



RESEARCH ARTICLE

Burden of Type 2 Diabetes Mellitus and associated factors among HIV negative and positive patients in two regional referral hospitals in the Manzini Region, Eswatini

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ABSTRACT

Background: Type 2 diabetes mellitus is an emerging non-communicable disease in low and middle-income countries in sub-Saharan Africa. Since the rollout of antiretroviral therapy in Eswatini, the burden of diabetes in human immunodeficiency virus infected people and comparison against HIV negative control population has not been evaluated in Eswatini.

Aim: This study aimed at assessing proximal and distal predictors of diabetes among HIV positive adults in comparison to HIV negative adults.

Material and Methods. We employed a cross-sectional study design with 498 subjects selected at random in each group. Face-to-face interviews were conducted to obtain socio-demographic and risk factors. Venous blood was collected, fasting blood glucose and 2-hour oral glucose tolerance test. Multivariable logistic regression was used to identify significant determinants of diabetes.

Results and Discussion. Prevalence of diabetes was 25.6% (95%CI: 22.6 – 28.2). A higher (36.1%; 95%CI: 31.9 – 40.4) prevalence of diabetes was observed in the HIV positive cohort compared to the HIV negative group (14.8%; 95%CI: 11.6 – 17.5). Being ≥40 years posed a higher risk (OR=1.04; 95%CI: 1.00 – 1.07, p=0.04) of developing T2DM compared to those <40 years. Overweight (OR=1.82; 95%CI: 1.06 – 3.10, p=0.029) and obesity (OR=3.73; 95%CI: 2.26 – 6.14, p<0.001) increased the risk of diabetes. Alcohol intake increased the risk of diabetes 15 folds (OR=15.05; 95%CI: 9.03 – 25.11, p<0.001) compared to not taking alcohol. Moderate (OR=0.4; 95%CI: 0.25 – 0.67, p<0.001) and vigorous physical activity (OR=0.1; 95%CI: 0.05 – 0.14, p<0.001) reduced the risk of diabetes. Being HIV positive increased the risk of T2DM (OR=3.43; 95%CI: 2.28 – 5.14; p<0.001) compared to being HIV negative.

Conclusions. HIV positive cohort had a higher prevalence of Type 2 diabetes mellitus and being HIV positive is a risk factor for diabetes; hence HIV care services need to include diabetes prevention and management.

Keywords: Eswatini, Type 2 Diabetes Mellitus, associated factors, HIV negative patients, HIV positive patients

List of abbreviations

ART	:antiretroviral therapy
ARV	:antiretroviral
BREC	:Biomedical Research Committee
CRP	:C-reactive protein
DTG	:Dolutegravir-based
FPG	:fasting plasma glucose
LMICs	:low and middle-income countries
NCD	:non-communicable disease
OGTT	:oral glucose tolerance test
OPD	:General Outpatient Departments
PASE	:Physical activity self-efficacy
PLHIV	:people living with HIV
PMTCT	:prevention of mother to child transmission
RFM	:Raleigh Fitkin Memorial Hospital
SEC	:Scientific and Ethics and Committee
ENNC	:Eswatini National Nutrition Council
SSA	:sub-Saharan Africa
T2DM	:Type 2 diabetes mellitus
TB	:tuberculosis
TNF- α	:tumour necrotic factor α
VCT	:Voluntary Testing and Counselling
WHO	:World Health Organisation

Introduction

Human immune-deficiency virus (HIV) infection remains a major global public health concern. The estimated number of people living with HIV (PLHIV) has increased, from 34 million in 2010 to 36.9 million in 2017¹. The sub-Saharan African (SSA) region is the most affected by HIV with more than 70% of global infections²⁻³. In 2015, the SSA contributed 46% of all new HIV infections globally, and 72% of all HIV related deaths globally⁴. Type 2 diabetes mellitus (T2DM) prevalence on the other hand has been increasing in the past decades, with the largest proportion of the disease occurring among people living in LMIC^{5,2} while it has been largely considered a disease of people in developed countries⁶. Even more concerning is that in middle and low-income countries T2DM affects the population below 50 years (59%)⁷, which is also the most sexually active group, that bears the largest burden of HIV infection². These data suggest a potential association between increase in PLHIV and T2DM, thus contributing to the double burden of HIV and T2DM in the middle and low-income countries.

Studies have described the process of T2DM development from HIV infection. HIV infection triggers a pro-inflammatory state evident by elevated inflammatory cytokines, such as TNF- α , interleukins, and C-reactive protein (CRP) levels⁸.

Elevation in inflammatory cytokines is associated with impaired insulin action in skeletal muscles⁹ and suppression of the production of adiponectin, an adipose-specific collagen-like molecule^{10,11}. The afore-said have been linked to the development of metabolic syndrome and subsequent T2DM¹², leading to HIV infection also causes mitochondrial dysfunction. This leads to cell apoptosis which consequently leads to an inflammatory response and subsequent release of inflammatory cytokines, such as interleukins, C reactive protein CRP, tumour necrotic factor α (TNF- α) levels¹⁰.

To counter the effects of HIV infection, antiretroviral therapy (ART) has been introduced to arrest HIV replication. The introduction of ART has improved the life expectancy for PLHIV. While ART has benefits such as increase in life expectancy of PLHIV, its initiation has adverse effects on the quality of life of PLHIV. Introduction of ART to the body leads to increased levels of TNF- α , which, in turn, impairs metabolism of fatty acids and lipid oxidation, resulting in suppressed lipolysis¹³.

This, in turn, results in altered fat distribution, subsequent changes in lipid profile, evident in an observed increase in the levels of triglycerides (hypertriglyceridemia) and low-density lipoprotein cholesterol, and a decrease in high-density lipoprotein cholesterol^{14,15}. Hypertriglyceridemia is associated with insulin resistance^{16,17}. This has been evident in South Africa where the prevalence of metabolic syndrome positively correlated to antiretroviral (ARV) exposure¹⁸ and incidence of dysglycaemia associated with the use of efavirenz¹⁹. The afore-said risk factors for T2DM among PLHIV are additional to the traditional risk factors which are obesity, poor dietary habits and physical inactivity²⁰. Apart from ART side effects, the emergence of T2DM and other chronic illnesses might simply be due to the increased life expectancy of HIV-infected patients on ART^{21,22}.

Eswatini is one of the countries in SSA with the highest HIV prevalence rates (26%) in the reproductive age group of 15–49 years²³, and has been implementing the World Health Organisation's guidelines on the use of ART. The first guidelines on the use of ART was used for HIV infected adults and for prevention of mother to child transmission (PMTCT) of HIV in 2002 and 2004, respectively^{24,25}. These guidelines were then updated in 2006 incorporating a concept of public health which preceded the development of the 2010 and finally the 2013 consolidated guidelines on the use of ART for treating and preventing HIV infection²⁶. Since 2016, testing and treating has been scaled up in many countries including Eswatini. These changes have increased the proportion of PLHIV on ART in Eswatini. Eswatini is among the SSA countries with more than 80% ART national coverage²⁷, and 83% coverage among pregnant women²⁸. According to the Ministry of Health²⁹, both protease inhibitors and non-nucleoside reverse transcriptase inhibitors form part of the ART regimen in Eswatini.

While results from developed countries strongly suggest that an association exists between ART and T2DM³⁰, results from middle- and low-income countries in SSA are inconclusive about this association³¹. Most studies on diabetes conducted in the African region only focused on the HIV positive cohort^{32,33} and were not comparative in nature. In view of the lack of clear evidence of association between ART uptake and HIV infection in LMICs, there is a need for further studies. Such information may be derived by determining the proportion of individuals on ART who also suffer T2DM after controlling for all the conventional factors, hence the necessity of this study. Since the rollout of universal ART access in Eswatini, the burden of T2DM among PLHIV has not been measured, making this study a significant contribution in improving the care provided to PLHIV in Eswatini. The main aim of

this study was to investigate the burden of T2DM among HIV positive adults in comparison to HIV negative adults to identify contextually relevant risk factors and determinants of T2DM.

Methods

STUDY POPULATION AND SETTING

A cross-sectional study was conducted to assess the burden of diabetes in HIV positive versus negative individuals between September 2016 and February 2017. The study was conducted in the Manzini region of Eswatini. This region was chosen because it has the highest (33%) HIV prevalence compared to all regions in Eswatini²³. Participants were recruited from the Raleigh Fitkin Memorial Hospital (RFM) and Mankayane Government Hospitals, from the Voluntary Testing and Counselling (VCT) and General Outpatient Departments (OPD). These two regional referral hospitals were chosen because they have the highest volume of patients³⁴. The HIV negative group consisted of patients seeking medical care from the OPD in the same health facilities.

SAMPLING STRATEGY AND SAMPLE SIZE

A total of 996 randomly selected participants, (498 HIV positive and 498 HIV negative), were recruited from the two study sites. To minimise selection bias, participants were selected randomly in each cohort as long as they met the inclusion criteria for each cohort. The research participants were found in the health facilities where the data was collected. Randomisation was done by using the register at VCT to obtain the list of all registered patients. HIV care numbers for patients were entered into Microsoft Excel and a computer-generated random sample was obtained. Randomisation for the HIV negative comparison cohort was obtained by assigning all patients from the HIV negative cohort group unique study identifiers which were also entered into Microsoft Excel and using a computer-generated random sample the sample was obtained. The sample size was calculated using PASS 12³⁵. Group sample sizes of 498 in group one and 498 in group two achieved 80% power to detect a minimum odds ratio of 1.45. The proportion in group one (control group) was assumed to be 0.50 or 50% (assume maximum variability) under the null hypothesis and 0.565 in group two under the alternative hypothesis i.e. minimum difference detectable of 6.5% between groups. The test statistic used is the two-sided Z test with continuity correction and pooled variance. The significance level of the test was 0.05 or 5%. The following eligibility criteria were employed: ≥ 18 years old, no mental disorders, receiving care at one of the two study sites and willing to participate. For the HIV positive cohort, both pre-ART and ART patients were enrolled as participants regardless of their ART status, and for participants on ART, data on the type of ART was collected. Participants selected for the HIV negative group had a confirmatory HIV test performed to confirm their status prior to recruitment. Participants also had to be willing to return to the hospital for a fasting blood glucose test if they did not meet the criteria for fasting at presentation. Randomisation and measurement of confounders were done to deal with selection bias.

DIAGNOSIS OF T2DM

According to the World Health Organisation (WHO) guidelines, T2DM should be diagnosed using oral glucose

tolerance test (OGTT) and should be differentiated from glucose intolerance. We therefore applied a two-test algorithm in this study to determine a participant's diabetes status. Venous blood was collected from participants for venous fasting plasma glucose (FPG) testing. Normal FPG levels were defined as glucose level ≤ 6.9 mmol/L, and high blood glucose was defined as glucose level ≥ 7 mmol/L, and this test was used to estimate the number of participants with beta cell dysfunction and classified as pre-diabetic. Thereafter, a participant was administered 75g bolus of glucose and was asked to wait for 2 hours. During these 2 hours, participants could continue with their main hospital visits in different departments of the hospital. At 2 hours, venous blood glucose was collected again from participants for OGTT in the laboratory. In the OGTT results, glucose level of ≤ 6.9 mmol/L was considered normal, and 7.0 – 11.0 mmol/L glucose level was considered as glucose intolerance but not diabetes. All participants with glucose intolerance were also considered as pre-diabetic. All participants who had a glucose level of ≥ 11.1 mmol/L based on OGTT results were considered diabetic.

DATA COLLECTION

Data was collected from study participants through face-to-face interviews using a structured questionnaire to obtain data on socio-demographic information. To minimise inter-interviewer variability, data collectors were trained on a standardized protocol for data collection and a structured questionnaire was developed to guide structured interviews. Physical activity self-efficacy (PASE) based on study tools was used^{36,37,33}. Physical activity was defined as any bodily movement produced by skeletal muscles that require energy expenditure³⁸. Physical activity included exercise and other activities which involve bodily movements done as part of playing, working, active transportation, house chores and recreational activities, and was classified as light (walking slowly, using computer, standing light work, selling goods), moderate (walking very fast, cleaning heavy, mowing lawn, driver (taxi/bus) and vagarious (jogging, shovelling, carrying heavy loads, farm work/teaching/waiter) as described in other studies³⁹⁻⁴¹.

Measurements performed included FPG level, weight, height, waist circumference and waist-hip-ratio. In the HIV positive cohort, data was also collected using a data abstraction tool to acquire medical information such as ART regimen, period living with HIV, ART status, period on ART. In the HIV negative cohort there was no abstraction of data from medical records, however, it was ascertained by checking their medical records if they were known cases of hypertension and or have been treated for tuberculosis (TB).

The waist circumference was measured using a tape-measure in centimetres. Measurements were made in the mid-axillary line midway between the last rib and the superior iliac crest to the nearest 0.1 cm. Hip measurement was also made using a tape-measure placed horizontally at the point of maximum circumference over the buttocks. Measurements were taken to the nearest 0.1 cm. Height was measured using the stadiometers height boards. Weight measurements were taken on a pre-calibrated weighing scale

(bathroom scale). The scales were daily calibrated using a known weight 1kg packet of salt. Participants were weighed dressed in light clothing and barefoot. Measurements were taken to the nearest 0.1kg⁴². The height board and scale were obtained from the Eswatini National Nutrition Council (ENNC) in the Ministry of Health.

Biochemical assessment included venous plasma glucose obtained from research participants. When measuring the blood glucose levels of participants, the nurse research assistant cleaned their hands using antiseptic sanitizers and cleaned the side on the participants' arm using antiseptic wipes with 70% isopropyl alcohol. Blood samples were collected into a blood specimen tube with glycolytic inhibitor and were placed in ice-water prior to laboratory testing. Laboratory testing of venous blood glucose was done on the same day of data collection. The laboratory research assistant performed the venous blood glucose testing using the Chemistry analysers: Beckman Coulter Synchron CX9 ALX (Beckman Introduces New SYNCHRON CX9 ALX Clinical System), at Eswatini National Referral Laboratory Services.

DATA ANALYSIS

Data analysis was performed in STATA 14.0⁴³ T2DM prevalence by HIV status were calculated with associated 95% confidence intervals. Categorical factors associated with T2DM were assessed using the standard Pearson's chi-square (χ^2) test. For comparison of continuous predictors by T2DM status we employed the standard t-test, and if the normality assumption was not upheld, then the non-parametric equivalent Wilcoxon rank-sum test was used instead. Factors associated with T2DM were

also assessed using bivariate and multivariate logistic regressions.

ETHICAL CONSIDERATIONS

Ethical clearance to conduct the study was obtained from the Scientific and Ethics Committee (SEC) in Eswatini Ministry of Health (REF: MH/599C/FWA 000 15267/IRB 000 9688) and from the Biomedical Research Ethics Committee (BREC) at the University of Kwa-Zulu Natal (REF BE 035/16).

Results

DEMOGRAPHIC AND LIFE-STYLE CHARACTERISTICS

A total of 996 participants were enrolled, 498 HIV negative and 498 HIV positive patients (Table 1). The mean age of participants was 45.6 ± 14.4 years, and 638 (64.1%) were females. The HIV positive group was older (46.3 ± 13.2 years (mean \pm standard deviation) compared to the HIV negative cohort (44.8 ± 15.5 years). The majority of participants (81.1%) were from the rural areas, and just less than half (41.8%) were employed. About 32.4% of males in the HIV positive cohort had a waist circumference of ≤ 100 cm compared to 9.7% in the HIV negative cohort. Among females, the HIV negative cohort had fewer (22.4%) participants below a waist circumference of 88cm compared to the HIV positive cohort (40.3%). Over a third (383 or 38.5%) were obese with 29.2% being classified as overweight. The majority of participants (88.5%) did not smoke, and similarly 84% reporting not drinking alcohol. Overall, 553 (55.5%) participants had vigorous physical activity, and the HIV negative group was more active (326 or 65.5%) compared to the HIV positive cohort (227 or 45.6%) (Table 1).

Table 1: Characteristics of participants enrolled from two regional hospitals in the Manzini Region, Eswatini¹

Characteristics	Total	HIV Negative	HIV Positive	P-Value
	n (%)	n (%)	n (%)	
Total number of patients	996 (100%)	498 (50.0%)	498 (50.0%)	
Gender				
Male	358 (35.9%)	185 (37.1%)	173 (34.7%)	0.234
Female	638 (64.1%)	313 (62.9%)	325 (65.3%)	
Age in years (N=996)				
≤ 40	398 (40.0%)	224 (45.0%)	174 (34.9%)	0.001
> 40	598 (60.0%)	274 (55.0%)	324 (65.1%)	
Educational level				
Illiterate	86 (8.6%)	43 (8.6%)	43 (8.6%)	0.030
Informal	15 (1.5%)	6 (1.2%)	9 (1.8%)	
Primary school	218 (21.9%)	109 (21.9%)	109 (21.9%)	
Secondary/high school	562 (56.4%)	268 (53.8%)	294 (59.0%)	
Tertiary	115 (11.5%)	72 (14.5%)	42 (8.4%)	
Type of residence				
Urban	188 (18.9%)	99 (19.9%)	89 (17.9%)	0.418
Rural	808 (81.1%)	399 (79.1%)	409 (82.1%)	
Employment status				
Employed	416 (41.8%)	192 (38.5%)	224 (45.0%)	0.046
Unemployed	580 (58.2%)	306 (61.5%)	274 (55.0%)	
Waist Circumference				
Males				
< 100 cm	284 (79.3%)	167 (90.3%)	117 (67.6%)	0.001

¹ Data represents demographic and clinical characteristics of participants from both hospitals. Variables include age, sex, HIV status, and relevant medical history. Continuous variables are presented as means \pm standard deviation, while categorical variables are expressed as frequencies and percentages.

Characteristics	Total	HIV Negative	HIV Positive	P-Value
≥100cm	74 (20.7%)	18 (9.7%)	56 (32.4%)	
Females				
<88cm	437 (68.5%)	243 (77.6%)	194 (59.7%)	0.001
≥88cm	201 (31.5)	70 (22.4%)	131 (40.3%)	
BMI				
Normal	321 (32.2%)	169 (33.9%)	153 (30.7%)	0.344
Overweight	291 (29.2%)	148 (29.7%)	143 (28.7%)	
Obese	383 (38.5%)	181 (36.4%)	202 (40.6%)	
Smoking				
Yes	115 (11.5%)	53 (10.6%)	62 (12.4%)	0.372
No	881 (88.5%)	445 (89.4%)	436 (87.6%)	
Alcohol intake				
Yes	159 (16.0%)	82 (16.5%)	77 (15.5%)	0.665
No	837 (84.0%)	416 (83.5%)	421 (84.5%)	
Physical Activity				
Light	293 (29.4%)	103 (20.6%)	190 (38.2%)	0.001
Moderate	150 (15.1%)	69 (13.9%)	81 (16.2%)	
Vigorous	553 (55.5%)	326 (65.5%)	227 (45.6%)	

p-values indicate significant differences between the HIV positive and HIV negative cohorts; assessed using the standard Pearson's chi-square (χ^2) test

PREVALENCE OF T2DM

The overall prevalence of impaired FPG was 29.3% (95%CI: 26.8– 32.8), and impaired glucose tolerance was 30.7% (95%CI:26.8-32.8). The overall prevalence of diabetes was estimated at 25.6% (95%CI: 22.6 – 28.2). The HIV positive group had a higher (35.7%; 95%CI: 31.9-38.3) prevalence of impaired FPG than the HIV negative group (22.9%; 95%CI: 19.9 – 26.9). The prevalence of impaired FPG differed significantly between the cohorts ($p<0.001$). The impaired glucose

tolerance prevalence was higher (35.1%; 95%CI: 31.5 – 37.9) in the HIV negative group compared to the HIV positive cohort (26.3%; 95%CI: 20.9 – 28.3). The prevalence of impaired glucose tolerance differed significantly between the cohorts ($p<0.001$). A higher (36.1%; 95%CI: 31.9 – 40.4) prevalence of diabetes was observed in the HIV positive cohort compared to the ($p<0.001$) HIV negative group (14.8%; 95%CI: 11.6 – 17.5) (Table 2).

Table 2: Prevalence of T2DM among HIV positive and negative participants in two regional hospitals in the Manzini Region, Eswatini²

Outcome	Overall		HIV Negative		HIV Positive		P-Value*
	n/ (%)	95% CI	n (%)	95% CI	n (%)	95% CI	
Prediabetes							
Impaired FPG	292/996 (29.3%)	26.8 – 32.8	114/498 (22.9%)	19.9 – 26.9	178/498 (35.7%)	31.9 – 38.3	<0.001
Impaired Glucose tolerance	306/996 (30.7%)	26.5 – 33.1	175/498 (35.1%)	31.5 – 37.9	131/498 (26.3%)	20.9 – 28.3	<0.001
Diabetes							
Diabetic	254/996 (25.6%)	22.6 – 28.2	74/498 (14.8%)	11.6 – 17.5	180/498 (36.1%)	31.9 – 40.4	<0.001

* p-Value indicates the significance of difference of prediabetes and diabetes prevalence between cohorts

PREVALENCE OF PREDIABETES AND DIABETES SEGREGATED BY PARTICIPANTS' CHARACTERISTICS PER COHORT

As shown in Table 3, the prevalence of prediabetes was higher (81.8%) among participants ≤40 years compared to those > 40 years (66.1%) in the HIV negative cohort. In the HIV positive cohort, a prediabetes prevalence of 52.0% was observed in those ≤40 years versus 37.4% in those > 40 years. The HIV positive cohort had higher (62.6% among those above the age of 40 years, and 48.0% among those below 40 years) diabetes prevalence compared to the HIV negative cohort (33.9% among those >40 years and 18.2% among those ≤40

years). The distribution of prediabetes and diabetes differed significantly between those below and above 40 years ($p<0.001$). The prevalence of prediabetes and diabetes also differed significantly by level of education ($p<0.001$), and employment status ($p<0.001$). Among males with a waist circumference below 100cm, very few (6.0% in the HIV negative cohort and 7.3% in the HIV positive cohort) had diabetes, while males with a waist circumference above 100 cm had a high (94.1% in the HIV negative cohort, and 100% in the HIV positive cohort) diabetes prevalence. Among females, a higher (85.2% in the HIV negative cohort and 95.9% in the HIV positive cohort) prevalence of diabetes was observed among

² Prevalence rates are calculated based on diagnostic criteria for Type 2 Diabetes Mellitus. Data are presented separately for HIV positive and negative participants.

those with a waist circumference of ≥ 88 cm compared to those with a waist circumference < 88 cm (1.9% in the HIV negative cohort and 3.8% in the HIV positive cohort). It was also observed that with the increase in physical activity, the diabetes prevalence decreased. For instance, in the HIV negative cohort, 43.5% diabetes prevalence was observed among those with light physical activity compared to 36.8% in moderate activity and 13.1% in

vigorous activity. A similar trend was observed in the HIV positive cohort, that is 72.0% among those with light physical activity; about 47.6% among those with moderate physical activity; and 40.7% (vigorous physical activity). The prevalence of prediabetes and diabetes differed significantly ($p < 0.001$) in each level of physical activity (Table 3)

Table 3: The prevalence of prediabetes and diabetes segregated by participants' characteristics per cohort in two regional hospitals in the Manzini Region, Eswatini³

Characteristics	HIV Negative			HIV Positive		
	Prediabetes n (%)	Diabetes n (%)	P-Value	Prediabetes n (%)	Diabetes n (%)	P-Value*
Age (in years)						
≤ 40	54/66(81.8%)	12/66(18.2%)	<0.001	52/100(52.0%)	48/100(48.0%)	<0.001
> 40	121/183 (66.1%)	62/183(33.9%)	0.001	79/211(37.4%)	132/211(62.6%)	<0.001
Educational Level						
Illiterate	20/29(69.0%)	9/29(31.0%)	<0.001	12/28(42.9%)	16/28(57.1%)	<0.001
Informal	3/4(75.0%)	1/4(25.0%)	0.001	2/4(50.0%)	2/4(50.0%)	<0.001
Primary school	34/56(60.7%)	22/56(39.2%)	0.001	32/72(44.4%)	40/72(55.6%)	<0.001
Secondary/high school	93/128(72.7%)	35/128(27.3%)	0.001	75/180(41.7%)	105/180(58.3%)	<0.001
Tertiary	25/32(78.1%)	7/32(21.9%)	0.001	10/27(37.0%)	17/27(63.0%)	<0.001
Employment status						
Employed	64/84(76.2%)	20/84(23.8%)	<0.001	55/134(41.0%)	79/134(59.0%)	<0.001
Unemployed	111/165(67.3%)	54/165(32.7%)	0.001	76/177(42.9%)	101/177(57.1%)	<0.001
Waist Circumference						
Males						
< 100 cm	63/67(94.0%)	4/67(6.0%)	0.527	51/55(92.7%)	4/55(7.3%)	0.233
≥ 100 cm	1/17(5.9%)	16/17(94.1%)	.078	0/56(0.0%)	56/56(100.0%)	0.563
Females						
< 88 cm	102/104(98.1%)	2/104(1.9%)	0.014	75/78(96.2%)	3/78(3.8%)	0.011
≥ 88 cm	9/61(14.8%)	52/61(85.2%)	.023	5/122(4.1%)	117/122(95.9%)	0.031
Physical Activity						
Light	52/92(56.5%)	40/92(43.5%)	<0.001	44/157(28.0%)	113/157(72.0%)	<0.001
Moderate	37/58(63.2%)	21/57(36.8%)	<0.001	33/63(52.4%)	30/63(47.6%)	<0.001
Vigorous	86/99(86.9%)	13/99(13.1%)	<0.001	54/91(59.3%)	37/91(40.7%)	<0.001

* p-Value indicates the significance of difference of T2DM prevalence between cohorts

RISK FACTORS FOR T2DM

As shown in Table 4, participants who were ≥ 40 years were more at risk (OR=1.04; 95%CI: 1.00 – 1.07, $p=0.04$) of developing T2DM compared to those < 40 years. Findings of this study did not show a significant (OR=1.15; 95%CI: 0.74 – 1.80, $p>0.05$) risk of diabetes among females compared to males. Compared to having normal BMI, being overweight (OR=1.82; 95%CI: 1.06 – 3.10, $p=0.029$) and obesity (OR=3.73; 95%CI: 2.26 – 6.14, $p<0.001$) increased the risk of diabetes. In this study, there was no significant risk of (OR=1.75; 95%CI: 0.91 – 3.37, $p>0.05$) diabetes among smokers compared to non-smokers. Alcohol intake increased the risk of diabetes 15 folds (OR=15.05; 95%CI: 9.03 – 25.11, $p<0.001$) compared to those not taking alcohol.

Compared to light physical activity, moderate (OR=0.4; 95%CI: 0.25 – 0.67, $p<0.001$) and vigorous physical activity (OR=0.1; 95%CI: 0.05 – 0.14, $p<0.001$) reduced the risk of diabetes. This study showed that being HIV positive increased the risk of diabetes by 3.4 folds (OR=3.43; 95%CI: 2.28 – 5.14; $p<0.001$) compared to being HIV negative. Among males, having a waist circumference of ≥ 100 cm increased the odds of having diabetes (OR=0.93; 95%CI: 0.88 – 0.99, $p=0.012$) compared to having a waist circumference below 100cm. Among females, compared to < 88 cm waist circumference, a waist circumference of ≥ 88 cm increased the risk of diabetes (OR=1.24; 95%CI: 1.19 – 1.30, $p<0.001$) (Table 4).

³ Data presented are based on a comparison of participants' characteristics across HIV positive and negative cohorts. Prediabetes and diabetes diagnoses were determined using standard clinical criteria.

Table 4: Predictors of T2DM among participants in two regional hospitals in the Manzini Region, Eswatini⁴

Characteristics	Total n (%)	T2DM	
		COR (95%CI)	p-Value
Total number of patients	996 (100%)		
Gender			
Male	358 (35.9%)	1	
Female	638 (64.1%)	1.15 (0.74 – 1.80)	0.526
Age in years (n=996)			
≤40	122 (12.2%)	1	
>40	219 (22.0%)	1.04 (1.00 – 1.07)	0.040
Educational level			
Illiterate	86 (8.6%)	1	
Informal	15 (1.5%)	2.29 (0.45 – 11.59)	0.316
Primary school	218 (21.9%)	1.29 (0.63 – 2.61)	0.485
Secondary/high school	562 (56.4%)	1.39 (0.65 – 2.66)	0.367
Vocational/Tertiary	115 (11.5%)	0.94 (0.37 – 2.37)	0.900
Type of residence			
Rural	808 (81.1%)	1	
Urban	188 (18.9%)	1.11 (0.68 – 1.81)	0.684
Employment status			
Employed	416 (41.8%)	1	
Unemployed	580 (58.2%)	1.34 (0.88 – 2.03)	0.178
BMI			
Normal	321 (32.2%)	1	
Overweight	291 (29.2%)	1.82 (1.06 – 3.10)	0.029
Obese	383 (38.5%)	3.73 (2.26 – 6.14)	<0.001
Smoking			
Yes	115 (11.5%)	1	
No	881 (88.5%)	1.75 (0.91 – 3.37)	0.092
Alcohol intake			
No	837 (84.0%)	1	
Yes	159 (16.0%)	15.05 (9.03 – 25.11)	<0.001
Physical Activity			
Light	293 (29.4%)	1	
Moderate	150 (15.1%)	0.40 (0.25 – 0.67)	<0.001
Vigorous	553 (55.5%)	0.10 (0.05 – 0.14)	<0.001
HIV status			
Negative	498 (50%)	1	
Positive	498 (50%)	3.43 (2.28 – 5.14)	<0.001

As shown in Table 5, compared to participants on ABC+3TC+ATVR regimen, TDF+3TC+KAL were more at risk (AOR= 2.44; 95%CI:1.27 – 4.7; p<0.001) of developing T2DM. Being on AZT+3TC+NVP increased the odds (AOR= 2.14; 95%CI:1.16 – 3.97; p<0.001) of developing T2DM compared to being on

ABC+3TC+ATVR regimen. Participants on AZT+3TC+EFV regimen also had a higher risk (AOR=2.14; 95%CI:1.21 – 3.77; p<0.001) of developing T2DM compared to those on ABC+3TC+ATVR regimen. All other regimens had an insignificant risk (p>0.05) of developing T2DM (Table 5).

Table 5: The prevalence of T2DM by ART regimen used by participant on ART in the HIV positive cohort ⁵

ART Regimen	Total n (%)	Adjusted Odds Ratio	
		AOR (95%CI)	p- value
ABC+3TC+ATVR	42/182 (23.1%)	1	
TDF+3TC+KAL	21/67 (31.3%)	2.44 (1.27 – 4.70)	<0.001
AZT+3TC+NVP	19/74 (25.7%)	2.14 (1.16 – 3.97)	<0.001
AZT+3TC+EFV	36/90 (40.0%)	2.14 (1.21 – 3.77)	<0.001
D4T+3TC+NVP	7/29 (24.1%)	0.93 (0.32 – 2.69)	0.894
TDF+3TC+NVP	4/14 (28.6%)	2.97 (0.71 – 12.42)	0.135
ABC+3TC+EFV	3/5 (60.0%)	2.98 (0.41 – 21.79)	0.283
ABC+3TC+NVP	2/13 (15.4%)	2.98 (0.41 – 21.79)	0.283
TDF+3TC+EFV	2/3 (66.0%)	0.60 (0.12 – 2.83)	0.514
TDF+3TC+AH	0/12 (0.0%)	5.95 (0.53 – 67.33)	0.150

⁴ Multivariate logistic regression analysis was used to identify predictors of Type 2 Diabetes Mellitus. Variables included in the model were age, sex, HIV status, BMI, and family history of diabetes. A significance level of $p < 0.05$ was applied.

⁵ Prevalence rates of Type 2 Diabetes Mellitus are categorized by antiretroviral therapy (ART) regimens among HIV positive participants. Data are presented as frequencies and percentages, with statistical significance assessed using Chi-square tests ($p < 0.05$).

Discussion

In this study, an overall high prevalence of diabetes was observed in the study participants. A number of factors could have caused the high prevalence. For instance, 60% of the participants were aged ≥ 40 years which increases the risk of diabetes as observed in the predictors of diabetes in this study. Also, the study showed a higher prevalence of impaired FPG in the HIV positive cohort compared to the HIV negative cohort. Both prediabetes and diabetes were higher in the HIV positive cohort compared to the HIV negative cohort. The findings are congruent with a recently published review that was carried out in Africa that showed a growing number of PLHIV becoming diabetic⁴⁴. This higher prevalence can be explained through the participants' HIV positive status. Participants in the HIV positive cohort who were on ART. HIV and ART can induce insulin resistance and metabolic syndrome which subsequently leads to diabetes^{45,20}. In this study, HIV status, adjusted for confounding factors, significantly increased the risk of diabetes. This shows being HIV positive poses a risk of developing diabetes and implies the need to include diabetes prevention and management into routine HIV care and management. Another recently conducted study in South Africa demonstrated that obese women who were HIV-positive had a lower prevalence of T2DM than their HIV-negative counterparts⁴⁶. The observed discrepancy may be explained by the fact that women living with HIV are already participating in dietary self-care as part of their healthcare regimen. The same study did not reveal any substantial disparity in the prevalence of T2DM between men who are HIV-positive and those who are not. This implies that additional research is required to fully understand the biology of sex-specific adipose tissue in the context of HIV and to clearly define its implications for diabetes risk, clinical phenotypes, management, and prognosis. The current study also showed that some ART regimens had a higher risk of developing T2DM than others, hence patients on ART need T2DM preventive health services.

The results are corroborated by data from other African countries, where Dolutegravir-based (DTG) regimens are swiftly emerging as the preferred first-line ART in this region⁴⁷. However, their use is correlated with hyperglycaemia in PLHIV in low and middle-income countries. Concerns are increasing regarding the development of hyperglycaemia and, in certain instances, diabetes mellitus in patients transitioned to DTG. Other traditional factors, such as age being ≥ 40 years, alcohol intake, being overweight and obese, light physical activity, having a waist circumference of ≥ 100 cm in males and ≥ 88 cm in females also increase the risk of diabetes. This implies that in the prevention and management of diabetes for both HIV positive and negative populations, these factors cannot be overlooked. A model of care that can be designed to address all these factors in the prevention and management of diabetes among PLHIV can reduce the high prevalence observed in this study.

This study reported a very high prevalence of T2DM among PLHIV compared to other previous studies. For instance, the prevalence of diabetes in HIV infected people was reported to range from 2% to 14% in the

United States^{48, 31}. One study conducted in China, reported a prevalence rate of hyperglycaemia of 19.99% among Chinese patients newly diagnosed with HIV. Some studies have also reported a lower prevalence of T2DM among PLHIV compared to the HIV negative population, that is, 14.9% in the HIV infected versus 21.4% in the HIV uninfected group⁴⁹ and 3.0% HIV infected individuals versus 3.7% among the negative comparison cohort⁵⁰. It is worth noting that these studies have been conducted in settings with low HIV prevalence and good health systems compared to the setting of the current study. Similar factors associated with T2DM have been identified by other studies⁵¹⁻⁵⁸. While HIV and certain ART regimens were associated with a risk of developing T2DM, traditional factors such as age, body weight, and level of physical activity also pose a significant risk to the development of T2DM, and these findings are similar to findings by other studies⁵⁹. Findings are congruent with those reported by a systematic showing an average incidence of diabetes at 13.7 per 1,000 person-years of follow-up where obesity, dyslipidemia, metabolic syndrome, and specific ART regimens have been identified as correlates⁶⁰. The major strength of this study is that it bridges a gap in diabetes research in Eswatini. The prevalence of T2DM has not been estimated. After the rollout of universal ART, the burden of T2DM has not been estimated among PLHIV hence this is the first study to estimate the burden of T2DM and the associated factors in the Manzini region in Eswatini. This study also highlights factors associated with T2DM burden in the context of Eswatini, one of the developing countries in SSA. While this study has useful findings for clinical care of patients in Eswatini, there are limitations. The observed higher prevalence of T2DM in the HIV positive group could be due to confounders other than HIV status alone; hence a case control study would be recommended to provide a clear effect of HIV on T2DM development. Since HIV and ART predispose individuals to T2DM, the cost of HIV and T2DM comorbidity can be high, and that T2DM has negative effects on the quality of life, measures to prevent T2DM among PLHIV are necessary. While many studies have shown the negative effects of HIV and ART in the development of T2DM and the benefits of preventing T2DM, a model of care for PLHIV to enhance the prevention of T2DM needs to be developed. Various organizations have focused on guidelines for diagnosis and management of T2DM in the general population. In the era of universal ART access and test and treat, there is a growing need for T2DM prevention among PLHIV and strengthening health systems to provide adequate preventive care. Successful implementation of T2DM prevention on a national scale requires careful planning and preparation. It is hoped that this model of care may provide a knowledge base, framework, and implementation procedures which may be adapted and used in other countries in the sub-Saharan region. It would be beneficial if the model of care gets tested in various settings so that it can be modified to fit the context of each setting beyond Eswatini. This study estimated the prevalence of T2DM in the Manzini region only, hence these findings cannot be generalised to the whole country. Refusal rate was not measured in the study. This study focused on participants in a hospital setting who are more likely to be sick, as a result it is likely that

different result could be obtained if the study was done in a community setting among individuals who consider themselves healthy.

Conclusion

In conclusion, this study showed a higher prevalence of T2DM in the HIV positive cohort hence there is a need to improve T2DM care among PLHIV. Both the traditional factors such as age ≥ 40 years, alcohol intake, lack of physical activity, being overweight or obese, and a high waist circumference increase the risk of diabetes. Being HIV positive also increases the risk of T2DM necessitating the inclusion of diabetes prevention and management among PLHIV. The overall high prevalence of diabetes observed in this study also indicate the need to improve surveillance of T2DM in the Swazi population, that is, both the HIV negative and positive population. Preventive measures should be advocated in clinical care to reduce the burden of T2DM. Developing and implementing a model of care that reinforces preventive measures and

active surveillance of T2DM in both the HIV negative populations can reduce the burden of T2DM in Eswatini.

Conflict of interest

The authors declare that they do not have any conflict of interest relating to the publication of this paper. This work has not been submitted elsewhere for publication.

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