Prevalence of depressive symptoms and quality of life among patients with diabetes mellitus with and without HIV infection: A South African study

By

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Dedication

The work is dedicated to the memory of my late father Nicholas Qubekile and late brother Sinethemba Qubekile. No matter where I am, your spirit will be beside me.

Declaration

I Yonela Qubekile declare that

(i) The research reported in this dissertation, except where otherwise indicated, and is my original work.

(ii) This dissertation has not been submitted for any degree or examination at any other university.

(iii) This dissertation does not contain other persons' data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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Overview of the thesis

South Africa (SA) has one of the highest prevalence of human immunodeficiency virus (HIV) infection globally with KwaZulu-Natal (KZN) province having the highest incidence rate in the country. Longevity has increased in the last decade mainly due to the availability and access to anti-retroviral treatment (ART). In combination with changes in demographic and environmental factors this has resulted in behavioral and nutritional transitions that have led to a higher risk of non-communicable diseases (NCDs). The most common NCDs in SA include cardiovascular disease, diabetes mellitus (DM), cancer, chronic respiratory disease, and mental illness. The prevention and treatment however of NCDs are still marginalized in SA because of the overwhelming prevalence of communicable diseases such as tuberculosis and HIV/acquired immunodeficiency syndrome (AIDS) and the current COVID-19 pandemic.

Psychological well-being is an important goal in management of chronic diseases, but little attention is paid to assessing and addressing the psychological aspect of patients living with HIV and other chronic medical disorders. It has been well documented that DM and HIV infection are both associated with increased risk of mood disorders and a poorer quality of life (QOL) but this has not been explored in those with the both co-morbidities.

This study set to highlight the need for mental health screening in patients with chronic medical illnesses so that they may be managed more holistically.

A cross-sectional pilot questionnaire survey was conducted among 101 adult patients living with DM with and without HIV infection attending a specialist medical outpatient service. The assessment consisted of a structured socio-demographic and clinical questionnaire for depressive symptoms and QOL. We aimed to explore the prevalence of depressive symptoms, measure QOL and their association with socio-demographic and clinical variables of DM and HIV. The patient health questionnaire 9 (PHQ-9) was used for depressive symptoms and the World Health Organization QOL scales utilized to assess QOL. HIV status and clinical markers of HIV and DM was confirmed from the clinical records.

In this study, the prevalence of depressive symptoms amongst all people living with DM (n=101) was 36%. Moderate to severe depressive symptoms (PHQ-9 score of 10 or more) was significantly associated with female gender and low educational level but not with HIV comorbidity or clinical characteristics of DM. Quality of life was influenced by moderate to severe depressive symptoms but not HIV status.

The high prevalence of depressive symptoms in patients with DM and its association with poor QOL highlights the need for integrated mental health access in medical outpatient services. The lack of association between comorbid HIV status and DM, depressive symptoms or QOL was surprising and may be due to the limited sample size and needs to be further explored.

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Literature Review

1.1 Introduction

This chapter reviews the literature on the prevalence and association of depression, diabetes mellitus (DM), HIV and the impact of these co-morbidities on quality of life. There are few studies that have examined the relationship between these comorbid disorders and especially limited data from sub-Saharan Africa. This pilot study aims to explore the relationship between these three diseases and the results will assist in guiding future screening and treatment guidelines.

1.2. Depression

Depression is a common illness worldwide, and the World Health Organization (WHO) estimates that more than 300 million (4.4%) of people of all ages worldwide suffer from depression with women (5.1%) usually more affected compared to men (3.6%) (1). Depression is a leading cause of disability worldwide and is a major contributor to the overall burden of disease (1). Globally, depressive disorders are ranked as the single largest contributor to non-fatal health loss with 7.5% of Years Lived with Disability (YLD). In 2015, depression alone contributed to over 50 million YLD globally (WHO 2015). The majority of this non-fatal disease burden occurs in low- and middle-income countries (1).

In a South African survey conducted between 2002 – 2004, which included 4351 adults the prevalence of major depressive disorder (MDD) was 9.7% for lifetime and 4.9% for the 12 months prior to the interview (2). The prevalence was significantly higher among woman (1.75 times higher) compared to men. Major depressive disorder was also found to be twice more common amongst those with a lower level of education (2). A later study from South Africa (SA) in 3840 persons aged 50 years and older showed a slightly lower overall prevalence of past 12-month depression at 4%, with women again having a higher prevalence at 55.9% compared to men (44.1%) (3). The prevalence of MDD in the South African general population is estimated to be 9.8%, with the lifetime prevalence of depression in KwaZulu-Natal (KZN) province being 9% (4).

Reasons for the variation in the prevalence of depression in studies include the use of different screening and diagnostic tools and cut-off values (5). In a systematic review of 66 studies on MDD prevalence, Bernard and colleagues found the majority of the studies used screening scales based on DSM-IV depression criteria to evaluate the severity of depressive symptoms (5). Among the 45 papers evaluating depressive symptoms, 14 (31.1%) used the Center for Epidemiological Studies – Depression (CES-D) scale, eight (17.8%) used the Patient Health Questionnaire (PHQ-9), eight (17.8%) papers used the Hopkins Symptom Checklist (HSCL-D) and the Beck Depression Inventory (BDI) a 21-item self-report measure was reported in six (13.3%) papers (5).

The PHQ-9 is a validated multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression, incorporating DSM-IV diagnostic criteria, to document depressive symptoms (6). The PHQ-9 uses a four-point Likert scale (0 not at all, 1 = several days, 2 = more than half the days, 3 = nearly every day) to gauge responses to questions asking about the respondents' emotional health over the previous two-week period. Scores on the PHQ-9 can range from 0 - 27; scores between 0 - 4 indicate no depression, 5 - 9 mild depression; 10 - 14 moderate depression, 15 - 19 moderately severe depression, and ≥20 severe depression (6). Scores of less than 10 seldom occur in individuals with MDD, while scores of 15 or greater usually signify the presence of MDD. The PHQ9 is simple and quick to use scale especially in resource limited countries (6).

Depression is a potentially treatable condition however despite the availability of cost-effective treatments for depressive disorders; fewer than half of those affected in the world receive treatment (1). Barriers to effective care include a lack of resources, inaccurate assessments, lack of trained health-care providers, and social stigma associated with mental disorders (1). Inadequately treated or undiagnosed depression itself can lead to additional stress, poorer quality of life and potentially to suicide (1).

In relation to depression in people living with HIV (PLWHIV) Arseniou and colleagues reported that depression has a negative impact on HIV progression, predicted faster progression to acquired immunodeficiency syndrome (AIDS), and increased mortality risk (7).Some of the implications of depression in PLWHIV are increased health facility utilization, reduced quality of life (QOL) and poor adherence to antiretroviral treatment (ART), which independently increase HIV progression (8). Quality of life impairments associated with depression are equal to or greater than those seen with other chronic disorders (9). The WHO also warns that one of the consequences of depression is suicide, which is the second leading cause of death in 15 - 29 year old people (1).

1.3 Diabetes Mellitus

Diabetes mellitus (DM) is a chronic disease caused by an inherited and/or acquired deficiency in the production of insulin by the pancreas or by the ineffectiveness of the insulin produced (10). It is a metabolic disorder with heterogeneous aetiologies, characterized by chronic hyperglycemia and disturbances of carbohydrate, fat and protein metabolism resulting from insulin secretion, insulin action or both (10).

The classification of DM is depicted in Table 1 (11) and is important for determining both treatment and outcomes.

Table 1 Classification of diabetes mellitus (11)

1. Type 1 diabetes (due to autoimmune β-cell destruction, usually leading to absolute
insulin deficiency, including latent autoimmune diabetes of adulthood)
2. Type 2 diabetes (due to a progressive loss of adequate b-cell insulin secretion
frequently on the background of insulin resistance)
3. Other specific types
Monogenic diabetes syndromes (such as neonatal diabetes and maturity-onset diabetes of the young
Diseases of the exocrine pancreas
Cystic fibrosis, pancreatitis, hemochromatosis, others
Drug- or Chemical-induced
Glucocorticoids, nicotinic acid, thyroid hormone, β-adrenergic agonists, thiazides, phenytoin, interferon, atypical antipsychotics, highly active antiretroviral therapy (HAART)
Endocrinopathies
Acromegaly, Cushing's syndrome, glucagonoma, phaeochromocytoma, hyperthyroidism, other
4. Hyperglycemia first detected in pregnancy
Gestational diabetes (diabetes diagnosed in the second or third trimester
of pregnancy that was not clearly overt diabetes prior to gestation)
Diabetes mellitus in pregnancy

Type 1 DM is a result of cellular-mediated autoimmune destruction of the Beta (β)-cell of the pancreas, with consequent insulin deficiency. The rate of β-cell destruction is quite variable and may be rapid or slow. Type 1 DM commonly occurs primarily in childhood and adolescence but can occur at any age and accounts for 5 - 10% of people with DM (12).

Type 2 DM is a consequence of the body's ineffective use of insulin; this is predominantly a consequence of physical inactivity and excess body weight. Type II DM is the most prevalent form of diabetes and has increased secondary to cultural and social change especially in developing countries (10). Type 2 DM may range from predominantly insulin resistance with relative insulin deficiency, to a predominantly secretory defect with insulin resistance. It may also include a subset that has ketosis-

prone diabetes (13). The clinical difference between type 1 and type 2 DM is illustrated in Table 2 (13) and the diagnostic criteria for DM are presented in Table 3 (11).

Table 2 Clinical differences between type 1 diabetes and type 2 diabetes (13)

Type 1 diabetes	Type 2 diabetes
Usually younger (<30 years*) but not always.	Usually older but prevalence in children, adolescents and young adults increasing
Usually lean weight	Mostly overweight or obese
Onset is acute	Onset is insidious / gradual
Almost always symptomatic (polyuria, polydipsia, weight loss)	Often asymptomatic
Prone to ketosis, often ketoacidotic at diagnosis	Not usually ketosis prone but ketoacidosis may be present at diagnosis
Diagnosis – usually has unequivocal hyperglycaemia	Diagnosis often during routine screening
Insulin necessary from diagnosis for survival	Usually controlled with non-insulin therapies, or may need insulin for symptom control
Otherwise normally healthy	Often have comorbidities (hypertension, dyslipidaemia, sleep apnoea, fatty liver disease, polycystic ovary syndrome); often diagnosed after emergency admission for myocardial infarction or stroke

*<35 years in African populations

Table 3 Diagnosis of diabetes mellitus (13)

FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*
OR
2-h PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT. The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*
OR
A1C ≥ 6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay*
OR
In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L)

DCCT, Diabetes Control and Complications Trial; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; WHO, World Health Organization; 2-h PG, 2-h plasma glucose. *In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Epidemiology of diabetes

As urbanization increases and populations age globally, type II DM will pose an ever-growing threat to public health (14). The prevalence of DM in the adult population is approximately nine percent worldwide and most of the adults with DM are aged between 40 - 59 years. Further approximately 80% of people affected with DM are living in low-and middle-income countries (15). The increase in urbanization and changing lifestyle habits which include, higher consumption of processed foods and a sedentary lifestyle has contributed to the rise in type 2 DM (16).

The prevalence of DM in adults (20 - 79 years) in Africa was 4.7% in 2019, with 19 million people living with the condition and this figure is estimated to increase to 47 million by 2045 (16). Africa has the lowest age-adjusted prevalence, which can be somewhat attributed to lower levels of urbanization, malnutrition, and lower levels of overweight and obesity individuals (16). South Africa has a higher estimated prevalence of DM than the rest of Africa at 9.3% (17), with a recent study from KZN province reporting an even higher prevalence of 14.3% in the public health sector. The majority of these individuals were from the mainly urban eThekwini district. (18). The authors also found the

prevalence of DM in the eThekwini district was the highest at 38% in KZN in keeping with its large Indian population (18).

Diabetes if not effectively controlled is associated with multi-system complications including macro and micro-vascular complications of coronary artery disease, peripheral arterial disease, stroke, diabetic nephropathy, neuropathy, and retinopathy (19). The risk of developing these complications depends on both the duration and the severity of hyperglycemia (19). These complications of DM may already be present in people with type 2 DM by the time they are diagnosed and may appear soon after in people with type 1 DM (16). Studies confirm a strong association between long term glucose control as measured by serum glycated hemoglobin (HbA1c) test and the risk of developing diabetic nephropathy (19). Diabetes mellitus is associated with several systemic complications of which the micro and macro-vascular complications are the most prevalent as summarised in Table 4 (19).

Table 4: Complications of diabetes mellitus (19)

Microvascular complications	Macrovascular complications
1. Diabetic retinopathy Non-proliferative retinopathy is the development of micro-aneurysms, venous loops, retinal hemorrhages, hard exudates, and soft exudates. Proliferative retinopathy is the presence of new blood vessels, with or without vitreous hemorrhage. It is a progression of non-proliferative retinopathy. 2. Diabetic nephropathy defined as persistent proteinuria (proteinuria > 500mg in 24 hours) with progressive decline in renal function. 3. Diabetic neuropathy heterogeneous condition includes focal, diffuse, sensory, motor, and autonomic neuropathy.	1. Atherosclerosis 2. Coronary artery disease 3. Cerebrovascular disease

The central pathological mechanism in microvascular disease is atherosclerosis, which leads to narrowing of arterial walls throughout the body (19). Cardiovascular disease is the primary cause of death in people with both type I and II DM (19). In a meta-analysis of 27 studies including type I and II diabetes, de Groot and colleagues found a significant association between depression and diabetes complications, including: diabetic retinopathy, nephropathy, neuropathy, macro vascular complications and sexual dysfunction (20).

The goal of treatment of DM is to control glucose and ultimately prevent or delay onset of microvascular and macrovascular complications as was shown in the United Kingdom Prospective Diabetes Study group (21). Insulin therapy is the mainstay of therapy in type 1 DM. In type 2 DM if hyperglycemia is mild, patients may be given a one month trial of diet, exercise and weight management. If this does not lead to adequate plasma glucose control, then an anti-hyperglycemic agent and/or insulin is commenced, depending on the patient profile and complication present. The markers of for DM control are home capillary glucose monitoring and HbA1c (21). For most patients, the recommended HbA1c target is less than 7% to prevent microvascular complications and macrovascular complications (13). For those who are frail, have multiple comorbidities, severe cardiac or vascular disease, advanced renal disease, limited life expectancy or hypoglycemic unawareness, an HbA1c target between 7.1% - 8.5% is acceptable (13).

1.4 Depression and diabetes mellitus

The association between depression and DM was described more than 300 years ago by Dr. Thomas Willis, a British physician and anatomist who commented “Diabetes is caused by sadness or long sorrow and other depressions” (22).

Worldwide estimates of depression in people with DM vary depending on the type of DM and socio-economic status of the country (23). In the United States of America (USA), the 2006 Behavioral Risk Factor Surveillance System (BRFSS) of adults aged 18 years and older which is large population based sample of 226,646 participants, found that 22990 (8.2%) reported having DM. Results from that study found an age adjusted rate of depression of 8.3% amongst American adults with DM, ranging from as low as two percent to a high of 28% among the 50 American states (24). The study also found that people with type II DM who were using insulin had a higher rate of MDD (24%), compared to people with type I DM (20.4%) or those with type II DM who were not using insulin (17.3%) (24). Further in the same cohort, the adjusted and unadjusted prevalence of undiagnosed depression was 8.7% and 9.2% respectively in patients with DM, with 45% of people with DM having undiagnosed depression (25).

In contrast, a Nigerian study found a much higher rate of depression of 30% in patients living with DM compared to 9.5% in the control group. Reasons for this higher rate included a low income and higher number of dependents as patients are faced with a burden of paying for health care whilst still meeting the needs of their dependents (26).

The inter-relationship between DM and depression is complex and authors have proposed that in addition to depression being a consequence of diabetes, depression may be a risk factor for the onset of diabetes (27). This suggests there may be a bi-directional association between the two diseases.

Diabetes mellitus and depression are both common chronic conditions that are significantly associated with increased odds of disability (28). The National Health Interview Survey (NHIS) in the USA found that the odds of functional disability were increased seven-fold amongst adults with DM and MDD compared to adults without diabetes and MDD (28). Diabetes mellitus and depression have an impact on occupational functioning, and adults with diabetes and depression are more likely to miss more than seven working days in any given year (28).

Similarly, in a South African study, 31% of adults with type II DM indicated poor well-being and were considered at risk for depressive features. Participants, who were married, had higher educational levels and were employed showed better well-being levels (29). Further DM places an extra financial burden on individuals and their families, apart from its substantial economic impact on countries and national health systems (30).

Despite practice guidelines from the International Diabetes Federation (IDF) indicating that patients with DM are more likely to be affected by depression and periodic assessment and monitoring of depression and other mental health conditions is required in the management of patients with DM (30), there are several challenges in implementing this policy. These challenges include both patient-related and health care related factors (23). Patient related factors include stigma and negative perceptions of any aspect of mental illness such as depression (23). Another barrier to early recognition and treatment of depression among individuals with DM is the difficulty in separating the overlapping symptoms of depression from the symptoms of poor management of diabetes e.g., fatigue, weight gain or loss, change in appetite and sleep disturbance are common symptoms of depression and poor DM control (31). Healthcare systems and providers may provide an additional barrier, as they separate general physical health and mental health services with poor integration of services. These factors have limited the effectiveness of treatments for depression and decreased the opportunity for patients with DM and depression to receive optimal care (31).

1.5 The burden of human immunodeficiency virus (HIV) infection

There were approximately 38 million people worldwide with HIV/AIDS at the end of 2019. In June 2020, 26 million people living with HIV were accessing ART. Further, an estimated 1.7 million individuals worldwide were newly infected with HIV in 2019, and 81% of people with HIV knew their status (32).

South Africa has been the center of the HIV epidemic globally with an estimated 7 million people living with HIV in 2015. In the same year there were 380,000 new infections, while 180,000 South Africans died of AIDS related illnesses (33). The prevalence although high in SA varies between

regions and HIV prevalence is highest at 40% in KZN province compared to 18% in the Northern Cape and Western Cape provinces (34).

A higher prevalence of depression has also been observed among PLWHIV (35), with those at highest risk being those that had not disclosed their seropositive status, lost a loved one, had advanced HIV disease stage and women (35). The exact prevalence of depression among PLWHIV remains unknown, as studies have generally not used standard diagnostic criteria according to DSM 5 or ICD-10 but have relied on physician reporting or screening surveys (36). In a South African study in patients initiating ART, the prevalence of depression was 25% (37). An association was observed between depression and duration of knowledge of HIV sero-positivity (OR 1.02, CI 1.01-1.03) and with those belonging to a support group being less likely to be depressed (37).

The aetiology of depression in PLWHIV is multifactorial and is likely determined by a combination of biological factors, history of comorbid mental illness and psychological factors (38). Biological risk factors include lesions in specific neuro-anatomic structures due to the HIV disease itself or other insults, such as those resulting from cerebrovascular changes or brain tumour which may contribute to development of secondary depression (39). Thus, it is important to exclude any contributory biological factors when treating depression.

A study on the lifetime prevalence of MDD or other psychiatric disorders found no difference at baseline between men living with HIV and control participants. However, a two year follow up found that those with symptomatic HIV disease were significantly more likely to experience a major depressive episode compared to the asymptomatic individuals living with HIV and control participants. After baseline disease stage and medical factors associated with HIV infection were controlled, a lifetime history of MDD or psychiatric comorbidity (the presence of two or more lifetime psychiatric disorders) predicted a subsequent major depressive episode (39). Other contributory factors that increase the risk of depression in PLWHIV include psychological factors such as HIV stigma, occupational disability, body image changes, isolation, and debilitation (40). Two recent studies from Ethiopia in PLWHIV found a strong association between depression and verbal stigma (41) and perceived HIV stigma and poor social support (42).

The impact of social stigma has also been noted in local study in SA. The authors reported the prevalence of depression was 25% in a study of 716 patients initiating ART in the Free State province. An association was observed between depression and duration of knowledge of HIV status. Participants who were in a support group were less likely to be depressed (43).

A cross-sectional study from SA, amongst 422 PLWHIV, aged 30 years and older, found that 42% had a depressive episode. Participants with a depressive episode were two to three times more likely to report poor health perceptions. Depressive symptoms were highest in older people who experienced

an HIV related death of an adult child in the two years prior to interview, followed by PLWHIV and had not commenced ART or who were on ART for less than three months (44).

The symptomatology of depression is thought to differ between PLWHIV and HIV negative patients (45). Studies have shown PLWHIV tend to have greater impairments in decisions making, sleep and appetite and cognitive functioning (45). Several studies have also shown a gender difference, and women living with HIV infection are at a higher risk of having more severe symptoms (46,47).

1.6 Quality of Life

The WHO defines QOL as "an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns" (48). It is a broad ranging and complex concept that is affected by the individual's physical health, psychological state, personal beliefs, social relationships, and their association with salient features of their environment (48). Quality of life impairments associated with depression are equal to or greater than those seen with other chronic disorders (9). Although clinical measures for DM provide an estimate for disease control, the objective of DM care is to improve the patient's QOL (49). Some of the implications of depression in PLWHIV are increased health facility utilization, reduced QOL and poor adherence to ART, which independently increase HIV progression (8).

The association between QOL of patients with DM has been studied in several settings. A review of the studies from primary health care in Norway found that QOL was moderately affected in diabetic patients. Strong positive predictive factors for a poorer QOL were macrovascular diseases; especially coronary heart disease and non-vascular diseases whilst microvascular complications were weaker predictors (50).

Purpose of the study

Although studies show that both HIV and DM are associated with depression and poorer QOL (36), this has not been explored in people living with the dual burden of both diseases. This pilot study aims to describe the prevalence of depressive symptoms among out-patients with DM living with and without HIV and explore their QOL. We also sought to describe any associations between depressive symptoms and participants' socio-demographic and clinical factors and QOL amongst patients with DM.

Aim

Our aim was to describe the prevalence of depression and QOL in patients with DM living with and without HIV.

Objectives

1. To describe the socio-demographic profile of PLWHIV and HIV negative patients with DM.
2. To determine the prevalence of depressive symptoms and QOL among PLWHIV and HIV negative patients with DM.
3. To determine any associations between depressive symptoms, QOL and socio-demographic and clinical correlates of HIV and DM.

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A submission ready manuscript

The manuscript is prepared according to the instructions for the
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The manuscript provides a report of pertinent results and recommendations of the study.

Manuscript

Prevalence of depressive symptoms and quality of life among patients with diabetes mellitus with and without HIV infection: A South African study

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Abstract

Background: Diabetes mellitus (DM) and human immunodeficiency virus (HIV) infection are both associated with increased risk of mood disorders and poorer quality of life (QOL), this association having not been explored in patients living with comorbid DM and HIV.

AIM: To describe the prevalence of depressive symptoms and QOL amongst patients with DM living with and without HIV attending a public sector hospital in South Africa.

Methods A cross-sectional questionnaire pilot survey was conducted among 101 patients with DM attending a specialist medical outpatient service. The assessment consisted of a structured socio-demographic and clinical questionnaire, the patient health questionnaire 9 (PHQ-9) for depressive symptoms and the World Health Organization quality of life (QOL) scale. HIV status was confirmed

from the clinical records. Correlates of depressive symptomatology in participants with DM living with and without HIV were identified using t-tests.

Results The prevalence of depressive symptoms in participants with DM was 36%. Moderate to severe depression was associated with female gender (p= 0.03) and low education educational level (p=0.02) but not with HIV comorbidity or clinical characteristics of DM. QOL was influenced by moderate to severe depressive symptoms (QOL in physical p<0.218 and environmental p<0.001 domains), but not HIV status (p= 0.218).

Conclusion The high prevalence of depressive symptoms in patients with DM and its association with poor QOL highlights the need for integrated mental health access in medical outpatient services. The lack of association between comorbid HIV status and DM with depression or QOL needs to be further explored.

Keywords: HIV, type 2 diabetes mellitus, depression, quality of life

Introduction

South Africa (SA) has one of the highest prevalence of human immunodeficiency virus (HIV) infections globally (1), with KwaZulu-Natal (KZN) province having the highest incidence rate in the country (2). Longevity amongst people living with HIV (PLWHIV) has increased in the last two decades mainly due to the availability and access to anti-retroviral treatment (ART). In combination with changes in demographic and environmental factors, this has resulted in behavioral and nutritional transitions that have led to a higher risk of non-communicable diseases (NCDs), including diabetes mellitus (DM) and mental illness (3). The prevention and treatment of NCDs are still marginalized in SA due to the overwhelming prevalence of communicable diseases, such as tuberculosis and HIV/acquired immunodeficiency syndrome (AIDS) (3).

The prevalence of DM in adults (20 -79 years) in Africa was 4.7% in 2019, with 19 million living with the condition, this figure being estimated to increase to 47 million by 2045 (4). South Africa has a higher estimated prevalence of DM than the rest of Africa at 9.3% (5), with a recent study from KZN reporting an even higher prevalence of 14.3% in the public health sector, the majority of these patients being from the mainly urban eThekwini District (6).

While depression affects more than 300 people million globally (4.4%) (7), the age adjusted rate of depression is higher in patients with DM (8.3%) in the United States of America (8), while a Nigerian study found a much higher rate of 30%. The reasons cited for this variation included lower income levels in Nigeria and the need to provide for a higher number of dependents (children), which resulted in patients being unable to pay for their own health care needs (9). The prevalence of major depressive disorder in the South African general population is 9.8%, with the lifetime prevalence of depression in KZN being 9% (10).

A higher prevalence of depression has also been observed among PLWHIV [(11)], with those at highest risk having not disclosed their seropositive status, lost a loved one, advanced HIV disease stage and being female (11). The exact prevalence of depression among PLWHIV remains unknown, as studies have generally not used standard diagnostic criteria according to DSM 5 or ICD-10 but have relied on physician reporting or screening surveys (12). In a South African study in patients initiating ART, the prevalence of depression was 25% (13). An association was observed between depression and duration of knowledge of HIV sero-positivity (OR =1.02, CI 1.01-1.03), with those belonging to a support group being less likely to be depressed (13).

The World Health Organization (WHO) defines Quality of life (QoL) as "*an individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns*". It is a broad ranging and complex concept that is affected by the individual's physical health, psychological state, personal beliefs, social relationships, and their association with salient features of their environment (14). Quality of life impairments associated with depression are equal to or greater than those seen with other chronic disorders (15). Although clinical measures for DM provide an estimate for disease control, the objective of DM care is to improve the patient's QoL (16). Some of the implications of depression in PLWHIV are increased health facility utilization, reduced QoL and poor adherence to ART, which independently increase HIV progression (17).

Although studies show that both HIV and DM are associated with depression and poorer QoL (12), this has not been explored in people living with the dual burden of both diseases. This pilot study aims to describe the prevalence of depressive symptoms in out-patients with DM living with and without HIV and explore their QoL. We also sought to describe any associations between depressive symptoms and participants' socio-demographic and clinical factors and QoL amongst patients with DM.

Methodology

A descriptive, cross–sectional study was conducted from January to December 2018 in the adult medical outpatient department at King Edward VIII hospital, eThekwini District, KZN, which offers a regional level specialist service in internal medicine and psychiatry.

Study participants

Adult patients aged 18 years and older from the medical out-patients with DM on treatment for a minimum of 12 months and living with HIV on treatment for at least six months were enrolled after obtaining informed consent. Control patients who were attending the same medical outpatient department, matched for gender, with DM, and who were HIV negative, as per clinical records either tested by ELISA or rapid HIV test (in the last six months), and consented, were also enrolled. Patients with other existing chronic medical conditions, such as hypertension and epilepsy, were excluded.

Measures

A structured questionnaire was used to collect socio-demographic information (age, gender, marital status, occupation, race, educational level, monthly income, and area of residence). Clinical data on the type of DM (type 1 or 2), DM complications, treatment, and control (glycated hemoglobin levels-

HBA1C) and HIV disease duration, treatment, and markers (CD4 cell count and viral load) within the last six months was recorded from the participants' charts.

The Patient Health Questionnaire 9 (PHQ 9), which is a validated multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression, incorporating DSM-IV diagnostic criteria, to document depressive symptoms (18). The PHQ 9 uses a four-point Likert scale (0 not at all, 1 = several days, 2 = more than half the days, 3 = nearly every day) to gauge responses to questions asking about the respondents' emotional health over the previous two-week period. Scores on the PHQ 9 can range from 0 - 27; scores between 0 - 4 indicate no depression, 5 - 9 mild depression; 10 - 14 moderate depression, 15 - 19 moderately severe depression, and ≥20 severe depression (18) .Scores of less than 10 seldom occur in individuals with major depression, while of 15 or greater usually signify the presence of major depression (18). For this study, 10 was used as the cut-off, as it has an overall sensitivity of 84% and a specificity of 72% (18), the tool having been used in various studies in SA (19,20,21).

The WHO Quality of Life-BREF (WHOQOL-BREF) is a person-centered instrument for subjective assessment and based on a cross culturally sensitive concept (22). It consists of a number of quality of life (QOL) items that are concerned with the meaning of different aspects of life and how satisfactory or problematic their experience is of them (22). The WHOQOL-BREF is an abbreviated 26 item version of the WHOQOL-100 that contains one item from each of the 24 facets of QOL, included in the WHOQOL-100, plus two benchmark items from the general facet on overall QOL and general health. The WHOQOL-BREF is scored in four domains that includes physical health, psychological, social relations and environmental domains (22), and has been used in several South African studies (23,24).

All interviews were conducted by the principal investigator (PI) after obtaining written informed consent. The PI is bilingual and conducted interviews in English and IsiZulu, with the tools being available in both.

Sample size

The required sample size calculated was 50 patients with DM and HIV and 50 as a control with DM and no HIV. The statistical parameters used to calculate the sample size were: effect size = 0.57 (medium), type I (α) error = 0.05 (the probability of falsely rejecting the null hypothesis=5%), type II (β) error = 0.2 (the probability of falsely retaining the null hypothesis). Statistical power= 1-β- 1- 0.2= 0.8 (statistical power of 80%).

Data Analysis

Descriptive statistics were used to describe the population frequency and percent to describe categorical variables. The frequency distributions of numeric variables were examine, and means with standard deviation or medians and inter-quartiles ranges were used as appropriate. The two groups were compared using the student t-test, while the categorical variables were compared using Pearson's chi square test and Fisher chi square test. A significance of $p<0.05$ was used for statistical significance testing, with the data being analyzed using program R version.

Ethical considerations

Ethical approval for this study (BE553/17) was granted by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (UKZN). Approval was obtained from the hospital and KZN provincial Department of Health. Those reporting psychological distress/ requesting mental health care support/ with moderate to severe depression were referred to the psychiatry services at the hospital.

Results

A total of 101 individuals participated and four refused to participate, of whom one was living with HIV and three were HIV negative. Their reasons for not participating included; lack of time or other commitments. The socio-demographic and clinical characteristics of the participants with DM living with and without HIV are described in Table 1. The median age of all the participants was 54.5 (IQR 48 - 61.3) years. The female to male ratio was 1.7:1 and most of the participants were Black (83%). People living with HIV were more likely to be younger ($p < 0.001$), Black (96%, $p < 0.001$), married (58%, $p=0.003$), more than two thirds lived in a township ($p=0.008$).

There were no significant differences in the type of DM, DM disease duration, treatment or control, as assessed by glycated hemoglobin level between the PLWHIV and the HIV negative group. Complications related to DM were similar between the two groups, except for cerebrovascular accidents, which were higher in the HIV negative than the PLWHIV group (16% vs. 3%, $p= 0.031$). Peripheral neuropathy was only found in PLWHIV and DM (14%, $p=0.012$).

Table 1: Socio-demographic and clinical characteristics of patients with diabetes mellitus with and without HIV infection (n=100)

Variables		Total n (%)	HIV negative n (%)	HIV positive n (%)	p- value
Age (years)*		54.5 (48.8-61.3)	59 (51.3-65)	51 (47.3-55)	**<0.001**
Gender	Men	37 (37)	17 (34)	20 (40)	0.534
	Women	63 (63)	33 (66)	30 (60)	
Race	Black	83 (83)	35 (70)	48 (96)	**<0.001**
Other		17 (17)	15 (30)	2 (4)	
Marital status	Single	34 (34)	17 (34)	17 (34)	**0.003**
	Married	45 (45)	16 (32)	29 (58)	
	Divorced/Widowed	21 (21)	17 (34)	4 (8%)	
Residence	Urban	39 (39)	24 (48)	15 (30)	**0.008**
	Rural	12 (12)	9 (18)	3 (6)	
	Township	49 (49)	17 (14)	32 (64)	
Education:	Grade 1-7	15 (11)	11 (22)	4 (8)	0.146
	Grade 8-12	72 (72)	33 (66)	39 (78)	
	Tertiary	13 (13)	6 (12)	7 (14)	
Occupation:	Employed	33 (33)	12 (24)	21 (42)	0.056
	Unemployed	67 (67)	38 (76)	29 (58)	
Income: < R1000		12 (12)	4 (8)	8 (16)	**0.041**
	R1001-R2500	50 (50)	31 (62)	19 (38)	
	R2501-R5000	13 (13)	3 (6)	10 (20)	
	R5001- R10000	14 (14)	5 (10)	9 (18)	
	R10000+	11 (11)	7 (14)	4 (8)	
DM	Type 1	12 (12)	7 (14)	5 (10)	0.538
	Type 2	88 (88)	43 (86)	45 (90)	
Diabetes duration (years)*		6 (3-11)	6 (3-11)	6 (3-12)	0.730
DM	Cardiac	15 (15)	9 (18)	6 (12)	0.401
Complications	CVA	9 (9)	8 (16)	1 (2)	**0.031**
	Nephropathy[#]	22 (22)	14 (28)	8 (16)	0.161
	Retinopathy	7 (7)	2 (4)	3 (6)	0.436
	Peripheral neuropathy	7 (7)	0 (0)	7 (14)	**0.012**
Treatment:	Insulin	36 (36)	21 (42)	15 (30))	0.451
	Oral	47 (47)	21 (42)	26 (52)	
	Dual	17 (17)	8 (16)	9 (18)	
HbA1C* (mmol/L)		7.8 (6.6-99)	7.8 (6.6-9.4)	7.7 (6.6-10.5)	0.461

*median (IQR)

[#]Nephropathy: estimated glomerular filtration rate <60 ml/min/1.73m^2 (Modification of diet in renal disease study equation)
DM diabetes mellitus, CVA: cerebrovascular accident**,** HbA1C: glycated hemoglobin 1C

Prevalence of depressive symptoms

A previous psychiatric history was reported in a eight (8%) participants of whom six (12%) were PLWHIV and two (4%) were HIV negative (p=1.00). Sixty four (63.3%) participants reported no to minimal depressive symptoms on PHQ 9 (0-4 score), while 24 (23.7%) reported mild (PHQ score 5-9) and 12 (11.8%) reported moderate to severe symptoms (PHQ score 10 or greater).

The HIV comorbidity amongst people living with DM and its clinical variables, such as type and complications or control, as assessed by the HBA1C, was not significantly associated with an increased risk of moderate to severe depressive symptoms. However female gender (p= 0.03) and those with lower educational level (p=0.02) were more likely to have moderate to severe depressive symptoms

For the PLWHIV, the median years since HIV diagnosis was five (IQR 3-9), median CD4 cell count was 492 cells/mm^3 (IQR 240-695) and 39 (78%) had a suppressed viral load. Forty-two (84%) PLWHIV were on first line ART regimen, which included Abacavir+lamuvidine+efaverens 3(6%), Zidovudine+lamuvidine+efaverens one (2%), Tenofovir+emtricitabine+efaverens 38 (76%), and eight (16%) were on second line/other ART regimens.

Table 2 summarizes the data comparing participants with DM with no or mild depressive symptoms to those with moderate to severe depressive symptoms and their associations with socio-demographic and clinical factors, including comorbid HIV status, which was not statistically significant.

Table 2: Association of depressive symptom score with socio-demographic and clinical variables of DM and HIV (n=100)

PHQ-9 total score		Total n (%)	PHQ ≤ 9.9 n (%)	PHQ ≥ 10 n (%)	p-value
Age (mean ±SD) years		53.7 (11.1)	53.3 (11.2)	56.6 (10.6)	0.343
Gender	Male	37 (37)	36 (40.9)	1 (8.3)	**0.030**
	Female	63 (63)	52 (59.1)	11 (91.7)	
Marital status	Single	34 (34)	32 (36.4)	2 (16.7)	0.172
	Married	45 (45)	40 (45.5)	5 (41.7)	
	Divorced/widowed	21 (21)	16 (18.2)	5 (41.7)	
Occupation	Employed	33 (33)	31 (35.2)	2 (16.7)	0.327
	Unemployed	67 (67)	57 (64.8)	10 (83.3)	
Race	Black	83 (83)	74 (84.1)	9 (75)	0.424
	Other	17 (17)	14 (15.9)	3 (25)	
Education	Grade 1-7	15 (15)	10 (11.4)	5 (41.7)	**0.020**
Level	Grade 8-12	72 (72)	65 (73.9)	7 (58.3)	
	Tertiary education	13 (13)	13 (14)	0 (0)	
Income	Under R1 000	12 (12)	10 (11.4)	2 (16.7)	0.406
	R1 001-R2 500	50 (50)	44 (50)	6 (50)	
	R2 501-R5 000	13 (13)	10 (11.4)	3 (25)	
	R5 001-R10 000	14 (14)	14 (15.9)	0 (0)	
	R10 000+	11 (11)	10 (11.4)	1 (8.3)	
DM	Type 1	12 (12)	12 (13.6)	0(0)	0.351
	Type 2	88 (88)	76 (86)	12 (100)	
Treatment	Insulin	36 (36)	30 (34)	6 (50)	0.503
	Oral	47 (47)	43 (49)	4 (33)	
	Dual	17 (17)	15 (17)	2 (17)	
*Duration of DM (years)		6 (3-11)	6 (3-11)	10 (3-11)	0.608
*HbA1c (mmol/L)		7.8 (6.6-10)	7.7 (6.6-9.8)	8.6 (7.6-11.2)	0.168
DM	Cardiac	15 (15)	13 (15)	2 (17)	1.000
Complications	CVA	9 (9)	7 (8)	2 (17)	0.294
	Nephropathy	22 (22)	19 (22)	3(25)	0.713
	Retinopathy	7 (7)	6 (7)	1 (8)	1.000
	Peripheral neuropathy	7 (7)	7 (8)	0 (0)	0.594
HIV status	Negative	50 (50)	42 (48)	8 (67)	0.218
	Positive	50 (50)	46 (52)	4 (33)	

DM diabetes mellitus, CVA: cerebrovascular accident**,** HIV Human immunodeficiency virus

*median (IQR)

Quality of Life and association with depressive symptoms

The WHO QoL BREF score for each domain did not differ significantly between the PLWHIV and HIV negative participants, as noted in Table 3. However, those who had moderate to severe depressive symptoms had a poorer QOL in the physical and environmental domains compared to those with no or mild depressive symptoms, as summarised in Table 4.

Table 3: Association of quality of life in patients with diabetes mellitus with and without HIV infection

	Total n (±SD)	**DM & HIV negative n (±SD)**	**DM & HIV positive n (±SD)**	**p-value**
Total physical [+]	23.6 (5.6)	23 (6)	24.1 (5.2)	0.592
Total psychological [+]	20.2 (2.4)	20.6 (2.6)	19.9 (2.2)	0.592
Total environmental [+]	27 (4.9)	26.9 (5.7)	27.6 (3.9)	0.766
Total social [+]	7.5 (1.5)	7.6 (1.6)	7.42 (1.4)	0.161

[+] Mean (±SD)

Table 3: Association between depressive symptom score (PHQ 9) and QoL in total cohort of patients with diabetes mellitus with and without HIV infection

QOL domains score	**Total n (±SD)**	**PHQ ≤ 9 n (±SD)**	**PHQ ≥ 10 n (±SD)**	**p-value**
Total physical [ϕ]	23.6 (5.6)	24.5 (4.9)	16.4 (5.8)	**<0.001**
Total psychological [ϕ]	20.2 (2.4)	20.5 (2.2)	18.1 (2.9)	0.005
Total social [ϕ]	7.5 (1.5)	7.7 (1.4)	6.6 (2)	0.092
Total environmental [ϕ]	27.3 (4.9)	28 (4.4)	22.1 (5.3)	**<0.001**

[ϕ] mean (±SD)

Discussion

This is a pilot case control study from SA to explore the prevalence of depressive symptoms in patients with DM and living with and without HIV and impact on quality of life. The study's key findings are that at least one third (36%) of participants with DM reported depressive symptoms, which were mainly undetected. While HIV infection and DM (type, complications or control) were not associated with moderate to severe depressive score, moderate to severe depressive symptoms

were associated with gender, educational level and poorer quality of life (physical and environmental domains) amongst all people with DM.

The prevalence of depression in our study was higher than that reported in the South African general population at 9.7% for lifetime and 4.9% for the 12 months prior to interview (25). A recent study similarly showed a much higher prevalence of depression (46%) amongst patients with type 2 DM attending a specialist diabetic clinic, which again suggests vulnerability to depressive symptoms amongst this group (21). Reasons for the variation in the prevalence of depression may include use of different measurement tools and cut-off points (26).

The current study finding, that depressive symptoms were associated with female gender and lower educational level, is supported by the literature. (21,7,27) Tomlinson and colleagues showed that the prevalence of depression was much higher amongst females, who were 1.75 times more likely to experience lifetime depression than males, and was significantly higher among those with low level of education (25). The Hunt study examined if a higher educational level protects against anxiety and/or depression and if this protection accumulates with time. The results showed that low educational levels were significantly associated with depression, while higher educational levels had a protective effect that accumulates throughout life (28).

The findings of this pilot study failed to establish any association between depressive symptoms and clinical features of HIV or DM, which suggest that they may not be the most pressing risk factors in individuals receiving chronic specialist medical care, and that socio-demographic factors, such as gender and educational level, remain driving factors that influence mood disorders. There is well documented evidence to support the interaction and outcomes between DM and depression, which is mediated by social contexts, especially among low-income countries (29). While Tesfaw and colleagues found that patients with stage III HIV were more likely to be depressed, they also identified that psycho-social factors, such as HIV stigma, poor social support and poor medicine adherence, increased the risk of depression (30). A Nigerian study found that 56% of PLWHIV had depressive symptoms, which these were also associated with psycho-social factors, such as female gender, below average schooling and poor economic status (27). This suggests the need to consider providing additional psychosocial support and mental health care access for the most vulnerable in our communities.

The association of QoL with the PHQ-9 score showed statistical differences in the physical and environmental domains, which suggests that comorbidity of HIV and DM was not impacting on QoL, but that mental health problems were. These findings are consistent with a previous study, which showed all four domains of QoL were associated with depression in patients with Type 2 DM (31).

Deshmuck and colleagues also noted that in PLWHIV, depression was associated with significantly lower QoL, particularly in the social and environmental domains (32). An Indonesian study reported a strong correlation of higher depression scores associated with lower QoL in PLWHIV (33). Finally, a study conducted in Uganda reported that although QoL improved overtime for PLWHIV, it was associated with depression, low education level and female gender (34). Thus, it is essential to screen and treat underlying mood disorders in patients with a medical disorder, as it could be impacting on QoL. The use of a simple screening tool, such as the PHQ 9, could be an initial important step towards addressing issues related to quality of life.

Limitations

The limitations of this study include that it took place at a single clinical site and small sample size, which limits its generalizability, although it provides a snapshot of current clinical public sector characteristics of patients with DM living with and without HIV. The study is urban- and hospital based, therefore findings may not be generalizable to other settings, and relies on self-reporting of symptoms, with the potential for patients under/over reporting symptoms. There is a need for a longitudinal larger community-based study to further explore the factors associated with depressive symptoms in this population.

Conclusion

The high prevalence of undetected depressive symptoms associated with gender and educational level, and that those with depression reported poorer quality of life in two domains amongst patients with DM with and without HIV, highlight the importance of screening for and treating underlying mood disorders in patients with chronic medical illness. This indicates the need for efficient mental health care screening and interventions to be integrated into routine clinical care in medical outpatient services to treat the person as a whole, and not just their medical condition.

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Competing interest

The authors have declared that no competing interest exists.

Author contributions

Y. Q developed the study concept and design, acquisition of patients and/or data analysis, interpretation of data, and preparation of manuscript.

S.P and FP developed the study concept and design, analysis and interpretation of data, and preparation of manuscript. All authors approved the final version of the manuscript.

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Data availability

Data is available from the corresponding author upon reasonable request.

Disclaimer

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Appendix 1

Final Protocol

Impact of human immunodeficiency virus infection on depression and quality of life in patients with diabetes mellitus attending a regional hospital in eThekwini, KwaZulu-Natal, South Africa.

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PURPOSE OF STUDY

To determine the impact of human immunodeficiency virus (HIV) infection on depressive symptoms and quality of life (QOL) in subjects with diabetes mellitus (DM) in the outpatient department of a regional hospital in eThekwini, Kwa-Zulu Natal (KZN).

South Africa (SA) has the highest burden of HIV infection globally and KZN is the epicenter of the HIV infection. Simultaneously change in environment due to urbanization have resulted in behavioral and nutritional transitions that have led to an increased risk of non-communicable disease (NCD) especially DM.

Diabetes mellitus is a chronic NCD, which has significant impact on morbidity, QOL and mortality. Human immunodeficiency virus infection is also associated with significant neuropsychiatric complications including increased suicidality, mood disorders and poorer QOL. The majority of patients with both these diseases are treated in the outpatient setting and studies have shown that the consistent recognition and treatment of mental health issues especially depression is less than optimal.

Psychological well-being is an important goal in management of chronic disease but little attention is paid to assessing and addressing the psychological aspect of patients living with HIV and another chronic medical disorder, therefore this study will highlight the need for mental health screening in our medical clinics so patients can be managed more holistically.

Background and literature review

Depression

Depression is a leading cause of disability worldwide, and is a major contributor to the overall burden of disease (World Health Organisation, Depression and Other Common Mental Disorders (Global Health Estimates), 2017). The World Health Organization (WHO) estimates that more than 300 million (4.4%) of people of all ages globally suffer from depression (World Health Organisation, Depression and Other Common Mental Disorders (Global Health Estimates), 2017) and women (5.1%) are usually more affected compared to men (3.6%) (World Health Organisation, Depression and Other Common Mental Disorders (Global Health Estimates), 2017).

Globally, depressive disorders are ranked as the single largest contributor to non-fatal health loss with 7.5% of Years Lived with Disability (YLD). In 2015, depression alone contributed to a global over 50

million YLD (WHO 2015). The majority of this non-fatal disease burden occurs in low and middle income countries (World Health Organisation, Depression and Other Common Mental Disorders (Global Health Estimates), 2017).

In a South African survey conducted between 2002 – 2004, which included 4351 adults the prevalence of major depression was 9.7% for lifetime and 4.9% for the 12 months prior to the interview. The prevalence was significantly higher among woman (1.75 times greater) compared to males. Depression was also found to be twice more common amongst those with a low level of education (Tomlinson, Grimsrud, Stein, William, & Myer, 2009). A further study from SA with a sample size of 3840 persons aged 50 years and above showed a slightly lower overall prevalence of past 12-month depression of 4% with women again having a higher prevalence at 55.9% compared to men 44.1% (Peltzer & Phaswana-Mafuya, 2013).

Further despite the availability of cost effective treatments being available for depression, fewer than half of those affected in the world receive such treatment (World Health Organisation, Depression and Other Common Mental Disorders (Global Health Estimates), 2017). Barriers to effective care include a lack of resources, inaccurate assessments, lack of trained health-care providers, and social stigma associated with mental disorders (World Health Organisation, Depression and Other Common Mental Disorders (Global Health Estimates), 2017).

Diabetes Mellitus

According to the WHO fact sheet diabetes mellitus is a chronic disease caused by inherited and/or acquired deficiency in production of insulin by the pancreas or by the ineffectiveness of the insulin produced (World Health Organisation, World Health Organisation - Diabetes, 2017).

Type II DM is the most prevalent form of diabetes and has increased alongside cultural and social change. As urbanization increases and populations age, type II DM will pose an ever growing threat (Whiting, Guariguata, Weil, & Shaw, 2011). The prevalence of DM in the adult population is approximately nine percent worldwide and the majority of the adults with DM are aged between 40-59 years. Further approximately 80% of people affected with DM are living in low and middle-income countries (Guariguata, Whiting, Hambleton, Beagley, Linnenkamp, & Shaw, 2014).

Studies from Africa estimate that about 39 000 people had type I diabetes in 2013 and the prevalence of type II diabetes was 4.9% in 2013.This number is expected to increase exponentially and it is expected by the year 2035 there will be 41.5 million adults with diabetes; this represents a 110% increase (Peer, Kengne, Motala, & Mbanya, 2014).

In SA, the estimated diabetes prevalence is 9.3% (Peer, Kengne, Motala, & Mbanya, 2014). A recent study in KZN found a prevalence of 14.3% in the public health sector and majority of these patients

were from the eThekwini district. The authors also found the prevalence in eThekwini district was the highest in at 38% in all of KZN in keeping with its large Indian population (Sahadew, Singaram, & Brown, 2016).

Diabetes if not effectively controlled is associated with multi-system complications including macro and micro-vascular complications of coronary artery disease, peripheral arterial disease, stroke, diabetic nephropathy, neuropathy, and retinopathy (Fowler, 2008). The risk of developing these complications depends on both the duration and the severity of hyperglycemia (Fowler, 2008). Studies confirm a strong association between glucose control as measured by glycated hemoglobin (HBA1c) and the risk of developing diabetic nephropathy (Fowler, 2008).

The central pathological mechanism in micro vascular disease is atherosclerosis, which leads to narrowing of arterial walls throughout the body (Fowler, 2008). Cardiovascular disease is the primary cause of death in people with both type I and II DM (Fowler, 2008). In a meta-analysis of 27 studies including type I and II diabetes, de Groot et al. found a significant association between depression and diabetes complications, including: diabetic retinopathy, nephropathy, neuropathy, macro vascular complications and sexual dysfunction (de Groot, Anderson, Freedland, Clouse, & Lustman, 2001).

Aetiology and prevalence of hypertension in diabetic patients

Several studies also show a higher prevalence of hypertension at approximately 1.5-2 times compared to non-diabetic matched controls. Further in type 2 diabetes; hypertension may often be co-diagnosed together or already present. The incidence of hypertension is proportionate to obesity, age and atherosclerotic disease and may often probably be essential hypertension.

Further studies have found an association of increased risk for cardiovascular mortality with the presence of depression in diabetes (van Dooren, Nefs, Schram, Verhey, Denollet, & Pouwer, 2013). Independent behavioral and clinical factors identified to be associated with depression amongst individuals with diabetes include severity of diabetes complications in men and higher HBA1C (> 8%) levels in patients less than 65 years of age (Katon, et al., 2004).

In a Cape Town study involving 243 patents in a primary care level assessing the complications of diabetes; 68% of patients had at least one of the following complications (retinopathy, proteinuria or diabetic foot problem). Although the prevalence of complications and glycemic control was largely unrecorded for the previous year, the prevalence rate was still high with retinopathy of any grade at approximately 55% ((Levitt, Bradshaw, Zwarenstein, Bawa, & Maphumolo, 1997). Similarly, a rural study KZN found that 46% of the subjects had been admitted on at least one occasion for a complication related to diabetes and retinopathy of any grade was present in 40% of the patients (Rotchford & Rotchford, 2002).

Further a prospective observational study found that the risk of diabetes complications was strongly associated with raised blood pressure. Any reduction in blood pressure was likely to reduce the risk of complications. On average each 10mmHg reduction in systolic blood pressure was associated with 12% decrease in endpoints (myocardial infarction, angina, stroke, renal failure, lower extremity amputation, micro vascular complications) and 15% reduction in risk of death related to diabetes ((Adler, 2000).

The association between QOL of patients with DM has been studied in several settings. A review of the studies from primary health care in Norway found that QOL was moderately affected in diabetic patients. Strong positive predictive factors for a poorer QOL were macro vascular diseases; especially coronary heart disease and non-vascular diseases whilst micro vascular complications were weaker predictors (Wandel, 2005).

Depression and diabetes

The association between depression and diabetes is well described for more than 300 years by Dr. Thomas Willis, a British physician and anatomist who commented “Diabetes is caused by “sadness or long sorrow and other depressions” (Willis, 1971).

Worldwide estimates of depression in people with diabetes mellitus vary depending on the type of diabetes, and socio-economic status of the country (Egede & Ellis, 2010). In the United States (U.S), the 2006 Behavioral Risk Factor Surveillance System (BRFSS) of adults aged 18 and older which is large population based sample of 226,646 participants, found that 22990 (8.2%) reported having diabetes. Results from the study found an age adjusted rate of depression of 8.3% amongst U.S adults with diabetes, ranging from a low of two percent to a high of 28% among the 50 states ((Li C. , Ford, Strine, & Mokdad, 2008). The study also found that people with type II diabetes who were using insulin had higher rate of major depression (24%) compared to people with type I diabetes (20.4%) or those with type II diabetes who were not using insulin (17.3%) (Li C. , Ford, Strine, & Mokdad, 2008). Further in the same cohort, the adjusted and unadjusted prevalence’s of undiagnosed depression was 8.7% and 9.2% respectively in patients with DM, and 45% of all diabetes patients had undiagnosed depression (Li C. , Ford, Zhao, Ahluwalia, Pearson, & Mokdad, 2009).

In contrast, a Nigerian study found a much higher rate of depression of 30% in diabetes patients compared to 9.5% in the control group. Reasons for this higher rate included a low income and higher number of dependents as patients are faced with a burden of paying for health care whilst still meeting the needs of the children. (James, Omoaregba, Eze, & Morakinyo, 2010).

The inter-relationship between DM and depression is complex and authors have proposed that in addition to depression being a consequence of diabetes, depression may be a risk factor for the onset of diabetes (Knol, Twisk, Beekman, Heine, Snoek, & Pouwer, 2006). This suggests there may be a bi-directional association between the two diseases.

Diabetes and depression are both common chronic conditions that are significantly associated with increased odds of disability (Egede L. E., 2004). The National Health Interview Survey (NHIS) in the US found that the odds of functional disability were increased 7-fold amongst adults with diabetes and major depression compared to adults without diabetes and depression (Egede L. E., 2004). Diabetes and depression have an impact on occupational functioning and adults with diabetes and depression are more likely to miss more than seven working days in any given year (Egede L. E., 2004).

Similarly, in a South African study, 31% of adults with type II DM indicated poor well-being and were considered at risk for depressive features. Participants, who were married, had higher educational levels and were employed showed better well-being levels (Ramkisson, Pillay, & Sartorious , 2016). Further DM places an extra financial burden on individuals and their families' as apart from its substantial economic impact on countries and national health systems (International Diabetes Federation , 2015).

Despite there being clear practice guidelines from the International Diabetes Federation (IDF) indicating that patients with diabetes are more likely to be affected by depression and periodic assessment and monitoring of depression and other mental health conditions is required in the management of patients with DM, (International Diabetes Federation , 2015) there are several challenges in implementing this policy. These include both patient-related and health care related factors (Egede & Ellis, 2010). Patient related factors include stigma and negative perceptions of any aspect of mental illness such as depression (Egede & Ellis, 2010). A barrier to early recognition and treatment of depression among individuals with DM is the difficulty in separating the symptoms of depression from the symptoms of poor management of diabetes e.g. fatigue weight gain or loss, change in appetite and sleep disturbance are common symptoms of depression and poor diabetes management (Ludman, et al., 2004).

Healthcare provider and healthcare system may provide an additional barrier, as they separate general physical health and mental health services with poor integration of services. These factors have

limited the effectiveness of treatments for depression and decreased the opportunity for patients with diabetes and depression to receive optimal care (Ludman, et al., 2004).

The added burden of human immunodeficiency virus infection

As per the United Nations Programme on Acquired Immune Deficiency Syndrome (UNAIDS) fact sheet, approximately 36.7 million people worldwide had HIV/AIDS at the end of 2015. In June 2016, 18.2 million people living with HIV were accessing antiretroviral therapy (ART). Further, an estimated 2.1 million individuals worldwide became newly infected with HIV in 2015 (UNAIDs report, 2015) and only 60% of people with HIV know their status, and the remaining 40% which is over 14 million people still need to access HIV testing services (UNAIDS, GLOBAL AIDS, 2016).

South Africa has the biggest and highest profile HIV epidemic in the world with an estimated 7 million people living with HIV in 2015. In the same year there were 380,000 new infections, while 180,000 South Africans died of AIDS related illnesses (UNAIDS, The Gap Report, 2014).

The prevalence although high in SA varies between regions and is 40% in KZN compared to 18% in the Northern Cape and Western Cape (South African National AIDS Council, 2015).

There is a high prevalence of mood disorders, particularly depression, associated with HIV disease (Dube, Benton, Cruess, & Evans, 2005). Individuals at highest risk for depression are those who have not disclosed their seropositive status, have lost a loved one, female gender and disease stage (Dube, Benton, Cruess, & Evans, 2005). The exact prevalence remains unknown as studies, have also generally not used diagnostic criteria according to DSM-V or ICD-10, but have relied on physician reporting or structured screening surveys (Klinkenberg, Sacks, & for the Hiv/aids Treatment Adherenc, 2004).

The etiology of depression in HIV patients is multifactorial and is likely determined by a combination of biological factors, history of comorbidity of psychiatric illness and psychological factors (Arseniou, Arvaniti, & Samakouri, 2011). Biological risk factors include lesions in specific neuro-anatomic structures due to disease itself or insult, such as those resulting from stroke or brain tumor which may contribute to development of secondary depression (Atkinson, et al., 2008). Thus it is important to exclude any contributory biological factors and then treat the depression.

Additionally, lifetime prevalence of major depression or other psychiatric disorder did not differ at baseline between HIV infected men and controls. However, a two year follow up found those with symptomatic HIV disease were significantly more likely to experience a major depressive episode compared to the asymptomatic HIV infected individuals and control patients. After baseline disease stage and medical variables associated with HIV infection were controlled, a lifetime history of major depression or psychiatric comorbidity (the presence of two or more lifetime psychiatric disorders) predicted subsequent major depressive episode (Atkinson, et al., 2008). Other contributory factors that increase the risk of depression in HIV infected patients include psychological factors such as HIV stigma, occupational disability, body image changes, isolation and debilitation (Olantunji, Mimiaga, O'Cleirigh, & Safren, 2006). Two recent studies from Ethiopia in HIV infected patients found a strong association between depression and verbal stigma (Mohammed & Mengistie, 2015) and perceived HIV stigma and poor social support (Tesfaw, et al., 2016).

The impact of social stigma has also been noted in local studies in SA, and in a study of 716 patients initiating ART in the Free State, the prevalence of depression was 25%. A positive association was observed between depression and duration of knowledge of HIV positivity. In contrast, participants who were in a support group were less likely to have been depressed (Pappin, Wouters, & Booysen, 2012).

A cross-sectional study in SA, amongst 422 HIV infected participants aged 30 years and older found that 42% had a depressive episode. Participants with a depressive episode were two to three times more likely to report poor health perceptions. Depressive symptoms were highest in older people who experienced an HIV related death of an adult child in the two years prior to interview, followed by people who were HIV infected and had not started ART or who were on ART for less than three months (Nyirenda, Chatterji, Rochat, Mutevedzi, & Newell, 2013).

The symptomatology of depression is thought to differ between HIV infected patients and HIV negative patients (Akena, Musisi, & Kinyanda, 2010). Studies show HIV infected patients tend to have greater impairments in decisions making, sleep and appetite and cognitive functioning (Akena, Musisi, & Kinyanda, 2010). Several studies have also shown that there is a gender difference and women with HIV infection are at a higher risk of having more severe symptoms (Wolff, Alvarado, & Wolff, 2010) (Reis, Haas, dos Santos, Teles, Galvão, & Gir, 2011).

In summary the current literature suggests that both HIV infection and DM are associated with depression and greater disability and poorer QOL. Thus, we wanted to understand the impact of HIV infection on depressive symptoms and QOL in patients with DM locally.

AIM:

To determine, the added impact of HIV infection on depression and quality of life in patients with diabetes mellitus in a regional hospital in KZN.

OBJECTIVES:

1. To describe the socio-demographic profile of the HIV infected and non-infected patients with diabetes mellitus.

2. To determine the prevalence of depressive symptoms and quality of life in HIV infected and non-infected patients with diabetes mellitus in the medical outpatient department in a regional hospital.

3. To determine the association between depressive symptoms and socio-demographic and clinical correlates of HIV infected and non-infected adults with diabetes mellitus.

HYPOTHESIS

There is a higher prevalence of depressive symptoms in HIV infected adult patients with diabetes mellitus compared to HIV non-infected adult patients with diabetes mellitus.

DEFINITIONS:

Human immunodeficiency virus infection: Human immunodeficiency virus infects cells of the immune system, destroying or impairing their function. Infection with virus results in progressive deterioration of the immune system leading to “immune deficiency”.

Diabetes Mellitus: Diagnostic criteria according to WHO guidelines (2006) for diabetes is if one or more of the following are met and must be confirmed on a subsequent day, symptoms with plasma glucose of ≥11.1 mmol/L confirmed on a subsequent day by fasting plasma glucose ≥7,0 mmol/L. An oral glucose tolerance test (OGTT) with two-hour post load value ≥11, 1 mmol/L or symptoms with plasma glucose ≥ 11,1mmol /L.

Quality of life (QOL): is the general well-being of individuals and societies, outlining negative and positive features of life. It observes life satisfaction, including everything from physical health, family, education, employment, wealth, religious beliefs, finance and the environment.

Depression: depression is described as a persistent depressed, irritable or decreased pleasure in activities for at least two weeks with five of nine criteria as per DSM V classification (American Psychiatric Association, 2014).

Method

This is a cross-sectional descriptive study of adult HIV infected patients with DM and an age, (± 3 years), gender and ethnic matched adult HIV non-infected patients with DM attending a medical outpatient department at a regional hospital.

A structured socio-demographic questionnaire and brief mental health screening tools will be used. All interviews will be conducted by the principal investigator after obtaining written informed consent.

Study Population

Human immunodeficiency virus infected adults with DM attending a medical outpatient service at King Edward Hospital will be invited to participate. A control group of HIV negative adults with DM who are matched for age (± 3 years) gender and ethnicity will also be enrolled.

Study Site

King Edward VIII Hospital is the second largest hospital in the southern hemisphere providing regional and tertiary services to the KZN and Eastern Cape. It is a 922 bedded hospital with ± 360000 outpatients. It has both medical and psychiatric specialist services. The outpatient medical clinics include a medical follow up clinic with ± 900 patients seen per month, family clinic which offers HIV services with approximately 2000 patients per month and acute medical unit with ± 3000 patients seen per month.

Study period

Data collection will commence after receiving full ethics approval from the UKZN BREC and permission from KEH VIII hospital management and provincial health department approval.

Data collection is anticipated to occur over 3 - 6months.

Sample size

The statistician Dr. W. Sibanda from UKZN College of Health Science was consulted. Two groups of patients with diabetes will be studied namely, HIV positive and HIV negative with respect to depression and QOL. We seek to determine if there are differences in QOL and depression in HIV positive and HIV negative diabetic patients. The null hypothesis is that there is no statistical difference in QOL and depression between HIV positive and HIV negative diabetic patients.

The statistical parameters were used to calculate the sample size, effect size = 0.57 (medium), type I (α) error = 0.05 (the probability of falsely rejecting the null hypothesis= 5%), type II (β) error = 0.2 (the probability of falsely retaining the null hypothesis).

-Statistical power= 1-β- 1- 0.2= 0.8 (statistical power of 80%).

On the basis of the above statistical parameters a total sample size was determined. This means 50 diabetic patients who are HIV positive and 50 diabetic patients who are HIV negative.

Sampling strategy

Consecutive adult patients with diabetes meeting inclusion/exclusion criteria will be invited to participate in the study.

Inclusion Criteria:

Case group: Adult (18 years and older) with diabetes mellitus on treatment for 12 months with or without hypertension.

- HIV infected on antiretroviral treatment for minimum of six months.
- Willing to participate in the study.
- Male or female
- Outpatients

Control group (matched for age, gender and ethnicity):

- Adult (18 years and older) with diabetes mellitus on treatment for 12 months with or without hypertension
- HIV negative test in the last six months
- Willingness to participate in the study
- Male or female
- Outpatient

Exclusion criteria :

Unable to consent/or refuse to participate.

HIV status unknown

Other underlying chronic medical disease such as epilepsy, arthritis and/ or chronic psychiatric disorders such as bipolar mood disorder or psychosis.

Data collection method and tools

Brief mental health case finding instruments that have been used in medically ill population with HIV infection will be used in the study.

The following tools will be used:

Socio-demographic questionnaire-designed for study

The Patient Health Questionnaire 9 (PHQ9) (Spitzer, 2000)

World Health Organization QOL BREF 7

The Patient Health Questionnaire (PHQ-9) (Kroenke, Spitzer, & Williams, 2001)

The PHQ-9 is a multipurpose instrument for screening, diagnosing, monitoring and measuring the severity of depression; it incorporates DSM-IV diagnostic criteria with other leading major depressive symptoms into a brief self-report tool (Kroenke, Spitzer, & Williams, 2001).

The PHQ9 was designed for use in clinical and medical settings, and uses a four-point Likert scale (0 not at all, 1= several days, 2=more than half the days, 3= nearly every day) to gauge responses to questions asking about the respondents mental/emotional health over the previous 2-week period (Kroenke, Spitzer, & Williams, 2001).

Scores on the PHQ9 can range from 0-27; scores between 0 and 4 indicate no depression, 5-9 indicate mild depression, 10-14 indicate moderate depression, 15-19 indicate moderately severe depression, and 20 or more indicate severe depression (Kroenke, Spitzer, & Williams, 2001) .

Reliability and validity studies of the PHQ9 have yielded results indicating sound psychometric properties. The diagnostic validity of the PHQ9 was established in studies and internal consistency of the PHQ9 has been shown to be high (Spitzer, 2000). A study involving two different patient populations with a total of 6000 participants produced Cronbach properties (Kroenke, Spitzer, & Williams, 2001).

Additionally, test-retest reliability had high correlation at r = 0.84 and discriminant validity was established via a ROC analysis that produced an area under the curve for the PHQ9 of 0.95 when diagnosing depression. Moreover, criterion validity was shown by both high sensitivity and specificity for the PHQ9. In addition, among the 6000 participants who completed the PHQ9, 580 were interviewed by mental health professionals, and results demonstrated strong agreement between diagnosis made by the PHQ9 and by the mental health professionals (Kroenke, Spitzer, & Williams, 2001).

The World Health Organization Quality of Life (WHOQOL)-BREF

The WHO defines QOL as gnosis made by the PHQ9 and by the mental health professionals and value systems in which they live, and in relation to their goals, expectations, standards and concerns." It is therefore important to be aware of how satisfied or dissatisfied people are with important aspects of their lives (Organisation, 1997) .

The WHOQOL-BREF is a person centered instrument for subjective assessment and is based on a cross culturally sensitive concept. It consists of QOL items that are concerned with the meaning of different aspects of life to the respondents and how satisfactory or problematic is their experience of them (Whoqol Group, 1994).

The WHOQOL-BREF is an abbreviated 26 item version of the WHOQOL-100; it contains one item from each of the 24 facets of QOL included in the WHOQOL-100, plus two benchmark items from the general facet on overall QOL and general health. The WHOQOL-BREF is scored in four domains which include; Physical health, psychological, social relations and environmental (Whoqol Group, 1994).

WHOQOL-BREF psychometric properties were analyzed using cross-sectional data obtained from a survey of adult carried out in 23 countries (n=11 830). Sick and well respondents were sampled from the general population, as well as from hospital, rehabilitation and primary care settings, serving patients with physical and mental disorder and with respect to quotas of important socio-demographic variables. The WHOQOL-BREF self-assessment was completed, together with socio-demographic and health status questions. Analyses of internal consistency, item-total correlations, discriminant validity and construct validity through confirmatory factor analysis indicate that the WHOQOL-BREF has excellent psychometric properties of reliability and performs well in preliminary tests of validity. These results indicate that overall, the WHOQOL-BREF is a sound, cross-culturally valid assessment of QOL (Whoqol Group, 1994) .

Data Analysis

Descriptive statics will be used to describe the population frequency and percent to describe categorical variables. The frequency distribution of numeric variables will be examined and means with standard deviation or medians and inter-quartiles ranges will be used as appropriate.

The two groups will be compared using the student t-test. Categorical variables will be compared using Pearson’s chi square test and Fisher chi square test.

LIMITATIONS OF STUDY

The study is urban based and hospital based, therefore findings may not be generalizable to other settings. Sample size may limit ability to find associations between depressive symptoms and clinical correlates. Study relies on self-reporting of symptoms and patients may under/over report symptoms. The study is conducted in the public sector so may not represent all ethnic groups or socio-economic strata.

ETHICAL CONSIDERATIONS

A research protocol will be submitted to the University of KwaZulu-Natal Ethics Committee for ethical approval.

Permission to conduct the research will be obtained from the medical manager of the hospital concerned after provisional BREC approval.

An information document for the participant will be provided in English and isiZulu

Informed written consent of the patient will be obtained prior to any study related procedure.

Patient confidentiality will be protected and anonymity ensured by assigning a study number to each patient and by recording patient data on coded data sheets which do not contain patient identifiers.

Data will be stored on a password protected computer and all patient records will be kept in a locked office with limited access to medical personnel only.

If participants are found to have any clinically significant finding that may impact on patient care, participants will be referred to the clinic doctor/psychiatric service for further assessment and care.

The study holds minimal risk to any patients as there is no intervention.

The risk of possible distress associated with questions asked is minimal and similar to a routine clinical interview. Participants will have option of refusing to answer questions that they may find distressing/intrusive. Counseling and referral for additional care will be provided if need arises.

Participants will receive the appropriate standard of care, irrespective of their participation in the study.

The results of the study will be made available to the clinic to enhance patient management and will assist in planning future programs particularly to guide screening.

No incentives will be provided for participation.

There will be no additional cost to the health facility.

The participants will be interviewed in a consulting room privately on day of routine visit.

PUBLICATION OF FINDINGS

A scientific report will be submitted to the Departments of Medicine and Psychiatry, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal and the hospital.

The results of the study will be submitted for presentation to scientific meetings and publication to local and/or international journals.

FEASIBILITY

Time lines and project management.

Protocol Submission to Post Graduate Office: August 2017

Submission of Protocol by Post Graduate Office to BREC by August 2017

BREC approval: 31 October 2017

Data collection : 1 November 2017-30 April 2018

Data Analysis and Review: 1 May 2018-31 May 2018

Write up of Journal Article: 1June 2018-30 September 2018

Study Team Contributors and Authorship

There are no co-investigators.

The study will be supervised by Dr. F. Paruk and Dr. S. Paruk who will serve as co-authors in the publication.

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Appendix 2:

The Guidelines for Authorship for the Journal selected: for submission of the manuscript to South African Journal of Psychiatry

SOUTH AFRICAN JOURNAL OF PSYCHIATRY

Overview

The author guidelines include information about the types of articles received for publication and preparing a manuscript for submission. Other relevant information about the journal's policies and the reviewing process can be found under the about section. The **compulsory cover letter** forms part of a submission and must be submitted together with all the required **forms.** All forms need to be completed in English.

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format. Systematic reviews should follow the same basic structure as other original research articles. The aim and objectives should focus on a clinical question that will be addressed in the review. The methods section should describe in detail the search strategy, criteria used to select or reject articles, attempts made to obtain all important and relevant studies and deal with publication bias (including grey and unpublished literature), how the quality of included studies was appraised, the methodology used to extract and/or analyse data. Results should describe the homogeneity of the different findings; clearly present the overall results and any meta-analysis.

Word limit	3000-4000 words (excluding the structured abstract and references)
Structured abstract	250 words to include a Background, Aim, Setting, Methods, Results and Conclusion
References	60 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate

Original Research Article full structure

Title: The article's full title should contain a maximum of 95 characters (including spaces).

Abstract: The abstract, written in English, should be no longer than 250 words and must be written in the past tense. The abstract should give a succinct account of the objectives, methods, results and significance of the matter. The structured abstract for an Original Research article should consist of six paragraphs labelled Background, Aim, Setting, Methods, Results and Conclusion.

- Background: Summarise the social value (importance, relevance) and scientific value (knowledge gap) that your study addresses.
- Aim: State the overall aim of the study.
- Setting: State the setting for the study.
- Methods: Clearly express the basic design of the study, and name or briefly describe the methods used without going into excessive detail.
- Results: State the main findings.
- Conclusion: State your conclusion and any key implications or recommendations.

Do not cite references and do not use abbreviations excessively in the abstract.

Introduction: The introduction must contain your argument for the social and scientific value of the study, as well as the aim and objectives:

- Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.
- Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic, and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.
- Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.
- Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design: This must address the following:

- Study design: An outline of the type of study design.

- Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.
- Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.
- Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.
- Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.
- Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used orsteps followed in qualitative data analysis.
- Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution’s name and permit numbers should be stated here.

Results: Present the results of your study in a logical sequence that addresses the aim and objectives of your study. Use tables and figures as required to present your findings. Use quotations as required to establish your interpretation of qualitative data. All units should conform to the **SI convention** and be abbreviated accordingly. Metric units and their international symbols are used throughout, as is the decimal point (not the decimal comma).

Discussion: The discussion section should address the following four elements:

- Key findings: Summarise the key findings without reiterating details of the results.
- Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.
- Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.
- Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

Conclusion: Provide a brief conclusion that summarises the results and their meaning or significance in relation to each objective of the study.

Acknowledgements: Those who contributed to the work but do not meet our authorship criteria should be listed in the Acknowledgments with a description of the contribution. Authors are responsible for ensuring that anyone named in the Acknowledgments agrees to be named. Refer to the acknowledgement structure guide on our *Formatting Requirements* page.

Also provide the following, each under their own heading:

- Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: *The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.* Read our **policy on competing interests**.
- Author contributions: All authors must meet the criteria for authorship as outlined in the **authorship** policy and **author contribution** statement policies.
- Funding: Provide information on funding if relevant
- Data availability: All research articles are encouraged to have a data availability statement.
- Disclaimer: A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

References: Authors should provide direct references to original research sources whenever possible. References should not be used by authors, editors, or peer reviewers to promote self-interests. Refer to the journal referencing style downloadable on our *Formatting Requirements* page.

Appendix 3: Ethics

1. Hospital Approval

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

OFFICE OF THE HOSPITAL CEO
KING EDWARD VIII HOSPITAL

Private Bag X02, CONGELLA, 4013
Corner of Rick Turner (Francois Road) & Sydney Road
Tel: 031-3603853, Fax:031-2061457; Email: rejoice.khuzwayo@kznhealth.gov.za
www.kznhealth.gov.za

Ref.: KE 2/7/1/(51/2017
Enq.: Mrs. R. Sibiya
Research Programming

13 October 2017

Dr. Y. Qubekile
Department of Internal Medicine
Nelson R. Mandela –School of Medicine
UNIVERSITY OF KWAZULU-NATAL

Dear Dr. Qubekile

Protocol: "Impact on human immunodeficiency virus infection on depression and quality of life in patients with diabetes mellitus attending a Regional Hospital in eThekwini, KwaZulu-Natal, South Africa"
Degree: MMed ; BREC REF. NO. BE553/17

Permission to conduct research at King Edward VIII Hospital is provisionally granted, pending receipt of approval by the Provincial Health Research Committee, KZN Department of Health.

Kindly note the following:-

- The research will only commence once confirmation from the Provincial Health Research Committee in the KZN Department of Health has been received.
- Signing of an indemnity form at Room 8, CEO Complex before commencement with your study.
- King Edward VIII Hospital received full acknowledgment in the study on all Publications and reports and also kindly present a copy of the publication or report on completion.

The Management of King Edward VIII Hospital reserves the right to terminate the permission for the study should circumstances so dictate.

Yours faithfully

[redacted] SUPPORTED/~~NOT SUPPORTED~~ 16/10/17

DR. SA MOODLEY
ACTING SENIOR MEDICAL MANAGER

DATE

2. KZN DoH Approval

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

330 Langalibalele street,
Private Bag X9051 PMB, 3200
Tel: 033 395 2805/3189/3123 Fax: 033 394 3782
E-mail: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management (HKRM)

Reference: HRKM420/17
KZ_201710_028

25 October 2017

Dear Dr Y Qubekile
(University of KwaZulu-Natal)

Subject: Approval of a Research Proposal

1. The research proposal titled **'Impact of human immunodeficiency virus infection on depression and quality of life in patients with diabetes mellitus attending a regional hospital in eThekwini, KwaZulu-Natal, South Africa'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at King Edward VIII Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facilities before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. **Your final report must be posted to HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Ms G Khumalo on 033-395 3189.

Yours Sincerely

[redacted]

Dr E Lutge
Chairperson, Health Research Committee
Date: 26/10/17

Fighting Disease, Fighting Poverty, Giving Hope

3. BREC ethics certificate

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

28 November 2017

Dr Y Qubekile (216076834)
School of Medicine
College of Health Science
yqubekile@yahoo.com

Dear Dr Qubekile

Protocol: Impact of human immunodeficiency virus infection on depression and quality of life in patients with diabetes mellitus attending a regional hospital in eThekwini, KwaZulu-Natal, South Africa. Degree: MMed
BREC Ref No: BE553/17

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 06 September 2017.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 15 November 2017 to BREC correspondence dated 06 October 2017 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval** and may begin as from 28 November 2017.

This approval is valid for one year from **28 November 2017.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be **RATIFIED** by a full Committee at its next meeting taking place on **12 December 2017.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

[redacted]

Prof VK Rambiritch
Deputy Chair: Biomedical Research Ethics Committee

cc: paruk@ukzn.ac.za myamod@telkomsa.net

Biomedical Research Ethics Committee
Professor J Tsoka-Gwegweni (Chair)
Westville Campus, Govan Mbeki Building
Postal Address: Private Bag X54001, Durban 4000
Telephone: +27 (0) 31 260 2486 Facsimile: +27 (0) 31 260 4609 Email: brec@ukzn.ac.za
Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

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4. Protocol Amendment

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI
RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

23 January 2020

Dr Y Qubekile (216076834)
School of Medicine
College of Health Science
yqubekile@yahoo.com

Dear Dr Qubekile

Protocol: Impact of human immunodeficiency virus infection on depression and quality of life in patients with diabetes mellitus attending a regional hospital in eThekwini, KwaZulu-Natal, South Africa. Degree: MMed
BREC Ref No: BE553/17

We wish to advise you that your correspondence received on 14 January 2020 submitting an application for amendments dated 13 January 2020 for the above study has been **noted and approved** by a subcommittee of the Biomedical Research Ethics Committee.

The committee will be notified of the above at its next meeting to be held on **11 February 2020.**

Yours sincerely

[redacted]

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

cc: paruk@ukzn.ac.za myamod@telkomsa.net

5. BREC Recertification

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

26 February 2021

Dr Y Qubekile (216076834)
School of Medicine
yqubekile@yahoo.com

Dear Dr Qubekile

Protocol: Impact of human immunodeficiency virus infection on depression and quality of life in patients with diabetes mellitus attending a regional hospital in eThekwini, KwaZulu-Natal, South Africa.
Degree: MMed
BREC Ref No: BE553/17

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved: 28 November 2020
Expiration of Ethical Approval: 27 November 2021

I wish to advise you that your application for Recertification received on 19 February 2021 for the above protocol has been **noted and approved** by a sub-committee of the Biomedical Research Ethics Committee (BREC) for another approval period. The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be notified of the above approval at its next meeting to be held on 09 March 2021.

Yours sincerely

[redacted]

Ms A Marimuthu
(for) Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Appendix 4: Data collection

1. Study questionnaire

Participant Study Number: 216076834

Site: King Edward Hospital

Section 1: Patient demographic characteristics

1.1 Age: ……years.

18- 25 years	
26 – 30 years	
31 – 40 years	
41- 45 years	

1.2 Gender:

Male	
Female	

1.3 Marital Status:

Single	
Married	
Divorced	
Widowed	
Separated	

1.4 Occupational Statuses:

Employed	
Unemployed	
Self employed	

1.5 Race:

Black	
White	
Indian	
Colored	
Other	

1.6 Educational level

Primary Education	
Secondary Education	
Tertiary Education	

1.7. Household Income:

< R1000	
R1001 – R2500	
R2501 – R5000	
>R5001- R10 000	
>R 10 000	

1.8. Area of residency

Rural/Urban/Township/Other

Section 2: Clinical features:

Diabetes Mellitus
2.1. Number of years since diagnosis……..
2.2. Type
2.3. Current treatment:

Insulin	
oral medication	
Dual therapy	

2.4. Complication of DM as per case files

Cardiac- ischemic heart disease	
Cerebrovascular disease	
Renal	
Other- specify	

2.5. Last HBA1C and date…….
2.6. Urine examination dipstick

Normal	
Abnormal- specify	

2.7. HIV Status

Positive	
Negative	
Unknown	

2.8. Diagnosis of HIV (no. of years)…….
2.9. CD4 count……

2.10. Viral load ……

Viral suppression	
Not virally suppressed	

.

2.11. ARV regimen specify……..

2.12. Date (year) HIV treatment started: ---------- years

2.13. Treatment interruption if any and length of period

Yes/no

Specify……

2.14. Opportunistic infection (current or previous)

Yes/no- past

Yes/no – current

Section 3: mental health

3.1. Past psychiatric history

Yes	
No	
If yes specify disorder	

3.2. Current psychiatric treatment

Yes- if yes specify diagnosis	
No	

3.3. Was there a psychiatric diagnosis before diagnosis of DM?

Yes (if yes specify diagnosis)	
No	

3.4 Was there a psychiatric diagnosis before diagnosis of HIV

Yes (if yes, specify diagnosis)	
No	

Factors influencing emotional distress

3.5. Family History of Mental Illness

Yes		Parent	
No		Sibling	
		Grandparent	
		Other	

3.6. Stigma experienced by patient (A set of negative and often unfair beliefs that a society or group of people have about something) around HIV/DM

Yes	
No	

3.7. Satisfaction with Medical Treatment

Yes	
No	

3.8. Support Systems:

Psychologist	
Social Worker	
School	
Family	

Friends	
Religious Organizations	

3.9 Suicide:

suicide history	yes	no	Comments (number and method)
Past suicide attempts (lifetime)			
Suicide attempts in past year			
Suicidal ideation in past			
Suicidal ideation currently			

2. PHQ-9

The Patient Health Questionnaire (PHQ-9)

Patient Name: Date of Visit:

(Use "✔" to indicate your answer)

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not At All	Several Days	More Than Half the Days	Nearly Every Day
1. Little interest or pleasure in doing things	0	1	2	3
2. Feeling down, depressed, or hopeless	0	1	2	3
3. Trouble falling or staying asleep, or sleeping too much	0	1	2	3
4. Feeling tired or having little energy	0	1	2	3
5. Poor appetite or overeating	0	1	2	3
6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down	0	1	2	3
7. Trouble concentrating on things, such as reading the newspaper or watching television	0	1	2	3
8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual	0	1	2	3
9. Thoughts that you would be better off dead or of hurting yourself in some way	0	1	2	3

Column Totals _____ + _____ + _____

=Total Score: _____

10. If you checked off any problems, how difficult have these problems made it for you to do your
Work, take care of things at home, or get along with other people?

☐Not difficult at all ☐Somewhat difficult ☐Very difficult
☐Extremely Difficult

Developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues, with an educational grant from
Pfizer Inc.

3. WHOQOL-BREF Questionnaire

The following questions ask how you feel about your quality of life. I will read out each question to you, along with the response options. **Please choose the answer that appears most appropriate**. If you are unsure about which response to give to a question, the first response you think of is often the best one.

Please keep in mind your standards, hopes, pleasures and concerns. We ask that you think about your **life in the last four weeks** (The overall quality of life and general health facet).

		Very poor	Poor	Neither poor nor good	Good	Very good
1.	How would you rate your quality of life?	1	2	3	4	5
		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
2.	How satisfied are you with your health?	1	2	3	4	5
The following questions ask about how much you have experienced certain things in the last four weeks.						
		Not at all	A little	A moderate amount	Very much	An extreme amount
3	To what extent do you feel that physical pain prevents you from doing what you need to do?	5	4	3	2	1
4.	How much do you need any medical treatment to function in your daily life?	5	4	3	2	1
5.	How much do you enjoy life?	1	2	3	4	5
6.	To what extent do you feel your life to be meaningful?	1	2	3	4	5
		Not at all	A little	A moderate amount	Very much	Extremely
7.	How well are you able to concentrate?	1	2	3	4	5

8.	How safe do you feel in your daily life?	1	2	3	4	5
9.	How healthy is your physical environment?	1	2	3	4	5

The following questions ask about how completely you experience or were able to do certain things in the last four weeks.

		Not at all	A little	Moderately	Mostly	Completely
10.	Do you have enough energy for everyday life?	1	2	3	4	5
11.	Are you able to accept your bodily appearance?	1	2	3	4	5
12.	Have you enough money to meet your needs?	1	2	3	4	5
13.	How available to you is the information that you need in your day-to-day life?	1	2	3	4	5
14.	To what extent do you have the opportunity for leisure activities?	1	2	3	4	5

		Very poor	Poor	Neither poor nor good	Good	Very good
15.	How well are you able to get around?	1	2	3	4	5

		Very dissatisfied	Dissatisfied	Neither satisfied nor dissatisfied	Satisfied	Very satisfied
16.	How satisfied are you with your sleep?	1	2	3	4	5
17.	• How satisfied are you with your ability to perform your daily living activities?	1	2	3	4	5
18.	How satisfied are you with your capacity for work?	1	2	3	4	5
19.	How satisfied are you with yourself?	1	2	3	4	5

20.	How satisfied are you with your personal relationships?	1	2	3	4	5
21.	How satisfied are you with the support you get from your friends?	1	2	3	4	5
22.	How satisfied are you with the conditions of your living place?	1	2	3	4	5
• 3.	• How satisfied are you with your access to health services?	1	2	3	4	5
24.	How satisfied are you with your transport?	1	2	3	4	5
• The following question refers to how often you have felt or experienced certain things in the last four weeks.						
		Never	Seldom	Quite often	Very often	Always
25.	How often do you have negative feelings such as blue mood, despair, anxiety, depression?	5	4	3	2	1
[Scoring method] Equations for computing domain raw scores:						
Domain 1 (physical) score = Q3 + Q4 + Q10 + Q15 + Q16 + Q17 + Q18						
Domain 2 (psychological) score = Q5 + Q6 + Q7 + Q11 + Q19 + Q25						
Domain 3 (social) score =Q20 + Q21						
Domain 4 (environmental) score = Q8 + Q9 + Q12 + Q13 + Q14 + Q22 + Q23 + Q24						

4. Information Document

Study title: Impact of human immunodeficiency virus infection on depression and quality of life in patients with diabetes mellitus attending a regional hospital in eThekwini, KwaZulu-Natal, South Africa.

Dear Sir/Mam

Good day

My name is Dr. Yonela Qubekile; a Registrar in the Department of Medicine at the University of KwaZulu-Natal and currently employed by the KwaZulu-Natal Department of Health.

You are invited to consider taking part in this study that involves research to identify depression and its associated risk factors in patients treated for diabetes with and without HIV. We want to find out if patients with HIV and diabetes have increased risk of psychological problems.

This study is being conducted at the king Edward hospital and we hope to enroll 100 outpatients.

It will involve an interview with the Principle Investigator, Dr. Qubekile, who will also look at your medical chart. The questionnaires are about depressive symptoms and how you feel diabetes with or without HIV infection has affected your life.

It is not experimental and does not include any procedures and administration of any treatment. If your answers suggest that you need assessment for depression, then we will refer you to the psychiatric clinic.

The study interview is expected to be approximately 20-30 minutes. The study is funded by the principle investigator and is for a MMed Degree (to become a physician).

RISKS

Risks of being in the study are possible inconvenience or distress at having to answer questions. You do not have to answer a question if you feel unable to.

POTENTIAL BENEFITS

Whist the study holds no direct immediate benefit to you or the patient; we hope that this study may contribute to improve knowledge on mental health in patients with diabetes and HIV.

Participation is entirely voluntary and refusal to participate will not affect your care and treatment. Your decision will not affect your further treatment or your relationship with those treating you at the hospital.

You may stop participation at any time without penalty or loss of benefits to which you are otherwise entitled.

COSTS and REIMBURSEMENTS

You will not be paid for participation in the study. There is also no cost involved for participating in study.

CONFIDENTIALITY Every effort will be made to keep personal information confidential. Absolute confidentiality cannot be guaranteed. Personal information may be disclosed if required by law.

The Biomedical research ethics committee may inspect or copy research records.

A subject identification list will be kept by the study doctors and all documents will be stored at the hospital. Study related staff will only have access to coded information (no names will be on the information).

You are encouraged to ask questions at any time during the study.

This study has been ethically reviewed and approved by the UKZN Biomedical Research Ethics Committee (approval number_____).

In the event of any problems or concerns/questions you may contact the researcher at 0727676809. (approval number_____). Or the BREC office at the following contact details:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION

Research Office, Westville Campus

Govan Mbeki Building

Private Bag X 54001
Durban 4000

KwaZulu-Natal, South Africa

Tel: 27 31 2604769 - Fax: 27 31 2604609

Email: BREC@ukzn.ac.za

Thank you for taking the time to read this information document.

Please feel free to ask doctor any additional questions

5. CONSENT DOCUMENT:

I _____ have been informed about the study entitled “Impact of human immunodeficiency virus infection on depression and quality of life in patients with diabetes mellitus attending a regional hospital in eThekwini, KwaZulu-Natal, South Africa.” and understand the purpose and procedures of the study.

I have been given an opportunity to answer questions about the study and have had answers to my satisfaction.

I declare that my participation in this study is entirely voluntary and that I may withdraw at any time without affecting any treatment or care that I would usually be entitled to.

If I have any further questions/concerns or queries related to the study I understand that I may contact the researcher Dr. Y. Qubekile at 0727676809, Dr. F. Paruk at 031 2604397 or Dr. S. Paruk 0312604321.

If I have any questions or concerns about my rights as a study participant, or if I am concerned about an aspect of the study or the researchers then I may contact:

BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Research Office, Westville Campus
Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za

_____ _____
Signature of Participant **Date**

_____ _____
Signature of Witness **Date**

_____ _____
Signature of Principle Investigator **Date**