UNIVERSITY OF THE WITSWATERSRAND

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QUALITY OF LIFE AND ASSOCIATED FACTORS AMONG PEOPLE LIVING WITH HIV RECEIVING SECOND LINE THERAPY IN JOHANNESBURG OVER 48 WEEKS

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1. DECLARATION

I, Nomcebo Oratile Mokgethi, 670495, declare that this Research Report is my own work and submitted in partial fulfillment of the requirements for the degree of MSc Epidemiology and Biostatics, in the University of the Witwatersrand, Johannesburg. I have made no use of sources, materials or assistance other than those which have been openly and fully acknowledged in the text. This report has not been submitted to this or any other university before, for any degree or examination.

Signature of Student…….....Date: …23 January 2020…….....

2. ABSTRACT

Background: Quality of life (QOL) has become an increasingly relevant outcome measure in antiretroviral therapeutic research and practice, giving a holistic picture of the well-being of patients living with HIV. The burden of HIV-related treatment challenges, such as side effects and pill burden has presented new public health challenges. Therefore, the aim of the study was to investigate direct and indirect pathways that affect the quality of life among PLWHA in Johannesburg, South Africa on second-line antiretroviral therapy over 48 weeks

Methods: The secondary data analysis utilized data from male and female HIV-1 positive participants receiving second-line Anti-Retroviral Therapy (ART) in Johannesburg over 48 weeks. Data were analyzed from a clinical trial which evaluated the non-inferiority of ritonavir-boosted darunavir (DRV/r 400/100 mg) compared to the current standard second-line therapy ritonavir-boosted lopinavir (LPV/r) over the period of 48 weeks . The analysis presented in this report was of data from a cohort of 293 HIV positive participants (at least 18 years old). QOL was measured using the eight domains from the ACTG (Aids Clinical Trial Group) questionnaire administered by a research nurse. Explanatory variables included: treatment regimen, pill burden, adverse events, substance use, and sociodemographic characteristics. A structural equation model using significant variables from the multivariate logistic regression analysis was performed based on an *a priori* conceptual framework and separate SEM models were developed for physical functioning, cognitive and mental QOL.

Results: QOL scores were very high, particularly in the cognitive domain, where the median score was 100/100 and the IQR was 100-100. The mental QOL domain presented with the lowest scores, with a mean score of 86.8 (SD21.1). Based on the logistic regression, pill burden and age were significant risk factors for lower QOL physical functioning and cognitive scores. Age was the only risk factor that predicted low mental health scores. Based on the SEM, pill burden was a mediator in physical functioning, cognitive and mental QOL domains. Adverse events was also an additional mediator in the mental health domain, and surprisingly were correlated with higher mental QOL scores. Participants on darunavir presented with a low pill burden and lower cognitive functioning scores.

Discussion: Overall, this study shows that pill burden decreases mental, cognitive and physical functioning QOL scores. Furthermore, this study revealed the impact of co-morbidities and pill burden amongst the older HIV participants, revealing the important needs of the aging HIV

population. The study supports the evidence that Duranavir has a better side effects profile, showing that participants on this regimen reported a lower pill burden and present with better cognitive functioning scores. Lastly, females report a higher number of pill burden and adverse events as compared to males, as a result, are vulnerable in experiencing lower mental, physical and cognitive QOL.

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AIDS	Acquired immunodeficiency syndrome
ACTG	Aids Clinical Trial Group
ADR	Adverse drug reaction
ART	Anti-retroviral therapy
DRV	Darunavir
HAART	Highly active antiretroviral therapy.
HIV	Human Immunodeficiency Virus
LPV/r	ritonavir-boosted lopinavir
PLWHA	People living with HIV/AIDS
QOL	Quality of Life
RCT	Randomized control trial
SAR	Severe adverse drug reactions
SSA	Sub-Saharan Africa
WHO	World Health Organisation
WRHI	Wits Reproductive Health and HIV Institute

8. DEFINITION OF TERMS

Quality of life	The World Health Organisation (WHO) defines QOL as ‘‘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’’(1) (WHO, 1997 p. 1403). There is an agreement that QOL includes aspects such as one's social, physical, cognitive function and overall wellbeing (2,3). The domains included in this report are:
a.General health perception:	general health and health outlook
b. Pain	both the intensity of bodily pain and the degree of interference with normal activities due to pain
c. Physical function	patients’ physical limitations
d. Role function	the impact of persons’ health on their ability to perform on the job, around the house or in school
e. Social function	the extent to which persons’ social activities are limited.
f. Cognitive function	the degree of difficulty persons have experienced in the past four weeks with respect to their cognitive abilities
g. Mental Health	a persons’ unusual or extreme shifts in mood
h. Energy:	assesses persons’ unusual or extreme shifts in energy
Pathways:	pathways are relationships of variables with an indication of directionality
Adverse event	An adverse event (also referred to as an adverse experience) can be any “unfavorable and unintended sign (e.g., an abnormal laboratory finding), symptom, or disease temporarily associated with the use of a drug, without any judgment about causality or relationship to the drug. An adverse event can arise from any use of the drug (e.g., off-label use, use in combination with another drug) and from any route of administration, formulation, or dose, including an overdose”. (CTSI, 2014, page.5)(4)
Tolerability	“The tolerability of the medical product represents the degree to which overt adverse effects can be tolerated by the subject”. (For example, how will this affect patient person’s day to day activities?) (FDA,2017, page. 13)(5)
Viral load	“The amount of HIV in a sample of blood. Viral load (VL) is reported as the number of HIV RNA copies per milliliter of blood” (AIDS info,2018, page 175) (6)
Drug resistance	“When a bacterium, virus, or another microorganism mutates (changes form) and becomes insensitive to (resistant to) a drug that was previously effective’ (AIDS info, 2018, page 2)(6)
Virologic failure	“The inability to achieve or maintain suppression of viral replication to an HIV RNA level <50 copies/mL” (AIDS info, 2018, page 181) (6)

1. CHAPTER ONE: INTRODUCTION

This chapter provides an overview of quality of life and the factors affecting it in people living with HIV/AIDS (PLWHA). In the literature review, aspects such as quality of life measures, treatment-related difficulties (adverse events, pill burden) and other factors such as gender differences are discussed in relation to how they impact quality of life in PLWHA. The problem statement and justification of the study are provided, and the chapter concludes with the aims and the objectives of this study

1.1. Introduction

In 2013 an estimated 35 million people were infected with the Human Immuno-deficiency Virus (HIV) worldwide. Sub-Saharan Africa (SSA) constitutes only 12% of the global population but contributes to 71% of the burden of the global rate of HIV infections(7). The number of new HIV infections in SSA decreased by more than 33% from 2005 to 2013 but remains relatively high(8). Major progress has been accomplished regarding the availability and access to antiretroviral therapy (ART) in the SSA region. By 2014, the majority of the 15 million people receiving ART were reported to be living in SSA(9). Despite these declines in new infections and the upscale of ART coverage, HIV incidence rates in SSA (2016) still mean that HIV is a public health concern, particularly in South Africa as it contributes to the largest number of new infections (23%)(8).

While HIV/AIDS remains one of the most common public health problems in developing countries, advancements in ART have largely contributed to the significant decrease in mortality in people living with HIV (PLWHA). HIV/AIDS can be managed as a chronic and treatable infection(10,11). Although PLWHA can live a longer life, the quality of their lives becomes a great concern (12). The World Health Organisation (WHO) defines quality of life (QOL) as ‘‘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’’ (1) (p. 1403). Reflecting on this, the concept of QOL is multi-faceted, reflecting different dimensions and experiences in a person’s life, such as their psychological, social and physical function. The psychological domain relates to emotional state, emphasizing moods, learning ability, concentration, and self-esteem. The physical domain focuses on physical and functional limitations while the social domain reflects personal relationships and practical social support(2,3).

Some of the factors affecting PLWHA lifestyles and overall QOL include clinical characteristics for example side effects due to medication and aging(13), presence of mental or medical

comorbidities(14), and the associated stigma and discrimination(15). Considering the variations in QOL among PLWHA which is influenced by sociodemographic and clinical characteristics, measuring QOL and determining associated factors has become important for implementing HIV treatment and health-related interventions(11,16).

Several studies have investigated factors that affect QOL among PLWHA in developed and developing countries(3,10,17). Previous studies have done this using traditional regression models and have been limited in their understanding of the inter-relationships between variables. This study used advanced structural equation models (SEM) to test the hypothesized factors and mediators affecting the quality of life in the South African population. Analysis using SEM enables us to explain interactions between sociodemographic and clinical factors in terms of direct and indirect effects (mediators and moderators) on QOL status that have not been previously thoroughly explored.

1.2. Literature review

PLWHA face comorbid conditions and have challenges associated with ART, co-medication and related adverse events or side effects. These factors affect QOL. Additional factors associated with QOL include gender, mental health, and stigma. For PLWHA, the effects of the disease and treatment thereof are far-reaching, profoundly impacting on day-to-day activities, relationships, and health status. As more people are initiated on antiretroviral therapy (ART) and new targeted treatments are being developed and evaluated (with a risk of severe side effects and toxicity), the importance of considering QOL as an outcome rises (18). This literature review aims to discuss the different QOL of life tools used to measure QOL and the challenges faced in comparing QOL scores. Subsequently, a review of the factors affecting QOL in prior studies will be discussed.

1.2.1. Quality of life measures

There are many measures of QOL that exist and that have been applied to a range of different populations and subgroups, including PLWHA. Available tools range from those which measure the generic quality of life, e.g. Nottingham Health Profile (18) to HIV-specific tools and domain-specific questionnaires within these, such as the SPF-36 and WHO-BREF (Table 1 below)(19,20).

A challenge emanating from the wide range of QOL instruments, which measure slightly different domains and are applied to diverse populations and subgroups, is comparability. The lack of comparability in metrics (e.g., raw summary scores vs. scaled scores) or among different instruments poses practical challenges in comparing scores across different studies(21,22). Table

1.1 below provides an overview of the commonly used HIV-specific QOL tools and the different domains measured, that assess QOL in HIV-infected people. Table 1.1 illustrates the QOL tools used, the domains measured and how the domains are scored.

Table 1:1: Commonly used QOL Tools in HIV Patients

QOL Tool name	Domains measured	Scoring
Medical Outcomes Study (MOS) including SF-12, SF-21, SF-36	This instrument measures eight scales: "physical function (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social function (SF), and role emotional (RE), and mental health (MH)" (22,23).	8 Scales are combined into the "physical component summary (PCS) and the mental component summary (MCS)" and range from 0 to 100. 3 scales (PF, RP, and BP) contribute most to the scoring of the PCS measure, and 3 scales (MH, RE, SF) contribute most to the scoring of the MCS measure. 2 of the scales (VT, GH,) have noteworthy correlations with both components.
World Health Organization Quality of Life Assessment Instrument (WHOQOL)-100 and WHOQOL-BREF	The instrument comprises of 26 items in a 4 domain structure: "physical health, psychological health, social relationships and environment" (22,23).	The domain scores range from 4 to 20 and are calculated by multiplying the average scores for all items in the domain by 4.
MOS-HIV health survey	Currently has 35 items classified into 10 domains: "physical function, pain, social function, role function, emotional well- being, energy/fatigue, cognitive function, health distress, health transition, general health and overall quality of life" (22).	Subscales are scored on a 0 – 100 scale.
HRQOL 601–602: AIDS Clinical Trials Group (ACTG)	Covers eight domains including physical function, energy/fatigue, social function, role function, cognition, pain, health perception and emotional well-being (23).	Subscales are scored on a 0 – 100 scale.

1.2.2. Antiretroviral therapy (ART) and quality of life

The QOL in HIV patients initiated on first-line ART varies with disease severity, demographics, geography or country and for most patients tends to improve over time after starting ART(10,24). ART improves QOL of PLWHA through viral suppression. It suppresses the virus and slows down its evolution. Viral suppression means PLWHA immune system recover and they can lead healthier lives (25,26). However, sometimes patients develop resistance to treatment, and the virus is not suppressed and continues to replicate. In a study by Torres and colleagues, using the ACTG SF-21

tool, individuals failing first-line ART showed lower QOL in most domains except role function and social function(27). Failing first-line ART and low QOL is associated with lower levels of adherence to treatment (24). The literature on first-line failures in South Africa is scanty, yet show that over 2% (which translates to over 10 000 of HIV patients) migrate to second-line therapy a year(28).

Lopinavir is the current standard of care for second-line treatment in South Africa and has been reported to contribute negatively to the QOL of PLWHA, considering that it has a low safety profile, a higher pill burden, twice-daily dosing (4 pills) and greater toxicity(29,30). Provision of a better tolerated second-line therapy, with a higher resistance barrier and low dosing (expected low toxicity), would be a major advance in the provision of antiretroviral care as well as overall QOL for the accumulating participants on second-line therapy. There is strong supportive evidence that darunavir (DRV), a protease inhibitor that can be dosed once daily with half the current levels (1 pill), can yield a better safety profile and better QOL(29–31).

1.2.3. Treatment factors associated with quality of life

1.2.3.1.Pill burden and quality of life

Several studies, that were conducted in the early stages of the HIV epidemic, emphasized the need for simplification of ART(7,8,32). Most recommendations included reducing the complexity of treatment such as the number of daily pills of ART, dosage timing and frequency(32,33). Strategies to simplify treatment include the use of fixed-dose regimens, taking on the “one pill per day” regimen with better tolerance, and improved maintenance approaches(1,2). Despite the progress that has been achieved in the advancement of ART regimen itself, the next therapeutic challenge has been the pill burden due to the number of prescription drugs required for multiple comorbid conditions(34,35). A Swiss study reported that 68% of its participants took ART concurrently with other medications and a US veteran cohort study that showed that 55% of study participants were taking five different medications daily(32). Furthermore, a study carried out in an urban clinic in Uganda reported 15.3% of the cohort was taking more than four non-HIV medications and argued that their prevalence might have been lower due to limited access to medication(36).

High pill burden can indicate drug interactions with anti-viral therapy as well as drug toxicity. Additionally, harms of a high pill burden can cause serious adverse events (SAE) and geriatric syndromes which include falls, fractures, cognitive decline, as well as death(34). However, the relationship between adverse events and pill burden is not only direct but has a bi-directional

nature. While comorbid conditions increase the risk of and exacerbate adverse effects, complex medication regimens administered in an attempt to manage these conditions may lead to additive toxicities and further increase adverse events and morbidity(37). This is illustrated by a study in Uganda that reported that most of the hospitalizations and outpatient clinic visits were associated with complications from co-medication(36).

In addition to adverse events, studies investigating co-medications have typically focused on adherence among the elderly(38,39). Research regarding the effect on pill burden is limited, however, a study in Spain, using MOS_HIV instrument to measure QOL, showed that better physical health and mental health scores were associated with less difficulty taking medication and lower pill burden(40).

1.2.3.2. Adverse drug reactions and Quality of life

ART can have undesirable adverse drug reactions ranging from mild to severe and short to long term. Adverse drug events are amongst the most important reason for non-adherence, treatment modifications or discontinuation and virologic failure(41–43). These consequences ultimately contribute to increased HIV virus resistance and costs to the public health system(44). Studies from developed and developing countries report the incidence of adverse drug reaction (ADR) among patients ranging between 37- 90% while serious adverse events (SAE) were as high as 30%(41–43). Most common symptoms were insomnia, fatigue, lipodystrophy, and depression (41–43). It has been noted that the aforementioned symptoms occur frequently, and patients report that these side effects negatively impact their daily routine and overall quality of life(45). The clinical importance of treatment side effects coupled with co-morbidities is especially important given the fact that patients commit to lifelong therapy(46).

Treatment side effects also add an extra layer of complexity in the management of HIV, by impairing a patients' willingness to adhere to their medication(9,47). A study conducted by Marzolini and colleagues showed that discontinuations of treatment due to drug toxicity occurred at a rate of 22.4 per 100 person-years(47). Furthermore, Rodriguez-Penney et al. reported that nearly half of the study participants had at least one co-morbid condition, reporting lower adherence and lower physical QOL across the lifespan using the Short Form Health Survey (SF-36)(9). A study, also using the SF-36 from the Medical Outcomes Study to assess the quality of life, reported that the physical and psychological demands of coping with ART side effects can be overwhelming to patients and decrease their quality of life(48).

1.2.4. Gender and quality of life

Studies that have focused on gender-specific differences in QOL outcomes have yielded different results. While several studies in India have observed females showing a significantly lower quality of life compared with males using the WHOQOL-HIV BREF(49–51), other studies conducted in western countries showed that gender had no major impact on QOL using Multidimensional QOL questionnaire for HIV/AIDS (MQOL-HIV)(52,53). There have been studies that have reported men having lower QOL scores than women in Estonia and South Africa, however, these differences have been marginal(54,55).

Studies that have reported lower QOL among women compared to these differences have been explained by the impact of women's expected social roles in their families and communities. A study conducted in a rural community in Ethiopia reported a lower quality of life in females in the physical, psychological, independence and environmental domains as compared to men using the ACTG-QOL tool. The authors emphasized that these differences were based on socioeconomic inequality in relationships(56), resulting in women having limited access to healthcare and treatment, especially in lower economic settings. Another study found similar results, showing that at week 40, females had scored lower in all domains except the general health perception using an ACTG-QOL Health Survey tool, however, argues that the responsibility of child-raising in women may have caused the lower quality of life observed in females(57). Additionally, a study conducted by Tesfay et al. (2015) using a WHOQOL-HIV BREF tool attributed the lower QOL observed in women to be as a result of HIV-related stigma and discrimination which tends to be harsher when directed at females in community settings. These barriers can make females suffer more under the physical burden of HIV(58).

What is more, is that studies have also shown that psychopathological symptoms are higher in women living with HIV than men, using the WHOQOL-HIV-Bref instrument(59,60). This is consistent with other literature that has shown that HIV-positive women report mental distress more often than male counterparts (using MOS-HIV tool), leading to an additional burden faced by women(61). Other factors that have been reported to be more common in females were illiteracy (less educated), higher unemployment rates, and more opportunistic diseases like tuberculosis, depression/anxiety, and malnutrition as compared to males which might be contributing to a reduced QOL(59). Additional studies are required to verify these conflicting results and investigate more potential factors that may be associated with gender differences in QOL.

1.2.5. Other factors associated with QOL

1.2.5.1. Mental health

Mental health disorders are common among PLWHA and such conditions tend to impact their QOL(62). The prevalence of mental disorders range from 32% to 78% amongst HIV positive individuals, and most of these patients show mental disorders such as depression, psychosis, and anxiety in developed countries(63,64). A meta-analysis conducted in African countries also reported that depressive symptoms were the most common with prevalence rates between 30% and 64%(65). Depression and anxiety have shown to negatively influence sleep, cognitive ability, and coping with skills reducing life satisfaction and quality of life(3,66).

Moreover, studies have shown that severe substance abuse and suicide attempts are prevalent amongst HIV positive people affected by mental disorders(62,67). Studies have shown that the use of substances facilitates HIV progression which leads to poor health outcomes and a lower QOL using the HIV Cost and Services Utilization Study (HCSUS) tool and WHOQOL- HIV BREF scale(62,66,68). In addition to this, patients who suffer from harmful substance abuse have been associated with lower compliance to ART, both in high-income countries and low/middle-income countries (LMIC)(68–70). Interventions to reduce HIV related stigma may be one of the potential routes to increase adherence in HIV care.

1.2.5.2. Stigma and quality of life

Stigma is a social and mental construct encompassing the occurrence of stereotypes and negative attitudes towards people living with HIV(63). Different cultures have reported that experiencing stigmatization based on living with HIV is related to poor quality of life using WHOQOL-HIV-BREF questionnaire, as it influences healthcare decision making, family and caregiver attitudes(63,64,67). A study by Levi-Mizi et al. shows that patients who had experienced stigma by being socially humiliated, rejected, and threatened by status exposure, had impaired QOL(67). Moreover, 89% of physicians, 88% of nurses and 73% of ward staff in a study of over 1000 healthcare-workers in India, would show discriminatory intent against PLWHA in situations that involved a high risk of bodily fluid exposure(71).

Even more concerning, reports have shown that experiences related to stigma tend to become a barrier towards treatment and prevention(72). Besides the fact that disease concealment affects adherence to treatment, it has been shown to indirectly increase the physical and mental stress of depression and anxiety. This, in turn, has an effect on the immune system and increases

vulnerability to other conditions(73,74). Additionally, the lack of social support and integration further contribute to depressive symptoms and have a negative influence on the quality of life(75). A study performed in South Africa and Zambia showed that HIV related stigma is a critical factor that may impede on the success of HIV prevention and treatment programs(76). This was supported by a meta-analysis conducted by Rueda et al. showing that patients that have experienced HIV-related stigma were 21% less likely to access or utilize health and social services(72). This leads to negative health outcomes and ultimately a reduced QOL

1.2.5.3. Adherence to ART and QOL

Strict lifelong adherence to ART is perhaps the most significant determinant of a regimen's success, leading to an enhanced quality of life(45). Adherence refers to "the extent to which the patient follows medical instructions" (77)(p. 3) and is usually measured by the percentage of patient behavior to the prescribed therapy. Low adherence means a consistent level of drug combinations is not maintained in the blood, which can lead to the development of viral mutations and subsequent resistance to treatment(45).On the contrary, benefits of adherence such as lower number of symptoms, suppression of viral load, reduction in HIV related co-morbidity and preservation of immunologic function lead to a higher chance of survival and good QOL(78).

Some studies have shown that adherence and QOL are positively correlated(79,80). In other words, QOL can also influence adherence since people with a higher QOL have a greater tendency of adhering to treatment(81). A study by Silva et al. using the WHOQOL HIV Bref tool, reported that individuals classified as non-adherent presented the worst scores in all the QOL domains(79). In the other direction, Luszczynska et al. using an SF-20 instrument, reported that increased QOL scores increased adherence(80). This highlights the importance of investigating factors that affect QOL since knowledge around those can help improve adherence to treatment and ultimately better health outcomes.

1.3. Problem statement

ART has allowed PLWHA to live longer, however, they may be living with health-challenges related to the clinical manifestation of HIV, the adverse events of treatment or emerging co-morbidities related to HIV. Therefore, despite living longer, PLWHA may not always experience a good quality of life. Although there's been evidence from studies from developed and developing countries that show how factors such as adverse events, gender, age, and pill burden directly affect

QOL, conceptualizing the complex relationship between these HIV related factors, how they affect each other and the QOL in PLWHA is less clear, especially in the South African context.

1.4. Justification

QOL has become a progressively relevant outcome measure in therapeutic research and practice, highlighting the challenges outside of clinical factors of the illness(59). This relevance is particularly empirical in the context of HIV. The burden of HIV-related challenges, such as treatment side effects and medical and mental co-morbidities, often result in clinic visits and hospitalizations that lead to higher usage of healthcare resources(11,82). Therefore, to understand a patient's experiences of living with this chronic infection and to lessen the increasing burden on the health system, direct and indirect factors influencing QOL need to be explored.

Furthermore, a research gap exists in South Africa, as we have so far identified few studies that have evaluated the interplay of factors that affect QOL in PLWHA. This research aims to assess the relationship of factors that impact QOL, which are important to understanding the effect of HIV and treatment-related challenges in PLWHA. In addition, the study will quantify and compare effects of different domains on QOL, and knowledge on these can allow guided interventions that can improve QOL, identify needs for health services developments as well as evaluate and monitor changes in the health status of PLWHA in South Africa.

1.5. Aim

The aim of the study was to investigate direct and indirect pathways that affect the quality of life among PLWHA in Johannesburg on second-line antiretroviral therapy

1.6. Objectives

i. To describe the quality of life across different domains amongst women and men living with HIV/AIDS on second-line ART in Johannesburg
ii. To examine associations between socio-demographic and other factors (pill burden, adverse events, substance use, and treatment regimen) and various domains of QOL among PLWHA in Johannesburg
iii. To determine the mediators and moderators of QOL domains among PLWHA in Johannesburg

2. CHAPTER TWO: METHODOLOGY

2.1. Background - primary study:

The primary study (Protocol number: WRHI052) was a randomized control trial (RCT) which investigated non-inferiority of ritonavir-boosted darunavir (DRV/r 400/100 mg) compared to the current standard second-line therapy ritonavir-boosted lopinavir (LPV/r). The study was conducted at the Wits Reproductive Health and HIV Institute (WRHI), one of the leading African research institutes(83). The study population was HIV-1 positive South Africans on the standard of care second-line therapy in Johannesburg studied between 2016 and 2018 for 48 weeks. The sample population included 300 male and female volunteers. An electronic randomization system assigned these participants to a 1:1 ratio with approximately 150 volunteered participants per treatment group.

Participants were included if:

≥18 years of age

weight ≥40 kg,

Within 60 days, the patient's plasma HIV-1 RNA level (VL) had to be <50 copies/ml

On ART containing LPV/r > 6 months (83)

Participants were excluded if:

On any ART other than LPV/r

They had a history of genetic protease inhibitor resistance

They were taking therapy along with major cytochrome P450 interactions (within the last month)

They were currently pregnant, breastfeeding or desiring pregnancy during the next year

They had a history of drug or alcohol abuse that may hinder strict adherence to protocol guidelines(83)

2.2.Study design

The secondary data analysis utilized a cohort study design of 293 participants from the RCT who were enrolled and followed up for 48 weeks.

2.3. Study population

The study population was HIV-1 positive South Africans receiving second-line antiretroviral therapy in Johannesburg over 48 weeks.

2.4. Sample

The secondary data analysis included all 293 participants. The inclusion criteria in this study were volunteered participants who are older than 18 years old at the time of being enrolled in the study and had QOL measured at Week 48 (End of study).

A retrospective sample size calculation was conducted, with adverse events as the exposure variable and physical function QOL as the outcome variable, using the STATA Sampsi (two proportion) command. P1 was the proportion of low QOL among those with at least 1 adverse event and P2 was the proportion of low QOL among those without any adverse events. A difference of 30% was observed among those with low and high QOL (65% vs. 35%). The sample size was calculated with a power of 90% and an alpha of 0.05. The minimum sample size required is 56 participants in each group, which was met.

2.5. Measurement

2.5.1. Outcome

The QOL data in the primary study was assessed using the ACTG (Aids Clinical Trial Group) questionnaire administered by a research nurse at enrolment and at 5 follow up visits from Week 4 to Week 48, with Week 48 being the end of study visit (EOS). In this study, QOL domains at Week 48 were used as the study outcomes. The questionnaire consisted of eight domains and 17 questions which focused on general health perceptions, physical function, role function, pain, social function, mental health, energy, cognitive function. Items in each domain were summed to create sub-score. A brief description of each domain is presented in Table 2.1.

Table 2:1: Description of the ACTG QOL Tool

Domains	No. of items	Item example	Scale
General health perception	1	In general, would you say your health is?	1-5 (Poor=1 to excellent=5)
Pain	1	How much bodily pain have you had in the past 4 weeks?	1-5 (None=1 to Severe=5)
Physical function	3	Does your health limit you are walking uphill /climbing stairs	1-3 (Yes limited a lot=1; Not limited at all=3)
Role function	2	Does your health keep you from getting a job?	1-3 (Yes, all the time=1; None of the time=3)
Social function	2	Has your physical or emotional health interfered with social activities?	1-5 (Not at all=1; Extremely= 5)
Cognitive function	3	Difficulty reasoning or solving problems	1-3 (All of the time=1; None of the time=3)
Mental Health	3	In the past four weeks, have you felt downhearted and blue?	1-3 (All of the time=1; None of the time=3)
Energy/fatigue	2	In the past 4 weeks, how often have you felt tired?	1-3 (All of the time=1; None of the time=3)

2.5.1.1. Transformation of the outcome variable

The standard ACTG-SF 21 (601-2) health survey manual was used to guide the scale construction of the QOL scores(84,85). Firstly, items had to be reverse-scored so that a higher score reflected better health on all QOL items. Secondly, values were verified and ensured there were no data entry errors. Thirdly, any missing items that respondents may have failed to complete were noted. For those items in a domain that were missing, a mean value of the items that were completed was assigned to them, provided that 50% of the items in the domain were completed. For example, if a participant missed one item in a 3-item social function scale, then an average of the two completed items would be substituted for the missing value.

The fourth step in the scale construction involved computation of raw scale scores, which meant summing up all the scored item values in a domain. For example, if a respondent had scored 3 for the two items in a domain, then the raw score of the respondent would be 6. Addition of all possible minimum and maximum item values gave the minimum and maximum range for the scale

respectively. The last step entails transforming the raw scale scores to a 0 to 100 scale where higher scores indicate better health. From this transformation, the 17 items were transformed into 8 domains using the formula in Table 2.2 below for each domain. For the 7 domains that present with different Likert- type response options and differences in the number of items, responses were weighted to maintain the 0-100 transformation.

An exploratory factor analysis was used to determine whether the number of items used in the WRHI questionnaire sufficiently measured the QOL domains, considering that the number of the items used in WRHI questionnaire was less than the number of items used in the ACTG-SF21 health survey manual. Based on the analysis, three domains were identified from the items presented, namely physical/functional quality (combined all items representing General Health perception, Physical function, Role function, Social function Pain and the Energy/Vitality domain), mental and cognitive domain. Table 2.2 presents the formula used to transform QOL sub-domain scores to a 0 to 100 scale.

Table 2:2 - Transformation of QOL sub-domain scales scores using the ACTG manual

Domains	Transformation Equation
General Health Perception a	= (100/ (5-1)) * (General Health Perception raw score -3)
Physical Function a	= (100/ (9-3)) * (Physical Function raw score - 4)
Role Function	= (100/ (9-3)) * (Role Function raw score - 2)
Social Function b	= (100/ (8-2)) * (Social Function raw score - 2)
Cognitive Function b	= (100/ (9-3)) * (Cognitive Function raw score - 3)
Pain a	= (100/ (6-1)) * (Pain - 2)
Mental Healthb	= (100/ (18-3)) *(Mental Health raw score - 3)
Energy/Fatigueb	= (100/ (6-2)) * (Energy/Fatigue raw score - 2)

[a] Equation was weighted differently based on the number of items present in the domains

[b] Equation was weighted differently based on Likert scales used

2.5.2. Explanatory variables

Demographic information including age, biological sex, race, marital status, education, and employment status was collected at screening visit in a screening form.

Other covariates included:

- Treatment regimens to which participants were randomly assigned.
- Pill burden counts were defined as medication taken additional to ART administered. The medication was taken from a concomitant medication source document that was regularly

updated at every study visit. This means that the number of co-medications was counted to give the total number of medications a participant administered over 48 weeks. This information could also be indicative of the co-morbidities that participants were facing. Most of the medication reported were analgesics, beta-blockers, antibiotics, chronic (hypertension, diabetes, and hypercholesterolemia), anti-depressants, vitamins/minerals, and non-pill-based medication.

- Adverse events were recorded at unscheduled and scheduled study visits. Adverse events were counted to give a total number of adverse events experienced over the 48 weeks period. The adverse events were graded as mild, moderate, severe or life-threatening, whether any treatment was required, and the outcome of the event (resolved, resolving, worsening or fatal).
- Substance abuse was assessed at the screening visit investigating alcohol, tobacco, and illicit drug use. Participants had to report whether they did or not engage in the use of the substance and the frequency thereof. “Are you a current smoker, a non-smoker or had other use for tobacco (e.g. snuff)?” is the question used to measure tobacco use. “Do you drink alcoholic beverages?” was the question asked for alcohol use and “Do you use illicit drugs for recreational, medicinal or other purposes?” and if so, “what is the purpose and frequency of use, was the question assessing illicit drug use.

2.6. Data Processing and Analysis

Data was extracted from source documents and converted into a format that Stata will recognize. All data was then imported into STATA version 15® for data cleaning and analysis. Data cleaning included checking for inconsistencies and outliers, in which case discrepancies or missing data were dropped from the data. Thereafter, a final sample size of 293 was established excluding patients that did not have QOL at Week 48 (Fig 2.1). Recoding and labelling variables were performed, and variables were categorized when the need arose.

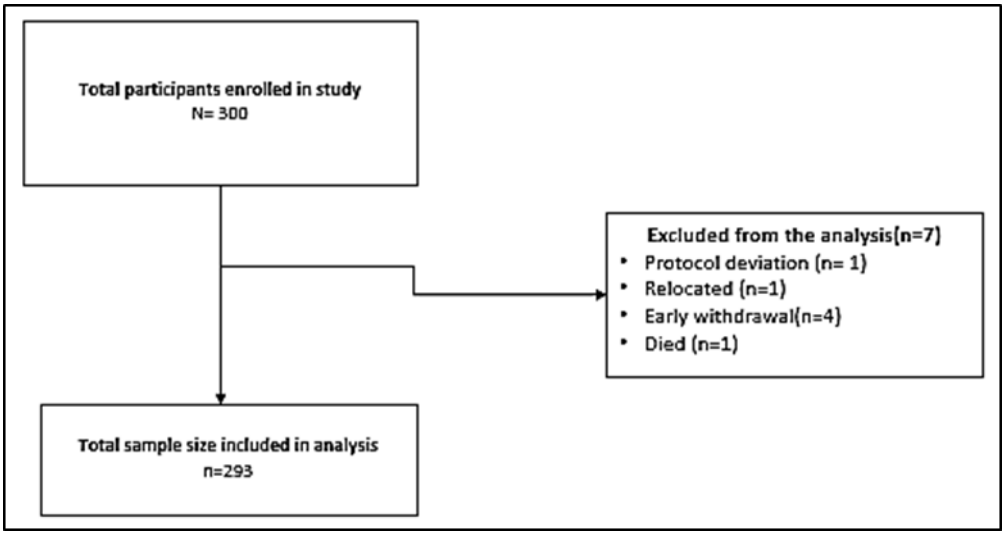

Figure 2-1: Diagram showing the number of participants dropped from the analysis

The data analysis that was conducted is presented in Table 2.3 by each objective.

Table 2:3: Descriptive of variables, types, and analysis conducted by objective

Specific objectives	Variables	Type	Analysis conducted
To describe the quality of life amongst PLWHA in Johannesburg	Quality of life	Continuous (score-based)	Mean and standard deviation are presented for the initial 8 domains and thereafter for the three QOL domains identified (following the exploratory factor analysis).
To examine associations of factors affecting overall and various domains of QOL in PLWHA in Johannesburg, aggregated for men and women	Outcome Quality of life: Covariates: Age Gender Marital status Educational level Employment status Treatment regimen Pill burden Adverse events Substance use	Continuous (score-based) Continuous Categorical Categorical Categorical Categorical Categorical Continuous Categorical Categorical	Student T-tests were used to compare the mean QOL scores between the explanatory variables that consisted of two groups, for example, sex. ANOVA test was used to determine the differences between the mean QOL scores and explanatory variables that consisted of two or more groups, for example, adverse events. Pearson's correlation coefficient test was used to determine a linear relationship between QOL scores and continuous variables, for example, age and pill burden Logistic regression models were performed for the three QOL domains identified after determining cut off points for low and high QOL. Odds ratios and confidence intervals were presented Link tests were used to check whether the assumptions of the ordinal logistic regression were met (model specification) VIF (variance inflation factors) were used to determine that the multi-collinearity assumption for the logistic regression was met
3. To develop a model of QOL involving mediators and moderators among PLWHA in Johannesburg aggregated for men and women.	Outcome Quality of life: Covariates: Age Gender SES Treatment regimen Pill burden Adverse events Substance use	 Latent variable Continuous Categorical Categorical Categorical Continuous Categorical Categorical	Exploratory factor analysis was conducted to determine the structure of items and evaluate the construct validity of the item scales Confirmatory factor analysis was used to test factor loadings and inter-correlations of latent outcome (QOL) A structural model was estimated using significant variables from the logistic regression analysis and based on the conceptual framework (Fig 1). Model fit was tested

2.6.1. Socio-demographic and clinical characteristics of PLWHA on second-line treatment

Descriptive statistics and frequency distribution of socio-demographic and clinical factors are presented in Table 3.1 and Table 3.2 respectively, aggregated by sex. Differences between males and females were determined using Pearson's Chi-Squared and Fisher's Exact tests.

2.6.2. QOL characteristics among men and women living with HIV

For objective 1, eight domains were produced representing an individual's QOL scores from 0 - 100, with higher scores indicating better health. Independent sample t-tests were used to determine differences in QOL scores in the different domains between males and females (Table 3.3).

2.6.3. Exploratory factor analysis

The ACTG SF-21 questionnaire administered in the primary study QOL omitted some items from the ACTG SF-21, resulting in only 17 items. From this, the researcher decided the best method would be to use exploratory factor analysis to examine the structure and the relationship between items, as well as evaluate the construct validity of the item scales. The factor analysis was conducted with the iterated principal axes (ipf option) initially exploring three factors then explored and retained four factors (factor (4) option). Kaiser's criteria(86) were used to extract factors with eigenvalues greater than 1 (Table 3.4). Although the fourth factor did not have an eigenvalue greater than 1, we chose to still extract it because following the varimax and promax rotations (minimal loadings of 0.3)(87), there were items that loaded on the factor that would have otherwise been dropped (Table 3.5). Finally, the domains identified were physical/functional quality, mental, cognitive and energy/fatigue. Mann Whitney tests were used to determine differences between males and females amongst the four identified domains (Table 3.6).

2.6.4. Confirmatory Factor analysis and pathway analysis

Initially, latent variables were created using the factors that were associated with the specified subset of items during exploratory factor analysis. Then the researcher looked at the measurement component of the output to verify that the observed variables load reasonably onto their corresponding latent constructs. Whilst creating the latent variables, the researcher collapsed the energy items with physical/functional items, and they loaded successfully. Reasonably, how energetic/fatigued you feel often affects your physical and functional capability. However, collapsing the mental and the cognitive with the physical/functional items was unsuccessful, confirming that physical/functional quality, mental and cognitive QOL should be analyzed as three separate latent variables.

2.6.5. Bivariate and multivariate logistic regression models

The first part of objective 2 was a bivariate analysis that analyzed socio-demographic and clinical factors in various QOL domains at Week 48. Student t-tests, ANOVA and Pearson's correlation coefficient tests were conducted to determine which socio-demographic and clinical characteristics were associated with the various QOL domains.

In the second part of objective 2, logistic regression models were conducted to determine sociodemographic and clinical predictors of QOL at Week 48. The distribution of the data was too skewed to conduct multiple regression models as anticipated, even after transforming each outcome variable (Physical/Function QOL, Cognitive QOL and mental QOL). In all the logistic models, adverse events and severity of adverse events were collinear, therefore it was decided that adverse events should be included in the model.

2.6.6. Physical and functional quality

The distribution of physical and functional QOL scores was determined using histograms with frequencies and overlaid normal density curve (Figure 2.2). After this, the researcher determined cut-off points that were used to categorize the physical and functional score into reasonable group sizes based on the distribution of the data. The scores were then classified into low and high as described in Table 2.4. A logistic regression was conducted to determine predictors of physical and functional QOL. The Independent variables that were included in the regression analysis comprised of variables that met the 0.2 significance level criteria in the bivariate analysis. Additionally, variables that were not significant but were commonly reported in the literature were also included in the model. The researcher then sequentially removed variables if they were not significant predictors of physical and functional QOL and did not change the odds ratios of the other variables by more than 10%, ruling out the possibility of confounding. A multi-collinearity test was conducted amongst the selected independent variables in the model using VIF (Variance inflation factors – an indicator of how much of the standard error inflation was caused by collinearity). As a rule of thumb, VIF's less than 10 do not warrant further investigation which was the case after the variable severity of adverse events was removed. Therefore, the assumption of independent variables in a logistic regression was met. Furthermore, a link function (command *linktest*) was used to determine whether the model was correctly specified. The link test uses the linear predicted value squared (_hatsq) as a predictor to rebuild the model. For a model that is correctly specified, the _hatsq should not be significant. In this model, the p-value for the –hatsq was 0.209, confirming

that the model was correctly specified. Final variables in the physical and functional QOL were age, sex, education, treatment regimen, pill burden, adverse events and severity of adverse events.

Table 2.4 and Figure 2.2 shows the cut off points and distribution of mental QOL scores

Table 2:4 - Physical and functional QOL cut-points based on the distribution of data

Classification	Cut off points	n (%)
Low	<87.5	83 (28.3)
High	≥87.5	210 (71.7)

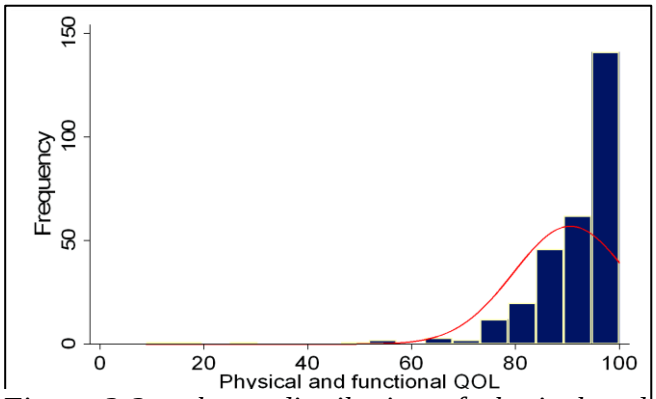

Figure 2-2 - shows distribution of physical and functional QOL

2.6.7. Cognitive QOL

Overall, Cognitive QOL scores were very high, with 94.5% participants scoring 100 (Figure 2.3). A dichotomous variable was formed by the researcher for those who scored less than 100 (low) and for those that scored 100 (high) (Table 2.5). The researcher then conducted a logistic regression to determine significant predictors of cognitive QOL. The independent variables that were included in the regression analysis comprised of variables that met the 0.2 significance level criteria in the bivariate analysis as well as variables of primary interest. To increase parsimony, variables that were not significant and did not change the odds ratios by more than 10% were removed. A multi-collinearity test conducted amongst independent variables showed that there was no collinearity considering that the VIF were all less than 10. The model was correctly specified as it had a non-significant _hatsq p-value of 0.197. Final variables in the physical and functional QOL were age, sex, education, treatment regimen, pill burden, adverse events and severity of adverse events

Table 2.5 and Figure 2.3 shows the cut off points and distribution of cognitive QOL scores

Table 2:5: Cognitive QOL cut-points based on the distribution of data

Classification	Cut off points	n (%)
Low	< 100	16 (5.5)
High	=100	277 (94.5)

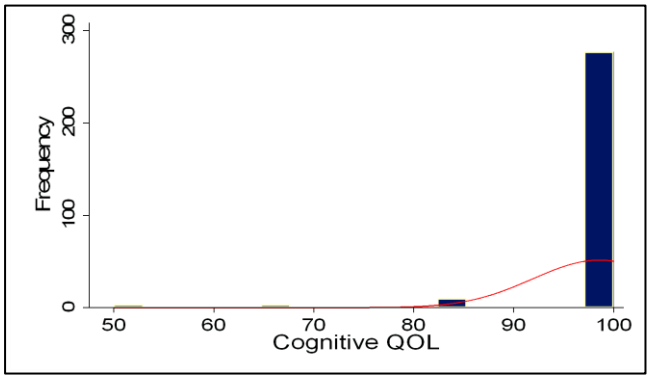

Figure 2-3 shows distribution of cognitive QOL scores

2.6.8. Mental QOL

The distribution of mental QOL scores was determined using histograms with frequencies and overlaid normal density curve (Figure 2.4). The mental QOL scores were classified into low and high QOL categories (Table 2.6). Following the selection of variables, a logistic regression was conducted to determine predictors of mental QOL. A multi-collinearity test showed no correlation between independent variables and the link test showed that the prediction squared did not have predictive power, confirming that the assumption of the logistic model was met (P=0.168).

Table 2.6 and Figure 2.4 below shows the cut off points and distribution of mental QOL scores

Table 2:6: mental QOL cut-points based on the distribution of data

Classification	Cut off point	n (%)
Low	≤ 70	76 (25.9)
High	> 70	217 (74.1)

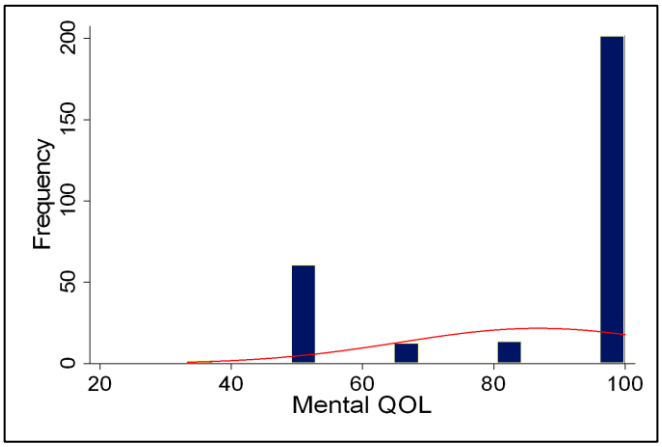

Figure 2-4: Distribution of mental QOL scores

2.7. Conceptual framework and *a priori* model

Figure 2.5 outlines the framework conceptualized for this study. The framework proposed that QOL was interrelated with the treatment regimen, socio-demographic and clinical factors among PLWHA. The conceptual framework is presented separately for each of the final QOL outcomes.

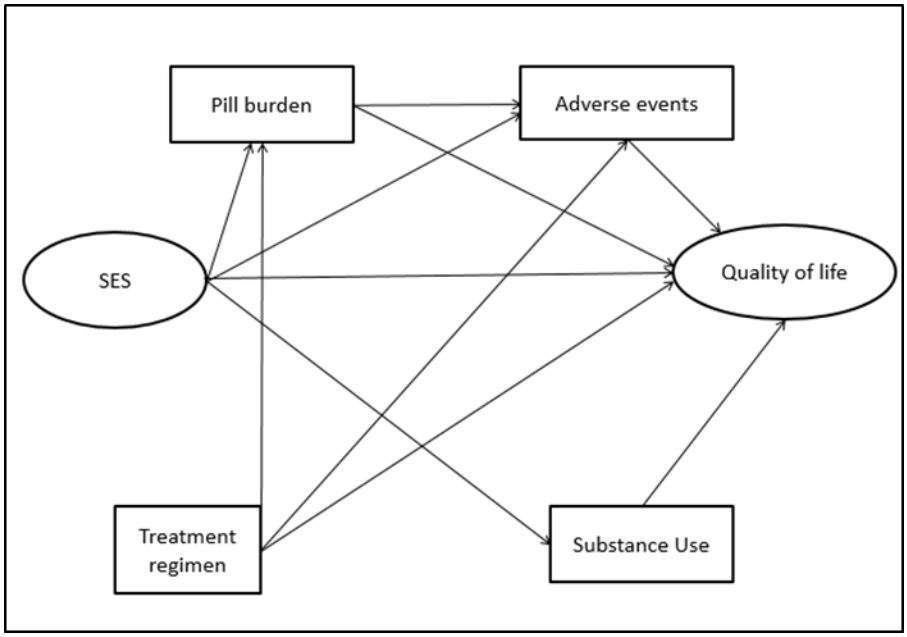

Figure 2-5: Conceptual model of interrelationships between factors leading to higher QOL among PLWHA

2.7.1. Pathway analysis

The researcher used a structural equation model (SEM) method to test the *a priori* pathways between variables. SEM is a powerful multivariate technique that is used to correlate groups of

interrelated variables into a single factor (latent variable) involving path analysis. This includes the direct effects of factors and correlations among them(88). SEMs are often presented graphically where direct effects are represented as straight arrows stemming from an independent variable (exposure) and pointing towards a dependent variable (outcome)(88). Contrary to the normal regression analysis that only explains the direct relationship between the dependent variable and independent variables, SEM is more flexible in that it allows multiple causal relationships to be modelled. This is advantageous given that the independent variables may not all affect the dependent variable directly and understanding how the dependent variables relate to each other also contributes significantly to understanding how certain variables moderate and mediate relationships. For this reason, an SEM was used to analyse the third objective.

For the SEM and pathway analysis, a confirmatory factor analysis on measurement models was initially conducted by the researcher, followed by assessing their goodness of fit to confirm the explanatory and outcome variables. All subset of items depicting the latent variables (3 QOL domains) had significant factor loadings. Next, she built and estimated the models separately for the three domains based on the apriori-hypothesis and on variables that were significant in the respective multivariate regression models. After that, each model was estimated and reviewed reiteratively to determine the pathways that did not contribute significantly. Insignificant pathways were then removed to increase the parsimony of the model. For the physical and functional domain, the following pathways were removed: adverse events and physical/functional QOL; pill burden and adverse events; age and physical/functional QOL; sex and physical/functional QOL as well as treatment regimen and adverse events. For the cognitive domain, the pathways removed were adverse events and cognitive QOL; treatment regimen and adverse events; pill burden and adverse events; age and cognitive QOL along with sex and cognitive QOL. For the mental domain, pathways between treatment regimen and adverse events; sex and mental QOL; age and mental QOL were removed.

Following this, the researcher used modification indices (*estat mindices*) to identify omitted pathways to improve the fit of each of the models. She added the following pathways in the physical and function domain: age and pill burden; pill burden and severity of adverse events in addition to two correlations between pill burden and adverse events as well as adverse events and severity of adverse events. Pathways that were added to cognitive QOL included sex and pill burden; sex and adverse events; age and pill burden; treatment regimen and cognitive QOL as well as a correlation between pill burden and adverse event. For the mental domain, pathways added were the severity

of adverse advents and mental QOL; age and pill burden; sex and pill burden; age and pill burden; pill burden and severity of adverse events along with two correlations between advents events and pill burden as well as adverse events and severity of adverse events. These pathways were added based on indices greater than 10 and through conceptual reasoning. In all three domains, education, employment, marital status (SES) and tobacco use as variables were dropped. Subsequent to the building of the model, the researcher conducted goodness of fit tests to determine the overall goodness of fit of the final model. RMSEA (root mean squared error of approximation), CFI (comparative fitness index), TFL (Tucker Lewis Index), LR chi (likelihood ratio chi-square tests) and RMSR (Root mean squared residual) were some of the goodness of fit statistics used to determine whether the models were of a good fit.

2.8. Ethics consideration

Ethics approval was obtained for the secondary data analysis through the Wits Human Research Ethics Committee (HREC) (Appendix 2). The primary study received ethics and regulatory approvals from the HREC and the South African Health Products Regulatory Authority (SAHPRA) and was overseen by the National Institutes of Health (NIH) Multinational Data and Safety Monitoring Board, and a Scientific Advisory Committee (SAC) (see Appendix B for the approval certificates). Permission from the Principal Investigator of the WRHI052 study was granted to perform the secondary data analysis (Appendix 3). Data received were de-identified and kept in a password-locked laptop. The student researcher and supervisors were the only people who had access to the data. It was agreed that the data will be kept for a two-year period after the publication of the study results. Thereafter the data will be destroyed

3. CHAPTER THREE: RESULTS

The overall aim of this study was to investigate the direct and indirect pathways that affect the quality of life among PLWHA in Johannesburg who was on second-line ART. This section presents the socio-demographic and clinical characteristics of the study aggregated by sex. Furthermore, logistic regressions were performed for the different QOL outcomes to guide the structural equation model.

3.1 Socio-demographic and behavioral characteristics of PLWHA in the study.

Table 3.1 presents the results of the Socio-demographic and behavioural characteristics of PLWHA in Johannesburg.

Table 3:1: Socio-demographic and behavioural characteristics of PLWHA in Johannesburg

Demographic Characteristics	Total (N=293)	Male(n=92)	Female(n=201)	P value
Age(years)				
18-30	15 (5.12)	4(4.26)	11(5.53)	0.003
31-40	129 (44.03)	29(30.85)	100(50.25)	
41-50	106 (36.18)	39(41.49)	67(33.67)	
51-75	43 (14.68)	22(23.40)	21(10.55)	
Mean (sd)	42.1(7.9)	44.5(8.9)	40.9(7.2)	
Education*				
Primary	23(7.85)	14(13.38)	11(5.03)	0.012
Secondary	246(83.96)	77(81.91)	169(84.92)	
Tertiary	24(8.19)	4(4.26)	20(10.05)	
Employment				
Employed	220(75.09)	79(84.04)	146(70.85)	0.015
Not Employed	73 (24.91)	15(15.96)	58(29.15)	
Marital status				
Single	164(55.97)	33(35.11)	131(65.83)	<0.001
Married	129(44.03)	61(64.69)	68(34.17)	
Behavioural characteristics				
Tobacco Use				
Non-Smoker	277(94.54)	83(88.30)	194(97.49)	0.001
Smoker	16(5.46)	11(11.70)	5(2.51)	
Alcohol use				
Yes	84(28.67)	34(36.19)	50(25.13)	0.051
No	209(71.33)	60(63.83)	149(74.87)	

*Fischer's Exact Test

A total of 293 study participants were included in the analysis, with 92(31%) males and 201 (69%) females (Table 3.1). The sample was relatively homogenous as far as race, where 99% were black Africans. The majority of the participants had received secondary education; males 77 (81.91%)

and females 169 (84.92%), however more females had reached tertiary level. Almost half of the females (29.15%) were unemployed as compared to males (15.96%), and one-third of females were single (66.67%) which was significantly different from the third of males (65.63%) that were married (p<0.001). Male participants seemed to engage more in smoking (11.46%) and alcohol use (37.50%) compared to female participants that presented with 2.45% and 25.00% of smoking and alcohol use respectively.

3.2 Clinical characteristics of PLWHA on second-line ART

Table 3.2 illustrates the clinical characteristics of PLWHA aggregated by sex

Table 3:2: Clinical characteristics of PLWHA in Johannesburg on second-line ART disaggregated by sex

Clinical Characteristics	Total (N= 293) n (%)	Male(n=92) n (%)	Female(n=201) n (%)	P-value
Treatment regimen				
DRV	144(49.15)	49(52.13)	95(47.74)	0.483
LPV	149(50.85)	45(47.87)	107(52.45)	
Number of Adverse events				
0	92(31.40)	37(39.36)	55(27.64)	0.061
1	85(29.01)	30(31.91)	55(27.64)	
2	62(21.16)	14(14.89)	48(24.12)	
3	54(18.43)	14(13.83)	41(20.60)	
Severity of adverse events				
None	92(31.40)	37(39.36)	55(27.64)	0.112
Mild	167(57.00)	46(48.92)	121(60.80)	
Moderate - severe	34(11.60)	11(11.70)	23(11.56)	
Pill burden				
0	41(13.99)	15(15.96)	26(13.07)	0.087
1	29(9.90)	14(14.89)	15(7.54)	
2	43(14.68)	15(15.96)	28(14.07)	
3	37(12.63)	11(11.70)	26(13.07)	
4+	143(48.81)	39(41.49)	104(52.26)	

Regarding the treatment-related characteristics, there were no significant differences between any of the clinical characteristics and sex (Table 3.2). A total of 201 study participants reported at least one adverse event, with the majority of the adverse events being reported by females (72.36%). Most of the adverse events reported were mild (57.00%), which was observed in both males and females while less than 2.00% went as far as severe. Serious adverse events were not common, with six (2.05%) cases reported, however amongst the six, females had experienced five (83.33%) of them. More than 85% reported at least one co-medication, with almost half of the sample

(48.81%) reporting a pill burden of more than four co-medications. Overall, a pill burden of three and more was higher in females

3.3 Dimensions of QOL aggregated by sex

Table 3.3 shows the mean scores and standard deviation for all eight dimensions of QOL. Overall, the mean QOL scores reported in the sample were very high, with the cognitive domain presenting with the highest scores (98.57 out of a possible 100) and general health perception presenting with the lowest (76.02 out of a possible 100). There were no statistically significant differences found between males and females in the general health perception, physical, role function, cognitive, mental and energy QOL scores. Pain scores were significantly higher in males than females, indicating that males had better QOL (P=0.043). Females had higher scores compared to males in the social domain, indicating better social engagement but did not yield statistical significance (p=0.095). Table 3.3 shows summary scores of the eight dimensions of QOL aggregated by sex

Table 3:3: Eight Dimensions of QOL overall and aggregated by sex at Week 48.

	Total N =293	Male n= 92	Female n=201	P value
General health perception				
Mean	76.02	76.59	75.75	0.744
sd	17.04	16.7	17.8	
Pain				
Mean	92.01	94.89	90.65	0.077
sd	19.2	16.1	20.38	
Physical				
Mean	97.73	96.99	98.07	0.450
sd	11.5	15.6	8.9	
Role				
Mean	97.70	97.07	98.0	0.563
sd	12.6	15.5	11.1	
Social				
Mean	97.03	95.21	97.8	0.095
sd	12.8	15.6	11.2	
Cognitive				
Mean	98.57	98.57	98.57	0.995
sd	6.7	7.6	6.2	
Mental				
Mean	86.82	88.65	85.94	0.305
sd	21.1	20.5	21.3	
Energy				
Mean	83.19	84.84	82.41	0.359
sd	21.1	20.5	21.4	

3.4 Exploratory Factor Analysis

Table 3.4 and Table 3.5 presents the results exploratory factor analysis

Table 3:4: Exploratory Factor Analysis

Factor	Eigenvalues
Factor 1	6.208
Factor 2	2.271
Factor 3	1.310
Factor 4	0.7475

The Kaiser test indicates that eigenvalues that are equal or greater than 1.0 are meaningful. Therefore factors 1, 2 and 3 (which have, respectively, eigenvalues of 6.208, 2.271 and 1.310) were worth keeping. While the fourth factor was less than 1. 0, it was retained based on the 2 items that had loaded on it (Table 3.4).

Table 3:5: Exploratory factor loadings

Domains	Items	Factor 1	Factor 2	Factor 3	Factor 4
General health	Item 1	0.4420			
Pain	Item 2	0.3857			
Physical function	Item 3	0.8983			
	Item 4	0.8516			
	Item 5	0.8597			
Role function	Item 6	0.9972			
	Item 7	0.9970			
Social function	Item 8	0.4568			
	Item 9	0.5030			
Cognitive function	Item 10			0.7237	
	Item 11			0.9064	
	Item 12			0.6334	
Mental Health	Item 13		0.9122		
	Item 14		0.8081		
	Item 15		0.9669		
Energy	Item 16				0.7904

	Item 17				0.4626

The results from the factor analysis (varimax rotation) with 17 items covered 4 discrete dimensions (Table 3.5). Factor 1 was mostly defined by 6 items, namely general health perception, pain, physical function, role function and social function, which overall measured physical and functional quality. Factors 2, 3 and 4 were defined by items measuring the cognitive, mental and energy/fatigue dimensions respectively.

Table 3.6 presents the breakdown of the QOL domains according to the exploratory factor analysis. As can be seen from the table, none of the mean QOL scores in the different domains showed any significant differences between males and females

Table 3:6: Newly established dimensions of QOL aggregated by sex

Domains	Total n= 293	Male n=293	Female n=293	P-value
Physical and functional QOL				
Mean	90.58	90.93	90.42	0.707
sd	(11.0)	(12.6)	(10.2)	
Cognitive QOL				
Mean	98.57	98.57	98.57	0.995
sd	6.7	7.6	6.2	
Mental well-being QOL				
Mean	86.82	88.65	85.94	0.305
sd	21.1	20.5	21.3	

3.5. Physical and functional QOL

3.5.1. Associations between socio-demographic factors and Physical/functional QOL

Table 3:7: Socio-demographic and clinical factors affecting QOL domain scores

Characteristic	Mean (SD)	P-value
Sex		
Male	90.94(1.3)	0.707
Female	90.342(0.7)	
Age*	90.58(11.0)	0.005
Education		
Primary	86.83(16.8)	0.137
Secondary	90.69(10.6)	
Tertiary	93.10(5.8)	
Treatment regimen		
DRV	90.8(11.6)	0.693
LPV	90.3(10.4)	
Number of Adverse events (AE)		
0	92.04(9.1)	0.005
1	91.04(8.0)	
2	91.94(6.0)	
3	85.84(18.7)	
Severity of AEs		
None	92.04(9.1)	0.018
Mild	90.74(8.5)	
Moderate-severe	85.87(20.9)	
Pill burden*	90.58(11.0)	<0.001

*Pearson's correlation test

Table 3.7 above presents the associations between physical function QOL and characteristics (socio-demographic and clinical) of the sample (n=293). There is a negative correlation between age and physical function QOL scores (r = -0.163); that is, physical function QOL scores decrease as age increases (p=0.005). Furthermore, physical function QOL decreased with an increase in the number of adverse events reported, wherein the highest physical function scores were among participants with no adverse events reported and the lowest scores were amongst participants who reported 3 adverse events over 48 weeks (p=0.005). An increase in the severity of adverse events also decreased physical function QOL. Participants who reported moderate to severe adverse events had the lowest physical function QOL scores (p=0.018). There was a weak negative association between pill burden and physical function QOL scores (r=-0.211). The higher the

number of medications administered over 48 weeks, the lower the physical function QOL scores (p<0.001).

3.5.2. Predictors of physical and functional QOL

When physical and function QOL was analysed using a logistic regression analysis, the researcher found that age and pill burden were significant predictors of QOL (Table 3.8). For a one-year increase in age the odds of lower physical function QOL were 6% higher (p = 0.011). In addition, as pill burden increased per unit, the odds of lower physical and functional QOL increased by 16% (P=0.006) adjusting for other variables. It was observed that the odds of lower physical QOL in females were nearly two-times higher than males, however, this did not reach statistical significance (p = 0.074).

Table 3:8: Logistic Regression of physical and functional QOL* (3.6.2.1)

Domains	AOR (95% CI)	P-value
Age	1.06 (1.01 – 1.10)	0.011
Sex		
Male	1	
Female	1.98(0.93 – 4.24)	0.074
Education		
Primary	1	
Secondary	1.31 (0.40 – 4.29)	0.665
Tertiary	0.52 (0.08 – 3.03)	0.465
Treatment regimen		
DRV	1	
LPR	1.00 (0.53 – 1.89)	0.831
Number of Adverse events (AE)		
0	1	
1	1.78(0.76 – 4.16)	0.167
2	0.71(0.25 – 2.00)	0.47
3	1.47 (0.52 – 4.14)	0.44
Pill burden	1.16(1.04 – 1.31)	0.006

*293 observations were included in the analysis with complete covariate information (p=0.001)

3.5.3. SEM and Pathway analysis of physical and functional QOL

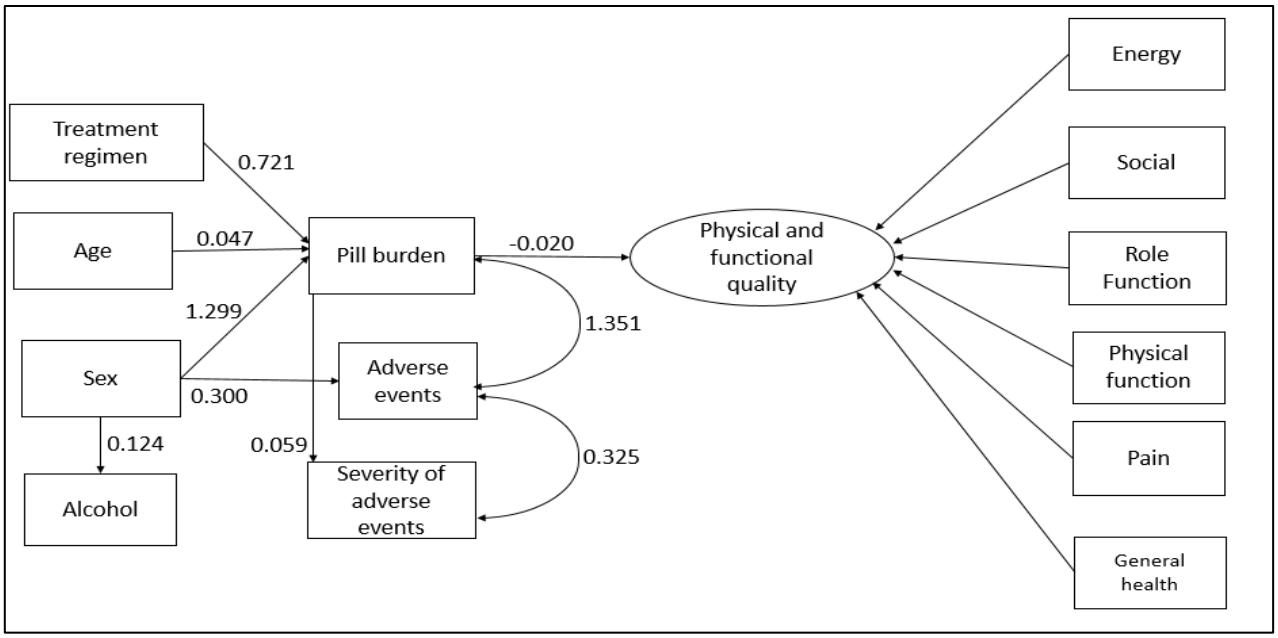

Figure 3-1: Final model of factors influencing physical and functional QOL among PLWHA on second-line antiretroviral therapy in Johannesburg. Box indicates an observed variable, and oval indicates the latent construct. Straight-line with one arrow denotes direct effect and curved line denotes correlation

As shown in Figure 3.1 and Table 3.9, treatment regimen (p=0.029) and age (p=0.020) have a direct positive effect on the pill burden. Sex has direct positive effect on pill burden (p=0.001), adverse events (p=0.014) (Table 16 below), and alcohol use (p=0.044). Pill burden has a direct positive effect on the severity of adverse events (p<0.001) and correlated with adverse events (p<0.001). Furthermore, the pill burden has a direct negative effect on physical function. Lastly, the number of adverse events correlated with the severity of adverse events (p<0.001).

Pill burden mediated the relationship between treatment regimen and physical/functional QOL (p=0.055), physical/functional QOL and age (p=0.054) as well as physical/functional QOL and sex (i.e. females) (p=0.019). Furthermore, pill burden mediated the relationship between treatment regimen (i.e. lopinavir) and severity of adverse events (p=0.032), age and severity of adverse events (p=0.030) as well as sex and severity of adverse events (i.e. females) (p=0.006).

Table 3:9: Statistically significant latent structure, direct and indirect effects of physical and functional QOL

Latent Variables		Estimate	SE	P-value
General health perception	Physical/functional QOL	1.220	0.148	<0.001
Pain→	Physical/functional QOL	1.613	0.206	<0.001
Vigorous activities limited→	Physical/functional QOL	1		
Normal activities limited→	Physical/functional QOL	0.953	0.034	<0.001
Daily activities limited→	Physical/functional QOL	0.659	0.032	<0.001
Role function limited→	Physical/functional QOL	0.959	0.028	<0.001
Role function at work→	Physical/functional QOL	1.008	0.025	<0.001
Interference of normal social activities→	Physical/functional QOL	0.968	0.120	<0.001
Family activities limited→	Physical/functional QOL	0.525	0.069	<0.001
Fatigue→	Physical/functional QOL	0.515	0.114	<0.001
Vitality→	Physical/functional QOL	0.551	0.105	<0.001
Direct effects				
Sex→	Alcohol use	0.124	0.061	0.044
Sex→	Adverse events	0.300	0.1.22	0.014
Pill burden→	Physical/functional QOL	-0.020	0.006	0.001
Age→	Pill burden	0.047	0.020	0.020
Treatment→	Pill burden	0.722	0.311	0.029
Sex→	Pill burden	1.298	0.401	0.001
Pill burden→	Severity of adverse events	0.059	0.011	<0.001
Indirect effects				
Age→Pill burden→Severity of adverse events		0.003	0.001	0.030
Treatment regimen→Pill burden→Severity of adverse events		0.043	0.020	0.032
Sex→Pill burden→Severity of adverse events		0.077	0.028	0.006
Age→Pill burden→Physical/functional QOL		-0.0009	0.0004	0.054
Treatment regimen→Pill burden→Physical/functional QOL		-0.014	0.007	0.055
Sex→Pill burden→Physical/functional QOL		-0.025	0.011	0.019
Correlations				
Number of Adverse events ←→Severity of adverse events		0.325	0.040	<0.001
Number of Adverse events←→Pill burden		1.351	0.210	<0.001

3.5.4. Goodness of fit tests for Physical and functional QOL

Table 3:10: Presenting fit statistics for the final SEM model

Fit statistic	Observed model fit	Criteria for good fit
Likelihood ratio chi-square	0.002	>0.05
RMSR	0.050	<0.05
CFI	0.982	Close to 1
TLI	0.978	Close t o1
RMSEA	0.040	<0.05

The model has a moderate fit, as the likelihood ratio test did not meet the criteria for a well-fitted model. However, other fit statistics met the criteria for a good fit. (CFI 0.982; TLI 0.978; RMSEA 0.040; RMSR 0.050 and LR chi2 0.002) (Table 3.10).

3.6.Cognitive QOL

3.6.1. Associations between socio-demographic factors and cognitive QOL

Table 3:11: Socio-demographic and behavioural factors affecting QOL domain scores

Characteristics	Mean (SD)	P-value
Sex		
Male	98.58(7.6)	0.995
Female	98.57(6.2)	
Age*	98.57(6.7)	0.001
Education		
Primary	94.93(14.6)	0.022
Secondary	98.85(5.6)	
Tertiary	99.31(3.4)	
Treatment regimen		
DRV	97.91(8.6)	0.096
LPR	99.22(4.0)	
Number of Adverse events (AE)		
None	98.42 (7.7)	0.094
1	98.75(5.8)	
2	99.74(2.1)	
3	97.22 (9.0)	
Severity of AEs		
None	98.37(7.8)	0.123
Mild	99.10(4.6)	
Moderate-Severe	96.57(10.7)	
Pill burden*	98.57(6.7)	<0.001

** Pearson Correlation test*

Table 3.11 presents the associations between cognitive QOL and characteristics (socio-demographic, and clinical) of the sample (n=293). There was a negative correlation between age and cognitive function QOL scores (r = -0.188), indicating that cognitive function decreased as age increased (P=0.001). Additionally, cognitive QOL scores increased with higher educational attainment. Participants with primary education had the lowest scores and participants with tertiary education had the highest scores (p=0.022). Furthermore, a negative correlation was found between cognitive function QOL scores and pill burden (r = -0.189), showing that as pill burden increased, cognitive QOL scores decreased (p< 0.001). Low cognitive QOL scores were reported amongst participants who were assigned to the treatment regimen, darunavir (P=0.096), and participants who had three or more adverse events over 48 weeks (p=0.094) but did not reach statistical significance.

3.6.2. Predictors of cognitive QOL

Table 3:12: Logistic regression model of Cognitive QOL* (3.7.2.1)

Cognitive	AOR (95% CI)	P value
Age	1.08(1.02 – 1.15)	0.027
Sex		
Male	1	
Female	2.48(0.57-8.38)	0.212
Education		
Primary	1	
Secondary	0.61 (0.12 – 3.42)	0.577
Tertiary	0.38 (0.02 – 6.15)	0.499
Treatment regimen		
LPR	1	
DRV	0.39(0.12 – 1.21)	0.130
Adverse events (AE)		
None	1	
1	1.31(0.20 – 8.61)	0.436
2	1(empty)	
3	1.78(0.28 – 11.34)	0.760
Pill burden	1.23 (1.05 – 1.44)	0.010

*231 observations were included in the final model, with 62 observation dropped in the adverse events category as it perfectly predicted failure (p=0.0035)

As indicated in Table 3.12, only age and pill burden were significant predictors of cognitive QOL. For a year increase in age, the odds of lower cognitive QOL increased by 8% (P=0.027). In addition, a unit increase in pill burden increased the odds of lower cognitive QOL by 23% (P=0.010).

3.6.3. SEM and pathway analysis for Cognitive QOL

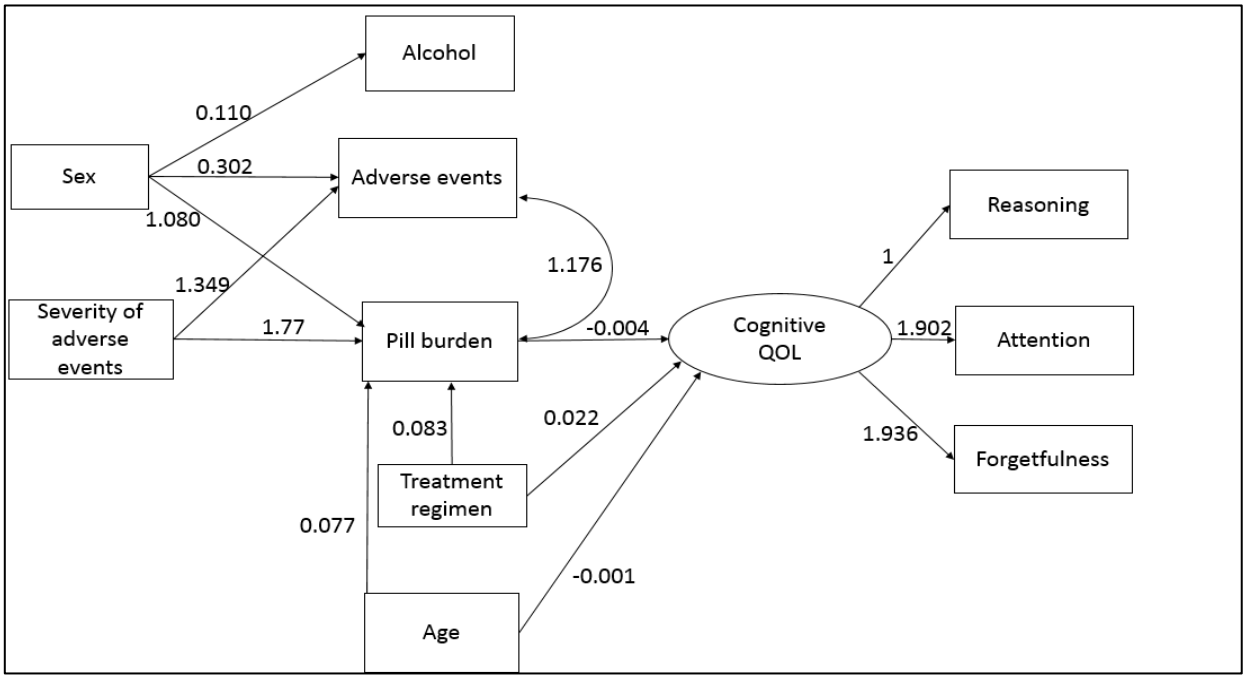

Figure 3-2: Final model of factors influencing cognitive QOL among PLWHA on second-line antiretroviral therapy in Johannesburg. Box indicates an observed variable, and oval indicates the latent construct. Straight-line with one arrow denotes direct effect and curved line denotes correlation

Sex had a direct and positive effect on pill burden (p= 0.003), adverse events (p=0.015) and on alcohol use (p=0.110) as observed in Figure 7. The severity of adverse events had a direct positive effect on the number of adverse events (p<0.001) and pill burden (p<0.001). In addition, age (p<0.001) and treatment regimen (lopinavir) (p=0.008) had a direct positive effect on pill burden. Pill burden (p=0.005) and age (p=0.046) had a direct negative effect on cognitive QOL, while treatment regimen had a direct positive effect on cognitive QOL (p=0.013. Furthermore, the pill burden correlated with the number of adverse events (p<0.001).

The results in Table 3.13 and Figure 3.2 show that pill burden mediated the relationship between sex and cognitive QOL (p=0.042), age and cognitive QOL (p=0.023), severity of adverse events and cognitive QOL (p= 0.010) as well as treatment regimen and cognitive QOL (p=0.050).

Table 3:13: Statistically significant latent structure, direct and indirect effects of Cognitive QOL

Latent Variables		Estimate	SE	P-value
Reasoning →	Cognitive QOL	1		
Attention→	Cognitive QOL	1.902	0.180	0.000
Forgetfulness→	Cognitive QOL	1.937	0.196	0.000
Direct effects				
Pill burden→	Cognitive QOL	-0.004	0.001	0.005
Age→	Cognitive QOL	-0.001	0.0006	0.046
Treatment regimen→	Cognitive QOL	0.023	0.009	0.013
Age→	Pill burden	0.077	0.019	0.000
Treatment regimen→	Pill burden	0.830	0.320	0.008
Severity of adverse events→	Pill burden	1.775	0.266	0.000
Sex→	Pill burden	1.080	0.363	0.003
Sex→	Adverse Events	0.302	0.124	0.015
Severity of Adverse Events→	Adverse Events	1.349	0.093	0.000
Sex	Alcohol	0.110	0.056	0.049
Indirect effects				
Age→Pill burden→Cognitive QOL		-0.0003	0.0001	0.023
Treatment regimen→Pill burden→Cognitive QOL		-0.003	0.002	0.050
Sex→Pill burden→Cognitive QOL		-0.004	0.002	0.042
Severity of adverse events→Pill burden→Cognitive QOL		-0.007	0.003	0.010
Correlations				
Number of Adverse events←→Pill burden		1.176	0.258	0.0000

3.6.4. Goodness of fit test for Cognitive QOL

Table 3:14: Model Fit statistics for Cognitive QOL SEM

The final SEM model for cognitive QOL had a good fit as all the criteria for a well-fitted model were met (CFI 0.992; TLI 0.0987; RMSEA 0.025; RMSR 0.034 and LR chi2 0.235) (Table 3.14)

Fit statistic	Observed model fit	Criteria for good fit
Likelihood ratio chi-square	0.235	>0.05
RMSR	0.034	<0.05
CFI	0.992	Close to 1
TLI	0.987	Close to 1
RMSEA	0.025	<0.05

3.7.Mental QOL

3.7.1. Associations between socio-demographic and clinical factors affecting Mental QOL

Table 3:15: Socio-demographic and clinical factors affecting QOL domain scores

Characteristic	Mean (SD)	P value
Sex		
Male	88.65(20.5)	0.305
Female	85.94(21.31)	
Age *		
	86.82(21.1)	0.637
Education		
Primary	82.61(24.3)	0.510
Secondary	87.4(20.7)	
Tertiary	84.7(21.3)	
Adverse events (AE)		
None	88.47 (20.6)	0.367
1	84.79(22.2)	
2	89.32(18.6)	
3	83.95 (22.7)	
Severity of AEs		
None	88.40(20.8)	0.087
Mild	87.45(20.5)	
Moderate - Severe	79.41(22.6)	
Pill burden*	86.82(21.1)	0.002

*Pearson correlation test

As described in Table 3.15, only pill burden was associated with mental QOL (p=0.002), presenting with a weak negative correlation (r =-0.178). Mental QOL scores decreased with an increase in pill burden. In addition, lower mental QOL scores were observed amongst participants who reported moderate to severe adverse events but was not statistically significant (p=0.087).

3.7.2. Predictors of Mental QOL

Table 3:16: Logistic Regression of Mental QOL (3.8.2.1)

	AOR (95% CI)	P value
Age	1.00 (0.96 – 1.03)	0.891
Sex		
Male	1	
Female	1.25(0.67 – 2.32)	0.477
Treatment regimen		
DRV	1	
LPV	1.02 (0.59 – 1.76)	0.934
Adverse events (AE)		
None	1	
1	1.03(0.51 – 2.07)	0.937
2	0.52(0.22 – 1.20)	0.124
3+	0.67 (0.27 – 1.69)	0.395
Pill burden	1.16(1.05 – 1.28) *	0.004

*293 observations were included in the analysis with complete covariate information (p=0.06)

The results of logistic regression as presented in Table 3.16, show pill burden as the only significant factor associated with lower cognitive QOL scores (p=0.004). The analysis shows that a unit increase in the number of medications increases the odds of lower mental QOL scores by 16%. No significant association was noted amongst other factors in the model.

3.7.3. SEM and pathway analysis of mental QOL

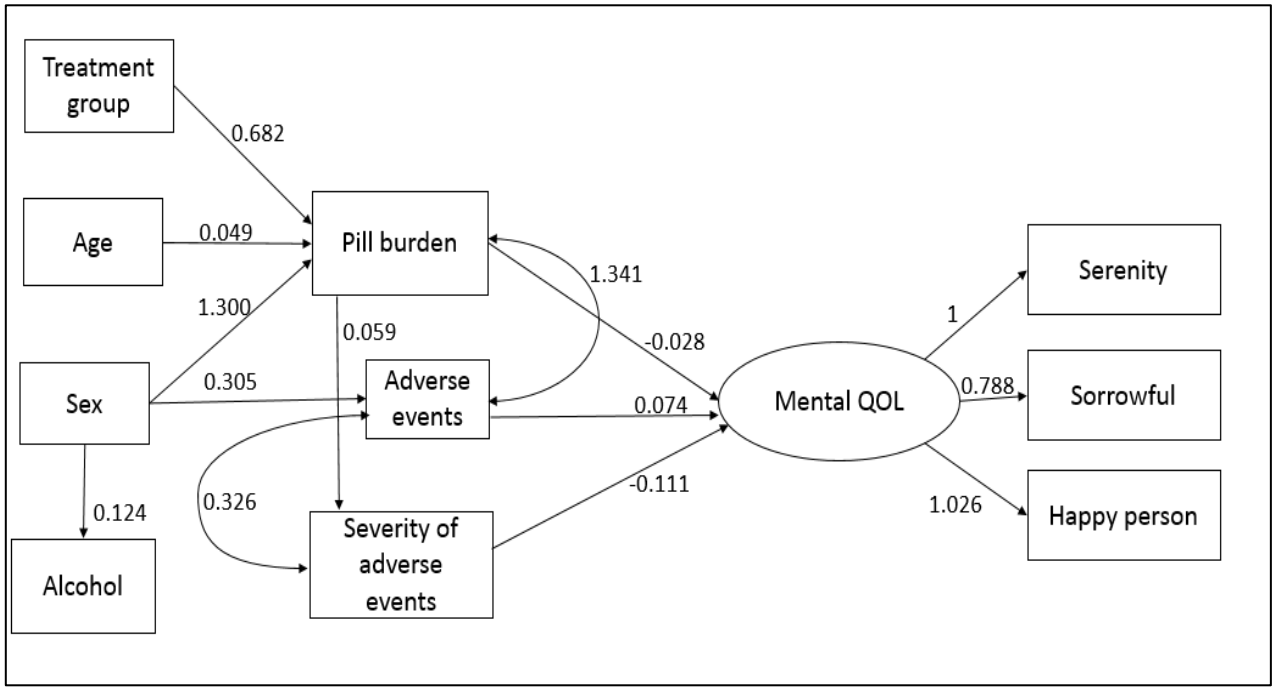

Figure 3-3: Final model of factors influencing mental QOL among PLWHA in Johannesburg on second-line antiretroviral therapy. Box indicates an observed variable, and oval indicates the latent construct. Straight-line with one arrow denotes direct effect and curved line denotes correlation

As shown in Figure 3.3 and Table 3.17, treatment regimen (p=0.029) and age (p=0.014) have a positive direct effect on pill burden. Sex has a direct positive effect on adverse events (p=0.022), pill burden (p=0.001) whereas sex (male participants) and alcohol use (0.044). Pill burden has a direct positive effect on the severity of adverse events (p<0.001). Pill burden also has a direct negative effect on mental QOL (p<0.001). In addition, the pill burden correlates to adverse events. Adverse events have a direct positive relationship on mental QOL (p=0.020) and correlate to the severity of adverse events (p<0.001). The severity of adverse has a direct positive effect on mental QOL (p=0.019).

Pill burden mediated the relationship between age and mental QOL (p=0.072), treatment regimen (p=0.092) and mental QOL in addition to sex (female participants) and mental QOL (p=0.041). In addition, pill burden mediated the relationship between age and severity of adverse events, treatment regimen, and severity of adverse events as well as sex (female participants) and severity of adverse events.

Table 3:17: Statistically significant latent structure, direct and indirect effects of Mental QOL

Latent Variables		**Estimate**	**SE**	**P-value**
Serenity→	Mental QOL	1		
Despondent →	Mental QOL	0.788	0.042	<0.001
Generally happy→	Mental QOL	1.027	0.042	<0.001
Direct effects				
Sex→	Alcohol use	0.124	0.061	0.044
Sex→	Adverse events	0.262	0.203	0.022
Pill burden→	Mental QOL	-0.028	0.010	0.010
Severity →	Mental QOL	-0.111	0.056	0.019
Adverse events →	Mental QOL	0.074	0.035	0.020
Age →	Pill burden	0.049	0.020	0.014
Treatment →	Pill burden	0.682	0.313	0.029
Sex →	Pill burden	1.300	0.402	0.001
Severity of adverse events→	Pill burden	0.059	0.011	<0.000
Indirect effects				
Age→Pill burden→Mental QOL		-0.001	0.0009	0.072
Treatment regimen→Pill burden→Mental QOL		-0.021	0.012	0.092
Sex→Pill burden→Mental		0.287	0.141	0.041
Sex→Adverse events→ Mental		-0.014	0.018	0.435

Alcohol→ Severity of Adverse Events →Mental QOL	-0.014	0.010	0.215
Correlations			
Number of Adverse events←→Severity of adverse events	0.326	0.040	<0.001
Number of Adverse events ←→Pill burden	1.341	0.209	<0.001

3.7.4. Goodness of fit tests for Mental QOL SEM

The model has a good fit as all the criteria for a well-fitted model were met (CFI 1.00; TLI 1.007; RMSEA 0.000; RMSR 0.034 and LR chi2 0.673) (Table 3.18).

Table 3:18: Model Fit statistics for Mental QOL SEM

Fit statistic	Observed model fit	Criteria for good fit
Likelihood ratio chi-square	0.673	>0.05
RMSR	0.034	<0.05
CFI	1.000	Close to 1
TLI	1.007	Close to 1
RMSEA	0.000	<0.05

4. CHAPTER FOUR: DISCUSSION

The overall aim of this study was to investigate direct and indirect pathways that affect the quality of life among PLWHA on second-line antiretroviral therapy in Johannesburg at Week 48. Overall, the study found that QOL scores were very high in all domains, particularly in the cognitive domain. The mental wellbeing domain presented with relatively lower scores. Pill burden and age were significant risk factors for the lower scores in the physical/functional domain and cognitive domain. Pill burden was the only risk factor that predicted lower mental health scores. Pill burden was a mediator in all three QOL domains. The number of adverse events also appeared to be an additional mediator in the mental health domain and surprisingly increased mental QOL scores.

4.1. Describing overall QOL

The first objective of the study was to describe the QOL among PLWHA in Johannesburg at Week 48. Overall, the average QOL scores were greater than 85 in this cohort. This finding was similar to the results of another clinical trial investigating QOL in HIV patients on second-line therapy(89). The clinical trial was conducted in resource-limited settings (Brazil, India, Kenya, Malawi, Peru, South Africa, Tanzania, Thailand, and Zimbabwe) and showed that at week 48 participants presented with average scores greater than 90(89). The first possible explanation for the higher QOL reported could be that participants in clinical trials have access to better care and constant supply of medication, which may have aided their adherence to treatment, and consequently improved QOL. There is evidence of lower quality of care in some HIV clinics where most PLWHA access treatment, compared to the high quality of care and monitoring that patients in clinical trials receive(54,90). Lower quality care in clinics has been associated with understaffing, high workloads and low service-provider morale in the public health sector(54). An example of this is a study conducted in a Ugandan cohort by Mutabazi-Mwesigire et al. which compared QOL at baseline and at six months. The study found that mental and physical health QOL scores were lower at baseline compared to six months. The authors partially attributed differences in QOL scores to changes in care, one of which was patients' participation in a clinical trial(10). Therefore, the generalisability of our study results may be limited.

Secondly, the overall well-being that was observed in cognitive, physical/functional and mental QOL may be attributed to the effectiveness of ART and HIV/AIDS becoming a manageable chronic condition.

With regard to the mental QOL domain, the scores were relatively lower compared to the physical function and cognitive domain. This may be an indication that PLWHA who do not have HIV-related physical illness, may experience symptoms of common mental disorders (e.g. depression) that can be a serious health challenge requiring clinical assessment and support(91). Other studies have reported that mental health in PLWHA may be negatively affected by factors such as lack of social support, substance abuse, and stigma(12). Another possible explanation for the lower mental scores observed in this study may be related to discomfort caused by failing first-line treatment and the fear of developing resistance to second-line treatment. The potential for viral rebound may have been worrisome to some of the participants in the study. Similarly, Torres et al. show that low QOL scores are observed in all the domains including mental health, in patients failing first-line therapy particularly in Malawi(27).This study, however, was unable to explore these factors in-depth as depression and anxiety were not measured in the primary study and therefore was beyond its scope. Nonetheless, the study analysed the use of substances (alcohol and tobacco) and found low use of these substances in this sample, which may explain why the researcher found no association with any of the domains of QOL. A limitation of the measures of substance use was that the frequency of consumption was not measured, which may have been the reason for its statistical non-significance.

On the other hand, the study found that participants reported higher QOL scores in the physical/functional and cognitive domains. These findings were contradictory to those of a Ugandan study which was conducted in 2007(92). These differences are likely due to the changes in HIV treatment guidelines at the time of the Ugandan study, where previously treatments were initiated at a specific CD4 count, by which time QOL would have been affected negatively. Currently, South African guidelines toward the test and treat policy allow early initiation of treatment despite CD4 count. This has clinical and immunological benefits that boost physical and cognitive function. A good example of this is a study conducted by Miner et al., who reported that patients diagnosed in more recent years had higher QOL scores, compared to those diagnosed in prior years(93). They argued that other factors explaining this result could be a more streamlined approach to taking medication, more favourable side effect profiles, increasing societal acceptance, and better life expectancy(93,94).

Another important finding was that there were no significant differences between males and females in the physical/function, cognitive and mental QOL domains. As mentioned earlier, the results of QOL differences in males and females are contradictory(49–53). Most cross-sectional

studies have reported that males were more likely to be employed and have more financial resources compared to women hence have a higher QOL(59,95). Other studies found that women were less likely to utilize HIV healthcare services as compared to men hence the lower QOL(96). However, the retention strategies employed in the primary study, such as improved patient waiting time, adherence counselling, development of positive relationships with healthcare professionals and the ease of access to services (reimbursement and transportation) may have aided in both male and females' overall adherence to treatment and ultimately improved QOL(97).

4.2. Factors that influence QOL in PLWHA on second-line treatment

4.2.1. Physical and functional QOL

The second objective of the study was to identify factors associated with the various domains of QOL. It was observed that as age increased, physical function QOL scores decreased significantly, despite adjusting for variables that differed between the groups (e.g., sex, treatment regimen). This was consistent with studies that reported lower physical QOL scores in older participants(10,98,99) associated with reduced ability to carry out physical day-to-day activities (e.g., eating, walking, running) when aging, may account for this observation.

This study used pill burden as a proxy measure for co-morbid conditions and found that lower physical function QOL scores were associated with a higher pill burden. A unit increase in pill burden resulted in a 16% decrease in physical function scores. These findings are similar to those from previous studies which investigated associations of co-morbid conditions and physical QOL(9,89). Torres et al. (2017) observed that an increase in the prevalence of comorbid conditions resulted in low physical function QOL scores. However, there was a limitation with pill burden as a proxy measure for co-morbid conditions because the pill burden in this study included medications for different conditions with different chronicity. For example, some of the medication may have been for transient or mild conditions while other conditions could have been chronic. Therefore, there was limited comparability in terms of the conditions considered in the different studies.

4.2.2. Cognitive QOL

Age and pill burden was also found to be associated with lower cognitive QOL scores. The odds of lower cognitive QOL scores in pill burden and age are 23% and 9% respectively per unit increase. With regard to age, previous research did not find age as a risk factor of low cognitive QOL(56,89). These differences may be attributable to the fact that the average age in these studies

was lower compared to the current study. On the contrary, other studies observed the cognitive decline in older participants and attributed the decline to poor medication management, financial difficulties and declines in daily living activities(100,101). However, the secondary data analysis presented in this study limited the possibility to adjust for these additional variables. Future studies must consider these to conclusively understand the relationships between cognitive QOL and these variables.

The researcher also found an association between lower cognitive scores and participants with a higher pill burden. This finding was consistent with Torres et al. who reported lower cognitive scores in participants on second-line treatment with 3 or more co-morbidities(89). It is likely that potential drug interactions, that result from co-medication, may complicate cognitive functional outcomes such as problems in attention, reasoning, solving problems and memory(102). Alternatively, changes in cognition may not be predicted by the number of medication but the presence of agents, such as cardiovascular agents, that have been shown to have a negative effect on cognitive function. Collectively, this highlights the importance of considering the risk/benefit ratio of medications before initiating them and should be tailored to minimize drug-to-drug interactions, specifically in HIV-infected patients. Interestingly, an interaction term between age and pill burden was tested and did not yield significance despite evidence of synergistic effects between older age and medical co-morbidity having been demonstrated by Rodriguez-penney et al (9).

4.2.3. Mental QOL

The results of this study show that pill burden was the only factor associated with lower mental QOL and thus highlighting pill burden as a risk factor consistently associated with all three QOL domains. Prior studies have implicated pill burden in PLWHA, reporting its significant effect in lowering the scores in various QOL domains such as role function, physical function and mental function(89). Mental QOL may be reduced by having several medications to take and as a result may be overwhelming to patients as it reminds them of their disease status(92). Rodriguez-penney et al. further suggest that greater comorbidity may lead to negative affective symptoms of mental health such as hopelessness, depression, and lethargy, especially in the younger population, although age was not associated with mental QOL in this study(9).

4.3. Interrelationship of risk factors in the QOL domains

While QOL has increasingly become accepted as an important outcome to be considered in the treatment of HIV/AIDS, relatively few efforts have been made to assess the interplay between various factors and how they affect QOL. The current study utilized structural equation modelling to examine a hypothesized model of QOL in PLWHA. Figures 6, 7, 8 show that adverse events and pill burden mediate the relationship between socio-economic status and QOL.

4.3.1. Risk factors common to Physical function, Cognitive and Mental QOL

In this study, pill burden was found to mediate the effects of age, treatment regimen, and sex in all three QOL domains. While the researcher found that age and pill burden were independently associated with QOL in the regression models, she also found that the relationship between age and QOL was mediated through pill burden. This is an advantage of using SEM as the researcher was able to see the relationship between age and pill burden that ultimately affects QOL. This can be explained by a higher prevalence of co-morbidities in older participants, which increases the number of medications, or pill burden, and thus impacting on QOL(9).

Participants on lopinavir (standard care of treatment) had a higher pill burden in this study, which was not consistent with other literature(89). As mentioned in the literature review, there's strong supportive evidence that the intervention drug, darunavir, is more tolerable and safer because of the lower dosage as compared to the standard line of treatment(29,31,32). This suggests less adverse events and consequently, less medication required to treat them. Having said this, the researcher had expected treatment regimen to also show a direct effect on adverse events, but this was not observed in this study. These present findings were not consistent with studies that found significantly lower adverse events reported in patients on darunavir(103,104). The inconsistent results might be that these studies used a larger sample size compared to this study.

Although there was no direct relationship observed between sex and QOL in the regression models, the researcher found that pill burden mediated the relationship between sex and QOL in SEM. Females reported a higher pill burden than males, which mirrored the results of a study conducted by Pereira et al. The study reported that opportunistic infections and co-morbidities such as tuberculosis, depression/anxiety, and malnutrition were more likely in female - which accords to why their pill burden would be higher (59). Interestingly, this argument would support why vitamins and supplements were included in the pill burden count, as they may be treatment administered to aid in treating malnutrition. Conversely, QOL in males may be affected by other

factors such as alcohol use as observed in the current study. Alcohol use has been linked to worsening co-morbidities, delayed access to ART, adherence difficulties and more importantly, decreased QOL (105,106). This study shows that a reduction in QOL may result from a myriad of factors including age-associated factors, gender as well as HIV treatment, which should be taken into consideration when reviewing treatment options and developing appropriate medication regimens.

Another result common to all three models is the correlation between pill burden and adverse events, which supports the cyclical nature of adverse events and pill burden highlighted in the literature review(37). The present findings seem to be consistent with other research, which found that treatment of adverse events leads to higher pill burden. As a result, patients are at a higher risk of adverse events secondary to this medication(37,47,107). Moreover, this cyclical relationship was highlighted in older patients, suggesting that long-term exposure to treatment could be the reason for the exacerbations in this age group. Similar results were found in this study since the pill burden has been consistently associated with age in all 3 QOL models. Thus, since the HIV population is aging, the impact of co-morbidities and pill burden need to be considered as these factors may have significant functional and public health implications.

4.3.2. Mediators and moderators affecting Physical function QOL

The fit statistics of the physical function model showed that the chi-squared p-value was significant, whereas a good model fit should not be so. However, the chi-squared statistic has been shown to be very sensitive to sample size and is no longer completely relied upon as a basis for acceptance or rejection(108,109).

Overall, physical function QOL was found to affect by age, sex and treatment regimen. These relationships were mediated by pill burden. Furthermore, in the physical function SEM, the researcher found that pill burden directly increased the severity of adverse events. Participants with a higher pill burden were more likely to report moderate to severe adverse events. This could account for the direct relationship observed between pill burden and physical function QOL.

4.3.3. Mediators and moderators affecting Mental QOL

In the mental QOL SEM, the researcher found that the number of adverse events was a mediator between sex and mental QOL. This observation further indicates that in this study, the effect of sex is mediated through other factors and may explain why other studies did not observe a direct relationship. In this case, females reported a higher number of adverse events, which unexpectedly

had a positive association with mental QOL. The findings of this current study do not support previous research(59,110). Wouters et al. conducted a structural equation model in South Africans on long-term changes in the physical and emotional QOL of patients on ART and reported that adverse events were negatively associated with emotional QOL (110). A different instrument was used to measure mental QOL, therefore making direct comparisons challenging. It is difficult to explain this relationship between adverse events and mental QOL, however, it is possible that the response and care that a study participant receives in the event of an adverse effect, may paradoxically contribute positively to their mental QOL. This would mean that, in a study setting, a patient may feel more valued and supported and this would impact positively on their mental well-being.

Although the number of adverse events increased mental QOL scores, the severity of adverse events lowered these scores. This finding was consistent with Anis et al. using data from the OPTIMA. The authors found that patients who experienced non-AIDS-related serious adverse events (defined as adverse events not related to the advanced stage of HIV/AIDS, resulting in death or significant disability/hospitalization) had a decrease in mental health summary scores within eight weeks of the study visit, and further decreased at week 16(111). Once more, the instrument used to measure QOL differed with our study, and comparisons should be interpreted with caution.

4.3.4. Mediators and moderators Cognitive QOL

Specific to the cognitive model, the researcher found that participants on darunavir had increased cognitive QOL scores. There is strong supportive evidence that darunavir has sustained high rates of viral suppression alongside a better side effect profile (better metabolic profile, lower impact on lipids)(22). In contrast, there have been studies that show that patients on lopinavir have commonly reported metabolic concerns(103,112,113). Gupta et al, in a study observing the effect of lopinavir on mice, reported that these metabolic abnormalities largely contributed to decreases in cognitive function (112). However, the relevance of this study to humans is currently unknown. Nonetheless, the studies mentioned are suggesting adverse events as a mediator of treatment regimen and cognitive QOL, a result the researcher did not find in this study. This may be attributed to the limitation of adverse events being described quantitively and not qualitatively in the current study.

4.4. Limitations

The results of the study should be interpreted in light of several limitations. One of the main limitations of the study is the arbitrary cut points that were applied to create QOL scores as a categorical variable, due to the highly skewed nature of the data. These cut off points were used to define lower and higher QOL classifications and used as the binary variable in the logistic regression models. Therefore, it was difficult to compare to other studies that used a similar instrument but applied a standard median cut-point.

Furthermore, the ACTG SF-21 questionnaire administered in the primary study included modifications that deviated from the validated tool as there was a reduction in the number of items scales used to comprehensively assess QOL dimensions. This resulted in the confirmatory factor analysis recognizing only three distinct domains rather than the standard eight QOL domains. Once more, this affected the comparisons made with other studies because the physical function domain incorporated other domains such as social, pain, energy, etc. Thus, comparisons may not have been credible.

The number of ART pills were not included as part of the pill burden but was adequately adjusted for in the logistic regression and SEM analysis through the inclusion of regimen as a variable. In light of this, it was unclear whether the decreased QOL was driven by the assigned treatment regimen or the additional co-medication.

The primary study was an open-label randomised clinical trial which was likely to subject measurement to biases such as response bias (i.e. a tendency for patients to report symptoms in a way they think is expected) as well as interviewer bias where a research assistants/nurses' knowledge may influence the structure and manner with which questions are administered and may subtly influence responses.

QOL is a self-reported measure and there could be measurement bias. However, there is no reason to believe that any groups e.g. males vs. female systematically reported higher or lower quality of life scores which would bias the result towards the null hypothesis.

The sample is a volunteer sample and as such the external validity of the results would be limited.

The primary study did not collect data on some variables that could be important in the pathway between sociodemographic/clinical factors and quality of life - such as psycho-social factors family support, level of health education, stigma, and history of ART including time on first-line

treatment, adherence data and frequency/dosage of alcohol and tobacco use. This is a limitation due to the secondary analysis of study data.

The small sample size did not allow us to disaggregate findings between males and females. The disaggregation resulted in inadequate power to detect different factors that contributed to QOL differences in male and females which present another limitation of the study. Furthermore, some of the findings were marginal and could show statistical significance with a bigger sample, and it would have been possible to detect the differences.

There were challenges in using non-parametric tests. Given the skewness of the data, the QOL median scores reported in the bivariate analysis were mostly 100 and the IQR range was zero. These results were difficult to present/interpret as there were no differences observed between groups. After conducting parametric tests and observed that the p-values were similar to the non-parametric tests and could give us more information through mean QOL scores, the researcher decided to use parametric tests.

5. Chapter 5. Conclusions and recommendations

5.1. Conclusion

Overall finding in this study shows that pill burden decreases mental, cognitive and physical function QOL scores. While this does not suggest that HIV positive patients should not be prescribed additional medications for acute and chronic comorbidities, it points out to a need for considering the risk/benefit ratio of medications before initiating them and tailoring these medications to reduce drug-to-drug interactions, if enhanced QOL is the desired goal. Additionally, clear guidelines and information should be made to patients, particularly amongst those older HIV patients.

Furthermore, this study revealed the impact of co-morbidities and pill burden amongst the older HIV participants, revealing the importance of guided functional and public health services that need to be tailored for the needs of the aging HIV population.

In addition, the study supports the evidence that darunavir has a better side effects profile, showing that participants on this regimen reported a lower pill burden and present with better cognitive function scores. These results can contribute to the additional safety data that is needed in some subpopulations before a large introduction in national treatment programs.

Females report a higher number of pill burden and adverse events as compared to males, as a result, are vulnerable in experiencing lower mental, physical and cognitive QOL. Therefore, to improve QOL of PLWHA due emphasis should be given to females, particularly those with co-morbidities and to enhanced integrated early detection and management of HIV-related and non-related co-morbidities among PLWHA in Johannesburg.

5.2 Recommendations

- Policy and program recommendations
  - Our findings highlight that mental health is still a concern in PLWHA and governments needs to do more to integrate mental health and HIV services to improve QOL.
  - HIV-infected individuals, particularly those who are older, should receive comprehensive medical evaluations to ensure early detection and remediation of conditions or symptoms to reduce co-morbidities and pill burden and improve overall health-related quality of life.
  - Strategies to prevent chronic diseases through lifestyle interventions (e.g exercise, salt intake, lower or no alcohol consumption) which reduce the risk of developing diseases such as hypertension and diabetes are important. In addition to the health benefits and reduced morbidity, prevention would limit the need for treatment later and this would lower the pill burden for PLWHA. Health programs should focus on food security and nutrition, provision of immune boosters and health checks via mobile clinics in order to prevent both chronic and acute infectious diseases. Additionally, awareness campaigns focusing on educating PLWHA and their family members about basic self-care and evidence-based complementary and alternative treatments should be considered (e.g. meditation and mindfulness). This would help to deal with the common side-effects of HIV/AIDS treatment like pain, diarrhea etc. and to encourage non-pharmacological approaches to reduce undue reliance on medications and consequences such as drug toxicities
  - It would also be beneficial to simplify treatment to one pill daily, which would also assist in reducing the pill burden experienced by PLWHA.
  - Current psychosocial initiatives, such as drug readiness training and support from community health workers should be scaled up among those presenting with high adverse events or high co-morbidities/pill burden (i.e older participants and females).
  - To reduce the QOL differences between sexes, retention strategies such as treatment buddies, support groups, transportation, should be reinforced among PLWHA.
- Measurement of QOL

- Researchers should avoid reducing the number of items in standard validated questionnaires in an attempt to lessen the completion time. This results in an inadequate number of items to comprehensively assess QOL domains and may result in missing out on the crucial domain affecting QOL in PLWHA.

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7. APPENDICES

7.1.Appendix 1: Quality of Life questionnaire

Questionnaire:
Assessing Quality of Life of Participants on 2nd Line ARVs

INSTRUCTIONS: Please mark "X" as answer in the appropriate box.

1. In general, would you say **your health** is: (Check One)
   - Excellent ..... 1 ☐
   - Very Good ..... 2 ☐
   - Good ..... 3 ☐
   - Fair ..... 4 ☐
   - Poor ..... 5 ☐

2. How much **bodily** pain have you had in the **past 4 weeks?** (Check One)
   - None ..... 1 ☐
   - Very Mild ..... 2 ☐
   - Mild ..... 3 ☐
   - Moderate ..... 4 ☐
   - Severe ..... 5 ☐
   - Very Severe ..... 6 ☐

3. Does your health now limit you in the following activities?

	Activities	Yes, limited a lot = 1	Yes, limited a little = 2	No= 3
a	Vigorous activities like lifting objects or doing sports	☐	☐	☐
b	Walking uphill or climbing the stairs	☐	☐	☐
c	Eating, dressing, bathing or using the toilet	☐	☐	☐

4. Does **your health** keep you from working around the house or at a job or going to school? (Check One)
   - Yes for all the time ..... 1 ☐
   - Yes for some of the time ..... 2 ☐
   - No ..... 3 ☐

5. Have you been unable to do **certain kinds or amounts** of work, at a job, housework, or schoolwork because of your health? (Check One)
   - Yes for all the time ..... 1 ☐
   - Yes for some of the time ..... 2 ☐
   - No ..... 3 ☐

   If **Yes**, specify kinds or amounts of work .....

   .....

WRHI052: Quality of Life Questionnaire
Version 1 dated 19 June 2015

Page **1** of **2**

Baseline (scr/Enr) ☐ Visit 3 (Week 24) ☐ PTD: __ __ __
Visit 1 (week 4) ☐ Visit 4 (Week 36) ☐
Visit 2 (week 12) ☐ Visit 5 (EOS/Week 48) ☐ Date: __ __/__ __ __/__ __

6. During the past 4 weeks, how much has your physical health or emotional problems interfered with your normal social activities? (Check One)
   - Not at all ..... 1 ☐
   - A little bit ..... 2 ☐
   - Moderately ..... 3 ☐
   - Quite a bit ..... 4 ☐
   - Extremely ..... 5 ☐

7. How much of the time, during the past 4 weeks has your physical health or emotional problems interfered with your social activities (like visiting with friends of relatives)? (Check One)
   - All of the time ..... 1 ☐
   - Some of the time ..... 2 ☐
   - None of the time ..... 3 ☐

	8. In the past 4 weeks, did you have	All of the time = 1	Some of the time =2	None of the time =3
a	Difficulty reasoning and solving problems, e.g. making plans, making decisions, learning new things?	☐	☐	☐
b	Trouble keeping your attention on any activity for long?	☐	☐	☐
c	Forget, e.g. things that happened recently, where you put things, appointments?	☐	☐	☐

	9. In the past 4 weeks, have you	All of the time = 1	Some of the time =2	None of the time =3
a	Felt calm and peaceful?	☐	☐	☐
b	Felt downhearted and blue?	☐	☐	☐
c	Been a happy person?	☐	☐	☐

	10. In the past 4 weeks, how often did you	All of the time = 1	Some of the time = 2	None of the time = 3
a	Feel tired?	☐	☐	☐
b	Have enough energy to do the things you want to do?	☐	☐	☐

7.2.Appendix 2: Ethics Clearance

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

Office of the Deputy Vice-Chancellor (Research & Post Graduate Affairs)

TO: Miss NO Mokgethi
School of Public Health
Medical School
University

E-mail: oratilemokgethi@gmail.com

CC: Supervisor: Professor N Christofides, et al <Nicola.Christofides@wits.ac.za> and <HREC-Medical.ResearchOffice@wits.ac.za>

FROM: Iain Burns
Human Research Ethics Committee (Medical)
Tel: 011 717 1252

E-mail: Iain.Burns@wits.ac.za

DATE: 28/11/2018

REF: *R14/49*

PROTOCOL NO: **M181001** *(This is your ethics application study reference number. Please quote this reference number in all correspondence relating to this study)*

PROJECT TITLE: *Quality of life and associated factors among people living with HIV receiving second line therapy in Johannesburg over 48 weeks*

Please find attached the Clearance Certificate for the above project. I hope it goes well and that an article in a recognized publication comes out of it. This will reflect well on your professional standing and contribute to the Government funding of the University.

MSWorks2000/Iain0007/Clearscan.wps

7.3.Appendix 3: Letter of permission

05 September 2018

Professor Francois Venter
Wits RHI

RE: Permission to use WRHI052 data for MSc Research

The purpose of this letter is to ask your permission to use some of the WRHI052 trial data for my MSc research report at the School of Public Health, Wits University.

The research will involve secondary data analysis to investigate pathways that affect the quality of life among PLHIV who are on second line anti-retroviral therapy in Johannesburg. Baseline and follow-up data for the following variables are required:

- Age
- Gender
- Marital status
- Educational level
- Employment status
- Treatment
- Substance abuse
- Concomitant medication
- Adverse events (on all follow up visits)
- Quality of life (baseline and follow up visits)

It's important to state that, if permission is granted:

- The data will not be passed on in whole or in part to a third party without permission from the Wits Reproductive Health and HIV institute.
- The student researcher and supervisors will be the only persons with access to the data and it will be kept for a two-year period after the publication of the results of the study and then it will be destroyed
- The data will not be used for any purposes other than that for which approval was given.

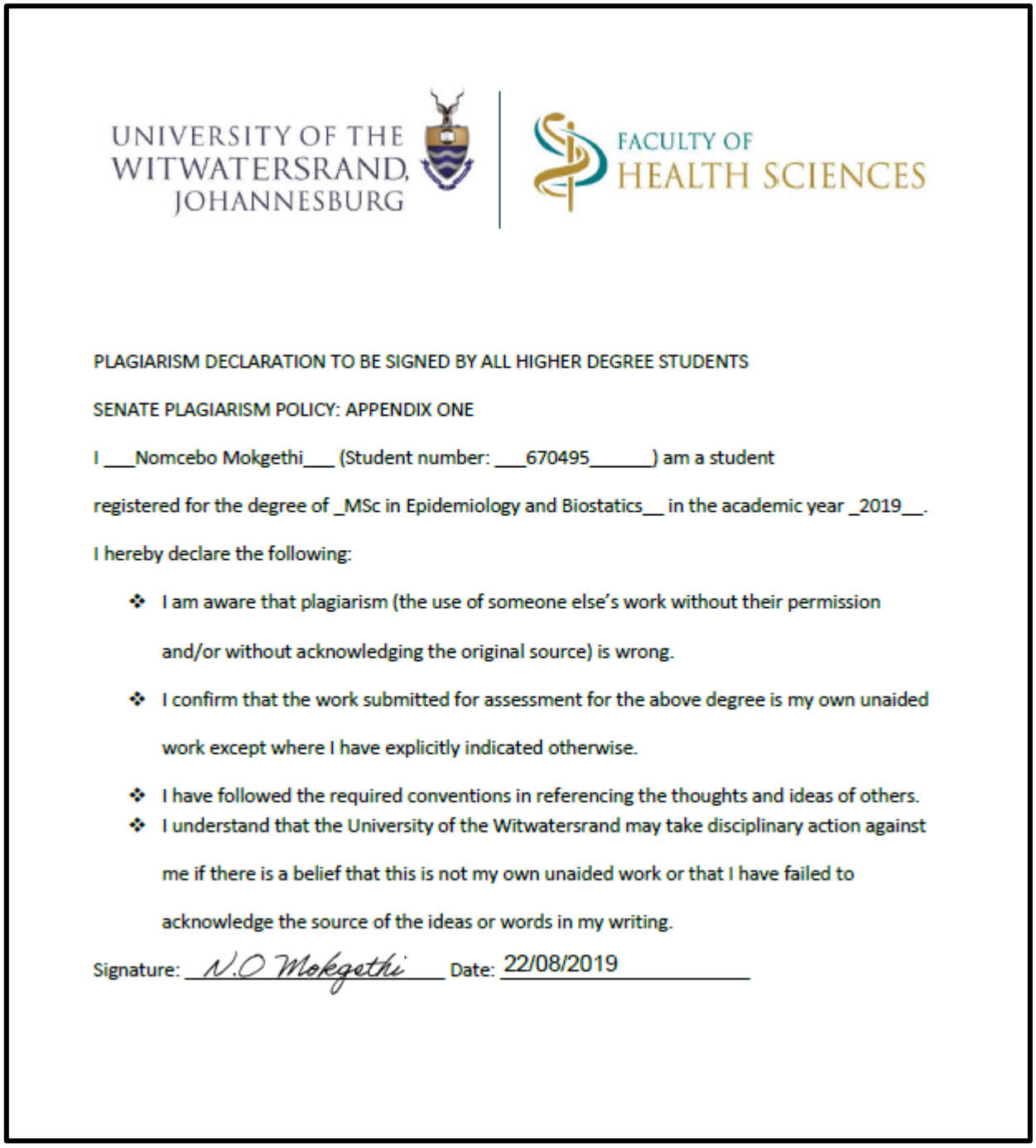
Applicant: Oratile Mokgethi; M.Sc. Student School of Public Health, University of the Witwatersrand)

Signature: N.Mokgethi.....

Approved by (WRHI052 Principal Investigator): .....

Date approved: |_0_|_6_|/|_0_|_9_|/|_2_|_0_|_1_|_8_|

7.4.Appendix 4: Plagiarism declaration



UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I ___Nomcebo Mokgethi___ (Student number: ___670495_____) am a student registered for the degree of _MSc in Epidemiology and Biostatics__ in the academic year _2019__.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.

Signature: N.O Mokgethi Date: 22/08/2019