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Diabetes Mellitus among Persons Living With HIV: Prevalence and Predictors

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DIABETES MELLITUS AMONG PERSONS LIVING WITH HIV: PREVALENCE AND PREDICTORS

By

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Author's Statement

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<u>Glodi K. Mutamba</u>
Signed by Author

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ABSTRACT

INTRODUCTION: Over the past years, there has been intense and sustained research interest in diabetes and its relationships with different health conditions and factors. Diabetes is defined as a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Without appropriate intervention, elevated blood glucose levels can cause several metabolic abnormalities and disabling complications such as cardiovascular disease, eye disease, neuropathy, and kidney failure. This study is particularly critical as the United States is among the highest diabetes prevalent nations among developed countries. The concentration of HIV and diabetes in the same subjects makes it essential to examine the magnitude of the burden and the predictors of diabetes among persons living with HIV. Nevertheless, the prevalence of type 2 diabetes among Persons Living With HIV (PLWHIV) and its predictors is not well understood.

AIM: This research was done to determine:

1. the prevalence of diabetes mellitus among PLWHIV,
2. odds of Diabetes Mellitus among PLWHIV,
3. predictors of diabetes among PLWHIV.

METHODS: Participants included 170 HIV-infected cases and 329 controls HIV uninfected. This cross-sectional study utilized the 1999–2018 data from the U.S. National Health and Nutrition Examination Surveys (NHANES).

ANALYSIS: Bivariate and multivariate logistic regression was performed to determine the association between diabetes mellitus and HIV status and estimate predictors of diabetes mellitus among PLWHIV. In the regression model, statistical adjustments were made for socio-demographic factors (age, sex, education, marital status, race/ethnicity, and family income), behavioral factors (smoking, physical activity, and alcohol use), metabolic and clinical factors (cholesterol, body mass index, and high blood pressure).

RESULTS: The mean age of HIV-infected participants was 40.8±9.8 years. HIV-infected subjects were older, male, non-Hispanic blacks, never married, had some college or associate degree, and family income to poverty ratio <5 compared with HIV uninfected controls. Apart from alcohol use, there were significant differences in behavioral factors by HIV status. The prevalence of diabetes mellitus was 7.19% in the HIV-infected group and 4.59% in the control group, but there was no statistically significant difference between those two groups (p-value=0.2294). Controlling for age, gender, race, marital status, family income to poverty ratio, education, smoking at least 100 cigarettes in his life, monthly alcohol use, cholesterol level, obesity, and high blood pressure in the model, those who are HIV positive had a non-significant increased odds of having diabetes than their counterparts (Adjusted Odd Ratio: 1.24, p-value = 0,715, 95% CI: 0.39, 3.90). In this study, increasing age, being married, hypertension, and obesity appear to be predictors of diabetes among persons living with HIV.

CONCLUSION: Overall, the findings showed that the prevalence of type 2 diabetes was higher among PLWHIV compared to HIV uninfected controls, but the difference was not statistically significant. Being infected with HIV was not associated with increased odds of type 2 diabetes. Increasing age, being married, having hypertension, and obesity were found to be predictors of type 2 diabetes among PLWHIV.

CHAPTER I

INTRODUCTION

1.1. Background

Over the past years, there has been intense and sustained research interest in diabetes and its relationships with different health conditions and factors. Diabetes is defined as a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both (American Diabetes, 2014). Without appropriate intervention, elevated blood glucose levels can cause several metabolic abnormalities and disabling complications such as cardiovascular disease, eye disease, neuropathy, and kidney failure. Ranked as the 7th leading cause of death, type 2 diabetes affects approximately 29.1 million people in the United States.

The availability and access of Highly Active Antiretroviral Therapy (HAART) and anti-infective therapy has dramatically improved the lifespan of Persons Living With HIV (PLWHIV) (Nakagawa et al., 2012). However, with the increase of life expectancy, PLWHIV are experiencing other chronic medical conditions (Corbett et al., 2003). Diabetes mellitus is one of these chronic comorbidities. Studies have reported changes in glucose homeostasis or fat redistribution in HIV-infected patients(Rasmussen et al., 2012). Identified risk factors associated with the development of diabetes in persons without HIV are the same as those in PLWHIV, including higher triglyceride, older age, obesity, genetic, and hypertension(Justman et al., 2003). In addition to those common risk factors, HIV-infected individuals have other risk factors specific to HIV and HIV medicines. Moreover, some HIV drugs like Nucleoside reverse transcriptase inhibitors (NRTI) and protease inhibitors (PI) have been identified as having diabetogenic effects (De Wit et al., 2008; Eastone & Decker, 1997).

1.2. Purpose of the study

There is limited evidence-based knowledge and insufficient documentation of type 2 diabetes in persons living with HIV. Diabetes is an emerging health problem in the HIV-infected population that is imperative to examine the magnitude and determine associated risk factors. Therefore, this thesis aims to determine:

- the prevalence of type 2 diabetes among PLWHIV,
- odds of type 2 diabetes among PLWHIV
- predictors of type 2 diabetes among PLWHIV.

1.3. Research questions

This study addressed three specific research questions:

1. Is the prevalence of type 2 diabetes in persons living with HIV different from the general population?
2. Is there an association between type 2 diabetes and HIV status among PLWHIV?
3. What are predictors of type 2 diabetes among PLWHIV?

CHAPTER II

REVIEW OF THE LITERATURE

Understanding the magnitude and risk factors of type 2 diabetes (T2D) among people living with human immunodeficiency virus (HIV) is essential to reduce mortality due to complications, improve the quality of life, and prevent harmful effects on managing the outcomes of HIV. A detailed review of the literature related to T2D and its predictors in persons living with HIV was conducted to explore information and research studies already gathered on this topic.

2.1. Type 2 Diabetes overview

Once considered a disease of older people, type 2 diabetes (T2D) has now spread to every category of human beings in the world. In 2014, type 2 diabetes ranked the 7th leading cause of death in the United States (American Diabetes, 2014). According to the 2017 National Diabetes Statistics Report, the prevalence of DM in the US population was 10.5%, and approximately 21,4% are undiagnosed(Centers for Disease Control and Prevention, 2020, August 28). (9) This chronic condition is generally associated with other comorbidities such as cardiovascular diseases, arthritis, HIV, Tuberculosis, and Alzheimer's that threaten and worsen the quality of life. Type 2 diabetes is rising as the major non-infectious comorbid health issue in HIV-infected patients, but very little evidence exists on its disease burden.

Estimating the prevalence of this disease among persons living with HIV will facilitate the assessment and implementation of preventive intervention strategies and contribute to managing this specific population. There is a lack of information about type 2 diabetes prevalence among HIV-infected persons in the USA. A cross-sectional study conducted by Alfonso C Hernandez-Romieu et al., which used data from the Medical Monitoring Project and the National Health and Nutrition Examination Survey, has determined the T2D prevalence among HIV-infected adults was 10.3%. The study also found that this prevalence was 3.8% higher in HIV-infected adults than in general population adults (Hernandez-Romieu, Garg, Rosenberg, Thompson-Paul, & Skarbinski, 2017). A Multicenter AIDS Cohort Study conducted from 1999 to 2003 reported 14% diabetes prevalence (Brown et al., 2005). In another study of 419 treatment-naive HIV-infected subjects, 2.6% had diabetes (El-Sadr et al., 2005). Among non-US studies, T2D prevalence among HIV-infected individuals tends to be lower. A recent work by David Mohammed and Panjasaram Naidoo was concerned about the prevalence of T2D among HIV-infected individuals in KwaZulu-Natal, South Africa, estimated that 9% of the participants who have HIV had diabetes (Umar & Naidoo, 2021). An additional cross-sectional study in an HIV clinic in Ethiopia found an overall prevalence of diabetes of 8% (Abebe et al., 2016). These studies have demonstrated that the prevalence of type 2 diabetes is higher among PLWHIV compared to the general population.

2.2. Predictors of type 2 diabetes

Several factors are associated with type 2 diabetes in persons living with HIV. Literature has demonstrated that common risk factors for diabetes mellitus in the general population remain prevalent in this population (American Diabetes, 2014). Sociodemographic characteristics, mental and behavioral factors, genetic aspects, clinical and metabolic factors simultaneously or separately play a significant role in developing of type 2 diabetes.

One study by Alfonso C Hernandez-Romieu et al. observed that older age and obesity among HIV-infected persons were strongly associated with a higher prevalence of diabetes(Hernandez-Romieu et al., 2017). These findings have also been observed in numerous studies around the world (Capeau et al., 2012; Paengsai et al., 2018). The North Ethiopia study, which assessed the prevalence of type 2 diabetes and associated factors among HIV-infected adults, found similar conclusions(Abebe et al., 2016). Also, some studies found an association between educational attainment and the prevalence of diabetes (Leonetti, Tsunehara, Wahl, & Fujimoto, 1992; Tang, Chen, & Krewski, 2003). Luisa N. Borrell et al. used the National Health Interview Survey (NHIS) to analyze this association in US adults. They observed a significant positive odds ratio of 1.6 among individuals with less than a high-school diploma compared to at least a bachelor's degree for diabetes (Borrell, Dallo, & White, 2006)

Multiple studies on HIV-specific predictors have been conducted over time. Some of them are associated with the development of glucose disorders and type 2 diabetes. The Multicenter AIDS Cohort Study examined untreated HIV-infected patients and HIV-negative. The study found that fasting glucose was similar between HIV-negative participants and untreated HIV-infected patients (Brown et al., 2005). However, one study by El-Sadr et al. also observed that a higher CD4 lymphocyte count was associated with less evidence of insulin resistance. Additionally, the cross-sectional study conducted by Alfonso C Hernandez-Romieu et al. also found that the CD4 count nadir, a marker of systemic inflammation, was not associated with increased prevalence of diabetes after controlling for covariates (Hernandez-Romieu et al., 2017). More studies that elucidate the interaction between acute or chronic inflammation of HIV and the development of type 2 diabetes are needed.

Before developing combination antiretroviral therapy, glucose disorders and type 2 diabetes were relatively rare in PLWHIV. A late nineties study of 1392 adult HIV-infected patients attending a university clinic found that the prevalence of hyperglycemia (random glucose >11.0 mmol/L) was 2%. The study also found that fasting glucose was significantly lower in untreated HIV patients than those treated with combination antiretroviral therapy (Kilby & Tabereaux, 1998). Today, research by Brown TT et al. represents the current state demonstrating that systemic inflammation due to the initiation of HIV-antiretroviral therapy is associated with the development of diabetes. The research found that patients with higher levels of inflammatory markers such as CRP, sTNFR1, and sTNFR2 at 48 weeks had an increased odd of subsequent diabetes after adjustment for covariates. The findings of this recent research show similar results to a retrospective cohort study conducted in Thailand on HIV-infected adults.

CHAPTER III

METHODS AND PROCEDURES

3.1. Study design

This is a cross-sectional study that used data from 1999 to 2018 of the National Health and Nutritional Examination Surveys (NHANES) to estimate type 2 diabetes prevalence, determine its predictors among HIV-infected adults, and the association between type 2 diabetes and HIV status. The NHANES is a cross-sectional health examination survey conducted by the National Center for Health Statistics (NCHS), under the Centers for Disease Control and Prevention (CDC), that assesses the health and nutritional status of the general non-institutionalized US population. Each year, the survey enrolls approximately a nationally representative sample of 5000 persons for interviews and physical examinations in 15 counties across the US. Participants were interviewed in their homes and subsequently received physical and laboratory examinations in mobile examination centers. Descriptions of the sampling plan and examination and interview protocol are published elsewhere (National Center for Health Statistics) and available at the National Center for Health Statistics (NCHS) website.

3.2. Inclusion criteria

The study was restricted to participants of 1999–2018 NHANES. Only adults 20 years and older tested for HIV antibody and with values for the following variables: sex, age, race/ethnicity, marital status, education, family income, Body Mass Index (BMI), blood pressure, total cholesterol level, alcohol use, smoking status, and physical activity were eligible for this study.

3.3. Study population

This study was restricted to adults 20 years and older with values for the following variables: sex, age, race/ethnicity, marital status, education, family income, Body Mass Index (BMI), blood pressure, total cholesterol level, alcohol use, smoking status, physical activity, and HIV antibody test. From 1999 to 2018 NHANES data, 170 participants who tested HIV positive were included in this study and considered as cases. We performed a simple random sampling from the same survey data, and 329 controls HIV uninfected participants were identified based on their age range.

3.4. Measures

The primary research outcome variable is diabetes mellitus. In NHANES, diabetes mellitus is defined using the following criteria: Participants who answered "yes" to the question: (i) "Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?"; or those answered "yes" to any of the following questions: (a) "Are you now taking insulin?"; or (b) "Are you now taking diabetic pills to lower your blood sugar?" Patients on Metformin monotherapy who answered "No" to question (i) were excluded because of the use of this medication for pre-diabetes and polycystic ovarian syndrome. HbA1c measurements have not been validated to diagnose type 2 diabetes among HIV-infected individuals.

Sociodemographic variables included age, gender, race/ethnicity, marital status, education, and family income to poverty ratio. We categorized age into four different classes (20-30, 31-40, 41-50, and 51-60 years old). Gender was dichotomized into male and female. We compared non-Hispanic whites with other racial subgroups (Non-Hispanic Blacks, Hispanics, and other Races). We also compared different marital statuses (widowed, divorced or separated, never married, living with a partner) with married. We included education on an increasing level as laid down by NHANES (Table 1A). Finally, we dichotomized the family income to poverty ratio as lower or higher than 5.00.

Clinical variables included body mass index (BMI), high blood pressure (HBP), total cholesterol level, and HIV antibody test. Body mass index (BMI) was measured using standardized techniques and equipment. BMI ≥30 kg/m2 was considered indicative of obesity. Normal weight was defined as a BMI value of less than 25 kg/m2 and greater than 18 kg/m2. High blood pressure was defined by participants who responded "yes" to the following question:" Have you ever been told by a doctor or other health professional that you had hypertension, also called high blood pressure?". Using the USA National Cholesterol Education Program, average+ cholesterol level was defined as values below 200 mg/dl (5.2mmol/l), and values higher than 200 mg/dl (5.2mmol/l) were indicative of hypercholesterolemia (National Cholesterol Education Program Expert Panel on Detection & Treatment of High Blood Cholesterol in, 2002). HIV serological and molecular blood test results were performed using the GS Combo Ag/Ab Enzyme Immunoassay (EIA) (Bio-Rad Laboratories, Redmond, WA) test method. This test simultaneously detects HIV-1 p24 antigen and antibodies to HIV-1, groups M and O, and HIV-2.

Behavioral variables include alcohol use, smoking status, and physical activity. Information on smoking status and alcohol consumption was obtained by questionnaire. Alcohol use was defined as the average number of drinks per month. Participants' smoking status was d by answering the question: "Have you smoked at least 100 cigarettes in your life?". Finally, physical activity was related to the answer to the question:" Over the past 30 days, have you walked or bicycled as part of getting to and from work, or school, or to do errands?"

3.5. Statistical Analysis

The Statistical Analysis System (SAS) software version 9.4 was used to download and analyze data. We compare sociodemographic, behavioral, metabolic, and clinical characteristics in the descriptive statistics by HIV positive and negative status. Bivariate and multivariate logistic regression were performed to determine the association between diabetes mellitus with HIV status and different risk factors. Multivariate logistic regression model adjusted for age, gender, race, marital status, family income to poverty ratio, education, smoking at least 100 cigarettes in his life, monthly alcohol use, cholesterol level, obesity, and high blood pressure. Results are presented as tables and figures. We considered p-values less than 0.05 and 95% confidence intervals statistically significant.

CHAPTER IV

RESULTS

4.1. Demographics

The total sample of this study consisted of 499 participants (170 HIV-infected subjects and 329 HIV uninfected controls). The mean age of HIV-infected participants was 40.8±9.8 years, with the majority (31.18%) between 41-50 years (Figure 1). The mean age of HIV controls was 36.8±10.9 years, with the majority (35.56%) aged 20 – 30 years (Figure1). HIV-infected persons were male (73.53%) and African American (65.88%), while HIV uninfected controls were female and Caucasian (53.19% and 36.78%, respectively). Among HIV-infected individuals, 37.65% had college or associate degrees, 25.29% were below 12th grade, 22.94% were high school graduates, and only 13.53% were college graduates or above. Among HIV controls, 28.27% had some college or associate degrees, 25.53% were college graduates or above, 23.71% were below 12th grade, and 22.49% were high school graduates. 46.11% of PLWHIV were "never married", and 51.99% of HIV uninfected persons were "married." Infected groups were significantly different by family income to poverty ratio (91.76% had a family income to poverty ratio <5.00) compared with HIV uninfected controls (83.89%). There were significant differences in all these demographic factors by HIV status or diagnosis. Thus, overall HIV-infected subjects were older, male, non-Hispanic black, never married, had some college or associate degree, and family income to poverty ratio <5 compared with HIV uninfected controls. The demographic distribution by HIV-infected and uninfected participants is shown in Table 1A.

4.2. Behavioral factors

Of the 170 HIV-infected participants, 101 (59.41%) reported to have smoked at least 100 cigarettes in their life, and 134 (40.73%) of 329 HIV uninfected participants reported that they smoked at least 100 cigarettes in their life (p-value < 0.0001). HIV-infected and uninfected groups were less likely to participate in physical activity (39.51% and 21.13%, respectively) and had less alcohol use (90.00% and 86.93%, respectively). Apart from alcohol use, there were significant differences in these behavioral factors by HIV status (Table 1A).

4.3. Diabetes Diagnosis

Participants were asked if a doctor had ever told them they had diabetes. Based on the response, the prevalence of type 2 diabetes was 7.19% in the HIV-infected group and 4.59% in the control group. Still, there was no statistically significant difference between those two groups (p-value=0.2294). HIV-infected subjects had less use of insulin, but more use of diabetic pills compared with HIV uninfected group. About 3.70% use insulin among HIV-infected participants compared to 1.55% among HIV controls. The Chi-square test of difference of insulin use showed no significance among these two groups (p-value = 0.1326). Of HIV-infected participants who had diabetes, 28.57% were under diabetic pills medication compared to 33.33% of their counterparts. The Chi-square test of difference also showed no significance among these two groups (p-value = 0.7240). (Table 1B)

4.4. Metabolic and Clinical factors

Among HIV-infected participants, 72.96% had cholesterol levels of less than 200mg/dl, and 27.04% had more than 200mg/dl. Among HIV uninfected subjects, 69.09% had normal cholesterol levels, and 30.91% had more than 200mg/dl. There was no statistically significant difference in cholesterol level between participants with HIV and without (p-value=0.1718). Among HIV-infected participants, 4.71% had a body mass index (BMI) less than 18.5kg/m^2, 37.06% were at the normal BMI (18.5-25kg/m^2), 31.76% were between 25-30 kg/m^2, and 26.47% were considered obese with a BMI more 30 kg/m^2. Among controls, 1.22% had a BMI less than 18.5kg/m^2, 29.97% were at the normal BMI limit (18.5-25kg/m^2), 32.11% were between 25-30 kg/m^2, and 36.70% were considered obese with a BMI more 30 kg/m^2. The Chi-square test difference showed significance between HIV-infected and uninfected groups (p-value =0.0124). HIV-infected participants appeared to have a lower mean BMI than HIV-infected controls. (Figure 4) Additionally, 31.76% of HIV-infected participants were more likely to have hypertension compared to 19.88% in the control group. The Chi-square test difference showed significance between HIV-infected and uninfected groups (p-value =0.0032). The metabolic and clinical factors distributed by HIV-infected and uninfected participants are shown in Table 1B.

4.5. Bivariate Analysis

In a bivariate logistic regression model, increased age was associated with an increased odds of type 2 diabetes (OR 1.09, 95% CI 1.05 - 1.14). A positive HIV result was associated with increased odds (OR=1.61; 95% CI =0.74-3.52) of type 2 diabetes, but there was no statistically significant difference. Compared with non-Hispanic whites racial/ethnic group; being of Hispanic, African-American, and other racial/ethnic groups were associated with increased odds of 1.65, 2.20, and 1.86, respectively. However, these associations were not statistically significant. Compared to college graduate degrees, non-college graduates presented a 63% much greater odds of type 2 diabetes, but no statistically significant. (Table 2A)

Additionally, the bivariate analysis results in Table 2B showed that increased age was associated with an increased odds of high cholesterol level (OR 1.02, 95% CI: 1.001, 1.04). (Table 2B)

In an unadjusted bivariate logistic regression, having a positive HIV status was associated with decreased odds (OR 0.62, 95% CI 0.41-0.93) of obesity compared the HIV-negative group. Compared to men, being females was associated with an odds ratio of 2.9 (p-value <0.0001, 95% CI: 1.97- 4.26) obesity. Subjects who smoked less than 100 cigarettes in their life were associated with an increased odds ratio of 1.79 (p-value= 0.0029, 95% CI: 1.22, 2.62) for having obesity than those who smoked more. In this analysis, increasing age, education, and alcohol use were respectively associated with obesity (OR=1.01, OR=1.22, OR=1.03), but they did not reach the significance level. (Table 2C)

Table 2D shows the result of bivariate logistic regression analysis. HIV-infected participants were 1.88 (p-value= 0.0034, 95% CI 1.23-2.86) times more likely to have a high blood pressure than HIV uninfected. Also, increased age was associated with an increased odds of high blood pressure (OR 1.08, 95% CI: 1.06 - 1.105). Non-Hispanic blacks were 94% more likely to have high blood pressure than non-Hispanic whites (p-value= 0.0101,95% CI: 1.06 - 1.105). (Table 2D)

4.6. Multivariate Analysis

The result of multivariate analysis is shown in Table 3. Participants with positive HIV results had an increased odds of type 2 diabetes compared to HIV-negative participants (AOR: 1.24, 95% CI: 0.39, 3.90), adjusting for age, gender, race, marital status, family income to poverty ratio, education, smoking at least 100 cigarettes in his life, monthly alcohol use, cholesterol level, obesity, and high blood pressure. Also, increased age was associated with odds of 1.078 (p-value = 0.026, 95% CI: 1.01, 1.15) for type 2 diabetes. Not being married was associated with a decreased odds of type 2 diabetes mellitus compared to the married group, adjusting for covariates (OR: 0.16, 95% CI: 0.05, 0.52). Participants with no high blood pressure were associated with a decreased odds of having (OR: 0.13, p-value=0.002, 95% CI: 0.04, 0.41) compared to those with hypertension. In the same model, those with obesity were at 473% (p-value = 0.0054, 95 % CI: 1.67, 19.63) with greater odds of having type 2 diabetes compared to non-obese subjects. Although race/ethnicity (OR: 2.32, 95% CI: 0.59 – 8.9), education (OR: 1.64, 95% CI: 0.37 – 7.32), alcohol use (OR: 1.51, 0.24 – 9.70), and cholesterol level (OR: 1.16, 95% CI: 0.39 – 3.42) appeared to have positive odds ratios of having type 2 diabetes controlling for all covariates; we did not find significant associations between diabetes diagnosis and these factors.

CHAPTER V

DISCUSSIONS

5.1. Discussions of Research Questions

The result of this study shows that the prevalence of type 2 diabetes was higher among HIV-infected participants (7.19%) than the controls (4.59%), but the rates were not statistically significant. This high prevalence could be attributed to the fact that HIV-infected individuals were older (40.8±9.8 years) than the controls (36.8±10.9 years). (Figure 2) Since diabetes is associated with an increase in age, this may play a factor or not. A recent cross-sectional study conducted in 2018 showed an increased prevalence of type 2 diabetes among PLWHIV (15.1%) in 2015 compared to 2005 (6.8%) (Duncan, Goff, & Peters, 2018). Another cross-sectional study, which used data from the Medical Monitoring Project and the National Health and Nutrition Examination Survey, has determined the diabetes prevalence among HIV-infected adults was 10.3% in 2010. This prevalence was 3.8% higher in HIV-infected adults than in the general population adults. (Hernandez-Romieu et al., 2017). One previous study exclusively limited to HIV-infected men that investigated the risk of T2D in PLWHIV receiving highly active antiretroviral therapy (HAART) estimated a prevalence of 14%, which was also higher than the rate in the general population (5%)(Brown et al., 2005). Conversely, a study of a large antiretroviral-naïve cohort in 2005 showed a low prevalence of 2.6% type 2 diabetes among HIV-infected subjects, but participants in this study were relatively young (El-Sadr et al., 2005). Another study conducted among HIV-infected and uninfected veterans in 2009 found a lower prevalence of type 2 diabetes (14.9% vs. 21.4%, respectively)(Butt et al., 2009). Some non-US studies have also shown the relatively high prevalence of type 2 diabetes among

PLWHIV compared to their counterparts, which is consistent with our finding. A recent work concerned about the prevalence of type 2 diabetes among HIV-infected individuals in KwaZulu-Natal, South-Africa, estimated that 9% of the participants suffering from HIV had diabetes compared to 5.4% in the population (Umar & Naidoo, 2021). In the San Raffaele Infectious Diseases Department in Milan, Italy, a cross-sectional study found a higher significant prevalence of type 2 diabetes in HIV-infected (4.1%) than healthy subjects (2.5 %) (Galli et al., 2012). The difference in type 2 diabetes prevalence between the US and non-US studies may be related to the demographic composition and regional divergence.

In the logistic model, we found a non-significant positive association between type 2 diabetes and HIV status. Participants who are HIV positive had a non-significant increased odds of having type 2 diabetes than their counterparts (AOR: 1.24, p-value = 0,7151, 95% CI: 0.39 -3.90). (Table 3) The Italian cross-sectional study obtained a significant increased odds of type 2 diabetes among PLWHIV. They found that those with HIV were associated with higher odds for type 2 diabetes (OR: 1.70, p-value= 0.009, 95 % CI: 1.12–2.51)(Galli et al., 2012). However, one recent study using information from the Veterans Aging Cohort Study aimed at determining the association between HIV infection and type 2 diabetes obtained a lower odd of diabetes (OR= 0.84, 95 % CI: 0.72-0.97) in HIV infected veterans (Butt et al., 2009). The difference between the Italian and Veterans study could be attributed to the fact that HIV-infected participants were younger in the Veteran's study, possibly resulting in a decreased likelihood for type 2 diabetes mellitus. Some studies, including complex factors, showed various associations between HIV infection and type 2 diabetes. The Danish Nationwide Population-Based Cohort Study analyzed whether there was an association before and after Highly Active Antiretroviral Therapy (HAART) initiation. They noticed a higher risk of T2D in PLWHIV from 1996 to 1999 both before and after initiation (ARR: 2.83; 95% CI: 1.57–5.09)(Rasmussen et al., 2012). In a recent Thailand cohort study, Ninutcha Paengsai and colleagues found that newly type 2 diabetes diagnosed individuals were more frequent after ART initiation (Paengsai et al., 2018). A hospital-based cross-sectional study in Northwest Ethiopia concluded that T2D was associated with HIV among subjects taking both pre-antiretroviral (13.2%; 95% CI 8.0% to 18.3%) and ART treatment (5.1%; 95% CI 2.6% to 7.6%) (Abebe et al., 2016). Additionally, multiple previous studies demonstrated that the initiation of some classes of antiretroviral drugs such as protease inhibitors (Behrens et al., 1999; Eastone & Decker, 1997; Salehian, Bilas, Bazargan, & Abbasian, 2005), Nucleoside reverse transcriptase inhibitors (De Wit et al., 2008) was associated with an increased risk of diabetes (Noubissi, Katte, & Sobngwi, 2018). Further investigations are needed to understand the different interactions of diabetic drugs with antiretroviral therapy. In our study, socio-demographic components, behavioral factors, and some metabolic and clinical aspects were involved in the process of determining the relationship of type 2 diabetes among PLWHIV.

Investigating whether HIV infection increases the risk for diabetes is challenging due to multiple confounders making the matching process difficult. A systematic review and meta-analysis by Xia Wang et al. on inflammatory markers and risk of type 2 diabetes showed that higher concentrations of IL-6 and C reactive protein (CRP) are significantly associated with the development of diabetes (Wang et al., 2013). Even low-grade inflammation has been shown to be positively associated with diabetes (Lontchi-Yimagou, Sobngwi, Matsha, & Kengne, 2013; Pitsavos et al., 2007; Wellen & Hotamisligil, 2005). Previous studies among PLWHIV showed a connection between the lower level of CD4 with increased CRP and Interleukin 6 (Brown et al., 2005; Capeau et al., 2012). On the other hand, El-Sadr et al. found that a higher CD4 lymphocyte count was associated with less evidence of insulin resistance (El-Sadr et al., 2005). A recent cross-sectional study focused on markers of systemic inflammation, which are known to be higher in HIV infected patients (Matuzkova et al., 2019), concluded that the CD4 count nadir was not associated with increased prevalence of diabetes after controlling for covariates (Hernandez-Romieu et al., 2017). More studies that elucidate the interaction between acute or chronic inflammation of HIV and the development of diabetes are needed.

Like anterior studies, we observed a strong association between increasing age, obesity, and hypertension among PLWHIV, indicating that these common risk factors considerably contribute to the occurrence of type 2 diabetes among HIV-infected individuals. Findings from our study showed that increasing age was associated with 1.078 greater odds of having diabetes mellitus, controlling for all covariates. (Table 3) HIV-infected subjects who have diabetes were older than any other subgroups. (Figure 3) One study aimed at investigating whether old age is a risk factor to chronic medical conditions in HIV-infected persons showed similar findings to our research. (Palella et al., 2019) Our result was also identical to that of the antiretroviral-naïve cohort, which found older age was associated with higher glucose levels (El-Sadr et al., 2005). Increasing age also had more effect on the risk of diabetes in the HIV infected than uninfected veterans. (Butt et al., 2009). Alfonso C Hernandez-Romieu et al. observed that older age and obesity among HIV-infected persons were strongly associated with a higher prevalence of diabetes. (Hernandez-Romieu et al., 2017). Furthermore, a non-US study conducted in Denmark also confirmed our result (Rasmussen et al., 2012).

Moreover, being married was found to be a predictor of diabetes in this study. Other marital statuses were 83.5% less likely to have diabetes than married subjects (Table 3). A recent long-term follow-up study by Azra Ramezankhani obtained similar results to our research. They found that never-married men and women had a significantly lower risk of type 2 diabetes. The risk of T2D substantially decreased among widowed women compared to married women after adjusting for age (Ramezankhani, Azizi, & Hadaegh, 2019). In this cohort study, never-married men and women were younger and had a lower mean BMI; this could explain the lower risk. On the other hand, some studies found that different subgroups were more significantly associated with the development of diabetes than married (Schwandt, Coresh, & Hindin, 2010). Although, Karamatollah Rahmanian et al., in their study on T2D in Iran, did not find a significant association between marital status and the development of diabetes (Rahmanian, Shojaei, & Sotoodeh Jahromi, 2013). Mechanisms underlying this relationship are not entirely understood, but some suggest they might be an effect of complex components such as health behaviors, biological factors, mental health outcomes (Whisman, Li, Sbarra, & Raison, 2014).

Additionally, our study found that BMI was significantly associated with type 2 diabetes. HIV-infected participants who have diabetes appear to have a BMI higher than 30kg/m^{2}. (Figure 4) Several previous studies demonstrated that obesity is one of the major risk factors for developing type 2 diabetes both in the general population and in persons living with HIV (Abebe et al., 2016; Buendia, Sears, Griffin, & Mgbere, 2021; Hernandez-Romieu et al., 2017; Lontchi-Yimagou et al., 2013). One Case-control study that assessed characteristics associated with the development of type 2 diabetes in HIV individuals showed that body mass index (BMI) was associated with type 2 diabetes (OR:1.13, p-value=

0.012, 95% CI: 1.03-1.23) (Yoon, Gulick, Hoover, Vaamonde, & Glesby, 2004). On the other hand, Faizal Samad et al. did not find a significant association between obesity (high BMI) and the development of T2D in PLWH (Samad et al., 2017). Multiple theories link and suggest several pathways in the process of developing diabetes mellitus among persons with obesity. Nowadays, insulin resistance and inflammatory cascade remain the most incriminated in the general and HIV-infected populations (Capeau et al., 2012; Noubissi et al., 2018).

Numerous past studies denoted that hypertension was one of the common predictors of type 2 diabetes in the general population. Recent advances in understanding the process in PLWHIV provided new insights and perspectives (Abebe et al., 2016; Duncan et al., 2018).

5.2. Strengths and limitations

Due to our study design, time-related relationships between T2D and HIV diagnosis as well as T2D and its predictors were impossible to determine. Longitudinal study design could provide further information on the time-related association between type 2 diabetes and HIV in HIV-infected individuals. Moreover, this study was designed as an observational cross-sectional, which means a firm causal relationship or association cannot be inferred. The sample size did not contain enough HIV infected participants and diabetic cases to provide further results of different predictors. Moreover, this study did not include certain potential confounders known to be associated with type 2 diabetes among HIV-infected individuals, such as diet, family history of diabetes, antiretroviral initiation, and inflammation markers.

Despite these limitations, the use of NHANES data remains a major and essential strength of the study. The NHANES, an extensive national survey with robust sampling methodology, contains demographic, lifestyle, clinical, and laboratory data needed for the purpose of this study. Survey sample weights in NHANES account for the differential probabilities of selection, nonresponse to survey instruments, and differences between the final sample and the total population.

5.3. Conclusions and recommendations

Overall, the findings showed that the prevalence of type 2 diabetes was higher among PLWHIV compared to HIV uninfected controls, but the difference was not statistically significant. HIV-infected participants were associated with a non-significant increased odds of developing diabetes mellitus. Increasing age, being married, hypertension, and obesity were found to be predictors of diabetes among PLWHIV.

It is essential to incorporate the diagnosis and care of non-communicable chronic diseases, including diabetes, into the current HIV management structure. This can potentially help maximize the use of available resources and improve the outcomes of diseases such as diabetes among persons living with HIV. Given that the prevalence and predictors of diabetes among PLWHIV are not well understood, this study can be informative and relevant for future research in that field.

Therefore, it is essential to monitor and screen for glycemic disorders to control and prevent the development of type 2 diabetes in the HIV-infected population. The study further proposes more future research to examine these conclusions.

Table 1A. Summary characteristics of HIV-infected (cases) and uninfected persons (controls).

Participant Characteristics N= 499	HIV+(n=170)		HIV-(n=329)		p-value
Socio-demographic characteristics					
Age, mean (SD) years	40.8 (9.8)		36.8 (10.9)		<.0001*
Age, years n (%)					
20 – 30	33	(19.41)	117	(35.56)	0.0026*
31 – 40	50	(29.41)	81	(24.62)	
41 – 50	53	(31.18)	84	(25.53)	
51 – 60	34	(20.00)	47	(14.29)	
Sex, n (%)					
Male	125	(73.53)	154	(46.81)	<.0001*
Female	45	(26.47)	175	(53.19)	
Race, n (%)					
Hispanic	26	(15.29)	103	(31.31)	<.0001*
Caucasian	29	(17.06)	121	(36.78)	
African American	112	(65.88)	75	(28.27)	
Other	3	(1.76)	30	(9.12)	
Education attainment, n (%)					
Below 12th grade	43	(25.29)	78	(23.71)	0.0128*
High school graduate	39	(22.94)	74	(22.49)	
Some college/AA degree	64	(37.65)	93	(28.27)	
College graduate or above	23	(13.53)	84	(25.53)	
Marital status, n (%)					
Married	38	(22.75)	170	(51.99)	<.0001*
Widowed	3	(1.8)	1	(0.31)	
Divorced/separated	24	(14.37)	35	(10.70)	
Never married	77	(46.11)	86	(26.30)	
Living with partner	25	(14.97)	35	(10.70)	
Ratio of family income, n (%)					
<5.00	156	(91.76)	276	(83.89)	0.0145*
=5.00	14	(8.24)	53	(16.11)	
Behavioral factors					
Smoking, (smoked at least 100 cigarettes in his life), n (%)					
Yes	101	(59.41)	134	(40.73)	<.0001*
No	69	(40.59)	195	(59.27)	
Physical Activity, n (%)					
Yes	32	(39.51)	30	21.13	0.0032*
No	49	(60.49)	112	78.87	
Alcohol use (average number of drinks per month), n (%)					
< 4	153	(90.00)	286	(86.93)	0.3878
4-15	15	(8.82)	41	(12.46)	
> 15	2	(1.18)	2	(0.61)	

* Significant result

Table 1B: Distribution of diabetes status and other metabolic/clinical factors by HIV

	HIV+(n=170)		HIV-(n=329)		p-value
Diabetic status, n (%)					
Yes	12	(7.19)	15	(4.59)	0.2294
No	155	(92.81)	312	(95.41)	
Insulin, n (%)					
Yes	6	(3.70)	5	(1.55)	0.1326
No	156	(96.30)	318	(98.45)	
Diabetic pills, n (%)					
Yes	6	(28.57)	9	(33.33)	0.7240
No	15	(71.43)	18	(66.67)	
Metabolic and clinical factors					
Cholesterol, mg/dl (%)					
< 200	116	(72.96)	195	(69.09)	0.1718
200 - 240	42	(26.42)	94	(30.91)	
> 240	1	(0.63)	-	-	
Body Mass Index, Kg/m^2 (%)					
<18.5	8	(4.71)	4	(1.22)	0.0124*
18.5-25	63	(37.06)	98	(29.97)	
25-30	54	(31.76)	105	(32.11)	
>30	45	(26.47)	120	(36.70)	
High Blood Pressure, n (%)					
Yes	54	(31.76)	65	(19.88)	0.0032*
No	116	(68.24)	262	(80.12)	

* Significant result

Table 2A: Bivariate analysis of diabetes regressed on sociodemographic and behavioral factors

Variables	Odds ratio	P-value	95% CI
1. Socio-demographic factors			
HIV Positive vs HIV Negative	1.61	0.2331	0.74 - 3.52
Age *	1.09	<.0001*	1.05 - 1.14*
Female vs Male	0.73	0.4344	0.33 - 1.62
Hispanic vs non-hisp white **African American** vs non-hisp white **Other races** vs non-hisp white	1.65 2.20 1.86	0.4012 0.1424 0.4712	0.38 - 5.34 0.77 - 6.32 0.34 - 10.02
Other marital status vs Married	0.49	0.0757	0.22 – 1.08
Ratio of family income	0.84	0.1995	0.65 - 1.09
Other educational level vs college degree	1.63	0.3761	0.55 - 4.82
2. Behavioral factors			
No smoking Vs Smoking	0.71	0.3829	0.32 - 1.54
Physical activity vs No physical activity	0.64	0.5849	0.13 - 3.12
Alcohol use	0.87	0.2976	0.67 - 1.13

* Significant result

Table 2B: Bivariate analysis of cholesterol regressed on sociodemographic and behavioral factors

Variables	Odds ratio	P-value	95% CI
1. Socio-demographic factors			
HIV Positive vs HIV Negative	0.77	0.229	0.50 - 1.20
Age*	1.02	0.036*	1.00 - 1.04*
Female vs Male	0.99	0.959	0.67 - 1.48
Hispanic vs non-hisp white **African American vs** non-hisp white **Other races vs** non-hisp white	0.91 0.68 1.3	0.742 0.123 0.525	0.53 - 1.56 0.41 - 1.11 0.58 - 2.95
Other marital status vs Married	0.84	0.396	0.56 - 1.26
Ratio of family income	0.997	0.966	0.88 - 1.13
Other educational level vs college	0.68	0.101	0.42 - 1.08
2. Behavioral factors			
No smoking Vs Smoking	0.8	0.289	0.54 - 1.2
Physical activity vs No physical activity	1.33	0.389	0.69 - 2.56
Alcohol use	1.02	0.7004	0.94 - 1.10

* Significant result

Table 2C: Bivariate analysis of obesity (BMI) regressed on sociodemographic and behavioral factors

Variables	Odds ratio	P-value	95% CI
1. Socio-demographic factors			
HIV Positive vs HIV Negative*	0.62	0.022*	0.41 - 0.93*
Age	1.01	0.154	0.99 - 1.03
Female vs Male*	2.9	<0.0001*	1.97 - 4.26*
Hispanic vs non-hisp white **African American** vs non-hisp white **Other races** vs non-hisp white	1.3 1.35 0.41	0.311 0.198 0.087	0.78 - 2.14 0.85 - 2.14 0.15 - 1.14
Other marital status vs Married	0.79	0.219	0.54 - 1.15
Ratio of family income	0.94	0.323	0.83 - 1.06
Other educational level vs college	1.22	0.353	0.80 - 1.84
2. Behavioral factors			
No smoking Vs Smoking *	1.79	0.0029*	1.22 - 2.62*
Physical activity vs No physical activity	1.12	0.729	0.60 - 2.08
Alcohol use	1.03	0.409	0.96 - 1.11

* Significant result

Table 2D: Bivariate analysis of high blood pressure (HBP) regressed on sociodemographic and behavioral factors

Variables	Odds ratio	P-value	95% CI
1. Socio-demographic factors			
HIV Positive vs HIV Negative*	1.88	0.0034*	1.23 - 2.86*
Age*	1.08	<.0001*	1.06 - 1.105*
Female vs Male	0.89	0.5713	0.58 - 1.34
Hispanic vs non-hisp white **African American** vs non-hisp white* **Other races** vs non-hisp white	0.96 1.94 0.43	0.8967 0.0101* 0.1863	0.53 - 1.74 1.17 - 3.2* 0.12 - 1.5
Other marital status vs Married	1.19	0.4065	0.78 - 1.82
Ratio of family income	0.95	0.4733	0.83 - 1.09
Other educational level vs college	1.10	0.7091	0.66 - 1.83
2. Behavioral factors			
No smoking Vs Smoking	0.77	0.228	0.51 - 1.17
Physical activity vs No physical activity	1.90	0.07	0.95 - 3.82
Alcohol use	0.99	0.8417	0.91 - 1.08

* Significant result

Table 3: Multivariate analysis of Diabetes on HIV status controlling for socio-demographic, behavioral, metabolic, and clinical factors.

Variables	Odds ratio	P-value	95% CI
HIV Positive vs HIV Negative	1.24	0.715	0.39 – 3.90
Age*	1.08	0.026*	1.01 - 1.15*
Female vs Male	0.38	0.101	0.12 – 1.21
All Other races vs non-hisp white	2.32	0.224	0.59 – 8.99
Other marital status vs Married *	0.16	0.002*	0.05 – 0.52*
Ratio of family income	0.77	0.186	0.53 – 1.13
Other educational level vs college	1.64	0.514	0.37 – 7.32
No smoking Vs Smoking	0.59	0.376	0.19 – 1.88
No Alcohol use vs alcohol use	1.51	0.663	0.24 – 9.70
Cholesterol	1.16	0.788	0.39 - 3.42
Obesity vs no obesity*	5.73	0.0054*	1.67 – 19.63*
High Blood Pressure*	0.13	0.0004*	0.04 – 0.41*

* Significant

Figure 1. Age group distribution by HIV status

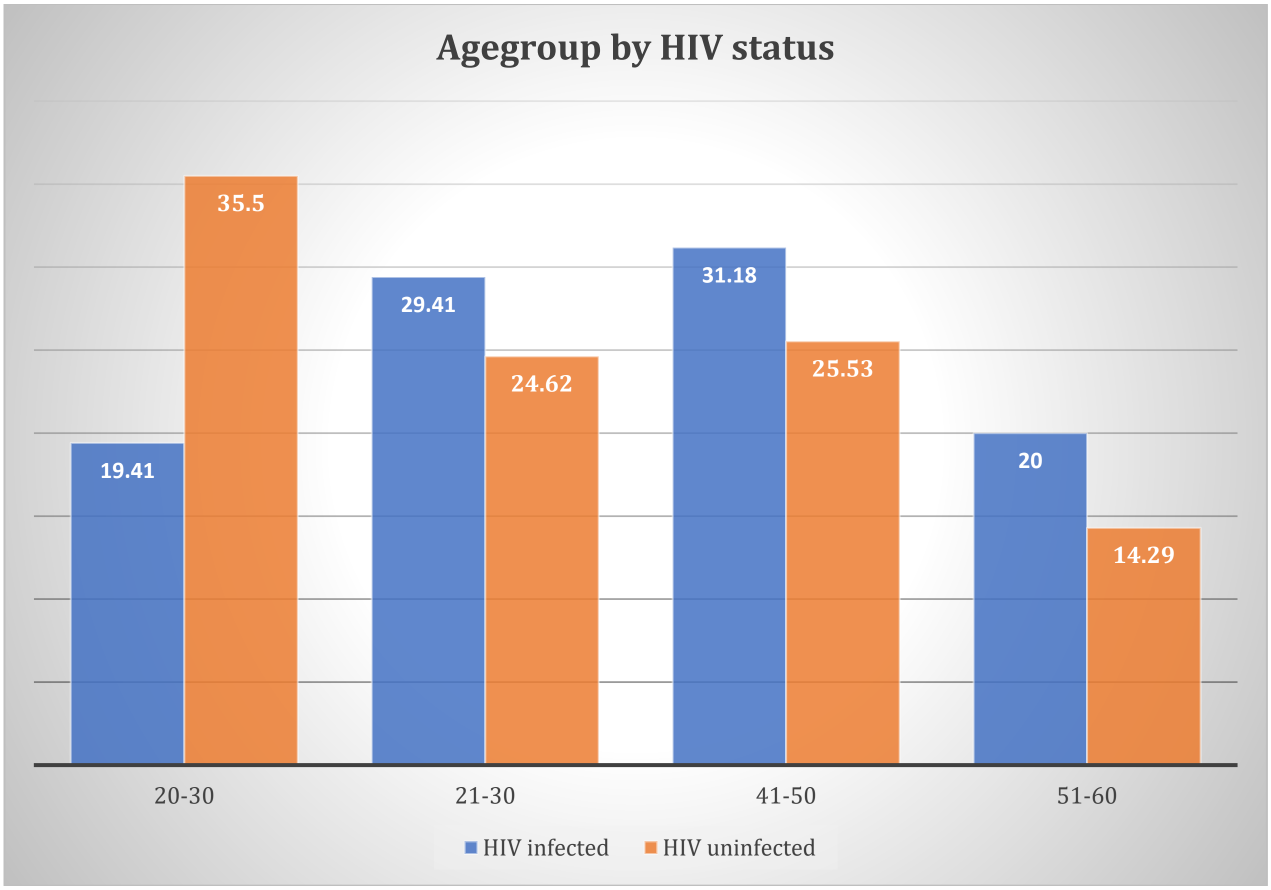


Figure 2: Boxplot of age distribution by HIV status

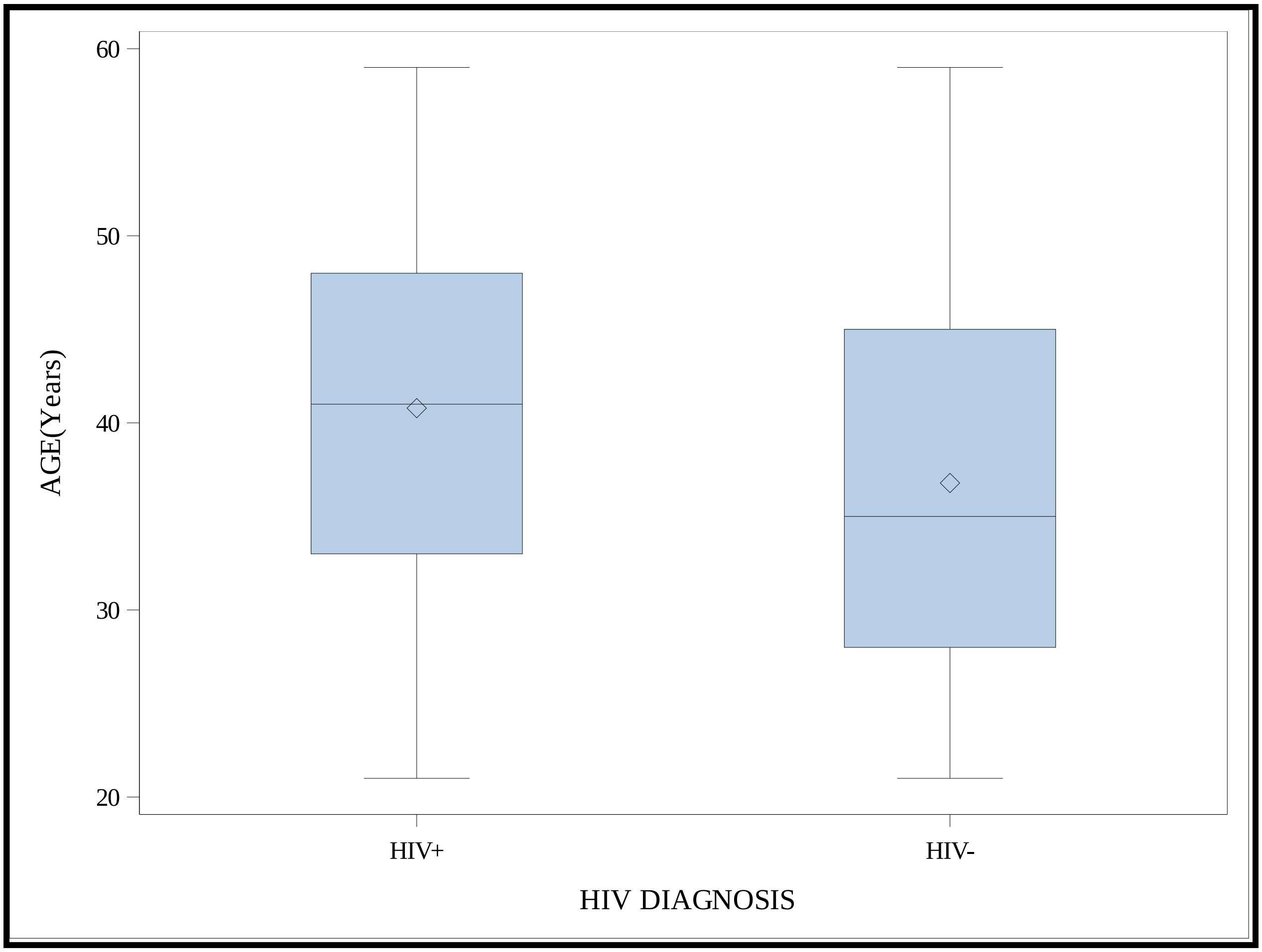


Figure 3: Box plot of age distribution by HIV status and diabetes status

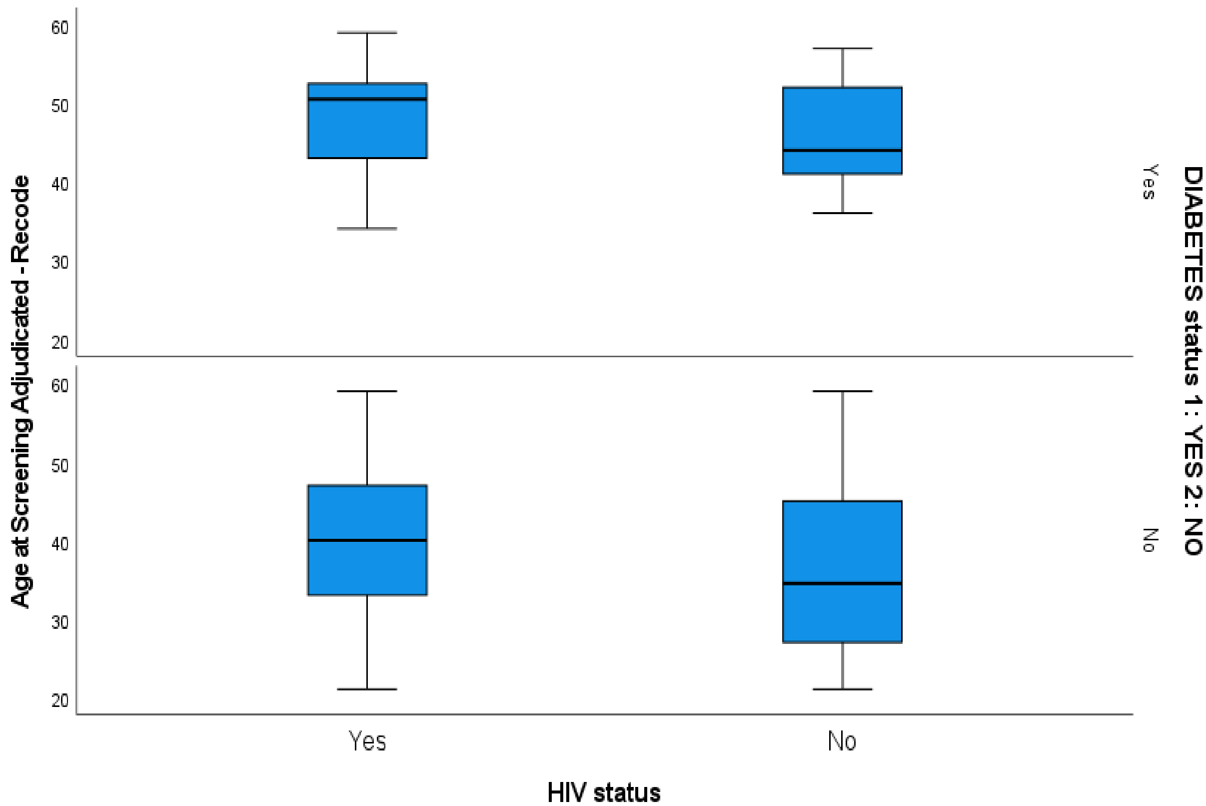
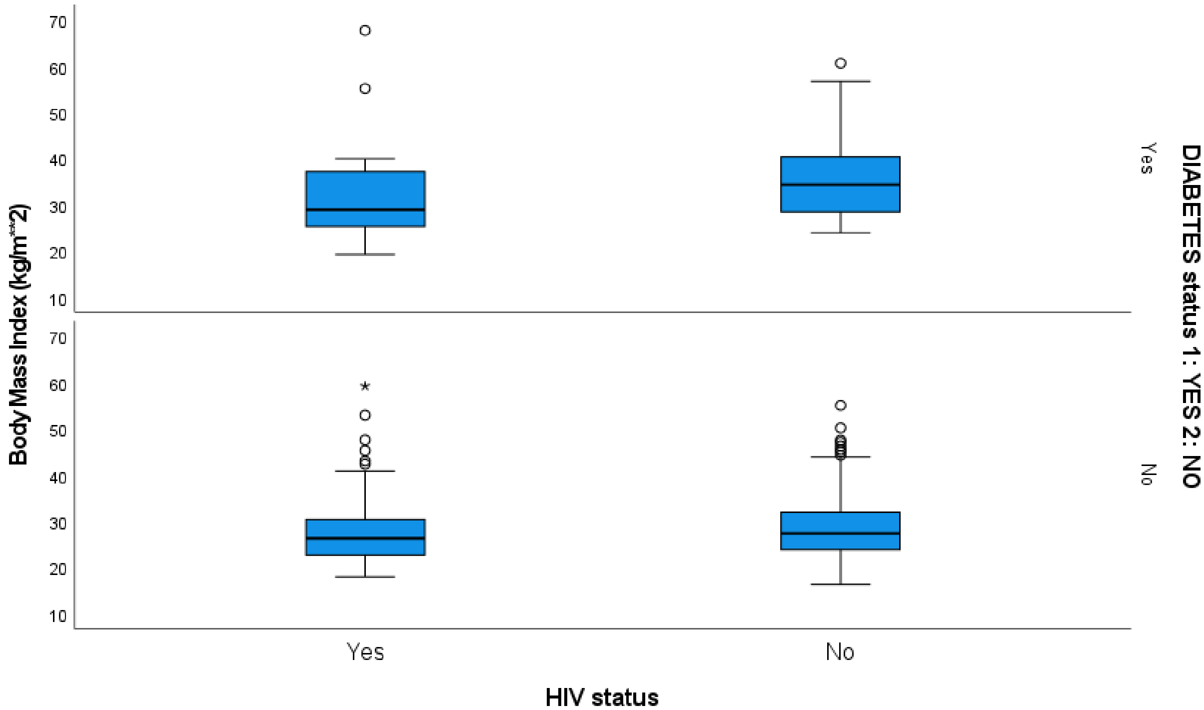


Figure 4: Distribution of Body Mass Index (BMI) by HIV status and diabetes status



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