blood pressure reductions in normotensive and hypertensive individuals, although the impact of exercise on HTN risk may partly depend on the short-term blood pressure response to exercise. [239, 240] The impact of PA frequency or type on HTN risk among PLWH remains to be fully investigated.

Our analysis also identified a 1.5-2.0 increased CVD risk with Low/Very Low PA, although PA was only associated with HDL-c and triglycerides laboratory values. An inverse association between PA levels and CVD risk factors/outcomes has been reported in HIV-infected and HIV-uninfected populations. [241, 242] PA is also associated with higher HDL-C and lower triglycerides in HIV-uninfected individuals, possibly due to augmentation of lipoprotein lipase (LPL) activity in skeletal muscle and adipose tissue. However, consistent with our results, two meta-analyses in HIV-uninfected individuals reported minimal declines in LDL-c and total cholesterol levels of 2900 men and 1715 women. [243, 244] We were unable to measure other factors that may impact CVD risk, such as LPL activity, LPL size, or apo-lipoprotein B levels. Future investigations are required to determine to what extent PA can reduce the risk of CVD, and the amount and types of PA required to meaningfully impact PLWH who have a higher-than-average risk for CVD.

Participants reporting Very Low PA tended to weigh more, have greater mortality, more exposure to d-drugs, and lower CD4+ T-cell counts than other groups. CD4+ counts are influenced by periods of rest and strenuous activity in HIV-infected and

-uninfected groups,[245] and PA interventions are associated with increased CD4+ count in PLWH in some, but not all, studies.[49, 246] The potential of exercise to complement ART-related immunologic reconstitution is an area that remains to be explored.

With regard to sex, race, and ethnicity, females had lower PA levels compared to males, and black participants more frequently reported Very Low/Low PA compared to other groups. Previous reports have identified similar patterns of sex or racial health disparities in PA levels in the general population and PLWH, [223, 247] confirming the need for programs to reduce sex and race disparities in PA. Interestingly, we also detected differences in PA for PLWH who identify as transgender among the 7200 participants reporting on transgender status. Within groups, only 9% of transgender participants identified as High PA compared to 13% of other participants, and 38% of transgender participants reported Very Low PA compared to 26% of others. Few investigations have explored unique aspects of health behaviors and risks among transgender individuals, particularly those with HIV. Fredriksen-Goldsen et al. [248] reported lower PA levels in transgender adults over age 50 compared to lesbian, gay, and bisexual older adults, while Bryant and colleagues found that compared to other members of the LGBT community, transgender women in particular were at risk for low PA and poor diet. [249]. The milieu of hormonal and body composition changes, combined with poor PA and dietary habits, could exacerbate CMD risk in this population. Unfortunately, our sample small limits the general applicability of these findings for transgender PLWH. Additional research is needed to identify barriers, facilitators, and metabolic factors that contribute to disparities in PA for the transgender community.

These findings are subject to certain limitations. Self-reported PA is less accurate than objectively measured PA and can underestimate Very Low/Low PA while overestimating High PA. However, this would possibly mean that Very Low/Low PA is present in more than the 68% of PLWH identified here and further serves to emphasize the need for PA promotion in this population. Additionally, as our PA data collection only began in 2008, we are unable to consider the impact of PA habits across the life course and throughout HIV infection, which is an area of significant interest in disease prevention.

Despite these limitations, the present study benefited from several strengths, including a large, diverse sample size inclusive of several geographic regions across the U.S., use of a validated PA assessment, and repeated PA measures assessed over 7.5 years of observation. The study included both biomarkers and outcomes of CMD and provides strong evidence that PA can have a meaningful impact on CMD in PLWH. These findings inform clinical practice by highlighting subgroups of PLWH that may benefit from additional PA promotion as well as risk factors that are more likely to be impacted when PA levels change. Additional scientific exploration that determines the appropriate types and dose-response of PA for specific CMD, as well as strategies to most effectively implement PA programs among PLWH, holds great potential to improve outcomes and reduce health disparities in CMD risk among individuals living and aging with HIV.

Notes. Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's website (www.jaids.com).

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Table 1. Demographic characteristics and laboratory values (mean ± SD or n (%)) at first physical activity assessment stratified by physical activity level for PLWH receiving care between 1/2008 and 7/2015.

Variable	Total n=11,719	Very Low n=3058	Low n=4957	Moderate n=2177	High n=1527	P value[a]
Demographics						
Age (yrs)	43.8 ± 10.7	44.9 ± 10.2	43.7 ± 10.9	42.8 ± 10.5	43.1 ± 10.8	< 0.01
Male Sex	9772 (83.4)	2409 (78.8)	4067 (82.1)	1956 (89.8)	1340 (87.8)	< 0.01
Transgender (yes)[b]	96 (1.3)	37 (2.0)	32 (1.1)	18 (1.2)	9 (0.9)	0.04
Race						<0.01
% Black	3917 (33.4)	991 (32.4)	1873 (37.8)	586 (26.9)	467 (30.6)	
% White	6735 (57.5)	1855 (60.7)	2643 (53.3)	1338 (61.5)	899 (58.9)	
% Other	1067 (9.1)	212 (6.9)	441 (8.9)	253 (11.6)	161 (10.5)	
% Hispanic ethnicity	1597 (13.7)	358 (11.8)	666 (13.5)	350 (16.2)	223 (14.8)	< 0.01
Body mass index	26.5 ± 5.5	27.0 ± 6.3	26.5 ± 5.5	26.3 ± 4.8	26.0 ± 4.7	< 0.01
Health insurance						< 0.01
Uninsured	1167 (9.9)	279 (9.1)	477 (9.6)	240 (11.0)	171 (11.2)	
Public	6171 (52.7)	1932 (63.2)	2552 (51.5)	1054 (48.4)	633 (41.5)	
Private	3083 (26.3)	455 (14.9)	1416 (28.6)	643 (29.5)	569 (37.3)	
Unknown	1298 (11.1)	392 (12.8)	512 (10.3)	240 (11.0)	154 (10.1)	
Transmission Risk Factor						< 0.01

IVDU	1771 (15.1)	579 (18.9)	697 (14.1)	324 (14.9)	171 (11.2)	
MSM	6976 (59.5)	1632 (53.4)	2956 (59.6)	1393 (64.0)	995 (65.2)	
Heterosexual	2615 (22.3)	725 (23.7)	1170 (23.6)	402 (18.5)	318 (20.8)	
Other/Unknown	357 (3.1)	122 (4.0)	134 (2.7)	58 (2.7)	43 (2.8)	
CD4+ T-cell count (cells/µl)	506.7 ± 294.3	488.6 ± 315.7	508.7 ± 293.3	517.0 ± 275.0	521.9 ± 278.2	< 0.01
Plasma HIV RNA < 200 copies/ml	7675 (70.5)	1928 (68.5)	3242 (70.1)	1472 (72.6)	1033 (72.5)	< 0.01
d-drug exposure (ever)	2533 (21.6)	724 (23.7)	1031 (20.8)	465 (21.4)	313 (20.5)	0.01
Death during observation period	510 (4.4)	216 (7.1)	204 (4.1)	55 (2.5)	35 (2.3)	< 0.01
Laboratory Values						
SBP (mmHg)	125.9 ± 15.4	125.2 ± 15.9	126.0 ± 15.6	126.4 ± 14.9	126.3 ± 14.1	< 0.01
DBP (mmHg)	78.7 ± 10.3	78.9 ± 10.5	78.9 ± 10.3	78.6 ± 10.2	78.2 ± 9.7	0.16
Total Cholesterol (mg/dL)	177.2 ± 42.7	176.4 ± 44.3	177.8 ± 43.3	177.5 ± 41.4	176.1 ± 39.2	0.60
LDL-c (mg/dL)	101.9 ± 33.7	100.6 ± 34.6	102.6 ± 33.4	102.4 ± 33.8	101.7 ± 32.6	0.20
HDL (mg/dL)	43.8 ± 16.4	41.7 ± 15.9	44.3 ± 16.2	44.3 ± 16.2	46.1 ± 17.7	<0.01
Triglycerides (mg/dL)	176.5 ± 180.5	196.2 ± 174.0	176.3 ± 211.6	164.7 ± 131.2	154.0 ± 130.8	<0.01
Glucose (mg/mL)	95.1 ± 30.9	97.8 ± 37.2	94.7 ± 30.2	94.2 ± 27.5	92.2 ± 22.9	<0.01

[a] – One-way ANOVA for continuous measures and chi-square for categorical measures
[b] – n(%) only for sites collecting data on transgender identify (n=7200)
Other = American Indian, Asian, Asian/Pacific Islander, Pacific Islander, Multiracial, Missing; d-drug = Didanosine, Stavudine, Zalcitabine
SBP = systolic blood pressure; DBP = diastolic blood pressure; LDL-c = low-density lipoprotein cholesterol; HDL = high-density lipoprotein cholesterol

Table 2. Demographic and clinical characteristics associated with cardiometabolic outcomes among PLWH in adjusted analyses. Each column shows adjusted odds ratios for separate multivariable logistic regression. All models also adjusted for site as a stratification factor.

	Obesity (n=9930, 3506 events)	**Hypertension (n=9525, 3828 events)**	**Cerebrovascular Disease (n=9525, 339 events)**	**Cardiovascular Disease (n=9525, 560 events)**	**Diabetes (n=9525, 976 events)**	**Multimorbidity (n=9933, 3252 events)**
PA Level						
High	Reference	Reference	Reference	Reference	Reference	Reference
Moderate	**1.34 (1.13-1.58)**	1.16 (0.98-1.38)	1.42 (0.87-2.31)	1.09 (0.74-1.60)	1.19 (0.87-1.62)	**1.32 (1.10-1.58)**
Low	**1.48 (1.28-1.71)**	**1.28 (1.10-1.49)**	1.38 (0.89-2.13)	**1.48 (1.07-2.06)**	**1.49 (1.14-1.94)**	**1.42 (1.21-1.66)**
Very Low	**1.92 (1.64-2.24)**	**1.43 (1.21-1.68)**	**1.76 (1.13-2.74)**	**1.92 (1.37-2.70)**	**2.32 (1.76-3.05)**	**2.12 (1.80-2.50)**
BMI Category [c]						
Normal wt.	--	Reference	Reference	Reference	Reference	--
Underweight	--	**0.65 (0.47-0.90)**	0.74 (0.35-1.56)	1.31 (0.78-2.20)	1.13 (0.69-1.86)	--
Overweight	--	**1.51 (1.35-1.68)**	1.00 (0.77-1.31)	1.01 (.082-1.25)	**1.36 (1.14-1.64)**	--
Obese	--	**2.89 (2.54-3.28)**	1.18 (0.88-1.60)	1.23 (0.96-1.56)	**3.73 (3.11-4.49)**	--
Race/Sex [a]						
WM	Reference	Reference	Reference	Reference	Reference	Reference
WF	**1.96 (1.61-2.39)**	**0.78 (0.62-0.98)**	1.36 (0.83-2.23)	**0.61 (0.39-0.98)**	1.02 (0.74-1.42)	1.11 (0.89-1.38)
BM	**1.41 (1.25-1.59)**	**1.73 (1.53-1.97)**	1.18 (0.86-1.61)	0.76 (0.60-0.98)	**1.56 (1.28-1.89)**	**1.75 (1.54-1.98)**

BF	**3.85 (3.20-4.64)**	**1.65 (1.34-2.02)**	1.53 (0.99-2.36)	**0.46 (0.30-0.69)**	1.23 (0.93-1.64)	**2.54 (2.09-3.09)**
OM	**0.72 (0.53-0.97)**	0.92 (0.67-1.27)	1.42 (0.66-3.02)	0.70 (0.34-1.47)	**2.09 (1.30-3.35)**	0.93 (0.66-1.29)
OF	**2.11 (1.16-3.84)**	1.13 (0.57-2.26)	0.79 (0.10-5.98)	1.27 (0.37-4.31)	0.92 (0.27-3.16)	1.36 (0.68-2.69)
Hispanic	**1.51 (1.29-1.77)**	1.04 (0.87-1.23)	0.85 (0.55-1.31)	0.81 (0.57-1.15)	**1.51 (1.17-1.96)**	**1.40 (1.18-1.67)**
Age						
19-29	reference	reference	reference	reference	reference	reference
30-39	**1.84 (1.55-2.18)**	**2.04 (1.66-2.51)**	1.63 (0.73-3.60)	2.26 (0.98-5.15)	**2.49 (1.50-4.13)**	**2.44 (1.93-3.08)**
40-49	**2.26 (1.92-2.67)**	**4.56 (3.74-5.56)**	**3.65 (1.75-7.60)**	**6.45 (3.00-13.90)**	**4.80 (2.98-7.75)**	**5.28 (4.23-6.59)**
50-59	**2.16 (1.82-2.58)**	**8.63 (7.02-10.61)**	**6.20 (2.97-12.92)**	**13.44 (6.25-28.92)**	**9.95 (6.16-16.08)**	**8.38 (6.67-10.52)**
≥ 60	**1.62 (1.28-2.04)**	**16.27 (12.46-21.25)**	**11.24 (5.23-24.16)**	**30.42 (13.92-66.44)**	**16.38 (9.86-27.19)**	**15.67 (11.93-20.57)**
Insurance						
Private	Reference	Reference	Reference	Reference	Reference	Reference
Public	0.91 (0.81-1.01)	1.02 (0.91-1.15)	**2.20 (1.59-3.06)**	**1.55 (1.22-1.95)**	1.19 (0.99-1.43)	1.06 (0.94-1.19)
Uninsured	0.83 (0.69-1.00)	0.85 (0.69-1.04)	0.85 (0.48-1.49)	0.98 (0.63-1.51)	0.90 (0.64-1.27)	**0.67 (0.55-0.83)**
Unknown	0.88 (0.73-1.06)	0.95 (0.78-1.16)	1.39 (0.76-2.54)	1.33 (0.86-2.06)	1.01 (0.72-1.43)	0.89 (0.72-1.09)
Risk Factor						
MSM[b]	Reference	Reference	Reference	Reference	Reference	Reference
Heterosexual	**1.21 (1.06-1.39)**	0.96 (0.83-1.11)	0.95 (0.67-1.35)	0.97 (0.73-1.29)	1.09 (0.88-1.36)	1.08 (0.93-1.25)
IV drug use	**1.17 (1.03-1.34)**	**0.87 (0.75-0.99)**	1.10 (0.79-1.51)	0.95 (0.73-1.23)	1.18 (0.95-1.46)	0.94 (0.81-1.08)

Unknown	1.08 (0.83-1.42)	0.78 (0.57-1.05)	1.33 (0.73-2.42)	0.84 (0.47-1.50)	1.24 (0.82-1.88)	1.08 (0.81-1.44)
d-drug use	1.09 (0.98-1.21)	**1.48 (1.32-1.65)**	**1.41 (1.11-1.79)**	**1.49 (1.23-1.80)**	**1.57 (1.34-1.83)**	**1.61 (1.44-1.79)**
Viral Load	1.03 (0.93-1.14)	**0.89 (0.80-0.99)**	**0.67 (0.51-0.89)**	**0.73 (0.58-0.93)**	**0.83 (0.69-0.99)**	**0.82 (0.73-0.91)**
>200 CD4:						
≥ 500	Reference	Reference	Reference	Reference	Reference	Reference
350-499	0.91 (0.81-1.02)	1.02 (0.91-1.16)	1.22 (0.90-1.65)	1.00 (0.79-1.27)	0.91 (0.75-1.09)	0.97 (0.86-1.10)
200-349	0.88 (0.77-0.99)	1.03 (0.90-1.17)	1.20 (0.87-1.68)	1.22 (0.96-1.56)	0.92 (0.75-1.12)	1.00 (0.87-1.14)
< 200	**0.66 (0.57-0.75)**	**0.84 (0.73-0.98)**	**2.06 (1.50-2.83)**	1.16 (0.87-1.53)	**0.77 (0.61-0.98)**	0.91 (0.78-1.05)

[a] – WM = white male; WF = white female; BM = black male; BF = black female; OM = other male; OF = other female

[b] – MSM = men who have sex with men

[c] – BMI categories: Underweight = <18.5; Normal Weight = 18.5-24.9; Overweight = 25.0-29.9; Obese = ≥30

Figures Legend

Figure 1. Associations between physical activity levels and laboratory values over time among PLWH. Values are GEE parameter estimates and 95% CI. Each model adjusted for site, first PA, race/sex, Hispanic ethnicity, age group, insurance status, HIV risk factor, d-drug use, viral load group, CD4 group, and lab specific non-ART medications prescribed

Figure 2. Prevalence (%) of multimorbidity and cardiometabolic disease by physical activity category for 11,719 PLWH diagnosed between 1/2008 and 12/2015

* = P<0.05; ** = P<0.01; *** = P<0.001

Figure 1.

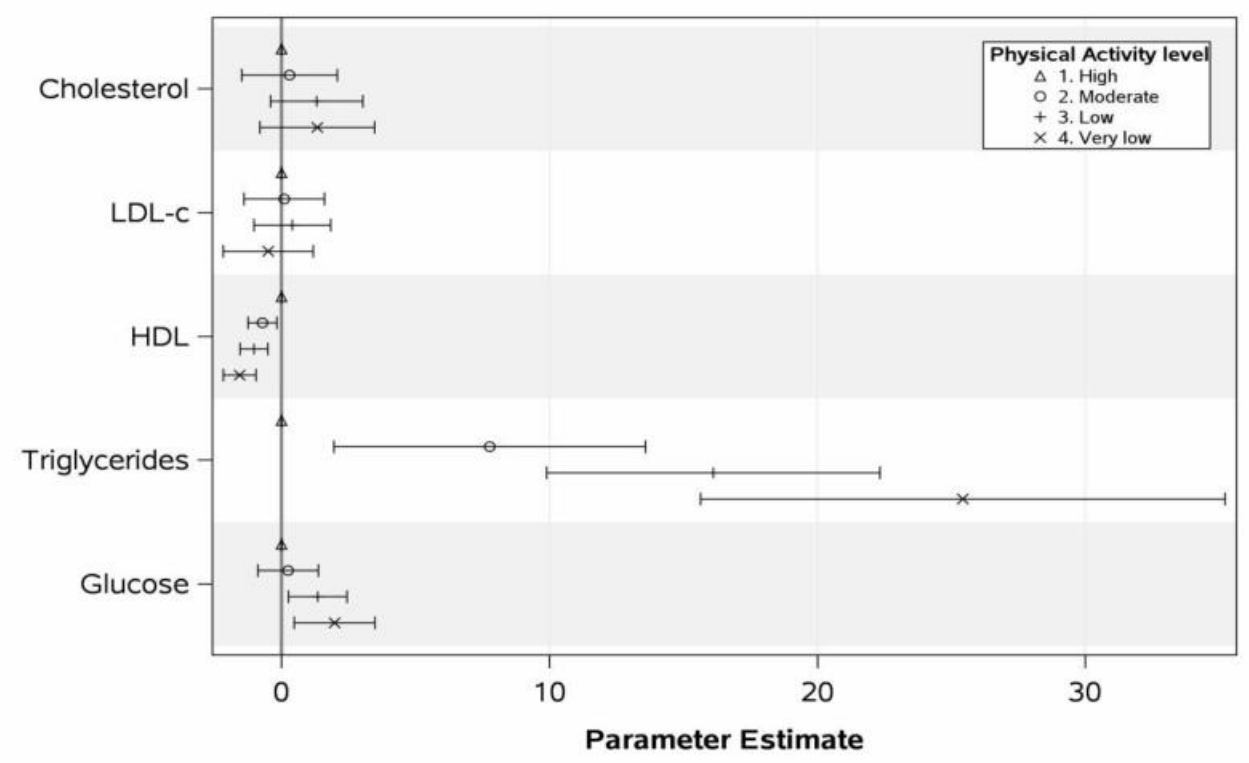
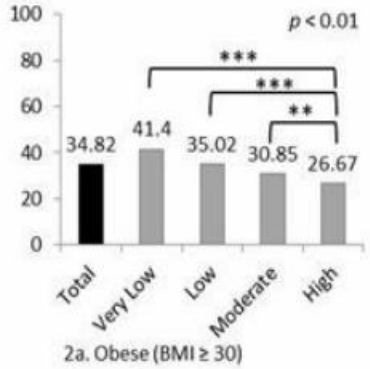
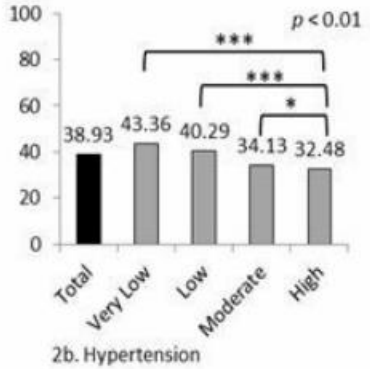

Physical Activity level
1. High
2. Moderate
3. Low
4. Very low
Cholesterol
LDL-c
HDL
Triglycerides
Glucose
0
10
20
30
Parameter Estimate

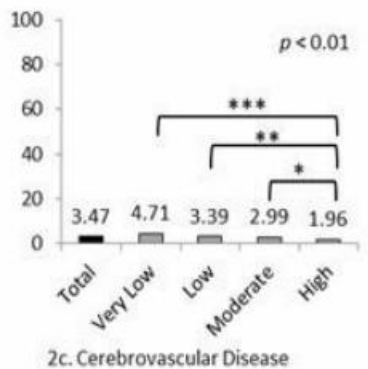
Figure 2.



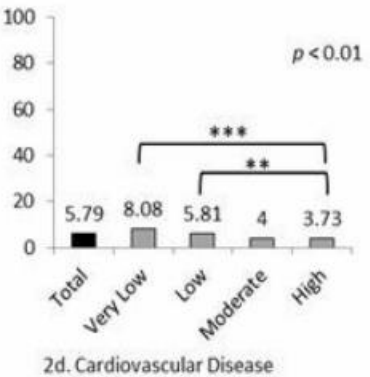
2a. Obese (BMI ≥ 30)



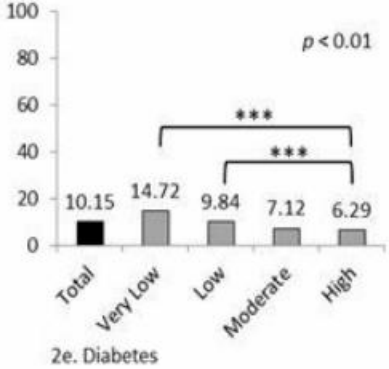
2b. Hypertension



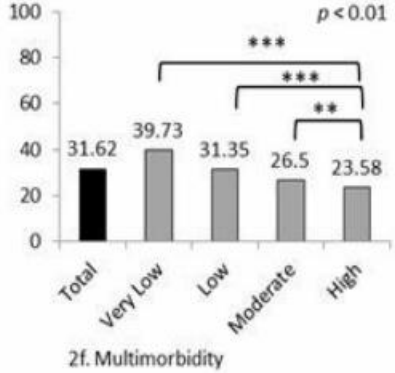
2c. Cerebrovascular Disease



2d. Cardiovascular Disease



2e. Diabetes



2f. Multimorbidity

SUMMARY AND CONCLUSIONS

People living with HIV have seen significant advancements in HIV-related outcomes since 1981 [10]. Today, cardiometabolic diseases threaten aging-related outcomes and quality of life even when HIV is well controlled with ART medication [23, 24]. As the number of older adults with HIV continues to expand and accumulate comorbidities, public health resources will become increasingly strained [13, 23, 133]. Therefore, healthy aging among PLWH requires immediate attention. As the scientific community converges on strategies for enhancing outcomes in this population, an investigation into the feasibility of existing lifestyle recommendations may be a practical first step and is warranted. Adequate diet, nutrition, and physical activity are each associated with reduced chronic disease risk among PLWH [4, 78, 90, 91, 122]. While lifestyle modifications are frequently recommended for the prevention of adverse health outcomes in the general population, specific guidelines have not been established for the adults who are HIV positive. The present project identified behavioral and physiological relationships that may better elucidate disease etiology and progression among persons who are HIV positive. In particular:

1) Persons who are aging with HIV face unique, multifaceted social burdens that impact nutrition [98, 134, 135]. Previous studies have investigated perceived stress, depression, perceived social support, and food insecurity in PLWH. However, our study is the first to investigate the associations of these factors with dietary intake and diet

quality. We identified food insecurity as a stronger driver of diet quality and selected micronutrients.

2) Metabolic changes, including dyslipidemia and vitamin D insufficiency, are common after antiretroviral (ART) initiation in persons who are treatment naïve. However, it is unclear whether daily, high-dose vitamin D and calcium supplementation improve metabolic changes associated with the initiation of an efavirenz/emtricitabine/tenofovir (EFV/FTC/TDF) ART regimen. We confirmed vitamin D and calcium supplementation does not significantly improve glucose metabolism, insulin resistance, lipid profiles, body composition measures, or prevalence of metabolic syndrome in our study population.

3) Physical activity (PA) is inversely associated with age-related declines in physical and mental health in the general population [39, 74]. However, patterns of physical activity and their longitudinal associations with chronic disease risk among PLWH have not been thoroughly investigated. We found most (68%) PLWH consistently report Very Low/Low levels of physical activity, which we found to be associated with higher glucose and triglyceride and lower HDL-c levels. Furthermore, we found those reporting Very Low PA have an increased risk for developing hypertension, diabetes, obesity, cerebrovascular disease, cardiovascular disease (CVD), or multimorbidity when compared to their High-PA counterparts.

A review of the relationships of diet, vitamin D sufficiency, and physical activity with cardiometabolic disease risk in persons aging with HIV is provided in the following general discussion.

Social Burden and Diet Quality

As non-HIV comorbidities proliferate among aged PLWH [10], nutritional concerns have shifted to the prevention of chronic diseases, such as diabetes [4]. Healthy diets are associated with improved health outcomes in both the general and study populations [44, 78, 89]. Diet quality is the product of multiple, interrelated factors, and there is limited clarity on which factor (psychosocial or economic) is more influential in people's food choices. Our study demonstrated that diet quality (DQ), as measured by the Alternative Healthy Eating Index (aHEI) and the Mediterranean Diet Score (MDS) is inversely associated with food insecurity. Leung and colleagues have previously reported similar findings in the general population [109], indicating the importance of considering economic forces as stronger drivers of diet quality than psychosocial wellness. Our study sample reported significantly lower income than the general population, suggesting that financial stability may supersede other issues in determining diet quality. A public health approach that considers income limitations may be required to address DQ among older PLWH. Fortunately, there are existing programs for disadvantaged people that could be adapted to assist PLWH in preventing chronic disease. For example, the Special Supplement Nutrition Program for Women Infants and Children (WIC) is a federal program established in 1974 for low-income pregnant women [163,164]. WIC provides vouchers for specific nutritious foods that our study population may not regularly consume, such as fresh fruits and vegetables and salmon. Unlike the Supplemental Nutrition Assistance Program (SNAP), commonly called "food stamps," WIC vouchers have no cash value,

are tightly monitored by merchants, and are regularly recertified by the issuing agency based on developmental milestones. Although the WIC program could serve as a model for a federal program designed to assist low-income PLWH, efforts should be directed toward initiatives where community service providers, social workers, and healthcare professionals collaborate to better assist patients who would benefit from additional nutritional support services.

The implications of our work regarding the importance of nutritional education among those at risk for chronic diseases cannot be minimized. Nutritional education programs have reported successful outcomes for low-SES patients with diabetes [136, 137]. Given the increased risk among aged PLWH for developing diabetes, incorporating a similar program into routine treatment may be an appropriate preventive measure to consider. Also, food assistance programs sponsored by charitable organizations in lower-income communities may help connect disadvantaged patients with nutritious meals and have additional benefits [138, 139]. Thus, if the need-seeking behavior is driving dietary intake, removing barriers and expanding access to affordable, nutritious foods may help improve diet quality.

The expansion of existing social programs provides a more immediate solution to nutritional disparities in lower-income communities; however, there may be alternatives that are more efficient and sustainable. Nonconventional approaches to remediating social inequities, such as urban farming, have reported successful outcomes in older PLWH who are food insecure [168]. While data on these studies are too limited to draw general conclusions, some initial findings are promising. In a small pilot study investigating the

feasibility of urban farming in PLWH, Shacham et al. reported positive results, most notably an increased access to healthy foods and greater self-efficacy [168]. Likewise, Palar et al. reported positive HIV and diabetes health outcomes in a pilot study investigating the feasibility of a comprehensive, medically appropriate food support program for food-insecure PLWH in San Francisco [169]. In both studies, self- efficacy is positively associated with healthful lifestyle habits [167]. Therefore, to encourage lifestyle modification among the disadvantaged, the qualitative preferences of the target community must be incorporated into any proposed intervention. Ultimately, the intended targets of the outreach must accept the intervention to fully participate.

Surprisingly, we did not observe an association of any variable of interest with diet quality as measured by the Recommended Food Score (RFS) [102]. We attribute the lack of connection to both limitations in the scale and the economic composition of our study sample [140, 141]. Based on previous studies investigating the restrictions of 12-month food frequency questionnaires, we believe the underlying FFQ upon which the RFS is based may not be designed to adequately assess irregular consumption of foodstuffs from disparate sources for food-insecure individuals [142-144]. Therefore, it may be plausible to suggest future studies evaluating diet quality carefully consider potential incongruities between inconsistent access to food and quality assessment methods.

The socioeconomic and demographic makeup of our study sample may have predisposed this cohort to certain risks [95, 149, 150], irrespective of their HIV status. Participants in our sample had poor diet quality, which confirms an increased risk in this population for developing cardiometabolic diseases. The average diet quality score for each index was lower than the respective national average in the general population

[145]. However, this may be partially attributable to geographic influence. Diet quality has been shown to be suboptimal in the Southern U.S., the location of our study [146, 147]. It is plausible that many of participants subscribed to a so-called Southern-style diet that has been shown to associate with increased chronic disease risk [148].

Revisiting the concept of psychosocial health, we hypothesized depression, perceived stress, and perceived social support would be the stronger influences on diet quality in our cohort. This is because previous studies in PLWH found these factors associated with longevity in PLWH [94, 98, 99, 134, 151, 152]. However, we found no associations between psychosocial variables with diet quality. Our findings suggest there is a hierarchy of needs among indigent, food-insecure populations where psychological needs are subordinate to food acquisition. This is especially true in the absence of excessive psychological distress. Perceived social support, for example, is believed to moderate depression in the presence of food insecurity [153-155] and is associated with longevity in geriatric populations [118]. In our sample, the total and subscale average scores on the MSPSS scale were consistent with high perceptions of social support. Furthermore, the average scores on the instrument measuring depression, below the diagnostic cut point, indicates major depression. We also reported average perceived stress scores that are comparable to those measured in the general population [113]. Further investigations under varying conditions are needed to clarify the relationship among psychological factors and how those factors mediate in the presence of food insecurity.

Metabolic Changes After ART Initiation

Dyslipidemia is common in PLWH and is a consequence of aging, poor diet, and other factors [62]. Recently, there has been increased interest in describing the role of vitamin D in lipid metabolism, especially in PLWH. Vitamin D has been hypothesized to beneficially affect cardiometabolic health in older PLWH [62]. While investigating aim 1, we confirmed quality was associated with very low intake of vitamin D in this population. Given the social and economic challenges facing older adults with HIV, a "diet only" approach to resolving nutritional imbalances may not be realistic. Therefore, for aim 2, we investigated the effects of daily high-dose vitamin D (4,000 IU) and calcium (1,000 mg) supplementation in treatment-naïve patients initiating an EFV/FTC/TDF ART regimen. We found supplementation did not meaningfully affect metabolic or lipid profiles in our sample. Our findings confirmed previous studies reporting vitamin D supplementation increased serum 25(OH)D levels in PLWH beginning ART regimens, but not calcitriol, 1, 25 (OH)2D [54, 56, 156, 157]. The respective findings seemingly indicate either discordant associations of serum 25(OH)D and the active hormone 1, 25 (OH)2D with individual lipid parameters or an HIV-related disruption in calcitriol synthesis. The literature supports either hypothesis or a combination thereof.

Karhapaa et al. reported a direct association of 1,25 (OH)2D with high-density lipoprotein cholesterol (HDL-c), but not other lipid parameters. He also reported an inverse association of serum 25 (OH)D with low-density lipoprotein cholesterol (LDL-c), triglycerides, and total cholesterol [107], but no association with HDL-c. Based on his

findings, we expected to see similar associations with serum 25 (OH)D. While we did report a substantial increase in serum 25 (OH) from baseline in the treatment arm, it was without significant between-group changes in LDL-c, triglycerides, or total cholesterol.

Demographic differences in respective cohorts may partially explain the divergent results. Unlike the Karhappa cohort, our study population was smaller and included a diverse admixture of risk characteristics, which may have shown that the intervention is not effective in the real world. All of our participants were HIV-positive, with the majority (65%) predisposed to vitamin D insufficiency based on at least one demographic risk factor [57, 105]. Also, participants in our study were younger, had lower BMI scores, and were vitamin D sufficient at baseline. Conversely, the Karhapaa cohort had fewer confounding factors; the sample size was much greater and considerably more homogenous. His study sample consisted entirely of European men who were HIV negative, nearly 25% of whom were vitamin D deficient (VDD) at baseline. Thus, the participants in the Karhapaa study were more likely to see stronger associations in relevant parameters. Further investigations in mediating/moderating factors affecting vitamin D sufficiency in the context of HIV infection are warranted.

Aside from demographic factors, there are biological considerations that may clarify our findings. Previous studies have shown HIV infection antagonistically affects calcitriol synthesis through alterations in the vitamin D receptor (VDR). Immune activation caused by HIV viremia is believed to propagate hypermethylation of CpG domains within vitamin D receptors (VDR-CpG), which cause attenuated expression of VDR and ultimately reduce the activity of its ligand, 1-25 (OH)2D [106, 158]. This activity may

explain why no changes were discernable in the lipid profiles of the study population despite increased serum 25(OH)D.

There is also evidence that suggests dyslipidemia commonly observed in treatment-naive patients may be attributed to other factors, such as baseline HIV viral load, rather than ART regimen. McComsey et al. reported patients with baseline HIV viral loads ≥100,000 copies/ml had significantly more gains in both subcutaneous (SAT) and visceral adiposity (VAT) when comparing cohorts with viral loads ≤100,000 copies/ml, irrespective of ART regimen [159]. Given that the relationship between fat deposition and dyslipidemia is well described [160], it is plausible to suggest this mechanism is a likely contributor. However, the role of the VAT and SAT in mediating/moderating vitamin D status is not well-understood in the general population [161] and even less in PLWH. Although supplementation did not significantly affect lipid profiles or metabolic parameters, other benefits were noted, particularly in bone health [62]. The lack of a significant association between vitamin D supplementation and lipid profiles is likely because mechanisms fully describing vitamin D insufficiency in PLWH remain unclear and are multifactorial. The role of dietary supplements in improving health outcomes in PLWH should be further investigated because persons from disadvantaged communities have limited access to healthcare and support services [85]. To better clarify associations leading to vitamin D insufficiency in this population, future studies that simultaneously investigate vitamin D supplementation within the context of overall nutritional status within a virally suppressed seropositive cohort are warranted.

Physical Activity

In addition to contributing to poor diet and nutritional deficiencies, the social burden may also limit opportunities for PLWH to participate in physical activities. Previous studies have shown physical activity to be protective against cardiometabolic disease risk in the general population and PLWH [49-51, 53, 74, 120, 132]; however, these studies did not compare respective levels of PA among infected versus noninfected populations. While PA levels in the general population are well- documented, such data in PLWH are lacking. Therefore, for aim 3, we investigated national trends in PA among PLWH to better understand potential causes of adverse health disparities in this community. It is plausible to suggest the higher rates of cardiometabolic disease among PLWH may be partially attributed to sedentary behavior. We hypothesized PLWH would have lower rates of PA because it is known attrition rates from PA interventions, for example, are higher in PLWH than in the general population [121]. This phenomenon may or may not be HIV-related but may affect PLWH more acutely given their predisposition to age-related comorbidities. Attaining adequate physical activity can be difficult for older adults, irrespective of HIV status. However, if there are unique barriers faced by PLWH which limit physical activity, it is important to first quantify the deficiency. Therefore, we wanted to first quantify patterns of PA before examining how these designs affect long-term disease risk in our study population.

We observed most participants (68%) in our study consistently reported Low/Very Low rates of PA. To our knowledge, our study is only the third one to characterize PA levels among PLWH and the first in a large, longitudinal investigation of a U.S. cohort. While it is known PLWH have decreased exercise capacity [120, 162] compared

to HIV-negative counterparts, we reviewed a meta-analysis performed by Vancampfort et al. [121] to clarify which environmental factors are likely associated with the exercise behaviors in our study sample. Vancampfort et al. reported a consistent, positive association of low PA with lipodystrophy, ART usage, and old age, among other factors. Gomes Neto et al. also reported similar results investigating aerobic capacity in PLWH [132]. Given these cumulative findings, decreased physical fitness in PLWH is likely associated with the reduced PA. Although previous studies have shown both aerobic and exercise training to be safe, feasible exercise options for older PLWH [49,51], our findings demonstrate current PA choices may not be practical or particularly appealing. Vancampfort observed facilitators of PA in this population included high self-efficacy, higher perceived benefits, and exercise motivation [121]. Therefore, interventions focusing on these qualitative areas, tailored to meet the specific needs of PLWH, may have a greater impact for PA promotion among PLWH. The transition from a sedentary to an active lifestyle may be intimidating, especially for older adults. A non-threatening approach to PA may be yoga, which has been shown to yield quality of life and HIV-related benefits [126, 128]. If practiced outdoors, yoga may also increase sun exposure to effect increased vitamin D production. There may also be psychosocial benefits to further facilitate healthy aging.

We also investigated longitudinal risk factors associated with one or more comorbidities. We found PLWH who report Very Low/Low PA are at an increased risk for developing obesity, cardiovascular disease, cerebrovascular disease, hypertension, diabetes, and multimorbidity.

Interestingly, we found African-American women were 3.85 times more likely to become obese, 1.65 times more likely to progress to hypertension, and 2.54 times more likely to develop multimorbidity than white males in our sample. The elevated risk of cardiometabolic disease among African-American women is further evidence why lifestyle interventions are required now. Despite ample evidence describing the multiple beneficial effects of PA [50, 52], African-American women remain an especially vulnerable subpopulation among PLWH and consistently exhibit lower levels of PA [83, 84] when compared to their male counterparts.

In total, our findings represent a critical first step in understanding associations of PA with disease risk in PLWH. Age-related disease risk among PLWH is a multifactorial challenge and a growing public health challenge, especially among African-American women. Further studies are needed to determine possible interventions that can increase enthusiasm and viability for PA among this vulnerable population.

Summary. Healthy dietary intake and regular physical exercise have each been shown to increase longevity and quality of life in aging PLWH. However, specific recommendations are needed to develop effective interventions for a population at increased risk for developing co-morbidities and multimorbidity in the context of well- controlled HIV infection. Our results from aim 1 suggest poor diet quality is a concern, especially among food-insecure, older PLWH. Furthermore, food insecurity is a stronger predictor of diet quality than perceived stress, depression, or perceived social support. In experimental aim 2, we found high-dose vitamin D and calcium supplementation does not attenuate metabolic changes seen after ART initiation. Results from goal 3 suggest most

PLWH engage in Very Low/Low levels of PA and are at increased risk of developing one or more co-morbidities or multimorbidity.

In summary, PLWH now live longer with increased access to healthcare. However, this study further elucidates the need to focus on lifestyle modifications as primary attenuators of chronic disease risk among PLWH, particularly among disadvantaged people living in the South. The results suggest there may be underutilized potential for lifestyle modifications to effect healthy aging in this sensitive population.

Future Directions. Multifactorial challenges await older PLWH, especially those who are 1) food insecure; 2) prescribed an efavirenz-based ART regimen; 3) vitamin D deficient; 4) physically inactive; 5) a minority; 6) live in the Southern U.S.; or 7) have low SES status. Studies investigating dose/response associations for diet and exercise regimens, the metabolic impact of specific dietary factors, and the impact of food security programs on diet quality are all warranted. Furthermore, qualitative studies investigating attitudes about exercise and nutrition are crucial for designing effective interventions that improve health outcomes in PLWH.

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APPENDIX A

DEMOGRAPHIC CHARACTERISTICS

Table A1: Demographic Characteristics (Mean (SD) or N (%)) Stratified by Perceived Stress in the Study Population

Characteristics	Study Sample (n=60)	Low Stress Group (n=31)	High Stress Group (n=29)	*p*-value
Age, mean years (SD)	55.87 (4.63)	56.32 (5.41)	55.38 (3.68)	0.87
Anthropometrics				
Height, mean (cm) (SD)	169.62 (9.83)	170.52 (10.71)	168.67 (8.88)	0.73
Weight, mean (kg) (SD)	81.13 (19.14)	80.75 (18.17)	81.54 (20.45)	0.65
BMI, mean (SD)	28.39 (7.21)	27.97 (6.89)	28.84 (7.63)	0.71
Demographic Information				
Women, %	31.67	19.35	44.83	**0.03**
Race, %				0.90
White	20	19.35	20.69	
African-American	80	80.65	79.31	
Education, %				0.50
< High School Diploma	20.00	16.13	24.14	

High school diploma	26.67	29.03	24.14	
> High School Diploma	53.33	54.84	51.72	
Income, %				0.23
<$10,000/year	41.67	38.71	44.83	
= $10-$19,999/year	35.00	32.26	37.93	
≥ $20,000/year	23.33	29.03	17.24	
Food Security %				**0.04**
Food Secure	45	54.84	34.48	
Food Insecure without Hunger	18.33	22.58	13.79	
Food Insecure with Hunger	36.67	22.58	51.72	
Marital status, %				0.89
Married	3.33	3.23	3.45	
Never Married	51.67	54.84	48.28	
Other	45.00	41.94	48.28	
Mean CD4 Count (SD)	528.30 (350.08)	486.52 (349.41)	596.41 (353.05)	0.29

Psychosocial Measures				
Perceived Stress Score, mean (SD)	15.70 (7.63)	9.87 (4.70)	21.93 (4.59)	**<.01**
Social Support Score, mean (SD)	3.13 (.582)	3.19 (0.57)	3.06 (0.59)	0.07
Friends	3.01 (0.58)	3.14 (0.60)	2.88 (0.76)	**<.01**
Significant Other	3.21 (0.73)	3.25 (0.72)	3.17 (0.75)	0.25
Family	3.16 (0.73)	3.19 (0.70)	3.13 (0.77)	0.66
Depression Score, mean (SD)	6.81 (5.75)	3.33 (3.42)	9.75 (5.72)	**<.01**
Diet Quality Scores				
Recommended Food Score (RFS), mean (SD)	10.58 (6.83)	10.03 (6.25)	11.17 (7.47)	0.65
Mediterranean Diet Score (MDS), mean (SD)	4.08 (1.70)	4.06 (1.75)	4.10 (1.68)	0.98
Alternative Healthy Eating Index (aHEI), mean (SD)	46.78 (11.73)	46.27 (12.13)	47.30 (11.47)	0.55

Table A2: Demographic Characteristics (Mean (SD) or N (%)) Stratified by Food Security Category in the Study Population

Characteristics	Study Sample (n=60)	Food Secure Group (n=27)	Food Insecure Group (n=33)	p-value
Age, mean years (SD)	55.87 (4.63)	55.93 (5.01)	55.82 (4.38)	0.75
Anthropometrics				
Height, mean (cm) (SD)	169.62 (9.83)	171.69 (9.35)	167.93 (10.04)	0.06
Weight, mean (kg) (SD)	81.13 (19.14)	84.20 (21.65)	78.63 (16.75)	0.09
BMI, mean (SD)	28.39 (7.21)	28.64 (7.33)	28.19 (7.22)	0.57
Demographic Information				
Women, %	31.67	25.92	36.36	0.28
Race, %				0.29
White	20	26	15	
African-American	80	74	85	

Education, %				0.09
< High School Diploma	20.00	18.52	21.21	
High school Diploma	26.67	18.52	33.33	
> High School Diploma	53.33	62.96	45.45	
Income, %				**0.02**
< $10,000/year	41.67	29.63	51.52	
=$10-$19,999/year	35.00	40.74	30.30	
≥ $20,000/year	23.33	29.63	18.18	
Marital status, %				0.70
Married	3.33	3.70	3.03	
Never Married	51.67	44.44	57.58	
Other	45.00	51.85	39.39	

Mean CD4 Count (SD)	528.30 (350.08)	517.74 (384.30)	536.94 (325.26)	0.48
Psychosocial Measures				
Perceived Stress Score, mean (SD)	15.70 (7.63)	13.67 (7.57)	17.36 (7.38)	**0.01**
Social Support Score, mean (SD)	3.13 (.582)	3.29 (0.69)	2.99 (0.44)	0.18
Friends	3.01 (0.58)	3.25 (0.72)	2.82 (0.60)	**0.03**
Significant Other	3.21 (0.73)	3.32 (0.75)	3.12 (0.71)	0.56
Family	3.16 (0.73)	3.30 (0.82)	3.05 (0.64)	0.56
Depression Score, mean (SD)	6.81 (5.75)	5.63 (5.62)	7.81 (5.76)	**0.04**

Diet Quality Scores				
Recommended Food Score (RFS), mean (SD)	10.58 (6.83)	9.81 (6.52)	11.21 (7.12)	0.46
Mediterra-nean Diet Score (MDS), mean (SD)	4.08 (1.70)	4.74 (1.65)	3.55 (1.56)	**<.01**
Alternative Healthy Eat-ing Index (aHEI), mean (SD)	46.78 (11.73)	48.79 (13.70)	45.12 (9.74)	**0.03**

APPENDIX B

CHANGES IN LAB VALUES DURING 48 WEEKS OF HIGH-DOSE VITAMIN D/CALCIUM SUPPLEMENTATION

	Baseline					Change over 24 weeks					Change over 48 weeks				
	VitD/Cal		**PBO**	**n**	**p**	**VitD/Cal**	**n**	**PBO**	**n**	**p**	**VitD/Cal**	**n**	**PBO**	**n**	**p**
Glucose	85 (80, 91)	73	85 (79, 92)	79	0.91	5 (-4, 12)*	70	5 (-3, 12)*	74	0.91	4 (1, 8)*	65	6 (-3, 12)*	72	0.91
HOMA-IR	0.97 (0.52,2.12)	72	0.94 (0.46, 1.81)	78		1.31 (0.69,2.24)*	69	1.49 (0.91,252)*	73	0.21	1.30 (0.81,2.69)	64	1.43 (0.82,2.49)	69	0.87
Total Chol	161 (138,182)	78	156 (135,184)	84		11 (-4, 29)	74	18 (1, 31)	80	0.22	13 (-6,28)	68	14 (-1, 37)	73	0.55
HDL-c	43 (34,50)	76	42 (33,49)	79		8 (0, 15) *	70	8 (2, 15) *	75	0.72	8 (1, 14) *	66	8 (1, 14)*	68	0.44
LDL-c	95 (80,112)	76	89 (72,115)	78		0 (-10, 17)	70	8 (-11,20)*	72		2 (-9, 14)	65	4 (-14, 27)	67	0.93
Tri-glycerides	99 (65,127)	78	96 (73,116)	82		3 (-17, 45)	74	4 (-18, 28)	78	0.90	3 (-14,31)	68	4 (-18, 39)	71	0.87
BMI (kg/m2)	25.7 (22.6,28.2)	76	24.0 (21.6,27.1)	84		0.0 (-0.5,1.1)	73	0.1 (-0.6,0.9)	82	0.67	0.1 (-0.8,1.1)	68	0.1 (-0.7,1.0)	78	0.98
Waist Circ. (cm)	88.3 (81.3,97.8)	77	84.1 (79.1,94.0)	86		0.0 (-2.5,3.0)	74	0.7 (-1.0,3.7)*	81	0.17	0.3 (-2.5,3.3)	68	0.9 (-2.0,4.8)*	80	0.38

All laboratory values were done in the fasting state and are given in mg/dL. VitD/Cal: Vitamin D/ Calcium Treatment Group, PBO: Placebo group.

APPENDIX C

ADDITIONAL ANALYSES OF PHYSICAL ACTIVITY DATA

Supplement Table. Demographic and clinical characteristics associated with longitudinal changes in blood pressure, lipid, and glucose values among PLWH. Each column shows parameter estimates and 95% confidence limits for separate generalized estimating equations. All models also adjusted for site as a stratification factor.

	SBP (mmHg)	**DBP (mmHg)**	**Total Cholesterol (mg/dl)**	**LDL-c (mg/dl)**	**HDL-c (mg/dl)**	**Triglycerides (mg/dl)**	**Glucose (mg/dl)**
PA Level							
High	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Moderate	0.21 (-0.22, 0.64)	0.41 (0.11, 0.71)‡	0.30 (-1.48, 2.08)	0.10 (-1.40, 1.61)	-0.71 (-1.25, -0.17)‡	7.78 (1.96, 13.59)‡	0.25 (-0.89, 1.38)
Low	-0.20 (-0.62, 0.21)	0.40 (0.13, 0.68)‡	1.31 (-0.41, 3.03)	0.41 (-1.03, 1.84)	-1.03 (-1.54, -0.51)†	16.12 (9.90, 22.34)†	1.35 (0.26, 2.45)*
Very Low	-0.64 (-1.11, -0.16)‡	0.32 (-0.01, 0.63)	1.34 (-0.81, 3.48)	-0.49 (-2.17, 1.18)	-1.56 (-2.17, -0.96)†	25.43 (15.64, 35.22)†	1.98 (0.47, 3.49)*
BMI Category							
Normal wt.	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Under-weight	-4.51 (-5.69, -3.33)†	-1.49 (-2.30, -0.69)‡	-4.51 (-5.69, -3.33)†	-9.03 (-12.77, -5.28)†	0.86 (-1.59, 3.31)	-21.47(-40.05,-2.90)*	1.43 (-1.66, 4.51)
Overweight	3.05(2.69, 3.40)†	1.85(0.12, 2.08)†	3.05(2.69, 3.40)†	3.98 (2.78, 5.17)†	-2.84 (-3.34, -2.34)†	27.52(18.60,36.44)†	1.09(-0.01, 2.19)
Obese	5.60 (5.09, 6.11)†	3.24 (2.91, 3.56)†	5.60 (5.09, 6.11)†	5.68 (4.01, 7.35)†	-5.61 (-6.28, -4.93)†	49.65(39.47,59.83)†	4.49 (2.90, 6.07)†
Race/Sex a							
WM	Reference	Reference	Reference	Reference	Reference	Reference	Reference
WF	-5.58 (-6.59, -4.56)†	-3.12 (-3.80, -2.45)†	6.87 (2.77, 10.98)†	2.18 (-1.16, 5.52)	8.79 (7.09, 10.49)†	-27.64(-40.32, -14.96)†	-4.00 (-6.18, -1.81)†

BM	0.43 (-0.14, 1.00)	0.57 (0.19, 0.95)‡	0.08 (-2.17, 2.32)	-0.94 (-2.84, 0.95)	5.64 (4.74, 6.54)†	-34.66 (-43.49, -25.82)† -2.44 (-3.78, -1.11)†	-2.44 (-3.78, -1.11)†
BF	-1.95 (-2.98, -0.91)†	-0.63 (-1.29, 0.02)	4.57 (0.79, 8.36)*	2.25 (-0.98, 5.49)	14.32(12.69, 15.95)†	-72.80 (-84.61, -60.98)†	-2.55 (-4.83, -0.28)*
OM	-0.07 (-1.26, 1.12)	0.31 (-0.57, 1.18)	0.97 (-3.41, 5.35)	-2.82 (-6.79, 1.14)	1.26 (-0.42, 2.94)	10.39 (-5.38, 26.16)	1.87 (-0.48, 4.22)
OF	-5.02 (-7.94, -2.10)†	-2.01 (-4.06, 0.05)	5.74 (-7.15, 18.63)	-0.59 (-12.80, 11.61)	8.04 (3.56, 12.51)†	-17.74 (-45.10, 9.62)	-2.77 (-7.39, 1.85)
Hispanic	-0.67 (-1.35, -0.01)*	-0.64 (-1.10, -0.18)‡	0.58 (-2.16, 3.33)	-2.40 (-4.60, -0.20)*	0.63 (-0.41, 1.67)	6.40 (-2.16, 14.95)	1.12 (-0.49, 2.74)
Age							
19-29	Reference	Reference	Reference	Reference	Reference	Reference	Reference
30-39	0.12 (-0.45, 0.69)	1.43 (1.00, 1.87)†	7.92 (4.92, 10.92)†	4.60 (2.20, 6.99)†	0.12 (-1.02, 1.26)	23.59 (16.39, 30.79)†	1.94 (-0.15, 4.02)
40-49	-0.19 (-0.81, 0.43)	1.98 (1.54, 2.43)†	11.86 (8.83, 14.89)†	6.00 (3.54, 8.47)†	1.75 (0.64, 2.87)‡	30.10 (22.81, 37.38)†	3.68 (1.54, 5.82)†
50-59	1.05 (0.35, 1.74)‡	2.05 (1.57, 2.54)†	10.09 (6.90, 13.28)†	3.56 (0.95, 6.17)‡	2.97 (1.81, 4.13)†	27.91 (19.71, 36.11)†	6.03 (3.89, 8.16)†
≥ 60	2.84 (1.81, 3.87)†	0.63 (-0.01, 1.27)	9.61 (5.58, 13.64)†	2.29 (-1.01, 5.59)	4.22 (2.83, 5.61)†	29.35 (14.69, 44.02)†	8.36 (5.65, 11.08)†
Insurance							
Private	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Public	-1.75 (-2.26, -1.24)†	-0.72 (-1.06, -0.38)†	-1.40 (-3.40, 0.60)	-3.06 (-4.70, -1.42)†	0.54 (-0.24, 1.33)	5.27 (-2.44, 12.98)	0.52 (-0.58, 1.61)

Uninsured	-1.06 (-1.97, -0.14)*	-0.22 (-0.86, 0.43)	0.18 (-3.51, 3.86)	-1.56 (-4.74, 1.63)	1.36 (-0.06, 2.78)	7.83 (-6.63, 22.29)	0.37 (-1.43, 2.17)
Unknown	-1.41 (-2.27, -0.54)‡	-0.48 (-1.08, 0.11)	-2.48 (-6.15, 1.18)	-1.49 (-4.52, 1.55)	0.01 (-1.36, 1.38)	-5.53 (-17.10, 6.05)	0.49 (-1.24, 2.23)
Risk Factor							
MSMb	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Hetero-sexual	-0.40 (-1.10, 0.30)	-0.69 (-1.14,- 0.23)‡	1.22 (-1.52, 3.95)	-0.76 (-3.08, 1.56)	1.15 (0.09, 2.22)*	5.13 (-5.13, 15.38)	0.51 (-1.09, 2.10)
IV drug use	-0.63 (-1.24, -0.02)*	-0.54 (-0.95, -0.11)*	-8.88 (-11.36, -6.39)†	-7.58 (-9.67, -5.49)†	-0.63 (-1.60, 0.34)	-5.74 (-13.79, 2.32)	0.56 (-0.93, 2.05)
Other/ Unknown	0.27 (-1.03, 1.56)	-0.18 (-1.03, 0.67)	-3.94 (-8.91, 1.04)	-2.76 (-7.01, 1.48)	-2.03 (-3.83, -0.22)*	1.51 (-12.29, 15.31)	0.97 (-2.30, 4.25)
d-drug use	-0.69 (-1.22, -0.17)†	-0.80 (-1.15, -0.45)†	-1.49 (-3.49, 0.50)	-2.28 (-3.92, -0.64)‡	-0.58 (-1.36, 0.20)	7.56 (-0.42, 15.55)	-1.03 (-2.35, 0.29)
Prescribed medicine	6.68 (6.21, 7.16)†	3.96 (3.64, 4.28)†	14.94 (13.01, 16.87)†	8.68 (7.06, 10.29)†	-3.31 (-3.87, -2.34)†	124.79 (107.36, 142.21)†	45.97 (42.39, 49.56)†
Viral Load >200	0.65 (0.29, -1.00)	0.62 (0.38, 0.85)†	-7.42 (-8.87, -5.96)†	-3.76 (-4.89, -2.64)†	-3.59 (-4.05, -3.13)†	9.49 (0.70, 18.28)*	-1.40 (-2.31, -0.49)
CD4:							
≥ 500	Reference	Reference	Reference	Reference	Reference	Reference	Reference
350-499	0.04 (-0.31, -0.38)	-0.09 (-0.30, 0.13)	-1.95 (-3.29, -0.62)‡	-0.91 (-1.96, 0.13)	-0.46 (-0.85, -0.07)*	-7.87 (-14.81, -0.92)*	1.72 (0.67, 2.77)‡
200-349	-0.06 (-0.52, 0.39)	-0.07 (-0.37, 0.22)	-3.25 (-5.04, -1.45)†	-1.99 (-3.47, -0.52)‡	-0.62 (-1.23, -0.02)*	-9.52 (-16.23, -2.81)*	1.58 (0.11, 3.06)*
< 200	-0.60(-1.20, -0.01)*	-0.43(-0.82, -0.04)*	-9.07 (-12.16, -5.97)†	-5.77 (-7.80, -3.74)†	-2.88 (-3.72, -2.04)†	-4.69(-23.75, 14.38)	5.56 (3.51, 7.60)†

a – WM = white male; WF = white female; BM = black male; BF = black female; OM = other male; OF = other female b – MSM = men who have sex with men

* = $p < 0.05$; ‡ = $p < 0.01$; † = $p < 0.001$

APPENDIX D

IRB APPROVAL

UAB

Project Revision/Amendment Form

Form version: June 26, 2012

RECEIVED
MAY 13 2016
IRB
INSTITUTIONAL REVIEW BOARD

In MS Word, click in the white boxes and type your text; double-click checkboxes to check/uncheck

- **Federal regulations require IRB approval before implementing proposed changes. See Section 14 of the IRB Guidebook for additional Investigators for additional information.**
- **Change means any change, in content or form, to the protocol, consent form, or any supportive materials (such as the Investigator's Brochure, questionnaires, surveys, advertisements, etc.). See Item 4 for more examples.**

1. Today's Date	5/10/2016	22371

2. Principal Investigator (PI)

Name (with degree)	Amanda Willig, PhD, RD	**Blazer ID**	mandyrd
Department	Medicine	**Division (if applicable)**	Infectious Diseases
Office Address	BBRB 203	**Office Phone**	5-5464
E-mail	mandyrd@uab.edu	**Fax Number**	4-5600

Contact person who should receive copies of IRB correspondence (Optional)

Name	Amanda Willig	**E-Mail**	
Phone		**Fax Number**	

3. UAB IRB Protocol Identification

3.a. Protocol Number F140813010

3.b. Protocol Title The microbiome, diet and incomplete CD4 recovery on antiretroviral therapy

3.c. Current Status of Protocol—Check ONE box at left; provide numbers and dates where applicable

- ☐ **Study has not yet begun** — **No participants, data, or specimens have been entered.**
- ☐ **In progress, open to accrual** — **Number of participants, data, or specimens entered:** 4
- ☐ **Enrollment temporarily suspended by sponsor**
- ☐ **Closed to accrual, but procedures continue as defined in the protocol (therapy, intervention, follow-up visits, etc.)**
  - **Date closed:**
  - **Number of participants receiving interventions:**
  - **Number of participants in long-term follow-up only:**
- ☒ **Closed to accrual, and only data analysis continues**
  - **Date closed:** 9/10/2015
  - **Total number of participants entered:** 60

4. Types of Change

Check all types of change that apply, and describe the changes in Item 5.c. or 5.d. as applicable. To help avoid delay in IRB review, please ensure that you provide the required materials and/or information for each type of change checked.

- ☐ **Protocol revision (change in the IRB-approved protocol)**
  In Item 5.c., if applicable, provide sponsor's protocol version number, amendment number, update number, etc.
- ☐ **Protocol amendment (addition to the IRB-approved protocol)**
  In Item 5.c., if applicable, provide funding application document from sponsor, as well as sponsor's protocol version number, amendment number, update number, etc.
- ☒ **Add or remove personnel**
  In Item 5.c., include name, title/degree, department/division, institutional affiliation, and role(s) in research, and address whether new personnel have any conflict of interest. See "Change in Principal Investigator" in the IRB Guidebook if the principal investigator is being changed.
  - ☒ **Add graduate student(s) or postdoctoral fellow(s) working toward thesis, dissertation, or publication**
    In Item 5.c., (a) identify these individuals by name; (b) provide the working title of the thesis, dissertation, or publication; and (c) indicate whether or not the student's analysis differs in any way from the purpose of the research described in the IRB-approved HSP (e.g., a secondary analysis of data obtained under this HSP).
- ☐ **Change in source of funding; change or add funding**
  In Item 5.c., describe the change or addition in detail, include the applicable OSP proposal number(s), and provide a copy of the application as funded (or as submitted to the sponsor if pending). Note that some changes in funding may require a new IRB application.
- ☐ **Add or remove performance sites**
  In Item 5.c., identify the site and location, and describe the research-related procedures performed there. If adding site(s), attach notification of permission or IRB approval to perform research there. Also include copy of subcontract, if applicable. If this protocol includes acting as the Coordinating Center for a study, attach IRB approval from any non-UAB site added.

☐ **Add or change a genetic component or storage of samples and/or data component—this could include data submissions for Genome-Wide Association Studies (GWAS)**
To assist you in revising or preparing your submission, please see the IRB Guidebook for Investigators or call the IRB office at 934-3789.

☐ **Suspend, re-open, or permanently close protocol to accrual of individuals, data, or samples (IRB approval to remain active)**
In Item 5.c., indicate the action, provide applicable dates and reasons for action; attach supporting documentation.

☐ **Report being forwarded to IRB (e.g., DSMB, sponsor or other monitor)**
In Item 5.c., include date and source of report, summarize findings, and indicate any recommendations.

☐ **Revise or amend consent, assent form(s)**
Complete Item 5.d.

☐ **Addendum (new) consent form**
Complete Item 5.d.

☐ **Add or revise recruitment materials**
Complete Item 5.d.

☐ **Other (e.g., investigator brochure)**
Indicate the type of change in the space below, and provide details in Item 5.c. or 5.d. as applicable.
Include a copy of all affected documents, with revisions highlighted as applicable.

▶

5. Description and Rationale

In Item 5.a. and 5.b, check Yes **or** No **and see instructions for** Yes **responses.**
In Item 5.c. and 5.d, describe—and explain the reason for—the change(s) noted in Item 4.

☐Yes ☒No **5.a. Are any of the participants enrolled as normal, healthy controls?**
If yes, describe in detail in Item 5.c. how this change will affect those participants.

☐Yes ☒No **5.b. Does the change affect subject participation, such as procedures, risks, costs, location of services, etc.?**
If yes, FAP-designated units complete a FAP submission and send to fap@uab.edu. Identify the FAP-designated unit in Item 5.c.
For more details on the UAB FAP, see www.uab.edu/cto.

5.c. Protocol Changes: In the space below, briefly describe—and explain the reason for—all change(s) to the protocol.

(a) Josh Muhammad is already added to this study protocol. He is a doctoral student in the Department of Nutrition Sciences and will complete his dissertation using existing data from this study.
(b) Title: Does perceived stress mediate diet quality, metabolism, and microbiome in older adult with HIV
(c) This dissertation is a secondary data analysis of data previously obtained under the approved study as seen in the attached proposal.

5.d. Consent and Recruitment Changes: In the space below,
(a) describe all changes to IRB-approved forms or recruitment materials and the reasons for them;
(b) describe the reasons for the addition of any materials (e.g., addendum consent, recruitment); and
(c) indicate either how and when you will reconsent enrolled participants or why reconsenting is not necessary (not applicable for recruitment materials).

Also, indicate the number of forms changed or added. For new forms, provide 1 copy. For revised documents, provide 3 copies:
- **a copy of the currently approved document (showing the IRB approval stamp, if applicable)**
- **a revised copy highlighting all proposed changes with "tracked" changes**
- **a revised copy for the IRB approval stamp.**

▶

Signature of Principal Investigator Amanda Willig Date 5/11/16

FOR IRB USE ONLY

☐ Received & Noted ☒ Approved Expedited* ☐ To Convened IRB

Sally Blake Headley, CIP — May 13, 2016

Signature (Chair, Vice-Chair, Designee) — Date

DOLA 10/7/15

Change to Expedited Category Y / N / NA

*No change to IRB's previous determination of approval criteria at 45 CFR 46.111 or 21 CFR 56.111