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Factors affecting ART adherence among HIV-positive adherence club members in Ekurhuleni, South Africa in 2016

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of MSc Epidemiology (Epidemiology and Biostatistics)

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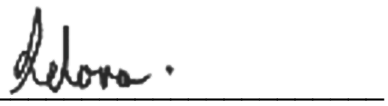
CANDIDATES DECLARATION

I, Tariro Ndoro, declare that this research report is my own work. It is being submitted in partial fulfilment of the requirements for the degree Master of Epidemiology (Epidemiology and Biostatistics) at the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.



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Student number: 1737299

On the 14th day of June 2021

DEDICATION

I dedicate this report to my mother Mrs. P Muchengwa and my sister, Tafadzwa Ndoro who have supported and encouraged me along this journey; and to God who makes everything possible.

ABSTRACT

Background

South Africa has the world's highest human immunodeficiency virus (HIV) prevalence. Free antiretroviral therapy (ART) is available to persons living with HIV/AIDS but low adherence to ART increases the burden of HIV on the public health system. ART adherence clubs were launched to improve ART adherence in communities. However, the drivers of ART adherence within these clubs have not been studied to date. This study aimed to determine the factors affecting ART adherence among HIV positive individuals attending adherence clubs in Ekurhuleni, Gauteng.

Methods

The study involved the secondary analysis of data collected in February 2016 through a cross-sectional study conducted amongst adherence club members in Ekurhuleni Metropolitan Municipality. Participants were sampled from a population of people living with HIV/AIDS (PLWHA) registered as members of adherence clubs in April 2015. Descriptive analysis was carried out by showing counts and frequencies, this was followed by bivariable analyses using a dichotomous outcome variable for ART adherence. Ordinal logistic regression was used for univariable and multivariable analyses to determine factors significantly associated with ordinal adherence scores. Significant determinants were then applied in a geometric structural equation model

(GSEM) to determine mediatory pathways between ART adherence determinants and ART adherence.

Results

There were 730 participants in this study, 96% of them were adherent to ART. The median age of the participants was 39 years (IQR = 20 - 69 years). Study participants had a median duration of adherence club membership of 3.4 years (IQR = 1.3 - 4.1 years). The odds of reporting high levels of adherence among participants with comorbidities were 0.5 times those of reporting high levels of ART adherence among participants without comorbidities (aOR: 0.5, 95% CI: 0.3 - 0.8, p = 0.005). The odds of reporting high levels of adherence among participants who were on combination ART were 1.8 times those of participants on a single tablet regimen (aOR: 1.8, 95% CI: 1.0 - 3.2, p <0.033).The odds of high ART adherence decreased by 20% for each additional year of adherence club membership (aOR: 0.8, 95% CI: 0.8 - 0.9, p < 0.001). None of the mediatory pathways hypothesised were found to be significant in GSEM analysis.

Conclusion

Increasing years spent as adherence club members, single tablet ART regimens and the presence of comorbidities were all significantly associated with nonadherence to ART among HIV positive individuals attending ART adherence clubs in Ekurhuleni. ART adherence amongst members could be improved by having regular and sustained counselling sessions for ART adherence club members. Adherence club facilitators

should have focused counselling sessions for adherence club members who have comorbidities, focusing on lifestyle modifications among PLWHA to manage concurrent illnesses. Further, screening tools for side effects and treatment fatigue should be developed and used regularly in adherence club settings.

Keywords: *models of care, antiretrovirals, medication adherence, fixed dose regimen, diabetes mellitus*

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ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immunodeficiency Syndrome
aOR	Adjusted Odds Ratio
ART	Antiretroviral Therapy
ARV	Antiretroviral
AZT	Zidovudine
BMI	Body Mass Index
CAG	Community Adherence Group
cART	Combination Antiretroviral Therapy
CD4	T-lymphocyte with a Cluster of Differentiation 4 receptor
CHW	Community Health Worker
CI	Confidence Interval
EFV	Efavirenz
FDC	Fixed-Dose Combination
FTC	Emtricitabine
GSEM	Geometric Structural Equation Modelling
HIV	Human Immunodeficiency Virus
INSTI	Integrase Strand Transfer Inhibitor
IQR	Interquartile Range
LMIC	Low to Medium-Income Countries
LPV/r	Lopinavir/ritonavir
LR	Likelihood Ratio
LTFU	Loss to Follow Up
MAC	Medication Adherence Club
MOC	Model of Care
MTR	Multi Tablet Regimen
NNRTI	Nonnucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor

NtRTI	Nucleotide Reverse Transcriptase Inhibitor
NVP	Nevirapine
PLWHA	Persons Living with HIV/AIDS
SA	South Africa
SD	Standard Deviation
STR	Single Tablet Regimen
TB	Tuberculosis
TDF	Tenofovir Disopril Fumarate
VIF	Variance Inflation Factor
VLS	Viral Load Suppression

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CHAPTER 1: INTRODUCTION

This chapter describes the history and background of community-based antiretroviral therapy (ART) adherence clubs in the South African context. This section includes a review of literature which expounds on the factors that affect ART adherence amongst PLWHA and fits them in a conceptual framework, highlighting the gaps in published literature. This chapter ends with the rationale of this study and its specific aims and objectives.

1.1 Background

Human immunodeficiency virus (HIV) is a virus that infects individuals, attacks their immune systems, thus making persons living with HIV/AIDS (PLWHA) susceptible to opportunistic infections (1). A total of 36 million people are infected with HIV globally and 7.6 million of these live in South Africa (SA), which has the world's largest HIV prevalence (2). Whilst antiretroviral (ARV) drugs slow the progression of HIV, they are not a cure for HIV and must be taken by PLWHA as a lifelong treatment (1).

The treatment cascade for HIV is dependent on positive testing, linkage to care, initiation to antiretroviral therapy (ART) and viral load suppression (VLS) to be successful. However, the HIV epidemic in SA was largely exacerbated by SA's late introduction of ARVs in the public sector (3) as ART only became available for free in the public sector in 2004 (4). At this time, only PLWHA with low cluster of differentiation type 4 (CD4) counts were initiated on ART. Subsequent changes to HIV guidelines resulted in the

scaling up of initiation to include more PLWHA on ART, including PLWHA with low viral loads and high CD4 cell counts (4,5). These changes improved the health outcomes of PLWHA and reduced viral transmission (6). By 2013, SA had the world's largest ART programme (7).

However, despite improvements in ART initiation, HIV eradication has been impeded by low ART adherence as retention in care decreased when ART initiation was scaled up (8). Retention in care refers to regular healthcare facility participation whilst medication adherence refers to the regular and continued uptake of ART as prescribed (8,9). For sustained VLS, it is vital that PLWHA take ART as a lifelong treatment, with adherence rates of 95% or higher i.e. PLWHA should be both retained in care, and adherent to ART (10).

Low retention in care results from the competing pressures the healthcare system faces with the need to initiate more PLWHA onto ART whilst maintaining those already in care (4). Low levels of retention consequently have grave consequences for PLWHA including increased morbidity, mortality, antiretroviral resistance and viral transmission (11).

1.1.2 Differentiated models of care and adherence club

To improve retention in care while initiating high volumes of newly eligible patients on ART, several differentiated models of care (MOCs) are being implemented in low to middle-income countries (LMICs) (12,13). In such MOCs, ART distribution is decentralised by shifting patients from hospitals to primary health clinics and community-based locations while shifting patient care from doctors to nurses and lay community health workers (CHWs) (8,13). Clinically stable patients are down-referred to

decentralised MOCs, thus reducing patient loads on clinics and allowing the prioritisation of critical patients by clinicians (14,15).

The community-based ART adherence club, affiliated with healthcare facilities but based in communal locations, is a differentiated MOC aimed at improving ART adherence among PLWHA (8). Adherence clubs are conducted in the form of meetings, which take place at two to three-month intervals. Each meeting consists of two activities: (i) medication distribution; and (ii) 'health talks' related to ART. CHWs distribute ART at meetings and facilitate the health talks, whilst pharmacists pre-pack medications before club meetings. Adherence club members are required to have their viral loads and CD4 counts measured every 6 months (14).

To be eligible for adherence clubs, PLWHA must be above the age of 18 years and clinically stable i.e. they must have been (i) on the same ART regimen for 18 months, (ii) have a high CD4 count, (iii) have an undetectable viral load, and (iv) have reasonably managed comorbidities (14). Adherence club members can be reverted to regular clinical care if they miss their meetings and fail to collect their medication within five days of the club meeting. Club members experiencing virological rebound or who develop complications with a comorbidity may also be up-referred to regular care, ensuring they receive specialised clinical treatment (8). Luque-Fernandez *et al.* demonstrated that the adherence club model improves ART adherence among HIV infected individuals (14). Based on these findings, adherence clubs have been subsequently implemented in the Cape Town Metropolitan Municipality and then in other SA provinces (16,17). Similar models have been applied in other sub Saharan countries (17–20).

1.2 Literature Review

The studies included in this review mostly highlight PLWHA in regular clinical care. Studies including various MOCs such as adherence clubs, community adherence groups (CAG) and medication adherence clubs (MAC) are also discussed. Community adherence groups involve HIV positive group members collecting ARVs on a rotational basis, while MACs host patients with a variety of chronic illnesses such as HIV, diabetes mellitus and heart disease in the same adherence clubs (8,18,19).

1.2.1 Patient-related factors that affect adherence

Personal factors such as (age, sex and educational attainment) have been associated with ART adherence (21–25). Masa and Chowa, observed that patient-related factors such as age and comorbidities are often interrelated (26).

Age

PLWHA aged less than 30 years old are more likely to disengage from care (27), while older PLWHA exhibit greater levels of adherence (28). Ramlagan *et al.* attributed this difference in adherence behaviour to sharp differences between paediatric and adult care for PLWHA. Adolescents and young adults have to adapt to new health care systems and the lack of dedicated services for this demographic is thought to increase their risk of nonadherence (21). Additionally, Larsen and colleagues observed that young PLWHA experience stigma from health care providers (22) which may result in disengagement from care and, therefore, nonadherence.

Sex and Marital status

In studies where sex has been investigated as a factor affecting ART adherence amongst PLWHA, women have been reported to exhibit better ART adherence than men (25,29,30). Moosa *et al.* have attributed this difference to the fact that men have poor health-seeking behaviour (29), while Stern and colleagues attributed this to men's difficulty in seeking social support (23) as PLWHA with limited social support are at high risk of nonadherence (31,32).

Many researchers have demonstrated that married PLWHA are more likely to adhere to ART than unmarried PLWHA (22,24,33–35). Adeniyi *et al*. hypothesised that this positive relationship results from the social support PLWHA receive from their spouses (24). Thus, although men have poor health-seeking behaviour (29), married men are likely to receive support from their spouses which could increase their likelihood of adhering to ART. Although women find it easier to disclose their status and therefore receive support, this support is not from their spouses who reject them but rather from their family members (36). It is important to note that PLWHA who are members of the adherence clubs also receive social support from CHWs and other club members (20).

Highest educational attainment

Researchers have reported conflicting findings about the relationship between the highest educational attainment and ART adherence amongst PLWHA. Several studies observed that educational attainment is positively associated with ART adherence (21,24,25,36,37). Most researchers found high ART adherence amongst PLWHA who had high educational attainment (21,25,36). Naidoo and Premdutt observed that PLWHA

with higher educational attainment were able to communicate effectively with clinicians, thus improving their treatment literacy (36). This argument may explain the association between educational attainment and ART adherence. However, a few researchers found a negative correlation between ART adherence and educational attainment (24,38,39). Mabunda *et al*. suggested that educational attainment in PLWHA does not always indicate high treatment literacy and, therefore, educated PLWHA with low treatment literacy may become nonadherent (39). However, Adeniyi and colleagues argued that educated PLWHA are more likely to be employed and therefore too busy to prioritise taking their ART (24).

Employment status

In studies where employment is investigated as a determinant of ART adherence amongst PLWHA, there have been mixed findings. Findings from a multi-site cohort study carried out in Uganda and South Africa, and a cross-sectional study carried out in Nigeria demonstrate that employed PLWHA are more likely to adhere to ART. However, PLWHA who have to travel for employment purposes often become nonadherent (23,24). Similarly, Tran and colleagues found that PLWHA with regular employment are more likely to adhere to ART whilst PLWHA who work during unorthodox hours are not (33). This suggests the stability of employment, in terms of both location and employment hours, is a factor to be considered in the reasons for adherence and nonadherence.

1.2.2 HIV Related factors that affect ART adherence

Patient morbidity has been associated with missing clinic appointments (38) which could result in nonadherence. However, some physically fit PLWHA become nonadherent as they see no need to be on ART (40). Patients undergoing co-treatment for other opportunistic infections also have lower adherence (25). Furthermore, Myezwa *et al.*, found that PLWHA who have been HIV positive for a long time face functional challenges, for instance, PLWHA experienced difficulty with moving freely and easily, while others displayed decreased participation in social activities (41). Thus, it is hypothesised that they are less likely to be adherent. However, PLWHA with low CD4 counts (≤350 cells/µL) are more likely to be retained in care than those with higher CD4 counts (40) and PLWHA with high CD4 counts have lower odds of ART adherence (42).

Undernourished PLWHA with a body mass index (BMI) of less than 25 are more susceptible to a progression from HIV to AIDS and are, therefore, at a greater risk of morbidity (43). Sick PLWHA often miss clinic appointments and, therefore, undernourished PLWHA may be susceptible to loss to follow up (LTFU) and, consequently, nonadherence.

1.2.3 Medication-related factors that affect ART adherence

ART regimen

There are different classes of ARVs that inhibit different stages of the HIV replication cycle. Nucleotide reverse transcriptase inhibitors (NtRTIs) such as tenofovir, nucleoside reverse transcriptase inhibitors (NRTIs) such as lamivudine, and non-nucleoside reverse transcriptase inhibitors (NNRTIs) such as efavirenz all prevent transcription of viral RNA.

Protease inhibitors impede HIV viral maturation, thus viral particles are unable to successfully infect new cells (1). It is for these reasons that PLWHA are prescribed a combination of ARVs to reduce their chances of developing resistance to a single drug class (44).

The default first-line treatment for adults living with HIV is currently a combination of tenofovir (TDF), lamivudine (3TC) and efavirenz (EFV). However, TDF has been associated with renal failure and therefore, TDF is replaced with zidovudine (AZT) or abacavir (ABC) where PLWHA have underlying renal comorbidities or are concurrently taking nephrotoxic drugs. EFV causes central nervous system dysfunction in some PLWHA therefore, for PLWHA with psychiatric comorbidities EFV is replaced with nevirapine (NVP) (45).

ART regimen has been reported to affect ART adherence amongst PLWHA. Evidence from a systemic review conducted by Altice *et al.* demonstrated that PLWHA on a single tablet regimen (STR) are more likely to adhere than PLWHA on multi-tablet regimens (MTR) (46). Dworkin and colleagues found similar results for integrase strand transfer inhibitor (INSTI) based ARVs but observed no difference in adherence between PLWHA taking NNRTI STRs and NNRTI MTRs (47). This observation may be due to differences in pill burden as PLWHA with a lower pill burden are more likely to adhere to treatment (48). Furthermore, the type of ARV a patient has been prescribed has been statistically associated with adherence as some regimens are more toxic than others (25), resulting in selective adherence (31) or complete disengagement from treatment (49) when PLWHA experience side effects.

ART duration and treatment fatigue

Numerous studies have examined the relationship between treatment duration and ART adherence. Several researchers observed that ART adherence decreases over time (44,50,51). Treatment fatigue, which has been defined as the “decreased desire and motivation to maintain vigilance adhering to prescribed treatment regimens” (52) has been observed as a barrier to ART adherence in several studies (24,53–55). Further, Phillips *et al*. observed that PLWHA experience greater side effects to ART over time (56), which may contribute to increasing nonadherence to ART. However, a retrospective cohort study carried out in Durban demonstrated that PLWHA become more adherent to ART over time (57). Similarly, evidence from a systematic review suggests that PLWHA who default on treatment are likely to become increasingly nonadherent over time while PLWHA who receive adequate adherence counselling are likely to become more adherent to ART over time (58).

1.2.4 Healthcare related factors that affect ART adherence

Despite the benefits of adherence clubs, some ART adherence club members feel that adherence clubs are less accessible than regular care (20). Additionally, retention in care within clubs also decreases as clubs mature. This is because as the club evolves facilitators focus only on medicine distribution and neglect health education and peer support (59,60). This is often the case when club numbers increase and CHWs become overwhelmed by their responsibilities (61).

In summary, the reviewed literature demonstrates that ART adherence has diverse determinants including sociodemographic, health status/clinical, and psychosocial factors. However, evidence for these determinants has been obtained from studying PLWHA in both regular care and differentiated MOCs. Additionally, findings from a wide range of study settings and designs informed the review above. Therefore, there remains a need to specifically investigate ART determinants, and quantify their interrelationships in an adherence club setting.

1.3. Conceptual Framework

The ART adherence determinants under consideration can be fitted into a Holistic Conceptual Framework for medication adherence originally designed for diabetic patients. Jaam *et al*., highlighted that medication adherence amongst chronically ill individuals is dependent on six types of factors: medication, healthcare system, patient, disease, healthcare provider and societal related factors (62). The Holistic Conceptual Framework is shown in Figure 1.1 below.

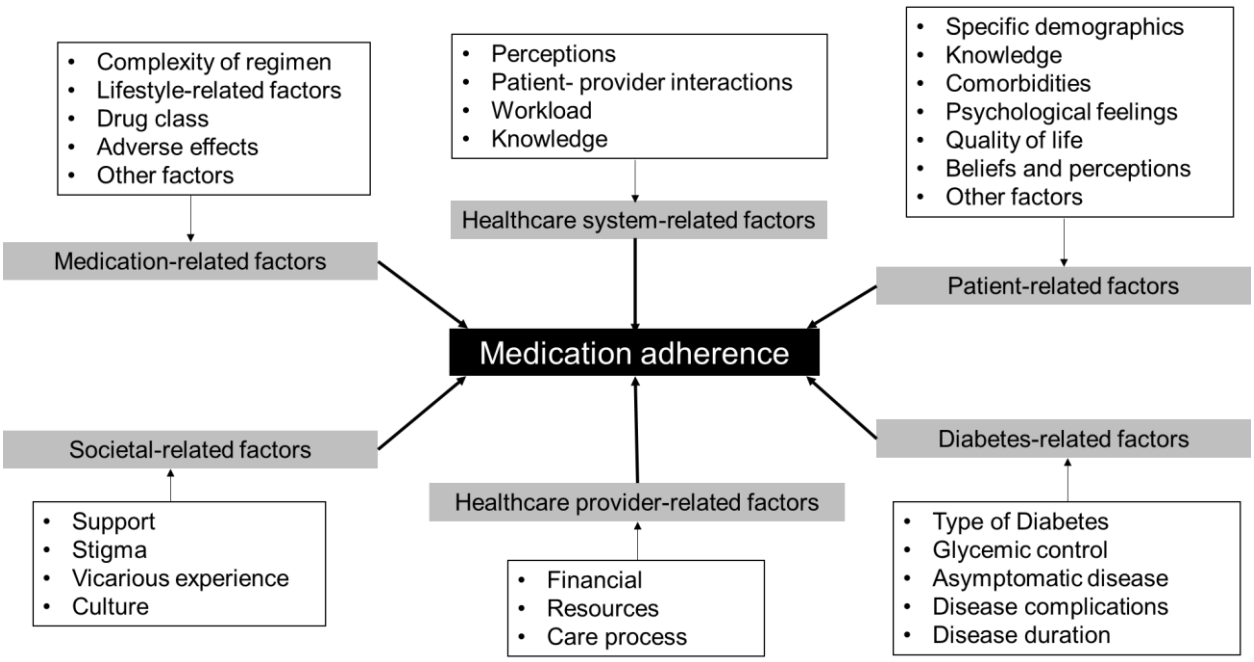

Figure 1.1: Adaption of medication adherence model by Jaam *et al.*(62)

However, this study involved secondary data analysis. Thus, while many of the variables included in the initial Holistic Framework are important, they were not captured during data collection. Therefore, the framework adopted for this study only includes HIV/AIDS, medication, and patient-related factors as these were the only variables available in the dataset in these three categories (Figure 1.2).

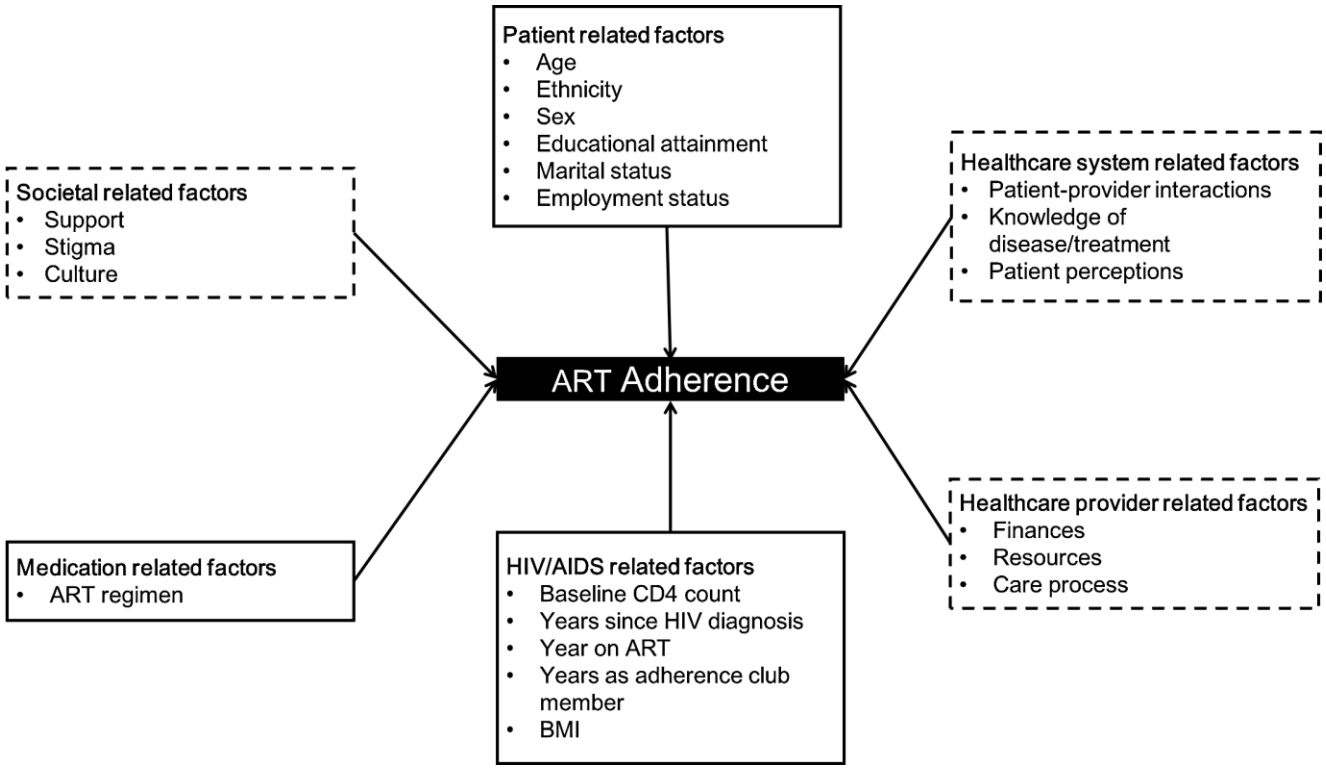

Figure 1.2: Conceptual framework of factors associated with ART adherence adapted from the holistic adherence model by Jaam *et al.* (62).

ART adherence can be affected by patient, medication, or HIV/AIDS-related factors (solid lines). Healthcare, health system and societal factors (broken lines) can also influence ART adherence, as stated in the Holistic Conceptual Framework (62). However, insufficient data was collected on stigma and treatment literacy and no data was collected for the rest of these factors.

Despite the paucity in variables analysed in this study compared to the Holistic Conceptual Framework, the variables in the current framework still address the objectives of this study as sociodemographic factors (age, sex, ethnicity, marital status, employment status and educational attainment) are included under patient-related factors. Additionally, HIV/AIDS, medication and patient-related factors can all potentially influence

adherence and, in some cases, be interrelated thus the current framework can be used to determine the factors affecting ART adherence among PLWHA and quantify any interrelationships between them (62).

1.4 Problem Statement

Despite the abundance of studies reporting the success of adherence clubs in improving VLS and retention in care (14,15,17,50,63), few studies have investigated factors influencing ART adherence within adherence clubs. Furthermore, recent studies have demonstrated suboptimal conditions in some adherence clubs. Thus, the adherence club model still has room for improvement (20,60). Gauteng's metropolitan municipalities have higher HIV prevalence than Cape Town's metropolitan municipalities. Ekurhuleni Municipality in Gauteng has the second-highest metropolitan municipal HIV prevalence in South Africa (7), providing a good opportunity to study the barriers and facilitators of ART adherence.

1.5 Justification

The consequences of poor ART adherence amongst PLWHA include increased mortality, morbidity, viral transmission and drug resistance, all of which exert a burden on the healthcare system (64). It is, therefore, crucial to determine factors that affect ART adherence in the adherence club setting to maintain optimal levels of ART adherence amongst adherence club members. Findings from this investigation will be used to improve future implementation of the adherence club model in Ekurhuleni Municipality and similar settings.

1.6 Research Question

What factors affected adherence to ART treatment among clinically stable HIV-positive patients who attend adherence clubs in Ekurhuleni Municipality in Gauteng, South Africa in 2016?

1.7 Aim

The purpose of this study was to determine factors affecting adherence to ART treatment among clinically stable HIV positive individuals attending ART adherence clubs in Ekurhuleni District in Gauteng, South Africa in February 2016.

1.8 Objectives

1. To describe the socio-demographic characteristics and levels of adherence of HIV-positive individuals attending adherence clubs based in Ekurhuleni.
2. To determine the factors that affect ART adherence among HIV-positive individuals attending adherence clubs based in Ekurhuleni.
3. To quantify interrelationships among factors significantly associated with ART adherence among HIV-positive individuals attending adherence clubs based in Ekurhuleni.

CHAPTER 2: METHODOLOGY

This chapter details the methodology used in this study. The chapter describes the cross-sectional design of the study, the setting of adherence clubs in Ekurhuleni and the population of HIV-positive club members studied. Additionally, the collection, management, and statistical analysis of the data used to determine factors associated with ART adherence are described in detail.

2.1 Study design

This was a cross sectional study using secondary data collected in February 2016.

2.2 Primary Study

The primary study was entitled, “Factors influencing health outcomes among adherence club members in Ekurhuleni district, South Africa” and conducted amongst adherence club members in Ekurhuleni Metropolitan Municipality. The participants were sampled from a population of PLWHA registered as members of adherence clubs affiliated with Community AIDS Response (CARe), a local nongovernmental organisation, in April 2015 (the organisation, ‘CARe’, ceased to exist towards the end of 2017). Data collection was carried out by trained research assistants, using a paper-based questionnaire administered in English.

2.3 Study Setting

The study site comprised 16 adherence clubs hosted in clinics within the City of Ekurhuleni. Ekurhuleni Metropolitan Municipality is one of the five health districts in

Gauteng Province and is composed of six sub-districts (65). The population of Ekurhuleni has a high HIV prevalence: in 2016, 12.4% of Gauteng's population was HIV positive and 14.3% of people in Ekurhuleni Metropolitan Municipality were HIV positive (7,66).

Adherence clubs were run at clinics with high volumes of patients on ART and each clinic had a designated room for adherence club members to meet. Each adherence club had a maximum of 40 members and was conducted in the morning to allow club members who were employed to go to work after adherence club sessions. These members collected their ARVs and then attended adherence counselling session. The topics discussed during counselling sessions were organised by the club members themselves. The adherence clubs in this study had been operating for more than a year at the time that data used in this study were collected.

2.4 Study population

The study population is composed of clinically stable HIV-positive adults, above 18 years of age, who were members of ART adherence clubs in Ekurhuleni Health District in February 2016. No adherence club members left or joined adherence clubs between April 2015 and February 2016 as club facilitators prioritised retention in care.

2.5 Sampling and sample size

All 730 patient records from the primary study were used in these analyses. The power of the study to detect differences in the proportion of at least 10% between groups was 97% for variables that had no missing observations and 92% when considering all missing

observations dropped from the multivariable and structural equation models. Power was calculated at an alpha level of 0.05 using STATA 15 (67).

2.6 Data collection

One questionnaire was used to collect data and the data collected were obtained from the investigator of the primary study and accessed in STATA 15 (67).

2.7 Data Management

Data management and analyses were carried out in STATA 15 (67). The dataset was checked for outliers and missing data before analyses were carried out. Some variables (recent CD4 count and income) had more than 30 % missing data. Little's test was used to determine whether data was missing at random. As the data were not missing completely at random, multiple imputation could not be used (68), and the data were not used in further analysis.

Variable definitions:

Outcome variable

The outcome variable for this study was self-reported ART adherence. ART adherence was originally measured using four items (e.g., adherence clubs make me take my medication at the right time) on a 5-point Likert scale (1= strongly disagree, 2=disagree, 3=neutral, 4=agree, 5=strongly agree).

The dichotomous outcome variable, "adherence" (0 =nonadherent; 1 = adherent was used for bivariable analyses. The dichotomous score was calculated by taking the mean of four five-point Likert scale questions rated 1 to 5. Values below a cut-off of 2.5 were designated 0 (nonadherent) while values of 2.5 or above were designated 1 (adherent).

The ordinal outcome variable “adherence score” was used for regression analysis and GSEM because (i) the initial data had a discrete/ordinal distribution, (ii) ordinal logistic models were better than logistic (binary models, and (iii) GSEM models created using the dichotomous variable failed to converge.

The ordinal “adherence score” was calculated by taking the mean of four five-point Likert scale questions on adherence. Ordinal scores were assigned as follows:

Table 2.2: Adherence scores of HIV positive adherence club members in Ekurhuleni district

Mean adherence value	Adherence score	Definition
0.5 -1.4	1	Highly nonadherent
1.5 - 2.4	2	Nonadherent
2.5 - 3.4	3	Neutral
3.5 - 4.4	4	Adherent
4.4 - 5	5	Highly adherent

The process outlined above is displayed in Figure 2.1 below.

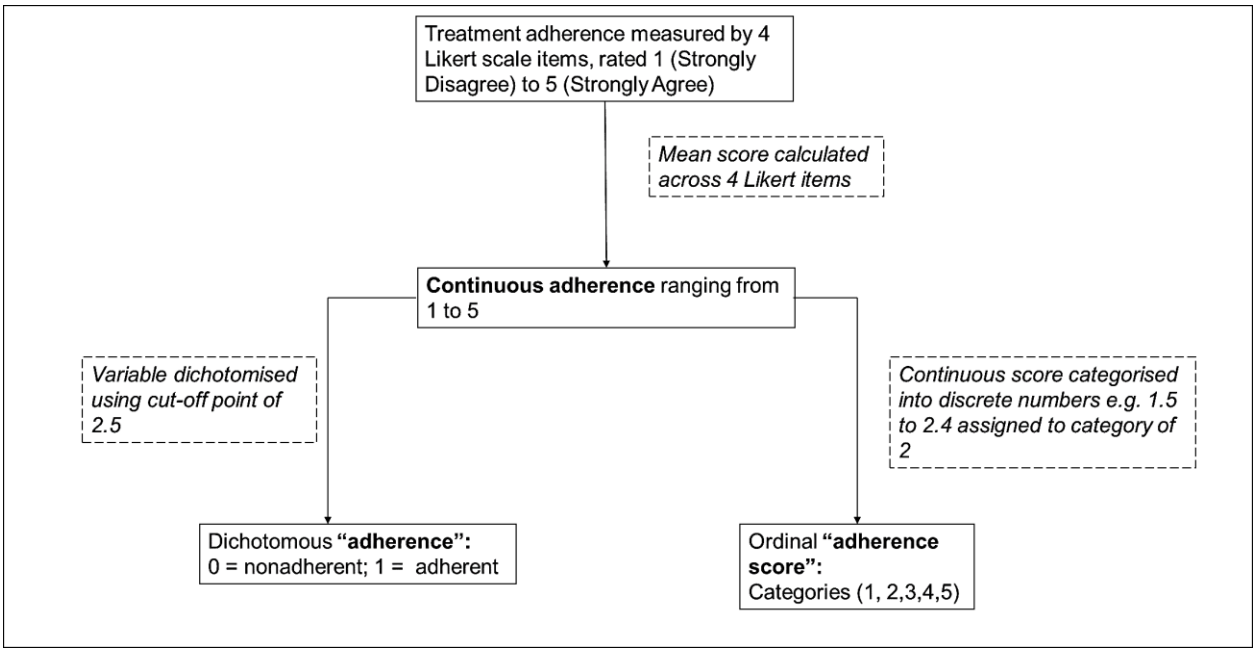

Figure 2.1 Schematic diagram of outcome variable manipulation

Exposure variables

The questionnaire collected data on participants' sociodemographic status and anthropometric measures. Age was defined as a continuous variable measured in years then divided into three categories: 18 – 30, 31 – 50, and >50 years. These categories were based on the existing data in literature that showed that PLWHA under 30 and PLWHA over 50 years old are more likely to disengage from ART than PLWHA between 30 and 50 years of age (27,38), the reasons for these findings have been highlighted in the section under "literature review" (Section 1.2.1, page 4). For this analysis, ethnicity was grouped into two categories, namely African and other (White, Asian, or Coloured) because of small numbers of other ethnic groups. Sex was categorized into male and female, whilst employment status was categorized into employed and unemployed.

Categorical variables with low numbers in some categories were merged into fewer categories. Highest education attained was merged from five categories (below grade 12, grade 12, certificate, diploma, and degree) to three (below grade 12, grade 12 and above grade 12). Marital status was merged from five categories (single, married, cohabiting, divorced and widowed) to three (single, married or cohabiting, and divorced or widowed). Participant height and weight were recorded during interviews and used to calculate BMI. BMI was categorised into three groups, namely underweight (<18.5), normal (18.5 – 24.9) and overweight and obese (>25.0).

Information on health status was also measured. The questionnaire collected the dates the participants tested positive for HIV, joined the adherence clubs, and started ART. Time since diagnosis, years on ART, and duration of adherence club membership were calculated by subtracting date tested HIV positive, date started ART and date started

clubs from the 29th of February 2016, when data collection was completed. Years since HIV diagnosis, years on ART and duration of adherence club membership were all measured in years.

Participants gave their baseline CD4 count from their adherence club records. Baseline CD4 count was measured in cells/µl and analysed as log CD4 count to correct for positive skewing inherent in CD4 counts as a continuous variable. Comorbidities were categorised into two groups: no comorbidities and comorbidities present (diabetes mellitus, cancer, obesity, heart disease or respiratory disease).

The daily ART pill count was a categorical variable of pills ranging from one to three tablets. Individual ART regimens were not recorded at the time of data collection. However, this study took place during a transition from combination ART (cART) to fixed-dose combinations (FDC) and the national ART guidelines were used to infer participant ART regimen based on daily pill count. Participants on cART took their ARVs as three separate tablets a day, while participants on a single tablet FDC took a single tablet containing TDF, 3TC and EFV daily. However, PLWHA with contraindications were prescribed one two-drug combination pill (3TC plus AZT, TDF or ABC) supplemented with one tablet of EFV or NVP. Patients on second-line treatment had similar drug combinations except EFV was replaced with lopinavir/ritonavir LPV/r and in some cases, 3TC was replaced with emtricitabine (FTC) (45,69) (Appendix 1).

2.8 Statistical Analysis

Descriptive Analysis

Descriptive analysis was carried out by displaying frequency distributions of categorical variables (age, sex, marital status, employment status, comorbidities, race, BMI, highest education, and ART regimen). Continuous variables were tested for normality and equal standard deviations using the normal probability plots, skewness kurtosis tests and variance ratio tests. The mean and standard deviation of log CD4 baseline are presented as log CD4 baseline followed a normal distribution. Age, years on ART, years since HIV diagnosis and duration of adherence club membership did not exhibit normal distributions, thus their medians and interquartile ranges were calculated.

Inferential statistics

Bivariable analysis was carried out using the Chi-squared (χ^2) test of independence for categorical variables (age, sex, marital status, employment status and comorbidities). Where variables had low observed frequencies in each cell of a two by two contingency table (≤5), the Fisher's exact test was used (race, BMI, highest education, and ART regimen). The Student's T-test was employed where data had an underlying normal distribution (log CD4 baseline); otherwise, a Wilcoxon rank-sum test was used (years on ART, years since HIV diagnosis and duration of adherence club membership). Variables with $p \leq 0.1$ were considered significant in bivariable analyses.

Since the outcome variable used in bivariable analyses (adherence) was different from the outcome variable used in regression (adherence score), all exposure variables

investigated in bivariable analysis were also investigated in regression analysis regardless of the p-value observed in bivariable analyses. Initially, the dichotomous outcome variable, adherence, was used as an outcome variable in logistic regression (Appendix 2). However, converting an outcome variable to a dichotomous measure may have resulted in loss of information (70), thus the continuous adherence variable was used as a continuous outcome measure in linear regression. However, the standardised residuals obtained did not satisfy the conditions of linear regression (residuals displayed heteroscedasticity) (71) therefore, the ordinal outcome variable, adherence level was used as an outcome variable as it reflects the initial ordinal nature of the variable.

Univariable ordinal regression analysis was used to determine relationships between individual exposure variables and ART adherence. Variables that were significant in univariable analyses with $p \leq 0.1$ were included in a multivariable model using ordinal regression. The stepwise backwards elimination was used to select variables that gave a parsimonious multivariable model. Variables with $p < 0.05$ were significant**.** The cut-off of $p \leq 0.1$ was employed in univariable analysis to assess variables associated with ART adherence at a 10% significance level for variable selection to be included in the multivariable analysis, while a p-value ≤ 0.05 was used for multivariable analyses to assess variables associated with ART adherence at a 5% significance level as it is an accepted standard (72). Collinearity between years on ART and duration of adherence club membership was investigated by examining the correlation coefficient between the two terms and the variance inflation factors.

Age and then sex were added to the final model and the Wald test, and the Likelihood Ratios test were used to determine whether they improved the model fit. Likelihood ratios were used to determine whether interaction terms between sex and the factors retained improved the model fit. Sex was also added to individual univariable models and the percentage change in odds ratios was used to identify confounding.

Structural equation modelling

Significant exposure variables were fitted to a geometric structural equation model (GSEM) model, with adherence score as the ordinal outcome variable with a logit link function. Structural equation modelling was used to test mediatory relationships hypothesised *a priori*. Relationships between age and comorbidity and ART regimen and comorbidity were hypothesised from previous findings (26). Since duration of ART has been associated with comorbidities and ART regimen (58), duration of adherence club membership and age were hypothesised to affect the relationship between ART adherence and these variables as duration of ART, duration of adherence club membership and age are all variables that have displayed temporality. The variable: case ratio of the model was 1:144, and overall case number was above 200. Therefore the sample size was sufficient to run a stable GSEM analysis (73). Model fit indices could not be calculated in the GSEM module.

2.9 Ethical Considerations

This study was approved by the University of Witwatersrand Human Research Ethics Committee (HREC) (Medical) (approval number: M200105) (Appendix 3). Secondary data obtained from CARe were anonymised and password protected.

CHAPTER 3: RESULTS

This chapter details the findings of this study. The sociodemographic and clinical characteristics of the study population are described. Factors affecting ART adherence are presented based on results from both univariable and multivariable ordinal logistic regression analyses. Finally, the interrelationships between factors affecting ART adherence obtained from GSEM are shown.

3.1 Description of study participants

Of the 730 adherence club members sampled, all of them participated in the study and none were excluded since adherence club members matched the inclusion criteria for this study.

Table 3.1: Characteristics of HIV positive individuals attending ART adherence clubs in Ekurhuleni district (N=730)

Variable		n (%)*
Age	18 – 30 years	108 (14.8)
	31 – 50 years	558 (76.4)
	>50 years	64 (8.8)
Race	African	712 (97.5)
	Other	18 (2.5)
Sex	Male	305 (41.8)
	Female	425 (58.2)
BMI	Underweight	14 (3.0)
	Normal	365 (77.5)
	Overweight/Obese	92(19.5)
	Missing	259 (35.5)
Marital Status	Single	436 (59.7)
	Married/Cohabiting	255 (34.9)
	Divorced/Widowed	39 (5.3)
Employment Status	Employed	311 (42.6)
	Unemployed	419 (57.4)
Highest Education	Below grade 12	361 (49.5)
	Grade 12	273 (37.4)
	Above grade 12	23 (3.2)
	Missing	73 (10.0)
ART regimen	Single tablet regimen	601 (82.3)
	Double tablet regimen	40 (5.5)
	cART	89 (12.9)
Comorbidity	Yes	79 (10.8)
	No	651 (89.2)

Note: Where totals amount to less than 730, there was missing data; * % calculated as n/N. cART – combination ART.

There were 730 participants in this study. Of these 58.2% (n=425) were females. The median age of the participants was 39 years, with an interquartile range of 20 to 69 years. Most study participants (n=712, 97.5%) were of African descent. Half of the study participants (365) had a normal BMI classification. Over half (57.4%, n=419) of the participants were unemployed and nearly 50% (n=361) of them left school before

completing Grade 12. Ninety-six percent (n=701; CI: 0.94 - 0.97) of the study participants were adherent to ART. The median years since HIV diagnosis of participants was 5.2 years (interquartile range = 3.7 - 6.8 years) and the median time on ART was 3.7 years (interquartile range=2.6 - 5.4). Study participants had a median duration of adherence club membership of 3.4 years (interquartile range = 1.3 - 4.1 years). The mean CD4 count at baseline was 545.6 cells/µl. Eighty-two percent (601) of study participants were on a single tablet ART regimen. Over 10% (n=79) of the participants had comorbidities, with diabetes mellitus (43, 5.9%) being the most common comorbidity (Table 3.1).

3.2 Bivariable analyses

Bivariate analyses were performed to obtain differences in adherence for each factor under investigation and are presented in Table 3.2 below.

Table 3.2: Comparison of sociodemographic and clinical factors with ART adherence of HIV positive individuals attending ART adherence clubs in Ekurhuleni district (N=730)

Factor		Adherent n/N(%)	Nonadherent n/N(%)	Test statistic	P-value
Number		701 (96%)	29 (4.0%)		
Age	18 – 30 years	102 (14.6)	6 (20.7)	χ^2= 4.0	0.135
	31 – 50 years	540 (77.0)	18 (62.1)		
	> 50 years	59 (8.4)	5 (17.2)		
Race	African	684 (97.6)	28 (96.55)		0.522†
	Other	17 (2.4)	1 (3.5)		
Sex	Male	291 (41.5)	14 (48.3)	χ^2= 0.5	0.469
	Female	410 (58.5)	15 (51.7)		
BMI	Underweight	14 (3.1)	0 (0.0)		1.000†
	Normal	355 (77.3)	10 (83.3)		
	Overweight/obese	90 (19.6)	2 (16.7)		
Marital Status	Single	421 (60.1)	15 (51.7)	χ^2= 14.1	0.001*
	Married/cohabiting	247 (35.2)	8 (27.6)		
	Divorced/widowed	33 (4.7)	6 (20.7)		
Employment Status	Employed	307 (43.8)	4 (13.8)	χ^2= 10.3	0.001*
	Unemployed	394 (56.2)	25 (86.2)		
Highest Education	Below grade 12	417 (59.5)	17 (58.6)	χ^2= 11.6	0.016* †
	Grade 12	265 (37.8)	8 (27.6)		
	Above grade 12	19 (2.7)	4 (13.8)		
ART regimen	Single tablet regimen	575 (82.0)	26 (89.7)		0.792†
	Double tablet regimen	39 (5.6)	1 (3.5)		
	cART	87 (12.4)	2 (6.9)		
Comorbidity	Yes	70 (10.0)	9 (31.0)	χ^2=12.8	<0.001*
	No	631 (90.0)	20 (69.0)		

*Variables with p≤0.1 were statistically significant; † p-values with no corresponding test statistic were obtained using Fisher's exact test.

The following variables were significantly associated with ART adherence amongst study participants: marital status (χ^2= 14.1, p = 0.001), employment status (χ^2= 10.3, p= 0.001), highest education (χ^2= 11.6, p=0.016) and presence of comorbidities (χ^2=12.8, p< 0.001) (Table 3.2).

3.3 Factors associated with ART adherence amongst HIV positive individuals attending ART adherence clubs in Ekurhuleni district

Univariable ordinal logistic regression models

Ordinal logistic regression was used to ascertain factors associated with ART adherence. Since bivariable analyses were carried out using a binary outcome variable and univariable analyses were carried out using an ordinal outcome variable, all variables considered in bivariate analyses were included in univariate analyses regardless of significance. Note: the dichotomous outcome variable (adherence) was used for simplicity in bivariable analyses. However, a table constructed using ordinal adherence scores is shown in Appendix 4.

Table 3.3: Factors associated with ART adherence amongst clinically stable, HIV positive individuals attending ART adherence clubs based in Ekurhuleni district (N=730)

Factor	n (%)	OR (95% CI)	P-value
Age			
18 – 30	108 (14.8)	1	
31 – 50	558 (76.4)	1.4 (0.9 - 2.1)	0.150
> 50	64 (8.8)	0.8 (0.4 -1.5)	0.460
Sex			
Male	305 (41.8)	1	
Female	425 (58.2)	1.4 (1.0 -1.9)	0.036
Marital Status			
Single	436 (59.7)	1	
Married/cohabiting	255 (34.9)	0.7 (0.5 - 0.9)	0.008
Divorced/widowed	39 (5.3)	0.8 (0.4 - 1.7)	0.601
Employment Status			
Employed	311 (42.6)	1	
Unemployed	419 (57.4)	0.8 (0.6 -1.1)	0.112
Highest Education			
Below grade 12	361 (49.5)	1	
Grade 12	273 (37.4)	1.2 (0.9 - 1.6)	0.304
Above grade 12	23 (3.2)	0.9 (0.4 - 2.3)	0.894
ART regimen			
Single tablet regimen	601 (82.3)	1	
Double tablet regimen	40 (5.5)	1.2 (0.6 - 2.3)	0.592
cART	89 (12.9)	1.8 (1.1 - 2.9)	0.022
Comorbidity			
No	651 (89.2)	1	
Yes	79 (10.8)	0.5 (0.3 - 0.8)	0.005

In the univariable analyses, the odds of reporting high levels of adherence among female participants were 1.4 times those of male participants (OR: 1.4, 95% CI: 1.0 - 1.9, p=0.036). The odds of reporting high levels of adherence among married and cohabiting participants were 0.7 times those of single participants (OR: 0.7, 95% CI: 0.5 - 0.9, p=

0.008). The odds of reporting high levels of adherence among participants on cART were 1.8 times those on a single tablet regimen (OR: 1.8, 95% CI: 1.1 - 2.9; p = 0.022). The odds of high adherence among participants who had comorbidities was 0.5 times those who had no comorbidities (OR: 0.5; 95% CI: 0.3 - 0.8, p=0.005) (Table 3.3).

Multivariable ordinal logistic regression model

The backward elimination approach of the stepwise regression technique was applied to variables that were found significant ($p \leq 0.1$) in univariable analyses. Age, ART regimen, presence of comorbidity, years on ART and duration of adherence club membership were retained in the model. For multivariable analysis, variables with $p<0.05$ were considered significant. These included daily ART pill count, presence of comorbidity, years on ART and time since HIV diagnosis. Despite being marginally significant, age was retained in the model as it improved the model fit (Likelihood ratio (LR) = 7.32, p = 0.026).

Despite being significant in univariable analysis, years on ART was removed from the final multivariable model as it displayed collinearity with the duration of adherence club membership (variance inflation factor (VIF): 16.76; correlation coefficient: 0.9696). The direction and magnitude of years on ART changed when the duration of adherence club duration was added to the model from (OR: 0.9, 95 CI: 0.9 – 1.0, p =0.013) to (aOR: 2.6, 95% CI: 1.8 - 3.7, p<0.001).

Due to its frequent inclusion in adherence models, sex was investigated as an effect modifier or confounder between the factors included in the multivariable model and ART adherence. Interaction terms including sex and each of the factors affecting ART

adherence did not improve the multivariable model. The addition of sex to individual univariable models changed odds ratios by less than 10%, thus ruling out confounding. The inclusion of the variable sex did not improve the fit of the multivariable model (Wald p-value = 0.4115). Therefore, sex was not included in the final multivariable logistic regression model.

Table 3.4: Multivariable model of factors associated with ART adherence among individuals attending ART adherence clubs based in Ekurhuleni district (N= 578)

Factor	**n (%)**	**aOR (95%CI)**	**P-value**
Age			
18 – 30	108 (14.8)	*1*	
31 – 50	558 (76.4)	1.6 (1.0 - 2.5)	0.073
> 50	64(8.8)	0.8 (0.4 -1.6)	0.583
ART regimen			
Single tablet regimen	601 (82.3)	1	
Double tablet regimen	40 (5.5)	1.3 (0.6 - 3.0)	0.489
cART	89 (12.9)	1.8 (1.0 - 3.2)	0.033
Comorbidity			
No	651 (89.2)	1	
Yes	79 (10.8)	0.5 (0.3 - 0.8)	0.005

The odds of reporting high levels of adherence among participants with comorbidities were 0.5 times those without comorbidities (aOR: 0.5, 95% CI: 0.3 - 0.8, p = 0.005), and the odds of high ART adherence levels in participants on cART were 1.8 times those on a single tablet regimen (aOR: 1.8, 95% CI: 1.0 - 3.2, p <0.033). The odds of reporting high levels of adherence among participants aged 31 to 50 years were 1.6 times those of participants below 31 years of age, although this association was only marginally significant (aOR: 1.6, 95% CI: 1.0 - 2.5, p-value<0.073) (Table 3.4).

3.3 Structural equation modelling of factors affecting ART adherence amongst individuals attending ART adherence clubs based in Ekurhuleni district

ART regimen, comorbidity, years on ART and duration of club membership remained significant in multivariable analysis. Therefore, interrelationships between these factors were investigated using path GSEM. The model was adjusted for age.

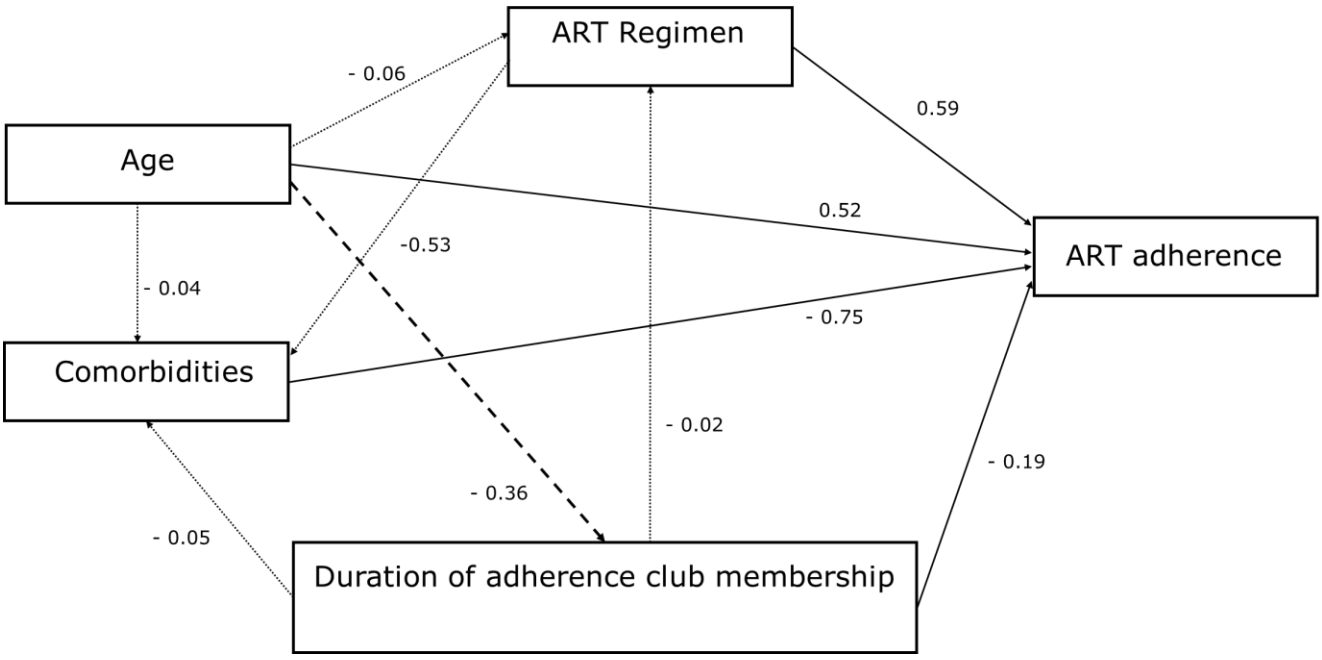

Figure 3.1: Geometric structural equation model of the factors affecting ART adherence amongst adherence club members in Ekurhuleni (n=578). Rectangular shapes represent variables and values represent β coefficients. Full lines represent significant pathways ($p<0.05$). Dashed lines (– – –) represent marginally significant pathways ($p\leq0.1$) and dotted lines (····) represent nonsignificant pathways ($p>0.1$) .

Each additional year of adherence club membership results in decreased ART adherence among study participants (β = - 0.2, 95 CI: -1.5 — -0.8; p< 0.001). Age was significantly associated with ART adherence levels. Participants aged 30 to 50 years reported higher

levels of adherence to ART than those aged 18 to 30 (β = 0.5, 95% CI: 0.1 - 0.9, p=0.008). ART regimen was significantly associated with ART adherence levels. Participants on cART reported higher levels of ART adherence than participants on a single tablet regimen (β = 0.6, 95% CI: 0.0 - 1.1, p=0.034). Comorbidities were significantly associated with ART adherence levels, and participants who had comorbidities reported lower ART adherence levels (β = -0.7, 95% CI: -1.3 - -0.2, p=0.005). The indirect effect of age on ART adherence via years on ART was only marginally significant (β = -0.4, 95 CI: -0.7 - 0.0, p=0.064) (Figure 2) (Appendix 5).

As described in the “Methods section”, several interrelationships (age and comorbidity; age and ART regimen; comorbidities and ART regimen; duration of adherence club membership and comorbidities, and duration of adherence club membership and ART regimen) were hypothesised *a priori*. None of these pathways were found to be significant.

Table 3.5: Path analysis model of factors affecting ART adherence amongst HIV positive individuals attending adherence clubs in Ekurhuleni district (N=578)

Outcome	Factor	β	95 % CI	P-value
Direct effects				
ART adherence	**Age**			
	18 – 30	1		
	31 – 50	0.5	0.1 - 0.9	0.008
	ART regimen			
	Single tablet regimen	1		
	cART	0.6	0.0 - 1.1	0.034
	Comorbidities			
	None	1		
	Yes	-0.7	-1.3 - -0.2	0.005
	Duration of adherence club membership	-0.2	-0.3 - -0.1	<0.001
Indirect effects				
Via duration of adherence club membership	**Age**			
	18 – 30	1		
	31 – 50	-0.4	-0.7 - 0.0	0.064

The total effects of age on ART adherence were 0.6. The rest of the factors only affected ART adherence directly, hence their total effects are equal to their direct effects (Table 3.5).

CHAPTER 4: DISCUSSION

The purpose of this study was to determine factors affecting ART adherence amongst members of ART adherence clubs in Ekurhuleni, Gauteng province. In this chapter, the findings obtained in this study are discussed as we draw lessons from previously published data. The chapter closes with a summary of the limitations faced during the study and recommendations for adherence club programmes and further research.

4.1 Key findings

ART adherence clubs were introduced as a MOC to reduce stigma through peer support and improve ART adherence (50). This study focussed on determining the factors affecting ART adherence amongst HIV positive members of such clubs. Ninety-six percent of the study participants reported that they were adherent to ART. A similar study of HIV positive individuals in regular care observed a lower prevalence of ART adherence (25).

Several crucial findings were obtained in this study: (i) individuals who had been adherence club members for long periods were associated with low levels of adherent behaviour, which was not ideal as adherence clubs were designed to improve a participant adherence (74); (ii) participants taking combination ART were associated with higher levels of adherence to ART than participants on a single tablet regimen which was unexpected as previous research has linked adherence with lower pill burdens (29); and (iii) the presence of comorbidities was associated with decreased odds of reporting high levels of ART adherence.

The association between comorbidities and ART adherence is important as PLWHA with comorbidities may need greater attention from healthcare workers to keep them adherent to ART. The most common comorbidity was diabetes mellitus, which may be a result of ART treatment (75).

Age was marginally associated with ART adherence. Participants aged 31 to 50 years were more likely to report high levels of ART adherence than participants aged 30 years and below. This finding reinforces findings from literature (22,44,76), indicating that younger PLWHA may need more targeted interventions (18,59,77). Marital status, employment and education were significantly associated with ART adherence in bivariate analyses. Although these variables did not remain significant in the multivariable model, they are worth mentioning as they indicate the sociodemographic profile of participants who are more likely to adhere to ART.

The inclusion of sex did not improve the multivariable model although previous studies reported significant differences in adherence behaviour between men and women (29,78). There was no evidence of mediatory pathways between comorbidities, pill count and adherence club membership duration as hypothesised.

The effect of length of adherence club membership on ART adherence

Individuals who had been adherence club members for long periods of time were associated with lower levels of ART adherence than individuals who had been adherence club members for shorter periods of time. This has not been reported before and therefore cannot be compared to previous studies. However, researchers have demonstrated that

the duration of treatment has a negative effect on treatment adherence which has mainly been attributed to treatment fatigue (44,50). A possible reason for this finding is that PLWHA on ART develop diabetes mellitus related comorbidities (75) and peripheral neuropathy (44). Many studies have also shown that ART is associated with the incidence of some chronic illnesses amongst PLWHA, hence individuals who have been taking ART for long periods of time may become nonadherent dues to increasing morbidity or increasing pill burdens (75,79).

Another possible explanation is that as adherence clubs grow, they become increasingly harder to manage. In some cases, this has led to a decrease in efficiency (59), which could result in decreased patient satisfaction and increased nonadherence amongst club members. Where adherence clubs lack the infrastructure to conduct health talks and explain club rules to new members, individuals do not benefit from social support and counselling (60). Furthermore, long term adherence requires motivation over and above treatment literacy (80). Thus, this finding underscores the need for adherence club facilitators to continually reinforce the benefits of ART adherence and the dangers of nonadherence, particularly to individuals who have been adherence club members for longer periods.

The effect of combination ART on ART adherence

About 82.3% of the study participants were on a single tablet regimen, which was much higher than the percentage of PLWHA on FDC previously reported in another Gauteng study (29.2 %) (81). The data revealed that multi pill regimens were associated with high levels of adherence to ART than individuals on single tablet regimens. This finding was

unexpected and inconsistent with previous findings (1). Numerous researchers have demonstrated that complex treatment regimens with high pill burdens result in nonadherence (29), therefore, participants on single tablet regimens were expected to demonstrate higher adherence than individuals on a multi pill regimen. A possible explanation of this result is that individuals on a single tablet regimen experienced positive health outcomes and became nonadherent, believing they were cured. A qualitative study carried out in Limpopo demonstrated that patients experiencing health improvements often abandon ART as they confuse VLS with being cured (82).

The effect of comorbidities on ART adherence

The presence of comorbidities was associated with a decrease in ART adherence levels. This finding is consistent with previous studies (25,83). Only 10.8% of study participants reported having a comorbidity. This was slightly lower than the percentage of participants with comorbidities (18.6%) in a similar study (84). It is worth noting that out of the chronic illnesses investigated, (diabetes mellitus) was the most prevalent comorbidity amongst study participants. ART has been linked with insulin resistance which leads to type 2 diabetes mellitus (75,79,85), therefore, some study participants may have developed diabetes mellitus as a consequence of taking ART. The presence of comorbidities has been associated with nonadherence and this association was attributed to pill fatigue as PLWHA with comorbidities undergo simultaneous treatment for HIV and comorbidities (25). The resulting polypharmacy amongst PLWHA concomitantly taking ART and other medication may result in drug interactions that pose a further threat to ART adherence (38,86). A cross-sectional study carried out in Mexico showed that PLWHA experiencing adverse drug reactions are likely to become nonadherent to ART (87).

The effect of age on ART adherence

HIV positive individuals aged 31 to 50 years had higher odds of reporting high ART adherence levels than HIV positive individuals aged 18 to 30. However, this association was marginally significant in the multivariable model. This finding is consistent with findings from other studies that have associated nonadherence with young age (22,44,59,76,77,88). Larsen and colleagues argued that young adults and adolescents often face discrimination in the healthcare system, this may result in disengagement from care (22). Another study demonstrated that younger adherence club members are intimidated by older club members and are therefore reluctant to participate during adherence club health talks (88). Thus, younger ART club members may not benefit from peer support and counselling. Researchers recommend specialised youth clubs for young adherence club members to address this challenge (20,59).

Mediatory pathways amongst factors affecting ART adherence

There was no evidence of mediatory relationships between the factors affecting ART adherence amongst adherence club members. While no researchers have created the same structural model, this finding is in contrast to the studies that were used to form hypotheses for the structural model (1,75). As these mediatory pathways were hypothesised from studies with different methodologies, it is likely that these relationships may not be significant in a club setting. Further, as some of these pathways are temporal, short club membership durations may have obscured any interrelationships (the median length of club membership was 3.4 years). Further studies may be needed to fully understand this finding.

The effect of sex on ART adherence

Despite previous studies highlighting differences in ART adherence between male and female PLWHA (8,14,21–23), female participants of this study were only marginally more adherent than male participants after adjusting for other variables. In addition, sex did not modify the effect of other factors associated with adherence. Sex did not significantly affect ART adherence amongst study participants and was excluded from the multivariable model as its inclusion did not improve the model fit. Researchers have previously associated high adherence with females, arguing that women generally exhibit better health-seeking behaviour than men (29). Researchers observed similar findings in Western Cape-based adherence clubs and postulated that this finding may be explained by selection bias as men must be clinically stable to be enrolled in adherence clubs and therefore appear to be more adherent than men in regular care (17). However, Mukumbang and colleagues demonstrated that men in differentiated MOCs exhibit better health-seeking behaviour than men in regular care as they receive greater social support in differentiated MOCs such as adherence clubs (89).

The effect of marital status, employment, and education on ART adherence

Marital status, employment and education were significantly associated with ART adherence in bivariate analyses. Single participants were more likely to report high levels of ART adherence than married/cohabiting participants. This finding differs from previous findings as married PLWHAs were shown to have high levels of adherence since they

receive social support from their spouses (24). It is likely that all adherence club members received peer support from other club members. Although these factors did not remain significant during univariable analyses, they provide easily identifiable target groups for intensive adherence counselling.

Participants who attained below grade 12 in high school and were unemployed were associated with high levels of adherence to ART. These results are in agreement with other studies that demonstrated a negative correlation between ART adherence and educational attainment (38,39). Mabunda *et al.* suggested that educational attainment does not always result in treatment literacy and therefore educated PLWHA with low adherence levels may need more health counselling, while employed PLWHA may be too busy to take ART (39).

4.2 Study limitations

This study highlights key factors to consider for improving and maintaining ART adherence among members of adherence clubs. While no mediatory pathways were observed using GSEM, structural equation modelling confirmed the results obtained from regression analysis (90). The use of an ordinal outcome variable in regression analysis yielded better estimates and reflected the nature of the data better than logistic regression (91).

Despite insufficient data being collected on participants' ART regimen (the questionnaire only collected information on the number of ARV tablets currently taken), I was able to infer ART regimens based on National Department of Health guidelines in use in 2015/2016 (45).

A few limitations were encountered while carrying out this study. Adherence clubs in different settings function differently as they generally have access to different resources (16) therefore results cannot be generalised to other ART adherence clubs in other settings. Additionally, adherence clubs are run differently from regular clinical care (92), therefore the findings of this study cannot be generalised to HIV positive individuals receiving regular clinical care. However, knowledge gained from this study can still be used to promote adherence in other clubs or highlight areas of adherence clubs that require constant evaluation.

Information bias presented a major limitation as the data were not complete and several variables (e.g. recent CD4 count) had to be disregarded from the study as their inclusion would have resulted in a smaller sample size, thereby minimising the power to detect meaningful differences in adherence behaviours of participants across categories. Multiple variables (educational attainment, BMI, and race) had to be recoded as some of the original categories had few participants. Thus, it is possible that underlying associations between these factors and ART adherence went undetected. In future, this limitation could be mitigated by using different sampling strategies.

Self-reported measures were used for both the outcome variable (ART adherence) and several exposure variables (comorbidities, income, and employment status). Thus, reporting bias could have occurred if participants reported inaccurate details, which could have resulted in biased results. Future studies can address this by using pill counts or viral loads as a proxy for adherence. Adherence club members who were lost to follow

up or absent in April 2015 were not sampled or included in the study, which could have resulted in selection bias if such club members had different adherence behaviours from club members who were present when participants were sampled. In future, more demographic information should be gathered about club members who were lost to follow up.

4.3 Conclusions

Adherence clubs are a crucial intervention for the decentralisation of ART distribution for PLWHA and also provide vital social support for club members. Findings from this study indicate that HIV positive individuals who had been adherence club members for long periods, individuals who were on single tablet regimens and individuals who had comorbidities were likely to report low levels of adherence to ART. Given the consequences of suboptimal adherence to ART discussed earlier (ART resistance and treatment failure), the findings of this study call for a greater emphasis to be placed on health education and targeted counselling within the adherence club setting to promote improved ART adherence amongst adherence club members who report low levels of treatment adherence.

4.4 Recommendations

There is a need for adherence club facilitators and clinicians to assess treatment fatigue among club members who have been on ART for long periods of time using short screening questionnaires. Facilitators should reinforce adherence counselling for club members experiencing moderate to high treatment fatigue.

In addition, intensive counselling should be provided for individuals who have been adherence club members for a long period of time, club members who are on single tablet regimens, or have comorbidities to ensure that they have the psychosocial skills necessary to remain adherent as findings from this study suggest that these groups of adherence club members were associated with reporting low levels of ART adherence.

ART adherence amongst adherence club members should be improved by placing greater emphasis on health information, education, and communication to ensure all club members have adequate treatment literacy. Further, programme coordinators should ensure that adherence club facilitators are equipped with relevant knowledge and prioritise peer support and health talks to the same degree they prioritise ART distribution.

Adherence club facilitators should have focused counselling sessions with adherence club members who have comorbidities, such as diabetes mellitus. Such discussions should focus on lifestyle modifications that PLWHA can make to manage concurrent illnesses. In addition, adherence club facilitators should equip their club members with strategies for coping with drug interactions that may result from the simultaneous use of multiple drugs.

Clinicians attending to PLWHA on ART should develop simple tools (questionnaires) to regularly assess side effects and adherence motivation among members on FDC treatments. Club facilitators should administer these regularly.

PLWHA who have comorbidities should seek assistance when they experience side effects and high pill burdens.

Training and staff briefings of adherence club facilitators working in adherence clubs should include briefing on recent findings from this, and other studies to ensure that they can best address challenges faced by adherence club members.

There is a need for ART programme directors to create age specific adherence clubs, allowing younger club members such as those 30 years and below to raise specific challenges they experience without fear of being stigmatised.

Given the high adherence scores reported in this study, more clinics, communities, and nongovernmental organisations should consider implementing or expanding adherence clubs to decongest health facilities where ART is distributed.

4.5 Suggestions for future research

This study highlighted a need to understand nonadherence amongst individuals on single tablet regimens within adherence clubs in order to provide the best care for adherence club members. A mixed method study should be carried out to reinforce quantitative information obtained in this study while explaining the unexpected associations (93,94) between multi-pill regimens and high adherence levels by conducting in-depth qualitative interviews with adherence club members and adherence club facilitators.

Future studies should include the collection of complete data on factors such as ART regimen, side effects and HIV status disclosure. Additionally, data on all the variables

included in the Holistic Framework of medication adherence should be collected and analysed to provide a more comprehensive view of ART adherence among adherence club members. These include societal, healthcare system and healthcare provider related factors (26).

There is also a need to understand strategies for helping HIV positive individuals experiencing treatment fatigue. Researchers should design studies aimed at assessing behavioural interventions for nonadherence due to treatment fatigue.

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6.0 Appendices

Appendix 1: ART regimens as per National Department of Health guidelines

Number of ARV tablets taken	Contraindication	Possible ART regimen
1 pill (Single tablet regimen (FDC))	n/a	**(TDF + FTC + EFV)** combination
2 pills (Double tablet regimen (FDC))	EFV	**(TDF + FTC)** combination + NVP
	TDF	**(AZT + 3TC)** combination + EFV
	TDF + EFV	**(AZT + 3TC)** combination + NVP
	TDF + AZT	**(ABC + 3TC)** combination + EFV
	TDF + AZT + EFV	**(ABC + 3TC)** combination + NVP
	Failing TDF based 1st line treatment	**(AZT + 3TC)** combination + LPV/r (2nd line)
3 pills (Combination ART)	n/a	TDF + FTC/3TC + EFV

***** *TDF – Tenofovir, FTC – Emtricitabine EFV – Efavirenz, NVP – Nevirapine, 3TC – Lamivudine, AZT – Zidovudine, ABC – Abacavir, LPV/r – Lopinavir/Ritonavir*

The following groups were given priority switch to FDC first:

- Newly diagnosed PLWHA
- Pregnant women
- PLWHA experiencing adverse reactions to stavudine based ART regimens
- PLWHA with tuberculosis (TB)
- PLWHA with other comorbidities

Hence some participants were on a single tablet TDF + FTC + EFV fixed-dose regimen while others were on a TDF + FTC + EFV multi-pill combination ART regimen.

Appendix 2: Univariable logistic regression analysis of factors associated with ART adherence level of HIV positive individuals attending ART adherence clubs in Ekurhuleni district

Factor		OR (p-value, 95% CI)	aOR (p-value, 95 % CI)
Race	Black	1	1
	Other	0.6959 (0.729, 0.0894-5.146)	0.6591 (0.693, 0.0829 – 5.2402)
Sex	Male	1	1
	Female	1.315 (0.470, 0.6251 -2.766)	1.22901 (0.589, 0.5816 -2.5972)
Marital Status	Single	1	1
	Married & cohabiting	1.100 (0.830, 0.4598 -2.6319)	1.220 (0.6559, 0.5037 – 2.956)
	Divorced & widowed	0.9411 (0.946, 0.1652-5.361)	0.2724 (0.023, 0.0888 – 0.8354)
Employment Status	Employed	1	1
	Unemployed	0.2053 (0.004, 0.0707 - 0.5962)	0.1930 (0.003, 0.0659 - 0.5646)
Age (years)	Mean (sd)	1.045 (0.026, 1.0056 -1.0936)	1.0478 (0.030, 1.004 -1.0930)
Highest Education	Below grade 12	1	1
	Grade 12	1.3504 (0.491, 0.5747 - 3.173)	1.1457 (0.760, 0.4782 -2.745)
	Above grade 12	0.1936 (0.006, 0.0594-0.6316)	0.1860 (0.006, 0.0563 -0.6145)
ART Regimen	Single tablet regimen	1	1
	Double tablet regimen	1.7635 (0.583, 0.2331 - 13.3397)	1.6667; (0.6220, 0.2192-12.6769)
	cART	1.9443 (0.371, 0.4534 - 8.3385)	1.8992 (0.389, 0.4414 - 8.1712)
Comorbidity	Yes	1	1
	No	0.2465 (0.001, 0.1081 -0.5623)	0.6249 (0.002, 0.1150 - 0.6100)
BMI	Underweight	1	1
	Normal	0.7889 (0.762, 0.1699 - 3.6641)	0.7838 (0.757, 0.1671 - 306763)
	Overweight & Obese	2.388 (0.252, 0.5385 - 10.5940)	1*

*The overweight and obese category was omitted from the model hence the absence of a p-value and confidence interval.

Appendix 3: Ethics clearance form

UNIVERSITY OF THE WITWATERSRAND JOHANNESBURG

R14/49 Ms T Ndoro

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200105

NAME: (Principal Investigator)	Ms T Ndoro
DEPARTMENT:	School of Public Health Division of Epidemiology and Biostatistics Medical School University
PROJECT TITLE:	Factors affecting antiretroviral therapy adherence amongst HIV-positive adherence club members in Ekurhuleni, South Africa in 2016
DATE CONSIDERED:	31/01/2020
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Prof P Nyasulu; Drs Z Ndlovu and N Tshuma
APPROVED BY:	CB Penny Dr CB Penny, Chairperson HREC (Medical)
DATE OF APPROVAL:	2020/03/20

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.

I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. I agree to submit a yearly progress report. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **January** and will therefore reports and re-certification will be due early in the month of **January** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

24/03/2020
Date

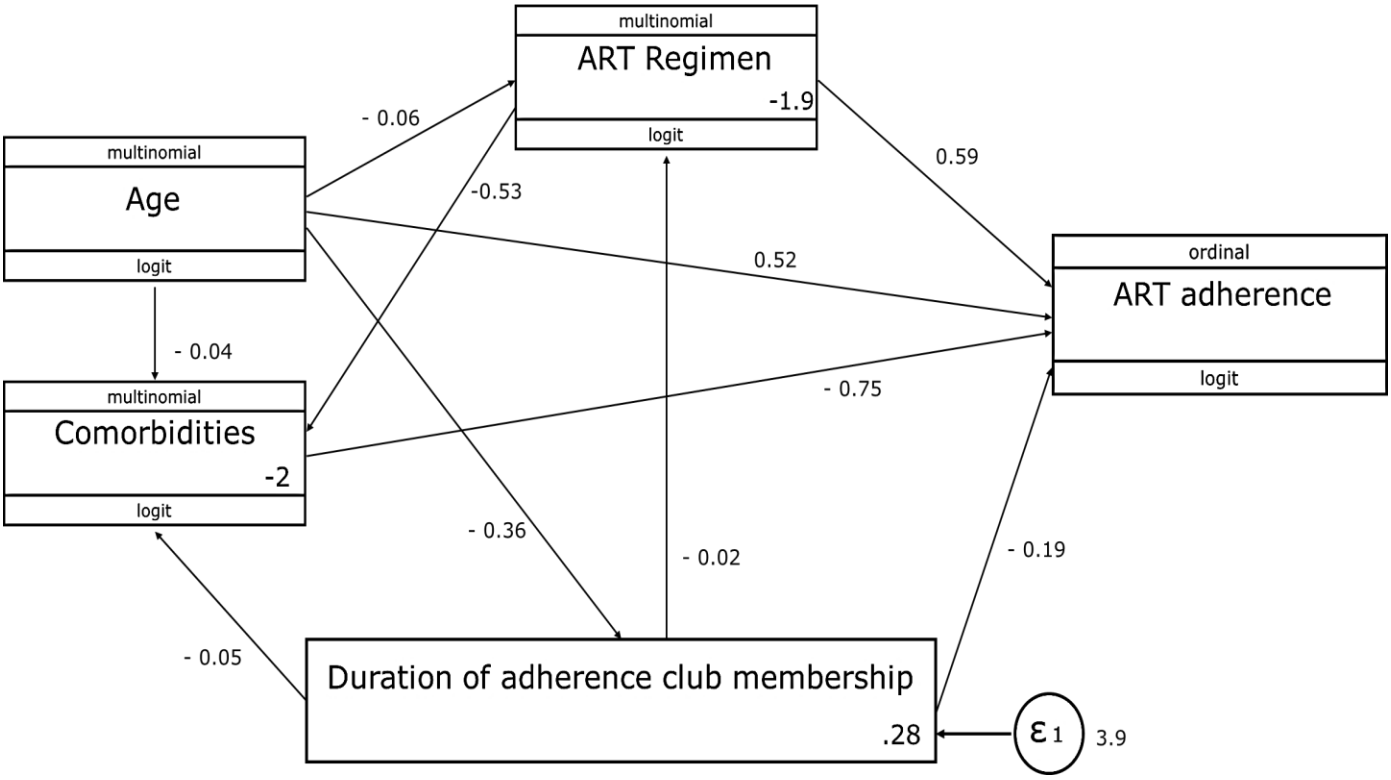
PLEASE QUOTE THE CLEARANCE CERTIFICATE NUMBER IN ALL ENQUIRIES

Appendix 4: Sociodemographic and clinical factors by level of ART adherence among HIV positive individuals attending ART adherence clubs in Ekurhuleni district

Factor		5	4	3	2	1	P-value
Number		446 (61.1)	241 (33.0)	27 (3.7)	14 (1.9)	2 (0.3)	
Age	18 – 30 years	62 (13.9)	35(14.5)	7(25.9)	3 (21.43)	1 (50.0)	0.043
	31 – 50 years	351(78.7)	182 (75.5)	17 (63.0)	7 (50.0)	1 (50.0)	
	> 50 years	33 (7.40)	24 (10.0)	3 (11.1)	4 (28.6)	0 (0.0)	
Race	African	437(98.0)	234 (97.1)	26 (96.3)	14 (100.0)	1 (50.0)	0.075
	Other	9 (2.0)	7 (2.9)	1 (3.7)	0 (0.0)	1 (50.0)	
Sex	Male	174 (39.0)	107 (44.4)	17 (63.0)	5 (35.7)	2 (100.0)	0.036
	Female	272 (61.0)	134 (55.6)	10 (37.0)	9 (64.3)	0 (0.0)	
BMI	Underweight	6 (2.2)	8 (4.7)	0 (0.0)	0 (0.0)	0 (0.0)	0.556
	Normal	211 (75.6)	136 (79.5)	12 (85.7)	5 (83.3)	1 (100.0)	
	Overweight/obese	62 (22.2)	27 (57.8)	2 (14.3)	1 (16.7)	0 (0.0)	
Marital Status	Single	282 (63.2)	134 (55.6)	11 (40.7)	9 (64.3)	0(0.0)	<0.001
	Married/cohabiting	138 (30.9)	102 (42.3)	12 (44.4)	2 (14.3)	1(50.0)	
	Divorced/widowed	26 (5.8)	5 (2.1)	4 (14.81)	3 (21.4)	1 (50.0)	
Employment Status	Employed	198 (44.4)	102 (42.3)	10 (37.0)	1 (7.1)	0 (0.0)	0.031
	Unemployed	248 (55.6)	139 (57.7)	17 (63.0)	13(92.9)	2 (100.0)	
Highest Education	Below grade 12	259 (58.10)	148 (61.4)	18 (66.7)	9 (64.3)	0 (0.0)	0.002
	Grade 12	172 (38.6)	90 (37.3)	6 (22.2)	5 (35.7)	0 (0.0)	
	Above grade 12	15 (3.36)	3 (1.2)	3 (11.1)	0 (0.0)	2 (100.0)	
ART regimen	Single tablet regimen	357 (80.2)	205 (85.1)	25 (92.6)	12 (85.7)	2 (100.0)	0.526
	Double tablet regimen	25 (5.6)	14 (5.81)	0 (0.0)	1 (7.1)	0 (0.0)	
	cART	63 (14.2)	22 (9.1)	2 (7.4)	1 (7.14)	0 (0.0)	
Comorbidity	Yes	0 (0.0)	4 (28.6)	8 (29.6)	28 (11.6)	39 (8.7)	0.004
	No	2 (100.0)	10 (71.4)	19 (70.4)	213 (88.4)	407 (91.3)	

*Where 1= highly nonadherent; 2 = nonadherent ; 3 = neutral; 4 = adherent; 5 = highly adherent.

Appendix 5: Full geometric structural equation model of the factors affecting ART adherence amongst adherence club members in Ekurhuleni including error terms and link functions.[1]



[1]Rectangles represent variables and circles represent error terms. Age, ART regimen and comorbidities were categorical variables and linked with logit functions to allow measurement of intermediary relationships.