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BMI at Diagnosis and its Association With Markers of HIV Disease Progression and Cardiovascular Disease Risk.

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DEDICATION

I dedicate my dissertation to my nephews, Jordyn and Braylon, my niece, Dallis, and my younger cousins. I pray you strive for the best and follow your dreams. The sky is the limit. I love you! “Live as if you were to die tomorrow. Learn as if you were to live forever” – Mahatma Gandhi

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ABSTRACT

Highly active antiretroviral treatment (HAART) has transformed the state of human immunodeficiency virus (HIV) from acute to chronic. As a result, the long-term effect of HAART has caused weight gain among HIV-infected individuals, leading to an increased prevalence of overweight and obesity. Increased Body Mass Index (BMI) has been associated with adverse health outcomes in non-HIV and HIV populations, yet among HIV-infected individuals, a higher BMI at diagnosis offers a slower progression from HIV to AIDS. Pre-HAART, studies reported that obese HIV-infected individuals have higher increases in CD4 count over time. However post-HAART, some report that overweight HIV-infected individuals with a higher BMI experience increased CD4 counts. In addition, HIV-infected treated individuals are now experiencing cardiovascular disease outcomes. Therefore, additional research is needed to support current evidence. Given that our study population consists of individuals from South Carolina, a state with a high prevalence of HIV and obesity, it is beneficial to explore the relationship between BMI at diagnosis and markers for HIV progression and cardiovascular disease risk. This cohort study consisted of 396 HIV-infected adults from the Ryan White Clinic in SC. The objectives of this study were to evaluate the relationship between BMI at diagnosis and CD4 count over time, to evaluate this relationship by gender, and to evaluate the relationship between BMI at diagnosis and cardiovascular disease risk markers (high-density lipoprotein(HDL), low-density lipoprotein (LD), systolic blood pressure (SBP), diastolic blood pressure (DBP), and fasting blood glucose).

TABLE OF CONTENTS

DEDICATION iii

ACKNOWLEDGMENTS iv

ABSTRACT v

LIST OF TABLES vii

LIST OF FIGURES x

CHAPTER 1: INTRODUCTION 1

CHAPTER 2: LITERATURE REVIEW 6

2.1 What is HIV? 6

2.2 Epidemiology of HIV/AIDS 7

2.3 Predictors of progression of HIV 8

2.4 Predictors of Cardiovascular related outcomes among HIV patients 14

2.5 Public Health Importance 19

CHAPTER 3: METHODS 20

3.1 Study Design 20

3.2 Study Population 20

3.3 Data Analysis 21

CHAPTER 4: Longitudinal Association between Body Mass Index (BMI) at Diagnosis and HIV Disease Progression 35

4.1 Introduction 35

4.2 Methods 36

4.3 Results 40

4.4 Discussion 43

CHAPTER 5: Longitudinal Association of the interaction of Gender and Body Mass Index (BMI) on HIV Disease Progression 54

5.1 Introduction 54

5.2 Methods 55

5.3 Results 59

5.4 Discussion 62

CHAPTER 6: Longitudinal Changes in Cardiovascular Disease Risk Markers and their association with Body Mass Index (BMI) in HIV-infected individuals 73

6.1 Introduction 73

6.2 Methods 75

6.3 Results 78

6.4 Discussion 84

CONCLUSIONS 100

REFERENCES 103

APPENDIX A: Protection of Human Subjects 109

LIST OF TABLES

Table 3.1 Independent variables for AIM 1 22

Table 3.2 Independent variables for AIM 2 25

Table 3.3 Independent variables for AIM 3 28

Table 3.4 Power Analysis: Average CD4 counts per BMI category 31

Table 3.5 Power Analysis: Number of HIV patients needed per BMI category at different powers 31

Table 4.1 Baseline characteristics of South Carolina HIV-infected individals diagnosed between 1997 and 2010 by Body Mass Index (BMI) category 49

Table 4.2 Mixed Model Analysis of the association between Body Mass Index (BMI) and CD4 count among HIV-infected individuals diagnosed in South Carolina between 1997 and 2010 51

Table 4.3 Mixed Model Analysis of the association between Body Mass Index (BMI) and CD4 count stratified by Baseline VL and Delayed entry into care among HIV-infected individuals in South Carolina diagnosed between 1997 and 2010 52

Table 5.1 Baseline characteristics of South Carolina HIV-infected individals diagnosed between 1997 and 2010 by Gender 68

Table 5.2 Mixed Model Analysis of the association between Body Mass Index (BMI) and CD4 count among HIV-infected individuals diagnosed in South Carolina between 1997 and 2010 stratified by Gender 70

Table 5.3 Mixed Model Analysis of the association between Body Mass Index (BMI) and CD4 count stratified by Baseline VL and Delayed entry into care among HIV-infected individuals in South Carolina diagnosed between 1997 and 2010 by Gender 71

Table 6.1 Baseline characteristics of South Carolina HIV-infected individals diagnosed between 1997 and 2010 by Body Mass Index (BMI) category 90

Table 6.2 Mixed Model Analysis of the association between Body Mass Index (BMI) and cardiovascular disease risk markers among HIV-infected individuals diagnosed in South Carolina between 1997-2010 92

Table 6.3 Mixed Model Analysis of the interaction between Body Mass Index (BMI) and highly active antiretroviral therapy (HAART) use and its association with cardiovascular disease risk markers among HIV-infected individuals diagnosed in South Carolina between 1997-2010 94

LIST OF FIGURES

Figure 4.1 Adjusted CD4 Count Mean by Body Mass Index (BMI) category.....53

Figure 4.2 Differences in Adjusted CD4 Count Mean by Body Mass Index (BMI) category.....53

Figure 5.1 Adjusted CD4 count Mean by BMI and Gender Categories.....72

Figure 5.2 Differences in Adjusted CD4 count Mean by BMI and Gender Categories....72

Figure 6.1 Adjusted Fasting Blood Glucose Mean by BMI category.....95

Figure 6.2 Differences in Adjusted Fasting Blood Glucose Mean by BMI category.....95

Figure 6.3 Adjusted HDL Mean by BMI category.....96

Figure 6.4 Differences in Adjusted HDL Mean by BMI category.....96

Figure 6.5 Adjusted LDL Mean by BMI category.....97

Figure 6.6 Differences in Adjusted LDL Mean by BMI category.....97

Figure 6.7 Adjusted SBP Mean by BMI category.....98

Figure 6.8 Differences in Adjusted SBP Mean by BMI category.....98

Figure 6.9 Adjusted DBP Mean by BMI category.....99

Figure 6.10 Differences in Adjusted DBP Mean by BMI category.....99

CHAPTER 1

INTRODUCTION

In HIV infection, CD4 count is used to determine treatment and monitor progression of HIV.[1 2 3] It also serves as the most important prognostic factor that correlates the most with disease progression. Furthermore, CD4 count also is associated with the risk of cardiovascular disease among HIV patients.[4 5 6] While the relationship between disease progression and CD4 has been proven, other factors such as HIV-RNA viral load, mode of transmission, age, gender and race also have been determined to be associated with disease progression.[7 8 9 10 11 12 13 14 15] Recent evidence suggests that nutritional status also impacts disease progression and the development of complications but this has not been extensively researched.

Body mass index (BMI) is an anthropometric indicator computed from height and weight and has been used to predict survival in non-HIV patients.[7 17 18] Those considered to be underweight (BMI<18.0) or obese (BMI≥30) are at higher risk of acquiring infections such as pneumonia, bacteraemia and lower respiratory infections.[18] A systematic review reported that obese individuals with infections had worst outcomes compared to the other BMI categories.[18] It is well documented that obesity leads to adverse health outcomes such as cardiovascular disease, diabetes, cancer and mortality.[19] Among HIV patients, those obese tend to have higher CD4 levels and lower HIV-RNA viral loads. A possible explanation of this effect is that the increased levels of leptin in

obese individuals, increases T-cell proliferation.[20] Since viral load has an inverse relationship with CD4 T-cells, it is possible that as CD4 count increases, viral load will decrease as a response to the relationship between leptin and CD4 T-cells. Those considered being underweight and malnutrioned at the time of starting treatment were associated with increased risk of survival. [20] Given obesity's effect on the immune system, it is logical to determine the association of BMI on progression of HIV. As the data needed to compute BMI are relatively easy and inexpensive to collect, it can be efficient to use BMI as an indicator to predict HIV progression.

Previous research on BMI and HIV disease progression has produced mixed results. Obese HIV patients during the pre-highly active antiretroviral therapy (HAART) era were seen to have a better survival rate or slower progression to AIDS compared to normal weight HIV patients as well as those who experienced the "wasting syndrome."[21] Studies have showed that HIV individuals who were obese at diagnosis have a decreased risk of disease progression and better survival compared to other BMI categories.[7 17 21 22 23 24 25] Obese HIV individuals at diagnosis also reportedly have higher CD4 counts and lower HIV-RNA viral loads over-time. HIV individuals with increasing BMIs over-time also have been associated with a decreased risk of disease progression. However during the era of HAART, recent studies report that the protective effect of obesity may no longer exist. It was reported that obese HIV patients now experience smaller increases in CD4, concluding that obesity may actually provide more harm to HIV patients. [26 27] There is limited evidence in this area of HIV, particularly in the era of HAART, and this study will provide a longitudinal analysis of this association.

As a result of the development of metabolic risk factors such as obesity, among HIV patients, the risk of cardiovascular disease (CVD) has increased. [21] After the initiation of HAART, more HIV patients became obese, leading to an increased chance of developing cardiovascular outcomes. [21] One study reported that BMI was useful in predicting CVD risk among their HIV population.[28] Using hsCRP, an established predictor of future coronary events, it was discovered that higher hsCRP levels were associated with higher BMIs, higher low-density lipoprotein (LDL) and triglyceride (TG) levels, and lower high-density lipoprotein (HDL) levels. However, they were limited due to the small sample size. Given the increased risk of CVD outcomes in non-HIV obese individuals, it is important to study this association among obese HIV individuals. One serum marker used to determine risk of CVD is cholesterol. In non-HIV patients, lower HDL levels and higher LDL and TG levels are associated with increased risk. [29] Among HIV patients, studies report that lower CD4 counts and higher HIV-RNA viral load at diagnosis are both associated with lower HDL levels and higher LDL and TG levels.[4 6] Among HAART naïve HIV patients, higher BMI was associated with higher total cholesterol. However, this association is higher among HAART treated HIV patients. [4 6] It is unclear whether BMI was measured at diagnosis or followed over-time.

To our knowledge, only five cohort studies (Boston, France, Miami, Nashville, and West Africa) have been conducted to determine how well baseline BMI predicts HIV disease progression.[17 22 23 24 25] These studies populations consisted of HIV individuals who were from sub-Saharan Africa[17], drug abusers[22], public hospitals patients from France[23], only women.[24], and those from an outpatient clinic in Nashville, TN.[25] Two of the studies used HIV-naïve patients as controls [22 24], while the other studies consisted of

only HIV patients.[17 23 25] These studies mainly focused on the association of BMI and mortality and determined that BMI was a strong predictor of survival among HIV. While these studies predicted survival and used certain AIDS defining events (e.g. first CD4 cell count <200 cells/mm^3) as outcomes, our study will focus on the longitudinal analysis of a marker of HIV progression (i.e. CD4 count) as our outcome. Some studies have used BMI as a time-dependent variable when determining the association with markers of disease progression.[20 21 22 24 25 30 31 32] However, this study will observe between disease progression and BMI at diagnosis. It is important to determine whether BMI at diagnosis has an association with markers of cardiovascular risk, as previous results have been inconclusive.[34 35 36 37 38 39 40 41 42] Recently, Koethe et al. discovered that patients classified as overweight may promote optimal immune reconstitution (i.e. higher levels of CD4) within 12 months of diagnosis once on HAART compared to those obese.[25] Therefore, it will be interesting to see if those results are repeated in the current study.

Data regarding the prognostic use of BMI in HIV patients are limited. The current study will help to clarify the prospective association between obesity and disease progression among HIV patients and, and the development of cardiovascular disease risk markers in this population. The results of this study will help clinicians gain a clearer risk profile of the HIV patient for more effective monitoring. The specific aims of this proposal are as followed:

Aim 1: To determine the association between BMI at diagnosis and a marker of disease progression (CD4 T cell count) over time.

Research Question 1.1: Is there a difference in mean CD4 between BMI categories?

Research Question 1.2: Do HIV patients who are obese at baseline have a slower progression of HIV (Higher CD4 T cell count) over time compared to those in the normal BMI categories?

Aim 2: To determine whether the association between BMI at diagnosis and a marker of disease progression (CD4 T cell count) over time differ by gender.

Research Question 2.1: Does the association between baseline BMI and disease progression over time (CD4 T cell count) vary by gender?

Aim 3: To determine the association between BMI at diagnosis and markers of cardiovascular disease risk (fasting blood glucose, HDL, LDL, SBP, and DBP) over time.

Research Question 3.1: Is there a difference in mean fasting blood glucose, mean HDL, mean LDL, mean SBP, and mean DBP between BMI categories?

Research Question 3.2: Do normal weight HIV patients at baseline have lower levels of these cardiovascular risk markers over time compared to obese HIV-patients?

CHAPTER 2

LITERATURE REVIEW

2.1 What is HIV?

The human immunodeficiency virus (HIV) is a sexually transmitted disease that leads to acquired immune deficiency syndrome (AIDS), the later stage of the HIV infection.[1] There are two different types of HIV are HIV-1 and HIV-2. In the United States (U.S.), HIV is primarily referred to only HIV-1.[1] HIV is spread by contact with infected blood through unprotected sex, the sharing of needles, from mother to child during pregnancy, childbirth, or breastfeeding.[1] HIV destroys specific blood cells called CD4+ T cells, also known as "helper cells", which are essential in helping a person's body fight diseases.[1] Once the immune system is weakened, the body's ability to fight organisms is diminished, leading to a greater chance of developing AIDS.

Several complications are related to the HIV infection. These include opportunistic infections such as tuberculosis, candidiasis, pneumonia, toxoplasmosis, kaposi's sarcoma, herpes simplex, and tuberculosis.[1] Other complications include different forms of cancer, lipodystrophy as well as chronic wasting. These infections can occur at different stages of HIV. People without HIV are also at risk of acquiring these infections. However, these infections occur at a higher rate and it takes longer to recover in those with HIV.[1]

2.2 Epidemiology of HIV/AIDS

2.2a Global

The number of people living with HIV worldwide has increased since its discovery. The number of people living with HIV increased from roughly 9 million people in 1990 to a total of 33.3 million people in 2009, with approximately 1.8 million deaths due to AIDS.[43] The majority of people living with HIV reside in Sub-Saharan Africa (68%), South and South-East Asia (12%), North America (5%), and Central and South America (4%), respectively. [43] A total of 2.6 million people were newly infected with HIV worldwide in 2009, with the majority being adults (85%). [43] The Joint United Nations Programme on HIV/AIDS reported that over 7000 new HIV infections occurred per day in 2009, with roughly 97% of those infections being mostly women (51%) and occurring in low and middle income countries.[44]

2.2b United States (U.S.)

The prevalence of HIV among people in the US was estimated to be approximately 1.1 million persons in 2006, with approximately 21% being undiagnosed. [1] The Centers for Disease Control and Prevention (CDC) reported that approximately 56,300 people were newly infected with HIV in 2006. [1] The majority of those new HIV cases (53%) occurred in men who have sex with men (MSM). [1] MSM account for nearly half of people living with HIV (48%), while heterosexuals account for only 25%.[26] African Americans account for 46% of people living with HIV in the US as well as 45% of new HIV infections. [1] The HIV incidence rate for African American men and women was 7 times higher than their Caucasian counterparts. [1] Hispanics/Latinos represent 15%

of the population but account for an estimated 17% of people living with HIV and 17% of new infections. [1]

2.2c South Carolina (SC)

In their 2007 surveillance report, the CDC reported that the Deep South (i.e. Alabama, Florida, Georgia, Mississippi, Louisiana, North Carolina, and South Carolina) were disproportionately affected by the HIV/AIDS epidemic. [1] In 2008, South Carolina was ranked 10th in the US in AIDS cases, with a rate of 15.5 per 100,000 persons. [1] South Carolina also ranked 7th in AIDS cases among females in the US, with a rate of 13.0 per 100,000. [1] The epidemic continues to increase in South Carolina with an average of 65 cases of HIV infections reported each month in 2009. [1] Furthermore, South Carolina has experienced a 52% increase in people living with HIV/AIDS from 1999 to 2009. [1] People who live with HIV in South Carolina are mostly men (69%), African American (73%), aged 20-44 (42%) and MSM (44%).[1 45]

2.3 Predictors of progression in HIV

HIV is broken down into four distinct stages: primary infection, clinically asymptomatic stage, symptomatic HIV infection and progression from HIV to AIDS. [1] Stage one, the primary infection stage, lasts for a few weeks and diagnosis is frequently missed. During this stage, the immune system begins to respond to the HIV in the blood, producing HIV antibodies and cytotoxic lymphocytes, which is known as seroconversion. Stage two represents the clinically asymptomatic stage and generally lasts for an average of ten years. HIV antibodies are detectable in the blood and diagnosis is usually evident during this stage. Stage three is the symptomatic HIV infection stage whereby the

immune system has become severely damaged. HIV also has mutated allowing for further destruction of the CD4 T-helper cells, which are needed to fight infection. Furthermore, symptomatic HIV is usually caused by the opportunistic infections described earlier. Finally, Stage four represents progression to AIDS which is caused by the low count of CD4 T-helper cells and the increased number of severe opportunistic infections.

Throughout HIV, there are several determinants that can be used to determine the progression HIV.[7] These determinants include immunological factors such as CD4+ T cells and CD8 T-lymphocytes, virological factor such as HIV-RNA viral load, and other factors such as age, gender, mode of transmission and body mass index. An understanding of these factors is essential in guiding patient management and treatment. While some of these prognostic factors are typically used to initiate treatment, track the progression of HIV infection (e.g. CD4 count and HIV-RNA viral load) and monitor response to treatment, others (e.g. BMI) are not used as much and could also possibly assist in tracking the progression of the disease and providing the best methods in treating each HIV patient. This could ultimately lead to a greater chance of survival.

2.3a CD4+ T-cells

Known as the most significant predictor of disease progression and survival in HIV patients, CD4 T-cell count takes precedent over any other predictors that are used when treatment guidelines are recommended.[2 3 7] CD4 T-cells are essential to the immune system as they serve as signals that activate the immune's response to organisms such as viruses and bacteria. HIV attaches to and infects the CD4 T-cells. Over the course of

HIV, CD4 T-cell count begins to decline. As a result, it is important that CD4 T-cell counts are maintained within the normal range, which is 500-1000 cells/mm^3. Treatment is generally recommended when a HIV patient's CD4 T-cell is ≤350 cells/mm^3 and when patients are in Stage 3 and 4 of the disease, irrespective of CD4 count.[1 3 4] Once the cell count is less than 200 cells/mm^3, the patient's immune system is severely weakened. This leads to a greater risk for developing HIV-related complications and opportunistic infections, including progression to AIDS.

Many studies have shown that CD4 count is highly associated with HIV progression.[2 7 8 46 47] The CASCADE collaboration reported that lower CD4 counts were associated with a greater risk of disease progression, with the greatest risk occurring as CD4 counts fall below 200 cells/mm^3.[48] This remains true when stratified by age. Van Leth et al. determined that baseline CD4 T-cell count is predictive of virological failure.[46] They showed that CD4 T-cell counts below 200 cells/mm^3 at time of HAART initiation are associated with an increasingly worse prognosis.[47]

2.3b CD8 T-cells

CD8 T-cells, also called cytotoxic T-lymphocytes, are white blood cells that find and destroy infected cells in the body.[1 7] In the case of HIV, CD8 T-cells are activated by CD4 T cells. It is thought that the anti-HIV specific CD8 T-cells are responsible for the demise of the infected CD4 T-cells, further increasing in response to ongoing viral replication. Evidence suggests that low absolute numbers of CD8 T-cell count correlate with poor survival outcomes in HIV patients.[7]

2.3c HIV-RNA viral load

HIV-RNA viral load is the second most important marker used to determine response to treatment.[3 7] In most HIV patients, HIV-RNA viral load has an inverse relationship with CD4 T-cell count. Higher HIV-RNA viral loads are correlated with a rapid decline of CD4 T-cells.[3 7] A four-fold increase in the risk of AIDS can be detected when HIV-RNA viral load is between 3000 copies/mL and 300,000 copies/mL, which also is seen when stratified by age groups.[7] In addition, there is an increase in risk of disease progression in HIV patients with HIV-RNA viral loads greater than 100,000 copies/mL across all age and CD4 T-cell strata.[7]

Higher HIV-RNA viral loads at diagnosis have been associated with faster CD4 T-cell decline over the first two years of infection.[2 7] Some evidence has suggested that HIV-RNA viral load serves as a better marker of disease progression when measured at later times than at diagnosis.[3 7] However, HIV-RNA viral load at diagnosis assists in providing treatment to HIV patients earlier. Van Leth et al. reported that treatment response was strongly related to HIV-RNA viral load at diagnosis, with HIV patients whose HIV-RNA viral loads that were greater than 100,000 copies/mL at diagnosis experiencing more virological failure after 48 weeks of treatment.[46] According to recent treatment guidelines, HIV-RNA viral load is only used to detect response to treatment and not to monitor progression of HIV.[3]

2.3d Age

Research has shown that as HIV patients get older, their risk of AIDS increases.[7] Age at seroconversion has been found to have significant impact on the future

progression of HIV. Previous studies found an age effect correlating with CD4 count and HIV-RNA viral load across all exposure categories.[8 49] Some have suggested that since older age is associated with lower CD4 counts at similar time from seroconversion, it may explain the relationship between age and HIV progression.[7 8] However, when HIV patients are on HAART, the age effect at seroconversion is attenuated.

2.3e Gender

Mixed results have been reported on the relationship between gender and HIV progression. Some studies report that gender differences in HIV disease progression has become larger and statistically significant in the era of HAART.[7 8 9 13 14 15 16] Women tend to have a higher HIV-RNA viral load at diagnosis compared to men, while HIV-RNA viral load over-time has reportedly varied.[7 9 10] Women also reportedly had an increased risk of death even after adjustment for HAART use. [7 9 10] Low levels of CD4 T-cells (<50 cells/mm^3) were found to be associated with higher HIV-RNA viral loads in women than in men within the same CD4 count.[9] Conversely, at higher CD4 T-cell levels (>350 cells/mm^3), mean HIV-RNA viral load has been noted to be lower in women compared to men in the same CD4 stratum.[8] Despite the variation in HIV-RNA viral load, disease progression has not been seen to differ between genders for CD4.[7 11] One study reported that disease progression was similar between genders. [11] Currently, there is no sex-specific treatment guideline for the initiation of treatment.[3]

2.3f Race

Research that has focused on the relationship between race and HIV progression has discovered that race mainly does not have an impact on the progression of HIV,

which is independent of confounders such as psychosocial factors, access to care and genetically driven response to therapy.[7] However, three studies discovered a difference between race and HIV disease progression.[12 14 16] Lemly et al. reported that the African Americans had an increased risk of death compared to Caucasians.[14] However, this association was no longer seen after adjustment for HAART use. Smith et al. reported that HIV-RNA viral load was discordantly low in African Americans compared to Caucasians stratified for CD4 count.[12] Finally, Meditz et al. reported that Non-Caucasian women were most likely to experience an HIV/AIDS related event compared to others ($p = .035$), even after adjustment for intravenous drug and HAART use.[16]

2.3g Mode of Transmission

Contradictory results have been reported on the effect of mode of transmission on HIV disease progression. An earlier study reported that homosexuals had a significantly faster progression compared to heterosexuals.[50] However, a recent study found no difference in disease progression between the different modes of HIV transmission.[51] It is important to note that injected drug users do have other-cause mortalities, which could confound the results of a study. This was seen in the CASCADE collaboration study where they determined in the post-HAART era, homosexual and heterosexual risk groups have a reduction in mortality, while no change was seen among injected drug users.[48] The higher risk in injected drug users can be due to lack of adherence to treatment and lack of access to treatment.

2.3h Body Mass Index (BMI)

Body mass index is a simple predictor that has been recently used to determine progression of HIV.[7] The association between BMI and HIV progression is important for two reasons. First, the "wasting syndrome", which is involuntary loss of more than 10% of body weight including more than 30 days of diarrhea, weakness, or fever, is considered an AIDS defining illness according to the CDC classification of disease.[1] Secondly, the simplicity of measuring BMI allows it to serve as a highly useful marker for the initiation of treatment in resource-limited countries. Past research has shown that long-term monitoring of BMI is predictive of disease progression.[7 20 21 22 23 24 25] A rapid decline in BMI among HIV patients has been shown six months preceding the diagnosis of AIDS.[7 24] Those considered underweight at diagnosis have been shown to be predictive of increased mortality, even in racially diverse cohorts.[7 17] One study discovered that a BMI < 17 kg/m^2 six months after initiation of treatment has been associated with a two-fold increase in risk of death.[6] Furthermore, a BMI < 18.5 kg/m^2 shows similar utility to CD4 count and HIV-RNA viral load based guidelines for the initiation of treatment. [7] Given these associations between BMI and survival among HIV patients, as well as BMI's correlation with infection in non-HIV patients[18], BMI may prove to be a valuable predictor for disease progression in HIV patients.

2.4 Predictors of cardiovascular related outcomes among HIV patients

During the early years of HIV/AIDS, the "wasting syndrome" was once the hallmark of HIV/AIDS.[1 21] Pronounced loss of weight, lean body mass and fat mass were attributed to an array of factors including opportunistic infection, living below the

poverty level, low CD4+ cell count and high viral load.[1] Today, HAART has transformed HIV disease into a chronic illness, which has caused incidence of wasting to decrease and the rates of obesity to increase.

People living with HIV are gaining weight and beginning to approach weight levels seen in the general U.S. population. Approximately two out of every three adults are overweight (i.e. BMI = 25-29.9) and one in every four adults are obese (i.e. BMI≥30) in the US.[21] Six states, including South Carolina (30.1%) had a prevalence of obesity equal to or greater than 30% in the general population.[19] Some studies have reported a lower prevalence of obesity among HIV-infected populations versus the general population,[52 53] whereas others have reported a higher prevalence .[24 54] Although the effect of HAART in causing obesity in HIV-infected patients may quantify the relatively slower progression to AIDS and provides the survival advantage afforded by elevated BMI,[24] certain problems have arose that has caused researchers question the mechanistic role of HAART.

Shortly after the introduction of HAART, several new metabolic abnormalities were reported and linked to its use.[55] Overweight and obesity are considered to be primarily responsible for the rising prevalence of these abnormalities. When taken together, these abnormalities form what is called the metabolic syndrome, which is seen in both non-HIV and HIV patients. Components of metabolic syndrome typically include abdominal obesity, hyperlipidemia, hypertension and diabetes.[56]

2.4a Cholesterol

Cholesterol is a waxy, fat-like substance that occurs naturally in the body.[57] Cholesterol is needed for the body to work properly, but if too much is in the blood, it can lead to plaque build-up in the arteries. This can lead to increased risk of developing heart disease, stroke, and other cardiovascular disease outcomes.

There are three types of cholesterol: Total Cholesterol (all cholesterol combined), High density lipoprotein (HDL) cholesterol (known as the good cholesterol), and Low density lipoprotein (LDL) cholesterol (known as the bad cholesterol).[57] Low levels of HDL combined with high levels of LDL and triglycerides indicate high cholesterol or what is better known as hyperlipidemia. Generally, high cholesterol levels are caused by unhealthy lifestyles, being overweight as well as certain medications such as diuretics and beta-blockers.[57] Approximately one in every six adults (~16%) of the U.S. adult population have high total cholesterol (> 240 mg/dL), with Hispanic men and Caucasian women displaying the highest levels of total cholesterol.[57] People with high total cholesterol have about twice the risk of heart disease as people with optimal levels.[57] Furthermore, certain conditions such as hypertension and diabetes can be exacerbated by high levels of cholesterol in the blood.

The amount of people affected by cholesterol among the HIV population seems to mirror the cholesterol levels among the general population. Low levels of HDL have been reported among HIV patients, and are associated with hypertriglyceridemia (i.e. high blood levels of triglycerides).[5 33 34] Furthermore, low CD4 T-cell counts and high levels of HIV-RNA viral load also are associated with low levels of HDL.[6 33 34] In 2006, El-

Sadr et al. compared cholesterol levels among obese HIV patients and non-obese HIV patients and determined that a higher BMI was associated with higher lipid levels.[6] Some research has suggested that the high levels of cholesterol in HIV patients is as a result of the HIV medication.[6 34] Additional research is needed to study the association between cholesterol and HIV progression.

2.4b Hypertension

Blood pressure is the force of blood against your artery walls as it circulates throughout your body.[58] Blood pressure is measured using two numbers. The first number is the systolic measurement and it represents the pressure in your blood vessels when your heart beats. The second number is the diastolic measurement and it represents the pressure in your vessels when your heart rests between beats. A normal blood pressure reading is 120/80 mmHg, while someone with high blood pressure (hypertension) will have a reading ≥ 140/90 mmHg.[58] Blood pressure tends to rise with age, but can be controlled by following a healthy lifestyle.[58] Hypertension can lead to increased risk of developing heart disease and stroke, which are the first and third leading causes of death in the U.S.[50] About one out of every three adults (~31%) in the U.S. has hypertension. Males, African Americans, and those of older age are more likely to develop hypertension.[58]

Among the HIV population, traditional risk factors are also associated with hypertension.[35 36] These factors include older age, overweight/obesity, family history of hypertension, and increased levels of triglycerides. CD4 counts below 200 cells/mm^3 show a tendency to be protective against hypertension in a univariate analysis, but this

association was no longer seen when included in the full model.[35] Most studies report that the prevalence of hypertension among HIV patients is anywhere between 25%-35%, which is very similar to the proportion of adults affected in the general population.[35 36 37 38 39] Some studies have raised the possibility that HAART may induce hypertension through hardening of the vessel walls,[36 39] however others report minimal effects.[37 38]

2.4c Diabetes

Diabetes is a disease in which blood glucose levels are above normal.[59] Your body either does not make enough insulin or cannot use its own insulin as well as it should, and can cause sugar build-up in the blood. Several risk factors are associated with getting diabetes such as genetics, poor diet, overweight/obesity, and the environment.[59] Tests such as the fasting blood glucose test, hemoglobin A1C, and oral glucose tolerance test are all used to determine diagnosis of diabetes. [59] However, it does require that two consecutive tests confirm this diagnosis.[60] A fasting blood glucose test with values higher than 126 mg/dL, a hemoglobin A1C test with values 6.5% or higher, and an oral glucose tolerance test with values higher than 200 mg/dL all constitutes a positive diagnosis of diabetes. [59 60] Risk factors for diabetes include older age, family history of diabetes, physical inactivity, and race/ethnicity. [59] Diabetes can lead to heart disease, blindness, kidney failure, and lower-extremity amputations. It is the seventh leading cause of death, and affects more than 20 million Americans. [59]

In HIV patients, mostly BMI, family history of diabetes, and certain HIV/AIDS medications are associated with diagnosis of diabetes.[40 41] The prevalence of diabetes among HIV patients has been reported to be between 1%-10%.[40 41] One study reported

that incidence of diabetes increases with cumulative exposure to HAART.[41] The HIV population also tends to have a greater chance for the development of complications due to diabetes when compared to HIV naïve patients.[42] Certain opportunistic infections, such as cytomegalovirus retinitis, can increase the chance of developing diabetic retinopathy in HIV patients. [42] Therefore, it may be possible that control of such opportunistic infections may help in reducing the diabetic complications seen in HIV patients.

2.5 Public Health Importance

Taken together, studying factors that influence progression of HIV is imperative. Non-traditional factors such as BMI may be useful to clinicians in providing the best clinical plan for each individual HIV patient. Furthermore, additional research on the risk of cardiovascular disease in HIV patients is needed. The populations sampled in past research have not provided the best population for studying this relationship. The population that will be sampled for our study will offer an array of HIV patients that will allow us to determine whether an association exists in the era of HAART.

CHAPTER 3

METHODS

3.1 Study design

The design of this study will be a retrospective cohort, determining how BMI (exposure) is associated with markers of HIV progression and cardiovascular disease risk. The marker for HIV progression includes CD4 T-cell count, while the markers of cardiovascular disease risk include fasting blood glucose, HDL, LDL, SBP and DBP. The inclusion criteria will be HIV positive individuals who are at least 18 years of age, with BMI being measured within three months of HIV diagnosis, and those with at least 1 follow-up after BMI was recorded at diagnosis. They will be grouped by their BMI status into the following four categories: underweight, normal, overweight and obese. Both the values and the measurement dates of CD4 T-cells, HIV-RNA viral load, fasting blood glucose, HDL, LDL, SBP and DBP will be collected.

3.2 Study Population

Setting: Medical records from the Ryan White HIV/AIDS Clinic in Columbia, SC will be reviewed to collect data for this study. The Ryan White HIV/AIDS program is a federally funded program that reaches more than 529,000 people a year in the United States.[35] It funds primary care and support services to low-income and underserved individuals and families living with HIV disease. [35] In 2007, the Ryan White program served 11,554 clients in South Carolina, with 100% of those clients being affected by

HIV. The majority of the clients served in the Ryan White Clinic in South Carolina are male (60%), African American (73%), and aged 25-44 (50.7%).[35]

Time Period: Since this study looks to determine the associations after HAART was introduced in 1996, we will include individuals who were newly diagnosed between January 1, 1997 and December 31, 2010, which is a total of 14 years.

3.3 Data Analysis

AIM 1: To determine the association between BMI at diagnosis and a marker of disease progression (CD4 T cell count) over time.

In order to determine the association between baseline BMI and markers of HIV, the following formula will be used to calculate BMI: (weight in lbs. * 703)/(height in inches^2). Descriptive analyses will be conducted. Statistical analyses will utilize Pearson's χ^2, Fisher's exact, or Kruskal-Wallis tests for categorical variables and t-test for continuous variables. A change between two test results is considered significant if it is a 30% change in absolute CD4 count or 3 percentage point change in CD4 percentage. A mixed regression analysis will be conducted to determine whether the mean values of the marker of HIV progression (CD4 count) are different over-time between BMI categories, after adjusting for the following confounding variables: race, gender, age, marital status, smoking, alcohol use, drug use, insurance, case manager, education, mode of transmission delayed entry into care, and HAART use. These variables were chosen due to their association between both BMI and the HIV disease. Tukey's multiple comparisons test will be used to determine which BMI categories' mean values, if any,

are different from each other. A loess fitting will be used if the data appears to be non-linear. Graphical comparisons will also be performed.

Table 3.1: Independent variables for AIM 1

Variables	**Date**	**Levels**	**Categories**
HIV seroconversion/diagnosis	Baseline	Date	Date
Race/Ethnicity	Baseline	4	White (ref) Black Hispanic Other
Gender	Baseline	2	Male (ref) Female
Age	Baseline	5	<20 21-29 (ref) 30-39 40-49 50-59 ≥60
Marital Status	Baseline	4	Single (ref) Married Divorced Widowed
Smoking Status	Baseline	2	No (ref) Yes
Alcohol Use	Baseline	2	No (ref)

			Yes
Drug Use	Baseline	2	No (ref) Yes
Insurance	Baseline	5	Medicare Medicaid Private Insurance Other None
Case Manager	Baseline	2	No (ref) Yes
Education	Baseline	4	High School diploma (ref) Some college College degree Graduate degree
Mode of Transmission	Baseline	4	Heterosexual (ref) MSM IDU NIR/NRR
Delayed entry into Care	Baseline	2	< 3 months (ref) ≥ 3 months
Weight	Baseline	Continuous	Continuous

Height	Baseline	Continuous	Continuous
ART/HAART use		2	No (ref) Yes
CD4 count	Baseline	Continuous	Continuous
CD4 count (outcome)	Overtime[1]	Continuous	Continuous
HIV-RNA viral load	Baseline	Continuous	Continuous

1The date that each variable is measured, after diagnosis of HIV, will be recorded as well.

AIM 2: To determine whether the association between BMI at diagnosis and a marker of disease progression (CD4 T cell count) over time differ by gender.

To determine whether AIM 1 varies by race and sex, investigators will use the same variables that will be used to analyze AIM 1, but will stratify the results by the gender (Male and Female). The following formula will be used to calculate BMI: (weight in lbs. * 703)/(height in inches^2). Gender differences in demographic and clinical characteristics will be assessed by using Pearson's χ^2, Fisher's exact, or Kruskal-Wallis tests for categorical variables and t-test for continuous variables. A change between two test results is considered significant if it is a 30% change in absolute CD4 count or 3 percentage point change in CD4 percentage. A mixed regression analysis will be conducted to determine whether the mean values of the marker of HIV progression (CD4 count) are different over-time between BMI categories vary by gender, after adjusting for the following confounding variables: age, race, marital status, smoking, alcohol use, drug use, insurance, case manager, education, mode of transmission, delayed entry into care and HAART use. Tukey's multiple comparisons test will be used to determine which

BMI categories' mean values, if any, are different from each other. A loess fitting will be used if the data appears to be non-linear. Graphical comparisons will also be performed.

Table 3.2: Independent variables for AIM 2

Variables	**Date**	**Levels**	**Categories**
HIV seroconversion/diagnosis	Baseline	Date	Date
Race/Ethnicity	Baseline	4	White Black Hispanic Other
Gender	Baseline	2	Male Female
Age	Baseline	5	<20 21-29 (ref) 30-39 40-49 50-59 ≥60
Marital Status	Baseline	4	Single (ref) Married Divorced Widowed
Smoking Status	Baseline	2	No (ref) Yes
Alcohol Use	Baseline	2	No (ref)

			Yes
Drug Use	Baseline	2	No (ref) Yes
Insurance	Baseline	5	Medicare Medicaid Private Insurance Other None
Case Manager	Baseline	2	No (ref) Yes
Education	Baseline	4	High School diploma (ref) Some college College degree Graduate degree
Mode of Transmission	Baseline	4	Heterosexual (ref) MSM IDU NIR/NRR
Delayed entry into Care	Baseline	2	< 3 months (ref) ≥ 3 months
Weight	Baseline	Continuous	Continuous

Height	Baseline	Continuous	Continuous
ART/HAART use		2	No (ref) Yes
CD4 count	Baseline	Continuous	Continuous
CD4 count	Overtime[1]	Continuous	Continuous
HIV-RNA viral load	Baseline	Continuous	Continuous

1The date that each variable is measured, after diagnosis of HIV, will be recorded as well.

AIM 3: To determine the association between BMI at diagnosis and markers of cardiovascular disease risk (Fasting blood glucose, HDL and LDL, and SBP and DBP) over time.

In order to determine the association between baseline BMI and markers of HIV, the following formula will be used to calculate BMI: (weight in lbs. * 703)/(height in inches^2). Descriptive analyses will be conducted as well. Statistical analyses will Pearson's χ^2, Fisher's exact, or Kruskal-Wallis tests for categorical variables and t-test for continuous variables. A mixed regression analysis will be conducted to determine whether the mean values of the markers of cardiovascular disease risk are different over-time between BMI categories, after adjusting for the following confounding variables: race, gender, age, marital status, smoking, alcohol use, drug use, insurance, case manager, education, mode of transmission, delayed entry into care, baseline CD4 count, baseline VL, baseline fasting blood glucose, baseline HDL, baseline LDL, baseline SBP and DBP, and HAART use. These variables were chosen due to their association between both BMI and the HIV disease. Tukey's multiple comparisons test will be used to determine which BMI categories' mean values, if any, are different from each other. A

loess fitting will be used if the data appears to be non-linear. Graphical comparisons will also be performed.

Those on cholesterol, hypertension and diabetic medications before diagnosis will be excluded from the analysis.

Table 3.3: Independent variables for AIM 3

Variables	**Date**	**Levels**	**Categories**
HIV seroconversion/diagnosis	Baseline	Date	Date
Race/Ethnicity	Baseline	4	White (ref) Black Hispanic Other
Gender	Baseline	2	Male (ref) Female
Age	Baseline	5	<20 21-29 (ref) 30-39 40-49 50-59 ≥60
Marital Status	Baseline	4	Single (ref) Married Divorced Widowed

Smoking Status	Baseline	2	No (ref) Yes
Alcohol Use	Baseline	2	No (ref) Yes
Drug Use	Baseline	2	No (ref) Yes
Insurance	Baseline	5	Medicare Medicaid Private Insurance Other None
Case Manager	Baseline	2	No (ref) Yes
Education	Baseline	4	High School diploma (ref) Some college College degree Graduate degree
Mode of Transmission	Baseline	4	Heterosexual (ref) MSM IDU
Weight	Baseline	Continuous	Continuous

Height	Baseline	Continuous	Continuous
ART/HAART use		2	No (ref) Yes
HDL and LDL	Baseline	Continuous	Continuous
Blood Pressure (Systolic and Diastolic)	Baseline	Continuous	Continuous
Fasting blood glucose	Baseline	Continuous	Continuous
HDL and LDL	Overtime[1]	Continuous	Continuous
Blood Pressure (Systolic and Diastolic)	Overtime[1]	2	Continuous
Blood Glucose Levels (fasting)	Overtime[1]	2	Continuous

1The date that each variable is measured, after diagnosis of HIV, will be recorded as well.

Data management and statistical analyses will be performed using SAS 9.2 software. Proc mixed will be used to perform the mixed model analyses.

Sample Size/Power Analysis

A power analysis was conducted using SAS Proc Power to determine sample size needed for each BMI category. Since each AIM will be analyzed using a mixed model analysis, mean values of CD4 count were used (Table 4). Compared to the other outcomes that will be analyzed in this dissertation, CD4 was also used since it had the largest standard deviation, which causes the sample size to be larger compared to smaller standard deviations. These numbers were averaged from previous studies reports of mean CD4 counts for each BMI category.[17 22 23 24 25] An average from these studies were calculated and used in the power analysis. Alpha was set to 0.05 and power was set to 0.80.

Table 3.4: Power Analysis: Average CD4 counts per BMI category

BMI Category	Average CD4 count
Underweight	**346**
Normal	**412**
Overweight	**451**
Obese	**473**

The power analysis determined that at least 85 HIV patients are needed in each group to ensure an 80% power for the study. We also determined how sample size affects power by computing sample size needed per group at different powers (Table 5)

Table 3.5: Power Analysis: Number (N) of HIV patients per BMI category needed at different powers

N Per Group	Power
5	0.082
10	0.127
15	0.176
20	0.228
25	0.282
30	0.336
35	0.390
40	0.442
45	0.492

50	0.541
55	0.586
60	0.629
65	0.668
70	0.705
75	0.738
80	0.769
85	0.796
90	0.821
95	0.843
100	0.863
105	0.881
110	0.897
115	0.911
120	0.923
125	0.933
130	0.943
135	0.951
140	0.958
145	0.964
150	0.969

Protection Measures

All study personnel will be trained and certified in federal and state policies regarding the protection of human subjects' participation in research. The human subjects data used in AIMS 1, 2, and 3 of this proposal are part of the University of South Carolina's Ryan White Clinic program. Careful consideration will be taken to ensure the anonymity of study participants. No individual will be identified in any publications resulting from this study. To further protect patient confidentiality, the researcher will have access to the medical records and will be required to sign a confidentiality agreement and attend a USC sponsored Health Insurance Portability and Accountability Act (HIPPA) training. The data will be abstracted from the medical records on forms that will not contain any identifying information. The abstracted data will be entered into an electronic database which will be used in the analysis. This investigation will pose only a minimal risk to the privacy of individuals, and the proposed research falls under Exemption 4 (AIM 1, AIM 2, and AIM 3) and Expedited Review Category 5 (AIM 1, AIM 2, and AIM 3). An application will be submitted to the University of South Carolina Institutional Review Board to approve this study (Please see Appendix A for a more detailed description of the Human Subjects Protection).

Strengths and Limitations

There is a strong need for simple and affordable clinical criteria (i.e. BMI) to guide interventions such as the initiation of treatment and monitor progression of HIV. This is of particular importance in resource-limited countries such as the sub-Saharan Africa, where tests to measure CD4 and HIV-RNA viral load may not be available due to

expenses. Ultimately, the use of BMI could aid in reducing the onset of morbidity and mortality.

Most of the studies that have investigated this relationship have studied BMI as a time-dependent variable. There are limited studies that have looked at the effect of BMI at diagnosis as a marker to determine disease progression. However, this proposal will determine its association with both disease progression and cardiovascular risk due to the recent evidence in this field of research.

A limitation to this proposal is that there is potential for missing data (CD4 cell count, HIV-RNA viral load, HDL, LDL, TG), but it is anticipated to be minimal.

Summary

This proposal outlined is significant because it looks to determine whether the use of BMI could be a basic prognostic factor used to measure HIV progression. Also, there is needed research in the field of nutrition and HIV to determine its relation as HIV continues to become more of a chronic disease. Dissertation committee chair, Dr. Anwar Merchant, has experience epidemiology, nutrition, and HIV research. Dr. Bo Cai, committee member, has experience in biostatistics. Dr. Kellee White, committee member, has experience in cardiovascular epidemiology. Dr. Wayne Duffus, committee member, has experience in HIV research. Combined, these investigators have an extensive background conducting epidemiological research and possess the methodological skills needed to successfully complete this study.

CHAPTER 4

LONGITUDINAL ASSOCIATION BETWEEN BODY MASS INDEX (BMI) AT DIAGNOSIS AND HIV DISEASE PROGRESSION

4.1 Introduction

Malnutrition and an underweight appearance were characteristics formerly associated with HIV/AIDS infection and were predictive of increased mortality.[21] However, since the introduction of Highly Active Antiretroviral Therapy (HAART) in 1996, mortality has decreased, the progression of HIV to AIDS has decelerated, and HAART treated individuals are experiencing weight gain and becoming more overweight (Body Mass Index (BMI): 25 – 29.9 kg/m^2) and obese (BMI: $\geq$ 30 kg/m^2).[7] Some studies report that the obesity prevalence among the HIV population is now beginning to mirror the obesity epidemic among the general population.[7 21]

Pre-HAART research evaluating the association between BMI and HIV progression has shown either no association[20 22] or that HIV-infected individuals with higher BMI levels are less likely to progress to AIDS and die as compared to those with normal weight individuals (BMI: $\leq$ 24.9 kg/m^2).[17 24 60] However, in the post-HAART era, the different increased BMI categories (overweight and obese) may be differentially associated with disease progression and survival. For example, overweight individuals are reported to have a slower progression to AIDS compared to those who were obese.[25] However, obese HIV-infected individuals on HAART are reported to experience smaller

increases in CD4-positive T-lymphocyte count (CD4), implying that obesity may actually be harmful.[26 27] These data suggest, that although HAART is associated with improvements in morbidity and mortality, progressive weight gain may additionally influence immune recovery, which may be reversed or slowed. However, there is a paucity of studies examining this relationship in the post HAART era.

This study is important because it was conducted in the southern United States, a region that suffers from one of the highest burdens of HIV-infected individuals,[1] and overweight and obese individuals.[19] Whereas previous studies have focused on mortality, this study investigates the longitudinal association of BMI at HIV diagnosis with disease progression as evaluated by CD4 counts obtained during routine medical care.

4.2 Methods

This is a cohort study of individuals who were receiving care at the Ryan White Clinic in Columbia, SC. Participants were eligible if they were diagnosed with HIV-infection from January 1, 1997 through December 31, 2010, were at least 18 years of age, had weight and height measurements within three months of HIV diagnosis, were HAART-naïve, and had at least one follow-up visit (within six months) after entering into care. Individuals who were pregnant when diagnosed and those diagnosed with AIDS at the initial visit were excluded. This study was approved by the University of South Carolina Institutional Review Board.

The power analysis, using the difference between mean CD4 counts by BMI category from past research, determined that at least 85 HIV-infected individuals are needed in each group to ensure an 80% power for the study. Investigators abstracted de-identified data from 409 medical records. However, since there were only 13 underweight

(BMI: <18.5 kg/m^2) HIV-infected individuals, this category was excluded from the analyses. A total of 396 individuals were included in the final analyses.

Variables

Outcome: The outcome evaluated for this study was CD4 cell count (cells/mm^3) assessed over the course of medical care follow-up. CD4 cell count was used to stage disease and is monitored routinely by providers to determine when to start HAART and to assess response to treatment. CD4 cell count was used as a continuous variable in the analysis.

Exposure: Body mass index at diagnosis was the main exposure variable. This was estimated by dividing weight in kg by height (measured at diagnosis) in m^2 measured within three months after diagnosis. BMI was grouped into three categories: normal (<25 kg/m^2), overweight (25-29.5 kg/m^2), and obese (≥30 kg/m^2).

Time varying covariates: HIV viral load (VL) (copies/mL) was collected at diagnosis and monitored over the course of follow-up to assess ongoing response to treatment. HAART use was defined as any prescription for HIV medication over the course of medical care. All data was extracted from the participants' medical records.

Other variables recorded at baseline include age, gender, race/ethnicity, marital status, education, type of insurance, use of case management, alcohol use, smoking status, drug use, mode of transmission, and delayed entry into care (defined later). Age was grouped into the following five categories when included in the multivariate analysis: < 20; 20-29; 30-39; 40-49; 50-59; and ≥ 60. The following categories were used for race/ethnicity: White, non-Hispanic; Black, non-Hispanic; Hispanic; Other; and Unknown. Education was grouped into these categories: no high school diploma, high

school diploma, associate degree, bachelor degree, master's degree, or doctoral degree. Type of insurance was based on primary insurance and was clustered into these categories: Medicare; Medicaid; Private Insurance or none (includes individuals enrolled in the AIDS Drug Assistance Program). Mode of transmission was grouped into four categories: heterosexual, men who have sex with men (MSM), injection drug users, or no identified risk/no reported risk (NIR/NRR). Given that timely linkage to care has the potential to improve health outcomes and prevent secondary HIV transmission,[61] the delayed entry into care variable was used as a covariate to adjust for differences between those who seek care early versus those who do not. Delayed entry into care was determined by subtracting the date of diagnosis from the date of first visit to the clinic, and was grouped into the two categories: $\leq$3 months and >3 months.[62] When an individual is diagnosed with HIV at the Ryan White Clinic, he or she is offered the services of a case manager to help the individual access care and other support services. Case management was defined as present if the individual had an assigned case manager and absent otherwise. We adjusted for this variable because there may be a difference in clinical care outcome associated with case management status. Current alcohol use, current smoking status, and current drug use were all assessed by yes or no questions. Visit number was entered into the analysis to control for time in study. Therefore, the first visit represented time point one, the second visit represented time point two, and so forth.

Statistical Analyses

Demographic and clinical characteristics of the participants were compared across the three BMI categories, using means and standard error (SE) for continuous variables

and number (n) and percent (%) for categorical variables. Differences in clinical characteristics were compared using F-test for continuous variables and Pearson χ^2, Fisher's exact, or Kruskal-Wallis tests for categorical variables as appropriate.

To determine the association between BMI at diagnosis and longitudinal CD4 cell counts, data were analyzed using mixed regression models. Age group, race/ethnicity, gender, use of case management, marital status, education, insurance type, delayed entry into care, mode of transmission, alcohol use, smoking status, drug use, CD4 count at diagnosis, and HIV VL at diagnosis and overtime were all adjusted for in the analysis given their relationship to BMI or HIV progression. Variables were included into the model sequentially: Model 1: BMI group, age group, race/ethnicity, gender, HAART use, baseline CD4 count, baseline HIV VL, HIV VL over time, and mode of transmission; Model 2: Model 1 + alcohol use, smoking status, and drug use; Model 3: Model 2 + marital status, education, and insurance type; Model 4: Model 3 + use of case management; Model 5: Model 4 + delayed entry into care. The mixed model analysis was also stratified by baseline VL and delayed entry into care. For this analysis, baseline VL was grouped into ≤100,000 copies/mL plasma and >100,000 copies/mL plasma. Adjusted CD4 count means were determined and graphed at five different time points by using an lsmeans statement in the mixed regression model, with tukey option to determine differences between BMI categories. The five time points were determined from quantiles obtained from a univariate analysis. Sensitivity analyses were conducted to test whether loss to follow-up (i.e. those with $\geq$ 6 months after the last documented visit) impacted the results and the data were re-analyzed using the inverse-probability weighting method as suggested by Hernan.[63] Statistical analyses were performed using

SAS 9.2 (SAS Institute; Cary, North Carolina). For all analyses, the α-level was set at 0.05.

4.3 Results

Baseline Characteristics

The overall study population's mean baseline BMI was 27.4 kg/m^2 (overweight) and mean age was 35 years. The study population were predominantly male (61.9%), black (74.2%), and single (61.1%); approximately 35.3% had at least a high school diploma,47.2% did not have insurance, 57.1% were not followed by a case manager, 60.9% used alcohol, 54.8% smoked, 59.8% did not report drug use, 55.8% were heterosexual, 56.8% entered care $\geq$ 3 months of diagnosis, and 88.1% were prescribed HAART during course of medical care (Table 1).

BMI categories were not related to age, race/ethnicity, marital status, educational attainment, type of insurance, use of case manager, and HAART use. However, gender, alcohol use, smoking status, drug use, mode of transmission, delayed entry into care, CD4 count at diagnosis, and HIV VL at diagnosis were all significantly different among the BMI categories. Obese HIV-infected individuals were more likely to be female (60.4%), non-alcohol users at diagnosis (44.3%), to non-smokers (53.8%), and had the lowest HIV VL at baseline (4.5 logs), and the highest CD4 count at baseline (575.6 cells/mm^3) compared to the normal and overweight weight individuals.

BMI and CD4 count over time

The overall mean follow-up time was 6.7 years and was similar across the BMI categories (P=0.108). The overall mean CD4 count over time was 579.3 cells/mm^3. Mean CD4 count was highest among obese individuals (611.2 cells/mm^3), followed by

overweight individuals (598.1 cells/mm^3) and normal weight individuals (550.5 cells/mm^3).

Mixed models were used to determine whether CD4 count change over time was different among BMI categories (Table 2). After adjusting for the variables listed in Table 1, there were significant differences in mean CD4 count for the overweight and obese categories when compared to the normal weight category. Models 1 thru 5 (full model) were all determined to be significant. Compared with the normal weight individuals in the full model, the obese category had significantly larger increases in CD4 count (5.5 cells/mm^3, P = <0.001) versus the decrease in CD4 count in the overweight category (-2.1 cells/mm^3, P = <0.001). For an example, after visit one, it is predicted that obese HIV-infected individuals at diagnosis will experience a 5.5 cells/mm^3 increase in CD4 count, while obese HIV-infected individuals will experience a 2.1 decrease in CD4 count. The results of the sensitivity analyses using the inverse-probability weighting method to account for loss to follow up (n=73) were qualitatively similar to the results presented.

Overall, mean CD4 count increased over time. Figure 1 shows a significant interaction between BMI and CD4 count using the adjusted mean CD4 counts. While the adjusted mean CD4 count was higher at the outset for the overweight and normal weight groups compared to the obese category, over time the CD4 count trend increased among the obese and normal weight categories and decreased for the overweight category (Figure 1). Figure 2 displays the differences in adjusted mean CD4 counts when compared to the normal weight group. The overweight category had the greatest difference in adjusted mean CD4 counts when compared to the normal weight group. The

adjusted mean CD4 counts at visit one, visit forty-two, and visit fifty-four among the overweight category were statistically different from the normal weight group's adjusted means.

The interaction between BMI and time among those with lower baseline VL values (<100,000 copies/mL plasma) were significant for the overweight and obese categories when compared to the normal weight individuals (time*overweight P <0.001, time*obese P <0.001) (Table 3). Significantly larger increases in CD4 count were seen in the obese category (3.3 cells/mm^3) versus the overweight category who experienced decreases in CD4 count (-1.8 cells/mm^3). Among those with higher baseline VL values (>100,000 copies/mL plasma), the interaction between BMI at time were significant for the overweight and obese categories when compared to normal weight individuals (time*overweight P <0.001, time*obese P <0.001). Significant decreases in CD4 count were seen in the obese category (-2.1 cells/mm^3) and the overweight category (-1.6 cells/mm^3).

For those individuals who entered care within three months of diagnosis, the interaction between BMI and time were significant when compared to the normal weight patients (time*overweight P <0.001, time*obese P <0.001) (Table 3). Significantly larger increases in CD4 count were seen in the obese category (9.4 cells/mm^3) versus the overweight category that experienced decreases in CD4 count (-2.9 cells/mm^3). In those who received care after three months of diagnosis, the interactions between BMI and time were significant (time*overweight P <0.001, time*obese P <0.001) when compared to the normal weight category, with the obese category experiencing increases in CD4 count (2.6 cells/mm^3) and the overweight category (-1.4

cells/mm^3) experiencing decreases in CD4 cell count when compared to the normal weight category.

4.4 Discussion

Within this cohort of HIV-infected individuals, CD4 counts were highest at time of diagnosis among those who were obese compared to those in the overweight and normal weight categories. CD4 counts at diagnosis also were higher for individuals who entered care within three months of diagnosis and those who had lower baseline VL values (<100,000 copies/mL). Over time CD4 count increases were highest for the obese followed by the normal weight groups, but decreased for the overweight category after adjusting for potential confounders. Although very high BMI among HIV-infected individuals is associated with increased CD4 count over time, moderately high BMI was not. Although our results are different from recent post-HAART studies that have evaluated this relationship, it suggests that obesity may still be beneficial to the immune recovery gained from HAART.

During the pre-HAART (before 1996) era, several studies reported that obese HIV-infected individuals had better survival over time.[17 22] Van der Sande et al. discovered that the median survival time of those presenting with BMI < 16 was significantly lower than the median survival time for those with a baseline BMI ≥ 22.[17] In the current investigation, we were unable to study those with BMI < 18.5 due to an insufficient number of underweight individuals. Shor-Posner et al. found that while CD4 cell count over time was higher for obese individuals compared with the non-obese group (376 cells/mm^3 vs. 364 cells/mm^3), the difference was not statistically significant.[22]

A few studies found that overweight individuals have larger increases in CD4 counts over time during the pre-HAART era.[24] [60]Jones et al. reported a significant difference in CD4 count among BMI categories, with the overweight group experiencing larger increases in CD4 counts, followed by those of normal weight and underweight.[24] With survival as the outcome, Shuter et al. found that overweight individuals progressed more slowly to AIDS, and CD4 count was not independently predictive of progression to AIDS. [60]

Whereas the results by Van der Sande et al. and Shor-Posner et al. are similar to our findings, these studies were conducted during the pre-HAART era and their population consisted of only women[24] or had a limited sample size.[60] Koethe et al. recently investigated the relationship between BMI and HIV progression by following HIV-infected adults starting treatment between 1998 and 2008 (post-HAART era) and discovered that overweight HIV-infected individuals experienced a 12-month CD4 count gain in women (+ 9 cells/ uL), but not in men (-1 cells/uL), while the normal weight (-65 cells/uL) and obese categories (-12 cells/uL) experienced a reduction.[25] They suggested that there may be an optimal BMI range for immune recovery once on treatment for a year, with immune reconstitution reaching a plateau in the range of BMI 25 to 30 kg/m^2. Crum-Cianflone et al. reported that in the HAART era, obese HIV-infected individuals had smaller increases in CD4 counts (+69 $cells/mm^3$) compared to those in the overweight (+116 $cells/mm^3$) and normal weight categories (+102 $cells/mm^3$).[26] Although previous post-HAART studies report different results, our results could be due to our study population being from South Carolina where high levels of HIV and obesity exist.

There are a few proposed clinical explanations for our results. First, leptin is a satiety hormone that circulates directly proportional to weight and is known to increase with inflammation.[64] Obese individuals have a higher concentration of leptin compared to overweight and normal weight individuals and given HIV causes inflammation and CD4 cells have leptin receptors and has a proliferation effect, it could explain the increase or higher levels of CD4 among obese individuals. Secondly, obesity is surplus of energy in the form of stored fat that acts to spare protein from being used as an energy source, which aids in preserving immune function.[19] This helps to neutralize the high metabolic rate of HIV and could explain the protective effect of obesity on CD4 levels. Thirdly, as Jones et al proposed, since untreated HIV-infection is associated with weight loss, individuals in the normal weight category are a mixed group consisting of both individuals who were normal weight pre-diagnosis, and those who were overweight but lost weight because of HIV-infection in the period preceding their diagnosis.[24] Furthermore, individuals in the overweight category are a mixed group consisting of both individuals who were overweight pre-diagnosis, and those who were obese but lost weight because of HIV-infection. These explanations are an example of reverse causality and a potential confounder in all studies evaluating this question.

To prevent the possibility of weight change being mis-classified into another BMI category, height and weight was collected within three months of diagnosis. If reverse causality is contributing to the association between BMI and HIV progression, then the BMI characteristics of the source population are likely important. As HIV is diagnosed at an earlier stage, before wasting sets in, the HIV-infected population is similar to the general population with respect to BMI. In our study population the mean BMI was 27.4

kg/m^2, and overweight and obesity prevalence was 30% and 26.8%, which is similar to the prevalence of overweight (35.4%) and obesity (31.5%) in general HIV-uninfected population in South Carolina.[19] However, the percentages differ the population of HIV-infected drug users in the report by Shor-Posner et al. (overweight or obese 18%),[4] or HIV-infected predominantly Latino population attending an urban health clinic in Bronx, NY in the report by Shuter et al. (overweight 21.7%),[60] or high risk women (history of injection drug use or high-risk sexual contact) in the report by Jones et al.(obesity 18.8%).[24] The characteristics of the study population in this report were similar for all HIV-infected individuals in the entire state of South Carolina, with respect to race (Black: 74.2% versus 76%) and mode of transmission (MSM: 33.1% versus 37.1%).[66] Given the similarities between our study cohort and the overall HIV-infected population in South Carolina, it is unlikely that reverse causality significantly impacted our results.

There are several limitations to our study. First, the secular change of CD4 count is impacted as more HIV-infected individuals are prescribed HAART and medication efficacy has increased, which could potentially attenuate the associations.[67] Second, our population consisted of mostly black HIV-infected individuals and the results may not be generalizable to other populations. Third, we were unable to make an assumption that included the underweight BMI category. However, past research has shown that underweight individuals generally have a faster progression to AIDS and death compared to other BMI categories.[17 24 25] Fourth, the treatment variable only measured whether individuals received HAART throughout the course of their HIV infection. We did not assess time spent on HAART. Fifth, there is the possibility of residual confounding.

Finally, the alcohol use and drug use variables only captured whether individuals were socially participating in these factors and not the frequency of use.

Our study has several strengths. First, we investigated the post-HAART longitudinal association between BMI at baseline and HIV progression in a southern state. In contrast, the majority of other studies from other regions focused on survival rather than continuous immune function. Second, unlike previous research, we adjusted for many potential confounders including delayed entry into HIV medical care and use of case management. Entry into HIV medical care is essential for access to antiretroviral therapy and facilitates the delivery of important prevention education to reduce HIV transmission. In addition, retention in care is necessary to monitor response to therapy. Therefore, adjusting for delayed entry into care is important to accurately determine the association between BMI and HIV progression as it relates to both. Whereas our results were similar to Koethe's et al. results in regards to mean CD4 counts, they were not able to adjust for educational attainment or insurance type.[25] The current study was able to gain an improved estimation of the relationship between BMI at diagnosis and CD4 count over time by adjusting for these variables. Third, our population of individuals with different stages of HIV disease, allows us to determine if the relationship under study exists in HIV-infected individuals with different levels of immune impairment. Fourth, the inverse probability weighting method used to evaluate the possible impact of loss to follow-up provided materially similar results to those reported. Finally, this investigation includes fourteen years of follow-up (i.e. those diagnosed in 1997) allowing us to assess CD4 count over a long period.

Our study results demonstrate that HIV-infected individuals who were obese at diagnosis had greater increases in CD4 counts over time when compared to HIV-infected individuals who were overweight and normal weight at diagnosis. This suggests that providers should pay closer attention to weight at diagnosis to predict the response to treatment. Additional studies are needed among different populations to support the conflicting results produced by studies that have evaluated this relationship. Because BMI at diagnosis may be an important factor in predicting disease trajectory in the post-HAART era, other studies are needed to evaluate immune impairment of those with high BMI and establish a biologic basis for the observed differences.

Table 4.1: Baseline characteristics of South Carolina HIV-infected individuals diagnosed between 1997 and 2010 by Body Mass Index (BMI) category.

Characteristic	Overall (n=396)	Normal (n=171)	Overweight (n=119)	Obese (n=106)	P^a
Body Mass Index	27.4 ± 6.3	22.3 ± 1.8	27.2 ± 1.5	35.9 ± 5.2	<0.001
Age	35.1 ± 10.6	34.5 ± 11.5	36.1 ± 9.5	34.5 ± 10.2	0.378
Gender					
Male	245 (61.9%)	126 (73.7%)	78 (65.6%)	41 (38.7%)	
Female	149 (37.6%)	44 (25.7%)	41 (34.5%)	64 (60.4%)	
Transgender	2 (0.5%)	1 (0.6%)		1 (0.9%)	<0.001
Race					
White, non-Hispanic	92 (23.2%)	38 (22.2%)	28 (23.6%)	26 (24.5%)	
Black, non-Hispanic	294 (74.2%)	127 (74.3%)	88 (74.0%)	79 (74.5%)	
Hispanic	3 (0.8%)	2 (1.2%)	1 (0.8%)		
Other	1 (0.3%)		1 (0.8%)		
Unknown	6 (1.5%)	4 (2.3%)	1 (0.8%)	1 (1.0%)	0.899
Marital Status					
Single	242 (61.1%)	111 (64.9%)	71 (59.7%)	60 (56.6%)	
Married	47 (11.9%)	15 (8.8%)	19 (16.0%)	13 (12.3%)	
Divorced	70 (17.7%)	25 (14.6%)	18 (15.1%)	27 (25.5%)	
Widowed	14 (3.5%)	7 (4.1%)	5 (4.2%)	2 (1.9%)	
Partnered	21 (5.3%)	12 (7.0%)	6 (5.0%)	3 (2.8%)	
Unknown	2 (0.5%)	1 (0.6%)		1 (0.9%)	0.166
Education					
No HS Diploma	63 (35.3%)	34 (19.9%)	13 (10.9%)	16 (15.1%)	
High School Diploma	140 (5.8%)	61 (35.6%)	45 (37.8%)	34 (32.1%)	
Associate Degree	23 (6.1%)	8 (4.7%)	4 (3.4%)	11 (10.4%)	
Bachelor Degree	24 (2.3%)	6 (3.5%)	8 (6.7%)	10 (9.4%)	
Master's Degree	9 (0.8%)	4 (2.3%)	3 (2.6%)	2 (1.9%)	
Doctorate Degree	3 (15.9%)	2 (1.2%)	1 (0.8%)		
Unknown	134 (33.8%)	56 (32.8%)	45 (37.8%)	33 (31.1%)	<0.001
Insurance					
Medicare	70 (17.7%)	33 (19.3%)	19 (16.0%)	18 (17.0%)	
Medicaid	43 (10.9%)	17 (9.9%)	10 (8.4%)	16 (15.1%)	
Private Insurance	96 (24.2%)	30 (17.6%)	35 (29.4%)	31 (29.3%)	
None	187 (47.2%)	91 (53.2%)	55 (46.2%)	41 (38.7%)	0.064
Followed by Case Manager					
Yes	170 (42.9%)	82 (47.9%)	44 (37.0%)	44 (41.5%)	
No	226 (57.1%)	89 (52.1%)	75 (63.0%)	62 (58.5%)	0.170
Alcohol Use					
Yes	241 (60.9%)	117 (68.4%)	73 (61.3%)	51 (48.1%)	
No	138 (34.8%)	49 (28.7%)	42 (35.3%)	47 (44.3%)	
Unknown	17 (4.3%)	5 (2.9%)	4 (3.4%)	8 (7.6%)	0.017
Smoking					
Yes	217 (54.8%)	114 (66.7%)	63 (53.0%)	40 (37.7%)	
No	162 (40.9%)	52 (30.4%)	53 (44.5%)	57 (53.8%)	
Unknown	17 (4.3%)	5 (2.9%)	3 (2.5%)	9 (8.5%)	<0.001
Drug Use					
Yes	141 (35.6%)	72 (42.1%)	44 (37.0%)	25 (23.6%)	
No	237 (59.8%)	94 (55.0%)	71 (59.7%)	72 (67.9%)	
Unknown	17 (4.6%)	5 (2.9%)	4 (3.3%)	9 (8.5%)	0.010
Delayed entry into care					
<3 months	171 (43.2%)	78 (45.6%)	39 (32.8%)	54 (50.9%)	
≥3 months	225 (56.8%)	93 (54.4%)	80 (67.2%)	52 (49.1%)	0.016

HAART use					
Yes	365 (88.1%)	161 (94.2%)	109 (91.6%)	95 (89.6%)	
No	31 (11.9%)	10 (5.8%)	10 (8.4%)	11 (10.4%)	0.109
CD4 count at diagnosis	499.3 ± 255.2	448.4 ± 229.1	498.4 ± 231.1	575.6 ± 296.2	0.019
Log HIV VL at diagnosis	4.1 ± 0.9	4.2 ± 0.9	4.2 ± 0.9	3.8 ± 0.9	<0.001

Abbreviations: MSM, men who have sex with men; IDU, injecting drug user; NIR/NRR, no identified/reported risk factor

NOTE: Mean and standard deviation are shown for Body mass Index, Age, CD4 count at diagnosis, HIV VL at diagnosis.

- Normal ($\leq$ 24.9 kg/m^2), Overweight (25.0-29.9 kg/m^2), Obese ($\geq$ 30.0 kg/m^2). Underweight individuals were excluded because numbers were too few for meaningful analysis.

[a] Comparison between baseline BMI strata

**Insurance – None: No insurance/ADAP Program

Table 4.2: Mixed Model Analysis of the association between Body Mass Index (BMI) and CD4 count among HIV-infected individuals diagnosed in South Carolina between 1997 and 2010.

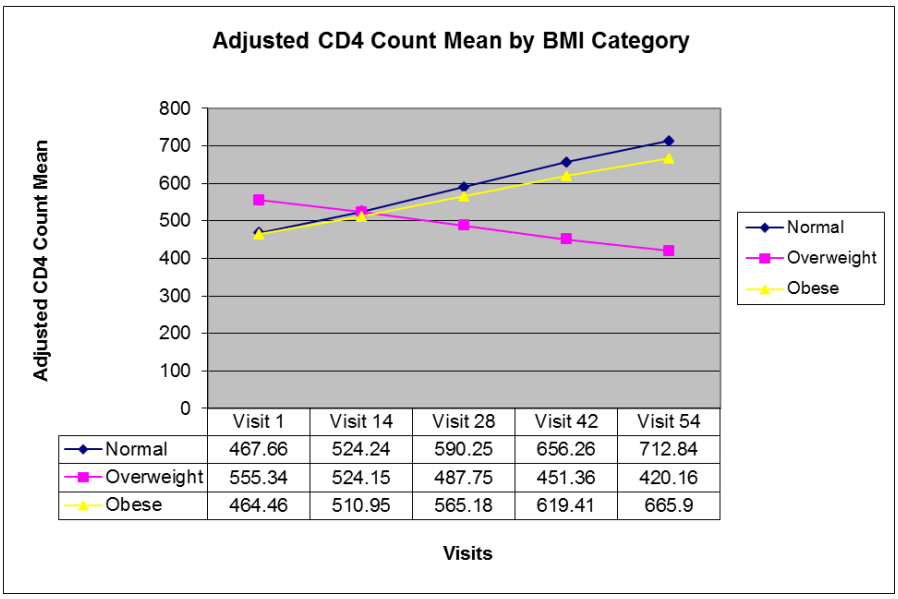
Model	Parameter Estimate	Standard Error (SE)	P^b
Model 1			
Time	4.9	0.002	<0.001
BMI			
Obese	20.8	0.07	<0.001
Overweight	124.2	0.07	<0.001
Normal	*	*	*
BMI*time			
time*Obese	0.8	0.004	<0.001
time*Overweight	-7.3	0.004	<0.001
time*Normal	*	*	*
Model 2			
Time	4.9	0.003	<0.001
BMI			
Obese	6.2	0.07	<0.001
Overweight	120.8	0.07	<0.001
Normal	*	*	*
BMI*time			
time*Obese	0.8	0.004	<0.001
time*Overweight	-7.5	0.004	<0.001
time*Normal	*	*	*
Model 3			
Time	4.9	0.003	<0.001
BMI			
Obese	-7.5	0.08	<0.001
Overweight	107.8	0.07	<0.001
Normal	*		*
BMI*time		*	
time*Obese	0.5	0.005	<0.001
time*Overweight	-7.2	0.005	<0.001
time*Normal	*	*	*
Model 4			
Time	5.0	0.003	<0.001
BMI			
Obese	-14.5	0.08	<0.001
Overweight	101.8	0.07	<0.001
Normal	*	*	*
BMI*time			
time*Obese	0.6	0.005	<0.001
time*Overweight	-7.2	0.004	<0.001
time*Normal	*	*	
Model 5 (Full model)			
Time	5.1	0.003	<0.001
BMI			
Obese	-13.3	0.08	<0.001
Overweight	106.7	0.07	<0.001
Normal	*	*	*
BMI*time			
time*Obese	0.4	0.005	<0.001
time*Overweight	-7.2	0.004	<0.001
time*Normal	*	*	*

Abbreviations: SE, standard error
NOTE: * Normal BMI category - reference group. The parameter estimates represent the difference in the adjusted mean CD4 count by BMI category. Those overweight has higher mean CD4 counts. b Comparison between baseline BMI categories.
- Normal (≤ 24.9 kg/m^2), Overweight (25.0-29.9 kg/m^2), Obese (≥ 30.0 kg/m^2)
- Underweight individuals were excluded because numbers were too few for meaningful analysis.
- Model 1 includes BMI, baseline CD4 count, baseline VL, viral load over time, age, gender, race, mode of transmission and treatment.
- Model 2 includes Model 1 + alcohol, smoking, and drug use.
- Model 3 includes Model 2 + marital status, education, and type of insurance
- Model 4 includes Model 3 + case management
- Model 5 includes Model 4 + delayed entry into care

Table 4.3: Mixed Model Analysis of the association between Body Mass Index (BMI) and CD4 count stratified by Baseline VL and Delayed entry into care among HIV-infected individuals in South Carolina diagnosed between 1997 and 2010.

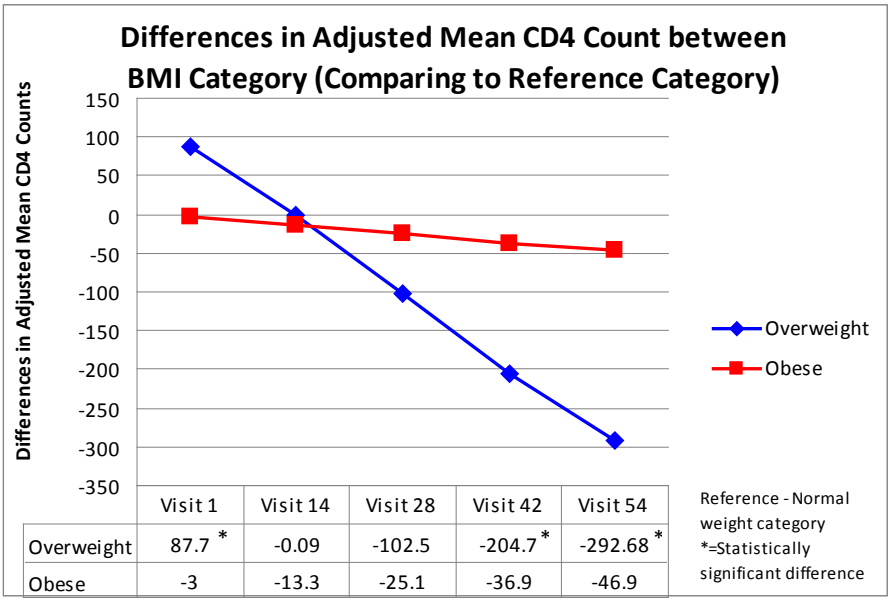
Model	Parameter Estimate (SE)- Baseline VL < 100,000	Parameter Estimate (SE)- Baseline VL > 100,000	Parameter Estimate (SE)- Delayed entry into care < 3 months	Parameter Estimate (SE)- Delayed entry into care > 3 months
Model 5 (Full model)				
Time	4.0 (0.003) [a]	5.3 (0.006) [a]	2.4 (0.004) [a]	6.5 (0.003) [a]
BMI				
Obese	-18.6 (0.08) [a]	63.4 (0.4) [a]	-30.1 (0.2) [a]	-33.1 (0.1) [a]
Overweight	119.0 (0.08) [a]	-97.8 (0.4) [a]	-9.5 (0.2) [a]	74.3 (0.08) [a]
Normal	*	*	*	*
Time*BMI				
time*Obese	-0.7 (0.4) [a]	-7.4 (0.01) [a]	7.0 (0.008) [a]	-3.9 (0.006) [a]
time*Overweight	-5.8 (0.5) [a]	-6.9 (0.008) [a]	-5.3 (0.009) [a]	-7.9 (0.005) [a]
time*Normal	*	*	*	*

Abbreviations: SE, standard error; VL, viral load
[a] p-value <0.001
Normal (≤ 24.9 kg/m^2), Overweight (25.0-29.9 kg/m^2), Obese (≥ 30.0 kg/m^2)
*Normal BMI category was used as the reference category.



	Visit 1	Visit 14	Visit 28	Visit 42	Visit 54
Normal	467.66	524.24	590.25	656.26	712.84
Overweight	555.34	524.15	487.75	451.36	420.16
Obese	464.46	510.95	565.18	619.41	665.9

Figure 4.1: Adjusted CD4 count means by Body Mass Index (BMI) category



	Visit 1	Visit 14	Visit 28	Visit 42	Visit 54
Overweight	87.7 *	-0.09	-102.5	-204.7 *	-292.68 *
Obese	-3	-13.3	-25.1	-36.9	-46.9

Reference - Normal weight category
*=Statistically significant difference

Figure 4.2: Differences in adjusted CD4 count means by Body Mass Index (BMI) category

CHAPTER 5

LONGITUDINAL ASSOCIATION OF THE INTERACTION OF GENDER AND BODY MASS INDEX (BMI) ON HIV DISEASE PROGRESSION

5.1 Introduction

Evidence to support an association between gender and HIV progression has varied. Some studies have found no association between gender and HIV progression, reporting that progression to AIDS was similar between men and women as was the risk of developing a CD4 cell count below 200 cells/mm^3 and the risk of dying of AIDS.[11 68] However, other studies have reported differences in CD4 count by gender.[8 14-16 25 69] Pre-HAART, progression to AIDS and to death was marginally slower in women than in men, suggesting higher CD4 cell counts offer no significance.[15] After HAART initiation, women had higher CD4 counts and the difference in CD4 count between men and women increased over time.[8 14 16 25 69] Some studies report that women were more likely to experience an HIV/AIDS-related event compared to men and had an increased risk of death even after adjustment for HAART use.[16] However, a recent study reported that post-HAART women have lower risks of HIV-AIDS-related events such as AIDS dementia, tuberculosis and Karposi's sarcoma.[8] While gender differences in HIV progression could be due to disparities in access to care, adherence, or retention, other factors such as BMI may play a greater role in explaining the difference.

Earlier studies that have assessed the relationship between BMI and HIV progression have produced mixed results. Pre-HAART research has shown either no association[20 22] or that HIV-infected individuals with higher BMI levels are less likely to progress to AIDS and die as compared to those individuals with normal weight (BMI: $\leq$ 24.9 kg/m^2).[17 24 60] However, in the post-HAART era, the overweight and obese categories may be differentially associated with disease progression and survival. It is unclear whether this association is different in females and males. While the calculation of BMI is not gender specific, the immune response to weight can be gender specific and could explain the difference in immunological response to HIV, treatment, and disease progression between men and women.[70]

This study is essential since it was conducted in the southern United States, an area that suffers from one of the highest burdens of HIV-infected individuals,[1] and overweight and obese individuals.[19] It investigates the gender differences in the longitudinal association of BMI at HIV diagnosis with disease progression as evaluated by CD4 counts obtained during routine medical care. To our knowledge, this is the first study to determine whether the association between BMI and HIV progression differs by gender.

5.2 Methods

Study Participants

Individuals included in this cohort study received care at the Ryan White Clinic in Columbia, SC. Participants were eligible if they were diagnosed with HIV-infection from January 1, 1997 through December 31, 2010, were at least 18 years of age, had weight and height measurements within three months of HIV diagnosis, were HAART-naïve,

and had at least one follow-up visit (within six months) after entering into care. Pregnant individuals and those diagnosed with AIDS at the initial visit were excluded. This study was approved by the University of South Carolina Institutional Review Board.

The power analysis, using the difference between mean CD4 counts by BMI category from past research, determined that at least 85 HIV-infected individuals are needed in each group to ensure an 80% power for the study. Investigators abstracted de-identified data from 409 medical records. However, since there were only 13 underweight (BMI: <18.5 kg/m^2) HIV-infected individuals and 2 transgendered HIV-infected individuals, they were excluded from the analyses. A total of 394 individuals were included in the final analyses.

Variables

Outcome: CD4 cell count (cells/mm^3) was the outcome evaluated for this study and was assessed over the course of medical care follow-up. CD4 cell count was used to stage disease and is examined routinely by providers to determine when to initiate HAART and to assess response to treatment. CD4 cell count was used as a continuous variable in the analysis.

Exposure: Body mass index at diagnosis and gender were the main exposure variables. BMI was estimated by dividing weight in kg by height (measured at diagnosis) in m^2 measured within three months after diagnosis, and was grouped into three categories: normal (<25 kg/m^2), overweight (25-29.5 kg/m^2), and obese (≥ 30 kg/m^2). Gender was grouped as male and female.

Time varying covariates: HIV viral load (VL) (copies/mL) was collected at diagnosis and monitored over the course of follow-up to assess ongoing response to

treatment. HAART use was defined as any prescription for HIV medication over the course of medical care. All data was extracted from the participants' medical records.

Other variables recorded at baseline include age, race/ethnicity, marital status, education, type of insurance, use of case management, alcohol use, smoking status, drug use, mode of transmission, and delayed entry into care (defined later). Age was grouped into the following five categories when included in the multivariate analysis: < 20; 20-29; 30-39; 40-49; 50-59; and $\geq$ 60. The following categories were used for race/ethnicity: White, non-Hispanic; Black, non-Hispanic; Hispanic; Other; and Unknown. Education was grouped into these categories: no high school diploma, high school diploma, associate degree, bachelor degree, master's degree, or doctoral degree. Type of insurance was based on primary insurance and was clustered into these categories: Medicare; Medicaid; Private Insurance or none (includes individuals enrolled in the AIDS Drug Assistance Program). Mode of transmission was grouped into four categories: heterosexual, men who have sex with men (MSM), injection drug users, or no identified risk/no reported risk (NIR/NRR). Given that timely linkage to care has the potential to improve health outcomes and prevent secondary HIV transmission,[61] the delayed entry into care variable was used as a covariate to adjust for differences between those who seek care early versus those who do not. Delayed entry into care was determined by subtracting the date of diagnosis from the date of first visit to the clinic, and was grouped into the two categories: $\leq$3 months and >3 months.[62] When an individual is diagnosed with HIV at the Ryan White Clinic, he or she is offered the services of a case manager to help the individual access care and other support services. Case management was defined as present if the individual had an assigned case manager and absent otherwise. We

adjusted for this variable because there may be a difference in clinical care outcome associated with case management status. Current alcohol use, current smoking status, and current drug use were all assessed by yes or no questions. Visit number was entered into the analysis to control for time in study and was measured in months. Therefore, the first visit represented time point one, the second visit represented time point two, and so forth.

Statistical Analyses

Demographic and clinical characteristics of the participants were compared across the two gender categories, using means and standard error (SE) for continuous variables and number (n) and percent (%) for categorical variables. Differences in clinical characteristics were compared using t-test for continuous variables and Pearson χ^2, Fisher's exact, or Kruskal-Wallis tests for categorical variables as appropriate.

To determine the effects of BMI at diagnosis and gender on longitudinal CD4 cell counts, data were analyzed using mixed regression models and were stratified by gender. Age group, race/ethnicity, use of case management, marital status, education, insurance type, delayed entry into care, mode of transmission, alcohol use, smoking status, drug use, CD4 count at diagnosis, and HIV VL at diagnosis and overtime were all adjusted for in the analysis given their relationship to BMI or HIV progression. The mixed model analysis was also stratified by baseline VL and delayed entry into care. For this analysis, baseline VL was grouped into ≤100,000 copies/mL plasma and >100,000 copies/mL plasma. Adjusted CD4 count means were determined and graphed at five different time points by using an lsmeans statement in the mixed regression model, with tukey option to determine differences between BMI categories by gender. The five time points were determined from quantiles obtained from a univariate analysis. Sensitivity analyses were

conducted to test whether loss to follow-up (i.e. those with $\geq$ 6 months after the last documented visit) impacted the results and the data were re-analyzed using the inverse-probability weighting method as suggested by Robins et al.[63] Statistical analyses were performed using SAS 9.2 (SAS Institute; Cary, North Carolina). For all analyses, the α-level was set at 0.05.

5.3 Results

The study population's mean BMI was 27.4 kg/m^2 and was higher in females (30.1 kg/m^2) than in males (25.8 kg/m^2). Gender was not related to age, race, educational attainment, use of case manager, smoking, and delayed entry into care. However, BMI, marital status, insurance, alcohol use, drug use, mode of transmission, HAART use, CD4 count at diagnosis, and HIV viral load at diagnosis were all significantly different among the gender categories. Females were more likely to be older (35.3 years of age), to be overweight (43.0% versus 16.8%), receive care after three months of diagnosis (57.7% versus 56.3%) have a higher overall mean CD4 count at diagnosis (551.4 cells/mm^3), and a lower log HIV viral load at diagnosis (8.7 logs) compared to males.

BMI and CD4 count (longitudinal)

Follow-up time was similar across gender (P=0.074), although females (7.5 years) had a marginally higher follow-up time compared to males (6.6 years). CD4 count mean was higher in females (517.3 cells/mm^3) than in males (473.6 cells/mm^3).

A mixed model was analyzed to determine whether CD4 count change over time is different among BMI between males and females (Table 2). There were significant differences in mean CD4 count for the overweight and obese categories when compared to the normal weight category among males and females. Among males, compared with

the normal weight individuals in the full model, the obese category had significantly larger increases in CD4 count (6.1 cells/mm^3, *P* = <0.001) versus the overweight category (0.5 cells/mm^3, *P* = <0.001). Among females, compared with the normal weight individuals in the full model, the obese category had significantly larger increases in CD4 count (4.9 cells/mm^3, *P* = <0.001) versus the significant decrease in CD4 count in the overweight category (-2.9 cells/mm^3, *P* = <0.001). For an example, after visit one, it is predicted that obese HIV-infected females at diagnosis will experience a 4.9 cells/mm^3 increase in CD4 count, while overweight HIV-infected females will experience a 2.9 decrease in CD4 count. The obese males had larger increases in CD4 count over time compared to obese females, but the overweight females had larger decreases in CD4 count over time compared to the increase in overweight males. The results of the sensitivity analyses using the inverse-probability weighting method to account for loss to follow up (n=73) were qualitatively similar to the results presented.

Overall, mean CD4 count increased over time for females and males. Figure 1 shows a significant interaction between BMI and CD4 count using the adjusted mean CD4 counts. The adjusted mean CD4 count was higher at the outset for the obese males, followed by overweight females and males. Over time the CD4 count trend increased among all groups, except the overweight female category, which decreased over time (Figure 1). The second graph (B) displays the differences in adjusted mean CD4 counts when compared to the normal weight group. The overweight males and females had the greatest difference in adjusted mean CD4 counts when compared to the normal weight males and females. The adjusted mean CD4 counts at each visit were not statistically different from the normal weight group's adjusted means.

The mixed model analysis among those with lower baseline VL values (<100,000 copies/mL plasma) showed a significant change in CD4 count over time between BMI categories among males and females (Table 3). In males, significantly larger increases in CD4 count were seen in the obese category (3.8 cells/mm^3) versus the overweight category who experienced decreases in CD4 count (-1.2 cells/mm^3). In females, significantly larger increases in CD4 count were seen in the obese category (3.4 cells/mm^3) versus the overweight category who experienced decreases in CD4 count (-3.8 cells/mm^3). Among those with higher baseline VL values (>100,000 copies/mL plasma), significant changes in CD4 count over time was seen between BMI categories among males and females. In males, significantly larger decreases in CD4 count were seen in the obese category (-2.6 cells/mm^3) and the overweight category (-0.5 cells/mm^3). In females, significant decreases in CD4 count were seen in the obese category (-13.2 cells/mm^3) and the overweight category (-2.0 cells/mm^3).

For those individuals who entered care within three months of diagnosis, significant changes in CD4 count over time was seen in the BMI categories when compared to the normal weight patients among males and females (Table 3). In males, significant increases in CD4 count were seen in the obese category (1.2 cells/mm^3) versus the overweight category that experienced decreases in CD4 count (-0.3 cells/mm^3). In females, significantly larger increases in CD4 count were seen in the obese category (3.3 cells/mm^3) versus the overweight category that experienced decreases in CD4 count (-4.0 cells/mm^3). In those who received care after three months of diagnosis, significant changes in CD4 count over time was seen in the BMI categories when compared to the normal weight patients among males and females. In males, significantly larger increases

in CD4 count were seen in the obese category (2.6 cells/mm^3) versus the overweight category that experienced decreases in CD4 count (-10.3 cells/mm^3). In females, significant increases in CD4 count were seen in the obese (9.9 cells/mm^3) versus the overweight category that experienced decreases in CD4 count (-2.3 cells/mm^3) when compared to the normal weight category.

5.4 Discussion

This cohort of HIV–infected individuals experienced CD4 counts that were highest at time of diagnosis among obese females, followed by overweight females and obese males. Over time, CD4 count increases were highest for the obese males, followed by the obese females and overweight males, but decreased for overweight females. While high BMI among HIV-infected individuals is linked to increased CD4 count over time in males and females, moderately high BMI was not, particularly among females. This implies that the immune recovery gained from HAART and the effect is different among males and females.

Several studies reported that obese HIV-infected individuals had better survival over time.[22 24 60] Shor-Posner et al. study population included men (n=82) and women (n=43) and had a higher proportion of obese men (69.6%) than obese females (30%). They discovered that CD4 cell count over time was higher for obese individuals compared with the non-obese group (376 cells/mm^3 vs. 364 cells/mm^3), although not statistically significant.[22] Another study included only women (n=871) and reported a significant difference in CD4 count among BMI categories, with the overweight group experiencing larger increases in CD4 counts, followed by those of normal weight and underweight.[24] The results of this study were different from the women in our study.

Shuter et al. study population included men (n=103) and women (86) and also had a higher proportion of women (32.5%) who were overweight compared to men (12.6%). They learned that overweight individuals progressed more slowly to AIDS, and CD4 count was not independently predictive of progression to AIDS. [60]

A post-HAART study recently investigated the relationship between BMI and HIV progression by following HIV-infected men (n=712) and women (n=203) starting treatment between 1998 and 2008 and discovered that overweight HIV-infected individuals experienced a 12-month CD4 count gain in women (+ 9 cells/ uL), but not in men (-1 cells/uL), while the normal weight (-65 cells/uL) and obese categories (-12 cells/uL) experienced a reduction.[25] In addition, they learned that the interaction of sex and BMI did not appear to be an important determinant of CD4 count change (*P*=0.16), which is different from our study results. Our study determined that the association between BMI and CD4 count change over time is distinct in men and women, with a significantly larger increase in CD4 counts in obese men compared to obese women.

One researcher proposed that there may be an ideal BMI range for immune recovery once on treatment for a year, with immune reconstitution reaching a plateau in the range of BMI 25 to 30 kg/m.[2 25] This could explain why overweight individuals are experiencing higher mean absolute CD4 counts compared to obese individuals. A recent post-HAART study included men (n=1556) and women (n=126) and reported that, obese HIV-infected individuals had smaller increases in CD4 counts (+69 cells/mm^3) compared to those in the overweight (+116 cells/mm^3) and normal weight categories (+102 cells/mm^3).[54]

The following explanations could validate our results. First, hormones, particularly estrogen, may be responsible for fat distribution and storage in non-HIV populations and could explain the difference in immune response in HIV-infected men and women.[70 71] Secondly, women reportedly have healthier behaviors and higher adherence rates to medication, which could explain higher overall mean CD4 count.[8] The women in our study had a higher CD4 count and lower VL at diagnosis compared to men, but were less likely to be on HAART. However, overweight males who had a baseline VL ≤100,000 and who entered care within three months of diagnosis had higher increases in CD4 count compared to overweight females. Thirdly, leptin is a satiety hormone that circulates directly proportional to weight.[64] Leptin is also known to increase with inflammation. Obese individuals have a higher concentration of leptin compared to overweight and normal weight individuals. Given HIV causes inflammation and CD4 cells have leptin receptors and has a proliferation effect, it could explain the increase or higher levels of CD4 among obese individuals. Fourthly, obesity is surplus of energy in the form of stored fat. [19] Obesity spares protein from being used as an energy source, which aids in maintaining immune function and helps to offset the high metabolic rate of HIV. This could explain the protective effect of obesity on CD4 levels. Lastly, some proclaim that since untreated HIV-infection is associated with weight loss, individuals in the normal weight category are a mixed group consisting of both individuals who were normal weight pre-diagnosis, and those who were overweight but lost weight because of HIV-infection in the period preceding their diagnosis.[24] This is an example of reverse causality and a potential confounder in all studies evaluating this question.

To avoid weight change being mis-classified into another BMI category, height and weight was collected within three months of diagnosis. If reverse causality is contributing to the association between BMI and HIV progression, then the BMI characteristics of the source population are likely important. As HIV is diagnosed at an earlier stage, before wasting sets in, the HIV-infected population is similar to the general population with respect to BMI. In our study population the mean BMI was 27.4 kg/m^2, and overweight and obesity prevalence was 30% and 26.8%, which is similar to the prevalence of overweight (35.4%) and obesity (31.5%) in general HIV-uninfected population in South Carolina.[19] Similar characteristics were discovered between our study population and all HIV-infected individuals in the entire state of South Carolina, with respect to race (Black: 74.2% versus 76%) and mode of transmission (MSM: 33.1% versus 37.1%).[66] Given the comparisons between our study cohort and the overall HIV-infected population in South Carolina, reverse causality most likely did not influence our results.

Several limitations may have impacted our results. First, we were unable to make an hypothesis that included the underweight BMI category. Nonetheless, past research has shown that underweight individuals normally have a faster progression to AIDS and death compared to other BMI categories.[17 24 25] Second, the treatment variable only measured whether individuals received HAART throughout the course of their HIV infection. We did not assess time spent on HAART. Third, the secular change of CD4 count is impacted as more HIV-infected individuals are prescribed HAART and medication efficacy has increased, which could potentially attenuate the associations.[68] Fourth, our population consisted of mostly black HIV-infected individuals and the results

may not be generalizable to other populations. Fifth, the alcohol use and drug use variables only captured whether individuals were socially participating in these factors and not the frequency of use. Sixth, we did not collect any information on gynecological factors (i.e. contraception use, menopause status) that could potentially confound our results. Finally, there is the likelihood of residual confounding such as measurement error of a particular variable.

Our study has several strengths. First, we examined the post-HAART longitudinal association between BMI at baseline and HIV progression in a southern state. In contrast, the majority of other studies from other regions focused on survival rather than continuous immune function. Second, unlike previous research, we adjusted for many potential confounders including delayed entry into HIV medical care and use of case management. Entry into HIV medical care is essential for access to antiretroviral therapy and facilitates the delivery of important prevention education to reduce HIV transmission. In addition, retention in care is necessary to monitor response to therapy. Therefore, adjusting for delayed entry into care is important to accurately determine the association between BMI and HIV progression as it relates to both. Whereas our results were similar to Koethe's et al. results in regards to mean CD4 counts, they were not able to adjust for educational attainment or insurance type.[25] The current study was able to gain an improved estimation of the relationship between BMI at diagnosis and CD4 count over time by adjusting for these variables. Third, our population of individuals with different stages of HIV disease, allows us to determine if the relationship under study exists in HIV-infected individuals with different levels of immune impairment. Fourth, this investigation includes fourteen years of follow-up (i.e. those diagnosed in 1997) allowing

us to assess CD4 count over a long period. Finally, the inverse probability weighting method used to evaluate the possible impact of loss to follow-up provided materially similar results to those reported.

Our study demonstrated that male HIV-infected individuals who were obese at diagnosis had greater increases in CD4 counts over time when compared to female HIV-infected individuals who were obese at diagnosis. Although obese males experience higher CD4 count increases over time, obese females who seek care early and have a lower at diagnosis VL experience a better prognosis of HIV. This suggests that innovative strategies are needed to determine ways to improve differences in immune response between genders. Future studies should evaluate differences in hormonal activity on CD4 counts over time between genders, especially among females, to learn more about the difference in progression between males and females.

Table 5.1: Baseline characteristics of South Carolina HIV-infected individuals diagnosed between 1997 and 2010 by Gender.

	Overall (n=394)		P^a
Characteristic	**Male (n=245)**	**Female (n=149)**	
Age	34.9 ± 10.4	35.3 ± 10.9	0.684
Body Mass Index			
Obese	126 (51.4%)	44 (29.5%)	
Overweight	41 (16.8%)	64 (43.0%)	
Normal	78 (31.8%)	41 (27.5%)	<0.001
Race			
White	65 (26.5%)	25 (16.8%)	
Black	172 (70.2%)	122 (81.9%)	
Hispanic	3 (1.2%)		
Other	5 (2.0%)	2 (1.3%)	0.090
Marital Status			
Single	163 (66.5%)	78 (52.3%)	
Married	19 (7.8%)	28 (18.8%)	
Divorced	36 (14.7%)	34 (22.8%)	
Widowed	6 (2.4%)	8 (5.4%)	
Partnered	20 (8.2%)		
Unknown	1 (0.4%)	1 (0.7%)	<0.001
Education			
No HS Diploma	31 (12.7%)	31 (20.8%)	
High School Diploma	100 (40.8%)	40 (26.8%)	
Associate Degree	11 (4.5%)	12 (8.0%)	
Bachelor Degree	16 (6.5%)	8 (5.4%)	
Master's Degree	5 (2.0%)	4 (2.7%)	
Doctorate Degree	2 (0.8%)	1 (0.7%)	
Unknown	80 (32.7%)	53 (35.6%)	0.071
Insurance			
Medicare	41 (16.7%)	29 (19.5%)	
Medicaid	9 (3.7%)	34 (22.8%)	
Private Insurance	58 (23.7%)	37 (24.8%)	
None	137 (55.9%)	49 (32.9%)	<0.001
Followed by Case Manager			
Yes	105 (42.9%)	65 (43.6%)	
No	140 (57.1%)	84 (56.4%)	0.882
Alcohol Use			
Yes	179 (73.0%)	62 (41.6%)	
No	58 (23.7%)	78 (52.4%)	
Unknown	8 (3.3%)	9 (6.0%)	<0.001
Smoking			
Yes	145 (59.2%)	72 (48.3%)	
No	91 (37.1%)	69 (46.3%)	
Unknown	9 (3.7%)	8 (5.4%)	0.104
Drug Use			
Yes	99 (40.4%)	42 (28.2%)	
No	137 (55.9%)	98 (65.8%)	
Unknown	9 (3.7%)	9 (6.0%)	0.039
Mode of Transmission			
Heterosexual	92 (37.5%)	135 (90.6%)	
MSM	123 (50.2%)		

IDU	16 (6.6%)	4 (2.7%)	
NIR/NRR	14 (5.7%)	10 (6.7%)	<0.001
Delayed entry into care			
< than 3 months	107 (43.7%)	63 (42.3%)	
> than 3 months	138 (56.3%)	86 (57.7%)	0.787
HAART use			
Yes	223 (91.0%)	124 (83.2%)	
No	22 (9.0%)	25 (16.8%)	0.021
CD4 count at diagnosis	465.6 ± 218.4	551.4 ± 297.2	<0.001
Log HIV Viral Load at diagnosis	4.3 ± 0.9	3.8 ± 1.0	<0.001

NOTE: Mean and standard deviation are shown for Body mass Index, Age, CD4 count at diagnosis, HIV Viral Load at diagnosis; Transgender was not included in the table.

Normal (≤ 24.9 kg/m^2), Overweight (25.0-29.9 kg/m^2), Obese (≥ 30.0 kg/m^2)

[a] Comparison between baseline BMI and gender stratas

Table 5.2: Mixed Model Analysis of the association between Body Mass Index (BMI) and CD4 count among HIV-infected individuals diagnosed in South Carolina between 1997 and 2010 stratified by Gender.

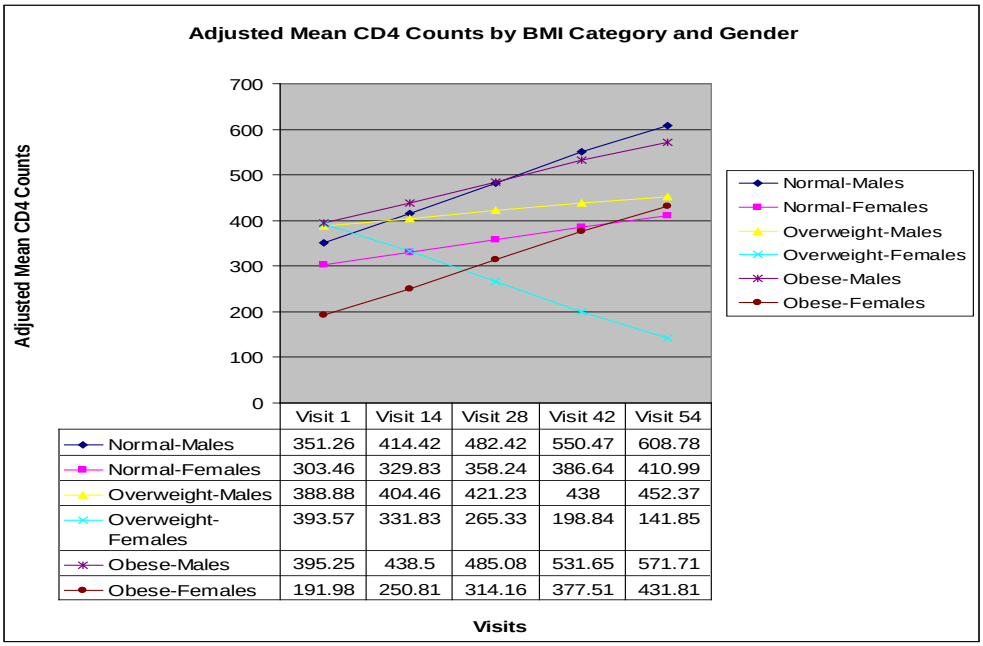
Model	Parameter Estimate	Standard Error (SE[a])	*P*[b]
MALES			
Full Model			
Time	5.2	0.003	<0.001
BMI			
Obese	-4.9	0.1	<0.001
Overweight	43.1	0.09	<0.001
Normal	*	*	*
time*BMI			
time*Obese	0.4	0.007	<0.001
time*Overweight	-5.7	0.006	<0.001
time*Normal	*	*	*
FEMALES			
Full Model			
Time	3.0	0.005	<0.001
BMI			
Obese	-123.9	0.1	<0.001
Overweight	94.5	0.1	<0.001
Normal	*	*	*
time*BMI			
time*Obese	1.9	0.008	<0.001
time*Overweight	-5.9	0.007	<0.001
time*Normal	*	*	*

NOTE: * Normal BMI category was used as the reference group. The parameter estimates represent the difference in the adjusted mean CD4 count by BMI category. Those overweight has higher mean CD4 counts.
Normal ($\leq$ 24.9 kg/m^2), Overweight (25.0-29.9 kg/m^2), Obese ($\geq$ 30.0 kg/m^2)
a SE=Standard Error
b Comparison between baseline BMI categories

Table 5.3: Mixed Model Analysis of the association between Body Mass Index (BMI) and CD4 count stratified by Baseline VL and Delayed entry into care among HIV-infected individuals in South Carolina diagnosed between 1997 and 2010 by Gender.

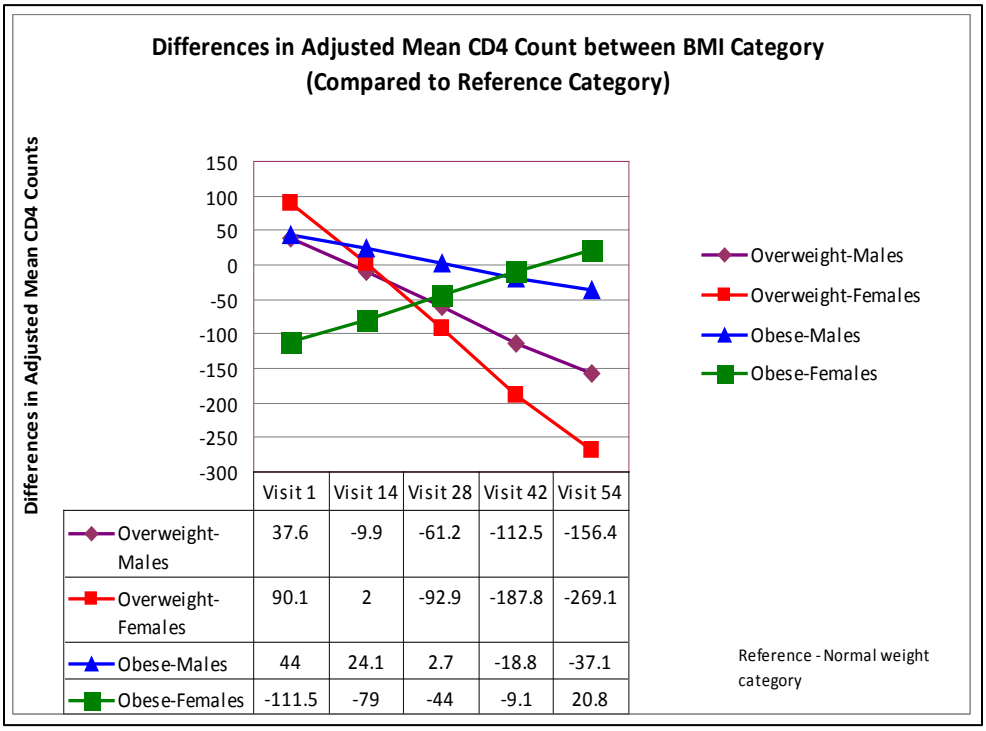
Model	Parameter Estimate (SE)- Baseline VL < 100,000	Parameter Estimate (SE)- Baseline VL > 100,000	Parameter Estimate (SE)- Delayed entry into care < 3 months	Parameter Estimate (SE)- Delayed entry into care > 3 months
Model 5 (Full model)				
Males				
Time	4.6 (0.004) [a]	5.8 (0.006) [a]	7.5 (0.004) [a]	2.2 (0.004) [a]
BMI				
Obese	-46.9 (0.1) [a]	154.7 (1.2) [a]	-1.7 (0.1) [a]	-205.7 (0.4) [a]
Overweight	117.7 (0.1) [a]	510.7 (0.4) [a]	64.0 (0.1) [a]	256.3 (0.4) [a]
Normal	*	*	*	*
Time*BMI				
time*Obese	-0.8 (0.009) [a]	-8.4 (0.02) [a]	-6.3 (0.01) [a]	0.4 (0.01) [a]
time*Overweight	-5.8 (0.006) [a]	-6.3 (0.01) [a]	-7.8 (0.006) [a]	-12.5 (0.03) [a]
time*Normal	*	*	*	*
Females				
Time	3.9 (0.005) [a]	-5.8 (0.06) [a]	2.4 (0.005) [a]	2.0 (0.01) [a]
BMI				
Obese	32.9 (0.1) [a]	-42.8 (1.4) [a]	-137.1 (0.2) [a]	-431.8 (2.5) [a]
Overweight	-96.2 (0.2) [a]	-114.4 (1.6) [a]	32.4 (0.2) [a]	-135.6 (2.7) [a]
Normal	*	*	*	*
Time*BMI				
time*Obese	-0.5 (0.008) [a]	-7.4 (0.08) [a]	0.9 (0.009) [a]	7.9 (0.02) [a]
time*Overweight	-6.1 (0.007) [a]	3.8 (0.06) [a]	-6.4 (0.008) [a]	-4.3 (0.02) [a]
time*Normal	*	*	*	*

Abbreviations: SE, standard error; VL, viral load
Normal ($\leq$ 24.9 kg/m^2), Overweight (25.0-29.9 kg/m^2), Obese ($\geq$ 30.0 kg/m^2)
[a] p-value <0.001
*Normal BMI category was used as the reference category.



	Visit 1	Visit 14	Visit 28	Visit 42	Visit 54
Normal-Males	351.26	414.42	482.42	550.47	608.78
Normal-Females	303.46	329.83	358.24	386.64	410.99
Overweight-Males	388.88	404.46	421.23	438	452.37
Overweight-Females	393.57	331.83	265.33	198.84	141.85
Obese-Males	395.25	438.5	485.08	531.65	571.71
Obese-Females	191.98	250.81	314.16	377.51	431.81

Figure 5.1: Adjusted CD4 count means by BMI and Gender Categories



	Visit 1	Visit 14	Visit 28	Visit 42	Visit 54
Overweight-Males	37.6	-9.9	-61.2	-112.5	-156.4
Overweight-Females	90.1	2	-92.9	-187.8	-269.1
Obese-Males	44	24.1	2.7	-18.8	-37.1
Obese-Females	-111.5	-79	-44	-9.1	20.8

Figure 5.2: Differences in adjusted CD4 count means by BMI and Gender categories

CHAPTER 6

LONGITUDINAL CHANGES IN CARDIOVASCULAR DISEASE RISK MARKERS AND THEIR ASSOCIATION WITH BODY MASS INDEX (BMI) IN HIV-INFECTED INDIVIDUALS

6.1 Introduction

Once highly active antiretroviral treatment (HAART) was initiated, the wasting syndrome became a decreased presence among HIV-infected population. One of the complications related to HAART was weight gain, which lead to an increased prevalence of overweight and obesity among HIV-infected individuals.[1 21] Approximately two out of every three adults are overweight (i.e. BMI = 25-29.9) and more than one-third of adults are obese (i.e. BMI ≥30), with non-Hispanic blacks having the highest age-adjusted rates of obesity in the US.[19] South Carolina (30.8%) is one of thirteen states that have a prevalence of obesity equal to or greater than 30% in the general population. Some studies have reported a lower prevalence of obesity among HIV-infected populations versus the general population,[52 53] whereas others have reported a higher prevalence.[24 30] Although the effect of HAART in causing obesity in HIV-infected patients may result in a moderately slower progression to AIDS due to the survival gain afforded by elevated BMI,[24] an increase in non-AIDS related outcomes, including metabolic abnormalities, have developed and has led to increased risk of morbidity and mortality.[54]

Abdominal obesity, hyperlipidemia, hypertension, and insulin resistance are examples of these abnormalities.[55] One of the primary causes for the rising prevalence of the abnormalities is the rising prevalence of overweight and obesity in non-HIV and HIV-infected individuals, leading to an increased chance of developing adverse cardiovascular outcomes such as myocardial infarction and stroke. [21] As suggested by some studies, inflammation caused by the long-term effects of HIV or HAART may also play a greater role in causing these outcomes among HIV-infected individuals, particularly because inflammation is known to be predictive of cardiovascular disease (CVD) outcomes among non-HIV populations.[72 73]

One study reported that BMI was useful in predicting cardiovascular disease (CVD) risk among their HIV population.[28] Given the increased risk of CVD outcomes in non-HIV obese individuals, it is important to study this association among various HIV-infected populations and determine if this association is differentially affected between BMI categories. The importance of this study is that it was conducted in the southern United States, a region that has the highest prevalence of HIV-infected individuals,[1] overweight and obese individuals, and cardiovascular disease.[19] A limited number of studies have evaluated the changes in metabolic abnormalities over time by BMI group. This study investigates the longitudinal association of BMI at HIV diagnosis with metabolic abnormalities as evaluated by markers of cardiovascular disease (i.e. fasting blood glucose, high-density lipoprotein (HDL) and low-density lipoprotein (LDL), and systolic and diastolic blood pressure measurements) obtained during routine medical care.

6.2 Methods

Study population and procedure

Individuals included in this cohort study received care at the Ryan White Clinic in Columbia, SC. Eligible participants were diagnosed with HIV-infection from January 1, 1997 through December 31, 2010, were at least 18 years of age, had weight and height measurements within three months of HIV diagnosis, were HAART-naïve, and had at least one follow-up visit (within six months) after entering into care. Individuals were excluded if pregnant when diagnosed or diagnosed with AIDS at the initial visit. The University of South Carolina Institutional Review Board approved this study.

Using the difference between mean CD4 counts by BMI category from past research, the power analysis determined that at least 85 HIV-infected individuals are needed in each group to ensure an 80% power for the study. Investigators extracted de-identified data from 409 medical records. However, since there were only 13 underweight (BMI: <18.5 kg/m^2) HIV-infected individuals, this category was excluded from the analyses. A total of 396 individuals were included in the final analyses.

Variables

Outcome: Five outcomes were evaluated for this study: Fasting blood glucose (mg/dL), HDL (mg/dL), LDL (mg/dL), Systolic blood pressure (SBP) (mmHg), and Diastolic blood pressure (DBP) (mmHg) levels were assessed over the course of medical care follow-up. These outcomes were used to determine risk of illness and cardiovascular disease, and the effects of HIV alone and with HAART. Each outcome was used as a continuous variable in the analysis.

Exposure: The main exposure variable was BMI at diagnosis and was estimated by dividing weight in kg by height (measured at diagnosis) in m^2 measured within three months after diagnosis. BMI was grouped into three categories: normal (<25 kg/m^2), overweight (25-29.5 kg/m^2), and obese (≥30 kg/m^2).

Time varying covariates: CD4 cell count (cells/mm^3) and HIV viral load (VL) (copies/mL) were collected at diagnosis and monitored over the course of follow-up to estimate disease stage, to determine when to start HAART, and to assess ongoing response to treatment. Fasting blood glucose, HDL, LDL, SBP, and DBP were also collected at diagnosis. HAART use and any medication prescribed for abnormalities in HDL/LDL, SBP/DBP measurements, and blood glucose levels were defined as any prescription for HIV medication, hyperlipidemia, hypertension or diabetes respectively, over the course of medical care. All data was extracted from the participants' medical records.

Additional variables documented at baseline include age, gender, race/ethnicity, marital status, education, type of insurance, use of case management, alcohol use, smoking status, drug use, mode of transmission, and delayed entry into care (defined later). Age was categorized into the following five categories when included in the multivariate analysis: < 20; 20-29; 30-39; 40-49; 50-59; and ≥ 60. The following categories were used for race/ethnicity: White, non-Hispanic; Black, non-Hispanic; Hispanic; Other; and Unknown. Education was grouped into these categories: no high school diploma, high school diploma, associate degree, bachelor degree, master's degree, or doctoral degree. Type of insurance was based on primary insurance and was clustered

into these categories: Medicare; Medicaid; Private Insurance or none (includes individuals enrolled in the AIDS Drug Assistance Program). Mode of transmission was grouped into four categories: heterosexual, men who have sex with men (MSM), injection drug users, or no identified risk/no reported risk (NIR/NRR). Timely linkage to care is likely to improve health outcomes and prevent secondary HIV transmission, [61] thus the delayed entry into care variable was added as a covariate to adjust for differences between those who seek care early versus those who do not. Delayed entry into care was determined by subtracting the date of diagnosis from the date of first visit to the clinic, and was categorized into two categories: $\leq$3 months and >3 months.[62] The services of a case manager are offered when a HIV-infected individual is referred to care and to help the individual access care and other support services. Case management was defined as present if the individual had an assigned case manager and absent otherwise. We adjusted for this variable because there may be a difference in clinical care outcome associated with case management status. Current alcohol use, current smoking status, and current drug use were all assessed by yes or no questions. Visit number was entered into the analysis to control for time in study, which was measured in months. Therefore, the first visit represented time point one, the second visit represented time point two, and so forth.

Statistical Analyses

Demographic and clinical characteristics of the participants were compared across the three BMI categories, using means and standard error (SE) for continuous variables and number (n) and percent (%) for categorical variables. Differences in clinical characteristics were compared using t-test for continuous variables and Pearson χ^2, Fisher's exact, or Kruskal-Wallis tests for categorical variables as appropriate.

To determine the association between BMI at diagnosis and the five metabolic abnormalities, data were analyzed using mixed regression models. Age group, race/ethnicity, gender, use of case management, marital status, education, insurance type, delayed entry into care, mode of transmission, alcohol use, smoking status, drug use, fasting blood glucose at diagnosis, HDL and LDL at diagnosis, and SBP and DBP measurements at diagnosis, HAART use, other medication uses, CD4 count at diagnosis and overtime, and HIV VL at diagnosis and overtime were all adjusted for in the analysis given their relationship to BMI and/or the metabolic abnormalities. The adjusted means for each outcome were calculated and graphed at five different time points by using an lsmeans statement in the mixed regression model, with tukey option to determine differences between BMI categories. The five time points were determined from quantiles obtained from a univariate analysis. Sensitivity analyses were conducted to test whether loss to follow-up (i.e. those with $\geq$ 6 months after the last documented visit) impacted the results and the data were re-analyzed using the inverse-probability weighting method as suggested by Robins et al.[63] Statistical analyses were performed using SAS 9.2 (SAS Institute; Cary, North Carolina). For all analyses, the α-level was set at 0.05.

6.3 Results

Baseline Characteristics

The study population was considered overweight, with a 27.4 kg/m^2 mean baseline BMI, and mean age was 35 years. This cohort was primarily male (61.9%), black (74.2%), and single (61.1%); approximately 35.3% had at least a high school diploma, 47.2% did not have insurance, 57.1% were not followed by a case manager,

60.9% used alcohol, 54.8% smoked, 59.8% did not report drug use, 55.8% were heterosexual, 56.8% entered care $\geq$ 6 months of diagnosis, and 88.1% were prescribed HAART throughout course of medical care (Table 1).

BMI categories were similar in regards to age, race/ethnicity, marital status, educational attainment, type of insurance, use of case manager, HAART use, cholesterol medication, blood glucose at diagnosis, HDL at diagnosis, LDL at diagnosis, SBP at diagnosis, and DBP at diagnosis. However, significant differences among the BMI categories were found in gender, alcohol use, smoking status, drug use, mode of transmission, delayed entry into care, CD4 count at diagnosis, HIV VL at diagnosis, diabetic medication, and BP medication. When compared to the normal and overweight HIV-infected individuals, obese HIV-infected individuals were more likely to be female (60.4%), non-alcohol users at diagnosis (44.3%), to be non-smokers (53.8%), and had the lowest HIV VL at baseline (4.5 logs), and the highest CD4 count at baseline (575.6 cells/mm^3), highest fasting blood glucose at baseline (106.6 mg/dL), highest HDL at baseline (49.2 mg/dL), highest SBP (130.7 mmHg), and highest DBP (83.3 mmHg).

BMI and fasting blood glucose over time

The overall mean follow-up time was 6.7 years and was similar across the BMI categories (P=0.108). The overall mean for fasting blood glucose over time was 100.3 mg/dL. Mean fasting blood glucose was highest among obese individuals (108.8 mg/dL), followed by overweight individuals (101.5 mg/dL) and normal weight individuals (95.2 mg/dL).

Figure 1 shows a significant interaction between BMI and fasting blood glucose. The adjusted mean fasting blood glucose was higher at the outset for the obese category,

but it decreased over time and was the lowest at the end of follow-up, followed by the overweight and normal weight categories (Figure 1). When compared to the normal weight category, differences in adjusted mean fasting blood glucose were greater among the obese category than the overweight category.

Mixed models were used to determine whether the main effect of fasting blood glucose and fasting blood glucose change over time was different among BMI categories (Table 2). After adjusting for the variables listed in Table 1, there were statistically significant differences in mean fasting blood glucose for the overweight and obese categories when compared to the normal weight category. Compared with the normal weight individuals in the full model, the obese category had significant decreases in fasting blood glucose levels (-0.2 mg/dL, P = <0.001) versus the increase in fasting blood glucose in the overweight category (0.1 mg/dL, P = <0.001). For an example, after visit one, it is predicted that obese HIV-infected individuals at diagnosis will experience a 0.2 mg/dL decrease in fasting blood glucose, while overweight HIV-infected individuals will experience a 0.1 increase in fasting blood glucose.

BMI and HDL over time

The overall mean for HDL over time was 48.1 mg/dL. Mean HDL was highest among overweight individuals (50.6 mg/dL), followed by obese individuals (47.7 mg/dL) and normal weight individuals (46.5 mg/dL).

Overall, HDL decreased slightly over time. Figure 2 shows a significant interaction using between BMI and the adjusted mean HDL. While the HDL was higher at the outset for the overweight and normal weight groups compared to the obese

category, over time the obese group had a larger increase in HDL compared to the overweight and normal weight categories (Figure 2). When compared to the normal weight category, differences in adjusted mean HDL were greater among the obese category than the overweight category.

Mixed models were used to determine whether the main effect of HDL and HDL change over time was different among BMI categories (Table 2). After adjusting for the variables listed in Table 1, there were statistically significant differences in mean HDL for the overweight and obese categories when compared to the normal weight category. Compared with the normal weight individuals in the full model, the obese (0.4 mg/dL, *P* = <0.001) and overweight categories (0.26 mg/dL, *P* = <0.001) had significant increases in HDL levels. For an example, after visit one, it is predicted that obese HIV-infected individuals at diagnosis will experience a 0.4 mg/dL increase in HDL, while overweight HIV-infected individuals will experience a 0.26 increase in HDL.

BMI and LDL over time

The overall mean for LDL over time was 110.5 mg/dL. Mean LDL was highest among overweight individuals (116.1 mg/dL), followed by obese individuals (113.7 mg/dL) and normal weight individuals (104.8 mg/dL).

Overall, LDL decreased over time. Figure 3 shows a significant interaction between BMI and the adjusted mean LDL. The overweight category had a higher LDL at the outset and had the largest decrease in LDL over time, followed by the obese and normal weight categories (Figure 3). When compared to the normal weight category, differences in adjusted mean LDL were greater among the overweight category than the obese category.

Mixed models were used to determine whether the main effect of LDL and LDL change over time was different among BMI categories (Table 2). After adjusting for the variables listed in Table 1, there were statistically significant differences in mean LDL for the overweight and obese categories when compared to the normal weight category. Compared with the normal weight individuals in the full model, the obese (-1.0 mg/dL, *P* = <0.001) and overweight categories (-1.4 mg/dL, *P* = <0.001) had significant decreases in LDL levels. For an example, after visit one, it is predicted that obese HIV-infected individuals at diagnosis will experience a 1.0 mg/dL decrease in LDL, while overweight HIV-infected individuals will experience a 1.4 decrease in LDL.

BMI and SBP over time

The overall mean for SBP over time was 128.9 mg/dL. Mean SBP was highest among obese individuals (132.0 mg/dL), followed by overweight individuals (130.3 mg/dL) and normal weight individuals (126.5 mg/dL).

Figure 4 shows a significant interaction between BMI and the adjusted mean SBP. The adjusted mean SBP was higher at the outset and remained the highest for the overweight category. Both the overweight and obese categories adjusted mean SBP decreased over time, compared to the increase in the normal weight category (Figure 4). When compared to the normal weight category, differences in adjusted mean SBP were greater among the obese category than the overweight category.

Mixed models were used to determine whether the main effect of SBP and SBP change over time was different among BMI categories (Table 2). After adjusting for the variables listed in Table 1, there were statistically significant differences in mean SBP for

the overweight and obese categories when compared to the normal weight category. Compared with the normal weight individuals in the full model, the obese (-1.96 mg/dL, *P* = <0.001) and overweight categories (0.96 mg/dL, *P* = <0.001) had significant decreases in SBP levels. For an example, after visit one, it is predicted that obese HIV-infected individuals at diagnosis will experience a 1.96 mg/dL increase in SBP, while overweight HIV-infected individuals will experience a 0.96 increase in SBP.

BMI and DBP over time

The overall mean for DBP over time was 81.6 mg/dL. Mean DBP was highest among obese individuals (84.2 mg/dL), followed by overweight individuals (82.1 mg/dL) and normal weight individuals (79.9 mg/dL).

Figure 5 shows a significant interaction between BMI and DBP. The adjusted mean DBP was slightly higher at the outset for the normal category, followed by the obese and overweight categories (Figure 5). However over time, the normal weight category had a larger decrease in DBP, while the overweight and obese categories experienced a slight decrease. When compared to the normal weight category, differences in adjusted mean DBP were roughly the same among the obese category and the overweight category.

Mixed models were used to determine whether the main effect of DBP and DBP change over time was different among BMI categories (Table 2). After adjusting for the variables listed in Table 1, there were statistically significant differences in mean DBP for the overweight and obese categories when compared to the normal weight category. Compared with the normal weight individuals in the full model, the obese category had no change in DBP levels (0.0 mg/dL, *P* = <0.001) versus the slight decrease in DBP in

the overweight category (-0.1 md/dL, P = <0.001). For an example, after visit one, it is predicted that obese HIV-infected individuals at diagnosis will experience relatively no change in DBP, while overweight HIV-infected individuals will experience a 0.1 decrease in DBP.

The mixed regression analysis results of the interaction between BMI category and HAART use on CD4 count over time are listed in Table 3. Obese HIV-infected individuals on HAART have significantly larger increases in fasting blood glucose (P = <0.001) and HDL (P = <0.001), and significantly larger decreases in LDL (P = <0.001) and SBP (P = <0.001) compared to overweight-HIV infected individual on HAART. Overweight HIV-infected individuals on HAART have larger decreases in DBP (P = <0.001) compared to obese HIV-infected individuals on HAART. The results of the sensitivity analyses using the inverse-probability weighting method to account for loss to follow up (n=73) were qualitatively similar to the results presented.

6.4 Discussion

The prevalence of overweight and obesity was considered high within this cohort, with nearly 57% being overweight and obese. Fasting blood glucose, HDL, and blood pressure levels were highest at time of diagnosis among those who were obese compared to those in the overweight and normal weight categories. Over time, the obese category had larger decreases in fasting blood glucose and SBP, and larger increases in HDL compared to the overweight and normal weight categories. The overweight category had larger decreases in LDL when compared to the obese and normal weight categories. Higher BMI among HIV-infected individuals is associated with increased CD4 count

over time and also appears to be protective against some cardiovascular disease risk markers.

Obesity is known to be one of the causes of increased glucose levels, which can result in the development of diabetes.[19] Other risk factors include race, age, physical inactivity, and family history of diabetes. Studies have shown that the incidence of diabetes increases with cumulative exposure to HAART,[41] particularly protease inhibitors, and that the HIV-infected individuals tend to have a greater chance for the development of diabetes morbidity when compared to HIV naïve patients.[42] Evidence has shown that HIV itself causes lipodystrophy, which can cause abnormally high levels of blood glucose.[74] One study reported an overall glucose mean of 87 mg/dL among their cohort of HIV-infected individuals and stated that higher BMI was associated with higher glucose concentrations.[6] In contrast, our study had a higher overall mean of fasting blood glucose (100.3 mg/dL) and had an overweight population, compared to the normal weight population seen in the El Sadr et al. study. Additionally, our study evaluated fasting blood glucose over time by looking at the difference between BMI categories. We showed that while the obese category had a higher decrease in fasting blood glucose over time compared to the increase among the overweight category, they both are significantly lower than the normal weight category. Therefore, this population behaves dissimilar to the non-HIV infected individuals where higher BMIs are associated with higher glucose levels.

Morbidity related to HDL and LDL levels are also associated with obesity,[56] although one study reported no association with LDL and that the negative association between BMI and HDL levels could be explained by insulin resistance.[75] While this may

be true, this association is slightly different among HIV-infected individuals. El Sadr et al. reports an overall HDL mean of 37 mg/dL and an overall LDL mean of 98.3 mg/dL, and only found a significant association between BMI and LDL.[6] Another study reported that 44.7% of their population had low HDL-C levels (<40 mg/dL), an overall LDL mean of 107.3, a negative significant association with BMI, and that low HDL-C levels were associated with antiretroviral therapy.[42] Our study had higher overall means for HDL and LDL compared to their study. We also adjusted for glucose levels in the mixed regression analyses and found significantly different associations between BMI and the lipid profiles (HDL and LDL). Unlike non-HIV infected individuals, our study found that at a positive association between the obese and overweight groups with HDL, and a negative association between the obese and overweight group with LDL.

Increased blood pressure is associated with the risk factors that affect both lipid levels and blood glucose levels, such as obesity among non-HIV infected individuals.[57] Overweight and obese individuals have higher systolic and DBP levels. Among HIV-infected individuals, traditional risk factors are also associated with increased blood pressure.[36] Most studies report a prevalence of hypertension among HIV-infected individuals to be between 25%-35% versus thirty-six percent of our population took blood pressure medication for hypertension over the course of follow-up.[35-39] Some studies have stated that HAART may induce hypertension through hardening of the vessel walls,[37 39] however others report minimal effects. [36 38] In our study, those on HAART had a small decrease in SBP (-2.1 ± 0.1) and an increase in DBP (7.7 ± 0.4). The obese individuals in our study had a higher overall mean for systolic and DBP, and larger

increases in SBP. Both the obese and overweight DBP levels were roughly the same over time.

The results of our study could be validated by several justifications. First, it has been reported that obesity is associated with improved outcomes and survival in patients on hemodialysis, pneumonia, heart transplant, renal failure and liver cirrhosis.[75] Therefore, the immune recovery afforded to HIV-infected individuals with higher BMI have with CD4 count over time could explain why obese individuals have larger increases in fasting blood glucose and HDL. Secondly, a potential confounder in all studies evaluating this question is the association between weight loss and untreated HIV-infection is called reverse causality. An example of reverse causality is when the normal weight category consist of individuals who were normal weight pre-diagnosis, and those who were overweight but lost weight because of HIV-infection in the period preceding their diagnosis, or when obese category includes individuals who lost weight before their diagnosis and were considered overweight at diagnosis.[24]

To prevent the possibility of reverse causality affecting the validity of our results, height and weight was collected within three months of diagnosis. If reverse causality is contributing to the association between BMI and cardiovascular disease risk markers, then the BMI characteristics of the source population are likely important. As HIV is diagnosed at an earlier stage, before wasting sets in, the HIV-infected population is similar to the general population with respect to BMI. In our study population the mean BMI was 27.4 kg/m^2, and overweight and obesity prevalence was 30% and 26.8%, which is similar to the prevalence of overweight (35.4%) and obesity (31.5%) in general HIV-uninfected population in South Carolina.[19] The characteristics of the study population in

this report were similar for all HIV-infected individuals in the entire state of South Carolina, with respect to race (Black: 74.2% versus 76%) and mode of transmission (MSM: 33.1% versus 37.1%).[62] Given the similarities between our study cohort and the overall HIV-infected population in South Carolina, it is unlikely that reverse causality significantly impacted our results.

This study has some limitations. First, the treatment variables only measured whether individuals received HAART, cholesterol medication, diabetic medication, or blood pressure medication throughout the course of their HIV infection. We did not assess time spent on these medications. Second, we were unable to make an assumption that included the underweight BMI category. However, past research has shown that underweight individuals generally are not associated with increased chances of diabetes, hypertension or dyslipidemia compared to other BMI categories, although some have reported that underweight may be associated with risk of developing these diseases. Third, the alcohol use and drug use variables only captured whether individuals were socially participating in these factors and not the frequency of use. Fourth, our population consisted of mostly black HIV-infected individuals and the results may not be generalizable to other populations. Finally, there is the possibility of residual confounding such as measurement error of a CD4.

This study has several strengths. First, we explored the post-HAART longitudinal association between BMI at baseline and cardiovascular risk markers in a southern state. Second, unlike previous research, we adjusted for many potential confounders including delayed entry into HIV medical care and use of case management. Entry into HIV medical care is imperative for access to antiretroviral therapy and facilitates the delivery

of important prevention education to reduce HIV transmission. In addition, retention in care is critical to monitor response to therapy. Finally, this investigation includes fourteen years of follow-up (i.e. those diagnosed in 1997) allowing us to assess the cardiovascular disease risk markers over a long period. Third, our population of individuals with different stages of HIV disease, allows us to determine if the relationship under study exists in HIV-infected individuals with different levels of immune impairment.

The results of this study revealed that HIV-infected individuals who were obese at diagnosis had greater decreases in fasting blood glucose and larger increases in HDL over time when compared to HIV-infected individuals who were overweight at diagnosis. Although higher BMI is associated with improved cardiovascular risk markers among this HIV-population, providers should monitor weight at diagnosis due to its correlation with inflammation. Because BMI plays an important role in causing metabolic abnormalities in non-HIV populations and because BMI at diagnosis may be an important factor in predicting the effects of HIV and treatment on metabolic abnormalities, additional studies are needed to evaluate markers of inflammation over time, particularly among different HIV-infected populations.

Table 6.1: Baseline characteristics of South Carolina HIV positive individuals diagnosed between 1997 and 2010 by Body Mass Index (BMI) category.

Characteristic	Overall (n=396)	Normal (n=171)	Overweight (n=119)	Obese (n=106)	P^a
Body Mass Index	27.4 ± 6.3	22.3 ± 1.8	27.2 ± 1.5	35.9 ± 5.2	<0.001
Age	35.1 ± 10.6	34.5 ± 11.5	36.1 ± 9.5	34.5 ± 10.2	0.378
Gender					
Male	245 (61.9%)	126 (73.7%)	78 (65.6%)	41 (38.7%)	
Female	149 (37.6%)	44 (25.7%)	41 (34.5%)	64 (60.4%)	
Transgender	2 (0.5%)	1 (0.6%)		1 (0.9%)	<0.001
Race					
White, non-Hispanic	92 (23.2%)	38 (22.2%)	28 (23.6%)	26 (24.5%)	
Black, non-Hispanic	294 (74.2%)	127 (74.3%)	88 (74.0%)	79 (74.5%)	
Hispanic	3 (0.8%)	2 (1.2%)	1 (0.8%)		
Other	1 (0.3%)		1 (0.8%)		
Unknown	6 (1.5%)	4 (2.3%)	1 (0.8%)	1 (1.0%)	0.899
Marital Status					
Single	242 (61.1%)	111 (64.9%)	71 (59.7%)	60 (56.6%)	
Married	47 (11.9%)	15 (8.8%)	19 (16.0%)	13 (12.3%)	
Divorced	70 (17.7%)	25 (14.6%)	18 (15.1%)	27 (25.5%)	
Widowed	14 (3.5%)	7 (4.1%)	5 (4.2%)	2 (1.9%)	
Partnered	21 (5.3%)	12 (7.0%)	6 (5.0%)	3 (2.8%)	
Unknown	2 (0.5%)	1 (0.6%)		1 (0.9%)	0.166
Education					
High School Diploma	140 (35.3%)	61 (35.6%)	45 (37.8%)	34 (32.1%)	
Associate Degree	23 (5.8%)	8 (4.7%)	4 (3.4%)	11 (10.4%)	
Bachelor Degree	24 (6.1%)	6 (3.5%)	8 (6.7%)	10 (9.4%)	
Master's Degree	9 (2.3%)	4 (2.3%)	3 (2.6%)	2 (1.9%)	
Doctorate Degree	3 (0.8%)	2 (1.2%)	1 (0.8%)		
No HS Diploma	63 (15.9%)	34 (19.9%)	13 (10.9%)	16 (15.1%)	
Unknown	134 (33.8%)	56 (32.8%)	45 (37.8%)	33 (31.1%)	0.207
Insurance					
Medicare	70 (17.7%)	33 (19.3%)	19 (16.0%)	18 (17.0%)	
Medicaid	43 (10.9%)	17 (9.9%)	10 (8.4%)	16 (15.1%)	
Private Insurance	96 (24.2%)	30 (17.6%)	35 (29.4%)	31 (29.3%)	
None	187 (47.2%)	91 (53.2%)	55 (46.2%)	41 (38.7%)	0.064
Followed by Case Manager					
Yes	170 (42.9%)	82 (47.9%)	44 (37.0%)	44 (41.5%)	
No	226 (57.1%)	89 (52.1%)	75 (63.0%)	62 (58.5%)	0.170
Alcohol Use					
Yes	241 (60.9%)	117 (68.4%)	73 (61.3%)	51 (48.1%)	
No	138 (34.8%)	49 (28.7%)	42 (35.3%)	47 (44.3%)	
Unknown	17 (4.3%)	5 (2.9%)	4 (3.4%)	8 (7.6%)	0.017
Smoking					
Yes	217 (54.8%)	114 (66.7%)	63 (53.0%)	40 (37.7%)	
No	162 (40.9%)	52 (30.4%)	53 (44.5%)	57 (53.8%)	
Unknown	17 (4.3%)	5 (2.9%)	3 (2.5%)	9 (8.5%)	<0.001
Drug Use					
Yes	141 (35.6%)	72 (42.1%)	44 (37.0%)	25 (23.6%)	
No	237 (59.8%)	94 (55.0%)	71 (59.7%)	72 (67.9%)	
Unknown	17 (4.6%)	5 (2.9%)	4 (3.3%)	9 (8.5%)	0.010
Mode of Transmission					
Heterosexual	221 (55.8%)	81 (47.4%)	66 (55.5%)	74 (69.8%)	
MSM	131 (33.1%)	72 (42.1%)	38 (31.9%)	21 (19.8%)	

IDU	20 (5.1%)	8 (4.7%)	7 (5.9%)	5 (4.7%)	
NIR/NRR	24 (6.1%)	10 (5.9%)	8 (6.7%)	6 (5.7%)	0.013
Delayed entry into care					
<3 months	171 (43.2%)	78 (45.6%)	39 (32.8%)	54 (50.9%)	
≥3 months	225 (56.8%)	93 (54.4%)	80 (67.2%)	52 (49.1%)	0.016
HAART use					
Yes	349 (88.1%)	161 (94.2%)	109 (91.6%)	95 (89.6%)	
No	47 (11.9%)	10 (5.8%)	10 (8.4%)	11 (10.4%)	0.109
Diabetic medication					
Yes	36 (9.1%)	11 (6.4%)	8 (6.7%)	17 (16.0%)	
No	360 (90.9%)	160 (93.6%)	111 (93.3%)	89 (84.0%)	0.015
Cholesterol medication					
Yes	62 (15.7%)	24 (14.0%)	20 (16.8%)	18 (17.0%)	
No	334 (84.3%)	147 (86.0%)	99 (83.2%)	88 (83.0%)	0.741
BP medication					
Yes	143 (36.1%)	50 (29.2%)	44 (37.0%)	49 (46.2%)	
No	253 (63.9%)	121 (70.8%)	75 (63.0%)	57 (53.8%)	0.016
CD4 count at diagnosis	499.3 ± 255.2	448.4 ± 229.1	498.4 ± 231.1	575.6 ± 296.2	0.019
Log HIV VL at diagnosis	4.1 ± 0.9	4.2 ± 0.9	4.2 ± 0.9	3.8 ± 0.9	<0.001
Fasting blood glucose at diagnosis	95.8 ± 40.4	90.8 ± 27.0	92.4 ± 20.4	106.6 ± 63.8	0.102
HDL at diagnosis	46.3 ± 19.1	46.2 ± 21.6	40.2 ± 4.4	49.2 ± 21.7	0.652
LDL at diagnosis	113.4 ± 37.2	94.4 ± 27.6	125.4 ± 49.7	123.4 ± 35.4	0.131
SBP at diagnosis	126.9 ± 16.3	125.7 ± 15.2	124.8 ± 16.9	130.7 ± 17.0	0.134
DBP at diagnosis	81.2 ± 11.3	80.2 ± 11.6	80.5 ± 12.4	83.3 ± 9.8	0.281

Abbreviations: MSM, men who have sex with men; IDU, injecting drug user; NIR/NRR, no identified/reported risk factor; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; DBP, diastolic blood pressure

NOTE: Mean and standard deviation are shown for Body mass Index, Age, CD4 count at diagnosis, HIV VL at diagnosis.

- Normal (≤ 24.9 kg/m^2), Overweight (25.0-29.9 kg/m^2), Obese (≥ 30.0 kg/m^2).

Underweight individuals were excluded because numbers were too few for meaningful analysis.

- Transgender was not included in the table.

[a] Comparison between baseline BMI strata

**Insurance – None: No insurance/ADAP Program

Table 6.2: Mixed Model Analysis of the association between Body Mass Index (BMI) and cardiovascular disease risk markers among HIV-infected individuals diagnosed in South Carolina between 1997-2010.

Model	Parameter Estimate	Standard Error (SE)	P^a
Blood Glucose			
Full Model			
Time	0.3	0.007	<0.001
BMI			
Obese	10.9	0.2	<0.001
Overweight	9.6	0.2	<0.001
Normal	*	*	*
time*BMI			
time*Obese	-0.5	0.01	<0.001
time*Overweight	-0.3	0.01	<0.001
time*Normal	*	*	*
HDL			
Full Model			
Time	0.2	0.008	<0.001
BMI			
Obese	-4.7	0.2	<0.001
Overweight	3.9	0.2	<0.001
Normal	*	*	*
time*BMI			
time*Obese	0.2	0.01	<0.001
time*Overweight	0.06	0.01	<0.001
time*Normal	*	*	*
LDL			
Full Model			
Time	-1.2	0.007	<0.001
BMI			
Obese	-2.7	0.2	<0.001
Overweight	3.0	0.2	<0.001
Normal	*	*	*
time*BMI			
time*Obese	0.2	0.01	<0.001
time*Overweight	-0.2	0.01	<0.001
time*Normal	*	*	*
SBP			
Full Model			
Time	0.04	0.008	<0.001
BMI			
Obese	1.8	0.2	<0.001
Overweight	7.0	0.2	<0.001
Normal	*	*	*
time*BMI			
time*Obese	-0.2	0.02	<0.001
time*Overweight	-0.1	0.01	<0.001
time*Normal	*	*	*
DBP			
Full Model			
Time	-0.3	0.008	<0.001
BMI			
Obese	-0.9	0.2	<0.001
Overweight	-2.1	0.2	<0.001
Normal	*	*	*

time*BMI			
time*Obese	0.3	0.02	<0.001
time*Overweight	0.2	0.01	<0.001
time*Normal	*	*	*

Abbreviations: SE, standard error; SBP, systolic blood pressure; DBP, diastolic blood pressure

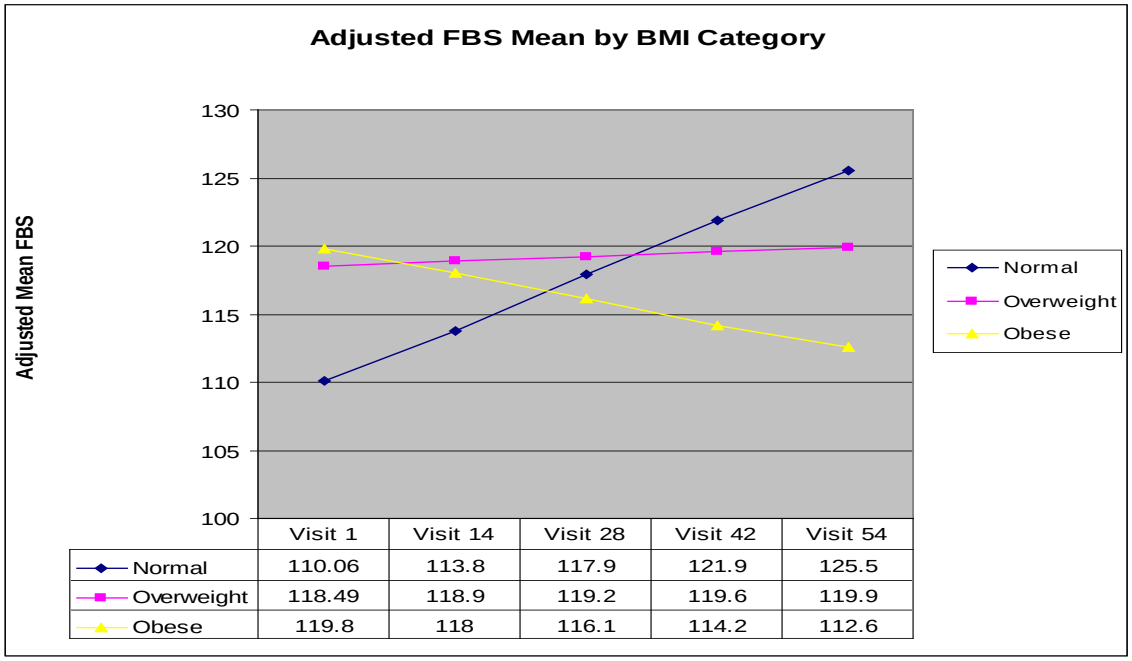
NOTE: * Normal BMI category - reference group. The parameter estimates represent the difference in the adjusted mean CD4 count by BMI category. Those overweight has higher mean CD4 counts. b Comparison between baseline BMI categories.

- Normal ($\leq$ 24.9 kg/m^2), Overweight (25.0-29.9 kg/m^2), Obese ($\geq$ 30.0 kg/m^2)
- Underweight individuals were excluded because numbers were too few for meaningful analysis.
- Models adjusted for, baseline CD4 count, CD4 count over time baseline VL, viral load over time, age, fasting blood glucose over time, HDL and LDL over time, SBP and DBP over time, gender, race, mode of transmission and treatment, alcohol use, smoking use, drug use, marital status, education, and type of insurance, case management, delayed entry into care, HAART use, cholesterol medication use, blood pressure medication use, and diabetes medication use.

Table 6.3: Mixed Model Analysis of the interaction between Body Mass Index (BMI) and highly active antiretroviral therapy (HAART) use and its association with cardiovascular disease risk markers among HIV-infected individuals diagnosed in South Carolina between 1997-2010.

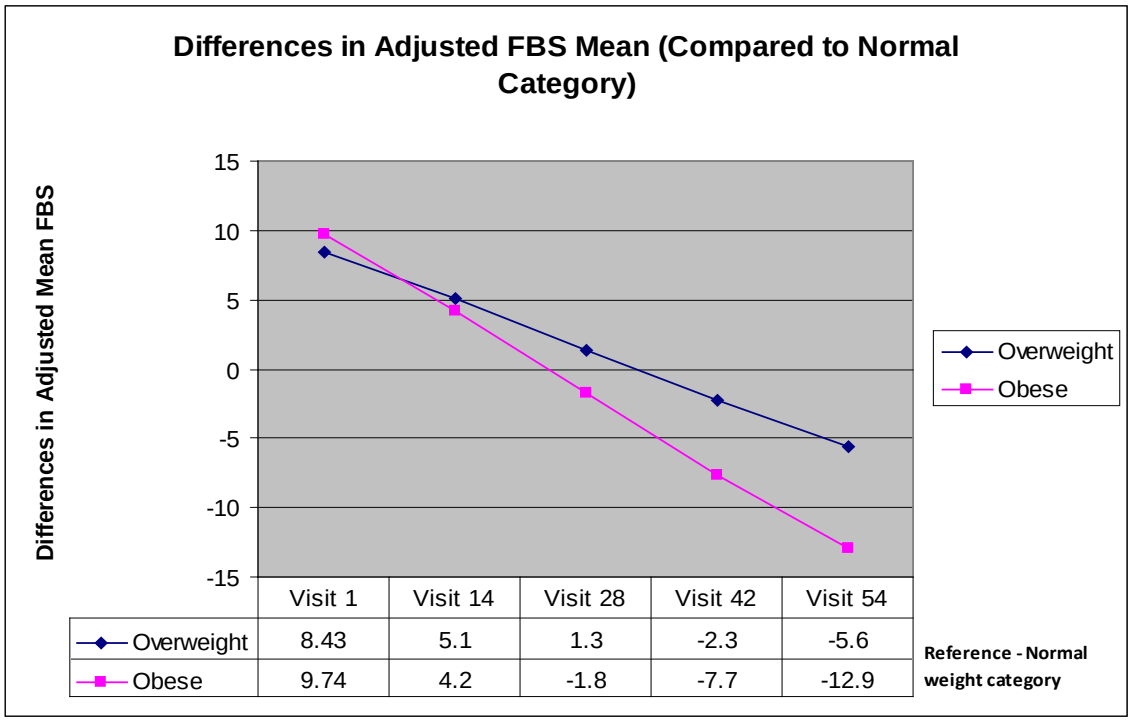
Model	Parameter Estimates (SE)	P^a
Blood Glucose		
BMI*HAART use		
Obese*Yes	4.5 (0.5)	<0.001
Obese*No	*	*
Overweight *Yes	-6.7 (0.6)	<0.001
Overweight *No	*	*
HDL		
BMI*HAART use		
Obese*Yes	9.9 (0.5)	<0.001
Obese*No	*	*
Overweight *Yes	-8.4 (0.6)	<0.001
Overweight *No	*	*
LDL		
BMI*HAART use		
Obese*Yes	-18.9 (0.5)	<0.001
Obese*No	*	*
Overweight *Yes	-13.2 (0.6)	<0.001
Overweight *No	*	*
SBP		
BMI*HAART use		
Obese*Yes	-5.5 (0.5)	<0.001
Obese*No	*	*
Overweight *Yes	1.0 (0.7)	0.113
Overweight *No	*	*
DBP		
BMI*HAART use		
Obese*Yes	-9.3 (0.5)	<0.001
Obese*No	*	*
Overweight *Yes	-12.3 (0.7)	<0.001
Overweight *No	*	*

Abbreviations: SE, standard error; SBP, systolic blood pressure; DBP, diastolic blood pressure
NOTE: * Normal BMI category and No HAART use- reference groups.
The parameter estimates represent the difference in the adjusted mean CD4 count by BMI category.
Those overweight has higher mean CD4 counts. b Comparison between baseline BMI categories.
- Normal ($\leq$ 24.9 kg/m^2), Overweight (25.0-29.9 kg/m^2), Obese ($\geq$ 30.0 kg/m^2)
- Underweight individuals were excluded because numbers were too few for meaningful analysis.
- Models adjusted for, baseline CD4 count, CD4 count over time baseline VL, viral load over time, age, fasting blood glucose over time, HDL and LDL over time, SBP and DBP over time, gender, race, mode of transmission and treatment, alcohol use, smoking use, drug use, marital status, education, and type of insurance, case management, delayed entry into care, HAART use, cholesterol medication use, blood pressure medication use, and diabetes medication use.



	Visit 1	Visit 14	Visit 28	Visit 42	Visit 54
Normal	110.06	113.8	117.9	121.9	125.5
Overweight	118.49	118.9	119.2	119.6	119.9
Obese	119.8	118	116.1	114.2	112.6

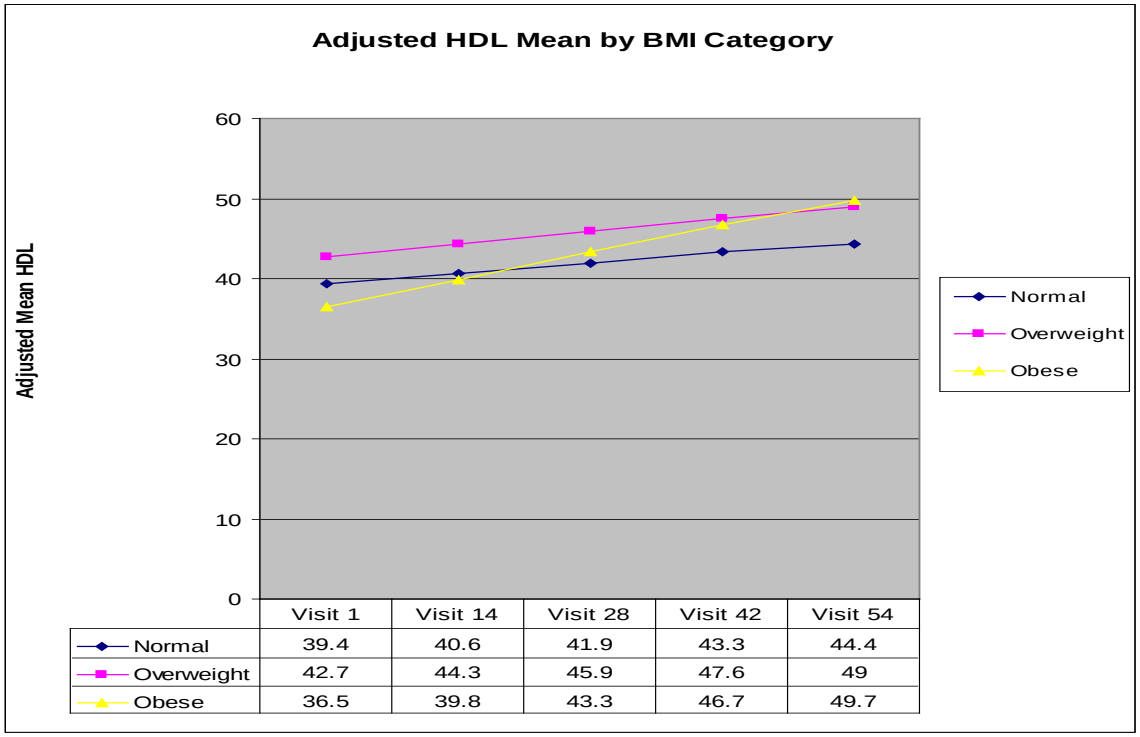
Figure 6.1: Adjusted fasting blood glucose means by BMI category



	Visit 1	Visit 14	Visit 28	Visit 42	Visit 54
Overweight	8.43	5.1	1.3	-2.3	-5.6
Obese	9.74	4.2	-1.8	-7.7	-12.9

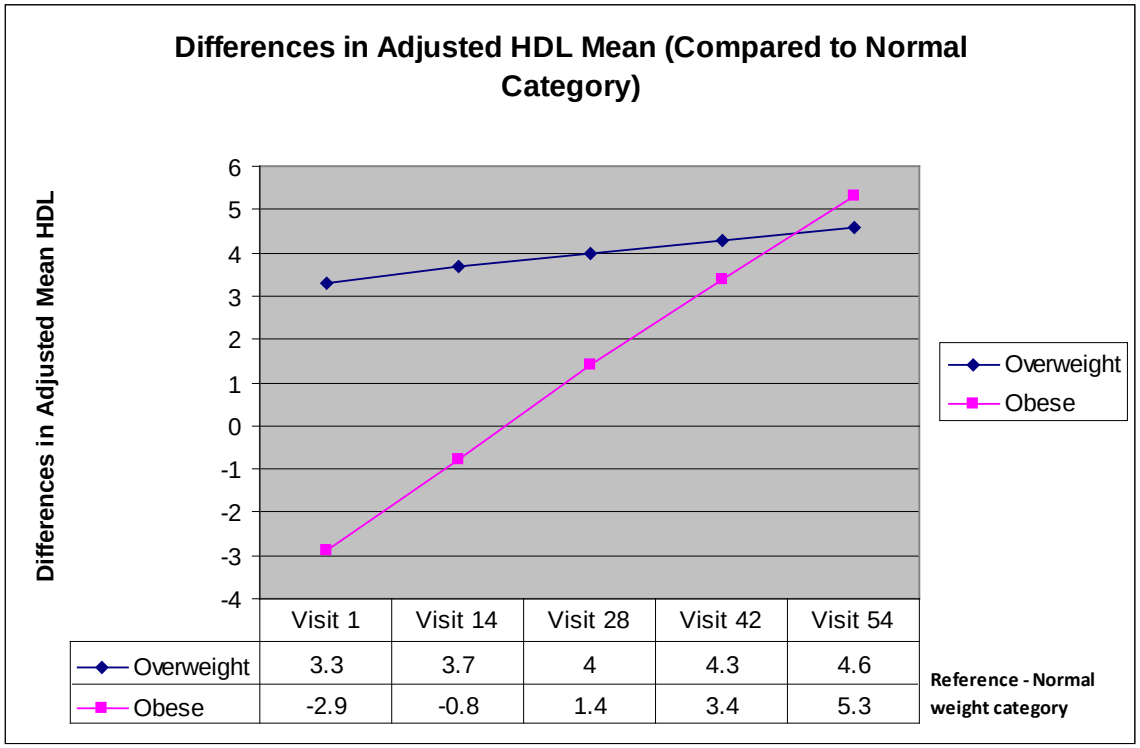
Reference - Normal weight category

Figure 6.2: Differences in the adjusted fasting blood glucose means by BMI category



	Visit 1	Visit 14	Visit 28	Visit 42	Visit 54
Normal	39.4	40.6	41.9	43.3	44.4
Overweight	42.7	44.3	45.9	47.6	49
Obese	36.5	39.8	43.3	46.7	49.7

Figure 6.3: Adjusted HDL means by BMI category



	Visit 1	Visit 14	Visit 28	Visit 42	Visit 54
Overweight	3.3	3.7	4	4.3	4.6
Obese	-2.9	-0.8	1.4	3.4	5.3

Reference - Normal weight category

Figure 6.4: Differences in the adjusted HDL means by BMI category

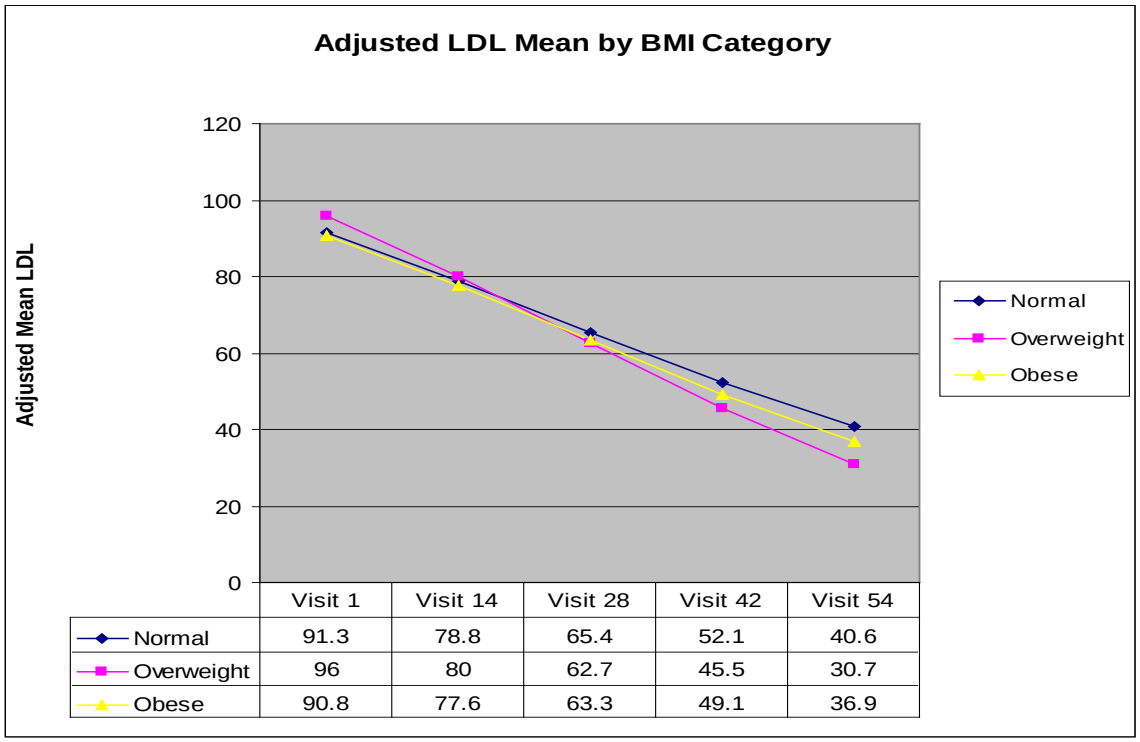


Figure 6.5: Adjusted LDL means by BMI category

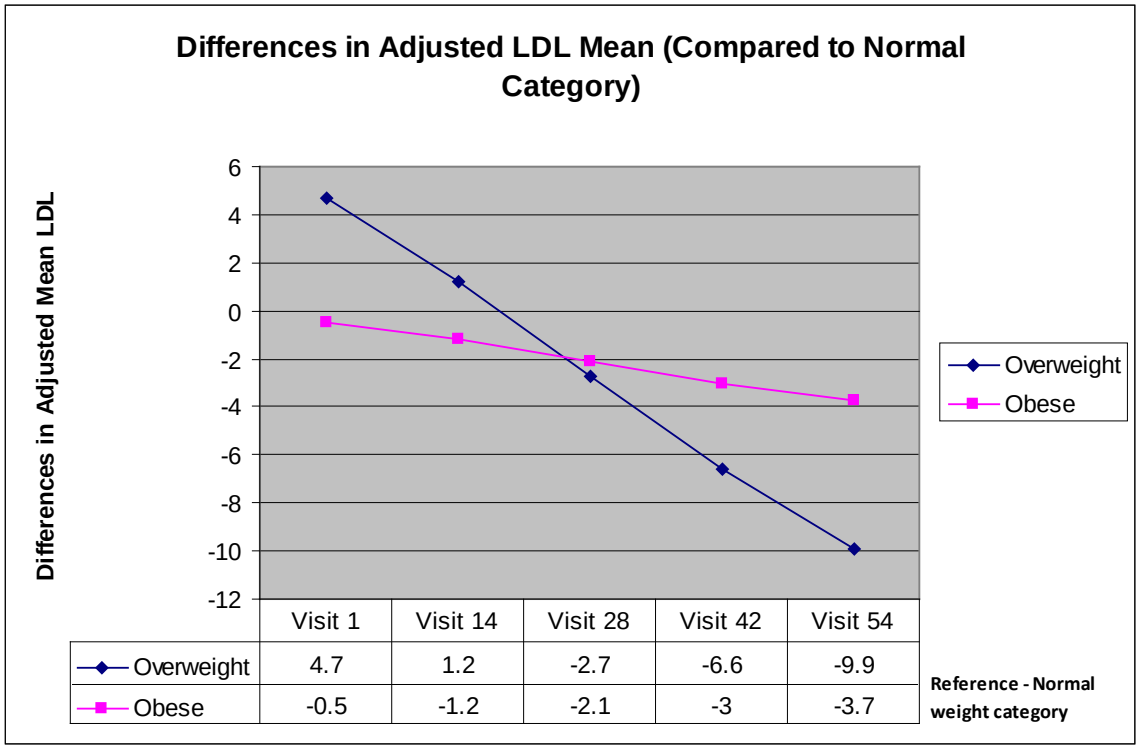
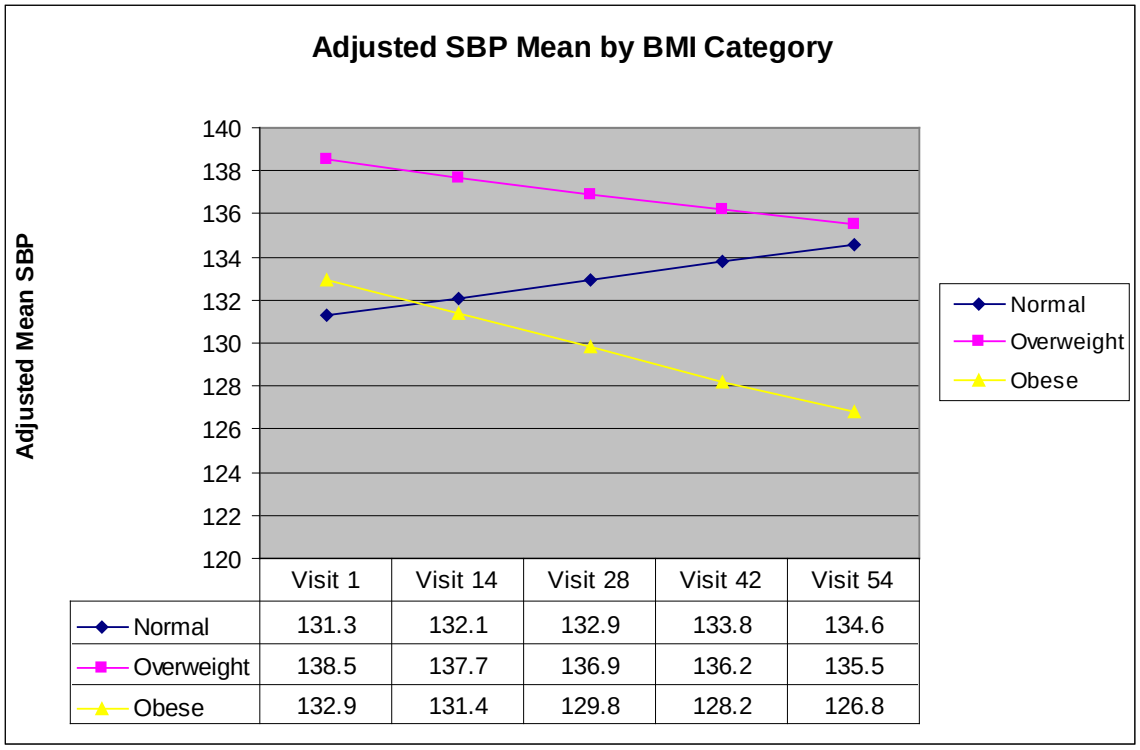
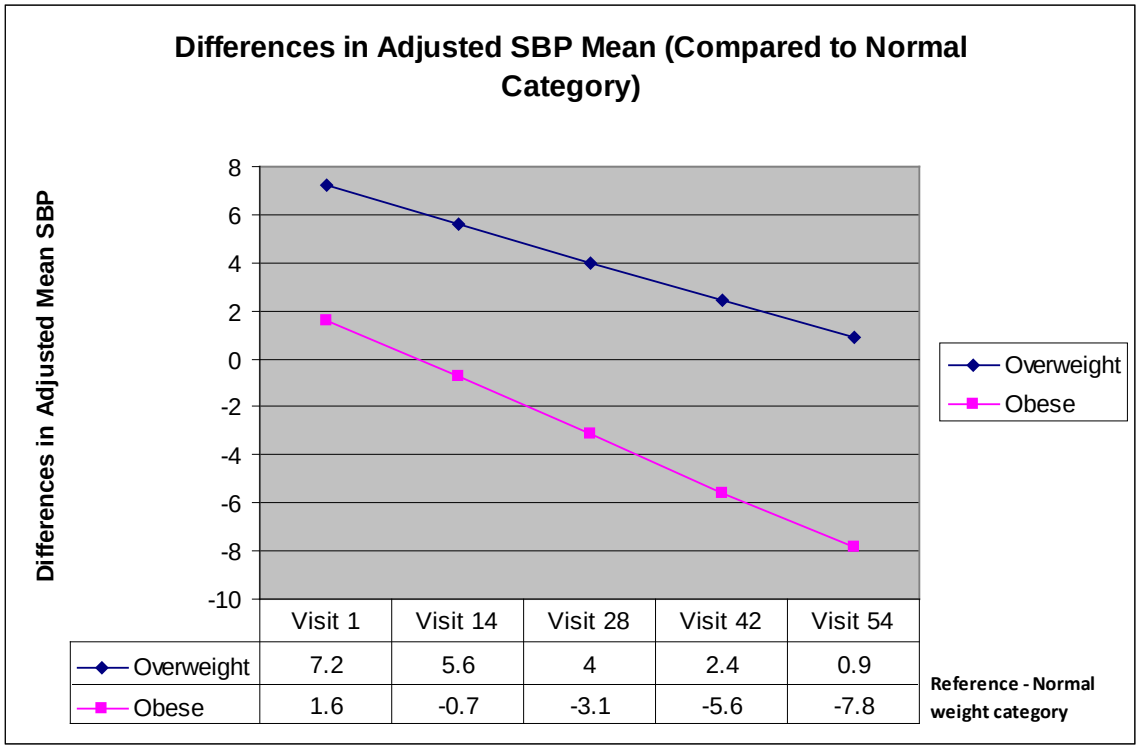


Figure 6.6: Differences in the adjusted LDL means by BMI category



	Visit 1	Visit 14	Visit 28	Visit 42	Visit 54
Normal	131.3	132.1	132.9	133.8	134.6
Overweight	138.5	137.7	136.9	136.2	135.5
Obese	132.9	131.4	129.8	128.2	126.8

Figure 6.7: Adjusted SBP means by BMI category



	Visit 1	Visit 14	Visit 28	Visit 42	Visit 54
Overweight	7.2	5.6	4	2.4	0.9
Obese	1.6	-0.7	-3.1	-5.6	-7.8

Reference - Normal weight category

Figure 6.8: Differences in the adjusted SBP means by BMI category

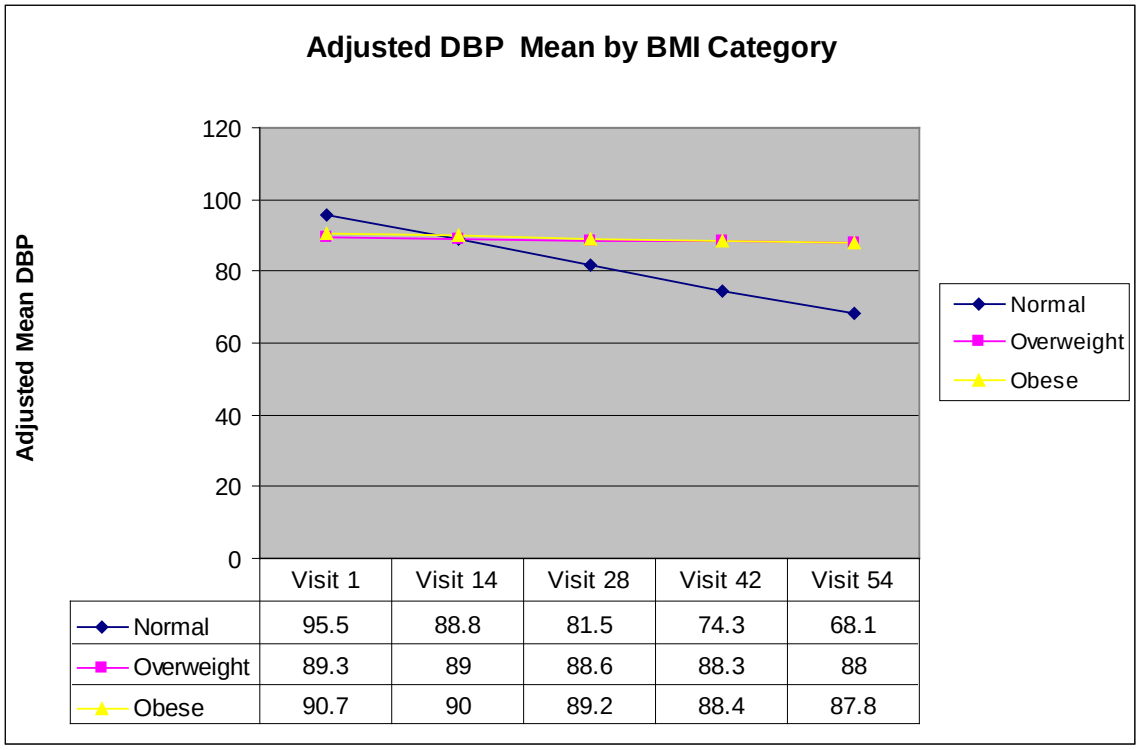


Figure 6.9: Adjusted DBP means by BMI category

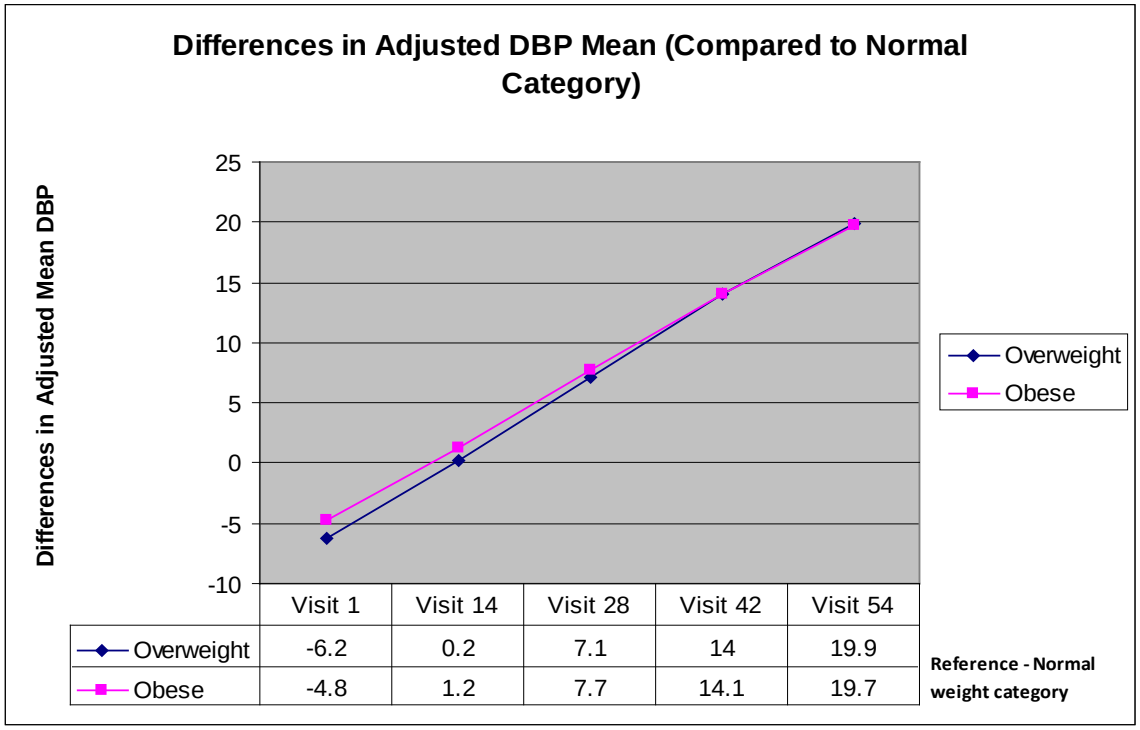


Figure 6.10: Differences in the adjusted DBP means by BMI category

CONCLUSIONS

As the prevalence of overweight and obesity continues to increase among HIV-infected individuals and as treated HIV-infected individuals continue to be plagued by metabolic abnormalities, additional research is needed to study this relationship among different HIV-infected populations and determine which factors are involved in creating these results. In this study, there were significant differences in CD4 count over time between overweight and obese individuals when compared to normal weight individuals. Overweight HIV-infected individuals, had larger increases in CD4 count and HDL over time and larger decreases in DBP over time. Obese HIV-infected individuals had larger increases in fasting blood glucose and SBP, which is indicative of the effects of obesity in causing inflammation. Female HIV-infected individuals had larger increases in CD4 count over time compared to males. The difference between females and males could be explained gynecological factors such as menopause or hormone replacement therapy. However, this study did not assess any gynecological factors and their association with progression of HIV.

HIV data is generally non-linear and the statistical analyses chosen are very essential to accurately estimate differences between groups. Our study used a mixed model analysis which allowed us to choose the best covariance structure that fit with the data. Spatial power was the covariance structure fitted to the mixed model analysis because it allows unequal measurements of data among individuals in the study. Future

researchers could use non-linear mixed model analyses to obtain better estimates for this relationship.

Several limitations affected our study. First, the secular change of CD4 count is impacted as more HIV-infected individuals are prescribed HAART and medication efficacy has increased, which could potentially attenuate the associations.[22] Second, our population consisted of mostly black HIV-infected individuals and the results may not be generalizable to other populations. Third, we were unable to make an assumption that included the underweight BMI category. However, past research has shown that underweight individuals generally are not associated with increased chances of diabetes, hypertension or dyslipidemia compared to other BMI categories, although some have reported that underweight may be associated with risk of developing these diseases. Fourth, the treatment variables only measured whether individuals received HAART, cholesterol medication, diabetic medication, or blood pressure medication throughout the course of their HIV infection. We did not assess time spent on these medications. Fifth, there is the possibility of residual confounding. Sixth, we did not collect any information on gynecological factors (i.e. contraception use, menopause status) that could potentially confound our results. Finally, the alcohol use and drug use variables only captured whether individuals were socially participating in these factors and not the frequency of use.

This study has several strengths. First, we explored the post-HAART longitudinal association between BMI at baseline and cardiovascular risk markers in a southern state. Second, unlike previous research, we adjusted for many potential confounders including delayed entry into HIV medical care and use of case management. Entry into HIV

medical care is imperative for access to antiretroviral therapy and facilitates the delivery of important prevention education to reduce HIV transmission. In addition, retention in care is critical to monitor response to therapy. Finally, this investigation includes fourteen years of follow-up (i.e. those diagnosed in 1997) allowing us to assess the cardiovascular disease risk markers over a long period. Third, our population of individuals with different stages of HIV disease, allows us to determine if the relationship under study exists in HIV-infected individuals with different levels of immune impairment.

In all, overweight and obese HIV-infected individuals have different associations with markers for HIV progression and cardiovascular disease risk. The causes of these associations are multifactorial and additional research should focus the interaction of these sources to understand the biological differences between overweight and obese HIV-infected individuals. Furthermore, this study illustrates the importance and the ability of BMI to predict response to treatment and potential long-term effects of the disease and medications.

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Appendix A: Protection of Human Subjects

Target Population

The target population for this proposal was individuals who were HIV-positive. Medical records from the Ryan White Clinic were reviewed for this study. The majority of the clients served in the Ryan White Clinic in South Carolina were male (60%), African American (73%), and aged 25-44 (50.7%).[35] For inclusion in the study, adults were at least 18 years of age, diagnosed with HIV from January 1, 1997-December 31, 2010 in the state of South Carolina and had at least one confirmatory Western Blot, had weight and height measured within three months of HIV diagnosis, and those with at least 1 follow-up appointment after BMI was recorded at diagnosis. HIV-positive individuals who are pregnant, or have taken either hypertensive, diabetic or cholesterol medication were excluded from this study. A total of 400 HIV-positive adults were included in this study. The sample size was determined using SAS 9.2 power analysis for ANOVA design. Given that the relationship under study is a relatively understudied area of research among HIV patients, this particularly study was necessary.

Recruiting Plans

Recruitment of individuals for this proposal was not necessary because the investigators used data that was already in existence. Only de-identified data were collected to prevent from exposing any private information.

Existing Data/Samples

Investigators of this proposal used existing data from medical records which are located in Ryan White HIV/AIDS Clinic to acquire the data listed in the data abstraction sheet. Although the medical records contained direct identifiers, none of that information was collected. The data was recorded in Epi Data with the pre-approved variables listed on the data abstraction sheet and exported into SAS.

Consent/Assent

For this proposal, consent from patients of the Ryan White Clinic was necessary because the investigators used data that was already in existence. Only de-identified data were collected to prevent from exposing any private information.

Potential Risks

We believe that there was minimal risk to study participants, because information that was collected did not contain any personal information and the investigator that collected the data was required to keep that information confidential. The proposed research fell under Exemption 4 (AIM 1, AIM 2, and AIM 3) and Expedited Review Category 5 (AIM 1, AIM 2, and AIM 3). An application for this study was approved by the University of South Carolina, Institutional Review Board. All study personnel were trained and certified in federal and state policies regarding the protection of human subjects' participation in research (CITI). The human subjects data used for AIMS 1, 2, and 3 of this proposal were part of the medical records from the Ryan White Clinic. Careful consideration was taken to ensure the anonymity of study participants. No individual will be identified in any publications resulting from this study. Furthermore,

we feel by blocking access to sensitive charts (i.e. charts from students and faculty of the University of South Carolina), further protected the confidentiality of all patients.

Potential Benefits

There was no direct benefit to participants as a result of this study. However, the information obtained from this study will add to the body of scientific knowledge about this important area of research. This proposed research will also provide information that can be used to inform intervention decisions, including when to initiate therapy and whether monitoring BMI could be a useful marker in assessing the success of such therapy, particularly in resource-limited countries. Given that the rates of obesity are increasing among HIV patients, the results of this study could potentially help in understanding the factors associated with increased rates of disease progression and cardiovascular risk in HIV patients. Using medical records enabled this research to provide a more comprehensive assessment of this relationship. These findings can provide the framework for clinicians to develop more appropriate HIV treatment strategies that can ultimately allow HIV-positive individuals to live longer.

Confidentiality

As mandated by the state and the Institutional Review Board (IRB) of the University of South Carolina, authorized persons trained in the Health Insurance Portability and Accountability Act (HIPAA) confidentiality procedures retrieved the data. Study investigators were required to abide by the guidelines set forth by the state and school with regards to the security and confidentiality of the data. To further protect confidentiality, access to patient charts who were deemed sensitive (i.e. students and

faculty of USC) were blocked. The principle investigator was the only person collecting the data. Unique identifiers were created for each patient. The definition of the unique identifier was located within the data abstraction sheet. The unique identifier and medical record for each patient was recorded on the patient list file. The data file and the patient list file was kept in a secure location, under lock and key at the Ryan White Clinic, under the supervision of Shirley Patterson. Only Mrs. Patterson and I had access to the data files. The data was not stored on a local hard drive or network drive. However, all data analysis by the investigators was conducted at University of South Carolina School of Public Health using password-protected computers once the data was exported to SAS.