Profile of South African HIV/AIDS patients in a medical scheme environment

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Dissertation submitted in fulfilment of the requirement for the degree Master of M Pharm in Pharmacy Practice at the North-West University

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Examination: March 2021

ACKNOWLEDGEMENTS

I want to extend my gratitude to Prof MS Lubbe for her endless patience, advice and efforts to complete this dissertation. She has been a great influencer and motivator during this time. Prof JR Burger has helped me grow as a writer and helped me develop critical thinking skills with lifelong value. Mrs A Naudé, thank you for your motivation and kind words when I needed it. Without these three supervisors, this dissertation would not have been a reality.

To Mrs Engela Oosthuizen, for assisting me with the technical editing of this dissertation. You always went above and beyond to help in any possible way. It was a privilege to work with you and a blessing to have your support and friendship.

I would like to extend my appreciation to Ms Helena Hoffman, for reference support, and both Mrs Elzet Blaauw and Mrs Elize Berman for language editing.

I am thankful to the pharmaceutical benefit management company for making the data available for this study.

I want to extend my gratitude to the North-West University, the National Research Foundation and the Water Research Commission for their financial support.

Brian and Ian Erasmus, my husband and son, stood by my side day and night to make this dream a reality. Your prayers, love and patience will always be cherished. All this would not have been possible without the motivation and encouragement from my family.

Matthew 6:33 says, “Seek ye first the kingdom of God and all these things shall be added unto you.” I am grateful that this verse has guided me through times when I felt discouraged. Jesus gave me direction and the faith to continue regardless of the hurdles I came across. Lord Jesus, I lift Your Name up high and give thanks to You always. Amen.

PREFACE

This dissertation, *Profile of South African HIV/AIDS patients in a medical scheme environment,* was written in an article format. The dissertation has four chapters outlined as follows:

- Chapter 1 introduces the methodology that was used to conduct this research. The background information, problem statement, research aims and objectives of the empirical investigation are stated in Chapter 1.

- The literature research in Chapter 2 was written to provide a comprehensive overview of the literature objectives.

- Two manuscripts were written for submission to the *Southern African Journal of HIV Medicine* and the *Journal of Clinical Pharmacology and Therapeutics*. The two manuscripts, presented in Chapter 3, contain results and discussions to answer the empirical objectives. They were written following each journal's author guidelines, and the reference lists of each manuscript were written according to the specified guidelines of each journal.

- Chapter 4 provides conclusions and recommendations for future studies

- The dissertation's references are listed at the end of this dissertation according to the Harvard referencing style guidelines of the North-West University.

The study supervisor and co-supervisors of this dissertation are referred to as co-authors in the manuscripts. Their contributions and permission to use the articles as part of the dissertation form part of this dissertation.

AUTHORS' CONTRIBUTIONS TO MANUSCRIPT 1

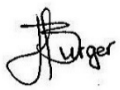
The contributions of each author of manuscript 1, "*Medicine claims profile of patients infected with HIV in the private healthcare environment of South Africa*", are listed below.

Author	**Role in this study**
Mrs T Erasmus	Planning, designing and implementation Writing dissertation and manuscript Data interpretation and statistical analysis
Prof MS Lubbe (Supervisor)	Supervision of manuscripts and concept of study Data and statistical analysis Study guidance and interpretation of results Revise and approve the manuscript and dissertation
Prof JR Burger	Co-supervision of study and manuscript Guidance on study and interpretation of results Revision and approval of the final manuscript version
Mrs A Naude	Co-supervision of study and manuscript Guidance on study and interpretation of results Revision and approval of the final manuscript version

This statement confirms the co-authors' role in this manuscript and permits that the manuscript may form part of this dissertation.

I hereby declare that I permit the above-mentioned manuscript to be published as part of the MPharm study of Mrs Tiffany Erasmus, and the representation of my contributions above is true.







Prof MS Lubbe **Prof JR Burger** **Mrs A Naude**

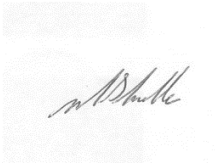
AUTHORS' CONTRIBUTIONS TO MANUSCRIPT 2

The contributions of each author of manuscript 2, "*Clinical profile of patients infected with HIV in the private healthcare sector of South Africa"*, are listed below.

Author	**Role in this study**
Mrs T Erasmus	Planning, designing and implementation Writing dissertation and manuscript Data interpretation and statistical analysis
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Prof JR Burger	Co-supervision of study and manuscript Guidance on study and interpretation of results Revision and approval of the final manuscript version
Mrs A Naude	Co-supervision of study and manuscript Guidance on study and interpretation of results Revision and approval of the final manuscript version

This statement confirms the co-authors' role in this manuscript and permits the manuscript to form part of this dissertation.

I hereby declare that I permit the above-mentioned manuscript to be published as part of the MPharm study of Mrs Tiffany Erasmus, and the representation of my contributions above is true.





Prof MS Lubbe	**Prof JR Burger**	**Mrs A Naude**

ABSTRACT

Title: Profile of South African HIV/AIDS patients in a medical scheme environment

Keywords: prevalence, HIV/AIDS, private healthcare sector, South Africa, antiretroviral treatment, co-existing chronic disease list (CDL) conditions

This study aimed to determine the demographic, clinical and medicine claims profile of people living with HIV/AIDS (PLWHA) in the private healthcare sector of South Africa using medicine claims data from 2016 obtained from a pharmaceutical benefit management (PBM) company. The demographic profile includes patients' demography, such as age, gender, geographic location, type of antiretroviral treatment (ART) prescriber and provider. The clinical profile includes the prevalence of co-existing chronic disease list (CDL) conditions and antiretroviral (ARV) prescribing patterns. The medicine claims profile focuses on the active ingredients of ARV medication prescribed, the type of medicine benefit claimed, the number of ARV prescriptions and medicine items claimed.

The study followed a cross-sectional study design using retrospective medicine claims data from 1 January 2016 to 31 December 2016 obtained from a PBM company. The study population included all PLWHA (N = 16 763) on the database with an International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnosis-code for HIV (diagnoses codes B20-B24) in conjunction with a claim for ARV medication.

The demographic and medicine claims profile were addressed in the **first manuscript**. The study population consisted of 8 871 female PLWHA (52.3%) and 7 992 male PLWHA (47.7%) with an average age of 42.3 years (SD 11.5; 95% CI 41.9–42.3). Female PLWHA were younger [40.21 years (SD 10.9; 95% CI 39.9–40.4)] than male PLWHA [44.3 years (SD 11.9; 95% CI 44.0–44.5)] (p < 0.0001; Cohen's d = 0.3). The highest prevalence rate (78 per 1 000) was in the age group ≥ 45 and < 65 years. The highest prevalence of PLWHA resided in the North West province (36.8 per 1 000 beneficiaries), followed by the Free State (29.7 per 1 000 medical scheme beneficiaries).

PLWHA received an average of 10.9 (SD 7.6; 95% CI 10.8–11.0) ART regimens (N = 175 317) during the study period, containing an average of 1.1 (SD 0.4; 95% CI 1.1–1.1) ARV items (N = 190 903). Of these items, 127 248 (66.4%) were fixed-dose combination products (FDC), 145 804 (76.1%) were generic products, and most (90.4%; n = 173 131) were reimbursed through the HIV-benefits of the patient's medical scheme. FDC products containing efavirenz, emtricitabine, and tenofovir were claimed the most (n = 71 251; 37.2%), followed by products

containing the single-active ingredient efavirenz (n = 19 359; 10.1%) and FDC products containing lopinavir and ritonavir (n = 16 577; 8.7%). The prescribers were mostly general medical practitioners (n = 152 308; 79.5%), paediatricians (n = 4 449; 2.3%) and other specialists (n = 34 784;18.2%). Community pharmacies provided most of the ARV medication (n = 190 903; 99.7%) followed by only 0.3% (n = 638) dispensing medical practitioners.

Manuscript two addressed the clinical profile of HIV/AIDS beneficiaries. The results showed that the median (IQR) number of CDL conditions per PLWHA was 0(0), indicating that the majority of PLWHA (n = 14 426; 86.1%) did not present with any CDL condition. Among those diagnosed with one or more CDL conditions (n = 2 337; 13.9%), the majority had one other CDL condition (n = 1 848; 79.1%), followed by 17.4% (n = 407) who had two, and 3.5% (n = 82) who had three.

A statistically significant association between gender and type of CDL conditions ($p < 0.0001$; Cramer's $V = 0.3$) was found, with hypertension more prevalent in female PLWHA compared to male PLWHA (n = 629, 56.8% vs n = 658, 53.5%). The same trend was experienced with asthma (n = 61, 5.5% vs 45, 3.6%) and epilepsy (n = 39, 3.5% vs 31, 2.5%). More men than women were diagnosed with hyperlipidaemia (n = 112, 9.1% vs 52, 4.7%) and with the combination of hyperlipidaemia and hypertension (n = 146, 11.9% vs 59, 5.3%). Based on analysis by age group, hypertension (n = 1 287; 55.1%), hyperlipidaemia (n = 164; 7.0%) or a combination of these (n = 205; 8.8%) were more prevalent among PLWHA ≥ 18 years ($p < 0.0001$; Cramér's $V = 0.3$). PLWHA <18 years presented with co-existing asthma and epilepsy. The majority of regimens contained one ARV item, primarily the FDC consisting of efavirenz, emtricitabine and tenofovir.

In conclusion, prescribing generic and FDC products through pharmacies and reimbursing these products from the HIV-benefit category of PLWHA's medical aid schemes are standard practices to decrease the possible risk profile of an increased number of PLWHA in the medical scheme environment. Prescribers followed the first- and second-line regimens suggested as per the standard treatment guidelines of the South African Department of Health and of the World Health Organization. Only 13.9% of PLWHA presented with co-existing CDL conditions that can influence their treatment patterns.

LIST OF ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired immune deficiency syndrome
ALT	Alanine transaminase
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV	Atazanavir
AZT	Zidovudine
BIC	Bictegravir
CCR5	Chemokine receptor antagonist
CDC	Centers for Disease Control and Prevention
CDL	Chronic disease list
CMS	Council for Medical Schemes
CrCl	Creatinine clearance
CI	Confidence interval
D4T	Stavudine
DALY	Disability-adjusted life years
DDI	Didanosine
DM2	Diabetes mellitus type 2
DNA	Deoxyribonucleic acid
DOH	Department of Health

DRV	Darunavir
DSP	Designated service provider
DTG	Dolutegravir
EDL	Essential medication list
EFV	Efavirenz
ETR	Etravirine
FDC	Fixed-dose combination
FI	Fusion inhibitor
FPV	Fosamprenavir
FTC	Emtricitabine
GDP	Gross domestic product
GFR	Glomerular filtration rate
GNR	Government notice number
GP	General practitioner
HAART	Highly active antiretroviral treatment
HIV	Human immunodeficiency virus
HTLv-3	Human T-cell lymph tropic virus 3
IQR	Interquartile range
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IDV	Indinavir
INH	Isoniazid
INSIGHT	International Network for Strategic initiatives in Global HIV Trails

IPM	International Partnership for Microbicides
IRIS	Immune reconstitution inflammatory syndrome
LAV	Lymphadenopathy-associated virus
LPV	Lopinavir
LPV/r	Lopinavir and ritonavir combination
MDR	Multi-medication resistant tuberculosis
MIC	Medicines Information Centre
MIMS®	Monthly Index of Medical Specialities
MPR	Medicine possession ratio
MSM	Men who have sex with men
MTCT	Mother-to-child-transmission
MUSA	Medicine Usage in South Africa
NAPPI	National Approved Product Pricing Index
NFV	Nelfinavir
NHI	National health insurance
NHRPL	National Health Reference Price Listing
NNRTI	Non-nucleotide reverse transcriptase inhibitor
No.	Number
NRTI	Nucleotide reverse transcriptase inhibitor
NVP	Nevirapine
OR	Odds ratio
PBM	Pharmaceutical benefit management company
PEPFAR	President's Emergency Plan for AIDS Relief

PI	Protease inhibitor
PLWHA	People living with HIV/AIDS
PMB	Prescribed minimum benefit
PMTCT	Prevention of mother-to-child-transmission
PrEP	Pre-exposure prophylaxis
PWHI	Patients with HIV infection (synonym of PLWHA used in Manuscript 1)
PZA	Pyrazinamide
RAL	Raltegravir
RIF	Rifampicin
RNA	Ribonucleic acid
RPV	Rilprivirine
RTV	Ritonavir
SANAC	South African National AIDS Council
SAPC	South African Pharmacy Council
SAS®	Statistical Analysis System®, SAS 9.4® (SAS Institute Inc., 2002-2012)
SD	Standard deviation
SQV	Saquinavir
START	Strategic timing of antiretroviral treatment
STD	Sexually transmitted disease
STG	Standard treatment guideline
TB	Tuberculosis
TDF	Tenofovir
UNAIDS	Joint United Nation Programme on AIDS

UNICEF	United Nations Children's Fund
WHO	World Health Organization

LIST OF DEFINITIONS

Authorised pharmacist prescriber:	Pharmacists issued a permit in terms of Section 22A(15) of the Medicines and Related Substances Act (101 of 1965) may prescribe schedule 3 and 4 medication. Authorised pharmacist prescribers must adhere to the Standard Treatment Guidelines and Essential Medicines List for South Africa when treating and diagnosing patients (Department of Health (DOH, 2017:1.1-23.28). Authorised pharmacist prescribers must be registered and adhere to the scope of practice in section 35A of the Pharmacy Act (53 of 1974).
Clinical profile:	In this study, HIV/AIDS patients' clinical profile includes their co-existing chronic disease list (CDL) conditions and their antiretroviral (ARV) treatment patterns based on the different regimens.
Chronic disease list (CDL) conditions:	The Medical Schemes Act (131 of 1998) published under Government Notice (No.) R.1262 of October 1999 and amended by Government No. R.570 of 5 June 2000, Government No. R.650 of 30 June 2000, Government No. R.247 of 1 March 2002 and Government No. R.1360 of 4 November 2002 identifies a list of 26 chronic diseases that are considered the most frequent and life-threatening diseases in South Africa. These diseases require treatment for 12 months or longer, or they may be treated with affordable medication that increases a patients' quality of life. In terms of the Medical Schemes Act (131 of 1998) as amended by Government No. R.570 of 5 June 2000, Government No. R.650 of 30 June 2000, Government No. R.247 of 1 March 2002 and Government No. R.1360 of 4 November 2002, these conditions enjoy prescribed minimum benefits where the medical scheme is required to cover physician consultation, medication cost and tests related to the disease as specified by law.

Demographic profile:	In this study, demographic profile refers to the patient's age, gender, the type of prescriber of the patient's ARV medication (e.g., specialist vs general practitioner), dispensing vs non-dispensing prescribers, provider of the medication and geographical location of the patient as determined by the postal code of the prescriber.
Designated service provider:	According to the Medical Schemes Act (131 of 1998), a medical scheme may appoint a designated service provider (DSP), a healthcare professional or provider appointed by the medical scheme to provide the patient with prescribed minimum benefit services. DSPs are specified in the medical scheme rules, and patients are encouraged to use DSPs to avoid co-payments. Medical schemes determined and manage financial strain and managed care provided by DSPs through contractual agreements.
Direct costs of a disease:	The direct costs of a disease are costs directly associated with the disease. Direct costs include costs for medication, laboratory tests, hospitals, clinics and consultations with nurses, doctors and specialists. These costs also include medical aid co-payments and levies.
Fixed-dose combination:	Two or more active ingredients are formulated in one dosage form.
Geographic location:	In this study, a patient's geographical location is determined by using the postal code of the prescriber's practice as a proxy.
Indirect non-medical costs of a disease:	Indirect non-medical costs are indirectly associated with a disease, which means that if there were no disease, these costs would not have affected the individual or family. These costs include but is not limited to travel, food and accommodation required to receive treatment as well as loans, selling belongings to be able to afford healthcare services, loss of income due to the death of the patient,

	and increased financial burden on the family due to the sickness and/or death of the patient.
Medicine claims profile:	In this study, the medicine claims profile of the HIV/AIDS patient includes the general prescribing patterns of ARVs.
Medicine prescribing patterns:	Medicine prescribing patterns refer to the benefits for which the medicine is claimed (acute, chronic and oncology), the generic indicator (original or generic medicine), and the general medicine use patterns of patients (fixed-dose or single-dose regimen).
Prescribed minimum benefits:	Prescribed minimum benefits (PMB) are a set of benefits specified in the Medical Schemes Act (131 of 1998) that must be paid in full by all medical schemes regardless of the benefit or plan beneficiaries have selected. These benefits include the diagnosis, medication and medical management of 270 conditions, 26 chronic diseases and HIV/AIDS as specified in the Medical Schemes Act (131 of 1998) published under Government Notice No. R. 1262 of October 1999, as amended by the following Government Notices: No. R.570 of 5 June 2000, No. R.650 of 30 June 2000, No. R.247 of 1 March 2002 and No. R.1360 of 4 November 2002.
Single-dose:	Only one active ingredient is formulated into a single dosage form.

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CHAPTER 1: INTRODUCTION AND STUDY OVERVIEW

1.1 Introduction

This study focused on profiling South African human immunodeficiency virus (HIV) and acquired immunodeficiency syndrome (AIDS) patients in the medical scheme environment in the private healthcare sector of South Africa.

1.2 Background and problem statement

The Joint United Nations Programme on HIV/AIDS (UNAIDS) has estimated that, in 2016, 36.7 million (30.8 million–42.7 million) people globally lived with HIV, but only 53% (39–65%) of these individuals received treatment (UNAIDS, 2016a:3). Patients who received antiretroviral treatment (ART) in that year numbered 19.5 million (UNAIDS, 2016a:5). In the same year, 1.8 million (1.6 million–2.1 million) people became newly infected with HIV, and 1 million (830 000–1.2 million) people died from AIDS-related conditions (UNAIDS, 2016:3). The effect of HIV/AIDS continues to be a global health concern, with 38 million people infected by the end of 2019 (WHO, 2020a). The global shortage of HIV health service availability resulted in 690 000 HIV-related deaths in 2019 and 1.7 million new HIV infections (WHO, 2020a). In 2019, 68% of adults received lifelong ART, enabling these people living with HIV/AIDS (PLWHA) to have better life quality (WHO, 2020a).

Sub-Saharan Africa is the region in the world that is affected the most, with 25.4 million PLWHA by 2015 (WHO, 2016a). In 2020, 64% of PLWHA were from sub-Saharan Africa (WHO, 2020a). The rapid increase in ART provision for HIV infections in sub-Saharan Africa over the past decade was a relieving achievement in the global fight against HIV/AIDS. Due to large investments from sources such as the Global Fund to Fight AIDS, Tuberculosis (TB), and Malaria, the President's Emergency Plan for AIDS Relief (PEPFAR) and bilateral donors, the number of PLWHA that received life-saving treatment in sub-Saharan Africa increased from 300 000 in 2004 to 6 million in 2015 (Hontelez *et al.*, 2016:30; UNAIDS, 2016a:3; PEPFAR, 2016:10). Consequently, HIV-related morbidity and mortality have decreased noticeably in this region (Hontelez *et al.*, 2016:22).

At the end of 2015, the UNAIDS (2016a:60) set the goal to eliminate HIV/AIDS as a global threat by 2030. Many countries, including South Africa, adopted the 2030 goal (PEPFAR, 2016:11; South Africa, 2016:1). To achieve this goal, the 90-90-90 target strategy was adopted, which means that 90% of people should know their HIV/AIDS status, 90% of diagnosed

HIV/AIDS patients should receive ongoing treatment and 90% of patients that receive ART should have sufficient viral suppression (South Africa, 2016:1-2).

Statistics South Africa (2016:7) estimated that the total number of PLWHA in South Africa has grown from 4.72 million in 2002 to 7.03 million people in 2016. The number of newly infected patients in South Africa decreased from 500 000 (470 000–530 000) patients in 2005 to 270 000 (240 000–290 000) in 2016 (UNAIDS, 2017a). South Africa had nearly 3.9 million people on treatment in 2016, more than any other country in the world (UNAIDS, 2016a:40).

The annual report of the Council for Medical Schemes (CMS) (2015a:7-9) for 2013/2014 indicated that HIV/AIDS prevalence among medical scheme patients in the private healthcare sector had grown from 6.6% in 2008 to 17.4% in 2013. According to the CMS, HIV/AIDS is the chronic disease that has increased the most (21.4%) from 2008 to 2013. The CMS 2015/16 annual report (2016:12) indicated that the number of patients treated for HIV/AIDS in the medical scheme environment of South Africa increased from 26.31 per 1 000 patients in 2015 to 27.95 per 1 000 patients in 2016.

According to a survey by Shisana *et al.* (2012:xxv-xxviii) done in the public sector in 2012, Kwazulu-Natal had an HIV/AIDS prevalence rate of 17%, with 14% each for the Free State and Mpumalanga. The Western Cape had the lowest HIV/AIDS prevalence rate of 5%, whereas prevalence was 7.4% in the Northern Cape and 13.3% in the North-West. The survey indicated that females had a higher prevalence of HIV/AIDS than males. Females with the highest prevalence rate were aged 30 to 34 years, and males with the highest prevalence rate were aged 35 to 49 years. The survey showed that the prevalence rate of HIV/AIDS was substantially different between provinces, age groups and genders (Shisana *et al.*, 2012:xxv).

As of 1 January 2004, the South African Government defined the chronic medicine management for HIV/AIDS as part of the prescribed minimum benefits (PMB), regardless of HIV/AIDS not being part of the chronic disease list (CDL) in the private healthcare sector. The CDL is a list of twenty-six diseases that have been identified by The Medical Schemes Act (131 of 1998) as life-threatening and most frequent conditions. The Medical Schemes Act (131 of 1998) entitles the beneficiaries of medical schemes to PMBs for all CDL conditions, including HIV/AIDS (CMS, 2017a; South Africa, 1998a). The CMS (2016:4-6) reported that HIV was the fifth most prevalent condition on the CDL in the medical schemes' environment in 2015. The other most prevalent CDL conditions were hypertension, hyperthyroidism, hyperlipidaemia, type 2 diabetes mellitus and asthma. The average growth rates in chronic diseases reported by the CMS (2015/16) are hypertension at 7.7%, type 2 diabetes mellitus at 11.1% and HIV-treated patients at 16.8% (CMS,

2016:8). Therefore, including HIV/AIDS as a CDL condition increased medical schemes costs because of its high prevalence (CMS, 2016:4-6; South Africa, 1998a).

No legislation guides HIV/AIDS treatment in South Africa's private healthcare sector. However, the treatment guidelines used in the South African public healthcare sector is a good example that can be used in the private healthcare sector of South Africa. The Department of Health (DOH) of South Africa, therefore, encourages the private healthcare sector to adopt the same standard treatment guidelines (STGs) prescribed for the public healthcare sector (DOH, 2018:1.1-23.29).

HIV/AIDS is a chronic, manageable disease that can be controlled through ART; treatment does not cure AIDS, but it suppresses viral replication chronically (UNAIDS, 2016b:1; WHO, 2016b:1). Therefore, the supply of ART globally and in South Africa is vital to achieving the UNAIDS goal to reduce HIV/AIDS (UNAIDS, 2014; WHO, 2016c:1; UNAIDS, 2016b:1-2).

In the past, developing countries often emphasised prevention over treatment with highly active antiretroviral treatment (HAART) (South Africa, 1996a:9). However, more recently, the use of three antiretroviral (ARV) medications in at least two or more ARV classes became a successful method of managing HIV/AIDS as a chronic disease instead of an acute lethal disease (Ferrando *et al.*, 2003:208-210). There are six major therapeutic classes of ARVs available: non-nucleotide reverse transcriptase inhibitors (NNRTIs), nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors (PIs), neuraminidase inhibitors and antiretroviral combinations, chemokine receptor antagonists (CCR5 antagonists) and fusion inhibitors (FIs) (Pray *et al.*, 2004:5).

Long-term use of ART may be associated with cognitive impairment, which leads to dementia in older patients (Slabbert *et al.*, 2015:9). The risk of developing cardiovascular diseases such as ischemic strokes and hypercoagulability is higher in HIV-positive patients (Zimba *et al.*, 2017:359). Ovbiagele and Nath (2011:444) found a relationship between older patients with HIV/AIDS and the prevalence of other chronic diseases such as diabetes, syndromic neurocognitive impairment, liver diseases, renal diseases and malignancy. Older patients with comorbidities and HIV-positive status were significantly and independently associated with worse physical and mental health-related quality of life than those without comorbidities (Rodriguez-Penney *et al.*, 2013:5-10).

Because HIV/AIDS affects the central nervous system, the patient presents with a higher tendency to develop major depression, which reduces adherence with ART (Grant, 2008:33-35; Wayburne & Da Silva, 2007:64-72). Due to the ART adherence-resistance relationship, failure of the patient to comply with the treatment dose as prescribed leads to increased viral replication

and selective resistance to specific ARV treatment (Bangsberg *et al.*, 2004:696). The disease and death progression is related to non-adherence to ARV treatment and the prescribed regimen (Kleeberger *et al.*, 2001:82). Adherence barriers to ARV treatment can lead to complications because of resistance to treatment and increased treatment cost (Bangsberg *et al.*, 2004:696).

HIV-patients' mental and physical health has been found to decrease as the number of chronic diseases they present with increases (Cramer *et al.*, 2008:44-47; Kleeberger *et al.*, 2001:82; Martin *et al.*, 2005:189). However, research about the prevalence of multiple CDL conditions in PLWHA in the private healthcare sector of South Africa is lacking. Information about the chronic medication treatment patterns of CDL conditions co-existing with HIV/AIDS is also lacking.

Despite the increasing prevalence rates of PLWHA in the South African medical scheme environment, little is known about these individuals' profiles. This background leads to research questions that require answers:

- What is the burden of HIV/AIDS globally, nationally and in the South African private healthcare sector?
- What is the current prevalence of HIV/AIDS stratified by age, gender and geographical location in the medical scheme environment of South Africa?
- Who prescribes ARVs to HIV/AIDS patients in the medical scheme environment?
- What co-existing diseases might HIV/AIDS patients have?
- How adherent are private healthcare sector patients to their ARV treatment?
- Do the prescribers of ART in the private healthcare sector of South Africa follow STGs?
- What other acute, chronic or oncology medication are claimed by HIV/AIDS patients?
- How many prescriptions and items do HIV/AIDS patients claim for in a specified period?
- What is the direct medicine treatment cost of HIV/AIDS patients in the private healthcare sector of South Africa?

1.3 Research aims and objectives

1.3.1 Research aims

This study aimed to determine the demographic, clinical and medicine claims profile of PLWHA in the private healthcare sector of South Africa using medicine claims data of 2016 obtained from a pharmaceutical benefit management (PBM) company.

The demographic profile includes patients' demography, such as age, gender, geographic location, prescriber type of ART and the ART provider. The clinical profile includes possible co-existing chronic conditions and ARV prescribing patterns. The medicine claims profile of HIV/AIDS patients includes the active ingredients of ARV medication prescribed, type of benefit medicine claimed (e.g., acute, chronic, oncology, PMB, HIV), the prescriber and provider of ARV, the number of ARV prescriptions and items.

1.3.2 Specific research objectives

The specific research objectives consisted of specific literature research objectives and specific empirical research objectives.

1.3.2.1 Specific literature research objectives

The specific literature research objectives were:

- To determine, from the literature, the burden of HIV/AIDS globally and in South Africa from a prevalence, clinical and social perspective.
- To conceptualise the treatment patterns[1] for HIV/AIDS globally and in South Africa.
- To determine the possible influence of co-existing chronic diseases, medicine adherence and economic factors on the implementation of STGs.

[1] A treatment pattern is a combination of medication used to treat patients with the same condition. This combination is repeated and used as a protocol.

1.3.2.2 Specific empirical research objectives

The specific research objectives for the empirical study were:

- To establish a demographic profile[2] of HIV/AIDS patients stratified by patients' age, gender, geographical location[3], type of prescriber, and ARV medication provider.
- To determine the clinical profile[4] of HIV/AIDS patients by identifying their co-existing CDL conditions (refer to paragraph 1.5.2.1) and ART patterns.
- To investigate the medicine claims profile[5] of HIV/AIDS patients by investigating the general medicine prescribing patterns of HIV/AIDS patients.

The study variables are categorised as per Table 1-2.

1.4 Research methodology

The research methodology included a literature review and an empirical study.

1.4.1 Literature review

A literature review of the impact of HIV/AIDS globally and in South Africa was performed. The HIV/AIDS burden was determined from a clinical, epidemiological, social and economic perspective. The medicine treatment patterns of HIV/AIDS globally and in South Africa were investigated, especially in key populations, factors influencing the medicine treatment pattern, medicine-related factors and patient-related factors.

The literature review was conducted via an internet search using reputable databases such as EBSCOhost®, Google Scholar®, PubMed®, Science Direct® and Scopus® and keywords. The keywords/phrases used to conduct the research were:

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[2] See definition in list of definitions and classification in Table 1-2.

[3] Geographical location will be determined using the postal code of the prescriber as a proxy.

[4] See definition in list of definitions and classification in Table 1-2.

[5] See definition in list of definitions and classification in Table 1-2.

- "HIV/AIDS in the private sector."
- "HIV/AIDS prevalence globally."
- "HIV/AIDS prevalence in South Africa."
- "HIV/AIDS in the public sector South Africa."
- "Treatment guidelines of HIV/AIDS in South Africa."
- "Treatment methods of HIV/AIDS globally."
- "Economic impact of HIV/AIDS."
- "HIV/AIDS mortality rates."
- "HIV/AIDS co-existing disease."
- "Adherence to antiretroviral medications."
- "Determine adherence to antiretroviral medications."
- "HIV/AIDS health expenditure."
- "HIV/AIDS and co-existing chronic diseases."
- "HIV/AIDS and other comorbidities."

1.4.2 Empirical investigation

1.4.3 Study design

A cross-sectional research design was implemented using retrospective medicine claims data from a PBM company. In a cross-sectional design, the prevalence of different variables is studied at a specific point in time (Kholmatova *et al.,* 2016:49-56). For this study, the point in time was from 1 January 2016 to 31 December 2016. Changes over time were not investigated; therefore, only one year's data was needed to achieve the empirical research objectives.

Retrospective (pre-existing) data from the medicine claims database of the PMB company were used. Retrospective data sources may include copies of prescriptions dispensed, treatment records kept at prescribers and/or patient information records kept at healthcare facilities

(Brink *et al.*, 2012:5; Kholmatova *et al.*, 2016:49-51). A limitation of retrospective data is that patients' information may be incomplete (Brink *et al.*, 2012:5; Kholmatova *et al.*, 2016:49-51). Therefore, all the data from 1 January 2016 to 31 December 2016 that met the inclusion criteria in Table 1-1 were used in this study. The PBM company verified the data obtained using the techniques listed in paragraph 1.4.5.1.

1.4.4 Study and target population

The target population consisted of all HIV/AIDS patients treated in the private healthcare sector in South Africa in the year 2016.

The study population included all HIV/AIDS patients on the PBM company database who claimed ARV medication during 2016. Patients were selected according to the inclusion and exclusion criteria as per Table 1-1.

Table 1-1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Study period: 1 January 2016 to 31 December 2016	All patients with incomplete data fields for age, gender, diagnosis code and postal code of the provider (needed for geographical location)
Ages: all	
Gender: male and female	
Diagnosis code: ICD-code B20–B24[6]	
Medication: antiretroviral medications	

No sampling was necessary as the information of all patients who met the inclusion criteria were included.

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[6] B20 Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases

B21 Human immunodeficiency virus [HIV] disease resulting in malignant neoplasms

B22 Human immunodeficiency virus [HIV] disease resulting in other specified diseases

B23 Human immunodeficiency virus [HIV] disease resulting in other conditions

B24 Unspecified human immunodeficiency virus [HIV] disease

1.4.5 Data source

A PBM company is a real-time electronic management system that manages patients' benefits and acts as a mediator between the healthcare provider and the medical scheme for all medicine claims submitted. The medicine claims database of a PBM company in South Africa whose name is withheld for confidentiality was used as the empirical study's data source.

1.4.5.1 Validity and reliability of the data source

The data used in the study were obtained from only one database, which leads to limited external validity because the data are only applicable to this database and study population.

All information was assumed to be correct and accurate. The PBM company performs internal validation checks through gatekeeping, eligibility, medicine utilisation management, fully integrated pre-authorisation management, management of medicines for CDL conditions, management of prescribed minimum benefits and other conditions, clinical management, pricing management and real-time benefit management, including reference pricing and formulary medication management. Duplicate claims and incomplete patient information were excluded from the data analysis. The statistician performed random data checks to verify the datasets. As per the confidentiality agreement with the PBM company, all identifiable information about medical schemes, patients, providers and prescribers were encrypted or deleted by the PBM company before providing the data for analysis.

1.4.6 Data fields used in this study

The following data fields were extracted from the database:

- Date of birth of the patient
- Gender indicated as male or female
- Postal code of the healthcare provider
- Type of medicine prescriber
- Dispensing vs non-dispensing medical practitioner
- Type of medicine provider
- Trade name of medications

- National Approved Product Pricing Index (NAPPI-[7]) of medications
- Dispensing date of prescription
- International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes
- Benefit category used for reimbursement

1.5 Study variables

The study variables for each profile are outlined in Table 1-2.

[7] The NAPPI-code, or National Approved Product Pricing Index code, is a unique, nine-digit long product code introduced to facilitate electronic transactions. Each code is unique for each medicine product name, registration, pack size, strength, manufacturer and dosage.

Table 1-2: Study variables per profile

Demographical profile	Clinical profile	Medicine claims profile
Gender: men or women **Age groups:** patients' ages were calculated for the year 2016 (i.e., the age that the patient was at the time the medication claim was submitted to the PBM company): Group 1: if age > 0 and < 2 years Group 2: if age ≥ 2 and < 12 years Group 3: if age ≥ 12 and < 18 years Group 4: if age ≥ 18 and < 25 years Groups 5: if age ≥ 25 and < 45 years Group 6: if age ≥ 45 and < 65 years Group 7: if age ≥ 65 years	**Prevalence of CDL conditions** diagnosed in PLWHA according to age, gender and product type of ARV medication claimed. The **active ingredient of ARV** medication was determined by NAPPI codes, ICD-10 codes and categorise according to the Monthly Index of Medical Specialities (MIMS®) classification system. **ARV item:** An ARV item claimed is a product containing one or more single active ingredient(s) used specifically to treat PLWHA.	**Benefit category**: The various benefit categories are acute, oncology, chronic, HIV and PMB. The PBM company distinguished between the benefit categories that covered the ARV medicine as HIV benefits, PMB benefits, chronic benefits and other benefits. **Active ingredients of medication:** NAPPI codes, ICD-10 codes and the MIMS® classification system were used to identify the top 10 active ingredients of the ARV medication claimed. **Medicine ARV provider**: medicine ARV providers were classified as a community pharmacy or a general practitioner or specialist practice (dispensing practice). **Prescriber type**: prescribers were categorised as general medical practitioners, paediatricians and other specialists). They were also categorised as dispensing or non-dispensing general practitioners or specialists depending if they also dispensed the ARV prescription.

Demographical profile	Clinical profile	Medicine claims profile
Geographical location: the antiretroviral (ARV) prescriber's postal code was **used as a** proxy for the patients' geographical location. Data were analysed on a provincial level. The nine provinces of South Africa are Eastern Cape, Free State, Gauteng, KwaZulu-Natal, Limpopo, Mpumalanga, Northern Cape, North West and Western Cape.	**ARV regimens:** ARV regimens were defined by a single or combination of ARV items (active ingredient(s)) claimed on one or more prescriptions on the same day.	**Generic status:** in cases where generic products were available, the generic state was used to determine if the generic alternative or the original product was dispensed. It was reported if no generic substitute was available. **Medicine product type**: medicine product type was used to distinguish between single-active ingredient and fixed-dose combination product (FDC) types dispensed to patients.

1.5.1 Demographic profile variables

The demographic variables considered were patients' age, gender and geographical location (by using the prescriber's postal code as a proxy) and the type of prescriber and provider of the medication.

1.5.1.1 Age

Patients' ages were calculated for the year 2016 (i.e., the patient's age when the claim was submitted to the PBM company) through the Statistical Analysis System®, SAS 9.4® (SAS Institute Inc., 2002-2017) programme. Ages were grouped as follows:

- Group 1: if age > 0 and < 2 years
- Group 2: if age ≥ 2 and < 12 years
- Group 3: if age ≥ 12 and < 18 years
- Group 4: if age ≥ 18 and < 25 years
- Groups 5: if age ≥ 25 and < 45 years
- Group 6: if age ≥ 45 and < 65 year
- Group 7: if age ≥ 65 years

1.5.1.2 Gender

Gender was divided into female and male. Patients whose gender was not indicated were excluded from the study.

1.5.1.3 Geographical location

The ARV prescriber's postal code was used as a proxy for patients' geographical location. Data were analysed at the provincial level. The nine SA provinces are Eastern Cape, Free State, Gauteng, KwaZulu-Natal, Limpopo, Mpumalanga, Northern Cape, North West and Western Cape.

1.5.1.4 Medicine provider

The PBM's data were divided into various medicine provider types classified as i) general medical or specialist practice, which is considered a dispensing practice; and ii) community pharmacies (Refer to paragraph 1.5.1.5).

1.5.1.5 Prescriber type

The PBM data were categorised according to prescriber type (i.e., the prescriber, practice, practitioner or specialist writing the prescription). The prescribers were divided into the following five categories:

- General medical practitioners: prescribers registered with the South African Health Professional Council as general medical practitioners (South Africa, 1998a).
- Paediatricians
- Specialised prescribers and practices: anaesthesiologists, cardiologists, clinical haematologists, dermatologists, diagnostic radiologists, gastroenterologists, neurologists, nuclear medicine specialists, gynaecologists, oncologists, ophthalmologists, oral pathologists, orthodontists, orthopaedists, otorhinolaryngology specialists, podiatrists, pathologists, periodontics specialists, urologists, surgeons, psychiatrists, physiatrists, plastic and reconstructive surgeons, prosthodontists, pulmonologists, radiographers, rheumatologists, thoracic surgeons, immunologists, nephrologists and endocrinologists.

1.5.1.6 Dispensing and non-dispensing prescriber

The PMB also categorised prescribers as a dispensing prescriber that dispenses his/her prescriptions or as a non-dispensing prescriber who gives the prescription to the patient to decide where to dispense the prescription.

1.5.2 Clinical profile variables

The clinical profile variables included identifying co-existing CDL conditions and prescribing patterns of the ARV medication.

1.5.2.1 Co-existing CDL conditions

The CDL conditions of South Africa were used to categorise co-existing non-communicable diseases (South Africa, 2003; South Africa, 2009). Co-existing CDL conditions were identified from the medicine claims data using the ICD-10 codes for CDLs. The ICD-10 code is an international classification system for all diseases used by healthcare providers, also in South Africa (WHO, 2016d).

The co-existing CDL conditions were grouped as follows using their ICD-10 codes:

- Cardiovascular diseases such as hypertension, hyperlipidaemia, coronary artery disease, cardiac failure, cardiomyopathy disease and dysrhythmia
- Central nervous system diseases such as epilepsy, Parkinson's disease and multiple sclerosis
- Chronic renal disease
- Diabetes insipidus
- Diabetes mellitus types 1 and 2
- Gastro-intestinal diseases such as Crohn's disease and ulcerative colitis
- Glaucoma
- Haematological diseases such as haemophilia A and B
- Hypothyroidism
- Psychiatric diseases such as bipolar mood disorder and schizophrenia

- Respiratory diseases such as asthma, chronic obstructive pulmonary disease and bronchiectasis
- Rheumatoid arthritis
- Systemic lupus erythematosus

The top ten co-existing CDL conditions or combinations present in HIV/AIDS patients were identified.

1.5.2.2 Prescribing patterns of ARV medication according to the active ingredient and ART regimen

The Monthly Index of Medical Specialities (MIMS®) lists the active ingredients and registered trade names of medication according to a pharmacological classification system (Snyman, 2016). A nine-digit product code is used in the real-time responses submitted to the PBM company. This nine-digit code is known as a National Approved Product Pricing Index code (NAPPI- codes). The NAPPI-code, ICD-10 code and MIMS® classification system from the data source were used to identify the active ingredient of the medicine claimed for by the HIV/AIDS patient (Snyman, 2016).

The prescribing patterns[8] for ARV medication were identified using active ingredients and combinations of active ingredients claimed per prescription per patient. These prescribing patterns were compared with the STGs suggested by WHO (2018a) and adopted by South Africa (DOH, 2018:1.1-23.29) to determine whether the prescribing patterns of South Africa's private healthcare complies with these regimens.

Table 1-3 indicates the medicines available to treat HIV/AIDS in South Africa until February 2017 (Rossiter *et al.*, 2016; WHO, 2015:1-2).

[8] Prescribing patterns include the most prevalent medication(s) and regimens, the percentage of fixed dosage combinations and types of medication (e.g., generic or original medications).

Table 1-3: HIV/AIDS medicine on the market in South Africa in 2017 per active ingredient and trade name

Active ingredient(s)	Trade name(s)	Single active ingredient products or fixed-dose combinations (FDC)
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)		
Abacavir (ABC)	Ziagen® Aspen Abacavir® Auro Abacavir® Cipla Abacavir® Adco Abacavir® Sonke Abacavir®	Single active ingredient products
Didanosine (DDI)	Videx® Aspen Didanosine® Sonke Didanosine®	Single active ingredient products
Emtricitabine (FTC)	Only available in FDC	FDC
Lamivudine (3TC)	3TC® Aspen Lamivudine® Auro Lamivudine® Cipla Lamivudine® Adco Lamivudine® Sonke Lamivudine®	Single active ingredient products
Stavudine (d4T)	Zerit® Aspen Stavudine® Auro Stavudine® Sonke Stavudine® Stavir®	Single active ingredient products
Tenofovir (TDF)	Viread® Aspen Tenofovir® Cipla Tenofovir®	Single active ingredient products
Zidovudine (AZT)	Retrovir® Adco Zidovudine® Aspen Zidovudine® Auro Zidovudine® Cipla Zidovudine® Sonke Zidovudine®	Single active ingredient products
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)		
Efavirenz (EFV)	Stocrin® Aspen Efavirenz®	Single active ingredient products

Active ingredient(s)	Trade name(s)	Single active ingredient products or fixed-dose combinations (FDC)
	Cipla Efavirenz® Adco Efavirenz® Auro Efavirenz® Sonke Efavirenz®	
Etravirine (ETR)	Intelence®	Single active ingredient products
Nevirapine (NVP)	Single active ingredient products	Single active ingredient products
Combined NRTIs/NNRTIs		
AZT/3TC	Combover® Aspen Lamzid® Auro Lamizido® Cipla Douvir® Sonke Lamivudine + Zidovudine®	FDC
AZT/3TC/ABC	Trizivar® Sonke Abaclamzid®	FDC
3TC/ABC	Kivexa® Dumiva®	FDC
Combined NRTIs/NNRTIs		
d4T/3TC/NVP	Triomune-30® Nevasta® Virtrium® Sonke-LamNevStav® Triomune-40®	FDC
TDF/FTC	Truvada® Adco Emtevir® Aspen Tenofovir & Emtricitabine® Didivir® Tencitab® Tenemine® Tyricten®	FDC

Active ingredient(s)	Trade name(s)	Single active ingredient products or fixed-dose combinations (FDC)
Combined NRTIs/NNRTIs		
FTC/TDF/EFV	Atripla® Atenef® Atreslawin® Atroiza® Odimue® Tribuss® Trivenz®	FDC
TDF/3TC/EFV	Eflaten® Tenarenz®	FDC
Dolutegravir (DTG)/ABC/3TC	Trelavue®	FDC
3TC/AZT/NVP	Triplavar®	FDC
Protease inhibitors (PIs)		
Atazanavir (ATV)	Reyataz® Atazor® Aspen Atazanavir®	Single active ingredient products
Darunavir (DRV)	Prezista®	Single active ingredient products
Fosamprenavir (FPV)	Telzir®	Single active ingredient products
Indinavir (IDV)	Crixivan®	Single active ingredient products
Nelfinavir (NFV)	Vira-cept®	Single active ingredient products
Protease inhibitors (PIs)		
Ritonavir (RTV)	Norvir®	Single active ingredient products
Lopinavir-ritonavir (LPV/r)	Aluvia® Kaletra®	FDC
Saquinavir (SQV)	Invirase®	Single active ingredient products

Active ingredient(s)	Trade name(s)	Single active ingredient products or fixed-dose combinations (FDC)
Other ARV		
Raltegravir (RAL)	Isentress®	Single active ingredient products
Dolutegravir	Tivicay®	Single active ingredient products
Rilpivirine (RPV)	Edurant®	Single active ingredient products

South Africa's DOH (2016:11.19-11.11) published standard treatment guidelines based on the WHO guidelines. Table 1-4 indicates the preferred regimens of South Africa's DOH (2016:11.1-11.10) and WHO (2016c).

Table 1-4: Regimens for first-line, second-line and third-line treatment according to the DOH and WHO

Regimen choice	Combination of regimen	Regimen no.	Regimen choice	Combination of regimen	Regimen no.
First-line treatment – DOH			First-line treatment – WHO		
All new patients including pregnant women as FDC	TDF+ FTC + EFV	Regimen 1-1	Fixed-dose combination	TDF+ FTC+ EFV TDF + 3TC+ EFV	Regimen 1-1 Regimen 1-2
EFV contra-indication	TDF + FTC+ NVP	Regimen 1-2	Alternative options	AZT+ 3TC + EFV AZT + 3TC + NVP	Regimen 1-7 Regimen 1-8
EFV+ NVP contra-indicated	TDF+ FTC+ LPV/r ABC+ 3TC+ NVP	Regimen 1-3 Regimen 1-4		TDF+ 3TC+ NVP TDF+ FTC+ NVP	Regimen 1-9 Regimen 1-2
TDF contra-indicated	ABC+ 3TC+ EFV ABC+ 3TC+ NVP	Regimen 1-5 Regimen 1-6		TDF+ FTC+ EFV_{400} TDF+ 3TC+ EFV_{400}	Regimen 1-10 Regimen 1-11
TDF and ABC contra-indicated	AZT+ 3TC+ EFV AZT+ 3TC+ NVP	Regimen 1-7 Regimen 1-8		TDF+ 3TC+ DTG TDF+ FTC+ DTG	Regimen 1-12 Regimen 1-13
Second-line treatment – DOH			**Second-line treatment – WHO**		
Failure of d4T or AZT base	TDF+ FTC + LPV/r	Regimen 2-1	Second-line suggestion	Should include 2 NRTIs + ATV/r or LPV/r	Regimen 2-1 and 2-3
			Alternative option	2 NRTIs + DRV/r	Regimen 2-4
Failure of TDF base	AZT+ 3TC+ LPV/r	Regimen 2-2			
Third-line treatment includes a referral to a specialist where the specific genotype must be tested, and specific resistance must be identified.			Third-line treatment includes a referral to a specialist where the specific genotype must be tested, and specific resistance must be identified.		

++3TC= lamivudine, ABC=abacavir, AZT=zidovudine, d4T= stavudine, DRV/r= darunavir/ritonavir combination, DTG=dolutegravir, EFV=efavirenz 600mg, EFV= efavirenz 400mg, FDC= fixed-dose combination, FTC= emtricitabine, LPV/r=lopinavir/ritonavir combination, NRTI=nucleotide reverse transcriptase inhibitor, NVP=nevirapine, RAL=raltrigravir, RPV=ritonavir, TDF= tenofovir

1.5.3 Medicine claims profile variables

The medicine claims profile variables considered include the general medicine prescribing patterns, the benefit category from which ARV medicine was reimbursed, the prescriber type that dispensed the medication, the medication provider and the generic indicator.

1.5.3.1 Prescribing patterns of ARV medication according to the active ingredient and ART regimen

Refer to section 1.5.2.2 for a detailed description of this variable.

1.5.3.2 General medicine prescribing patterns

The data source was used to determine the total number of ARV prescriptions and items HIV/AIDS patients claimed during the one-year study period. The total number of prescriptions claimed was categorised according to the benefit for which the medication was claimed (paragraph refer 1.5.3.3).

1.5.3.3 Benefit category

The medical scheme has various benefit categories, namely acute, oncology, chronic, HIV and PMB.

1.5.3.4 Generic indicator

Antiretroviral medications were also categorised according to their generic status using the generic status indicator assigned by the PMB to all medicine products on their database. Cases where there was no generic substitute available were reported. Generic status was categorised as: i) an original medication with generic equivalent(s); ii) an original medication with no generic equivalent(s), or iii) a generic equivalent.

1.5.3.5 Medicine product type

This study distinguished between FDC products and single active ingredient products dispensed as determined from the ART items claimed. Research has found that FDC helped increase correct and efficient ART usage (Bea *et al.,* 2011: 279-280). The benefits associated with the use of FDC products can be a motivator for healthcare providers to prescribe it (Cihlar & Fordyce, 2019:56).

1.5.4 Statistical analysis

The Statistical Analysis System, SAS 9.4® (SAS Institute, 2002-2017) was used to analyse the data according to the empirical study's research objectives. The statistical analysis was performed in consultation with the Statistical Consultation Services of the North-West University. The statistical analysis used for the specific study objectives is described in Table 1-5 and outlined below:

1.5.4.1 Descriptive statistics

Descriptive statistics were applied by determining frequencies/counts (n) as a percentage (%), means, standard deviations (SD), 95% confidence intervals (CI), median and interquartile range (IQR). In this study, frequency and prevalence are used as synonyms to indicate the number of HIV/AIDS prescriptions, ARV items claimed by the patients and the number of patients in the study period.

1.5.4.2 Inferential statistics

- The two-sample independent *t*-test was used to compare the size of the difference between the means of the two groups. Cohen's *d*-value was considered for practical significance; the magnitude of the *d*-values was interpreted as follows: ≤ 0.2 is a small effect with no significant difference, > 0.2 and ≤ 0.8 is a medium effect with an observable significance, and > 0.8 is a large effect with a significant difference. (Banerjee, 2003:99; Steyn, 1999:18-19).

- Chi-square test (χ^2), a non-parametric test, was used to determine if a statistically significant association exists between two categorical variables, for example, the age groups and gender of the HIV/AIDS patients. The statistical significance was determined using a two-sided probability of $p < 0.05$. Cramér's V was used to determine the associations' practical significance, with Cramér's $V \geq 0.5$ defined as practically significant. A Cramér's V equal to 0 indicates no association between two groups regardless of the study population's size (Pagano & Gauvreau, 2000:345; Steyn, 1999:18-19; Swanepoel *et al.*, 2010:262).

Table 1-5: Statistical analysis plan

Objectives	Measurements	Variables		Statistical analysis		
		Independent	**Dependant**	**Descriptive**	**Inferential**	**Statistical and practical significance**
Determine the demographical profile of the HIV/AIDS patient	Total number of patients with HIV/AIDS in the database		Number of HIV/AIDS patients	Frequency (%) Presented as per 1 000 beneficiaries		
	Age group distribution of HIV/AIDS patients	Age group	Number of HIV/AIDS patients	Frequency (%) Presented as per 1 000 beneficiaries		
	Gender distribution of HIV/AIDS patients	Gender	Number of HIV/AIDS patients	Frequency (%) Presented as per 1 000 beneficiaries		
	Difference in the mean age of HIV/AIDS patients stratified according to gender	Gender	Age	Mean (SD), 95% CI	Two-sample independent *t*-test	*p*-value < 0.05 *d*-value
	Geographical location (determined on the provincial level) of HIV/AIDS patients	The geographical location of the HIV/AIDS patient (determined on the provincial level, refer Table 1-2)	Number of HIV/AIDS patients	Frequency (%) Presented as per 1 000 beneficiaries		

Objectives	Measurements	Variables		Statistical analysis		
		Independent	**Dependant**	**Descriptive**	**Inferential**	**Statistical and practical significance**
	Geographical distribution of HIV/AIDS patients stratified by age group and gender	Geographical distribution on the provincial level (refer Table 1-2)	Age group Gender	Cross tabulate Frequency (%)	Chi-square	*p*-value < 0.05 Cramér's *V*
	Prescriber-type responsible for issuing prescriptions	Prescriber	Number of ARV medicine items	Frequency (%)		
	Medicine (ARV) provider responsible for dispensing the prescription	Medicine (ARV) provider	Number of ARV medicine items	Frequency (%)		
Determine the clinical profile of the HIV/AIDS patient	Number of CDL conditions per HIV/AIDS patient		Number of CDL conditions per patient	Frequency (%)		
			Number of CDL conditions per patient	Median Interquartile range (IQR)		
	Top 15 most prevalent CDL conditions diagnosed in patients with HIV/AIDS		Type of CDL condition	Frequency (%)		

Objectives	Measurements	Variables		Statistical analysis		
		Independent	**Dependant**	**Descriptive**	**Inferential**	**Statistical and practical significance**
	Type of co-existing CDL conditions per HIV/AIDS patient stratified by age group and gender	Gender Age group	Type of co-existing CDL conditions	Cross tabulate Frequency (%)	Chi-square	*p*-value < 0.05 Cramér's *V*
	General medicine prescribing patterns of ARV medication		Number of ARV medicine items	Frequency (%)		
Investigate the medicine claims profile of HIV/AIDS patients	General medicine prescribing patterns of ARV medication	ARV-items	Number of ARV-items per prescription	Mean ±SD, 95% CI		
			Number of ARV prescriptions per patient	Mean ±SD, 95% CI		
		Top 10 ARV products according to active ingredients	Number of ARV medicine items	Frequency (%)		
		Medicine product type: Fixed-dosage combination vs single-dose products in combinations Benefit category:	Number of ARV medicine items	Frequency (%)		

Objectives	Measurements	Variables		Statistical analysis		
		Independent	**Dependant**	**Descriptive**	**Inferential**	**Statistical and practical significance**
		Type of medicine (generic, original, etc.) Prescriber types: Dispensing medical practitioner Non-dispensing medical practitioner Type of provider				
		Medicine product type: Fixed-dosage combination vs single-dose products in combinations Benefit category: Prescriber types: Dispensing medical practitioner Non-dispensing medical practitioner Type of provider	Type of medicine (generic, original, etc.)	Cross tabulate Frequency (%)	Chi-square	*p*-value < 0.05 Cramér's V

1.6 Ethical considerations

This study was conducted after ethical approval was obtained from the Health Research Ethics Committee of the Faculty of Health Science, North-West University (Ethics number NWU- 00179- 14-A1-07).

Informed consent was not required from patients, medical schemes, prescribers, or medication providers because none were identified in the study.

1.7 Chapter summary

The study background emphasises the burden of HIV/AIDS in South Africa. The chapter also contains the problem statement, research aims and objectives, and the research methodology. The validity and reliability of the data source, the data fields and study variables were discussed. The ethical considerations were also included.

CHAPTER 2: BURDEN OF THE HUMAN IMMUNODEFICIENCY VIRUS (HIV) AND ACQUIRED IMMUNODEFICIENCY SYNDROME (AIDS)

2.1 Introduction

Chapter 2 discusses the burden of HIV and AIDS considering clinical, epidemiological, economic and social perspectives. HIV/AIDS medicine treatment patterns and factors influencing medicine treatment guidelines for PLWHA are also considered.

The clinical and epidemiological aspects provide a background on the prevalence, mortality and morbidity rates of HIV/AIDS globally, in sub-Saharan African countries and South Africa. The social and economic aspects of HIV/AIDS are also reviewed in the literature, considering the direct and indirect financial aspects of HIV/AIDS globally, the African region, South Africa, the patient and the family members involved.

2.2 Origin of HIV/AIDS

The first appearance of HIV/AIDS can be traced back as early as 1930-1950 where people were infected by handling and eating the meat of HIV-infected chimpanzees in Central West Africa (Kirk, 1996:746-759). HIV/AIDS began spreading in the Congo and central parts of Africa and then to the United States of America, from where it spread to other countries worldwide (Kaslow *et al.*, 2014:1003; Sharp & Hahn, 2011:3-8; Taylor, 2016:267).

In 1982–1983, a cluster of men having sex with men (MSM) presented with haemophilia and/or opportunistic diseases such as Kaposi's sarcoma and *Pneumocystis carinii* pneumonia, and, at the time, this presentation became known as the "gay syndrome" (Gottlieb *et al.*, 1981:1425-1431; Taylor, 2016:267). With time, it became noticeable that HIV/AIDS was an infectious disease transmitted by sexual contact with an HIV/AIDS infected person, the use of contaminated needles or exposure to contaminated blood or bodily fluids (Greene, 2007:S96; Kaslow *et al.*, 2014:1001; Yarchoan *et al.*, 2014:3). In 1983–1984, Montagnier at the Pasteur Institute isolated the lymphadenopathy-associated virus and Robert Gallo isolated the human T-cell lymph tropic as the cause of "the gay syndrome" (Greene, 2007:S96; Taylor, 2016:267). After these discoveries, the virus was called the human immunodeficiency virus, or HIV, and was known to be the cause of acquired immunodeficiency syndrome, or AIDS (Greene, 2007:S94-S97; Jones & Salazar, 2016:23-25; Kaslow *et al.*, 2014:1002).

HIV infection has four stages: acute HIV infection, the asymptomatic period, the symptomatic period, and the AIDS stage. About two to four weeks after HIV infection, a person develops flu-like symptoms (Zolopa, 2014:1276). In the acute stage, HIV duplicates and increases rapidly by resembling the duplicating mechanisms of retroviruses in that it attaches and fuses itself to the host cell, primarily the T-lymphocytes (CD4-cells) (Greene, 2007:S96; Jones & Salazar, 2016:23- 25; Taylor *et al.*, 2007:267). From inside the host cell, the virus uses the synthesis processes of the cell to multiply by turning ribonucleic acid (RNA) into deoxyribonucleic acid (DNA) (Levy, 2007:1). It reduces CD4-cells, which causes a weak immune response and a widespread state of inflammation (Freed, 2001:13-33). Not only does HIV damage CD4-cells, it also damages B-lymphocyte cells. B-lymphocyte damage results in autoimmunity, allergic and hypersensitivity reactions (Zolopa, 2014:1275-1276). During the acute stage of HIV, the level of virus concentration rapidly increases, and the risk for transmission is very high (Pope & Haase, 2003:847-849; Zolopa, 2014:1276).

During the second stage, known as the persistent or asymptomatic period, HIV reaches a stage of clinical latency. This stage is mostly asymptomatic as HIV continues to multiply in the body at a slower pace (Connor & Ho, 1994:4405-4406). Transmission can also occur during this stage, but transmission risk is lower because some cells have gone into a latent stage (Connor & Ho, 1994:4405-4406). Latent cells remain in the host cells forming a latent reservoir that may become active and start multiplying at any time (Zolopa, 2014:1276).

The third stage of HIV infection, the symptomatic period, produces severe weight loss, chronic diarrhoea with a duration of more than a month, persistent fever, oral candidiasis, oral hairy leucoplakia, pulmonary tuberculosis (TB) and bacterial infections such as pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia (DOH, 2018:11.13-11.15). Other infections and symptoms occurring in this stage include acute necrotising ulcerative stomatitis, gingivitis or periodontitis, anaemia, neutropenia and/or chronic thrombocytopenia (DOH, 2018:11.13-11.15).

AIDS is the last and most severe stage of HIV infection, where more than 20 HIV-related opportunistic diseases or cancers may be present (Centers for Disease Control and Prevention [CDC], 1993:507-514; Katzung & Trevor, 2015:835; Zolopa, 2014:1273-1275).

ART regimens have been shown to reduce HIV's mortality rate and the number of infections, particularly in the early stages of the disease (Greene, 2007:S96; Zolopa *et al.*, 2009:e5575). ART works by suppressing HIV in different stages of the HIV life cycle and stopping the progression of HIV/AIDS (Freedberg *et al.*, 2001:824-831). Therefore, all patients diagnosed with HIV infection should receive ART as soon as possible, regardless of their CD4-cell count. In an attempt to achieve comprehensive prevention, ART can even be given as pre-exposure prophylaxis (PrEP) to people at risk of HIV infection (Eholié *et al.*, 2016:27; Holodniy *et al.*, 2007:28).

ART is divided into different pharmacological classes (Eaton & Kalichman, 2016:4-13). ART typically combines two or more antiretroviral (ARV) medications from at least two different pharmacological classes to make the treatment regimen more potent and effective (World Health Organization [WHO], 2017a; Zolopa, 2014:1294-1296). ART helps reduce the risk of HIV transmission and increases the quality of life of PLWHA by suppressing HIV and the progression of the disease (Ledergerber *et al.*, 1999:863-868; Mamedicationa *et al.*, 2007:49-58). A variety of ARV medications that controls the progression and prevents disease transmission are available on the market. Regardless of the ART available, continuous attempts are made to create a vaccine against HIV/AIDS (Freedberg *et al.*, 2001:491; Rerks-Ngarm *et al.*, 2009:2214-2218).

The first ARV medication, zidovudine (AZT), was introduced in 1987 (Zolopa, 2010:1274). Despite the available treatment, the disease spread rapidly worldwide and infected 30 million people by 1995–1996 (Greene, 2007:S96). By 2006, a total of 23 million people had died from, and 40 million people were infected with HIV (Greene, 2007:S100). In 2006, once-a-day tablet treatments in the form of Atripla® (efavirenz (EFV), emtricitabine (FTC) and tenofovir (TDF)) were released on the market (Airoldi *et al.*, 2010:115-116; Taylor, 2016:267). Since the FDC tablet became available, the clinical outcomes of PLWHA improved rapidly (Pujari *et al.*, 2008:196).

Globally, the number of people receiving ART has increased from 611 000 in 2000 to 21.7 million in 2017 (WHO, 2017b). In eight out of 10 countries where ART enrolment increased, a reduction of HIV/AIDS prevalence was observed (Auld *et al.*, 2017:558-562). The target globally is that 33 million PLWHA receive ART by the year 2030 (WHO, 2017b). A total of 25.4 million people were receiving ART in 2019, comprised of 17.8 million in Africa, 2.5 million in the Americas, 2 million in Europe and 1.5 million in the Western Pacific (WHO, 2019a).

2.3 The burden of HIV/AIDS

Hessel (2008:94-96) describes the burden of disease as the entire collective outcomes of a specific disease or collection of harmful diseases concerning infirmities or disabilities in society. These outcomes include clinical or health aspects, economic implications to society and the social impact of the disease. The disease burden depends on identifying the associated risk factors and quantifying the estimations of mortality and morbidity by age, gender, and region (geographical location) (Hessel, 2008:94-96). Every disease and age group have risk factors that increase the clinical burden associated with the disease (Ezzati *et al.*, 2002:1347; Lopez *et al.*, 2006:1747-1748).

According to Lim *et al.* (2012:2225-2227), the risk factors associated with the disease burden of HIV/AIDS include behavioural factors (smoking, alcohol and substance abuse), lifestyle (sanitation, vitamin deficiency due to food supply), physiological factors, occupational risk factors and exposure to violence and abuse. Gore *et al.* (2011:2093) studied the global and regional burden of disease by investigating how the young adults' behaviour impacts disability-adjusted life years (DALYs), incidence and prevalence rate associated with HIV/AIDS. The study found that demographic factors, risk factors, age, sex, morbidity rate, and DALYs all contribute to disease burden. From a morbidity and mortality perspective, the factors mentioned above relating to the disease burden are important, but they do not reflect a complete picture of the harmful impact of a disease on human wellbeing (Lopez *et al.*, 2006:1747-1748).

From an economic perspective, the burden of disease and illness also relates to the indirect and direct costs of the disease (Russell, 2004:147-155) that affect the patient and the surrounding family members and dependants (Krentz & Gill, 2012:2). Direct costs affecting PLWHA include hospitalisation, utilisation of specialist services, consultations and laboratory testing (Krentz *et al.*, 2003:108-109; Russell, 2004:147-155). Indirect costs include expenses for caregivers, transportation fees, and income loss due to absenteeism or premature mortality (Marcellusi *et al.*, 2016:A523; Sarlon *et al.*, 2012:269).

Before combination ART was available, hospitalisation was a significant direct cost for HIV/AIDS (Krentz & Gill, 2012:1). Since the availability of combination ART, most of the expenses for PLWHA changed from in-hospital direct costs to out-patient direct costs due to combination ART, laboratory tests and healthcare provider visits (Krentz & Gill, 2012:2). Even where HIV/AIDS ART testing and consultation services with healthcare providers are provided for free at public health facilities in countries such as South Africa, patients still carry indirect costs such as travelling to

clinics, food, overnight accommodation, and loss of income due to leave or absenteeism (Chimbindi *et al.*, 2015:e52-e60).

There is a correlation between the prevalence of PLWHA, life expectancy, socioeconomic and health factors of a country (Mondal & Shitan, 2013:308). A country's economic growth depends on the workforce's health status and the life expectancy of the population, i.e., an increase in life expectancy improves a country's economic growth (Ogundari & Awokuse, 2018:131-133). Economic growth also relies on the workforce's health because it impacts their physical and mental capacity, productivity, the number of days worked and increases in wage costs (Ogundari & Awokuse, 2018:131).

The burden of HIV/AIDS in this study is discussed in subsequent paragraphs according to clinical and epidemiological impact, social impact, and financial and economic impact, as shown in Figure 2-1.

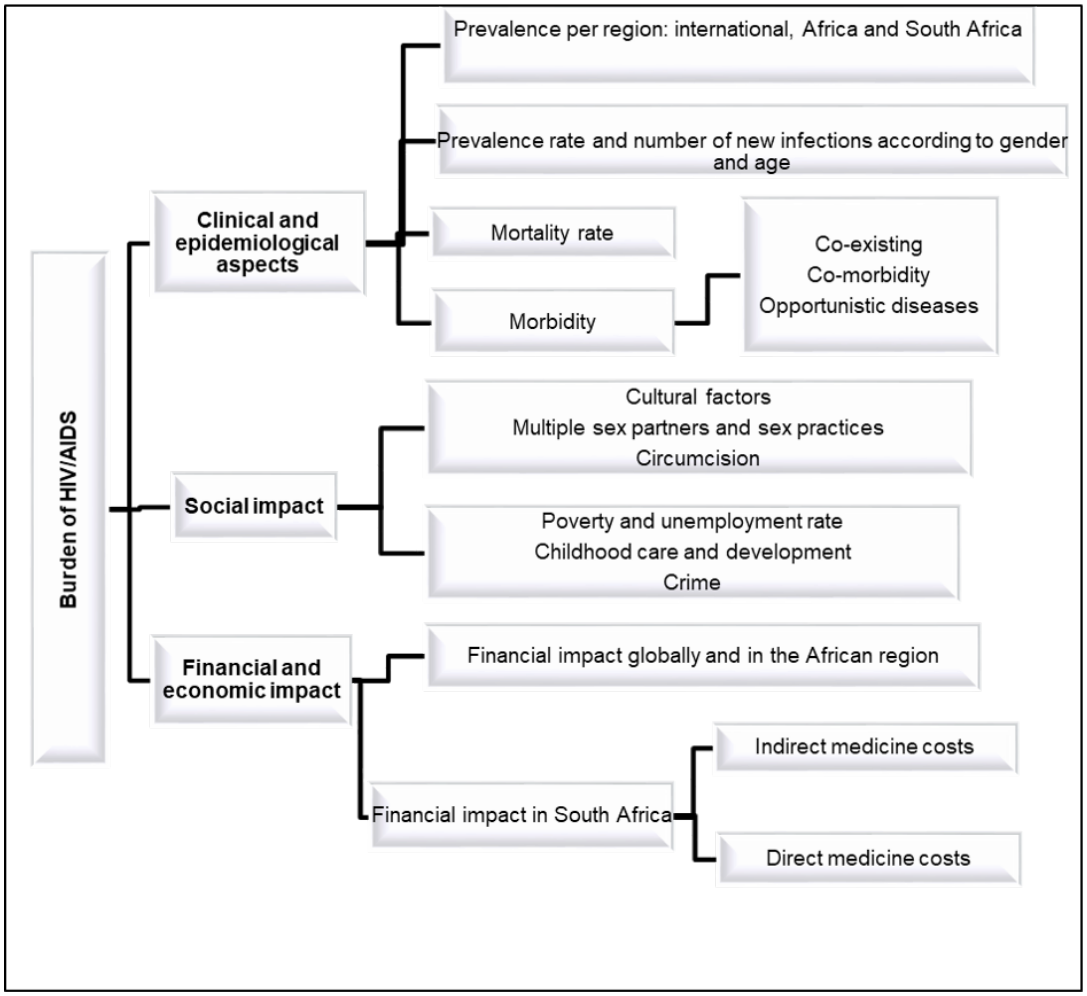


Figure 2-1: The burden of HIV/AIDS

2.3.1 Clinical and epidemiological aspects

Epidemiology includes the distribution of disease as well as the risk and environmental factors linked to the disease (Williams *et al.*, 2000:123-142). The prevalence and incidence of HIV/AIDS internationally in Africa and South Africa are discussed in subsequent paragraphs. The different age and gender groups affected by HIV/AIDS and the mortality and morbidity rates due to HIV/AIDS are also considered.

2.3.1.1 Prevalence per region

2.3.1.1.1 International prevalence

Since the HIV/AIDS pandemic started in the early 1980s until 2016, a total of 76.1 million people became infected with HIV/AIDS globally (UNAIDS, 2017a:1). The number of newly HIV-infected patients decreased steeply from 2.8 million in 2000 to 1.8 million in 2017 (WHO, 2018b). In 2017, the WHO aimed to reduce the number of new HIV/AIDS infections to less than 500 000 by 2020 and less than 200 000 by 2030 (WHO, 2017a). However, this aim seems to be out of reach, as the global number of new infections were only down to 1.7 million in 2019 (WHO, 2019a). Globally, there were 37.3 million PLWHA in 2018, a 20% increase since 2010 (WHO, 2018b; WHO, 2019a). The growing trend continues, with the number of PLWHA in 2019 estimated to be 38 million (WHO, 2019a).

Table 2-1 shows the number of PLWHA in 1990, 2005 and 2016 and the number of newly infected patients and HIV/AIDS mortalities in 2016 for international populations[9] as indicated by the UNAIDS (2017b). There was a decrease in the number of mortalities between 2016 and 2017, likely due to new post-2015 targets for ART treatment upscale globally (UNAIDS, 2020a; Meintjes *et al.*, 2017:1). The total HIV/AIDS-related adult and child deaths reported in 2016 were 1.1 million, of whom 10% were children under 15 years (UNAIDS, 2017a:1). The global estimates for children under the age of 15 increased to 1.8 million by 2019, with 150 000 new HIV infections and 95 000 AIDS-related deaths (UNAIDS, 2020a:29). According to WHO (2019a), 400 000

[9] The international population is divided into different regions by the UNAIDS (2017a). The regions include Asia and the Pacific, the Caribbean, Eastern Europe and Central Asia, East and Southern Africa, Latin America, the Middle East and North Africa, West and Central Africa, West and Central Europe, and North America.

PLWHA lived in the Eastern Mediterranean, 1.9 million in the Western Pacific, 2.5 million in Europe, 3.7 million in the Americas, 3.7 million in South-East Asia and 25.7 million in Africa.

The African region had 25.7 million PLWHA in 2017; the rate of new HIV infections in Africa had decreased 24% annually from 2000, and HIV-related deaths had declined 35% annually (UNAIDS, 2019a). Due to the reduced number of new HIV infections, no increase in the number of PLWHA in the African region by the year 2019 was reported by UNAIDS (2019a). Table 2-1 shows that the East and Southern African region accounted for the highest HIV prevalence (52.8% in 2016) and the highest number of infections (71% in 2017). In 2019, the UNAIDS (2020b:30) indicated that this region had 20.7 million PLWHA, with 730 000 adults and children infected with HIV and 300 000 deaths due to AIDS. Western and Central Africa had the second-highest HIV prevalence (16.6% in 2016) and the number of new incidences (28.2% in 2017). West and Central Africa have also shown high growth in its number of PLWHA, increasing from 1.9 million in 1990 to 6.1 million in 2016. By 2019, West and Central Africa had 4.9 million adults and children living with HIV/AIDS and 140 000 deaths were reported due to AIDS (UNAIDS, 2020b:30). Table 2-1 shows that the most newly-infected people in 2017 were in East and Southern Africa (790 000) and West and Central Africa (370 000). The number of HIV/AIDS-related mortalities was 420 000 in East and Southern Africa and 310 000 in West and Central Africa.

Europe had 2.3 million PLWHA in 2017. Relative to 2000, the number of new infections increased by 20% annually, whereas the number of HIV-related deaths decreased by 5% (WHO, 2017b). For 2019, the UNAIDS (2020b:30) reported that Eastern Europe and Central Asia had 1.7 million adults and children living with HIV, 35 000 adults and child deaths due to AIDS and 170 000 adults and children newly infected. In the same report, Western and Central Europe and North America had 2.2 million adults and children living with HIV, 65 000 adults and children newly infected with HIV and 12 000 deaths due to AIDS (UNAIDS, 2020b:30). The UNAIDS (2020b:30) indicated that Latin America had 2.1 million PLWHA,120 000 adults and children newly infected with HIV and 6900 deaths related to AIDS in 2019.

In Asia and the Pacific, high growth in the number of PLWHA was observed, growing from 440 000 to 4.5 million people from 1990 to 2005 and further increasing to 5.1 million people in 2016. In 2019, Asia and the Pacific accounted for the second-highest number of adults and children living with HIV (5.8 million), and it had 300 000 people newly infected with HIV and 160 000 deaths due to AIDS in 2019 (UNAIDS, 2020b:30). Table 2-1 shows that the number of newly HIV-infected people in 2017 was 270 000, with 170 000 AIDS-related deaths in the region in 2016 (refer to Table 2-1).

Table 2-1: The number of PLWHA in 1990, 2005 and 2016, the number of new infections in 2017, and the number of HIV-related mortalities in 2016

Region	Nr PLWHA, 1990	Nr PLWHA, 2005	Nr PLWHA, 2016	Nr new HIV/AIDS infections, 2017	Nr HIV/AIDS-related mortalities, 2016
Asia and the Pacific	440 000	4 500 000	5 100 000	270 000	170 000
The Caribbean	170 000	290 000	310 000	18 000	9 400
Eastern Europe and Central Asia	53 000	560 000	1 600 000	190 000	40 000
East and Southern Africa	4 800 000	16 200 000	19 400 000	790 000	420 000
Latin America	410 000	1 200 000	1 800 000	97 000	36 000
The Middle East and North Africa	15 000	150 000	230 000	18 000	11 000
West and Central Africa	1 900 000	6 500 000	6 100 000	370 000	310 000
Western and Central Europe and North America	1 100 000	1 600 000	2 100 000	73 000	18 000
Global totals	8 900 000	31 000 000	36 700 000	1 800 000	1 100 000

2.3.1.1.2 Prevalence in the African regions

The UNAIDS (2017a:3) divided the African continent into three regions: Eastern and Southern Africa, West and Central Africa, and the Middle East and North Africa. Table 2-2 shows the prevalence of HIV/AIDS in these regions, the number of new incidences (newly infected patients) and the number of HIV/AIDS-related deaths in 2005 and 2016.

From all African countries, the Western and Central African region accounted for the second-highest number of PLWHA (6.1 million people), representing 17% of PLWHA globally in 2016 (UNAIDS, 2017a:2-3), as is evident in Table 2-2. In the Middle East and North Africa region, the number of new HIV-infected incidences rose by 4%. According to the UNAIDS (2016c:5), Eastern and Southern Africa accounted for 53% of PLWHA globally in 2016. This high prevalence is despite the fact that from 2010 to 2016, the number of newly HIV-infected people in Eastern and

Southern Africa decreased by 29% and the number of HIV-illness-related deaths dropped by 42% (UNAIDS, 2017a).

Table 2-2: Frequency, number of newly infected people and the number of HIV-related deaths in 2005 and 2016 for Eastern and Southern Africa, West and Central Africa, and the Middle East and North Africa

Nations	2005			2016		
	Frequency of HIV/AIDS	Number of people newly infected with HIV	Number of HIV/AIDS-related deaths	Frequency of HIV/AIDS	Number of people newly infected with HIV	Number of HIV/AIDS-related deaths
Eastern and Southern African region						
Angola	140 000	21 000	7 600	280 000	25 000	11 000
Eritrea	21 000	750	1 700	15 000	520	540
Lesotho	240 000	20 000	15 000	330 000	21 000	9 900
Rwanda	210 000	13 000	15 000	220 000	7 500	3 300
South Sudan	150 000	17 000	8 100	200 000	16 000	13 000
United Republic of Tanzania	1 400 000	91 000	120 000	1 400 000	55 000	33 000
Botswana	300 000	15 000	13 000	360 000	10 000	3 900
Ethiopia	920 000	30 000	85 000	710 000	30 000	20 000
Madagascar	19 000	1 400	1 100	31 000	4 300	1 600
Mozambique	1 400 000	170 000	78 000	1 800 000	83 000	62 000
Swaziland	170 000	1 300	10 000	220 000	8 800	3 900
Zambia	920 000	69 000	64 000	1 200 000	59 000	21 000
Comoros	100	10	10	130	10	10
Kenya	1 600 000	91 000	130 000	1 600 000	62 000	36 000
Malawi	950 000	74 000	73 000	1 000 000	36 000	24 000
Namibia	180 000	13 000	11 000	230 000	9 600	4 300
South Africa	5 100 000	500 000	270 000	7 100 000	270 00	110 000
Uganda	1 200 000	110 000	84 000	1 400 00	52 000	28 000
Zimbabwe	1 300 000	91 000	100 000	920 000	40 000	30 000
Total	16 200 000	1 300 000	1 100 000	19 400 000	790 000	420 000

Nations	2005			2016		
	Frequency of HIV/AIDS	Number of people newly infected with HIV	Number of HIV/AIDS-related deaths	Frequency of HIV/AIDS	Number of people newly infected with HIV	Number of HIV/AIDS-related deaths
West and Central Africa						
Benin	58 000	4 600	4 100	67 000	3 600	2900
Chad	100 000	9 100	6 900	110 000	4 800	2800
Democratic Republic of the Congo	520 000	35 000	40 000	370 000	13 000	19 000
Guinea-Bissau	37 000	5 100	1 700	36 000	1 300	2 000
Gambia	16 000	2 200	820	20 000	1 300	1 100
Togo	130 000	8 500	8500	100 00	4 100	5100
Burkina Faso	120 000	4 400	11 000	95 000	3 400	3 100
Cameron	520 000	50 000	28 000	560 000	32 000	29 000
Congo	69 000	5 200	6 000	91 000	7 600	3 800
Equatorial Guinea	18 000	2 500	990	35 000	2 300	980
Ghana	380 000	18 000	34 000	290 000	20 000	5 000
Liberia	56 000	2 500	4 900	43 000	2 900	2 800
Niger	68 000	4 200	4 900	48 000	1 800	3 400
Senegal	45 000	3 900	2 500	41 000	1 100	1 900
Burundi	110 000	3 900	8 700	84 000	2 200	2 900
Central African Republic	160 000	8 100	14 000	130 000	8 700	7 300
Cote d'Ivoire	590 000	33 000	43 000	460 000	20 000	25 000
Gabon	53 000	3 600	3 200	48 000	1 700	1 500
Guinea	99 000	9 900	7 000	120 000	8 300	5 800
Mali	110 000	9 500	6 900	110 000	5 900	6 100
Nigeria	3 100 000	260 000	200 000	3 200 000	220 000	160 000
Sierra Leone	44 000	No available	2 200	67 000	5 300	2 800
Total	6 500 000	490 000	440 000	6 100 000	370 000	310 000

Nations	2005			2016		
	Frequency of HIV/AIDS	Number of people newly infected with HIV	Number of HIV/AIDS-related deaths	Frequency of HIV/AIDS	Number of people newly infected with HIV	Number of HIV/AIDS-related deaths
Middle East and North Africa						
Algeria	6 400	860	310	13 000	880	170
Egypt	3 500	530	160	11 000	1 600	320
Jordan	170	20	10	440	30	10
Sudan	28 000	4 600	1 200	56 000	5 000	3 000
Morocco	14 000	1 700	41	22 000	950	640
Saudi Arabia	4 900	540	80	8 200	430	210
Yemen	4 300	560	230	9 900	1 100	360
Djibouti	12 000	590	770	8 600	500	550
Islamic Republic of Iran	48 000	8 300	1 700	66 000	5 000	4 000
Lebanon	1 200	110	50	2 200	140	80
Somalia	27 000	2 300	1 800	24 000	1 800	1 700
Tunisia	810	130	20	2 900	320	80
Total	230 000	21 000	6 900	230 000	18 000	11 000

In the Middle East and North Africa region, the Islamic Republic of Iran had the highest rate of PLWHA (48 000 in 2005 and 66 000 in 2016). Sudan, where the number of people infected with HIV has increased from 28 000 in 2005 to 56 000 in 2016, was the country with the highest increase in the number of people infected with HIV from 2005 to 2016. From all countries in the Middle East and North Africa regions, Jordan and Tunisia had the least number of PLWHA.

In the West and Central Africa region, 6.5 million people lived with HIV/AIDS in 2005, decreasing to 6.1 million people in 2016. Nigeria had a total of 3.1 million PLWHA in 2005, increasing slightly to 3.2 million in 2016. Nigeria accounted for around 47.7% of the total PLWHA in the West and Central Africa region, making it the country with the highest prevalence rate. Equatorial Guinea and Gambia are the countries in this region with the least number of PLWHA.

In the Eastern and Southern Africa region (also refer to paragraph 2.3.1.1.3), South Africa had the highest number of people infected with HIV and the highest prevalence rate among all the

African countries and globally (Table 2-1 and Table 2-2). Kenya had 1.6 million PLWHA in 2005 with no increase in 2016, whereas the Republic of Tanzania and Mozambique each had 1.4 million PLWHA in 2005. In Mozambique, the number of PLWHA increased from 1.4 million in 2005 to 1.8 million in 2016. The Republic of Tanzania stayed at 1.4 million PLWHA. Eritrea and Comoros had the least number of PLWHA in the Eastern and Southern Africa region.

2.3.1.1.3 Prevalence in South Africa

South Africa represented 17% of the global HIV/AIDS burden in 2009, regardless of only representing 0.7% of the global population (Karim *et al.,* 2009:921). In 2016, South Africa had the highest HIV prevalence (19%) than other global countries (UNAIDS, 2017a). In 2019, it had 38 million PLWHA (UNAIDS, 2020b:2), representing 20.9% of PLWHA globally. South Africa's representation of the global prevalence rate increase from 17% to 20% in ten years (Karim *et al.,* 2009:921; UNAIDS, 2020b:2). In South Africa, 13.5% or 7.97 million people from the total population lived with HIV/AIDS in the year 2019 (Statistics South Africa, 2019:v).

In 2018, 9.4 million South Africans, or 16.4% of the population, were served by the private healthcare sector, compared to 83.6% of the population who received healthcare from the public sector (South Africa, 2015a:17; Statistics South Africa, 2018a). The private healthcare sector in South Africa is responsible for more than half of the country's total health expenditure (Mayosi *et al.*, 2012:2031; DOH, 2011:23). The CMS's annual report for 2018/2019 showed that PLWHA accounted for the fourth highest portion of beneficiaries registered for chronic disease management in the private healthcare sector (CMS, 2019:168).

In 2016, South Africa accounted for 15% of the global new HIV/AIDS infections and 11% of the global AIDS-related deaths (UNAIDS 2017a:2-3). However, from 2010 to 2016, South Africa's number of new HIV infections decreased by 49%, and AIDS-related deaths decreased by 29% (UNAIDS, 2017a:2-3). According to the mid-year population estimates for 2017, the rate of newly HIV-infected people had declined from 1.9% in 2002 to 0.9% in 2017 (Statistics South Africa, 2017:8).

In South Africa, the HIV/AIDS prevalence rate differs between settlement types, with the highest HIV/AIDS prevalence rate found in urban-informal settings (Gibbs *et al.,* 2020:e0230105). Factors contributing to the disproportionate HIV/AIDS prevalence rate between formal settlements and informal settlements may include lower access to education, higher unemployment rates and increased poverty (Gibbs *et al.*, 2020:e0230105; Hargreaves *et al.,* 2008:4003; Magadi, 2013:1645). The risk of acquiring HIV/AIDS is also dependent on settlement type, and settlement type ratios are different for each province (Gibbs *et al.*, 2020:e0230105).

There is a shortage of studies that reports the geographic distribution of PLWHA in South Africa (Gibbs *et al.,* 2020:e0230105). Table 2-3 lists the HIV/AIDS prevalence based on the nine provinces in South Africa in 2016, as reported by Statistics South Africa (2017:7-9).

Table 2-3: HIV/AIDS prevalence in the nine provinces of South Africa

Province	HIV/AIDS prevalence rate	
	2012	2016
KwaZulu-Natal	17.8%	18%
Mpumalanga	14.9%	15.2%
Free State	12.9%	12.9%
North West	12.5%	12.3%
Gauteng	12.9%	13.1%
Eastern Cape	11.2%	12.1%
Limpopo	7.9%	8.3%
Northern Cape	6.6%	6.8%
Western Cape	6.2%	6.6%

Table 2-3 makes it evident that the provinces contributing the most to the HIV/AIDS prevalence in South Africa were KwaZulu-Natal (18%), Mpumalanga (15.2%), Gauteng (13.1%) and Free State (12.9%). The North West province was the only province where prevalence declined by 0.2% from 2012 to 2016. The Eastern Cape had the highest increase in prevalence rate, whereas the Free State stayed the same. The prevalence in the rest of the provinces increased by 0.2% to 0.4%.

Medical schemes play an essential role in the private healthcare sector of South Africa. The private healthcare sector is mainly funded by patients who use medical schemes to cover their medical expenses. Sponsors of the private healthcare sector include health insurers, healthcare providers, employers, administrators, managed care organisations, brokers and patients who pay out of their own pockets for their medical and healthcare needs (Wayburne & Da Silva, 2007:63).

According to the CMS (2015b:8-11), HIV/AIDS was the chronic disease that showed the most growth compared to the other CDL conditions in the private healthcare sector of South Africa. The CMS 2015/2016 annual report (2015a:7-9) shows that the number of patients treated for HIV/AIDS in the medical scheme environment of South Africa increased as follows from 2008 to 2015: 6.6 cases per 1 000 in 2008, 14.6 per 1 000 in 2012, 17.4 per 1 000 in 2013, 27.7 per 1 000 in 2014 and 30.7 per 1 000 patients in 2015. In 2016, the number of PLWHA in treatment ranked

fourth among chronic diseases in the medical scheme environment. In 2016 and 2017, the HIV/AIDS coverage[10] ratio in the medical schemes' environment was 60%, the highest of all CDL conditions (CMS, 2016:139). The CMS (2018a:140) reported that HIV/AIDS coverage increased to 80% by 2018.

2.3.1.2 Prevalence according to age and gender group

Globally, 35.1 million adults and 1.8 million children lived with HIV/AIDS in 2017, and the majority (18.2 million) were women (WHO, 2017b). Each age group have unique challenges that can increase their risk of being infected with HIV (UNAIDS 2016c: 7). The life cycle approach from UNAIDS aims to identify factors that can increase HIV infections to help personalise and find effective strategies to reduce new incidences (UNAIDS 2016c:7-9).

Young adults are a vulnerable group globally and, in some cases, have grown up in challenging circumstances because of a lack of food and education as well as exposure to violence and crime at a very early age (UNAIDS, 2016c:6). Students tend to be exposed to risky sexual practices, harmful injectable medications and increased alcohol consumption (Alamrew *et al.*, 2013:2-8; UNAIDS, 2016c:6). The prevalence rate of HIV among youth aged 15–24 reduced from 7.3% in 2002 to 4.6% in 2017 (Statistics South Africa, 2017:7). In 2019, males aged 15-24 years represented 9% of new HIV infections in sub-Saharan Africa and females 24% (UNAIDS, 2019:19).

From 2002 to 2017, the HIV/AIDS incidence in women continuously stayed higher than that of men, whereas the prevalence in youth aged 15–24 years declined from 7.31% to 4.64% (refer to Table 2-4). The overall incidence rate for both men and women declined from 1.90% in 2002 to 0.91% in 2017 (refer to Table 2-4). Table 2-4 depicts that the global prevalence for women was higher than the worldwide prevalence of men in the 15–49 years age group (WHO, 2017b). This trend is similar to South Africa's prevalence rate according to gender in Table 2-6.

[10] Coverage refers to the benefits provided or paid by the medical schemes under PMB.

Table 2-4: HIV/AIDS global prevalence rate for different gender and age groups and the incidence rate for the age group 15-49 years from 2002 to 2017

Year	Incidence rate (%)			Prevalence rate (%)
	Women aged 15–49 years	Men aged 15–49 years	Youth aged 15–24 years	Adults aged 15–49 years
2002	20.23	17.65	7.31	1.90
2005	20.65	17.89	6.78	1.86
2008	21.00	18.11	6.56	1.74
2012	21.53	18.43	5.82	1.21
2015	21.34	18.17	4.92	1.01
2017	21.17	17.98	4.64	0.91

Table 2-5 shows the global HIV/AIDS prevalence rate according to gender and age, as indicated by UNAIDS (2016c:78).

Table 2-5: Global prevalence rate of HIV/AIDS in men and women ages 0-60+ years in 2008 and 2012 globally

Age (Years)	Global prevalence rate (%)			
	2008		2012	
	Men	Women	Men	Women
0–14	3.1	2.4	2.3	2.4
15–19	2.5	6.7	0.7	5.6
20–24	5.1	21.1	5.1	17.4
25–29	17.3	32.7	17.3	28.4
30–34	25.8	29.1	25.6	36.0
35-39	18.5	28.4	28.8	31.6
40–44	19.2	16.3	15.8	28.0
45–49	8.4	14.1	13.4	19.7
50–54	10.4	10.2	15.5	14.8
55–59	5.5	7.7	5.5	9.7
60+	3.5	1.8	4.6	2.4

Table 2-5 shows that the highest global HIV/AIDS prevalence rate for both men and women in 2008 and 2012 was 25–39 years. The prevalence in women was as high as 32.7% in 2008 for the 25–29 year age group, which reduced to 28.4% in 2012. The prevalence in women was higher in the age groups 30–34 years (36% in 2012), 25–29 years (32.7% in 2008 and 28.4% in 2012), and 35–39 years (31.6% in 2012). The prevalence for men was higher for the age groups 30–39 years: 25.8% in 2008 and 25.6% in 2012 for ages 30–34 years and 28.8% for ages 35–39 years in 2012.

Table 2-5 shows that adults' global HIV/AIDS prevalence was the lowest for men 55-59 years and women above the age of 60. Age is a factor that contributes to co-existing diseases and comorbidities (Al-Dakkak *et al.*, 2013:413; Wing, 2016:64). Regardless of the effective ARV medications that increase life expectancy and reduce AIDS-related deaths, HIV/AIDS may accelerate the ageing process (Lopez-Otin *et al.,* 2013:1216; Wing, 2016:61). The ageing process in people affects numerous biological mechanisms, including mitochondrial function, stem cell exhaustion, intercellular communication, immune function (due to CD4-cell depletion) and loss of proteostasis, among others (Lopez-Otin *et al.,* 2013:1194-1210; Horvath & Levine, 2015:1573). Globally, ART's availability led to improved prognoses for PLWHA, causing a change in demographics as this population group was ageing (O'Keefe *et al.,* 2010:1145; Wing, 2016:63). At the end of 2010, more than half of the PLWHA in San Francisco were older than 50 years, and predictions suggest that by 2030, more than three-quarters of the PLWHA in San Francisco would be older than 50 years of ages (O'Keefe *et al.*, 2010:1145).

Table 2-6 indicates that globally and in South Africa, women aged 15–49 years had a higher HIV/AIDS prevalence than men of that age (UNAIDS, 2016b).

Table 2-6: Gender and age of PLWHA

Gender and age in years of PLWHA	HIV/AIDS prevalence globally	HIV/AIDS prevalence in South Africa
Females aged 15–49	17 800 000	4 100 000
Males aged 15–49	16 700 000	2 600 000
Children aged 0–14	2 100 000	320 000

In 2017, the WHO (2017b:30) estimated that 12.6% of the total population in South Africa is HIV/AIDS-infected. In 2012, South Africa's prevalence rate was the highest in women aged 30–34 years and men aged 35–49 years (Shisana *et al.*, 2012:7-8). One in every five women aged 15–49 years were living with HIV in 2012, and the number of new incidences was 1.7 times higher

in women than in men for that age group (Statistics South Africa, 2017:7). Shisana *et al.* (2012:7 - 8) suggested that the age discrepancy might be because young girls aged 15–19 years may have older sex partners, leading to a cycle where older men would spread HIV to these girls. As the girls mature, they spread HIV to their partners (Shisana *et al.*,2012:137). In the age group of 25-49, women represented 25% of the new HIV infections in sub-Saharan Africa in 2019, and men around 23% (UNAIDS, 2019:19). In sub-Saharan Africa, girls between the ages of 15 and 19 years are twice as likely as boys to be living with HIV (UNAIDS, 2020b).

The prevalence of children with HIV infection is concerning both globally and in South Africa (refer to table 2-6). Although the number of newly infected children aged 0–14 years dropped by 51% from 2010 to 2015, the increase in global coverage of services is important to prevent mother-to-child HIV transmission (Liamputtong, 2013:6-7; UNAIDS, 2016c:6). In 2019, children represented 24% of new HIV infections, and these infections were linked to the mothers not having access to healthcare services during pregnancy or breastfeeding (UNAIDS, 2019:174). In sub-Saharan Africa, the UNAIDS (2019:19) reported that boys 0-14 years accounted for 7% of new HIV infections and girls of the same age group for 6%.

Similar to global HIV/AIDS prevalence rates (Table 2-5), the prevalence rate for female medical aid beneficiaries in South Africa aged 25–54 years was higher than in males in the same age group from 2008 to 2013 (CMS, 2015a:42-44). Male beneficiaries aged 40–44 years had the highest HIV/AIDS prevalence than other male age groups (CMS, 2015a:43). In the medical scheme environment, the number of females treated for HIV was 17.45 per 1 000 women beneficiaries, whereas the male beneficiaries were lower at 15.34 per 1 000 male beneficiaries for all ages (CMS, 2017b:50-51).

2.3.1.3 Mortality rate

In the United States, the HIV/AIDS mortality rate increased rapidly for the first ten years into the early 1990s. By 1992, HIV/AIDS was the leading cause of death in men aged 25–44 years in the country (Kaslow *et al.,* 2014:1015). From 1980 to 2006, the mortality rate increased annually by 19.4%, reaching its peak in 2006. However, from 2006, AIDS-related mortality reduced at a rate of 4.17% annually, most likely due to increased ART coverage globally. Only 28 000 deaths related to HIV/AIDS occurred in North America, Western America and Central America in 2011 (Kaslow *et al.*, 2014:1015).

Globally, by the year 2010, HIV/AIDS was the fifth-highest disease burden globally as measured by DALYs; as it constituted 2.8% of global deaths and made up 3.3% of the worldwide disease burden (Ortblad *et al.*, 2013:2005-2015).

In 2016, the three regions accounting for the highest mortality rates due to HIV/AIDS were Eastern and Southern Africa (470 000), Central and West Africa (330 000), and Asia and the Pacific (180 000) (UNAIDS, 2016a:4) (refer to Table 2-2). Out of the 470 000 deaths in the Eastern and Southern African region in 2016, South Africa accounted for 26.1% or 110 000 deaths. In 2015 and 2016, HIV/AIDS was the fifth-highest cause of mortality in South Africa (Statistics South Africa, 2018b:32). Table 2-7 shows the percentage of deaths due to HIV/AIDS in South Africa from 2002 to 2016 (Statistics South Africa, 2018b:32).

Table 2-7: The HIV/AIDS mortality rate in South Africa from 2002 to 2016

Year	HIV/AIDS mortality rate (%)
2002	39.6
2004	45.8
2006	47.7
2008	43.8
2010	40.8
2012	33.0
2014	28.8
2016	27.9

In sub-Saharan Africa, there has been a correlation between the number of AIDS-related deaths, that decreased from 1 million in 2006 to 580 000 in 2018, and the decrease in treatment interruption, reported to be 100% in 2006 and reduced to 20% by 2018 (UNAIDS, 2019:22). Table 2-7 indicates that the mortality rate in South Africa due to HIV/AIDS increased until 2006 and then started reducing.

The average life expectancy at birth for a person without HIV/AIDS in South Africa is 65 years for males and 71 years for females (Statistics South Africa, 2017:7-8). Life expectancy in South Africa decreased to 49.5 years between 1990 and 2000 due to AIDS-related mortalities (Teeraananchai *et al.*, 2017:256-257). The life expectancy of PLWHA is affected by factors such as gender, region, lifestyle (alcohol use, smoking, and nutrition), comorbidities, co-existing diseases, infections not related to HIV/AIDS, renal disease, violence, medication abuse and suicide (French *et al.,* 2009:399; Rodger *et al.*, 2013:979; Wandeler *et al.,*2016:499-500; Wing, 2016:62). The reduced mortality rate portrayed in Table 2-7, could have been the result of the introduction of once-a-day tablet ARV treatments were released on the market in 2006 (Airoldi *et al.*, 2010:527; Taylor, 2016:446).

The use of ART in middle- and low-income countries has shown to improve life expectancy in PLWHA by ten years for women and eight years for men (Teeraananchai *et al.*, 2017:257-263). In South Africa between 2002 and 2012, the mortality rate of men on ART up to ten years after HIV infection was higher than that of women (Shisana *et al.*, 2012:xxix). In 2012, within ten years of HIV infection, 19% of women had died, while 34% of men had died (UNAIDS, 2017c:3).

In South Africa in 2001, Statistics South Africa (2017:4) estimated that 40% of adult deaths for the age group 15-49 years were due to HIV/AIDS, and it accounted for 25% of overall deaths for all ages. However, from 2005 to 2016, the number of AIDS-related deaths in South Africa decreased from 270 000 to 110 000 (refer to Table 2-2). The mid-year population statistics in 2016 indicated that the number of deaths due to HIV/AIDS reached a turning point in 2005-2006 at 47.4-47.7%, decreasing to 25.03% in 2017 (Statistics South Africa, 2017:8). At its height in 2005, HIV/AIDS was the third leading cause of death in males and the fifth leading cause of death in South Africa (Statistics South Africa, 2018b:55).

AIDS-related deaths in the early 21st century were due to HIV/AIDS-related infections and malignancies, but this trend reduced as ART emerged and usage increased (Wing, 2016:62). The death rates of HIV/AIDS patients with co-existing diseases such as liver disease and cardiovascular disease, among others, reduced with increased ART (Wing, 2016:62; The Antiretroviral Therapy Cohort Collaboration*,* 2010: 1390-1391; Smith *et al.,* 2014:248).

2.3.1.4 Comorbidities as well as co-existing and opportunistic diseases in PLWHA

PLWHA has an immune dysfunction due to depletion of CD4-cells, immune cell deterioration with age and chronic inflammation, regardless of successful viral suppression (Silverberg, 2015:517- 518; Simard *et al.,* 2011:1089). Over time, the immune dysfunction leads to co-infection with organisms such as bacteria (TB, bacterial pneumonia, staphylococcal skin infections), viruses (cytomegalovirus, hepatitis A, B, C, D and F), parasites (cryptosporidium, *pneumocystis jirovecii*) or fungi (candidiasis, cryptococcus, coccidioidomycosis) (Sonenklar, 2011:41-45; WHO, 2016d:1). In a healthy patient where the immune system is not weakened, patients would be able to recover from these infections, referred to as opportunistic diseases (Sonenklar, 2011:41-45).

Jonsson *et al.* (2013:155-159) found that patients with a low CD4 cell count presented with opportunistic infections or diseases. Some viruses such as human papillomavirus (HPV) can cause cervical cancer in women, and human herpesvirus 8 can cause Kaposi's sarcoma (Sonenklar, 2011:45). Kaposi's sarcoma and non-Hodgkin B cell lymphoma are higher in PLWHA (Patel *et al.,* 2008:728). Primary central nervous system lymphoma, lung, live- and anal cancer,

cervix carcinoma, Hodgkin's lymphoma, as well as breast, colon and prostate cancers are all related to PLWHA and ART (Franceschi *et al.,* 2010:421-422*;* Patel *et al.*, 2008:728; Rasmussen *et al.,* 2012:e297-e298; Silverberg, 2015:517-518; Simard *et al.,*2011:1089).

The list of potential HIV/AIDS-related comorbidities that are dependent on the clinical HIV/AIDS stage, as found in the STGs of South Africa (DOH, 2018:11.13-11.15) is given in Table 2-8.

Table 2-8: Clinical stages of HIV/AIDs and related comorbidities

Clinical stage	Related comorbidities and infection
Stage 1	Asymptomatic HIV infection, persistent Generalised lymphadenopathy
Stage 2	Persistent respiratory tract infections (sinusitis, otitis media and pharyngitis) Herpes zoster (shingles) Angular stomatitis Persistent oral ulceration Papular pruritic eruption Seborrhoeic dermatitis *Candida albicans*
Stage 3	Persistent oral candidiasis (thrush) Oral hairy leucoplakia Pulmonary TB Severe bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis or bacteraemia) Acute necrotising ulcerative stomatitis, gingivitis or periodontitis Unexplained anaemia (< 8 g/dL), neutropenia (< 0.5 × 109/L) and/or chronic thrombocytopaenia (< 50 × 109/L)
Stage 4	HIV wasting syndrome Extrapulmonary tuberculosis *Pneumocystis* pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital or anorectal, or visceral at any site) Oesophageal candidiasis (or candidiasis of trachea, bronchi or lungs) Kaposi’s sarcoma Cytomegalovirus infection (retinitis or infection of other organs) Central nervous system toxoplasmosis HIV encephalopathy Extrapulmonary cryptococcosis including meningitis Disseminated non-tuberculous mycobacterial infection Progressive multifocal leukoencephalopathy

A study by Oni *et al.* (2015:20) investigated the distribution of comorbidities in the medical scheme environment in South Africa. The study found that 94% of patients presented with two morbidities, where diabetes mellitus type 2 (DM2) and hypertension were the most common, and 5% presented with three morbidities, where DM2, hypertension and HIV were the most common. Among TB patients, HIV was the most common comorbidity followed by hypertension and DM2 (Oni *et al.*, 2015:20).

According to the 2013/2014 CMS annual report, the number of medical scheme beneficiaries with two CDL conditions increased by 29.3% from 2008 to 2013, and beneficiaries with three CDL conditions increased by 50% from 2008 to 2013, indicating an upward trend in beneficiaries with multiple CDL conditions (CMS, 2015b:42). The prevalence of CDL conditions in the medical scheme environment was ranked as follows: hypertension (1st), hyperlipidaemia (2nd), DM2 (3rd) and HIV/AIDS (4th)[11] (CMS, 2018b:7-8).

2.3.2 Financial and economic impact

2.3.2.1 Global financial burden

Recognising the HIV/AIDS epidemic as a severe threat and targeting it as one of the millennium development goals have resulted in increased global investment and funding (Masur *et al.*, 2014:1310-1311; Zolopa *et al.*, 2009:e5575-e5576). However, HIV/AIDS funding already started increasing in the 1990s, at least in some countries, and federal funding continued to grow each year. The AIDS Medication Assistance Program was established in 1987 in the USA and expanded dramatically in 1997, assisting low-income patients by providing them ART (Sonenklar, 2011:103). The US's National Institutes of Health's programme increased its budget by 35% from US$738.5 million in 1996 to US$996.3 million in 1997 (Sonenklar, 2011:102-105). Funding towards the HIV/AIDS programmes was primarily invested in treatment and prevention of HIV/AIDS (Schneider, 2016:1475). HIV/AIDS response funding has been provided with US$109.8 billion between 2000 and 2015, globally. All over the world, HIV/AIDS funding for development increased annually by 22.8% since 2000 but dropped to 1.3% between 2010 and 2015 (Schneider, 2016:1475).

[11] HIV/AIDS is not considered a CDL condition, but the purpose of the ranking the CMS included it to indicate that medical scheme beneficiaries showed an increase in co-existing diseases, and HIV/AIDS formed part of the PMB benefits.

Apart from global alliances such as the World Bank, private non-profit groups and foundations such as the PEPFAR program, American Foundation for AIDS Research, the National Institutes of Health Office and AIDS Research, Black AIDS Institute, the Elizabeth Glaser Paediatric AIDS Foundation, American Academy of HIV Medicine and Bill and Melinda Gates foundation were contributing financially toward HIV/AIDS (Sonenklar, 2011:103-107). In 2009, the United States of America was the largest donor in the world, followed by the United Kingdom, Germany, the Netherlands, France and Denmark (Sonenklar, 2011:104). However, since 2008, the number of donations has decreased (Sonenklar, 2011:104). The decline of the United States bilateral funding had the greatest impact on reduced donations, with a decline of more than US$1 billion since 2010 (UNAIDS, 2020c). Despite this decrease, the United States government was the main donor toward HIV-funding in 2019, followed by the United Kingdom, France, the Netherlands and Germany (UNAIDS, 2020c).

By 2007, it was found that local governments of low-income countries will need to fund at least 12% of their total resources for the management of HIV/AIDS (Amico *et al.*, 2010:e12997). Lower- to middle-income countries is estimated to fund 45% of their HIV-related needs, and middle- to upper-income countries funds 95% of their HIV-related needs (Amico *et al.*, 2010:e12997). Private and public international donors, the World Bank, PEPFAR and the Global Fund help fund middle- and low-income countries affected by HIV/AIDS (Amico *et al.*, 2010:12997). This funding supplements each country's internal national budget for HIV/AIDS and required public health services according to its needs and the size of its budget (Mayosi & Benatar, 2014:1344-1345). By 2019, US$18.6 billion were made available for HIV/AIDS response in low- and middle-income countries (UNAIDS, 2020d). The UNAIDS estimated HIV funding required by the end of 2020 to be US$26.2 billion, compared to the $19.8 billion that was available by the middle of 2020 (UNAIDS, 2020d).

Because of the decrease in funding from donors, Harman (2010:1-2) recommended low- and middle-income countries to fund their own HIV needs by targeted budget allocations, increasing tax revenue and improve efficiency. Examples of innovative funding that has been implemented by various countries include special tax levies such as levies on remittances, mobile phone usage, alcohol and tobacco purchases, or air passenger travel (Harman, 2010:3-13). These innovative funding methods help reduce the country's dependence on international assistance. Another recommendation is to partner with private sectors and multilateral funding (Haman, 2019:3-13; UNAIDS, 2016b:67-69).

2.3.2.2 Financial impact on Africa

According to Harman (2010:6-7), HIV/AIDS reduces the development of the African economy, with the impact greatest on small businesses in productive sectors due to the reduction of the adult workforce. This reduction in the workforce due to high morbidity and mortality rates also leaves children orphaned and households without income. Poverty rates increase as breadwinners are unable to work and provide for their families. The resulting economic strain on small businesses increases retrenchment, reduces job opportunities and consumer spending and thus slows business investments (Amico *et al.*, 2010:e12997).

Harman (2010:6) argues that reduced GDP rates can measure the great effect of HIV/AIDS on reducing the development of the African economy. The fiscal demands on African governments are high, leaving minimal resources in needed areas to minimise the impact of HIV/AIDS (Harman, 2010:6). Socioeconomic challenges such as poverty, food shortage, lack of sanitation, limited access to healthcare and social inequities are all factors that further increase vulnerability to the spread of HIV/AIDS (Harman, 2010:6). For this reason, Harman (2010:6-7) argues that emphasis should be placed on socioeconomic factors associated with HIV/AIDS. Healthcare provision should be increased, and long-term strategic plans to prevent the spread of HIV/AIDS and reduce mortality should be implemented. Educational and training programmes should be implemented and infrastructure provided regardless of the limited financial resources.

The African region accounted for 45% of the fiscal HIV burden[12] globally in 2015 (Atun *et al.*, 2016:e009656; Collier & Sterck, 2018:357). In West and Central Africa, HIV/AIDS funding peaked in 2013, followed by an annual reduction of 14% between 2015 and 2019 (UNAIDS, 2020a:103). In 2019, the sources of funding for HIV/AIDS response in this region included domestic spending (36%), bilateral contributions from the United States Government (35%), and the Global Fund (20%) (UNAIDS 2020a:103). In the Middle East and North Africa in 2019, domestic funding was the main funder for HIV response (77%), followed by the Global Fund (14%), the United States Government (2%) and international sources (7%) (UNAIDS, 2020a:305). HIV/AIDS funding for Eastern and Southern Africa peaked in 2017(UNAIDS, 2020a:47). In 2019, domestic funding was responsible for 41% of the HIV funding in this region, followed by United States Government bilateral funding (40%) and the Global Fund (10%) (UNAIDS,2020a:47).

[12] Atun *et al.* (2016:e009656) used cost, cost-effectiveness, coverage and epidemiological data to determine the HIV-burden

The increasing financial responsibility to treat all HIV-infected patients is evident, especially in the sub-Saharan Africa region (Atun *et al.*, 2016:e009656). Treating all HIV-infected patients has an ethical as well as an economic impact. However, these countries have other responsibilities to sustain the poor and less fortunate people, making it problematic to balance (Remme *et al.*, 2016:66-67).

2.3.2.3 Financial impact on South Africa

In 2004/2005, the South African government allocated R1.2 billion toward HIV/AIDS, which gradually increased to R17.5 billion in 2016/2017 (Blecher *et al.,* 2016:207*)*. The South African government subsidy increased from R4.5 billion in 2009/2010 to R8.4 billion in 2010/2011 due to extending ART, enhancing prevention of mother-to-child transmission (PMTCT) programmes, promoting HIV and TB treatment integration, and increasing investments in HIV prevention programmes (Mayosi *et al.,* 2012:2030). The government continuously switch thousands of patients from treatment programmes funded by the United States' PEPFAR to South African government services (Mayosi *et al.*, 2012:2030).

PEPFAR initiated HIV/AIDS funding in South Africa in 2004 with US$89 million, and it peaked in 2008 at over US$590 million (Lodge, 2015:1573). PEPFAR funds decreased annually and reached US$250 million by the year 2017. PEPFAR funded treatment for both HIV and TB, specifically the public sector (Lodge, 2015:1573). In 2019, 40% of HIV-funding in the Eastern and Southern Africa region came from global funding, with South Africa accounting for the highest percentage of domestic spending (UNAIDS, 2020a:47). The National Revenue Fund of South Africa increased the allocated budget for primary healthcare to help relieve HIV/AIDS (UNICEF, 2018:14-17; WHO, 2016b:1).

The United Nations Children's Fund (UNICEF, 2018:7) has shown that conditional grants help prevent HIV/AIDS through reducing poverty and increasing education (school attendance), which are the main drivers in behavioural changes. South Africa's budget for HIV/AIDS, TB and maternal and child development reflects this finding, with an increase of 7.6% for the 2017/2018 fiscal year (Pettifor *et al.* 2012:1729-1738). South Africa's budget for conditional grants for the 2017/2018 fiscal year ranged from R500 million in Mpumalanga to R1.4 billion in Kwa-Zulu Natal. Gauteng and the Western Cape had the lowest budgeted amount allocated to primary healthcare (about 26%) as these provinces had a larger number of individuals that have access to private healthcare and medical aid services (UNICEF, 2018:8-9). Each province has a limited budget to achieve comprehensive care, but other priorities that also needs attention cause substantial variation in

all areas. For example, in 2015, Mpumalanga spent 25% of its budget on healthcare services, whereas the Western Cape spent 36% of its budget on health (UNICEF, 2018:11-12).

Similar to the rest of Africa, as discussed in paragraph 2.3.2.2, South Africa's economy is negatively impacted by high fiscal demands and socioeconomic challenges. Health spending of a government is determined by the country's economic growth (Blecher *et al.,* 2016:209*)*. In 2013/2014, 4.4% of South Africa's GDP, or R148.9 billion, was spent by the public healthcare sector, compared to R155.7 billion spent by the private healthcare sector (South Africa, 2015b:48). The largest public healthcare spending was by the provincial DOH and the medical schemes in private healthcare spending (South Africa, 2015b:48). South Africa spent 8.5% of its GDP on health in 2015/2016, of which 4.1% was allocated to the public health sector (South Africa, 2015b:17). These inequities in health funding in South Africa benefits the rich, and the government's contribution of large amounts to medical schemes for staff increases the inequity (South Africa 2015b:18).

The 90-90-90 target to expand treatment to all HIV-infected people aims to have 90% of all HIV-infected diagnosed, with 90% of those diagnosed on ART, and 90% of those treated to have viral suppression (UNICEF, 2018:14-17; UNAIDS, 2020a). This target challenges both the public and the private healthcare sector in South Africa. Within a reduced fiscal space, increased HIV/AIDS prevention, screening and treatment procedures were required, and the higher demand for healthcare staff and facilities raised financial responsibilities (Atun *et al.,* 2016:e009656; Blecher *et al.,* 2016:216-217).

The Medical Schemes Act (31 of 1998) was amended to include HIV/AIDS as a PMB in 2004, benefitting medical schemes beneficiaries but increasing the fiscal burden for medical schemes (South Africa, 2003; South Africa, 2009)). The increase in stipulated benefits of HIV-infected beneficiaries is likely to increase expenses (CMS, 2018b:19-20). Expenses of beneficiaries with HIV/AIDS and/or other CDL conditions include general practitioner and specialist visits, medicine usage and hospital admissions (Wayburne & Da Silva, 2007:63). Prevention of HIV and other chronic diseases is important to reduce the fiscal burden on medical schemes (CMS, 2017a:34).

According to the CMS report on CDL condition prevalence and expenditure for 2016/17, HIV was the fourth most prevalent condition after hypertension, hyperlipidaemia, and type 2 diabetes mellitus (CMS, 2017a:34). While elderly patients have a higher tendency to have one or more chronic diseases that are costly to medical schemes (CMS, 2017c:34), younger and sexually active individuals are more likely to be infected with HIV/AIDS, which can also lead to high expenditure for the medical scheme (CMS, 2017a:141).

The HIV/AIDS coverage provided for medical scheme members in 2017 was 81% for ART, 74% for monitoring and diagnostic tests and 75% for viral load and CD4 cell count testing (CMS, 2017a:146). In 2015, the expenditure on medicines for the treatment of two or more CDL conditions increased from R 2 800 per beneficiary for a single condition to R4 200 for two CDL conditions, R6 400 for three CDL conditions, and R13 900 and more for five (or more) conditions per medical aid beneficiary[13] (CMS, 2017a:136).

Thus, the 90-90-90 target overburdens South Africa's healthcare sector due to the high prevalence of PLWHA that requires treatment (Mayosi & Benatar, 2014:1345; UNAIDS, 2020a). There are different responses to help curb this HIV epidemic in South Africa. One response is implementing universal healthcare services to all South Africans through National Health insurance (NHI) (Osler *et al.*, 2018:S118-S122; UNAIDS, 2016b:3-11). The NHI will require financing mechanisms to raise national revenue (Blecher *et al.,* 2016:215*)*. Due to South Africa's low economy and high debt, and reduced financial support, health spending can be constrained (Blecher *et al.,* 2016:215*)*. These fiscal constraints can reduce HIV/AIDS spending (Blecher *et al.,* 2016:215*)*. From a fiscal viewpoint, the reduction of ART-cost per unit was beneficial as it led to substantial savings (Blecher *et al.,* 2016:217*)*. Furthermore, fiscal constraints require effective allocation toward HIV/AIDS service delivery to achieve greater value for money for both the public and the private healthcare sector (Blecher *et al.,* 2016:217*)*. The private healthcare sector in South Africa is costly while the public healthcare system is overburdened and inequity is prominent, particularly in the rural areas (Mayosi & Benatar, 2014:1344; WHO, 2016e).

From a business perspective, the increase in PLWHA and other chronic diseases in the work environment increases absenteeism, employees' possible death, and incapability to work, directly impacting recruitment and retention (Wayburne & Da Silva, 2007:64). The Overseas Development Institute (2007:30) has indicated that the reduction in workforce negatively impacts small businesses, and investors are less attracted to invest in the economy. It results in increased job losses and poverty, driving other factors that increase vulnerability to HIV/AIDS. Mortality and morbidity caused by HIV/AIDS deprive the economy of labour supply and productivity, reducing human development achievements, increasing gender inequality and making families more vulnerable to poverty. Poverty reduces access to treatment and care, worsening the morbidity and mortality caused by HIV/AIDS (Poku, 2017:xxix). The mortality rate in children is higher in

[13] This expenditure applies to all CDL conditions and HIV/AIDS, and not only to HIV/AIDS.

poorer countries, and the lower the socioeconomic level of a household, the higher the mortality rates in children (Liamputtong, 2013:vii).

2.3.2.3.1 Direct costs of HIV/AIDS in South Africa

Direct costs are the costs that are directly associated with treating a disease. It includes but is not limited to medication, utilisation of healthcare services (medical practitioner, nurse, traditional healer, specialist doctor, etc.), hospitalisation costs and medical aid costs (levies, co-payments, etc.) (Drimie, 2002:2). The devastating effects of the HIV/AIDS pandemic on the lives of individuals, families, whole population groups and society increase the financial burden on PLWHA. The financial burden on PLWHA is driven by utilising healthcare resources other than public healthcare services, such as private doctors, the use of medicines obtained from community pharmacies and traditional healers (Chimbindi *et al.*, 2015:e52-e60; Mayosi *et al.*, 2012:2052).

Initially, before the availability of ART, the direct costs of HIV/AIDS were driven by hospitalisation (Krentz & Gill, 2012:2-3). After ART became available, direct costs were mainly driven by ART (Krentz & Gill, 2012:2-6). Patients who prefer to use private healthcare services and hospitals need to cover the costs for medication, doctors, medical specialists, etc., out of their own pockets or by using a medical scheme (Mayosi *et al.*, 2012:2032).

Patients using medical schemes and medical insurers feel the financial burden due to the continuous rise in premiums and the ongoing restriction of benefits provided by medical schemes (Chimbindi *et al.*, 2015:e52-e60). In the private healthcare system, the average cost of ART was R373 per item in 2014 an increase of 22.7% from R304 in 2013 (Bester *et al.*, 2016:25). Patients with HIV/AIDS consumed an average of 14.9 items in 2016, resulting in a cost of R5 608 per beneficiary with HIV/AIDS (Bester *et al.*, 2014:9; Bester *et al.*, 2016:8). The co-payments that had to be paid by the beneficiary for all providers were R16.42 per item overall, R17.90 per item for retail pharmacies, R11.26 per item for courier pharmacies, R16.27 per item for medical specialists and R6.19 per item for general practitioners. Co-payments were not only driven by medicine prices but also overall diagnostic tests or levies charged due to doctors charging more than the rates paid by medical schemes amongst other possibilities (Bester *et al.*, 2016:25). In addition to monthly premiums payable, these co-payments, are the result of charges above the medical scheme rates or reference pricing, the product or item not being part of the medical aid formulary, not using designated service providers (DSPs), the maximum value per individual or prescription having been reached and because of co-payments on selected benefits (Bester *et al.*, 2016:25).

2.3.2.3.2 Indirect costs of HIV/AIDS in South Africa

Indirect costs are costs that could have been avoided in the absence of the disease. In South Africa, public healthcare services provide most of the direct costs associated with HIV/AIDS, but patients still have high indirect costs, such as transport, accommodation and food required to receive treatment (Krentz & Gill, 2012:2-3). PLWHA who depend on public healthcare services face financial challenges such as transport to the clinic or hospital, the loss of income and time by going to the clinic as well as paying for food and accommodation near the clinic or hospital (Krentz & Gill, 2012:2-3; Walensky & Kuritzkes, 2010:274). The financial impact of HIV/AIDS on families may lead to borrowing money or selling belongings to enable them to keep up with the financial pressure (Chimbindi *et al.*, 2015:6-7; Sinofsky & Rice, 1987:11; Wilensky & Kibitzes, 2010:274).

The greatest impact on PLWHA is due to mortality and increased morbidity, which results in the loss of income for the family and places a spiritual, emotional and financial burden on the family of such a patient (Walensky & Kuritzkes, 2010:274). The death of HIV-infected adults reduces the household's income, leaves children orphaned or in care of an elderly caregiver, relocates domestic responsibilities and reduces access to education, which, in turn, increases poverty (Chimbindi *et al.*, 2015:e52-e60).

2.3.3 Social impact

Social circumstances such as mental and physical health; nutritional state, educational opportunities and care of children and young adults; and literacy in children and pregnant women have a significant impact on the general health of a population (Benatar, 2013:154-155; Shisana *et al*., 2012:2-5; UNAIDS, 2015:7). Provision of basic needs such as water, sanitation, housing and basic healthcare services are needed for all. Poverty leads to behavioural factors such as an increase in sex work, crime, violence and medication and substance abuse that increase vulnerability to diseases such as HIV/AIDS (Bentar, 2013:154-155; Shisana *et al*., 2012:2-5; UNAIDS, 2015:25).

Cultural beliefs and practices such as polygamy, multiple sex partners, traditional healing and cultural sacrifices are challenges contributing to the spread of HIV/AIDS that are difficult to overcome (Scitovsky & Rice, 1987:11). Stigmatism and exceptionalism keep PLWHA from seeking medical attention or support from family members (Benatar, 2013:154-155; Shisana *et al.*, 2012:2-5; UNAIDS, 2015:6-28).

According to the WHO (2016a:26), socioeconomic differences occur in all countries and have significant influences on health. In almost all countries, groups of lower socioeconomic status show higher mortality rates and inferior self-assessment of health (WHO, 2016a:26-27). Socioeconomic differences also result in behaviour that affects health negatively (WHO, 2016a:26-27). The accessibility of reproductive and maternal health interventions is lower among countries with lower socioeconomic status, resulting in an increase in the HIV/AIDS prevalence rate (Smith & Whiteside, 2010:47; UNAIDS, 2019:174).

Individuals' socioeconomic status influences the prevalence of PLWHA due to lack of access to education and a lack of knowledge about safe sex practices and HIV preventative actions (WHO, 2016f:26). Lack of education prevents the household from obtaining skills to improve the probabilities of employment to increase the household's income (Tladi, 2006:369). The poverty rate increases in an HIV/AIDS-affected household due to medical costs, caregiving, absenteeism from work and, eventually, high memorial service expenses (Tladi, 2006:369).

2.3.3.1 Cultural practices

According to the UNAIDS (2017c:2-4), the greatest challenges facing South Africa in overcoming the HIV/AIDS epidemic are gender inequities as well as strong gender standards and traditions. Certain traditions and norms are harmful as it strips women of educational access and thus the same decision-making or economic autonomy as men. More than half of the women in the Gauteng province of South Africa have been exposed to gender-based violence at least once in their lifetime (Tladi, 2006:370). Women are disadvantaged by gender inequality, the denial of HIV/AIDS, the lack of authority in sexual decision-making, the worth of fertility, sexual cleansing practices, polygamy and stigmatisation and loathing of condom use (Alamrew *et al.*, 2013:2-3). Because of their vulnerability to pregnancy, gender-based violence, rape and gender inequities, several support programmes for women and children affected by HIV/AIDS are offered (UNAIDS 2017c:2-4).

While health and social service programmes support women and young girls, support for men and young boys with HIV/AIDS is lacking in South Africa (UNAIDS, 2017c:1). The belief systems and standards of masculinity in South Africa discourage men and boys from accessing healthcare services (UNAIDS, 2017c:1-2). Therefore, men are less likely to know their HIV/AIDS status, and they are more ill by the time they seek healthcare (UNAIDS, 2017c:2). Because of young girls' preferences for having sexual relationships with older men, young girls have the highest number of new infections. As these girls get older, they spread the virus to future sexual partners (UNAIDS, 2016c:78). The high rate of alcohol use in men with multiple sex partners and the lack

of condom use are risk factors that make men vulnerable to HIV/AIDS exposure (Shisana *et al.*, 2012; UNAIDS, 2017c:2). Stigmatism and exceptionalism hinder men and women from seeking medical care, which, in its turn, leads to negative social and economic impacts, repeating the HIV/AIDS cycle (UNAIDS, 2017c:2).

In sub-Saharan Africa, certain cultures believe that sexually transmitted diseases (STDs) and HIV/AIDS are not spread by unsafe sex practices but rather by witchcraft or sorcery and, thus, the spread of HIV infection via bodily fluids is fallacious (Smith & Whiteside, 2010:1-7). In certain African cultures, traditional healers order men to have sexual intercourse with girls who are virgins to remedy HIV/AIDS (Scott, 2010:83-85). Another cultural challenge is life-enhancing beliefs that encourage fertility and reduce the use of condoms (Falola & Heaton, 2007:369). Gender inequality in relationships, the great worth of fertility, liberality of male promiscuity, and land inheritance or ownership obtained through marriage are factors that also increase unsafe sex practices (Liddell *et al.*, 2005:697-698). Traditional rituals that promote unsafe sex practices include circumcision, mixing of blood and sex without condoms, are standard practices that increase the risk of HIV infection (Falola & Heaton, 2007:361).

2.3.3.2 Circumcision

Male circumcision is a cultural tradition in some religions and ethnic groups in South Africa (Falola & Heaton, 2007:369). The prevalence rate of HIV/AIDS is lower in circumcising ethnic groups than in non-circumcising ethnic groups (Williams *et al*., 2000:130). However, the cultural practice of male circumcision increases the risk of HIV infection because of how it is done. Medical male circumcision has become a primary driver of HIV prevention in South Africa. Therefore, voluntary medical male circumcision should preferably be implemented (UNAIDS, 2016a:44) to provide men with partial protection against HIV/AIDS (Urassa *et al*., 1997:78-80). The number of medical male circumcisions in South Africa rose substantially between 2008 and 2011 (Mayosi *et al*., 2012:2030). Shisana *et al.* (2012: xxx-xxxi) reported that in 2012, 46.4% of men aged 15 years and older were circumcised. Since 2008, more than 11 million adolescent boys have been voluntarily circumcised in 14 different countries in the Eastern and Southern African regions (UNAIDS, 2016d).

2.3.3.3 Multiple sex partners and unsafe sex practices

One of the noticeable risk factors of HIV/AIDS is unsafe sex, followed by alcohol use (Probst *et al*., 2016:853). These factors specifically affect low-income countries, especially in South-East Asia and sub-Saharan Africa (Probst *et al.,* 2016:853)).

Practising safe sex is one of the ways in which people can protect themselves from HIV/AIDS. However, in sub-Saharan Africa, cultural factors and belief systems cause people to be less likely to use condoms (Ezzati *et al.*, 2002:1350-1351). The likelihood of unsafe sex practises increases with alcohol use, as it may reduce cognitive ability. Students who consume alcohol are two times less likely to use condoms (Probst *et al.*, 2016:846-847; Scott, 2010:83-84). Alcohol consumption also increases HIV mortality rates as it reduces patients' adherence to ART (Alamrew *et al.*, 2013:1-3).

Unprotected sex, multiple sex partners and premarital sex are high-risk factors for transmitting STDs and HIV/AIDS. In 2012–2013, a survey of students at a private college in Bahir Dar city showed that 50.7% of the students were sexually active, and 45.3% of these students were practising unprotected sex (Alamrew *et al.*, 2013:1-3). Among all sexually active students, 39% had two sexual partners, and 12% of females and 16% of males had three or more sexual partners. Alamrew *et al.* (2013:1) attributed this risky sex practises to peer pressure and alcohol consumption. A study by Shisana *et al.* (2012:xxxii) found that 10.7% of young adults in South Africa in 2012 aged 15–24 years had sex for the first time before the age of 15 years, and 12.6% of the young adults surveyed reported that they had more than one sexual partner in the past year. One third (33.7%) of females aged 15–19 years reported having a sex partner five years older[14] than them. The females aged 15-19 years were at higher risk due to multiple sex partners and a tendency of alcohol and medication use (Shisana *et al.,* 2012:xxxii-xxxiii).

Married women and women older than 50 years are sexually vulnerable due to patriarchal culture and society, specifically in Mpumalanga (Madiba & Ngwenya, 2017:1341597). Men refuse to use condoms due to the practice of *lobola*[15], reduced sexual pleasure and stigmatism, which increases women's vulnerability (Madiba & Ngwenya, 2017:1341597). Sexual practices with the opposite gender and the same gender simultaneously are other reasons for unsafe sex practices

[14] These older partners have a higher risk of HIV/AIDS due to multiple sex partners (Shisanna *et al.*, 2012: xxxii).

[15] *Lobola* is a price that men pay to the bride's family to marry her. Due to the price these men pay, they regard women as subordinates and feel entitled to have sex with their bride without a condom (Parker, 2015:187)

(Shefer, 2016:211-219). Only 65% of men with two or more sexual partners were found to use condoms (UNAIDS, 2017c). In South Africa in 2016, 26% of people aged 20–24 years had two or more sexual partners in less than one year (UNAIDS, 2017c:2-3). In less than a year, 17% of South African men aged 15-49 years had two or more sexual partners, four times more than women of the same age (UNAIDS, 2017c:1-3). Older men who have sexual relationships with younger women cause a high incidence rate in these women, who then spread the infection to men in their age group when they mature[16] (UNAIDS, 2017c:1-3).

2.3.3.4 Poverty and rate of unemployment

Basic elements outside the health sector such as poverty, unemployment and poor housing increase HIV and TB prevalence (Agardh *et al.*, 2011:527; Alamrew *et al.*, 2013:4). In developing countries such as South Africa, the high rate of poverty, unemployment, rural-urban migration and the lack of education and healthcare are factors that enable the spread of HIV/AIDS (South Africa, 2016:12). Poverty aggravates the transmission and progression of HIV/AIDS due to the lack of access to healthcare services or financial restrictions to maintain healthcare. Poverty furthermore increases with gender inequality, rapid population growth, civil unrest and war, high incidences of rape and gender violence, reduced land ownership and ethnic and geographical isolation (Melkote *et al.*, 2000:17-18). To cope with poverty, families sell land and livestock and increase labour migration (Latré-Gato Lawson, 1999:391-396).

Young, bachelor men travelling from Lesotho, Botswana, Swaziland, Mozambique, Zimbabwe and Zambia to South Africa to pursue job opportunities in the mining industry led to the increased spread of HIV infections (Drimie, 2002:8; Marcus, 2001:110). Migrants residing in single-sex lodgings who use sex workers spread HIV infections rapidly when they return home. Truck drivers are vulnerable to exposure to HIV/AIDS due to their recurrent use of sex workers while transporting products (Tladi, 2006:372). Labourers that reside away from homes, such as construction workers, soldiers, wildlife rangers and agricultural workers, are also susceptible to HIV/AIDS (Drimie, 2002:8; Marcus, 2001:110). Due to a lack of formal education and entertainment, these labourers rely on sex and homemade alcohol for leisure (Poku, 2017:xx; UNAIDS, 2016c).

[16] Women that mature will have intercourse with men the same age.

One of the devastating consequences of HIV/AIDS is the high mortality rate of adults aged 25–45 years (Yu, Roos & Barker, 2018:2.6.1). These adults are responsible for providing and supporting families and are the most productive labour workforce (Drimie, 2002:8; Yu, Roos & Barker, 2018:2.6.1). The resulting financial burden on households, orphaned children and single mothers are drivers of transactional sex to help provide and improve income, leaving women particularly vulnerable (Drimie, 2002:7-8). Gender inequality also forces women into transactional sex or commercial sex work because of employment instability, lack of education and job opportunities, and lack of knowledge on safe sex practises and HIV/AIDS (Melkote *et al.*, 2000:17). Young girls engage in sexual relationships or transactional sex with older men that promise them security as well as financial and social benefits (Shisana *et al.*, 2012:131).

2.3.3.5 Childhood care and development

HIV prevalence is higher in orphans, suggesting that prevalence increases due to vulnerability and other risk factors associated with orphan hood (UNAIDS, 2016d). Mother-to-child transmission (MTCT) of HIV/AIDS makes children more vulnerable and increases the mortality rate of children (Sanders *et al.*, 2012:103; UNAIDS, 2016d). In 1998, the maternal death rate in South Africa per 1 000 pregnancies was 150, increasing to 650 in 2007 (Mayosi *et al.*, 2012:2033). Of the 34 million PLWHA in 2010, two million were children and half were women, many of whom had children and were still of reproductive age (Liamputtong, 2013:1-2). Reducing the mortality rate in a country increases protection against orphanhood and children's vulnerability (Shisana *et al.*, 2012:102-103).

Even though the transmission rate of HIV/AIDS in Botswana is high, half of the youth in Botswana could not identify how HIV/AIDS is transmitted (Sinkamba & Moseki-Lowani, 2016:250). The tradition and religion in which a child is raised determine whether they are taught that sex is only practised during a marriage or that sex play in childhood and sexual activity in adolescence is normal (Coovadia *et al.*, 2009:822; Sinkamba & Moseki-Lowani, 2016:247). Traditional healers in certain African cultures further put the youth at risk as they encourage men to have sex with virgins to remedy HIV/AIDS (Sinkamba & Moseki-Lowani, 2016:247).

Child neglect and abuse lead to mental and physical health problems, which results in these young children becoming involved in violence and crime (Coovadia *et al.*, 2009:823). Children not raised with parents seek acceptance and protection elsewhere, which may lead them to participate in gangsterism. Gang culture promotes participation in criminal and risky sexual activities, victimises female gang members and increases the vulnerability of children in both

urban and rural areas (Coovadia *et al.*, 2009:823; Sanders *et al.*, 2012:7). Cycles of poverty, absent parents, crime and abuse during children's development may hinder children from becoming disciplined and responsible adults (Coovadia *et al.*, 2009:822-823; Sanders *et al.*, 2012:65-66). Absent fathers also play a role in the sexual activity of children; for example, young girls are more likely to be pressured into transactional intercourse with older partners due to the financial burden on the family (Sinkamba & Moseki-Lowani, 2016:247).

To reduce the financial burden on HIV/AIDS-affected families and in turn reduce further vulnerability to HIV/AIDS, the South African government provides social grants for unemployment, grants to help support children and grants for families of people affected by HIV/AIDS (Coovadia *et al.*, 2009:823). As part of the HIV/AIDS response, more attention is given to pregnant and breastfeeding women. To assist PMTCT, pregnant women have access to prevention and ART programmes (Mayosi & Benatar, 2014:1346). ART programmes have improved the quality of life for many mothers, pregnant women, infants and children (Mayosi *et al.*, 2012:2033). Mothers are important to help provide for and nurture their children (Liamputtong, 2013:27). The increase in accessibility and availability of lifelong ART plays a role to help prevent infant mortality and HIV progression (Marmot, 2005:1099-1100).

Empowerment of the youth depends on education about HIV/AIDS, safe sex practices, specifically condom use, and human rights at school, local clinics or hospitals (UNAIDS, 2016d:14-25). Encouraging voluntary circumcision in young adults is key in reducing vulnerability to HIV/AIDS (refer to paragraph 2.3.3.2). Children who live with HIV/AIDS need to be educated on adherence to ART, safe sex practises and PMTCT to ensure that they do not spread HIV/AIDS to other peers or their children at a later stage in life (UNAIDS, 2016c:30-43).

2.3.3.6 Crime

A high unemployment rate increases poverty which, in turn, increases crime (Coovadia *et al.*, 2009:819-821; Pettifor *et al.*, 2012:1729). In poor socioeconomic environments, young adults are more inclined to risky sexual behaviour, medication and alcohol abuse, teenage pregnancies and criminal activities (Coovadia *et al.*, 2009:819-821; Pettifor *et al.*, 2012:1729; UNAIDS, 2016c:32-35). Poverty increases the tendency of teenagers and young adults to participate in gangsterism and criminal activity (Sinkamba & Moseki-Lowani, 2016:240). At-risk groups such as gang members, homeless people and young convicts and offenders are exposed to health risks due to their behaviours (Coovadia *et al.*, 2009:821-822; Sanders *et al.*, 2012:2). These behaviours include assault, rape, intimate partner violence, and homicide due to medication and/or substance abuse and crime (Sanders *et al.*, 2012:2).

Children who experienced abandonment are more likely to become involved in crime and violence (Sanders *et al.*, 2012:46) (refer to paragraph 2.3.3.5). According to the UNAIDS (2016d:32), children and young adults with exposure to violence promote HIV-related risk behaviour among adolescent girls. The chances of acquiring HIV are 50% higher in women exposed to intimate partner violence than those who are not (Coovadia *et al.*, 2009:822). The relationship between medication abuse, unsafe sex practises and crime promotes the spread of HIV (UNAIDS, 2016d:32).

Naidoo (2005:2-4) found that education and literacy reduce inequality, improve household income and reduce unemployment. These aspects reduce crime rates and the risk of HIV/AIDS (Naidoo, 2005:1-3; UNAIDS, 2016d:32).

2.4 HIV/AIDS medicine treatment patterns

This section reviews the medicine treatment patterns for ARV medications and the influences of different prescribing patterns. Figure 2-2 gives an overview of the factors that influence medicine treatment patterns for PLWHA.

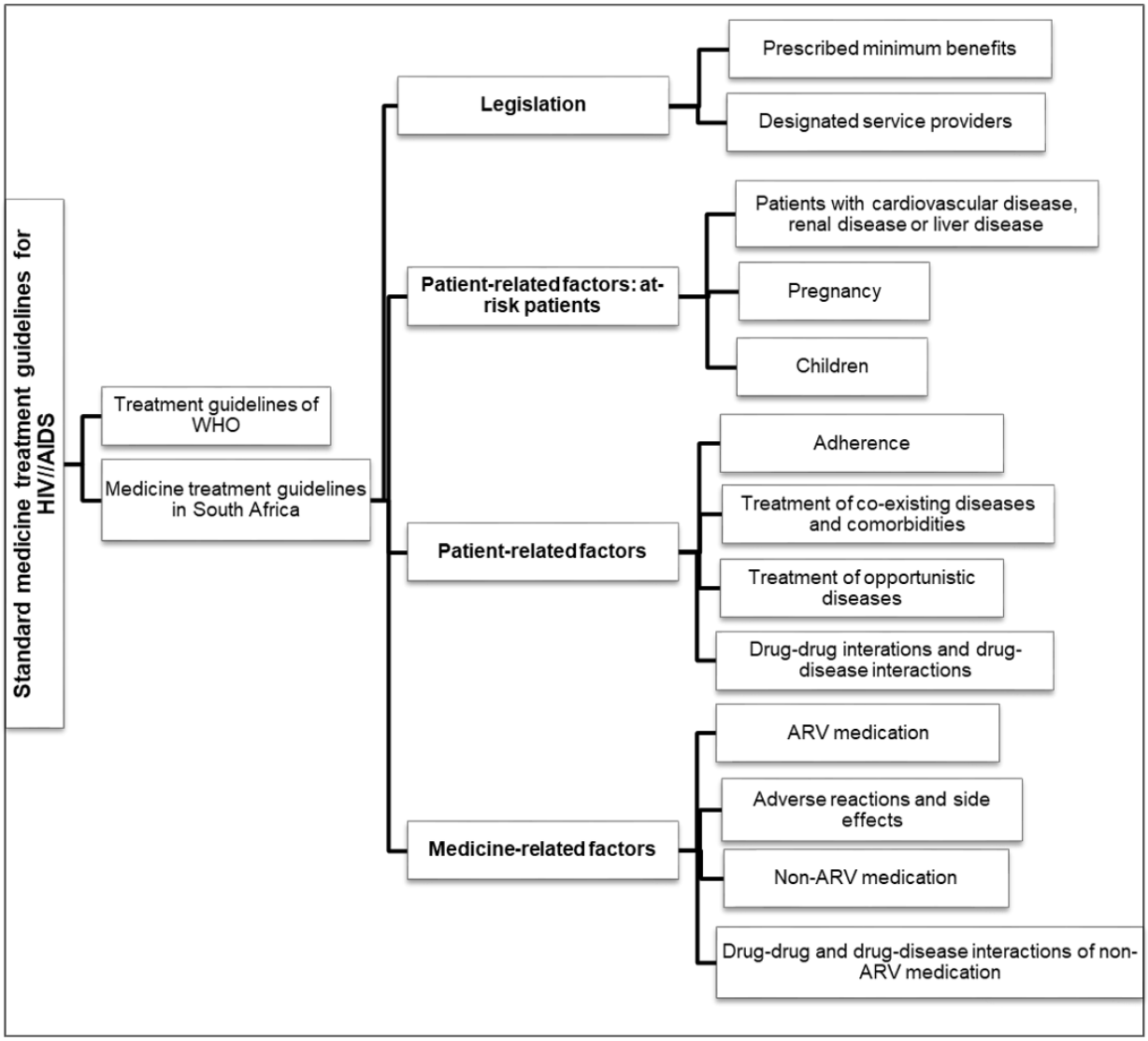


Figure 2-2: Factors that influence medicine treatment patterns for PLWHA

2.4.1 Standard medicine treatment guideline for HIV/AIDS

The WHO Expert Committee on the Selection and Use of Essential Medicines stipulates a list of essential medicine and treatment guidelines that serve as a guide for countries to institute an essential medicine list (EML) and STG (WHO, 2018c). The WHO EML serves as a guide for the procurement and supply of medicine in South Africa's public healthcare sector (DOH, 2018). The STG determined by South African's National Medication Policy (South Africa, 1996b:11-12) and the government of South Africa are based on the availability and accessibility of essential medications, safety, efficacy and quality of medications (DOH, 2018:xx-xxii). The STG ensure good prescribing and dispensing practices, rational use of medications and informed decision-making when prescribing medication (DOH, 2018:xx-xxi). The EML is used as a reference to

determine good quality medicine that is effective and affordable for public health care facilities and the patient (DOH, 2018:xx-xxi). In cases where there are no protocols in place, the latest worldwide, evidence-based studies are used as a guideline (DOH, 2018:xxxii-xxxiii).

2.4.1.1 World Health Organization

The WHO provides treatment guidelines for individuals diagnosed with HIV and treated with ARV (WHO, 2018a:14). Initiating ART increases quality of life, preserves immune function, minimises morbidity and mortality due to HIV/AIDS, achieves maximum and continual viral suppression, and reduces the spread of HIV to HIV-negative individuals, including unborn babies (Medicines Information Centre [MIC], 2016:13).

Some treatment choices are based on the Strategic Timing of Antiretroviral Treatment (START) study conducted by the International Network for Strategic Initiatives in Global HIV Trials (International Network for Strategic Initiatives in Global HIV Trails [INSIGHT], 2015) and the MIC (2016:13). The START study addressed the risks and benefits of initiating ART and assessing ART's clinical management, and it is used to help form treatment guidelines (Babiker *et al.*, 2013:S6-S8).

The earliest treatment regimens for HIV/AIDS were complicated and involved a large pill burden with challenging dose schedules (Bae *et al.*, 2011:279). Therefore, the WHO (2015:44-45) recommended standard medicine treatment guidelines based on the availability of fixed-dose combinations, convenience for the patient and compatibility with co-existing diseases. The combination of TDF with 3TC (lamivudine) and EFV (efavirenz) was preferred because this combination was the most affordable and uncomplicated fixed-dose combination (Bae *et al.*, 2011:279). The MIC (2016:13-14) indicated the following guidelines of when to start ART:

- All pregnant women living with HIV regardless of CD4 cell count
- If TB is diagnosed, starting ART within two weeks if the patient is ill, otherwise when the patient is stable on TB treatment
- When the patient has severe HIV-related disorders, e.g., immune thrombocytopenia, thrombotic thrombocytopenic purpura, polymyositis, or lymphocytic interstitial pneumonitis; and
- In cases where non-HIV-related disorders are present, e.g., hepatitis B, hepatitis C, malignancies and any other diseases that require immunosuppressive treatment.

In June 2017, the WHO (2017b) changed the STG to a medication regime with high potency, lower cost, lower toxicity and a genetic barrier to resistance. The four medications recommended were dolutegravir (DTG), raltegravir (RAL), EFV 400 mg and darunavir/ritonavir (DRV/r). DTG and EFV 400 mg are considered for first-line regimens. These medications have high tolerability, high efficacy and low resistance. Despite these advantages, implementing this guideline in low- and middle-income countries is challenging (WHO, 2017c) because RAL and DRV/r are expensive due to a lack of generic products for this fixed-dose combination, making it unsustainable to add to the standard treatment guidelines of low- and middle-income countries (WHO, 2017c).

2.4.1.2 Antiretroviral treatment guidelines in South Africa

Healthcare providers in the private healthcare sector of South Africa do not have to adhere to any law, rule or regulation in treating HIV-positive patients (DOH, 2018:1.1-23.29; WHO, 2015). They are, however, encouraged to adhere to the WHO guidelines (WHO, 2015) (Table 1-4) and the preferred treatment guidelines of South Africa's DOH (DOH, 2018). The public healthcare sector follows the EDL guidelines (refer to paragraph 2.4.1).

The Medical Schemes Act (131 of 1998) allows medical schemes to implement formulary lists to treat HIV/AIDS based on the EML and guideline recommendation as per WHO (refer to paragraph 2.4.1.1). Medical practitioners may motivate to treat patients with medication that is not on the formulary or suggested treatment guidelines when they provide evidence-based published studies (refer to paragraph 2.4.1.1).

2.4.2 Key populations

Eaton and Kalichman (2016:31) and the UNAIDS (2016d:21-20) identified the following key populations that need attention in South Africa when it comes to HIV/AIDS:

- Young women between the ages of 15 and 24 years
- People living in informal settlements and next to national roads
- Adolescents not attending school
- People with low socioeconomic standing
- Uncircumcised men
- Disabled people

- Sex workers and their customers
- Persons who abuse alcohol and other substances
- Men who have sex with men (MSM)
- Transgender individuals
- Prisoners

The HIV National Strategic Plan for South Africa includes strategies to help prevent HIV/AIDS, STDs and TB. These strategies include prevention efforts that focus on geographical areas where the transmission risk of HIV/AIDS is the highest to help prevent HIV/AIDS in these key populations in particular (UNAIDS, 2014:10). Between 2000 and 2014 in the African region, key populations contributed 30% to new HIV/AIDS infections in Kenya, 25% in South Africa, 20% in Mozambique, and 12% in the Kingdom of Eswatini (formerly known as Swaziland) (UNAIDS, 2015:92). Focusing on key populations is important in reducing the epidemic due to these populations' vulnerability to HIV/AIDS exposure (UNAIDS, 2015:113). Methods and prevention services to help reduce HIV/AIDS among the key population (UNAIDS, 2015:106,107) are:

- HIV testing
- Condom use for MSM, sex workers and persons who abuse injectable substances
- Distribution of needles and syringes among persons injecting substances
- Increased availability of condoms in prisons
- Improving PrEP availability to key populations
- Engaging key populations in national AIDS response[17]

[17] Engagement with national AIDS response includes policy development, implementation of services, budgeting, interventions, monitoring and evaluation (UNAIDS, 2015:107).

2.4.2.1 Prisoners

Prisoners are one of the key populations (refer to paragraph 2.4.2) due to the high prevalence rate of HIV/AIDS among them. Focussing on them is therefore important in preventing HIV/AIDS globally (UNAIDS, 2016c:57). Since the beginning of the HIV/AIDS epidemic, HIV/AIDS prevalence in prisons has been high (Dolan *et al.*, 2016:1089). The UNAIDS indicated that the prevalence rate of HIV/AIDS among prisoners is 50 times higher than among the general population (UNAIDS, 2016d:33). This high prevalence may be due to increased exposure to HIV/AIDS because prisoners are exposed to violent victimisation, high prevalence of injectable drug use and sexual assault (Sanders *et al.*, 2012:40). The lack of policies, laws and preventative measures by governing authorities decreases access to healthcare services in prisons (Rubenstein *et al.*, 2016:1202). The right to receive healthcare is in some cases unlawfully withheld from prisoners when they do not respect authorities or when they engage in conflicts with other inmates, authorities or healthcare providers (Rubenstein *et al.*, 2016:1211).

Despite South Africa's Correctional Services Act (111 of 1998), the social environment, unsanitary conditions, discrimination and stigmatism reduce prisoners' access to ARV medication (South Africa, 1998b; UNAIDS, 2016b:57). Prisoners fail to seek healthcare services due to the fear of being harassed or arrested by police officers and challenging conditions in most prisons (Dolan *et al.*, 2016:1809; Rubenstein *et al.*, 2016:1202). Because of the prison environment, which includes poor ventilation and large populations in small areas, co-existing infections such as hepatitis C and TB are more prevalent (UNAIDS, 2016d:57).

2.4.2.2 Men having sex with men

In high-, middle- and low-income countries, MSM[18] is an exceptional population group because HIV/AIDS prevalence increased for this group when the overall HIV/AIDS prevalence decreases worldwide (Beyrer *et al.*, 2012:367). MSM accounted for 26.8% of the HIV/AIDS prevalence rate in South Africa in 2016 (UNAIDS, 2016c).

Biologically, the probability of HIV-transition in anal penetration is 18 times higher than in vaginal penetration (Beyrer *et al.*, 2012:371). Other risk factors that also increase the prevalence of and vulnerability to HIV-transition for MSM are possible subareas such as injectable medications, alcohol use, sex trading, frequency of unprotected sex and multiple sex partners

[18] MSM describes males who have sex with males, regardless whether they have sex with women as well or of their sexual identity (bisexual, gay, etc.) (UNAIDS, 2015:114).

(Beyrer *et al.*, 2012:368-372; UNAIDS, 2016d:52). Other risk factors include peer abuse, compulsive sexual behaviour, mental health, lack of social support and lack of sexual education (Newcomb *et al.*, 2011:223-224).

Discrimination, harassment, rejection, violence, criminalisation and self-stigmatism lead to negative physical and mental health outcomes in MSM (UNAIDS, 2016d:52). Younger MSM was found to be more vulnerable to homophobia[19] (UNAIDS, 2015:55) and to have a higher risk to be infected with HIV/AIDS compared to heterosexual young men or older MSM (UNAIDS, 2016d:55). Due to religious and cultural beliefs and fear of discrimination or blackmail, MSM tends to avoid healthcare providers (Lane *et al.*, 2011:626-630). The same study found that MSM in Soweto, South Africa, were trading sex for food, housing or income because of poverty (Lane *et al.*, 2011:626-630). Circumcision in men has a protective benefit in preventing HIV infection among MSM (Beyrer *et al.*, 2012:371).

ARV medication is suggested as prophylaxis for patients who are potentially at high risk, even if they are HIV-negative (Sullivan *et al.*, 2012:388-389). A study on pre-exposure prophylaxis (PrEP) initiatives reported that MSM and transgender women who received tenofovir and emtricitabine had 44% less risk of being infected with HIV/AIDS than those using the placebo, despite compliance of less than 89% (Sullivan *et al.*, 2012:390-391).

2.4.2.3 Sex workers

Despite the number of new infections in sex workers remaining the same from 2011 to 2015 globally (WHO, 2016a), sex workers are an attributable population group to new HIV infections in the sub-Saharan African region (Beyrer *et al.*, 2015:72). In 2015, HIV prevalence among female sex workers in Johannesburg, South Africa, was 71.8% (UNAIDS, 2016c). Eakle *et al.* (2017:e1002444) reported that, in 2017, three out of four female sex workers in South Africa were already infected with HIV/AIDS. Social, religious and cultural factors around male sex workers and MSM (refer to paragraph 2.4.2.2) make it more difficult to report the prevalence for male sex workers (Baral *et al.*, 2015:262-264). However, in 2015, Baral *et al.* (2015:262-264) indicated the HIV/AIDS prevalence rate of male sex workers in the African region to be around 12.5%.

[19] Homophobia includes social isolation, family discarding, harassment, intimidation, discrimination and/or violence (CDC, 2020).

The risk of HIV infection in sex workers is higher because of their high number of sexual partners and increased likelihood of anal intercourse (Baral *et al.*, 2012:546). Sex workers are often exposed to risky sexual practices and social environments that include violence, abuse and use of injectable medications and alcohol (Baral *et al.*, 2012:376; Beyrer *et al.*, 2012:538-539). Due to these high-risk factors, sex workers' human rights are key to help reduce HIV-transmission (Eakle *et al.*, 2017:e1002444).

The South African government implemented the PrEP guidelines for sex workers, regardless of their CD4-count, in June 2016 (Eakle *et al.*, 2017:1002444). Sex workers can currently receive counselling, testing and treatment for HIV/AIDS at any healthcare clinic, and they can gain access to ART regardless of their CD4 cell count if they are HIV-positive or PrEP if they are HIV-negative (Eakle *et al.*, 2017:1002444). Among the 692 sex workers Eakle *et al.* (2017:1002444) surveyed, they found that 93% qualified for PrEP or ART but the compliance rate was 22% for PrEP was 22% and 60% for ART.

2.4.3 Legislation

South Africa's Medical Schemes Act (131 of 1998) describes the compulsory costs for which medical schemes are liable. Section 29 of the Medical Schemes Act (131 of 1998) indicates that a medical scheme may determine the level and scope of the minimum benefits that the medical scheme will implement. However, these rules should be submitted to the CMS and may not be less than what is available through public healthcare services. Internal rules may also determine the level and scope of minimum benefits (refer to paragraph 2.4.3.1).

To ensure that patients do not deplete limited benefits, the Medical Schemes Act (131 of 1998) provides for PMB (refer to paragraph 2.4.3.1). Regulation 8 of the Medical Schemes Act (131 of 1998) identify 270 conditions that include 26 chronic conditions, defined as the CDL, to form part of the PMB (South Africa, 2003; South Africa, 2009). An amendment to PMB legislation published in Notice No. 1360 of 2002 and implemented on 1 January 2004 stipulated that HIV should be considered part of the PMB and should be funded from the medical schemes' risk pool and not from patients' medical savings. Refer to Annexure A for the amendment as published under Government Notice Number (GNR) 1360 of 2002 with effect from 1 January 2004, by GNR 1397 of 2003 with effect from 6 October 2003 and by GNR 1410 of 2004 with effect from 1 January 2005 in the Medical Schemes Act (131 of 1998).

2.4.3.1 Prescribed minimum benefits

PMB are a set of benefits to ensure that all medical scheme members have access to certain minimum health services, regardless of the benefit option they have selected (South Africa, 1998a). Amendments to the Medical Schemes Act (131 of 1998) as per GNR 1262 of 20 October 1999, which were effective 1 January 2000, require medical aids to provide compulsory cover for diagnosis, treatment and care of defined chronic conditions (South Africa, 1999). For each chronic disease, the Medical Schemes Act (131 of 1998) defines an algorithm that should be considered as a protocol for the disease.

Due to the legislative changes in the Medical Schemes Act (131 of 1998) (refer to paragraph 2.4.3), all registered medical scheme options are obligated to include HIV/AIDS in PMB (CMS, 2015b:34). The benefits enforced for patients with HIV/AIDS as per the Medical Schemes Act (131 of 1998) include medical and surgical management of opportunistic infections and possible malignancies, hospitalisation, broader cover for PMTCT, counselling and testing, PrEP and provision of ARVs (Wayburne & Da Silva, 2007:110).

The private healthcare sector does not have enforced treatment guidelines; however, they are encouraged to adhere to national and provincial guidelines and protocols in the STG and EML of South Africa (DOH, 2018). Formularies and guidelines are evidence-based, and the affordability of treatment must be considered (CMS, 2020; South Africa, 1999). Patients may insist on taking medication or treatment not included in the formulary or guidelines, but they may then be subject to a co-payment. In most cases, medical schemes pay for patients' chronic benefits; however, if their chronic benefits are capped with a maximum amount specified by the medical scheme in their terms, the beneficiary is liable to pay for pharmaceutical expenses of PMB conditions (CMS, 2020; South Africa, 1999).

The submission of ICD-10 codes is compulsory when registering chronic or PMB conditions so that the medical scheme can fund the service provided from their risk pool (CMS, 2017c; South Africa, 1999). Should the incorrect ICD-10 code be submitted or if the medical scheme cannot identify the service as part of PMB, costs will be paid from the patient's medical savings (CMS, 2020; South Africa, 1999). The ICD-10 codes associated with HIV/AIDS are listed in Table 2-9 (MIC, 2016:156-158; South Africa, 1999).

Table 2-9: ICD-10 codes for HIV/AIDS-associated conditions

ICD-10 codes	Description
HIV/AIDS-associated conditions	
B22.0	HIV resulting in encephalopathy
B22.1	HIV resulting in lymphoid interstitial pneumonitis
B23.1	HIV resulting in lymphadenopathy
B22.7	HIV resulting in multiple diseases classified elsewhere
B22.2	HIV resulting in wasting syndrome
B23.8	HIV resulting in other specified conditions
B24	Unspecified HIV disease
HIV/AIDS-related infections	
B23.0	Acute HIV syndrome
B20.4	Candidiasis
B20.2	Cytomegaloviral disease
B23.2	Haematological and immunological abnormalities
B20.0	Mycobacterial infection
B20.6	*Pneumocystis carinii* pneumonia
B20.1	Bacterial infection (other)
B20.5	Mycoses (other)
B20.3	Viral infections (other)
B20.8	Parasitic infectious diseases (other)
B20.9	Parasitic infectious diseases (unspecified)
B20.7	Multiple infections
Malignancies	
B21.1	Burkitt's lymphoma
B21.0	Kaposi's syndrome
B21.2	Non-Hodgkin's lymphoma (other types)
B21.7	Multiple malignant neoplasms
B21.3	HIV resulting in other malignant neoplasms of lymphoid, haematopoietic and related tissue
B21.8	Other malignant neoplasms
B21.9	Unspecified malignant neoplasms

ICD-10 codes	Description
Screening	
Z21	HIV asymptomatic infection status
Z11.4	Special screening examination for HIV
Z20.6	Contact with and exposure to HIV
Z71.7	Counselling for HIV
Z11.1	Special screening examination for respiratory tuberculosis
Gonococcal infections	
A54.1	Gonococcal infection of the lower genitourinary tract with periurethral and accessory gland abscess
A54.0	Gonococcal infection of the lower genitourinary tract without periurethral and accessory gland abscess
A54.2 + N51.0	Gonococcal infection with a disorder of the prostate
Gonococcal infections	
A54.2 + N51.1	Gonococcal infection with epididymitis or orchitis
A54.2 + N74.3	Gonococcal infection with female pelvic inflammatory disease
Chlamydial infections	
A55	Lymphogranuloma
A56.3	Chlamydial infection of anus and rectum
A56.2	Chlamydial infection of the genitourinary tract (unspecified)
A56.0	Chlamydial infection of the lower genitourinary tract
A56.4	Chlamydial infection of the pharynx
A56.1 + N51.1	Chlamydial infection with epididymitis/orchitis
A56.1 + N 74.4	Chlamydial infection with female pelvic inflammatory disease
A56.8	Chlamydial infection of other sites: sexually transmitted chlamydial infection
Herpes viral infections	
A60.0	Herpes viral infection of genitalia and urogenital tract
A60.1	Herpes viral infection of perianal skin and rectum
A60.9	Anogenital infection, unspecified

ICD-10 codes	Description
Other predominantly sexually transmitted diseases	
A63.0	Anogenital warts
A57	Chancroid
A58	Granuloma inguinale
A59.0	Urogenital trichomoniasis
A63.8	Other
A64	Unspecified

2.4.3.2 Designated service providers

Designated service providers (DSPs) are service providers such as doctors, pharmacies and hospitals, groups of doctors or clinics preferred and authorised by the medical scheme that the patient belongs to (CMS, 2017c). PMBs should be delivered by a DSP specified by the medical scheme rules to avoid co-payments and access unlimited benefits (CMS, 2017c; South Africa, 1999). The Medical Schemes Act (101 of 1998) allows medical schemes to contract with a DSP to provide PMB services to members of the specific medical scheme (refer to paragraph 2.4.3.1).

According to the Medical Schemes Act (101 of 1998), the DSP selection must be transparent and fair. However, the decision may be influenced by price, quality, preserved kickbacks and, sometimes, incentives. DSP selection ensures that PMB services are provided according to legislation. The selection of DSPs entails advantages that include (CMS, 2010:1-3; Meintjes *et al.*, 2017:1-14).

- Financial negotiation that leads to better prices at which services are provided
- Treatment guidelines and formularies arranged with DSPs that lead to cost-effectiveness
- Exploring risk management options with providers
- Assuring members of the availability of services

In cases where a medical scheme has not selected a DSP, the member may use a non-DSP, and the medical scheme will be liable to pay for 100% of the medical scheme rate. In cases where the patient is involuntarily obliged to use a non-DSP due to emergency, other DSPs cannot provide the service or had an unreasonable delay or the medical scheme that did not appoint a DSP, the

same applies. When a patient decides to use a non-DSP by choice, the medical scheme may levy a co-payment (CMS, 2017c; South Africa, 1999).

2.5 Patient-related factors

Patient-related factors that influence the choice of treatment regimens are discussed below, including at-risk patients (pregnancy, children, elderly patients and patients with renal disease), adherence to treatment regimens, co-existing diseases and drug-drug interactions.

2.5.1 At-risk patients

Patient's treatment regimens may be influenced by risk factors that prevent the standard regimen from being followed. A discussion of these factors follows in subsequent paragraphs.

2.5.1.1 Pregnancy

Pregnant women need to be aware of their HIV-status to ensure that they receive and adhere to ARV treatment to prevent complications and MTCT (Ethier *et al.*, 2016:138-140). ART given to pregnant women can be associated with an increase in premature births, which, in turn, increases the risk of mortality (Thorne *et al.*, 2004:2337-2338).

Medical care-seeking behaviour and treatment adherence of pregnant women depend significantly on whether the pregnancy was planned or not (Ethier *et al.*, 2016:138-141). Mothers in Cape Town, South Africa, who received postnatal HIV healthcare showed improved viral suppression over 12 months (Myer *et al.,* 2018, e1002547). Initiating new ART for pregnant and breastfeeding women is done steadily to reduce possible toxicity (WHO, 2017c). An active ARV toxicity monitoring system is used to monitor congenital anomalies in mothers and infants using ART through a register of adverse medication reactions (WHO, 2017d).

Zidovudine (ZDV) is known to reduce viral transmission from mother to child by 70%, but anaemia in both mothers and neonates is one of the adverse medication effects associated with its use (Lorenzi *et al.*, 1998:F242). The WHO's initial ART guidelines in 2016 included DTG as first-line treatment, but these guidelines have been changed due to lack of data and possible adverse medication effects, such as neural tube defects in neonates (WHO, 2018a:18). Treatment with RAL has shown to be superior to EFV and LPV/r for neonates with HIV due to less evidence of adverse medication effects and increased adherence (WHO, 2018a:18). DTG is known to cause central nervous system toxicity, immune reconstitution inflammatory syndrome (IRIS) and unexpected toxicity during pregnancy (WHO, 2017c). DRV/r and RAL may cause hepatotoxicity,

whereas RAL is also associated with central nervous system toxicity, myopathy and IRIS in pregnant and breastfeeding women (WHO, 2017c).

The STG for pregnant women includes placing them on long-term ARV medications regardless of gestational age (DOH, 2018:6.32). The first line of treatment for pregnant women or are at risk of pregnancy includes an NNRTI (EFV or NVP) and two NRTIs (DOH, 2018:6.32-36.36). EFV is preferred, as it is better tolerated with lower hepatotoxicity and is also well tolerated with tuberculosis treatment. For second-line treatment, LPV/r (PI) replace NNRTIs in cases where medication resistance or hepatotoxicity is suspected (Deeks & Phillips, 2009:69-70). In cases where HIV-positive pregnant women are not indicated to use ARV treatment, 3TC 300 mg is given 12 hourly from 28 weeks of pregnancy and NVP 200 mg once off four hours before the baby's birth (DOH, 2018:6.33-36.35). Birth through caesarean sections can be a method to help PMTCT.

The recommended STG for pregnant women (DOH, 2018:6.33-36.35) are:

- Women of all gestational ages who are not on ART can start with an FDC containing TDF 300 mg, FTC 200 mg and EFV 600 mg once a day before bedtime.
- EFV may be contra-indicated due to its psychiatric side effects. EFV may be substituted with NVP 200 mg twice a day or LPV/r 400 mg/100 mg in these cases. Therefore, the regimen will include TDF 300 mg, FTC 200 mg, NVP 200 mg or LPV/r 400 mg.
- TDF may be contra-indicated due to renal insufficiency. In these cases, TDF may be substituted with ABC 600 mg. FTC 200 mg may be substituted with 3TC 300 mg daily. The regimen will, therefore, include ABC 600 mg, 3TC 300 mg and EFV 600 mg.
- Women that have not been on ART but were tested positive during labour should be given NVP 200 mg as soon as possible, AZT 300 mg intrapartum during labour, TDF 300 mg as a single dose and FTC 200 mg as a single dose. Within 24 hours after labour, the mother should be started on lifelong FDC as per STG.

2.5.1.2 Children

As a preventative measure, early HIV-testing in children exposed to HIV is required and, if possible, exclusive breastfeeding is recommended (UNAIDS 2016c:6). If a child is exposed to HIV, the child should be given NVP for 12 weeks after birth, and mothers are encouraged to continue on ART, especially when breastfeeding (DOH, 2018:11.23-11.27). The DOH treatment guidelines for children without complications (DOH, 2018:11.28-11.38) are listed in Table 2-10.

Table 2-10: Treatment guidelines for children and adolescents

Age	Regimen	Active ingredients
Starting age 0-3 years	Regimen 1	ABC, 3TC, LPV/r or EFV
	Regimen 2	TDF + 3TC or FTC + EFV or LPV/r
Starting age 3 years and older and more than 10 kg	Regimen 1	ABC, 3TC and EFV (do not exceed adult dose)
Adolescents	Regimen 1	TDF + 3TC or FTC + EFV (only initiate treatment with no psychiatric comorbidity or renal insufficiency or co-administration with nephrotoxic medication)

In cases where children are exposed to HIV, cotrimoxazole is given as prophylaxis for *Pneumocystis jiroveci* pneumonia from four to six weeks of age. In cases where the patient experiences side-effects with cotrimoxazole, dapsone may be used. Children with TB may be treated with tuberculostatics and pyridoxine, and a multivitamin may be used. Children living with HIV/AIDS may not be administered the Bacille Calmette-Guérin (BCG) vaccine during the administration of routine immunisations (MIC, 2016:22-27). The risk associated with vaccinating children living with HIV/AIDS is greater than the benefits of preventing severe TB in children and is, therefore, contra-indicated in this case (WHO, 2007).

First-line treatment for children is ABC, 3TC and LPV/r for those older than three years and weighing less than 10 kg and for children weighing more than 10 kg but less than 40 kg it is ABC, 3TC and EFV. Second-line treatment is dependent on the failed first-line treatment. Children that failed on ABC, 3TC and LPV/r and TDF, 3TC or FTC and LPV/r or EFV should consult a specialist. According to the MIC (2016:22-27), failed treatment regimens on ABC, 3TC and EFV (or NVP) are recommended AZT, 3TC and LPV/r, and failed treatment regimens on D4T, 3TC, and EVF (or NVP) are recommended AZT, ABC and LPV/r.

2.5.1.3 Patients with cardiovascular, renal or liver disease

HIV/AIDS has been associated with increased morbidity and mortality rates (Baker *et al.*, 2008:841-842; Silverberg *et al.*, 2007:1957-1959). PLWHA have an increased risk for cardiovascular disease, renal disease and liver disease, all of which are considered non-AIDS-related diseases (Deeks & Phillips, 2009:288; Günthard *et al.*, 2016:192-193). Multiple factors such as the ageing of patients, lifestyle choices such as smoking, medication (especially immunosuppressant), and ART's side effects further increase the risk (Baker *et al.*, 2008:841- 842; INSIGHT START Study Group, 2015:805). It is important to

establish a balance between the advantages and risks of using ART for patients with other non-AIDS-related diseases (Baker *et al.*, 2008:1-2). Timely and correct use of ART reduces the risk of complications caused by HIV/AIDS (Deeks & Phillips, 2009:288).

Patients with renal disease receiving dialysis have a higher risk of mortality because HIV/AIDS progression increases as renal function deteriorate (Günthard *et al.*, 2016:196). Dialysis should not be withheld from the patient due to HIV/AIDS or its treatment (MIC, 2016:62-64). ARVs must be adapted according to patients' needs to accommodate renal dysfunction (Günthard *et al.*, 2016:196). TDF causes renal tubular dysfunction in patients that use PIs, especially LPV/r. For these patients, urine dipsticks should be performed to determine urea, creatinine, calcium/magnesium/phosphate and possible proteinuria (Günthard *et al.*, 2016:196). Results of patients' creatinine clearance (CrCl) will indicate the dosage of TDF that may be prescribed to the patient (refer to Table 2-11).

Kidney transplantation and dialysis are recommended for patients with HIV/AIDS who meet specific criteria. The criteria include stability and good adherence to ART for at least six months with a viral load of fewer than 50 copies/mL and a CD4 cell count of more than 400 cells/µl as well as an absence of opportunistic diseases or AIDS-defining conditions (Meintjes *et al.*, 2017:15; MIC, 2016:62-64). The exclusion criteria for transplantation are the presence of cardiopulmonary disease, uncontrolled malignancy, HPV infection, untreated hepatitis B, hepatitis C or liver cirrhosis, active diseases such as infections with Epstein-Barr virus, human herpesvirus and cytomegalovirus as well as Kaposi's sarcoma, multifocal leukoencephalopathy or any life-threatening infections that may be induced by the use of immunosuppressants (Günthard *et al.*, 2016:192-195; MIC, 2016:62-64).

For patients who have renal dysfunctions, such as kidney transplant patients, patients receiving dialyses or patients with chronic kidney diseases, the dosage of medication should be adjusted according to their creatinine clearance, the type of dialysis they are receiving and their body weight (Baker *et al.*, 2008:4-7; Günthard *et al.*, 2016:192-195). Table 2-11 depicts the normal dose for ART and the adjustments required according to the patient's creatinine clearance (MIC, 2016:62-64; Southern African HIV Clinicians Society, 2008:34-39; WHO, 2016b:84)**.**

Table 2-11: Normal ART doses and adjustments required according to body weight, creatinine clearance and type of dialysis[20]

Medication	Dose adjustment according to body weight	Dose adjustment according to creatinine clearance (CrCl)	Dose adjustment for patients receiving haemodialysis or peritoneal dialysis
3TC (lamivudine)	150 mg given twice a day or 300 mg once a day as standard adult dose[21]	CrCl ≥ 50 ml/min: 150 mg daily CrCl = 30 ≥ 49 ml/min: 150 mg initial dose and then 100 mg daily CrCl = 15 ≥ 29 ml/min: 150 mg initial dose and then 50 mg daily CrCl = 14 ≤ 5 ml or less: 50 mg initial dose and then 25 mg daily	Initial dose of 50 mg and then 25 mg daily[22]
AZT (zidovudine)	The usual adult dose of 300 mg twice a day	CrCl less than 15ml/min: 300 mg once a day	100 mg every 6 to 8 hours
D4T (stavudine)	The usual adult dose of 30 mg twice a day	CrCl ≥ 50 ml/min: no adjustments CrCl = less than 5 ≥ 49 ml/min: weight more than 60 kg to use 20 mg twice a day, weight less than 60 kg to use 15 mg twice a day	Weight 60 kg and more to use 20 mg twice a day Weight less than 60 kg to use 15 mg once a day No adjustments for peritoneal dialysis, to use with caution and monitor the patient closely

[20] (MIC, 2016: 62-64; South African HIV Clinicians Society, 2008:205-212; WHO, 2016c:84)

[21] An adult dose is given to patients over the age of 12 years and weighing more than 40 kg.

[22] After haemodialysis is completed, the patient may use the usual adult dose dependent on weight.

Medication	Dose adjustment according to body weight	Dose adjustment according to creatinine clearance (CrCl)	Dose adjustment for patients receiving haemodialysis or peritoneal dialysis
DDI (didanosine) buffered tablet	For patients above 60 kg, usual adult dose of 200 mg twice a day	CrCl ≤ 59 ≥ 30 ml/min: 200 mg once daily CrCl ≤ 29 ≥ 10 ml/min: 150 mg once a day CrCl less than 10 ml/min: 100 mg once a day	100 mg once a day
DDI (didanosine) enteric-coated	Adult patient weight of less than 60 kg, 125 mg twice a day	CrCl ≤ 59 ≥ 30 ml/min: 150 mg once daily CrCl ≤ 29 ≥ 10 ml/min: 100 mg once a day Cr/Cl less than 10 ml/min: 75 mg once a day	75 mg once a day
FTC (emtricitabine)	Usual adult dose of 200 mg once a day	CrCl ≤ 49 ≥ 30 ml/min: 200 mg every 48 hours CrCl ≤ 29 ≥ 15 ml/min: 200 mg every 72 hours CrCl less than 15 ml/min: 200 mg every 96 hours	200 mg every 96 hours
NVP (nevirapine)	The usual adult dose of 200 mg twice a day	No adjustment	No adjustment For patients receiving peritoneal dialysis, the dose is unknown but should be used with caution
TDF (tenofovir)	The usual adult dose of 300 mg once a day	No adjustment Not recommended with CrCl less than 49 ml/min	Not recommended
TDF and FTC combination (tenofovir and emtricitabine)	The usual adult dose of 300 mg for tenofovir / 200 mg for emtricitabine once a day	No adjustment Not recommended with CrCl less than 49 ml/min	Not recommended

2.6 Factors influencing medicine treatment patterns for HIV/AIDS

Healthcare professionals use evidence-based treatment guidelines to decide the correct medical care that patients require (Günthard *et al.*, 2016:191-192; Holodniy *et al.*, 2007:20). The quality of healthcare provided by healthcare professionals is related to their adherence to published, evidence-based information (Holodniy *et al.*, 2007:20). Factors influencing treatment patterns for HIV/AIDS include adherence to ART, side effects of ART, drug-drug or drug-disease interactions, and treatment of opportunistic diseases, co-existing diseases and comorbidities (Benson *et al.*, 2009:3-4; Cihlar & Fordyce, 2016:50-52; Fonsah *et al.*, 2017:e0170893; Holodniy *et al.*, 2007:20-22).

2.6.1 Adherence

According to Cramer *et al.* (2008:44-45), the health outcomes of patients is determined by adherence to the treatment prescribed and persistence with treatment for the required period. Adherence is the extent to which the prescribed treatment regimen and dose interval is adhered to, whereas persistence is the time duration from treatment initiation to the time treatment is discontinued (Touchette & Shapiro, 2008:S2-S4). Due to the nature of HIV, chronic management of the disease is obtained by chronic use of ART, and treatment persistence is essential for improved life quality of PLWHA (Touchette & Shapiro, 2008:S2-S4). Adherence is important for HIV-infected patients as failure to adhere to treatment may lead to treatment failure, viral mutations due to insufficient viral suppression and increased resistance to treatment (Airoldi *et al.,* 2010:115; Bangsberg *et al.*, 2004:696-699). Patients who do not adhere to ART may also have increased treatment costs because of increased morbidity (Cramer *et al.*, 2008:44- 45).

Several factors cause patients to be non-adherent to their treatment regimen (DOH, 2018:xxii- xxiv). Identified factors include busy lifestyles, socio-economic-related issues, lack of resources, cultural beliefs, denial of disease, healthcare professionals who do not provide information or help patients understand the treatment, side effects of medication, pill burden or complicated treatment regimens (DOH, 2018:xxii-xxiv). Patient-specific factors that affect adherence are age, gender and race (Al-Dakkak *et al.*, 2013:413). Socio-economic-, behaviour- and treatment-related factors all result in patients not being adherent and not persisting with their treatment (Airoldi *et al.*, 2010:414; Vervoort *et al.*, 2007:271-281).

New medication developments, such as combination medications that simplify treatment regimens and dose frequency, are intended to improve safety, reduce resistance profile and enhance adherence (Cihlar & Fordyce, 2016:50-51). Patients adhere better to newer generations

of NRTIs such as TDF, 3TC, FTC and ABC compared to DDI, ZDV and D4T (MacArthur *et al.*, 2006:2125-2135; Springer *et al.*, 2007:205-212). Long-term use of DRV and ATV results in the reduced possibility of medication toxicity, while LPV, saquinavir (SQV) and RPV are associated with a change in regimens or non-adherence to treatment regimens (Bae *et al.*, 2011:287; Monforte *et al.*, 2000:499-507; Sax *et al.*, 2009:2230-2240; Springer *et al.*, 2007:205-212). Incorrect use of ART negatively impacts a patient's health outcomes and cause adverse medication reactions, both of which have cost implications (Demeke *et al.*, 2015:344-346).

Despite progress in ART for children, ART formulations for children and infants need to be prioritised (Penazzato *et al.,* 2019:e263). Treatment for children with HIV/AIDS should be tolerable and effective (Penazzato *et al.,* 2019:e263). PMTCT is halted in some cases as some mothers do not continue with their ART during pregnancy and breastfeeding, and the lack of adherence results in children and infants becoming newly infected with HIV (WHO, 2019b). Treatment of HIV/AIDS is especially challenging for children and their caregivers, negatively impacting adherence in children. Due to a lack of child-friendly formulations, children often dislike the taste of medications causing them to spit it out, and administration times may conflict with caregivers' working hours (Biadgilign *et al.*, 2009:150; WHO, 2019b). Poverty, nutritional shortage, lack of support, stigmatism and discrimination may also lead to non-adherence to ARV treatment in children (Biadgilign *et al.*, 2009:148-152).

2.6.2 Treatment and co-existing diseases and comorbidities

The treatment of patients with HIV/AIDS is affected by co-existing diseases and comorbidities (Cihlar & Fordyce, 2016:54). Long-term use of ART increases the risk of comorbidities and drug-drug interaction with the treatment of other chronic and opportunistic diseases (Günthard *et al.*, 2016:194-196). The use of PIs such as RTV causes dyslipidaemia and, in the long term, increases the risk of developing cardiovascular diseases, which, in turn, increase the incidence of myocardial infarction (Mallon *et al.*, 2006:1004). A study by Ovbiagele and Nath (2011:449) reported an increase in the number of patients hospitalised for ischemic stroke with co-existing HIV/AIDS. HIV/AIDS worsens hypercoagulability due to vascular abnormalities and coagulopathies (Zimba *et al.*, 2017:354). Cardiovascular disease accounts for 10% of mortalities in patients with HIV/AIDS (Reust, 2011:1450).

Some patients, usually older patients, have co-existing diseases and comorbidities that require treatment (Oni *et al.*, 2015:20). In South Africa, hypertension and DM2 are the two most prevalent co-existing diseases in PLWHA co-infected with TB (Oni *et al.*, 2015:20). Young et al. (2009:1- 2) reported that HIV and TB were the two most common infectious diseases in South Africa in 2009. PIs cause glucose intolerance; thus, 6% of patients using PIs develop DM2 (Reust, 2011:1447). Both PIs and NNRTIs increase the risk of metabolic syndrome in HIV-positive patients (Young *et al.*, 2009:3-9). Patients on NRTI-based treatment with co-existing metabolic syndrome should be closely monitored so that they do not develop lactic acidosis (refer to paragraph 2.6.3.4 (Reust, 2011:1444).

Günthard *et al.* (2016:192-196) recommend that patients with co-existing HIV/AIDS and hepatitis B should receive an ART regimen that includes TDF or TAF, 3TC or FTC with a third ARV medication, depending on the patient's medical history. In patients with HIV/AIDS with hepatitis B, entecavir may only be used if the viral load of HIV has been suppressed (Günthard *et al.*, 2016:192-193). NVP-based ART regimens has been reported to cause severe hepatotoxicity and liver failure in these patients (Reust, 2011:1446).

In PLWHA, the risk of developing osteoporosis, osteopenia, and vitamin D deficiency is increased through increased use of NNRTIs such as DDI or TDF as it reduces bone density by 2-6% (Günthard *et al.*, 2016:192-196; Reust, 2011:1450).

The Strategies for Management of Antiretroviral Therapy Study Group (SMART) study investigated the use of CD4 cell count as a guide to associate the risk of liver diseases, cardiovascular diseases, renal insufficiency and cancer events with the episodic use of ART versus the long-term use of ART (SMART Study Group, 2008:1145-1455). The strategy was to interrupt ART when the CD4 cell count reached a certain threshold to reduce adverse effects and comorbidities. The study resulted in patients with an increase in opportunistic infections, low CD4 cell counts and high viral loads (SMART study group, 2008:1145-1455). The outcome showed that, despite the increased risk from non-AIDS diseases associated with ART, the risk of leaving HIV/AIDS untreated is greater (Baker *et al.*, 2008:842; MacArthur *et al.*, 2001:177-181; Silverberg *et al.*, 2007:1957-1958).

PLWHA with co-existing diseases and comorbidities should be treated according to the STG of the DOH (2018:11.1-11.45) so that a suitable ARV regimen with reduced drug-drug interactions and drug-disease interactions can be selected (refer to paragraph 2.6.2.2)

2.6.2.1 Treatment of opportunistic diseases

Opportunistic diseases present more often and more severely in immunosuppressed patients, such as those with HIV/AIDS (Benson *et al.*, 2009:4). Treatment of opportunistic infections in PLWHA is complex due to possible toxicities, development of ART resistance and possible IRIS. IRIS is observed mostly in TB infections, toxoplasmosis, cytomegalovirus, hepatitis A, hepatitis B, varicella-zoster, Cryptococci infection, *Pneumocystis jirovecii* pneumonia and histoplasmosis (Benson *et al.*, 2009:3-4). IRIS may present only weeks after initiating ART, making it more challenging to determine other clinical manifestations (Benson *et al.*, 2009:4).

Table 2-12 (DOH, 2018:11.12-11.21) lists the treatment and prevention of opportunistic diseases in PLWHA.

Table 2-12: Treatment and prevention of opportunistic diseases in PLWHA

Active ingredient	Dosage[23]	Opportunistic disease
Cotrimoxazole	160/800 mg twice a day (320/1600 mg 12-hourly for 4 weeks and then 160/800 mg for 12 weeks for treatment of toxoplasmosis)	Given as preventative treatment for *pneumocystis jirovecii* pneumonia, toxoplasmosis, bacteraemia, isosporiasis, HIV-associated diarrhoea and bacterial pneumonia
Tetracaine	5% topically every six hours	Aphthous ulcers
Fluconazole	200 mg daily for two weeks	Oral or oesophageal candidiasis
Fluconazole	800 mg for 2 weeks, 400 mg for the next 8 weeks, and maintain with 200 mg for 12 months afterwards	Cryptococcal infection
Acyclovir	400 mg 5 times a day	Chronic herpes simplex mouth ulcers
Acyclovir	800 mg 5 times a day	Shingles (herpes zoster)
Isoniazid and pyridoxine	300 mg isoniazid and 25 mg pyridoxine daily for 12 months	Preventative TB treatment
Cetirizine and hydrocortisone	10 mg daily (cetirizine) and 1% topical cream (hydrocortisone) for 7 days	Papular pruritic eruption

[23] These dosages apply to adults only.

PLWHA may develop cancers such as Kaposi's sarcoma, non-Hodgkin's lymphoma, Hodgkin's lymphoma, cervical-, anal-, hepatic-, oral-, oesophageal-, lung-, testicular- and colorectal cancer, as well as types of skin cancer including basal cell carcinoma, squamous cell carcinoma and melanoma (Silverberg *et al.*, 2007:1961-1962; Yarchoan *et al.*, 2014:64-75).

Kaposi's sarcoma is related to human herpesvirus 8, which results in a type of cancer that forms lesions on the cells that line the blood vessels or lymph. All HIV-positive patients diagnosed with Kaposi's sarcoma are recommended to start ARV-treatment irrespective of their CD4 cell count. Cotrimoxazole is given to PLWHA as prophylactic treatment against Kaposi's sarcoma. ART also assists with tumour regression if the patient is adherent and has no history of opportunistic diseases and a normal CD4 cell count (above 200 cells/µl). Chemotherapy is suggested for patients with a lower prognosis, specifically in cases where systemic lesions are present in lymph nodes and the gastro-intestinal tract (Krown *et al.*, 1997:3085; Yarchoan *et al.*, 2014:64-75).

PLWHA are at risk of developing lymphatic cancer cells that can be classified as non-Hodgkin's lymphoma or Hodgkin's lymphoma (Armitage *et al.*, 2017:298; Sonenklar, 2011:45). Non-Hodgkin's lymphoma is cancer present in the lymph system (Armitage *et al.*, 2017:300). The lymph nodes of the armpits, groin and neck become enlarged; they are asymptomatic initially, but later, patients present with symptoms such as drenching night sweats, weight loss, severe itching and fever (Armitage *et al.*, 2017:301). Treatment differs for each type of lymphoma in PLWHA, but generally, these patients respond to chemotherapy and effective management of HIV/AIDS with ART treatment (MIC, 2016:63).

Cervical cancer is caused by the human papillomavirus (Menon *et al.*, 2018:3). The stage of cervical cancer can be determined by performing a pap smear (Menon *et al.*, 2018:3). The human papillomavirus causes uncontrolled growth of infected cells in the cervix and produces a protein that interferes with the normal function of the cervix cells (Menon *et al.*, 2018:4). Vaccines can prevent human papillomavirus if administered before exposure or before becoming sexually active (Menon *et al.*, 2018; MIC, 2016:63).

In 2009, the comorbid conditions associated with HIV and TB were the cause of 13% of HIV-related mortalities (Benson *et al.*, 2009:19). Preventative treatment for TB is isoniazid 300 mg with pyridoxine 25 mg daily for 12 months. In HIV-infected patients that present with a CD4 cell count of less than 50 cells/µL, prophylactic isoniazid is given two weeks after ART initiation. Alternatively, if a patient's CD4 cell count is more than 50 cells/µL, isoniazid is given eight weeks after ART initiation (DOH, 2018:11.12-11.13). All patients diagnosed with TB must be referred for treatment by a specialist or hospital facility (DOH, 2018: 10.16-10.18). In cases where TB is

diagnosed, patients are required to use standard tuberculostatics, which include rifampicin, ethambutol, pyrazinamide and isoniazid, for two months followed by rifabutin and isoniazid for an additional four months (Benson *et al.*, 2009:22). In cases where rifampicin for the treatment of TB is co-administered with NVP-based ARV treatment, it increases adverse effects such as hepatitis and skin rash (Sapkota *et al.*, 2012:17).

Resistance to antibiotics, tuberculostatic medications and medications used to treat opportunistic infections due to HIV/AIDS is a major concern globally. The increasing use of second- and third-line medicine can become unsustainable because of its financial impact (McLeod *et al.*, 2003:78).

2.6.2.2 Drug-drug interaction with ARV medication

Table 2-13 lists the drug-drug interactions between ARV medication and other medication on the market (AIDSinfo, 2019:L-7-L-51; De Maat *et al.*, 2003:228-272; MIC, 2016:61-88; DOH, 2018:11.11-11.21; University of California San Francisco, 2016).

Table 2-13: Drug-drug interactions between ARV medication and non-ARV medication

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
ABC (abacavir)	• **Carbamazepine** levels are decreased because ABC competes for glucuronidation. • **Interferon-alpha** or ribavirin has a lower response when used with ABC and might lead to hepatic decompensation and anaemia. • **Metronidazole** inhibits alcohol dehydrogenase and increases ABC levels. • **Phenobarbitone** decreases ABC levels. • **Phenytoin** or **rifampicin** reduces ABC concentration.
DDI (didanosine)	• **Allopurinol** increases DDI effects. • **Amphotericin** is nephrotoxic and requires dosage adjustments and close monitoring when administered with DDI. • Co-administration of DDI and **metronidazole, nitrofurantoin, paclitaxel, phenytoin, chloramphenicol or cisplatin** cause peripheral neuropathy. • The buffer in DDI tablets reduces **chlorpromazine, pyrimethamine, sulfadoxine** and **rifabutin** absorption when taken at the same time. • The buffer in DDI tablets decreases the effect **of ciprofloxacin** and **tetracyclines** due to decreased absorption and possible chelation. • DDI and **dapsone** increase neuropathy when used together. • DDI dispersible tablets and powder contains antacid that reduces the absorption of **dexamethasone**. • **Ganciclovir** leads to DDI toxicity (neuropathy, diarrhoea, pancreatitis) due to increased serum concentration, and the buffer in DDI reduces ganciclovir concentration. • **INH** and DDI can both cause neuropathy when used together. • DDI reduces the efficacy of **itraconazole**. • Co-administration of DDI and **metformin** may cause lactic acidosis. • The risk of liver toxicity is increased when **methotrexate** is used with DDI.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
DDI (didanosine)	• Co-administration of DDI and **methyldopa** may cause pancreatitis. • The buffer in DDI tablets changes **moxifloxacin's** bioavailability. • The buffer in DDI reduces the concentration of **nalidixic acid** and ofloxacin when co-administered with DDI. • Arthralgia is caused by co-administration of DDI and **pyrazinamide**, as DDI increases the exposure of **pyrazinamide**. • When DDI and **ribavirin** are used together, the risk of pancreatitis, hyperlactatemia, peripheral neuropathy, lactic acidosis and hepatic failure is increased due to mitochondrial toxicity. • Co-administration of DDI and **trimethoprim** or **sulfamethoxazole** may increase the risk of pancreatitis. • DDI and **valproic acid** used together lead to fatty liver, so the liver function must be monitored. • **Vincristine** and DDI used together may lead to peripheral neuropathy.
ARV medication	**Active ingredients of non-ARV medication that interact with ARV medication**
EFV (efavirenz)	• EFV reduces the levels of the active metabolite **albendazole sulfoxide**. • EFV decreases **alfentanil** levels, **medroxyprogesterone (oral), phenobarbitone, tacrolimus, trazodone, diltiazem** and **vincristine**. • EFV reduces exposure to **pravastatin, alprazolam, rifabutin** and **omeprazole**. • EFV may increase or decrease the concentration of **amiodarone** and **triazolam.** • **Artemether** and **lumefantrine** levels are reduced by EFV. • **Atorvastatin** concentration is decreased by EFV due to enzyme induction. • **Atovaquone** plasma concentration may be reduced by 75% due to EFV. • **Budesonide** and EFV levels are decreased with oral co-administration. • **Bupropion** concentration is reduced by 55% due to the induction of CYP2B6 by EFV. • EFV reduces **itraconazole's** efficacy when co-administered.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
EFV (efavirenz)	• Co-administration of **carbamazepine** and EFV causes reduced concentrations for both medications. • **Chloramphenicol** and **dexamethasone** increase EFV concentration. EFV reduces dexamethasone concentrations. • EFV decreases **chlordiazepoxide's** pharmacological action. • The co-administration of **cisapride** and EFV increases cardiotoxicity. • Induction of CYP3A4 results in the reduction of **clarithromycin** levels when administered with EFV and causes a rash in patients who receive both medications. • EFV reduces concentrations of **clonazepam, glibenclamide, colchicine, haloperidol, mebendazole, codeine, mianserin, nifedipine, praziquantel, quetiapine, quinidine, risperidone, sildenafil, verapamil** and **clozapine**. • The active metabolite of **ethinylestradiol** is increased when used with EFV. • **Levonorgestrel** levels are reduced when used with EFV. • EFV increases the efficacy and toxicity of **cyclophosphamide**. • **Diazepam's** sedation effects are extended with the use of EFV. • Risk of sedation and respiratory depression is increased by co-administration of **midazolam** and EFV. • **Fluoxetine** inhibits the metabolism of EFV and may lead to serotonin syndrome. • EFV increases the levels of **flurazepam, phenytoin, piroxicam** and **gliclazide**. • EFV may increase **flurazepam** levels. • EFV and **fluticasone** reduce each other's levels. • **Garlic supplements** contain allicin that reduces levels of EFV. • Plasma levels of EFV are reduced when used with griseofulvin due to induced enzymes. • EFV reduces the active metabolite of **tamoxifen**. • EFV and oral **hydrocortisone** decrease each other's concentration. • EFV reduces the pharmacological action of **ifosfamide** but increases its toxicity.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
EFV (efavirenz)	• EFV reduces (via inducing CYP3A4**) isotretinoin** or increases (via inhibiting CYP2C8) **isotretinoin,** leading to toxicity. • **Lidocaine** and **loratadine** concentrations are reduced when used with EFV • Competition for or inhibition of UGT2B7 during co-administration with EFV increases **morphine** concentration and opiate toxicity. • Because the metabolites of **olanzapine** and EFV undergo **glucuronidation**, EFV could interfere with the concentration of these medications. • EFV inhibits CYP2C8 and may increase **paclitaxel** when co-administered. • Because EFV induces CYP2B6 and CYP3A4 increases **pethidine** concentration, co-administration increases the risk of CNS side effects such as seizures and the risk increases when pethidine and EFV are used together for long periods. • EFV reduces or increases the plasma concentration of **phenytoin**, and phenytoin reduces EFV concentration. • The risk of arrhythmias is increased by co-administration of **pimozide** and EFV. • EFV shortens the half-life of **prednisone**, and prednisone levels may fluctuate. • CYP3A4 induction caused by EFV leads to decreased concentration of **quinine**. • **Simvastatin** levels are increased when used with EFV. • **Sirolimus'** concentration is reduced when used with EFV. • **St John's Wort** may reduce the plasma concentration of EFV and reduce the efficacy of EFV. • EFV may lead to additive PR-interval (of electrocardiography) prolongation when used with timolol due to increased **timolol** concentration. • EFV levels increase when used with **voriconazole**, and voriconazole's effects are decreased.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
EFV (efavirenz)	• Using **warfarin** with EFV increases the risk of bleeding or clotting, so international normalised ratio tests are required to determine levels and monitor them regularly. • **Zolpidem** may cause withdrawal symptoms when used with EFV due to decreases in zolpidem levels.
ETR (etravirine)	• ETR reduces the active metabolite **albendazole sulfoxide.** • ETR decreases levels of **alfentanil, lidocaine, diltiazem, medroxyprogesterone (oral), disopyramide, phenytoin, pimozide, praziquantel, phenobarbitone, quinidine, quinine, risperidone, tacrolimus, trazodone, verapamil** and **cisapride.** • Co-administration with ETR reduces the exposure of **alfuzosin, sildenafil, vincristine** and **rifampicin.** • **Griseofulvin** induces enzymes that may cause increased ETR levels. • ETR induces CYP3A4, which decreases the exposure of **alprazolam, nifedipine** and **midazolam.** • ETR increases **nitric oxide** (due to CYP3A4) when co-administered with **isosorbide dinitrate**. • ETR reduces the plasma concentration of **amiodarone** and **sirolimus.** • **Artemether** and **lumefantrine** levels are reduced with ETR. • ETR reduces **atorvastatin** exposure. • Both ETR and **budesonide** levels are decreased when co-administered orally. • **Carbamazepine** reduces ETR concentration. • Etravirine could decrease **carvedilol** concentrations via induction of glucuronidation or increase carvedilol concentrations via CYP2C9 inhibition. • ETR reduces **chlordiazepoxide's** pharmacological action. • Exposure to ETR produces the hydroxy metabolite of **clarithromycin**, reducing clarithromycin levels and increasing ETR levels. • **Diltiazem** increases ETR levels. •

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
ETR (etravirine)	• ETR reduces concentrations of **clozapine, mebendazole, colchicine, quetiapine** and **codeine.** • **Cyclophosphamide's** neurotoxic metabolite is increased when used with ETR. • The plasma concentrations of **cyclosporine** and **disopyramide** are reduced when used with ETR. • ETR increases the plasma concentration of **digoxin**. • ETR decreases **dexamethasone** concentration, and **dexamethasone** decreases ETR concentration. • ETR reduces the active metabolite of **tamoxifen** when co-administered. • ETR increases levels of **diazepam, ibuprofen, piroxicam** and **gliclazide**. • **Fluconazole** increases the plasma concentration of ETR by 86%. • **Garlic supplements** reduce ETR levels due to the **allicin** in the supplements. • ETR reduces **itraconazole** concentration, and itraconazole increase ETR concentration. • Co-administration of ETR and **prednisone** reduce each other's levels. • **Rifabutin** reduces ETR exposure by 37%. • ETR reduces **simvastatin** exposure when used together. • **St John's** Wort used with ETR may reduce ETR levels. • ETR can decrease **triazolam** exposure when used together. • ETR and **voriconazole** exposure are both increased when used together. • ETR leads to increased plasma concentrations of **warfarin**, so the international normalised ratio of patients using ETR and warfarin should be monitored regularly. • **Zolpidem** may cause withdrawal symptoms when used with ETR due to decreases in zolpidem levels.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
3TC/FTC (lamivudine/ emtricitabine)	• **Acetazolamide** may compete for active renal transport with 3TC/FTC and may increase the concentration of 3TC/FTC levels. • **Amikacin** is nephrotoxic, and the dosage of 3TC should be adjusted accordingly. • 3TC/FTC competes for OCT2 with **cisplatin, pyrimethamine** (also compete for MATE1) or ofloxacin, which results in slow renal elimination and impaired renal function. • 3TC renal elimination is decreased with **disopyramide**. • Co-administration of **methotrexate** and 3TC/FTC causes increased competition for renal elimination and potentially increases both medications' toxicity. • 3TC/FTC used with **ribavirin** increases the risk of lactic acidosis and hepatic decompensation. • **Trimethoprim/sulfamethoxazole** increases 3TC/FTC exposure, and high doses should be avoided when co-administered. • **3TC/FTC** and **valproic acid** used together lead to fatty liver.
PIs (protease inhibitors) - LPV/r, ATV, DRV, RTV (lopinavir/ ritonavir combination, atazanavir, darunavir, and ritonavir, indinavir)[24]	• RTV reduces the active metabolite **albendazole** sulfoxide. • PIs increase levels of **alfentanil, triazolam** and **clonazepam.** • PIs increase the plasma concentration of **alfuzosin** and **disopyramide.** • **Alimemazine** and RTV levels may be increased if used together. • **Alprazolam** levels increase with the initiation of LPV/r or LPV and ATV combination, which stabilises ten days after initiation. • Aluminium hydroxide decreases ATV absorption and solubility as the stomach's pH increases. • RTV increases **prednisolone** levels up to 30% when used together.

[24] The whole group of LPV/r, ATV, DRV and RTV are referred to as PIs.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
PIs (protease inhibitors) - LPV/r, ATV, DRV, RTV (lopinavir/ ritonavir combination, atazanavir, darunavir, and ritonavir, indinavir)[25]	• RTV increases levels **of amiodarone** and **glibenclamide**. • The plasma concentration and effects of **amitriptyline** and **mefloquine** are increased with PIs, and co-administration with LPV/r has a risk of increased QT interval[26] prolongation. • Co-administration of **quinine** and LPV/r decreases quinine exposure by 50%, where if quinine is given with RTV alone, quinine levels increase four times and the half-life of RTV increases by 20%. • RTV increases levels of **propafenone** and **promethazine**, which leads to *torsade de pointes*. • **Amlodipine** concentration is increased with RTV and ATV, which can cause an increased risk of PR interval[27] prolongation. • PIs reduce artemether levels and increases **lumefantrine** levels. • Cardiac and neurological events have been reported in cases where RTV and **beta-blockers** have been co-administered, and they may cause prolongation of the PR interval. • PIs increase **timolol** and **verapamil** concentration when co-administered, increasing the risk of PR prolongation. • RTV increases levels of **loperamide**. • PIs increase **norpethidine** concentrations and CNS side effects when PIs are co-administered with **pethidine**. • PIs may increase levels of **atorvastatin** up to fivefold. • LPV/r may decrease **atovaquone** levels.

[25] The whole group of LPV/r, ATV, DRV and RTV are referred to as PIs.

[26] QT interval prolongation is a measure of delayed ventricular repolarisation, which can trigger tachycardias due to heart muscles that take longer than normal to recharge between beats (Katzung & Trevor, 2015:139).

[27] PR interval that is prolonged is an indication that there is a delay in the conduction of the sinoatrial nodal impulse to the heart ventricle (Katzung & Trevor, 2015:139).

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
PIs (protease inhibitors) - LPV/r, ATV, DRV, RTV (lopinavir/ ritonavir combination, atazanavir, darunavir, and ritonavir, indinavir)[28]	• Co-administration of PIs and **azithromycin, lithium, fluconazole, ofloxacin, promethazine, propafenone** or **ciprofloxaci**n may cause prolongation of the QT interval. • **Lithium** levels are decreased when used with ATV and RTV. • Co-administration with **beclomethasone** reduces the active metabolite of DRV/RTV by 11-19%. • **Betamethasone** levels are increased and PI levels are decreased by co-administration. • **Budesonide** decreases levels of PIs, and RTV increases budesonide levels due to enzyme inhibition. • PIs reduce the active metabolite of **tamoxifen**, resulting in lower efficacy. • PIs reduce concentrations of **bupivacaine**, **medroxyprogesterone** (oral), **morphine**, **sirolimus**, **theophylline** and **ibuprofen**. • PIs increase levels of **captopril, chlorphenamine/chlorpheniramine, chlorpromazine** and **haloperidol.** • PIs increase levels of **carbamazepine, mianserin, risperidone, simvastatin, tacrolimus** or **rifabutin** when co-administered. • **Carbamazepine** decreases levels of PIs. • Oral LPV/r solutions may cause a disulfiram reaction when used with **metronidazole**. • Co-administration of PIs and **carvedilol nifedipine, diltiazem, propranolol** or **digoxin** can cause a prolonged PR interval and increase in the concentration of PIs. • ATV increases **diltiazem** plasma concentration 2.25 times. • **Carvedilol** concentrations increase due to CYP2D6 inhibition or decrease via induction of **glucuronidation** when co-administered with PIs.

[28] The whole group of LPV/r, ATV, DRV and RTV are referred to as PIs.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
PIs (protease inhibitors) - LPV/r, ATV, DRV, RTV (lopinavir/ ritonavir combination, atazanavir, darunavir, and ritonavir, indinavir)[29]	• PIs increase the exposure and half-life of **cetirizine**, which may cause drowsiness. • PIs increase the pharmacological action of **chlordiazepoxide**. • **Chloroquine, moxifloxacin, quinine** and **citalopram** levels may be increased with PIs, increasing the risk of QT interval prolongation. • **Fluphenazine** levels are increased by RTV and may lead to QT interval prolongation. • PIs increase **cisapride** levels, potentially leading to cardiotoxicity. • **Clarithromycin** and PI co-administration should be avoided due to cardiotoxicity (QT interval prolongation) and a potential increase in clarithromycin concentration. • RTV increases the concentration of **clindamycin** or **prochlorperazine** when used together. • PIs reduce the active metabolite of **ATV** and **RTV**. • **Analgetic** effects of codeine may be reduced when used with PIs. • PIs cause significant changes in **colchicine**, and dosages should be amended when co-administered. RTV and colchicine are contra-indicated in patients with renal impairment. • High doses of oral contraceptives are suggested when co-administered with PIs as **ethinylestradiol** concentration is either increased or decreased. • Cushing's syndrome may be caused by co-administration of inhaled **fluticasone** and RTV. • **Corticosteroids** reduce LPV/RTV's concentration, and systemic **corticosteroids** are increased. • The efficacy and toxicity of **cyclophosphamide** are increased with the use of PIs.

[29] The whole group of LPV/r, ATV, DRV and RTV are referred to as PIs.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
PIs (protease inhibitors) - LPV/r, ATV, DRV, RTV (lopinavir/ ritonavir combination, atazanavir, darunavir, and ritonavir, indinavir)[30]	• Immunosuppression and renal toxicity are increased due to the increased concentration of **cyclosporine** when used with PIs. • PIs inhibit or induce p-glycoprotein, and **dabigatran** is a substrate of p-glycoprotein. • **ATV** and **dapsone** increased the risk of hemolytic anaemia and hyperbilirubinemia. • Cardiotoxicity risk is high when PIs are used with **daunorubicin**. • **Dexamethasone's** levels and pharmacological action are increased with PIs, and dexamethasone reduces LPV, RTV and DRV concentrations. • Cardiac arrhythmias may be caused when **flecainide** or pimozide is co-administered with PIs. • The use of **fluoxetine** with PIs increases **fluoxetine** and toxicity. RTV with **fluoxetine** may cause serotonin syndrome. • Sedation, confusion and respiratory suppression may be caused by co-administration of PIs and **midazolam**. • Cushing's syndrome and adrenal suppression result from decreased plasma cortisol caused by increased **fluticasone** levels when used with PIs. • Both **fusidic acid** and RTV levels increase when co-administered, increasing the risk of hepatoxicity. • **Allicin** in garlic supplements reduces PI levels. • LPV/RTV decreases the plasma concentration of **gemfibrozil** by 41%. • RTV induces CYP2C9, which reduces **gliclazide**. • PIs' concentration is reduced with oral **hydrocortisone**, and oral **hydrocortisone** levels may be increased. • PIs reduce **ifosfamide's** pharmacological action, and **ifosfamide** reduces PI levels.

[30] The whole group of LPV/r, ATV, DRV and RTV are referred to as PIs.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
PIs (protease inhibitors) - LPV/r, ATV, DRV, RTV (lopinavir/ ritonavir combination, atazanavir, darunavir, and ritonavir, indinavir)[31]	• PIs increase **imipramine** concentrations. • Co-administration of PIs and **isosorbide dinitrate** decreases the active metabolite (nitric oxide) and **nitric oxide** efficacy. • **Isotretinoin** levels are increased when used with PIs as it increases CYP2C8 and CYP3A4. • The efficacy of PIs and **itraconazole** is increased when used together. • PI efficacy is possibly increased or decreased when used with **ketoconazole**, and **ketoconazole's** effects are increased. • PIs (except ATV) decrease **lamotrigine** blood levels by half due to glucuronidation induction. • LPV/RTV decreases **lansoprazole**, and ATV decreases when used with **lansoprazole**. • Severe dyskinesia has been reported with co-administration of **levodopa** and indinavir. • PIs increase thyroid-stimulating hormone levels, so the dosage of **levothyroxine** should be monitored. • PIs increase **omeprazole's** metabolism, and **omeprazole** reduce ATV exposure. • PIs increase systemic **lidocaine** and side effects such as hypotension and cardiac arrhythmias. • PIs increase levels of **loratadine**. • ATV absorption is decreased when pH increases, and it cannot be used with antacids. • RTV reduces the efficacy of **mebendazole** and **olanzapine**.

[31] The whole group of LPV/r, ATV, DRV and RTV are referred to as PIs.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
PIs (protease inhibitors) - LPV/r, ATV, DRV, RTV (lopinavir/ ritonavir combination, atazanavir, darunavir, and ritonavir, indinavir)[32]	• Co-administration of **metoprolol** and PIs increases the plasma concentration of **metoprolol**, increasing neurological and cardiovascular side effects (PR interval prolongation). • PIs and **mycophenolate mofetil's** metabolite undergo glucuronidation and therefore both could alter each other's concentration. • PIs reduce concentrations of **naloxone**. • Co-administration of PIs and **paclitaxel** increases toxicity, leading to myelosuppression and peripheral neuropathy. • PI concentration is reduced by **phenobarbitone**. • CYP3A4 inhibition caused by PIs increases **quetiapine's** concentration. • Co-administration of **phenytoin** and PIs decreases concentrations of both. • **Pravastatin** increases the exposure of RTV and DRV up to five times. • Co-administration of **ranitidine** and ATV reduces the absorption of ATV. • **Rifampicin** reduces levels of ATV, DRV and LPV, leading to increased alanine transferase and aspartate transaminase. • PIs increase **colchicine** levels severely. • **St John's Wort** reduces the plasma concentration of PIs. • RTV levels are increased when co-administered with **pyrimethamine**. • PIs may increase **tramadol** exposure but reduce its active metabolite. • PIs increase **trazodone** side effects such as nausea, hypotension and syncope due to increased trazodone levels. • LPV and **valproic acid** reduce each other's concentration when co-administered.

[32] The whole group of LPV/r, ATV, DRV and RTV are referred to as PIs.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
PIs (protease inhibitors) - LPV/r, ATV, DRV, RTV (lopinavir/ ritonavir combination, atazanavir, darunavir, and ritonavir, indinavir)[33]	• Co-administration of PIs and vincristine lead to the risk of neurotoxicity because PIs cause increased levels of **vincristine**. • **Voriconazole** concentration is potentially decreased or increased and LPV/RTV levels are possibly increased when used together. • PIs used with **warfarin** leads to increased risk of bleeding or clotting, and therefore international normalised ratio should be monitored. • Side effects such as sedation should be monitored when zolpidem is used with PIs because PIs lead to an increased **zolpidem** concentration.
NVP (nevirapine)	• NVP reduces the active metabolite **albendazole sulfoxide**. • NVP reduces the effects of **alprazolam**. • The plasma concentrations of amiodarone or **sirolimus** are potentially increased when co-administered with NVP. • The effect of both NVP and **artemether** is reduced when used together. • **Griseofulvin** causes enzyme induction which decreases the concentration of NVP. • NVP decreases the concentration of **atorvastatin, medroxyprogesterone (oral), itraconazole, paclitaxel, pimozide, midazolam, praziquantel, mianserin, propafenone, quinine, trazodone** and **haloperidol.** • NVP and **budesonide** levels are decreased when co-administered. • NVP and **carbamazepine** levels are reduced when co-administered. • **Chloramphenicol** increases NVP levels. • NVP decreases the pharmacological action of **chlordiazepoxide** and **diltiazem**. • NVP increases **clarithromycin's** active metabolite, and co-administration may lead to an increase in NVP levels.

[33] The whole group of LPV/r, ATV, DRV and RTV are referred to as PIs.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
NVP (nevirapine)	• NVP causes a reduction in the concentration of **clonazepam** when co-administered, which may lead to **clonazepam** withdrawal symptoms. • NVP decreases levels of **ethinylestradiol** and **norethisterone**. • NVP and **corticosteroids** levels are reduced by co-administration. • NVP used with **cyclophosphamide** increases the active metabolite of cyclophosphamide, increasing neurotoxicity. • NVP and **dexamethasone** reduce the efficacy of each other. • **Diazepam** concentration is reduced when used with NVP. • The plasma concentration and clinical effect of **disopyramide** are reduced when used with NVP. • **Fluconazole** increases NVP exposure by 100% and may cause raised ALT. • NVP reduces concentrations of **fluoxetine, glibenclamide, mebendazole, flurazepam** and **fluticasone.** • **Fluticasone** and NVP reduce each other's concentration. • **Garlic supplements** contain allicin which reduces PI levels. • Oral **hydrocortisone** and NVP levels are reduced by co-administration. • The risk of **ifosfamide** toxicity is increased when used with NVP. • NVP and **ketoconazole** efficacy is increased when co-administered. • NVP decreases concentrations of **lidocaine, verapamil** and **simvastatin** when used together. • NVP and **mycophenolate mofetil's** metabolite undergo glucuronidation, and therefore both could alter each other's concentration. • Because CYP2B6 and CYP3A4 are induced when NVP is co-administered with **pethidine** (increases the active metabolite norpethidine), it increases the risk of CNS toxicity. • NVP levels are decreased when used with **phenobarbitone** and **phenytoin**. • NVP increases **rifabutin** exposure, increasing toxicity.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
NVP (nevirapine)	• **Rifampicin** reduces NVP exposure when co-administered. • **St John's Wort** reduces the plasma concentrations and efficacy of NVP. • NVP reduces **tamoxifen** levels and increases the active metabolite of tamoxifen, and co-administration should be monitored for toxicity. • NVP decreases **triazolam's** concentration and may result in withdrawal symptoms. • When administering **trimethoprim/sulfamethoxazole** with NVP, the risk of developing a rash is increased. • NVP reduces **vincristine** concentration when co-administered. • **Voriconazole** increases NVP levels, and NVP decreases voriconazole levels when co-administered. • NVP may decrease or increase **warfarin** levels when used together. • Withdrawal symptoms may be caused in patients that use NVP and **zolpidem** together for an extended period, as NVP reduces **zolpidem's** concentration.
RAL (raltegravir)	• **Aluminium** hydroxide decreases RAL exposure. • Using RAL with **carbamazepine** should be monitored as both medications' concentration may be reduced due to glucuronidation induction. • RAL increases **gemfibrozil** concentration. • **Paclitaxel** may reduce RAL concentration.
RAL (raltegravir)	• RAL exposure increases when used with **omeprazole**. • RAL levels increase when used with **rifabutin**. • **Rifampicin** decreases exposure to RAL when used together.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
D4T (stavudine)	• **Acetazolamide** completes active renal transport with D4T, which may lead to increased concentrations of either medication. • **Amikacin** may be nephrotoxic when used with D4T, and co-administration must be monitored or avoided. • **Amphotericin B** or **streptomycin** may be nephrotoxic when used with D4T, and dose adjustment is required. • Co-administration of **aurothioglucose**, **paclitaxel, paracetamol, chloramphenicol, metronidazole, phenytoin** or **cisplatin** with D4T causes peripheral neuropathy. • D4T may lead to neuropathy when used with **dapsone**. • Co-administration of **INH** or **nitrofurantoin** and D4T may cause peripheral neuropathy. • Co-administration of **D4T** and **metformin** may cause lactic acidosis. • Co-administration of **methotrexate** and D4T causes increased competition for renal elimination, potentially increasing both medications' toxicity. • The risk of pancreatitis is increased when D4T and **methyldopa** or **trimethoprim/sulfamethoxazole** are used together. • Co-administration of D4T and **ribavirin** may cause lactic acidosis and hepatic decompensation. • Active tubular toxicity is increased when D4T is used with **sirolimus**. • Using D4T and **valproic acid** together increases the risk of fatty liver.
TDF (tenofovir)	• **Acetazolamide** competes for active renal transport with TDF and may increase the concentration of either medication. • Competition for active renal transport between TDF and **acyclovir** may increase the concentration of either medication. • TDF co-administered with **amikacin**, **cyclosporin**, **kanamycin**, **cisplatin**, **tacrolimus**, or **streptomycin** leads to additive nephrotoxicity.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
TDF (tenofovir)	• Additive nephrotoxicity has been reported when TDF is used with NSAIDs such as **aspirin**; therefore, dosage adjustments are required. • **Furosemide** may reduce the renal elimination of TDF. • Nephrotoxicity risk is increased when TDF and **NSAIDs** are used together for long periods. • Co-administration of TDF and **metformin** may cause lactic acidosis. • Co-administration of **methotrexate** and TDF causes increased competition for renal elimination, potentially increasing both medications' toxicity. • TD4 and **mycophenolate mofetil** increase each other's concentration because active tubular secretion and **mycophenolic mofetile's** metabolite inhibit the renal transporters QAT1 and QAT3. • TDF used with **ribavirin** increases the risk of lactic acidosis.
AZT (zidovudine)	• **Acetazolamide, vincristine or nitrofurantoin** causes additive myelosuppression when used with AZT. • **Aciclovir** may lead to profound lethargy when used with AZT. • **Albendazole** has an additive bone marrow suppression when used with AZT. • **Amphotericin B** has the same toxicity profile as AZT, and co-administration should be monitored closely. • **Aspirin** increases the concentration of AZT. • **Atovaquone, estradiol** and **ethinyl** inhibit glucuronidation and increases AZT levels. • AZT may increase **carbamazepine** concentration due to competition for glucuronidation. • AZT increases **chloramphenicol** concentration due to glucuronidation. **Chloramphenicol** and AZT are both bone marrow toxins and should be monitored. • Co-administration of AZT with **cisplatin**, **ibuprofen**, **ifosfamide**, **methyldopa**, **paclitaxel**, **clozapine**, **prochlorperazine** or **dapsone** lead to hematotoxicity. • **Clarithromycin** reduces AZT concentration.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
AZT (zidovudine)	• **Cimetidine** reduces the absorption of AZT. • Additive myelosuppression is caused when **cyclophosphamide** or **daunorubicin** is co-administered with AZT. • AZT's effect and toxicity are increased with the use of **fluconazole**. • **Interferon-alpha** increases AZT levels, and the two have similar toxicity profiles, potentially causing hematological toxicity, impaired renal function and hepatic decompensation. • AZT and **lorazepam** used together increase the concentration of AZT and may cause headaches. • **Magnesium hydroxide** increases AZT levels which causes diarrhoea. • **Mycophenolate mofetil** concentrations could be altered when used with AZT. • AZT's bioavailability is increased when used with **oxazepam** and, therefore, can cause increased headaches. • The use of **paracetamol** with AZT increases hematotoxicity and hepatotoxicity. • AZT levels are decreased when used with **phenobarbitone**. • Co-administration of ATZ and **phenytoin** decreases AZT's clearance and toxicity and may increase or reduce phenytoin concentration. • AZT decreases the concentration of **pyrazinamide** when co-administered. • Risk of lactic acidosis, hepatic decompensation, neutropenia and anaemia increases when AZT is used with **ribavirin**. • **Rifabutin** or **rifampicin** decreases AZT levels when used together. • AZT causes additive hematotoxicity when co-administered with **PIs**. • When AZT is used with **trimethoprim/sulfamethoxazole**, AZT's toxicity is increased, especially hepatic failure. • AZT's toxicity increases when used with **valproic acid** because **valproic acid** inhibits the breakdown of AZT; therefore, co-administration may increase the risk of fatty liver.

ARV medication	Active ingredients of non-ARV medication that interact with ARV medication
All ARV medications	• **Activated charcoal** and **liquid paraffin** may reduce the absorption of all ARV medication. • No interactions have been reported between ARV medications and **Vitamin A, Vitamin B-complex, Vitamin C, Vitamin K** or **zinc oxide.**

2.6.3 Medicine-related factors

Medicine-related factors include ARV medications used to treat patients with HIV/AIDS, suggested regimens, resistance caused by ARVs, the reasons for such resistance, and adverse drug reactions and drug-drug interactions that may present during treatment.

2.6.3.1 Antiretroviral medication

The ART's goal is to provide continuous effective viral suppression, sustain and rebuild the immune system, minimise morbidity, increase life expectancy and quality of life, help prevent transmission, and ensure minimal adverse effects of treatment (Meintjes *et al.*, 2017:1). The following five classes of ARV medication listed were available in South Africa at the time of writing (Katzung & Trevor, 2015:1631-1661; Meintjes *et al.*, 2017:1-2):

- NRTIs initiate reverse transcriptase inhibition where viral RNA transcription to DNA is reduced by nucleic acid analogues that imitate the regular building blocks of DNA.
- NNRTIs cause reverse transcriptase inhibition by modifying the catalytic site and therefore inhibit its action.
- PIs inhibit the last phases of HIV duplication and yields the formation of non-infective viral particles.
- Integrase inhibitors block the distribution of viral DNA strands into the host chromosomal DNA.
- Entry inhibitors trigger attachment to viral gp41, gp120, host CD4 cell or chemokine (CCR5) receptors.

Table 2-14 lists the active ingredients, dosage, side effects and contra-indications as well as information regarding the various ARV medications (Katzung & Trevor, 2015:1631-1661; MIC, 2016:60-88; Reust, 2011:1444-1450; Rossiter *et al.*, 2016:60-88).

Table 2-14: Active ingredients, dosage, side effects and contra-indications, as well as information regarding ARV medication

Active ingredients	Dosage	Side effects and contra-indication	Information regarding the active ingredient
Abacavir (ABC)	Adult: 600 mg daily or 300 mg twice a day Paediatric (3 months to 12 years): 16 mg/kg once daily or 8 mg/kg twice a day	Hypersensitivity Increased liver enzymes leukopenia and lymphopenia Sleep disorders Headache Hyperlactatemia and hepatic steatosis Anaemia Neutropenia Increase in creatine phosphokinase and pancreatitis Myocardial infarction	It cannot be used as a single agent Causes life-threatening hypersensitivity reaction Discontinued when the patient develops lactic acidosis Contra-indicated for severe hepatic impairment Contra-indicated for hereditary fructose intolerance Safety in neonates and infants under three months not established
Lamivudine (3TC)	Adult: 300 mg daily or 150 mg twice a day Paediatric (3 months to 12 years): 4 mg/kg twice a day (with a maximum of 150 mg twice a day); for less than 10 kg, 8 mg/kg once a day Neonates (younger than 30 days): 2 mg/kg twice a day	Gastro-intestinal side effects like nausea, vomiting and diarrhoea Headache, fever, malaise, fatigue, upper abdominal pain, rash, alopecia, paraesthesia, muscle disorders Pure red cell aplasia in scarce situations Peripheral neuropathy and pancreatitis Hyperlactatemia and hepatic stenosis	Must be used in combination with other ARVs Rebound hepatitis infection possible when the patient had a hepatitis infection Used for post-exposure prophylaxis and to prevent MTCT

Active ingredients	Dosage	Side effects and contra-indication	Information regarding the active ingredient
Atazanavir (ATV)	Adult: 300 mg plus RTV 100 mg once a day with meals; dose adjustment for moderate liver impairment to 300 mg once a day Paediatric: dependent on body weight for ages 6 to 18 years – 15 to 20 kg to take 150 mg once a day with 100 mg RTV; 20 to 40 kg to take 200 mg ATV with 100 mg RTV; 40 kg or more to take the adult dose During pregnancy: only use RTV-boosted ATV	Dyslipidaemia and GI-tract effects Nausea, abdominal pain, diarrhoea, vomiting, dyspepsia, insomnia, rash, dizziness, peripheral neuropathy and headache Jaundice (due to unconjugated hyperbilirubinemia) Mild to moderate maculopapular rashes in the first three weeks of treatment	Not to be used alone A high potential of medication interactions when combined with RTV It cannot be used with rifampicin (RIF) Difficult to develop viral resistance due to several viral mutations required and cross-resistance with other protease inhibitors (PI) Potentially significant interaction with antacids and proton pump inhibitors Cardiac conduction abnormalities or administration with other medications may prolong PR interval Asymptomatic increases in indirect bilirubin experienced by most patients, but when treatment is stopped

Active ingredients	Dosage	Side effects and contra-indication	Information regarding the active ingredient
Darunavir (DRV)	Adult: PI naïve patients to use 800 mg daily taken with RTV 100 mg Paediatric: weight-based treatment for children aged 6 to 18 years – 20 to 30 kg to take 375 mg DRV with 50 mg RTV; 30 to 40 kg to take 450 mg DRV with 60 mg RTV twice a day with	Diarrhoea, skin rash, nausea, vomiting, hepatitis and headache Dyslipidaemia and, in some cases, Stevens-Johnson syndrome	To be used in combination with other ARV medication Difficult to form viral resistance due to several viral mutations needed and cross-resistance with other protease inhibitors (PI) Has the highest genetic barrier to resistance and therefore is still active when other PIs are not Patients allergic to sulphonamide groups may be allergic to DRV It cannot be used with RIF
Darunavir (DRV)	food; more than 40 kg to take 600 mg DRV with 100 mg RVT twice a day with food Pregnancy: safety is limited, and use is suggested only when other ARVs cannot be used		

Active ingredients	Dosage	Side effects and contra-indication	Information regarding the active ingredient
Didanosine (DDI)	Indicated only for adults and children older than 12 years weighing at least 40 kg For patients who are treatment naïve to integrase strand transfer inhibitors, 50 mg once daily When co-administered with EFV and FPV/r, TPV/r or RIF, which are UGT1A/CYP3A inducers, to use 50 mg twice a day	Insomnia and headache Hypersensitivity reactions, including rash, constitutional findings and sometimes organ dysfunction	Transaminase caused by DDI may worsen underlying hepatitis B and hepatitis C Co-administration with dofetilide contra-indicated Medication interaction with metabolic inducers may decrease the plasma concentration of DTG

Active ingredients	Dosage	Side effects and contra-indication	Information regarding the active ingredient
Efavirenz (EFV)	Adults: those weighing more than 40 kg to use 600 mg daily at night and those weighing less than 40 kg to use 400 mg daily Paediatric (more than 10 kg and older than 3 years): 10–13.9 kg to take 200 mg at night, 14–24.9 kg to take 300 mg at night, 25–39.9 kg to take 400 mg at night	Abnormal dreams, impaired concentration, headache, dizziness and insomnia Mild to moderate maculopapular rashes common; must be stopped in patients developing rash associated with blistering, desquamation, mucosal involvement or fever Nausea, vomiting, diarrhoea, gynaecomastia and raised liver enzymes	Neural tube defects can be caused in the first trimester and distributed to human milk Cross-resistance with NVP Not to be used as a single agent Taken at night on an empty stomach to make the side effects more tolerable May cause impaired function during the day Contra-indicated in severe renal impairment and severe liver disease.
Emtricitabine (FTC)	Adults: 200 mg daily Paediatric: children less than 35 kg (TDF and FTC) or less than 40 kg (TDF, FTC and EFV)	Headache, nausea, vomiting, rash, hyperpigmentation Hyperlactatemia and hepatic steatosis	Similar to 3TC, only available in combination with TDF and EFV Must be used in combination with other ARVs and not as a single treatment Also used as post-exposure prophylaxis for chronic hepatitis B infection and to reduce MTCT
Etravirine (ETR)	Adult: 200 mg twice a day Paediatric: 16–19.9 kg to take 100 mg twice a day, 20–24.9 kg to take 125 mg twice a day, 25–	Mild to moderate rash when treatment is initiated Severe hypersensitivity	Only used in ART-experienced patients Not to be used with RIF or ATV Tablets dissolvable in water but not to be chewed

Active ingredients	Dosage	Side effects and contra-indication	Information regarding the active ingredient
	29.9 kg to take 150 mg twice a day, 30 kg or more to take 200 mg twice a day		
Lopinavir/ritonavir (LPV/r)	Adult: 400 mg/100 mg (two tablets) twice a day or 800 mg/200 mg (four tablets) Paediatric: available as oral solution from postnatal age of 14 days if the infant is not premature; 7–14 kg to be given 12 mg/3 mg per kg every 12 hours, 15–40 kg to be given 10 mg/2.5 mg per kg every 12 hours	Diarrhoea, nausea and vomiting Elevated triglycerides and LDL-cholesterol leads to dyslipidaemia Prolongation of QT interval and PR interval Hepatotoxicity	Only to be used as a single agent if no other option is available Cross-resistance with other PIs Difficult to form viral resistance due to several viral mutations needed and cross-resistance with other PIs

Active ingredients	Dosage	Side effects and contra-indication	Information regarding the active ingredient
Nevirapine (NVP)	Adult: oral 200 mg daily for 14 days, followed by 200 mg 12-hourly Paediatric: from 2 months to 8 years, 4 mg/kg once a day for two weeks then 7 mg/kg twice daily; for those older than 8 years, 4 mg/kg once daily for two weeks, then 4 mg/kg twice a day (maximum 400 mg/day)	Rash that dissolves after the first six weeks Rash accompanied by fever and other manifestations may cause life-threatening systemic hypersensitivity Clinical hepatitis and abnormal liver function	Resistance to NVP develops quickly, and cross-resistance with EFV is evident

Active ingredients	Dosage	Side effects and contra-indication	Information regarding the active ingredient
Raltegravir (RAL)	Adult: 400 mg twice a day, including for children above the age of 12 years and weighing at least 25 kg Paediatric: available in chewable tablets for children; 10–14 kg to receive 75 mg twice a day; 14–20 kg to receive 100 mg twice a day; 20–28 kg to receive 150 mg twice a day; 28–40 kg to receive 200 mg twice a day; above 40 kg to receive 300 mg twice a day	Headache, nausea, vomiting, insomnia, dizziness Hepatitis Rash Stevens-Johnson syndrome Rhabdomyolysis	Lowers the viral load faster than any other regimen May be used with an NRTI in first-line treatment as well as second-line treatment if boosted with a PI when other medications are not tolerated Low potential for medication interactions Dosage adjustments not required in patients with renal disease
Rilpivirine (RPV)	Adult: 25 mg once a day with meals Paediatric: not recommended for children younger than 18 years	Depression, insomnia, headache and rash Doses higher than 25 mg prolong the QT interval	It cannot be administrated with proton pump inhibitors Antacids to be administered two hours after RPV Metabolised by cytochrome P450 enzyme CYP3A4

Active ingredients	Dosage	Side effects and contra-indication	Information regarding the active ingredient
Ritonavir (RTV)	100 mg tablets, 80 mg/mL oral solution and 100 mg oral power available Adult: 600 mg twice a day. Dosage titration required starting with at least 300 mg twice a day and increasing dose at 2- to 3-day intervals with 100 mg twice a day Paediatrics: patients older than 1 month to receive 350 mg to 450 mg per m^2 twice daily per mouth and should not exceed 600 mg twice a day.	Diarrhoea, nausea and vomiting Elevated triglyceride and LDL-cholesterol that leads to dyslipidaemia PR interval prolongation Hepatotoxicity Orthostatic hypotension, vasodilation, pancreatitis, dyspepsia, oral ulceration, dry mouth, hyperaesthesia, hypersensitivity reactions Hyperglycaemia	Only recommended with PIs Added to LPV/r in children who also take RIF Cross-resistance with other PIs Contra-indicated in porphyria and hypersensitivity May lead to anaphylaxis Adult dose: often used as a booster Paediatric dose: the bitter taste of the oral solution can be improved with milk or by coating the mouth with peanut butter
Ritonavir (RTV)	Titration for paediatric patients is required starting with 250 mg per m^2 and increasing at 2- or 3-day intervals with 50 mg per m^2.		

Active ingredients	Dosage	Side effects and contra-indication	Information regarding the active ingredient
Stavudine (D4T)	Adult: Patients weighing up to 60 kg, 30 mg every 12 hours. Patients weighing 60 kg and above, 40 mg every 12 hours Paediatric: no longer recommended for use in children because of the high rate of side effects	May lead to lipoatrophy of the face and limbs, hyperlactatemia and hepatic steatosis Jaundice, dark-coloured urine, right-abdominal pain, swelling of the stomach, loss of appetite, nausea, vomiting, fever Peripheral neuropathy, pancreatitis, hypertriglyceridemia, headache, GI intolerance Neutropenia, thrombocytopenia and myalgia	Due to lactic acidosis, peripheral neuropathy and pancreatitis should only be used in patients who cannot tolerate other ARVs May not be used with AZT It cannot be used in patients with porphyria, a history of pancreatitis or peripheral neuropathy, hepatic disease or renal impairment Should be avoided with another medication that could cause pancreatitis or peripheral neuropathy (e.g., metronidazole, isoniazid and vincristine)
Tenofovir (TDF)	Adult: 300 mg once daily Paediatric: no suitable preparation for children	Nausea, diarrhoea and vomiting Nephrotoxicity that may lead to renal impairment, proteinuria and Fanconi's syndrome Reduction in bone mineral density Hypersensitivity reactions, hyperlactatemia and hepatic steatosis	Renal function should be monitored closely and cannot be taken with other nephrotoxic medications Recurrent acute hepatitis B may occur on discontinuation and must be monitored for at least one year after treatment discontinuation

Active ingredients	Dosage	Side effects and contra-indication	Information regarding the active ingredient
Zidovudine (AZT)	Adult: 300 mg twice a day, can be reduced to 200 mg if needed for haematological toxicity Pregnancy and birth: as PMTCT, 300 mg 12-hourly from week 14 of pregnancy; 300 mg 3-hourly from the onset of labour to delivery Neonates: within 12 hours of birth, 2 mg/kg 6-hourly or 4 mg/kg 12-hourly Paediatric: 1 month to 12 years, 180 mg/kg 12-hourly to a maximum of 600 mg/day	Nausea, vomiting, headache and myalgia Anaemia and neutropenia Hyperlactatemia Hepatic steatosis Lipoatrophy	Used in combination with other ARVs Avoid D4T use while on AZT

Adverse effects were higher in FDC with three therapeutic classes and dual PI therapeutic regimens than in single PI therapeutic regimens (Fellay *et al.*, 2001:1325). Lipodystrophy was found to be associated with the use of D4T. Mood disorders were prevalent with 3TC and thrombocytopenia was a side effect associated with SQV (Fellay *et al.*, 2001:1325). Hyperlactatemia was an adverse effect associated with D4T and DDI, IDV caused unconjugated bilirubin anaemia and ZDV caused anaemia (Fellay *et al.*, 2001:1325). Increased creatine phosphokinase was prevalent among users of D4T and ABC (Fellay *et al.*, 2001:1325.

2.6.3.2 Regimens

Tables 2-15 and 2-16 provide the DOH's STGs based on the WHO guidelines (DOH, 2018:11.11- 11.21). Bangsberg (2004:696-697) highlighted that regimen choices are dependent on cost, clinical efficiency, tolerability and possible medication resistance present in regimens.

ART's primary goals are to achieve and maintain virological suppression, reduce opportunistic infections, minimise treatment resistance and decrease morbidity and mortality (DOH, 2019:2). Combination ART containing three active ingredients is needed to provide sufficient viral suppression, improved prognosis and clinical outcomes (Cihlar & Fordyce, 2016:50). Tolerance and product safety are important considerations when choosing a regimen as patients will be exposed to the medication for an extended period. In cases where patients cannot use ABC, TDF or TAF, regimes with two medications are recommended (Günthard *et al.*, 2016:193).

2.6.3.2.1 First-line treatment regimens

Table 2-15 lists the first-line treatment regimens according to the ART clinical guidelines for managing HIV in adults, pregnancy, adolescents, children, infants and neonates for 2019 issued by the South African DOH (DOH, 2019:10-14).

Table 2-15: First-line ARV treatment regimens for 2019*

Gender and age group	Regimen	Qualifying guidelines
Adults and adolescents weighing more than 35 kg or older than 10 years of age	If the regimen is TDF + 3TC or FTC + EFV or NVP, switch to TDF + 3TC or FTC + DTG.	Women of childbearing potential who are pregnant in the first trimester or who wish to become pregnant and do not qualify for contraception may not use DTG.
Adult women and adolescent girls older than 10 years and weighing more than 35 kg	TDF + 3TC + DTG	Women with no childbearing potential, who are not pregnant, using contraceptives or in the second/third trimester of pregnancy
Adult men and boys older than 10 years and weighing more than 35 kg	TDF + 3TC + DTG	All boys with no active-ingredient-specific contra-indications
Neonate, infants and children aged 0 to less than 10 years	AZT + 3TC + NVP ABC + 3TC + LPV/r ABC + 3TC + DTG TDF + 3TC + DTG	Neonates between 2.5 and 3 kg from 0 weeks to less than 4 weeks of age Infants and children between 3 and 20 kg older than 4 weeks and older than 42 weeks of gestational age Children between 20 and 35 kg or younger than 10 years of age Adolescents weighing more than 35 kg and older than 10 years of age

In cases where treatment is interrupted, patients may continue with the regimen they were on at the time of interruption if the side-effects are not the reason for the interruption and the viral load is sufficiently suppressed. If the treatment is stopped due to side-effects or being ill, a new regimen is to be considered (DOH, 2019:11). The options for switching between first-line regimens are listed in Table 2-16 (DOH, 2019:13-14).

Table 2-16: Switching between first-line ARV regimens

Gender and age group	Regimen	Qualifying guidelines
Adults and adolescents weighing more than 35 kg or older than 10 years of age	If the regimen is TDF + 3TC or FTC + EFV or NVP, switch to TDF + 3TC or FTC + DTG.	Women of childbearing potential who are pregnant in the first trimester or who wish to become pregnant and do not qualify for contraception may not use DTG.

Gender and age group	Regimen	Qualifying guidelines
Adults and adolescents weighing more than 35 kg or older than 10 years of age	If the regimen is AZT or ABC + 3TC + EFV or NVP, switch to AZT or ABC + 3TC + DTG.	If the use of TDF is not contra-indicated due to nephrotoxicity. DTG is not suggested for women of childbearing potential who are pregnant in the first trimester or who wish to become pregnant.
Children and adolescents weighing less than 20 kg	If the regimen is ABC + 3TC + LPV/r, switch to ABC + 3TC + DTG. If the regimen is ABC + 3TC + LPV/r, switch to TDF + 3TC + DTG.	If the viral load is ≥ 50 cells/µl or ≥ 1 000 cell/µl. Women with no childbearing potential, who are not pregnant, using contraceptives or in the second/third trimester of pregnancy. If the caregiver or adolescent chooses to switch to DTG. If the weight of the patient is more than 20 kg and less than 35 kg. If the renal function of the patient is abnormal. Same guidelines as in number 1, but the renal function is normal. Before switching to TDF, check eGFR/creatinine to ensure adequate renal function.
Children and adolescents weighing less than 20 kg	If the regimen is ABC + 3TC + EFV, switch to ABC + 3TC + DTG. If the regimen is ABC + 3TC + EFV, switch to TDF + 3TC + DTG.	Suppose viral load is ≥ 50 cells/µl or ≥ 1 000 cell/µl. Women with no childbearing potential, who are not pregnant, using contraceptives or in the second/third trimester of pregnancy. If the caregiver or adolescent chooses to switch to DTG. If the weight of the patient is more than 20 kg and less than 35 kg. If the renal function of the patient is abnormal. Same guidelines as in number 1, but the renal function is normal. Before switching to TDF, check eGFR/creatinine to ensure adequate renal function.

2.6.3.2.2 Second-line and third-line ART treatment regimens

Second-line treatment should be based on the exposure of the first-line treatment (MIC, 2016:18). The preferred PIs in second-line treatment, according to the DOH (2019:17-19) is listed in Table 2-17.

Table 2-17: Second-line and third-line ARV regimens for children and adolescents

Gender and age group	Regimen	Qualifying guidelines
Adults and adolescents weighing more than 35 kg or older than 10 years with confirmed virological failure	If the first-line regimen is TDF + 3TC or FTC + EFV or NVP, switch to AZT or TDF + 3TC or FTC + LPV/r or ATV/r.	Address any adherence failure. Refer to a third-line committee on regimen if results of resistance have been determined.
Adults and adolescents weighing more than 35 kg or older than 10 years with confirmed virological failure	If the first-line regimen is AZT or TDF + 3TC or FTC + LPV/r or DTG, switch to AZT or TDF + 3TC or FTC + LPV/r or ATV/r.	Test resistance to DTG on a case-by-case basis. HIV-positive patients are not eligible to use TDF. Address any adherence failure. Refer to a third-line committee on regimen if results of resistance have been determined.
Adolescents and children weighing less than 35 kg but more than 20 kg	If the first-line regimen is ABC or AZT or TDF + 3TC or FTC + EFV or NVP, switch to ABC or ATZ or TDF + 3TC or FTC +DTG.	Women of childbearing potential who are pregnant in the first trimester, who wish to become pregnant or who do not qualify for contraception may not use DTG.
Adolescents and children weighing less than 35 kg but more than 20 kg	If the first-line regimen is ABC or AZT + 3TC or FTC + LPV/r or ATV/r, switch to ABC or AZT + 3TC or FTC + DTG or refer to third-line committee.	PI-based regimens require resistance testing. If there is no PI resistance, in consultation with an expert, ensure that at least one NRTI is active. If PI resistance of genotype is unsuccessful, refer to a third-line committee.
Adolescents and children weighing less than 35 kg but more than 20 kg	If the first-line regimen is ABC or AZT + 3TC or FTC + DTG, refer to an expert or third-line committee.	Determine if one NRTI is active and consult with a specialist.
Adolescents and children weighing less than 20 kg	If the first-line regimen is ABC or AZT + 3TC or FTC + EFV or NVP, switch to ABC or AZT or TDF + 3TC or FTC + DTG.	Determine if one NRTI is active and consult with an expert or refer to a third-line committee for the regimen.

Gender and age group	Regimen	Qualifying guidelines
Adolescents and children weighing less than 20 kg	If the first-line regimen is ABC or AZT + 3TC + EFV or LVP/r, switch to ABC or AZT + 3TC + DTG.	PI-based regimens require resistance testing. If there is no PI resistance, in consultation with an expert, ensure that at least one NRTI is active. If PI resistance of genotype is unsuccessful, refer to a third-line committee on regimen.

2.6.3.3 Resistance

Adherence among HIV-infected people highly impacts their quality of life, immune function and life-expectancy (Kleeberger *et al.*, 2001:82). Non-adherence to ART leads to continuous viral replication (Bangsberg *et al.*, 2004:696). If a patient has low, ineffective ART concentration while viral replication occurs, the new strains are resistant against the specific ART present (Bangsberg *et al.*, 2004:696). Bangsberg *et al.* (2004:696-697) suggested that certain ARV-classes are more susceptible to resistance than others; for example, PI requires multiple viral mutations, which reduces enzyme ability, whereas NNRTIs are more fragile to viral mutation. Transmission of medication-resistant viruses increases resistance in individuals and the population (Kleeberger *et al.*, 2001:82).

Medication-resistance testing is recommended when first-line treatment has failed. The resistance test serves two purposes: to conclude treatment adherence and a suitable second-line regimen (Conradie *et al.*, 2012:163). Changing treatment regimens is not recommended if ART has been interrupted, but there is still sufficient viral suppression from the first-line treatment (Conradie *et al.*, 2012:163). The medication-resistance for ART-experienced persons should be considered when viral loads are more than 1 000 copies/µl, for patients with suboptimal viral load reduction and patients who experience virologic failure when receiving a DTG-based regimen (AIDSinfo, 2019:C-13). Medication-resistance testing is required for patients taking ART who are experiencing virologic failure and in cases when a new regimen is constructed for a patient, i.e., for second-line treatment or third-line treatment (AIDSinfo, 2019:C-13).

Resistance to first-line regimens used for HIV/AIDS treatment is a major concern globally, as the use of second- and third-line medicine is expensive and difficult to sustain (Mayosi *et al.*, 2012:2030). Among the integrase strand transfer inhibitors, RAL-containing regimens have the most extended clinical experience and have durable virologic efficacy (AIDSinfo, 2019:F-7). RAL has a lower genetic barrier to resistance than bictegravir (BIC) and

DTG. According to AIDSinfo (2019:F-7), the transmission of resistance with treatments based on BIC and DTG is therefore rare.

2.6.3.4 Adverse medication reactions and side-effects

The MIC (2016:43-48) and DOH (2015a:43-48) indicated that the most common side effects of ARV medication are lactic acidosis or hyperlactatemia, haematological toxicity, hepatotoxicity, lipodystrophy, dyslipidaemia, peripheral neuropathy, renal failure, gynecomastia and lipomastia, neuropsychiatric toxicity and medication hypersensitivity reactions.

Lactic acidosis or severe hyperlactatemia is common in patients who use NRTIs and are asymptomatic (DOH, 2015: 79-80). Lactic acidosis becomes severe as soon as the mitochondrial DNA polymerase enzyme inhibition occurs, resulting in increased serum lactate concentration and increased steatohepatitis. D4T, DDI, AZT, 3TC, ABC and TDF are medications that cause lactic acidosis, usually around six months after treatment initiation (DOH, 2015: 79-80). Non-specific lactic acidosis symptoms may include lethargy, weight-loss, nausea, vomiting, pain and discomfort in the abdomen, and tachycardia. Kussmaul breathing, hypotension, and decreased consciousness levels indicate severe lactic acidosis (MIC, 2016:44-51). Management of lactic acidosis includes discontinuation of NRTIs or changing the regimen to low-risk NRTIs (ABC or 3TC). Alternatively, NNRTIs can be given with PIs as a booster; however, regular monitoring is required to ensure the correct treatment to reduce the risk of developing lactic acidosis (Meintjes *et al.*, 2017:18; MIC, 2016:44-51).

Peripheral neuropathy is common among patients with HIV/AIDS using D4T and DDI (MIC, 2016:44-51). Peripheral neuropathy is the loss of sensation, with paraesthesia presenting late in the disease (MIC, 2016:44-51).

TDF can be co-administered with a PI, but it may cause renal failure (DOH, 2015:81-83). TDF is eliminated by glomerular filtration and excretion via the renal tubule in patients that use PIs (LPV/r), and PIs increase TDF concentrations (DOH, 2015: 81-83; Foy *et al.*, 2015: 214-215). Patients receiving TDF may present with Fanconi's syndrome and acute renal failure, and TDF should not be prescribed to patients with a glomerular filtration rate (GFR) lower than 50 ml/min (AIDSinfo, 2019:F-14; Meintjes *et al.*, 2017:18; MIC, 2016:44-51).

AZT causes haematological toxicity such as anaemia and neutropenia, especially when co-administered with cotrimoxazole because AZT and cotrimoxazole cause bone marrow suppression (AIDSinfo, 2019:F-14; MIC, 2016:44). Because anaemia only becomes prevalent in the late stages of HIV/AIDS, haemoglobin testing is required before initiating treatment with AZT, and haemoglobin and neutrophil monitoring are required (Meintjes *et al.*, 2017:17). If the

haemoglobin count is below 6.5 g/dl or neutrophils are below 0.5 g/dl, an alternative NRTI such as ABC should be used (DOH, 2015a:79-81). Cytopenias may occur in patients with HIV/AIDS without ART, and macrocytosis is common in patients using D4T and AZT (Meintjes *et al.*, 2017:17).

All ART classes may lead to hepatotoxicity, but NNRTIs are the most likely cause (Meintjes *et al.*, 2017:17). Hepatotoxicity is a concern in patients on tuberculostatics and azoles (Meintjes *et al.*, 2017:18). In females with a CD4 cell count of more than 250 cell/µl, NVP causes hepatotoxicity. NVP may cause medication-induced liver injury within three months of initiation, and, therefore, it requires monitoring of alanine aminotransferase (ALT) (Meintjes *et al.*, 2017:18). NRTIs, especially D4T and DDI, cause steatohepatitis after long-term use. In cases where patients have underlying hepatitis B or hepatitis C, ART initiation causes hepatitis symptoms to worsen due to IRIS. Because 3TC and TDF act against hepatitis B, stopping this treatment also results in worsening hepatitis. ATV leads to isolated unconjugated hyperbilirubinaemia, a benign condition, but patients may opt to change to alternative options because of the cosmetic change it causes (AIDSinfo, 2019:F-14; Meintjes *et al.*, 2017:18). ALT, gamma-glutamyl trans-peptidase (GGT) or alkaline phosphatase (AP) and conjugated bilirubin tests should be done to monitor the patient, and hepatotoxic medications should be stopped in the case of hepatotoxicity (Meintjes *et al.*, 2017:18; MIC, 2016:44-51; DOH, 2015a:81-83).

Lipodystrophy takes place when patients use ART over a long period. Due to the physical changes it causes (visceral obesity, 'buffalo hump', lipomata or lipoatrophy), patients' compliance with ART reduces (MIC, 2016:44-48). Lipoatrophy in the limb and facial fat are side effects associated with NRTIs such as D4T and DDI. These effects improve when D4T, DDI and AZT are substituted with TDF and ABC (AIDSinfo, 2019:F-14; Meintjes *et al.*, 2017:20). The treatment of HIV/AIDS with ART is generally associated with gaining weight, but it can be managed with a healthy lifestyle and diet (Meintjes *et al.*, 2017:20). Visceral fat accumulation increases insulin resistance and dyslipidaemia. Management includes reducing cardiovascular risk factors, and metformin is prescribed for patients with metabolic syndrome or isolated dysglycaemia as it reduces insulin resistance (Meintjes *et al.*, 2017:20). Older PIs and EFV, AZT and D4T may lead to diabetes due to the risk of dysglycaemia and should be monitored when prescribed to patients at risk (Meintjes *et al.*, 2017:20-21).

Dyslipidaemia is a side effect of ART, such as LPV/r and RTV (refer to Table 2-14). LDL cholesterol and triglyceride levels increase in patients using PIs, especially RTV (Meintjes *et al.*, 2017:19). The increased serum concentration of low-density lipoprotein cholesterol is associated with EFV (MIC, 2016:45-46). ATV and DRV are the only PIs associated with less severe dyslipidaemia in patients (Meintjes *et al.,* 2017:19*)*. Diet and lifestyle

modifications are advised for patients with a confirmed diagnosis of dyslipidaemia, especially in patients with other cardiovascular risks (Meintjes *et al.,* 2017:19*)*. PIs, such as RTV and indinavir, should be switched for ART options with little or no effect on cholesterol and triglyceride levels (MIC, 2016: 46-48). Many statins, except for pravastatin and fluvastatin, have interactions with PIs that lead to statin toxicity (Meintjes *et al.,* 2017:19). Patients that suffer from HIV lipodystrophy or metabolic syndrome with glucose intolerance must be monitored because NRTIs and metformin may cause lactic acidosis (DOH, 2015a:79-81).

Neuropsychiatric toxicity is associated with the use of RAL and AZT. It presents as headaches that later resolve. Side effects of EFV include dizziness, vivid dreams, insomnia, and both dysphoria and euphoria may occur. In severe cases where patients cannot tolerate these side effects, EFV may be switched to NVP, RPV or RAL (SANAC, 2013:113-119).

Patients with HIV/AIDS experience bone density reduction associated with the use of TDF, which may lead to fractures (e.g., hip, rib, vertebral, wrist) (MIC, 2016:46-47).

Gynaecomastia and lipomastia have been reported in both male and female adolescents using EFV (DOH, 2015: 79-81), reducing adherence to EFV. Some patients who are severely influenced may require surgical intervention (MIC, 2016:44-48).

2.6.3.5 Drug-drug interactions between antiretroviral and other medication

Due to ARV treatments' life-long use, PLWHA tends to develop other comorbid conditions (Foy *et al.,* 2015:212). For example, common drug-drug interactions occur in patients using PIs or NNRTIs as they alter the p-glycoprotein medication transporter and/or the cytochrome P-450 enzyme systems (Foy *et al.,* 2015:212). Detailed interactions are presented in Table 2-13 and discussed in the overview below.

Immunosuppression treatment is given to patients who receive kidney transplants. Monoclonal antibodies (basiliximab/daclizumab) are considered safe, whereas polyclonal antibodies should be avoided (MIC, 2016:41-53). In kidney transplants patients, first-line immunosuppressing treatment should be cyclosporine and prednisone (MIC, 2016:41-53). There are multiple ARV-immunosuppressant medication interactions (refer to Table 2-13), such as (MIC, 2016:44-53):

- EFV, which reduces the efficacy of cyclosporine, sirolimus and tacrolimus
- RTV, which increases the efficacy and plasma concentration of cyclosporine, tacrolimus and sirolimus
- D4T and AZT, which have shared toxicities with immunosuppressants and should be avoided

Medication-induced liver injury is present in 5–33% of patients with HIV/AIDS being treated for complicated TB with isoniazid (INH), RIF and pyrazinamide (PZA) (Meintjes *et al.*, 2017:13). EFV is the preferred NNRTI when patients are receiving rifampicin. NVP is an alternative but increases the risk of hepatitis (Meintjes *et al.*, 2017:13). Rifampicin reduces the efficacy of PI-boosted ART, so dose adjustments are required. However, high levels of LPV/r increase the risk of hepatotoxicity (Meintjes *et al.*, 2017:13). Tuberculostatics and ARV medications share many side-effects, including (Meintjes *et al.*, 2017:13):

- AZT, DDI, PIs, PZA and ethionamide cause nausea.
- NVP, EFV, PIs, RIF, rifabutin, INH, PZA and bedaquiline may cause hepatitis.
- D4T, DDI, INH, ethionamide, linezolid and terizidone/cycloserine may lead to peripheral neuropathy.
- TDF, aminoglycosides and RIF increase the risk of developing renal impairment.
- NVP, EFV, RAL, RIF, INH, PZA, streptomycin, ethambutol and quinolones lead to a rash.
- EFV, DTG, terizidone/cycloserine, INH and quinolones may lead to neuropsychiatric complications.
- AZT, rifabutin and linezolid may increase myelosuppression.

Hepatotoxicity may result from the direct toxicity, a metabolite of the medication or an immunologically mediated response that affects the hepatocytes, biliary epithelial cells and/or liver vasculature (MIC, 2016:44-53). Risk factors include alcohol use, hepatitis B surface antigen, malnutrition, hepatitis C co-infection and an increase in baseline ALT (MIC, 2016:44-53). Treatment of hepatitis C infection led to potential drug-drug interaction in PLWHA, including DRV/r, LPV/r, RPV, EFV, NVP, ETR, TDF and NS3/4A protease inhibitors such as telaprevir, boceprevir and simeprevir (Foy *et al.*,2015:220-222).

Many statins have interactions with PIs due to the inhibition of the CYP3A4 iso-enzyme that increases statin levels. Atorvastatin and rosuvastatin are significantly increased by PIs but may be reduced in lower doses, whereas simvastatin and lovastatin should not be used with PIs at all. ART absorption is reduced with bile acid sequestrates such as cholestyramine and, therefore, contra-indicated (DOH, 2015:79-81; Foy *et al.*, 2015:220-222; MIC, 2016:44-46).

Most of the drug-drug interactions between ARV medication and non-ARV medication are due to ARV medications' metabolism with cytochrome P450 in the liver and intestines (Meintjes *et al.*, 2017:12). Induction or inhibition due to enzyme systems and medication transportation are listed in Table 2-13.

In May 2019, a significant change in the STGs for ART in South Africa, including the use of DTG, was released (DOH, 2019:9). Medications such as rifampicin, polyvalent cations (antacids, sucralfate, multivitamins and nutritional supplements) and anticonvulsants (carbamazepine, phenobarbitone, phenytoin, and valproate) reduce DTG concentration, and co-administration with metformin increases metformin levels (DOH, 2019:8-9).

2.7 Finding a cure

Regardless of the advantages of chronic HIV/AIDS management, the high toxicity of antiretroviral medications may affect patients' quality of life (Sonenklar, 2011:118-119). In 2019, high ARV medication resistance levels to first-line treatment regimens were found in infants born from mothers living with HIV/AIDS. It has emphasised the need for newer first-line medication regimens, increased surveillance of ARV medication resistance, and improved patient prognosis (WHO, 2020b).

Because of the need to find improved treatment methods for all PLWHA, research is being conducted to provide alternatives such as strengthening the immune system, gene therapy and vaccines (Sonenklar, 2011:116; WHO, 2020c). In Thailand, studies to prove the efficacy of the ALVAC-HIV and AIDSVAX B/E vaccine regimen have shown limited success and became a stepping stone for further research on producing AIDS vaccines (Rerks-Ngarm *et al.*, 2009:2209- 2220). Regardless of many attempts to develop vaccines, no vaccine so far has proven effective (WHO, 2020c). Continuous investments are being made around the globe in an attempt to develop an HIV vaccine (WHO, 2020c),

Besides vaccines, more focus has been placed on gene therapy to cure HIV/AIDS (Benjamin *et al.*, 2016:1059-1070; Cornu *et al.*, 2015:117-130; Peterson & Kiem, 2019:685-687). Gene therapy research search for methods to manipulate T-cell function to interfere with the production of HIV and modify stem cells in PLWHA to improve their immune system (Benjamin *et al.*, 2016:1059-1070; Cornu *et al.*, 2015:117-130; Peterson & Kiem, 2019:685-687; Sonenklar, 2011:118).

2.8 Chapter summary

This chapter discussed the burden of HIV/AIDS from a clinical, social and economic perspective. The factors that impacted the burden of HIV/AIDS and treatment patterns of PLWHA in SA and, more specifically, the private health sector.

CHAPTER 3: RESULTS AND DISCUSSION

3.1 Introduction

- This chapter contains two manuscripts that present the study's empirical review in the form of academic journal articles.

- The empirical objectives addressed in this chapter are:

1. To establish a demographic profile of HIV/AIDS patients stratified by patients' age, gender, geographical location, type of prescriber, and ARV medication provider.

2. To investigate the medicine claims profile of HIV/AIDS patients by investigating the general medicine prescribing patterns of HIV/AIDS patients.

3. To determine the clinical profile of HIV/AIDS patients by identifying their co-existing CDL conditions (refer to paragraph 1.5.2.1) and ART patterns.

The first two objectives are met by Manuscript 1, and the third objective is discussed in Manuscript 2.

Each manuscript was written according to the author guidelines of the journal. Manuscript 1 was prepared for the *Southern African Journal of HIV Medicine*, and the author guidelines are attached in ANNEXURE B. Manuscript 2 was prepared for the *Journal of Clinical Pharmacy and Therapeutics*, and the author guidelines and referencing guidelines are attached in ANNEXURE C.

The *Southern African Journal of HIV Medicine* prefers the term "patients with HIV infection" (PWHI) over "people living with HIV/AIDS" (PLWHA). Therefore, Manuscript 1 refers to PWHI, while Manuscript 2 and the rest of the dissertation refer to PLWHA. The two terms are used synonymously in this study.

3.2 Manuscript One

MEDICINE CLAIMS PROFILE OF PATIENTS INFECTED WITH HIV IN THE PRIVATE HEALTHCARE ENVIRONMENT OF SOUTH AFRICA

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Word count

Article (without references): 3813

Abstract: 245 words

Abstract

Background: Although patients with HIV infection (PWHI) may negatively impact the risk profile of medical schemes in South Africa, limited information is available regarding their demographic profile and medication prescribing patterns.

Objective: To portray the demographic and medication prescribing profile of PWHI.

Methods: A cross-sectional research design was followed to analyse retrospective medicine claims data of 858 590 patients, obtained from a pharmaceutical benefit management (PBM) company from 1 January 2016 to 31 December 2016. PWHI were identified using the International Classification of Diseases, 10th Revision (ICD-10) diagnosis codes for HIV (B20, B21, B22, B23 and B24), which is associated with the medicine claim and indorsed by the pre-authorization process

Results: A total of 16 763 (19.5 per 1 000) PWHI were identified, with the highest prevalence rate (78 per 1000) in the age group ≥ 45 and < 65 years. Women were younger [40.21 years (SD 10.9; 95% CI 39.9–40.4)] than men [44.3 years (SD 11.9; 95% CI 44.0–44.5)] (p < .0001; Cohen's d = 0.3). Most PWHI resided in the North West province (36.8 per 1000 medical scheme beneficiaries). PWHI received 175 317 individual regimens with 190 903 antiretroviral (ARV) items. Of these items, 127 248 (66.4%) were fixed-dose combination products (FDC), 145 804 (76.1%) were generic products, and most (90.4%; n = 173 131) were reimbursed through HIV-benefits.

Conclusion: Prescribing generic and FDC products through pharmacies and reimbursing these products from the patient's HIV-benefit category are standard practices to decrease the possible risk-profile of an increased number of PWHI in the medical scheme environment.

Keywords: HIV, AIDS, private healthcare, fixed-dose combination, ARV, benefit category, demographic profile, prescribing patterns, South Africa, medical schemes, claims data.

Introduction

The human immunodeficiency virus (HIV) is a significant health concern in South Africa (SA), with a total of 7.97 million people (13.5% of the population) being infected in 2019.[1] HIV infection was the cause of 5% of annual deaths in the country from 2014 to 2016, despite the decrease in newly infected cases from 1.9% (2002) to 0.9% (2017).[2,3] HIV infection, thus, has a devastating effect on health services and has the potential to overburden the healthcare system of SA.[4]

The SA healthcare system consists of a public health sector, which serves the majority of the population, and a private health sector.[5,6] However, health expenditure in the private health sector, mostly through medical schemes, is six times more than that in the public health sector.[6,7] To contain medical expenditure in the private health sector, the SA Government has enacted, *inter alia*, a set amount of benefits, or so-called prescribed minimum benefits (PMBs) as stipulated in SA's Medical Schemes Act (131 of 1998).[8] The PMBs originally comprised a list of 270 medical conditions that included 25 chronic conditions, designated as the chronic disease list (CDL).[8] Later amendments to the Medical Schemes Act (131 of 1998) included HIV-infection as a CDL among the PMBs.[9]

From 2011 to 2016 HIV-infection was the most rapidly increasing PMB condition, with an annual growth of 18%.[10] In 2018, HIV-infection formed part of the top five CDL conditions, whilst its treatment accounted for 4.1% of the PMB medicine expenditure in SA.[11] The direct costs of HIV-infection are mostly driven by specialist and doctor consultations, hospitalisation, laboratory tests and antiretroviral therapy.[12-14] Apart from hospitalisation, medicines dispensed accounted for the second-highest expenditure of total benefits paid by medical schemes in 2018.[10] It resulted in a negative impact on the risk profile of medical schemes in SA[10] and led to an increased financial burden for the private health sector.[10]

A factor contributing to medical schemes' increased medicine expenditure is the use of original products (in some cases, new chemical entities have no generic products) with high average costs compared to generic equivalents or alternatives.[15] Generic substitution, which is becoming more acceptable for stakeholders, provides cost-saving solutions to healthcare systems without impeding healthcare provision.[11] General practitioners who dispensed have a higher tendency to dispense generic products compared to pharmacists from courier pharmacies, retail pharmacies and other providers.[11]

Healthcare providers in the private health sector of SA do not have to follow specific guidelines when treating PWHI;[16,17] however, they are encouraged to adhere to the World Health Organization and the Standard Treatment Guidelines (STG) of SA's Department of Health (DOH).[16-18] There is a shortage of studies that delineate the profile of PWHI in the private health sector in SA from a demographic and medication perspective.[19-21] This study aimed to enlighten the demographic and medicine claims profile of PWHI in the SA private health sector.

Methods

Study design

A cross-sectional research design was followed using retrospective medicine claims data obtained from the database of a SA pharmaceutical benefit management (PBM) company. The study period covered one year from 1 January 2016 to 31 December 2016.

Study population

The study population included all patients on the database with an International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) diagnosis code for HIV infection (ICD-10 codes B20–B24), [22,23] who were on the database between 1 January 2016 to 31 December 2016.

Data source

Medicine claims data were obtained from the database of an independent privately-owned pharmaceutical benefit management (PBM) company in SA. The PBM company uses a real-time electronic management system to administer and manage various medicine benefit categories and capitation plans on behalf of medical schemes in SA. The different medical schemes develop specific medicine claims processing rules and authorisations, determining the medicine benefit allocation by the PBM company. The PBM company applies several automated validation processes to ensure the quality and integrity of claims data and compliance with medicine claims processing rules.

The following data fields were extracted from the database: date of birth and gender of the patient, postal code of prescriber, type of prescriber, type of ARV medication provider, the trade name of drugs, National Approved Product Pricing Index (NAPPI-code)[24] of drugs, dispensing date of

prescription, ICD-10 codes and the benefit category used for reimbursement of ART (ARV treatment). Duplicate claims and incomplete data were excluded from the data analysis.

Study variables

The demographic and medicine claims profile variables are listed in Table 1.

Table 1 Study variables of the demographic profile and medicine claims profile of HIV-infected patients in SA

Demographic profile	Medicine claims profile
Gender: men or women **Age groups:** patients' ages were calculated for the year 2016 (i.e. the age that the patient was at the time the medication claim was submitted to the PBM company): Group 1: if age > 0 and < 2 years Group 2: if age ≥ 2 and < 12 years Group 3: if age ≥ 12 and < 18 years Group 4: if age ≥ 18 and < 25 years Groups 5: if age ≥ 25 and < 45 years Group 6: if age ≥ 45 and < 65 years Group 7: if age ≥ 65 years **Geographical location:** the antiretroviral (ARV) prescriber's postal code was used as a proxy for the patients' geographical location. Data were analysed on a provincial level. The nine SA provinces are Eastern Cape, Free State, Gauteng, KwaZulu-Natal, Limpopo, Mpumalanga, Northern Cape, North West and Western Cape.	**Benefit category:** The various benefit categories are acute, oncology, chronic, HIV and PMB. The PBM company distinguished between the benefit categories that covered the ARV medicine as HIV benefits, PMB benefits, chronic benefits and other benefits. **Active ingredients of medication:** NAPPI codes, ICD-10 codes, and the Monthly Index of Medical Specialities (MIMS®) classification system was used to identify the top 10 active ingredients of the ARV medication that was claimed. **Medicine ARV provider:** medicine ARV providers were classified as a community pharmacy or a general practitioner or specialist practice (dispensing practice). **Prescriber type:** prescribers were categorised as general medical practitioners, paediatricians and other specialists). They were also categorised as dispensing or non-dispensing general practitioner or specialist, depending if they have dispensed the ARV prescriptions. **Generic status:** in cases where generic products were available, the generic state was used to determine if the generic alternative or the original product was dispensed. It was reported if no generic substitute was available. **Medicine product type:** distinguishes between the single-active ingredient and

Demographic profile	Medicine claims profile
	fixed-dose combination product (FDC) types dispensed to patients. **ARV item:** an ARV item claimed is a product containing one or more single active ingredient(s) used specifically to treat PWHI. **ARV regimens:** ARV regimens were defined by a single or combination of ARV items (active ingredient(s)) claimed on one or more prescriptions on the same day.

Statistical analysis

The Statistical Analysis System, Version 9.4® (SAS Institute, 2002–2012) was used for data management and analysis.[25]

Variables were expressed using descriptive statistics, which include frequencies (*n*) presented as percentages (%), arithmetic means, standard deviations (SD) and 95% confidence intervals (CI). Statistical significance was determined using a probability value (*p*) denoted as $p \leq 0.05$.

The chi-square (χ^2) test was used to establish whether an association existed between proportions of two or more groups. The Cramér's *V* statistic was used to test the practical significance of these associations, with Cramér's $V \geq 0.5$ defined as practically significant.[26]

The two-sample independent *t*-test was used to compare the size of the difference between the means of the two groups. Cohen's *d*-value was considered for practical significance; the magnitude of the *d*-values was interpreted as follows: ≤ 0.2 is a small effect with no significant difference, > 0.2 and ≤ 0.8 is a medium effect with an observable significance, and > 0.8 is a large effect with a significant difference.[27]

Ethical considerations

Ethics approval was obtained from the North-West University Health Research Ethics Committee (NWU-00179-14-A1-07). The PBM company granted goodwill permission to use the data.

Results

Demographic profile

The demographic profile of PWHI (n = 16 763) against the profile of all patients on the database (N = 858 590) reveals that approximately 53% of patients on the database (n = 454 966) and 52%

of PWHI (n = 8 871) were women (Table 2). A total of 16 763 (19.5 per 1 000) PWHI claimed one or more ARV prescriptions during the study period. No difference was found between the number of patients infected with HIV per 1 000 beneficiaries, at 19.8 per 1 000 for men and 19.5 per 1 000 for women.

The average age of PWHI was 42.13 years (SD 11.5; 95% CI: 42.0.95–42.3). Women infected with HIV [40.2 years (SD 10.9; 95% CI 39.9–40.4)] were statistically significantly younger ($p < 0.001$; Cohen's $d = 0.3$) than the men [44.27 years (SD 11.9; 95% CI 44.0–44.5)].

Of the 79 333 patients (92.4 per 1 000) younger than two years, only 0.5 per 1 000 beneficiaries were HIV-infected, and of those aged ≥ 18 and < 25 years (n = 255 671, 297.8 per 1 000 beneficiaries) only 1.3 per 1 000 beneficiaries were infected with HIV. Patients in the age group five (≥ 25 and < 45 years) accounted for a prevalence rate of 38.2 PWHI per 1 000 beneficiaries. The prevalence rate of PWHI was the highest in patients ≥45 and <65 years, at 78 per 1 000 beneficiaries

Table 2 Demographic profile of patients infected with HIV on the PBM database

	Number of patients infected with HIV		Total number of patients on the database	
	n (%)	Per 1 000 beneficiaries	n (%)	Per 1 000 beneficiaries
Patients				
Total number of patients (n)	16 763 (100)	19.5	858 590 (100)	1 000
Gender				
Men	7 992 (47.7)	19.8	403 624 (47.0)	470.1
Women	8 871 (52.3)	19.5	454 966 (53.0)	529.9
Age groups (years)				
≥ 0 and < 2	37 (0.1)	0.5	79 333 (9.2)	92.4
≥ 2 and < 12	284 (1.7)	3.9	73 364 (8.5)	85.4
≥ 12 and < 18	336 (2.0)	5.8	58 021 (6.8)	67.6
≥ 18 and < 25	330 (2.0)	1.3	255 671 (29.8)	297.8
≥ 25 and < 45	9 322 (55.6)	38.2	243 878 (28.4)	284.0
≥ 45 and < 65	6 146 (36.7)	78.0	78 797 (9.2)	91.8
≥ 65	308 (1.8)	4.4	69 526 (8.1)	81.0
Provinces				
Eastern Cape	924 (5.5)	21.6	42 716 (5.0)	49.8
Free State	1 388 (8.3)	29.7	46 695 (5.4)	54.4
Gauteng	5 209 (31.1)	17.7	294 284 (34.3)	342.8
KwaZulu-Natal	2 374 (14.2)	24.1	98 483 (11.5)	114.7
Limpopo	638 (3.8)	17.4	36 565 (4.3)	42.6
Mpumalanga	1 472 (8.8)	30.5	48 197 (5.4)	56.1
North West	1 407 (8.4)	36.8	38 262 (4.5)	44.6

Northern Cape	274 (1.6)	16.1	17 004 (2.0)	19.8
Western Cape	3 077 (18.4)	13.0	236 384 (27.5)	275.3

Source: own data compilation based on the medicine claims data for 1 January 2016 to 31 December 2016

Based on the prescriber's postal code as a proxy for the geographical area, most patients in the database were from Gauteng (n = 294 284, 342.8 per 1 000); however, only 17.7 per 1 000 beneficiaries from Gauteng were HIV-infected. The province with the highest prevalence rate of PWHI was the North West (36.8 per 1 000) (Table 2).

Medicine claims profile

The 16 763 PWHI received 175 317 regimens, and 191 541 ARV items were prescribed. An average of 10.9 (SD 7.6; 95% CI 10.8–11.0) ART regimens were claimed per PWHI during the study period, containing an average of 1.1 (SD 0.4; 95% CI 1.1–1.1) ARV items.

Table 3 Medicine claims profile of patients infected with HIV

	Number of ARV drugs	
	n	%
Medicine (ARV) provider		
Community pharmacy	190 903	99.7
General medical practice	633	0.3
Specialist family medicine	5	0.003
Type of prescriber		
Dispensing medical practitioner	638	0.3
Non-dispensing medical practitioner	190 903	99.7
Medicine product type		
Single-active ingredient	64 293	33.6
FDC	127 248	66.4
Generic status		

No generic option available	27 693	14.5
Original (other generic options available)	18 044	9.4
Generic option	145 804	76.1
Benefit category		
HIV	173 131	90.4
PMB	18 011	9.4
Other	371	0.2
Chronic	28	0.01

PMB: Prescribed minimum benefits

Source: own data compilation based on the medicine claims data for 1 January 2016 to 31 December 2016

Community pharmacies provided almost all ARV medication (n = 190 903; 99.7%) (Table 3). Most ARV items dispensed were FDC products (n = 127 248; 66.4%) compared to single-active ingredient products (n = 64 293; 33.6%). More generic ARV medicines (n = 145 804; 76.1%) were dispensed compared to original ARV medicines (n = 18 044; 9.4%). No generic option was available for 14.5% (n = 27 693) of the ARV medicine dispensed. The majority of ARV medication was covered under the HIV-benefit category (n = 173 131; 90.4%), followed by the PMB category (n = 18 011; 9.4%). The prescribers were mostly general medical practitioners (n = 152 308; 79.5%), paediatricians (n = 4 449; 2.3%) and other specialists (n = 34 784;18.2%). The prescribers were mostly non-dispensing medical practitioners or specialists (n = 190 903; 99.7%).

Table 4 **Association between the generic status of ARV items and medicine product type, benefit category, type of prescriber and type of provider**

	Generic status					
	Generic option	**No generic option available**	**Original**	**Total**	***p*-value**	**Cramér's *V***
	n (%)	**n (%)**	**n (%)**	**n (%)**		
Total number of ARV items	145 804 (76.1)	27 693 (14.5)	18 044 (9.4)	191 541 (100)		
Medicine product type						
Fixed-dose combination (FDC)	93 977 (73.9)	16 650 (13.1)	16 621 (13.0)	127 248 (100)	<0.0001	0.2
Single- active ingredient	51 827 (80.6)	11 043 (17.2)	1 423 (2.2)	64 293 (100)		
Benefit category						
HIV	132 879 (76.8)	24 946 (14.4)	15 306 (8.8)	173 131 (100)	< 0.0001	0.1
PMB	12 667 (70.3)	2 697 (15.0)	2 647 (14.7)	18 011 (100)		
Other	230 (62.1)	50 (13.4)	91 (24.5)	371 (100)		
Chronic	28 (100)	0	0	28 (100)		
Typy of prescriber (Dispensing vs non-dispensing prescriber)						
Dispensing medical practitioner	417 (65.9)	74 (11.7)	147 (22.4)	638 (100)	< 0.0001	0.03
Non-dispensing medical practitioner	145 387 (76.1)	27 619 (14.5)	17 897 (9.4)	190 903 (100)		

Source: own data compilation based on the medicine claims data for 1 January 2016 to 31 December 2016

	Generic status					
	Generic option	No generic option available	Original	Total	*p*-value	Cramér's *V*
	n (%)	n (%)	n (%)	n (%)		
Type of provider						
Community Pharmacy	145 387 (76.1)	27 619 (14.5)	17 897 (9.4)	190 903 (100)	< 0.0001	0.1
General medical practice	417 (65.9)	74 (11.7)	142 (22.4)	633 (100)		
Specialist family medicine	0	0	5 (100)	5 (100)		

The association between ARV items' generic status and other factors such as the medicine product type, benefit category, ARV medicine prescriber, and ARV medicine provider are presented in Table 4. For the majority of FDC products (n = 93 977; 73.9%) and single-active ingredient products (n = 51 827; 80.6%), the generic option was dispensed. No practically significant association ($p < 0.0001$; Cramér's $V = 0.2$) was found between the generic status and the medicine product type (single-dose vs fixed-dose combination). In the HIV benefit category, 76.8% (n = 132 879) of ARV items were generic products, 14.4% (n = 24 946) of ARV items did not have a generic substitute available and only 8.8% (n = 15 306) were original products. The majority of ARV items in the PMB (n = 12 667; 70.3%) and other benefit (n = 230; 62.1%) categories were generic products, and all of those in the chronic category (n = 28; 100%) were generic products.

No practically significant association was found between the generic substitution status and the ARV reimbursement benefit category ($p < 0.0001$; Cramér's $V = 0.2$) or between the generic substitution status and ARV medicine prescriber ($p < 0.001$; Cramér's $V = 0.03$). However, most ARV items provided by community pharmacist (n = 145 387; 76.1%) and dispensing practitioners (n = 417; 65.9%) were generic options, and most dispensed ARV items were generics (n=145 804; 76.1%).

Table 5 Prevalence of the top 10 ARV products prescribed according to active ingredients, n = 191 541

Top 10 ARV products according to active ingredients	Number of ARV drugs	
	n	%
Efavirenz/emtricitabine/tenofovir	71 251	37.2
Efavirenz	19 359	10.1
Lopinavir/ritonavir	16 577	8.7
Lamivudine/zidovudine	14 806	7.7
Emtricitabine/tenofovir	14 241	7.4
Ritonavir	7 235	3.8
Lamivudine	6 549	3.4
Nevirapine	5 382	2.8
Atazanavir	5 327	2.8
Abacavir/lamivudine	5 071	2.7

Source: own data compilation based on the medicine claims data for 1 January 2016 to 31 December 2016

Among all the ARV drugs claimed on the database, the FDC products containing efavirenz/emtricitabine/tenofovir were claimed the most (n = 71 251; 37.2%), followed by the single-active ingredient efavirenz-containing products (n = 19 359; 10.1%) and the FDC lopinavir/ritonavir-containing products (n = 16 577; 8.7%). The other single-active ingredient products claimed included ritonavir (n = 7 235; 3.8%) and lamivudine (n = 6 549; 3.4%) (Table 5).

Discussion

Compared to the number of PWHI in the South African private health sector in 2016 reported by the Council for Medical Schemes[28] (22.1 per 1 000 patients), the number of PWHI in this study

was slightly less. The medicine claims database used in this study represents only a section of the medical schemes environment in SA and should be considered in the interpretation of the results. We noted that although there was no significant difference in the total number of men and women with HIV-infection, the total number of men in the study population was slightly more than the women. Furthermore, women with HIV-infection were significantly younger than men with HIV-infection. International trends show that the probability of young women getting infected with HIV is 60% higher than in men of the same age group.[29] In SA, men are considered to be vulnerable to HIV-infection because of behavioural factors such as alcohol use as well as lower likelihood to use condoms and make use of the healthcare system to help test or treat HIV-infection.[30] In 2016, 37% of SA men older than 15 years of age were infected with HIV.[30] In 2017, one-fifth of South Africans in their reproductive ages (15 to 49 years) were HIV-infected.[21] Women younger than 25 years had a higher predisposition to get infected with HIV due to their tendency to have sexual relationships with older men.[31]

Both men and women in the age group 45 to 65 years were more likely to be HIV-infected due to the continuation of their sexual behaviour from when they were younger, contributing to a continuing cycle where older men spread the virus to younger women.[31] This cycle explains why HIV-prevalence peaks in age groups 45 to 65 years.[31] The private health sector in SA has shown similar trends as the results from these studies, with a low prevalence rate of HIV-infected patients between 1 and 19 years (an average of 8.6 per 1 000).[25] Globally, the prevalence of HIV in children from birth to 14 years of age has shown a 51% decline from 2010 to 2015.[31,32]

Our analysis showed that the highest prevalence of patients with HIV-infection on the database resided in the North West province, Mpumalanga and KwaZulu-Natal. Our findings were similar to studies done in 2012, which showed that provinces with the highest HIV-prevalence rate in the public health sector were KwaZulu-Natal (18%), Mpumalanga (15.2%), Gauteng (12.9%) and Free State (12.9%).[19,20] The variance in the number of PWHI within countries and geographical areas in countries can be related to social aspects such as poverty, unemployment, poor public health conditions, the lack of infrastructure and the lack of access to healthcare services.[33,34] In the public health sector of SA, the HIV-prevalence rate is higher in rural than in urban areas.[20] Around 53% of South Africans have full access to healthcare services, with higher access in urban areas than rural areas.[6] In the private health sector, however, most medical scheme beneficiaries residing in urban areas are educated and employed, contributing to discrepancies in geographic locations.[6,35]

Our analysis showed that an average of 10.9 ARV prescription fills per PWHI was claimed during the study period (2016), containing an average number of 1.1 ARV items. The medicine product type of choice mainly was FDC (n=127 248). Generally, an FDC treatment regimen has been associated with improved quality of life, increased adherence, cost-effectiveness and limited toxicity.[36,37] Apart from the regimen simplifications, other advantages of FDC include cost-saving for ARV, improved efficacy and increased adherence.[38] The preferred first-line FDC product recommended by the STG of the public health sector (in the year 2018) in SA contains 300 mg tenofovir, 200 mg emtricitabine and 600 mg efavirenz.[16] The top 10 ARV products dispensed during the study period were dispensed according to the STG of the DOH in SA,[16] as is evident in the top three ARV products that included the FDC efavirenz/emtricitabine/tenofovir and lopinavir/ritonavir and the single-active ingredient efavirenz-containing products.

Generic substitution is defined as dispensing a generic product when the original product's generic equivalent is available.[11] The generic substitution of ARV items in this study was high (n = 145 804), with only a few (n = 18 044) ARV items being original products. The remainder of ARV items had no generic option available. High generic uptake is associated with cost-saving benefits for the funder.[36] Non-dispensing general practitioners were responsible for prescribing most (n = 190 903; 99.7%) ARV items. Patients made use of community pharmacies as the leading providers of ARV items, and the generic uptake for these pharmacies was as high as 84%.

The ARV items claimed were predominantly categorised as an HIV benefit (n = 173 131; 90.4%), followed by the PMB category (n = 18 011, 9.4%). From the total healthcare benefits paid to beneficiaries in the SA private health sector in 2018, 15.6% were spent on medicines (and consumables) provided by pharmacies and other healthcare providers.[10] Of these healthcare benefits paid, 88.7% were paid to pharmacies, 5% to dispensing general practitioners and the remaining to clinics, nurses and other specialist services.[10] In this study, most ARV medication (n = 190 903, 99.7%) were prescribed by non-dispensing practitioners and dispensed by community pharmacists. The remaining 0.3% (n = 633) were prescribed and dispensed by dispensing doctors, which is similar to trends for the medical scheme environment.[10]

A significant limitation of this study was that the data were obtained from only one PBM company in SA. Therefore, it is impossible to generalise the results to the entire SA medical scheme population, the private health sector or the public healthcare sector.

Conclusion

This study showed that the PWHI on the database were mainly older adults residing in the North-West province. The highest prevalence rate of PWHI for both genders was in the age group 45 to 65 years. Almost all ARV items were generic FDC items provided by pharmacies and paid from the HIV-benefit category. These findings suggest that PWHI in older age groups will claim more ARV items, which increase medication costs for the medical scheme.

Therefore, it is suggested that medical schemes' policies should focus on managing the financial burden of a possible increased number of PWHI in the medical scheme environment in SA.[31].

Acknowledgements

The authors would like to extend their gratitude to Ms Helena Hoffman and Ms Elzet Blaauw for proofreading and editing this manuscript. We are appreciative to Ms Anne-Marie Bekker for assisting us with data management

Conflict of interests

None to declare.

Funding information

Financial support was received from the North-West University (21975310), the National Research Foundation (Grant no. 85315) and the Water Research Commission (Project No. K5-2594e)

Data availability statement

The authors acknowledge the PBM company's generous act for permitting the use of its database to perform this study.

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3.3 Manuscript Two

CLINICAL PROFILE OF PATIENTS INFECTED WITH HIV IN THE PRIVATE HEALTHCARE ENVIRONMENT OF SOUTH AFRICA

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Declarations of interest:

None to declare.

Funding source:

Financial support was received in the form of a bursary from the Faculty of Health Science, North-West University (Grant no. 21975310), the National Research Foundation (Grant no. 85315) and the Water Research Commission (Project no. K5-2594e).

Word count: 3949 (article)

Word count: 258

Keywords:

Clinical profile, patients with HIV infection, South African private health sector, chronic disease list (CDL) conditions, medicine claims data

ABSTRACT

This cross-sectional study aimed to determine the clinical profile of human immunodeficiency virus (HIV)-infected medical scheme beneficiaries in South Africa using retrospective medicine claims data (1 January 2016 to 31 December 2016). The clinical profile of patients with HIV infections (PWHI) included the prevalence of co-existing chronic disease list (CDL) conditions and antiretroviral treatment (ART) patterns. A total of 16 763 PWHI (n = 8 871, 52.3% female; n = 7 992, 47.7% male) were registered on the database. The majority of PWHI (n = 14 426, 86.1%) did not present with CDL condition. Amongst those diagnosed with one or more CDL conditions (n = 2 337, 13.9%), 79.1% (n = 1 848) had one other CDL condition, 17.4% (n = 407) had two and 3.5% (n = 82) had three. Hypertension (n = 1 287, 55.1%), hyperlipidaemia (n = 164, 7.0%) or a combination of the two (n = 205, 8.8%) were the most prevalent CDL conditions amongst PWHI ≥18 years. PWHI <18 years presented with asthma and epilepsy. ART regimens consisted of an average of 1.1 antiretroviral (ARV) items (SD 0.38, 95%; CI 1.08–1.09) per regimen with the majority of regimens containing one ARV item—which was primarily a fixed-dose combination product consisting of tenofovir, emtricitabine and efavirenz. It can be concluded that only 13.9% of PWHI are diagnosed with co-existing CDL conditions that can influence these patients' treatment patterns. The prevalence of co-existing CDL conditions and ART treatment patterns in this PWHI population concurs with existing literature and suggested national and international standard treatment guidelines.

CLINICAL PROFILE OF PATIENTS INFECTED WITH HIV IN THE PRIVATE HEALTH SECTOR OF SOUTH AFRICA

INTRODUCTION

The global response to the human immunodeficiency virus (HIV) pandemic through increased access to antiretroviral treatment (ART) has improved quality of life and reduced both new HIV-incidence and HIV-related deaths in patients with HIV infections (PWHI).[1,2] In South Africa, the number of new HIV infections declined by 39% between 2000 and 2019.[1] HIV infections, however, continue to be a global public health concern, spreading rapidly around the world with 38 million PWHI by the end of 2019.[1]

ART regimens are prescribed to provide successful viral suppression, reduce transmission, lessen morbidity and increase life expectancy.[3] Since fixed-dose combinations (FDC) became available to PWHI with the launch of Atripla® in 2006,[4,5] the advantage of FDCs has led to improved clinical outcomes of patients.[6] The Southern African HIV Clinicians Society[7] outlined FDCs benefits as simplified dosing schedules and regimens, improved adherence, increased efficacy, reduced treatment cost and decreased risk of dispensing errors.

The health sector of South Africa is divided into a public sector providing for the majority of indigent people in the country and a private sector[8] providing services to around 16% of the population.[9] National standard treatment guidelines (STG) are implemented in the private health sector in South Africa.[10] These guidelines are based on those suggested by the World Health Organization (WHO).[11] However, no compulsory guidelines for HIV care and treatment exist for the private health sector. The South African Department of Health (DOH),[10] encourages healthcare professionals across all sectors to follow the national STG and protocols.

The choice of the treatment regimen, however, is subject to various factors, including the presence of co-existing diseases and comorbidities, treatment of opportunistic diseases, drug-drug or drug-disease interactions, adherence to ART and side effects of ART.[12,13,14,15]

PWHI have an increased risk of developing co-existing diseases and comorbidities.[16] The number of co-existing conditions is more likely to rise in elderly PWHI and may be aggravated by the side effects of antiretroviral (ARV) medication.[16] There is an association between the characteristics of older PWHI (such as age and mental and physical health) and the prevalence of other co-existing chronic diseases such as diabetes, syndromic neurocognitive impairment, liver diseases, renal diseases, and malignancies.[17] Older PWHI with comorbidities were significantly and independently associated with deteriorated physical and mental health-related quality of life when compared to those without comorbidities.[18] Furthermore, the possibility of developing premature onset of comorbidities when ageing is greater in PWHI, which decreases their health-related quality of life.[19] People from different age groups have unique circumstances influencing their risk of acquiring HIV. [20] Younger, sexually active individuals are primarily infected with HIV due to behavioural aspects.[21]

Because of the ART adherence-resistance relationship, failure of the patient to comply with the treatment dosing schedule as prescribed leads to selective resistance to specific ART, influencing the choice of treatment regimens.[22] The progression of the disease and mortality are also related to non-adherence to the prescribed ART regimen, which results in fewer options for treatment regimens.[17] The more chronic diseases a patient presents with, and the worse the mental and physical health of the PWHI, the lower the adherence to ART may be.[21,23,24,25,26] Understanding the clinical profile of PWHI can support medical schemes to identify possible risk factors and develop policies to mitigate the effect of a growing PWHI population in a managed care environment.[20,27]

There is limited information about the clinical profile of PWHI in the South African private health sector. This study aims to determine the prevalence of chronic disease list (CDL) conditions and ART patterns in PWHI in the South African medical scheme environment.

METHODS

Ethical considerations

Ethics approval was obtained from the North-West University Health Research Ethics Committee (NWU-00179-14-A1-07). A pharmaceutical benefit management (PBM) company granted goodwill permission to use the data for this study.

Study design

A cross-sectional research design was implemented to analyse retrospective medicine claims data of 2016, obtained from a South African PBM company's database.

Study population

The study population included all PWHI on the database with an International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnosis code for HIV (diagnoses code B20-B24) in conjunction with a claim for ARV medication. Patients with incomplete demographic information, such as age and gender, were excluded from datasets.

Study variables

The clinical profile of PWHI includes the existence of CDL conditions, age, gender and ARV regimens claimed according to product type (FDC or a single active ingredient product).

The day (in 2016) the ARV medicine was claimed (in other words, the date the medicine claim was submitted to the PBM company) was used to calculate the patients' ages. Patients

were categorised into seven age groups: ≥0 and<2 years, ≥2 and <12 years, ≥12 and <18 years, ≥18 and <25 years, ≥25 and <45 years, ≥45 and <65 years and over 65 years.

FDCs were defined as a product with two or more active ingredients formulated in one dosage form. In contrast, single active ingredient products contain only one active ingredient in a specific dosage form.

ARVs were identified according to their National Approved Product Pricing Index codes[28] and classified according to the Monthly Index of Medical Specialties[29] classification system.

An ARV regimen is a treatment plan with suggested active ingredient(s) and a specified dosage prescribed for a specified duration (usually lifelong). ARV regimens were defined as a single ARV item or a combination of ARV items (active ingredient(s)—single or FDC) claimed on one or more prescriptions on the same day. The type of ART regimens prescribed in this study was compared to the suggested STG of the DOH[10] and WHO[11]. This comparison served as an indicator for the compliance of healthcare professionals with suggested STGs.

In South Africa, the Medical Schemes Act (No. 131 of 1998) includes prescribed minimum benefits (PMBs) for 270 conditions that include 26 chronic conditions (defined as the CDL) to ensure that all medical scheme members are continuously provided with certain minimum health services, irrespective of their selected benefit option.[27] Effective from 1 January 2004, PWHI received PMBs for their condition, even though it is not classified in the Medical Scheme Act as a CDL condition.[30] Each CDL has a specific ICD-10 code; the ICD-10 codes are used to identify other CDL conditions in PWHI.

Data analysis

The Statistical Analysis System, SAS 9.4® (SAS Institute, 2002-2017)[31], was used for data analysis.

Categorical variables are presented as numbers or frequencies (n) and percentages (%). The age of PWHI and the number of ARV items per regimen are presented as a mean and standard deviation (SD). The number of CDL conditions per patient is presented as a median (interquartile range (IQR)).

The chi-square (x^2) test was used to test for association between the type of CDL condition and gender or age group. Statistical significance was established using a probability value (*P*), represented as $P \leq 0.0500$. The Cramér's *V* statistic was used to test the associations' practical significance, with Cramér's $V \geq 0.5$ defined as practically significant.[27]

RESULTS

A total of 16 763 PWHI (n = 8 871, 52.3% female; n = 7 992, 47.7% male), with an average age of 42.3 years (SD 11.5, 95%; confidence interval (CI) 41.9–42.3), were included in this study.

Table 1 depicts the number of PWHI who presented with CDL conditions. The median (IQR) number of CDL conditions per PWHI was 0(0), indicating that the majority of PWHI (n = 14 426, 86.1%) did not present with any CDL condition. Only 13.9% (n = 2 337) of PWHI were diagnosed with one or more CDL condition during the study period. Amongst these, 79.1% (n = 1 848) had one CDL condition, 17.4% (n = 407) had two CDL conditions, and 3.5% (n = 82) had three or more CDL conditions.

Table 1 Number of PWHI diagnosed with one or more CDL condition (N = 2 337)

Number of PWHI diagnosed with CDL conditions	Frequency n (%)
1	1 848 (79.1)
2	407 (17.4)
3 or more	82 (3.5)

The prevalence of the top 15 co-existing CDL conditions or combinations in PWHI is shown in **Table 2.** Hypertension was documented in more than half (n = 1 287, 55.1%) of the PWHI who had one or more co-existing CDL conditions, followed by hyperlipidaemia in 7.0% (n=164) and both hypertension and hyperlipidaemia in 8.8% (n = 205). Hypertension was also found in combination with several other CDL conditions: chronic renal disease (n = 33; 1.4%), asthma (n = 28, 1.2%), epilepsy (n = 20, 0.9%) and hypothyroidism (n = 19, 0.8%).

Table 2 The top 15 most prevalent CDL condition(s) diagnosed in PWHI (N = 2 337)

Chronic diseases	**n (%)**
Hypertension	1 287 (55.1)
Hyperlipideamia and hypertension	205 (8.8)
Hyperlipidaemia	164 (7.0)
Asthma	106 (4.5)
Epilepsy	70 (3.0)
Chronic renal failure	45 (1.9)
Hyperthyroidism	41 (1.8)
Bipolar disease	39 (1.7)
Chronic renal disease and hypertension	33 (1.4)
Asthma and hypertension	28 (1.2)
Cardiac failure	28 (1.2)
Diabetes mellitus type 1	24 (1.0)
Hypertension and epilepsy	20 (0.9)
Hypertension and hyperthyroidism	19 (0.8)
Glaucoma	17 (0.7)

The results in **Table 3** indicate a statistically significant association between gender and the type of CDL condition ($P < 0.001$; Cramér's $V = 0.2902$). A larger percentage of women compared to men were diagnosed with hypertension (n = 629, 56.8% vs n = 658, 53.5%), asthma (n = 61, 5.5% vs 45, n = 3.6%) and epilepsy (n = 39, 3.5% vs n = 31, 2.5%). More men than women were diagnosed with hyperlipidaemia (n = 112, 9.1% vs. n = 52, 4.7%) and the combination of hyperlipidaemia and hypertension (n = 146, 11.9% vs. n = 59, 5.3%).

The majority of PWHI (n = 1 451, 62.1%) diagnosed with one or more CDL conditions were aged between ≥45 and <65 years, followed by the age group ≥25 and <45 (n = 682, 29.2%). HIV-infected children under the age of two (<2) had no co-existing CDL conditions. A statistically significant association ($P < 0.0001$; Cramér's $V = 0.3327$) was also found between age groups and the types of co-existing CDL conditions. PWHI in the age group ≥45 and <65 years had the highest prevalence of hypertension (n = 834; 57.5%), hypertension and hyperlipidaemia (n = 148; 10.2%), hyperlipidaemia (n = 106; 7.3%), asthma (n = 45; 3.1%) and epilepsy (n = 33; 2.3%). More than 50% (n = 385) of PWHI aged ≥25 and <45 years were diagnosed with hypertension. The majority of elder PWHI (≥65 years and above) were diagnosed with hypertension (n = 68, 39.1%), followed by hyperlipidaemia (n = 32, 18.4%) and hypertension and hyperlipidaemia together (n = 17, 9.7%). In PWHI <18 years (n = 17), asthma (n = 9, 52.9%) was the most prevalent CDL condition, followed by epilepsy (n = 5, 29,4%).

Table 3 Prevalence of the different types or combination of CDL conditions in PWHI (n = 2 337) stratified by gender and age group

PWHI with CDL condition	Hypertension	Hypertension and hyperlipidaemia	Hyperlipidaemia	Asthma	Epilepsy	Other	*P* value	Cramér's *V*
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)		
Total number of (N = 2 337)	1 287 (55.1)	205 (8.8)	164 (7.0)	106 (4.5)	70 (3.0)	505 (21.6%)		
Gender								
Men (n = 1229)	658 (53.5)	146 (11.9)	112 (9.1)	45 (3.6)	31 (2.5)	237 (19.3)	< 0.001	0.2902
Women (n = 1108)	629 (56.8)	59 (5.3)	52 (4.7)	61 (5.5)	39 (3.5)	268 (24.2)		
Age groups (years)								
> 0 and < 2 (n = 0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	< 0.001	0.3327
≥ 2 and < 12 (n = 5)	0 (0)	0 (0)	0 (0)	3 (60.0)	0 (0)	2 (40.0)		
≥12 and <18 (n = 12)	0 (0)	0 (0)	0 (0)	6 (50.0)	5 (41.7)	1 (8.3)		
≥18 and <25 (n = 13)	0 (0)	0 (0)	0 (0)	8 (61.5)	2 (15.4)	3 (23.1)		

Age groups (years)						
≥25 and <45 (n = 682)	385 (56.5)	25 (3.7)	41 (6.0)	43 (6.3)	30 (4.4)	158 (23.1)
≥45 and <65 (n = 1451)	834 (57.5)	148 (10.2)	106 (7.3)	45 (3.1)	33 (2.3)	285 (19.6)
≥65 and above (n = 174)	68 (39.1)	32 (18.4)	17 (9.7)	1 (0.6)	0 (0)	56 (32.2)

For the study period (1 January 2016 to 31 December 2016), a total of 175 317 individual treatment regimens containing 191 541 ARV items were claimed. An average of 1.1 ARV items (SD 0.38, 95%; CI 1.08–1.09) were claimed per regimen (on one or more prescriptions on the same day). **Figure 1** indicates that most regimens contained one ARV item (n = 163 154, 92.3%), followed by two ARV items (n = 8 550, 4.8%). A further 3 613 (2.1%) regimens contained three and more ARV items.

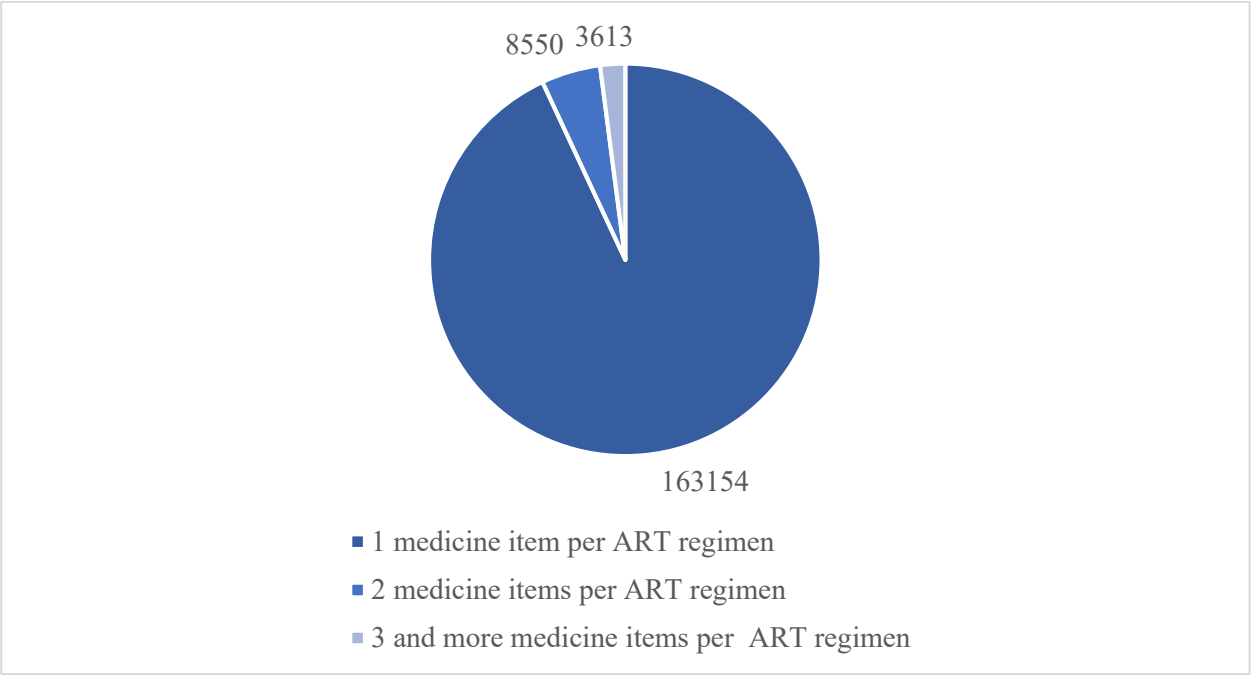


Figure 1 Frequency of number of ARV items claimed per regimen (N = 175 317)

Table 4 Top five regimens according to the number of ARV items

Regimen	Product type	Number of ARV regimen
One medicine item	**FDC/ single active ingredient product**	**N (100%)** **N = 176 768**
EFV + FTC + TDF	FDC	71 251 (40.3)
LPV/r	FDC	16 448 (9.3)
3TC +AZT	FDC	14 789 (8.4)
FTC + TDF	FDC	14 241 (8.1)
EFV	Single active ingredient	13 643 (7.7)
Two medicine item	**FDC/ single active ingredient product**	**N (%)** **N = 8 550**
EFV + 3TC + AZT	Single active ingredient + FDC	1 764 (1.0)
ABC + 3TC	2 Single active ingredients	1 174 (0.7)
RPV + RTV	2 Single active ingredients	1 095 (0.6)

Regimen	Product type	Number of ARV regimen
ARV + RPV	2 Single active ingredients	827 (0.5)
NVP + TDF	2 Single active ingredients	599 (0.3)
Three medicine item	**FDC/ single active ingredient product**	**(%)** **N = 3 613**
ABC + EFV + 3TC	3 Single active ingredients	1 720 (1.0)
EFV + 3TC + d4T	3 Single active ingredients	414 (0.2)
EFV + 3TC +AZT	3 Single active ingredients	289 (0.2)
NVP + 3TC + TDF	3 Single active ingredients	171 (0.1)
EFV + 3TC+ TDF	3 Single active ingredients	165 (0.1)
Four medicine item	**FDC/ single active ingredient product**	**N (%)** **N = 2**
EFV + 3TC + AZT+ ABC	4 Single active ingredients	1 (0.0)
3TC + EFV + D4T + D4T	4 Single active ingredients	1 (0.0)

Regimen	Product type	Number of ARV regimen

++3TC=lamivudine, ABC=abacavir, AZT=zidovudine, d4T=stavudine, DRV/r=darunavir/ritonavir combination, DTG=dolutegravir, EFV=efavirenz, FDC=fixed-dose combination, FTC=emtricitabine, LPV/r=lopinavir/ritonavir combination, NRTI=nucleotide reverse transcriptase inhibitor, NVP=nevirapine, RAL=raltrigravir, RTV=ritonavir, TDF=tenofovir

Table 4 shows that the one-item regimen in the form of an FDC were predominantly prescribed and contained mostly EFV+FTC +TDF (n = 71 251, 40.3%), followed by LPV/r (n = 16 448, 9.3%) and 3TC + AZT (n = 14 789, 8.4%). EFV (n = 13 643, 7.7%) was the only one-item regimen that was a single active ingredient product type, being part of the top five one-item regimens. Prescriptions consisting of two-item regimens with active ingredients EFV + 3TC + AZT (n = 1 764, 1.0%) had the highest number of claims; second was ABC + 3TC (n = 1 174, 0.7%) and third RPV + RTV (n = 1095, 0.7%). The product type for three and four-item regimens was only FDC. Among the three-item regimens, ABC + EFV + 3TC (n = 1 720, 1.0%), EFV + 3TC + d4T (n = 414, 0.2%), and EFV + 3TC +D4T (n = 289, 0.2%) were most frequently claimed.

DISCUSSION

In response to HIV infection and acquired immunodeficiency syndrome (AIDS), increased health coverage globally led to 25.4 million PWHI receiving ART in 2019.[1] Since the introduction of ART, life expectancy increased and morbidity and mortality rates reduced.[32] This present study identifies the clinical profile of PWHI, which include co-existing CDL conditions and the ARV treatment patterns, by identifying the most prevalent ARV regime and product type dispensed to PWHI in the South African medical scheme environment.

Similar to this study's findings, the most common co-existing diseases amongst PWHI in the United States are hypertension, hyperlipidaemia and endocrine disease, with increased prevalence among the ageing population.[33] There is also an increased risk of developing multiple co-existing chronic diseases with the prolonged use of ART. This study showed an association between age group and the type of CDL conditions PWHI were diagnosed with ($P < 0.001$; Cramér's $V = 0.3327$).

This study indicated that more HIV-infected women than men with were diagnosed with hypertension (n = 629, 56.8% vs n = 658, 53.5%). Men have a higher tendency of being

diagnosed with hyperlipidaemia than women with HIV infection.[34,35] This is also confirmed in this study.

Adults between the ages of 25 and 49 years tend to have a higher prevalence rate of HIV infections than adults older than 55.[20] This study alluded that PWHI ≥18 years and diagnosed with co-existing CDL conditions had a higher probability of hypertension, hyperlipidaemia or a combination of both than younger age groups. A study conducted in Poland suggested that the cardiovascular risk of PWHI is associated with the duration of HIV infection and increased age of the patient.[36] Both hypertension and hyperlipidaemia are risk factors associated with cardiovascular diseases, making HIV-infection management more complex in these patients.[37] The side effects of ART can increase the likelihood of getting co-existing diseases and comorbidities—and vice versa.[16] An example of a drug-disease interaction is the use of protease inhibitors (PI) in PWHI that could lead to dyslipidaemia.[38] Abnormalities associated with HIV infection and ART use include changes in the lipid blood concentration and insulin resistance, resulting in older patients developing metabolic syndrome.[36,37,39] The three most common comorbidities found in PWHI in South Africa were tuberculosis co-infection, diabetes mellitus type 2 and hypertension.[40,41]

HIV-infected children younger than two years were most likely infected due to mother-to-child transmission.[42,43] As soon as these children are diagnosed, they must receive lifelong ART to improve their quality of life.[1] HIV-infected children are subject to limited treatment options due to contraindications.[1] In this study, HIV-infected children and adolescents below 18 years presented with either asthma or epilepsy. Asthma and epilepsy were amongst the top five most prevalent co-existing CDL condition in this study.[44] PWHI are five times more likely to be diagnosed with epilepsy than patients without HIV infection.[44] The increased prevalence of seizures in PWHI can be associated with the progression of HIV disease, which leads to metabolic irregularities and the presence of specific opportunistic diseases such as

toxoplasmosis.[44] Of the 70 PWHI diagnosed with epilepsy in this study, 10% (n = 7) were younger than 18 years. Lack of child-friendly, simplified ARV dosing formulations lead to reduced adherence and failure to suppress viral count in children living with HIV.[45,46] The management of HIV-infected children diagnosed with epilepsy is more complex, reducing the already-limited ARV simplified formulation options.[44,45,46] Furthermore, previous studies found that there is an increasing incidence rate of asthma in HIV-infected children and adolescents who are treated with ARV.[47,48,49] The escalated incidence rate of asthma may be influenced by immune-reconstitution of $CD4^+$ T cells in children living with HIV who receive ART.[49]

Adherence to ART in PWHI is a crucial factor in improving the general health outcomes of patients.[50] Reduced dose frequency and improved dose scheduling were achieved by combining the active ingredients into a single tablet taken once a day as FDC.[13,50] An average of 1.1 ARV items per regimen was claimed, and more than nine out of 10 regimens contained one ARV item, which was primarily an FDC product. FDC help to improve correct and efficient ART usage.[13] The benefits associated with using FDC products can be a motivator for healthcare providers to prescribe it.[6] Medical schemes in South Africa stipulate formularies—which are lists of medication based on the suggested guidelines by the DOH[10]—that are paid from the risk pool; should the patients or prescribers choose alternative treatment options, it may be subject to a co-payment.[51]

Ineffective and incorrect use of ART can lead to adverse drug reactions and impact the clinical prognosis of PWHI.[13,52,53] The ART suggested to achieve viral suppression contains a combination of three or more ARV active ingredients, which should be taken chronically.[1] By 2016, the suggested regimen both globally and in South Africa included TDF, FTC and EFV in cases where these drugs were not otherwise contraindicated.[10,11] Treatment regimens are adapted to accommodate PWHI with pre-existing conditions.[10] Reasons for changes in ART regimens could not be identified in this study because they were not indicated in the database.

The FDC consisting of TDF, FTC and EFV was the highest-claimed ARV regimen during the study period. For both the WHO[11] and DOH[10], TDF, FTC and EFV were part of the first-line treatment options—as per their guidelines. This indicated that medical professionals were likely to adhere to these stipulated first-line regimens. The WHO[11] recommended guidelines which include prescribing two NRTI with a PI can serve as alternatives to failure or contraindicated first-line treatment. The DOH[10] guidelines specify that if a TDF-based first-line treatment is contraindicated, treatment should be replaced by AZT, 3TC and EFV or NVP combination.[10,11] EFV, AZT and 3TC were amongst the top five highest-claimed single active ingredient ARV items, suggesting that medical professionals prescribed the alternative suggested first and second-line regimen guidelines.[10,11] This study's results indicated that medical professionals were more likely to follow first and second-line suggested regimens as per STG of the DOH[10] and WHO[11] when compared to the three- and four-item regimens, as indicated in **Table 4.**

This study sought to determine the clinical profile of HIV-infected medical scheme beneficiaries in South Africa. This cross-sectional study employed retrospective medicine claims data from one PBM company that leads to limited external validity. The results are only applicable to this database and study population, and the researcher was not able to compare the findings with other PBMs in South Africa.

STUDY HIGHLIGHTS

What is the current knowledge on the topic?

Previous studies indicate how risk factors such as gender, ageing and comorbidities affect the treatment patterns and clinical outcome of PWHI.

What question did this study address?

This study addresses the clinical profile of HIV-infected medical scheme beneficiaries in South Africa. The clinical profile includes the trends in the prevalence of co-existing CDL conditions in PWHI and their ART patterns.

What does this study add to your knowledge?

Only 13.9% of PWHI presented with co-existing CDL conditions; 79.1% were diagnosed with one CDL condition, and 17.4% presented with two or more CDL conditions. Asthma and epilepsy were the most prevalent co-existing CDL conditions in PWHI younger than 18 years. In PWHI ≥younger than 18 years, co-existing CDL conditions were most likely hypertension and hyperlipidaemia. Most PWHI were treated with one ARV item and most probably FDC products. The FDC most claimed were a TDF, FTC and EFV combination, which formed part of the South African DOH HIV STG.

How might this change pharmacology or translational science?

Profiling PWHI based on the type of co-existing diseases and treatment patterns can help healthcare providers personalise future treatment plans according to characteristics such as age, gender and the probability of co-existing CDL conditions. PWHI have a high probability of being treated with FDC products containing TDF, FTC and EFV. Only 13.9% of PWHI are diagnosed with co-existing CDL conditions that can influence these patients' treatment patterns.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS

The authors wish to acknowledge the PBM company for providing the database to conduct this study. The authors would like to extend our gratitude to Ms H.Hoffman and Ms E. Berman to proofread and edit this manuscript. We thank Ms A. Bekker for helping with the data management.

AUTHOR CONTRIBUTIONS

M.S.L., J.R.B., T.E. and A.N. conceived the study. M.S.L. analysed the data under the guidance of the Statistical Consultation Services, North-West University. T.E. interpreted the findings and, under the supervision of M.S.L., J.R.B. and A.N., drafted the report. All authors reviewed and approved the final version.

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FIGURE LEGENDS

Figure 1 Frequency of number of ARV items claimed per regimen (N = 175 317)

3.4 Chapter summary

This chapter addressed the specified empirical objectives of this study in the form of two manuscripts.

CHAPTER 4: CONCLUSION OF DISSERTATION

4.1 Overview of the dissertation

This final chapter of the dissertation focuses on concluding the study in relation to the specific objectives outlined. A synopsis of the content of the dissertation is provided. The study's strengths and limitations are outlined, and recommendations are made for future studies.

4.2 Conclusions from the literature study

The objectives of the literature study were:

- To determine, from the literature, the burden of HIV/AIDS globally and in South Africa from a prevalence, clinical and social perspective.
- To conceptualise the treatment patterns for HIV/AIDS globally and in South Africa.
- To determine the possible influence of co-existing chronic diseases, medicine adherence and economic factors on the implementation of STGs.

4.2.1 Burden of HIV/AIDS globally and in South Africa from a prevalence, clinical and social perspective

The burden of HIV/AIDS both globally and specifically in South Africa were addressed in Chapter 2. HIV/AIDS continues to be a global health concern, with an estimated 38 million PLWHA in 2019 (WHO, 2019a). The African region had the largest number of PLWHA compared to other regions in 2019 (UNAIDS, 2020b), and women had a higher incidence rate than men from 2002 to 2017 (WHO, 2017b). Eastern and Southern Africa had the highest number of PLWHA, followed by Western and Central Africa (UNAIDS, 2017a:2-3).

In 2016, more than half (53%) of the PLWHA globally resided in Southern and Eastern Africa, despite the number of new infections in the region that had declined by 29% from 2010 to 2016 (UNAIDS, 2016b:5; UNAIDS, 2017a:2-3). Sub-Saharan Africa had the highest prevalence rate in the African region and globally (UNAIDS, 2017a:2-3). Women in the Eastern and Southern Africa region accounted for 60% of new HIV infections and were more than twice as likely to get infected with HIV than their male peers (UNAIDS, 2020b). AIDS-related mortalities in the Eastern and Southern Africa region decreased by 49% from 2010 to 2019 (UNAIDS, 2020b).

In South Africa, 13.5% of the population lived with HIV/AIDS in 2019 (Statistics South Africa, 2019:v). Women aged 25–49 years accounted for 25% of new HIV infections in the same year (UNAIDS, 2019a:19). Around 24% of new infections were children who acquired HIV infection due to mothers not having access to healthcare during gestation or breastfeeding (UNAIDS, 2019:a174). These high prevalence rates were even though the HIV infection rate declined from 1.9% in 2002 to 0.9% in 2017 (Statistics South Africa, 2017:8). HIV/AIDS-related deaths reached a high of 47.7% before an FDC ARV treatment became available on the market in 2006 (Airoldi *et al.*, 2010:115-116; Statistics South Africa, 2018:32; Taylor, 2016:445-450). The HIV/AIDS mortality rate reduced to 27.9% by 2016 (Statistics South Africa, 2018:32).

Among the nine provinces of South Africa in 2016, KwaZulu-Natal contributed 18% to the HIV/AIDS prevalence rate, followed by Mpumalanga (15.2%) and Gauteng (13.1%) (Statistics South Africa, 2017:7-9). One of the reasons for the unequal HIV/AIDS prevalence rate among the provinces is the difference between the ratio of formal and informal settlement types in the provinces, which also reflects differences in education access and socio-economic factors such as income levels (Gibbs *et al.*, 2020:e0230105; Hargreaves *et al.,* 2008:27).

Funding for HIV/AIDS response started to grow globally in the 1990s (Soneklar, 2011:102-105; UNAIDS, 2020d). Funding from private and public international donors, the World Bank and the Global Fund, among others, was made available to low- and middle-income countries affected by HIV/AIDS (Amico *et al.*, 2010:e12997). In African countries, small businesses experienced financial strains due to HIV/AIDS due to reduced adult workforces, job opportunities and business investments (Harman, 2010:6-7). The resultant slowing of economies in African countries with the increased HIV/AIDS prevalence rates increased the fiscal demand on African governments (Harman, 2010:6).

The South African government's funding allocated toward HIV/AIDS increased from R1.2 billion in 2004/2005 to 17.5 in 2016/2017 (Blecher *et al.,* 2016:207). Apart from government funding, PEPFAR donated funds that reached US$250 million by 2017 (Lodge, 2015:1573). Conditional grants alleviated the fiscal burden of HIV/AIDS on households and amounted to R1.4 billion spent in 2017/2018 (UNICEF, 2018:8-9).

HIV/AIDS was the chronic disease that showed the most significant growth in the private medical scheme environment in South Africa from 2008 (6.6 cases per 1 000 beneficiaries) to 2015 (30.7 per 1 000 beneficiaries) (CMS, 2015b:8-11). When HIV/AIDS had to be treated as part of

prescribed minimum benefits (PMB) as indicated in the regulatory amendments in 2004 (South Africa, 2003; South Africa, 2009), medical schemes' fiscal burden increased.

HIV/AIDS has financial consequences for families because of the direct costs of treatment (medication, medical practitioners, hospitalisation and medical aid levies or co-payments) (Drimie, 2002:2; Chimbindi *et al.*, 2015:e52-e60). Apart from these direct costs, which are covered by public healthcare services in South Africa, patients experience indirect costs such as transport, accommodation, food and income loss (Bester *et al.*, 2014:2-25; Chimbindi *et al.*, 2015:e52-e60; Sinofsky & Rice, 1987:11; Wilensky & Kibitzes, 2010:274). The death of caregivers or breadwinners reduces education access for dependants and leaves children orphaned, leading to poverty (Chimbindi *et al.*, 2015:e52-e60; Walensky & Kuritzkes, 2010:274).

Poverty leads to risky behaviour, such as sex work, crime, and substance and drug abuse, contributing to acquiring HIV infection (Benatar, 2013:154-155; Shisana *et al*., 2012:2-5; UNAIDS, 2015:25). Social aspects such as cultural beliefs, multiple sex partners, stigmatism and violence occur in all countries, leaving groups from lower socio-economic groups more vulnerable to getting infected (Benatar, 2013:154-155; Shisana *et al.*, 2012:2-5; UNAIDS, 2015:6-28). Poverty can be a barrier that reduces access to education, resulting in households lacking employment probabilities to improve their financial status (Tladi, 2006:369).

4.2.2 Conceptualise the treatment patterns for HIV/AIDS globally and in South Africa

The treatment pattern of HIV/AIDS both globally and in South Africa was discussed in Chapter 2. The availability of a one-a-day ARV tablet increased patient adherence, reduced-dose schedule and improved affordability, which all have the potential to reduce HIV/AIDS mortality rates (Babiker *et al.,* 2013:55-58; Bae *et al*., 2011:279). The treatment regimens for patients with HIV/AIDS are influenced by guidelines determined by the World Health Organization (WHO), the South African Department of Health (DOH), legislation, patients at risk, patient-related factors and medicine-related factors. (Refer to paragraph 2.4.)

South Africa's STGs serve as an outline of good treatment practices that include quality and affordable medication (DOH, 2018:xx-xxii). The STGs for HIV/AIDS used in South Africa is based on the WHO's treatment guidelines (WHO, 2018a:14). The uncomplicated FDC recommended includes TDF, 3TC and EFV (DOH, 2018:11.1-11.21; WHO, 2016c; WHO, 2018a:14).

The legislative amendments that included HIV/AIDS in the PMB have made medical schemes liable for a set of predefined healthcare services for patients using medical schemes (CMS, 2015b:34; South Africa, 2003; South Africa, 2009). The change increased the risk profile of medical schemes as these services must be covered from the medical scheme's risk pool and not the medical savings of patients (CMS, 2015b:34; South Africa, 2003; South Africa, 2009).

Among PLWHA, key populations that require attention were found to include prisoners, MSM and sex workers (Eaton & Kalichman, 2016:31; WHO, 2017a:55). These key populations constituted 25% of the new HIV infections between 2000 and 2014 (UNAIDS, 2015:92). Prisoners are 50 times more likely to acquire HIV/AIDS than the general population due to violent victimisation, the high prevalence of injectable drug use and sexual assault in prisons (UNAIDS, 2016d:33; Sander *et al.,* 2012:40). MSM accounted for 26.8% of the South African HIV/AIDS prevalence rate in 2016, and they are at higher risk because the probability of HIV transition through anal penetration is 18 times higher than vaginal penetration (Beyrer *et al.,* 2012:367). In South Africa in 2015, 75% of sex workers lived with HIV/AIDS. Risky sexual behaviour and a social environment that increases exposure to violence, abuse, and substance and drug abuse contribute to the high HIV/AIDS prevalence rate in this population group (Baral *et al.,* 2015:263- 264; Beyer *et al.,* 2015:292; UNAIDS, 2016c).

Patient-related factors that can change the choice of treatment regimens include treating at-risk patients. For this study, at-risk patients include pregnant women, children, the elderly, and renal or cardiovascular disease patients. (Refer to paragraph 2.5.1.)

In pregnant women, the early diagnosis and onset of treatment with ART help reduce MTCT. The STG for pregnant women of all gestational stages starts with the fixed-dose combination TDF, FTC and EFV. If EFV is contra-indicated due to psychiatric side effects, NVP or LPV/r are suggested. In cases where TDF is contra-indicated, the regimen changes to ABC, 3TC and EFV. Women who test positive during labour but were not on ART during pregnancy should be given NVP as soon as possible and AZT during labour, TDF and FTC. The use of FDC is recommended during breastfeeding to reduce MTCT.

The recommendation for children exposed to HIV is to treat with NVP for 12 weeks after birth. When children are diagnosed with HIV/AIDS, the first-line regimen for children below 3 years old includes ABC, 3TC and LPV/r or EFV. An alternative regimen includes TDF, 3TC or FTC and EFV or LPV/r. For children older than 3 years and with a weight of more than 10 kg, the regimen choice includes ABC, 3TC and EFV. In adolescents with the absence if comorbidities or other nephrotoxic medication, the treatment regimen includes TDF, 3TC or FTC and EFV.

PLWHA are associated with an increased risk of developing renal, cardiovascular and/or liver diseases, which are non-AIDS related diseases (Deeks & Phillips, 2009:a01780893; Günthard *et al.*, 2016:192-193). Patients with these diseases require adjustments from the STG regimens, including changes of dose according to body weight, creatinine clearance or changing the choice of active ingredients (MIC, 2016:62-64; Southern African HIV Clinicians Society, 2008:34-39; WHO, 2016c:84).

4.2.3 Determine the possible influence of co-existing chronic diseases, medicine adherence and economic factors on the implementation of STGs

Specific factors that influence treatment patterns of PLWHA were discussed in Chapter 2. They include patient adherence to ART, drug-resistance, side-effects, drug-drug interactions, drug-disease interactions, treatment of opportunistic disease, co-existing diseases and comorbidities (Benson *et al.*, 2009:3-4; Cihlar & Fordyce, 2016:50-52; Fonsah *et al.*, 2017:e0170893; Holodniy *et al.*, 2007:20-22).

Adherence to ART is an important factor required to achieve optimal viral suppression and reduce possible resistance to treatment due to viral mutation (Airoldi *et al.*, 2010:115; Bangsberg *et al.*, 2004:696-699; Touchette & Shapiro, 2008:S2-S4). Reduced adherence to ART is related to increased costs due to increased morbidity (Cramer *et al.,* 2008:44-45). Patient-specific factors such as age, gender, race, culture, and socio-economic, behaviour and treatment-related factors can reduce ART adherence (Airoldi *et al.*, 2010:116; Al-Dakkak *et al.*, 2013:413; Vervoort *et al.*, 2007:271-281). Non-adherence to ART results in suboptimum ART concentrations, viral replication and resistance against the ART (Bangsberg *et al.*, 2004:696; Kleeberger *et al.*, 2001:82), which affects the treatment regimen choice for the specific patient (Kleeberger *et al.*, 2001:82).

Co-existing diseases and comorbidities in PLWHA also affect treatment patterns (Cihlar & Fordyce, 2016:54). PIs and NNRTIs are associated with an increased risk of metabolic syndrome (Oni *et al.*, 2015:20). NNRTIs leads to reduced bone density, and patients may develop osteoporosis, osteopenia and vitamin D deficiency (Günthard *et al.*, 2016:192-196; Reust, 2011:1450). Long-term use of PIs leads to dyslipidaemia and increases cardiovascular disease risk, increasing myocardial infarction risk (Mallon *et al.*, 2006:1004).

In PLWHA, severely immunosuppressed individuals have a greater risk of acquiring opportunistic diseases (Benson *et al.,* 2009:4). The presence of opportunistic diseases requires additional treatment apart from ART, leading to drug-drug interactions and a higher tendency of ARV regimens to be contra-indicated (De Maat *et al.*, 2003:228-272; Sapkota *et al.*, 2012:17).

ART active ingredients have numerous side effects and possible toxicities for patients, even those without comorbidities. (Refer to Table 2-14.) The most common side effects include lactic acidosis, haematology toxicity, hepatotoxicity, lipoatrophy, dyslipidaemia, peripheral neuropathy, neuropsychiatric toxicity and hypersensitivity reactions to ART (DOH, 2015a:78-80; MIC, 2016:43-48). Drug-drug interactions between ART and non-ARV medication are listed in Table 2-13. Due to competition for metabolic enzymes or elimination, the concentration of ART or non-ARV medication can be decreased or increased, which jeopardises treatment outcomes and results in limited treatment options (AIDSinfo, 2019:L-7-L-51; De Maat *et al.*, 2003:228-272; MIC, 2016:61-88; DOH, 2018:11.11-11.21; University of California San Francisco, 2016).

ART requires a combination of three active ingredients to achieve the desired clinical outcome; however, more ingredients can result in a higher probability of side effects and toxicity (Cihlar & Fordyce, 2016:50; DOH, 2019:2). The regimens identified by South Africa's STGs and the WHO guidelines aim to increase clinical efficiency and tolerance and avoid costly treatment options (Bangsberg, 2004:696-697; DOH, 2018:11.11-11.21).

Resistance or contra-indications to first-line treatment options result in second- and third-line treatment regimens, which can become costly and challenging to maintain (Mayosi *et al.*, 2012:2030). Benefits such as reduced morbidity, viral suppression, improved quality of life and reduced mortality rates for PLWHA on chronic ART outweigh the risks of high toxicity and side-effects; however, these concerns leave the need to find alternatives to treat HIV/AIDs (Benjamin *et al.*, 2016:1059-1070; Sonenklar, 2011:118).

4.3 Conclusions from the empirical study

The research objectives for the empirical study were:

- To establish a demographic profile of HIV/AIDS patients stratified by patients' age, gender, geographical location, type of prescriber, and ARV medication provider.
- To investigate the medicine claims profile of HIV/AIDS patients by investigating the general medicine prescribing patterns of HIV/AIDS patients.
- To determine the clinical profile of HIV/AIDS patients by identifying their co-existing CDL conditions (refer to paragraph 1.5.2.1) and ART patterns.

4.3.1 Demographic and medicine claims profile of HIV/AIDS patients stratified by patients' age and gender, geographical location, type of prescriber and provider of ARV medication

The demographic and medicine claims profile of PWHI[34] was portrayed in Manuscript 1 in Chapter 3. Manuscript 1 is titled "Medicine claims profile of patients infected with HIV in the private healthcare environment of South Africa." The first two research objectives for this empirical study were addressed by Manuscript 1.

Healthcare expenses in the private healthcare system of South Africa are six times higher than in public healthcare (Mayosi & Benatar, 2014: 1345; Burger & Christian, 2020: 45). Because HIV is treated chronically, the medical schemes environment is legally obligated to cover the set PMB for HIV from their risk pool (South Africa, 2009; McIntyre, Doherty & Ataguba, 2012: 433-482). Because PWHI impact medical schemes' risk profile, understanding these beneficiaries' demographic profile and medicine claim patterns is beneficial for stakeholders (Shisana *et al.,*2012:7-8; SANAC, 2016:113; Statistic South Africa, 2017:7-9).

From a demographic profile perspective, a total of 16 763 (19.5 per 1 000) PWHI, with an average age of 42.3 years (SD 11.5; 95% CI 41.9–42.3), were identified, consisting of 8 871 female PWHI (52.3%) and 7 992 male PWHI (47.7%). Female PWHI were younger than male PWHI *(p* < 0.0001; Cohen's *d* = 0.3). The prevalence rate of PWHI was the highest in patients ≥ 45 and

[34] PWHI (patients with HIV infection) is preferred over PLWHA (people living with HIV/AIDS) in the journal where this manuscript was submitted. In this study, the terms are used synonymously.

< 65 years at 78 per 1 000 beneficiaries. Although most patients in the database were from Gauteng, only 17.7 per 1 000 medical scheme beneficiaries from the province were HIV-infected. The highest prevalence of PWH resided in the North West province (36.8 per 1 000 beneficiaries), followed by the Free State (29.7 per 1 000 medical scheme beneficiaries).

From a medicine claims perspective, the profile of PWHI indicated that they received an average of 10.9 (SD 7.6; 95% CI 10.8–11.0) ART regimens (N = 175 317) during the study period. The ART regimens contained an average of 1.1 (SD 0.4; 95% CI 1.1–1.1) ARV items (N = 190 903). Almost all (99.7%) ARV-items were prescribed by non-dispensing medical practitioners and dispensed in community pharmacies. The medical schemes mainly reimbursed the ARV items through patients' HIV-benefits. Medical schemes were found to use mostly generic medication (n = 145 804; 76.1%) and FDC products (n = 127 248; 66.4%). These practices can help reduce the risk profile for medical schemes.

4.3.2 Clinical profile of HIV/AIDS patients according to co-existing CDL conditions and ARV treatment patterns

Manuscript 2 in Chapter 3 discussed the clinical profile of HIV/AIDS patients. The manuscript is titled "Clinical profile of patients infected with HIV in the private health sector of South Africa".

To reduce HIV infections spreading more rapidly, the global focus shifted toward increasing access to effective ART (Greene, 2017; WHO, 2020a). In South Africa, the number of new HIV infections has decreased rapidly since 2000 due to increased ART access (WHO, 2020a). Since the approval of the FDC containing EFV, TDF and FTC, the clinical outcomes of HIV-infected patients rapidly increased (Meintjes *et al.*, 2017:2-4; Pujari *et al.*, 2008:196). Due to its evidence-based benefits, the FDC of EFV, FTC and TDF form part of the first-line STG of South African DOH (2016:11.1-11.26) and the WHO (2016c).

This study found that an average of 1.1 ARV items per regimen was claimed, and more than 9 out of 10 regimens contained one ARV item, which was primarily an FDC product. The most predominant FDCs contained EFV, FTC and TDF (n = 71 251; 43.7%), followed by LPV/r (n = 16 448; 10.1%) and 3TC and AZT (n = 14 789; 9.1%).

According to the WHO (2016c) recommended guidelines, two NRTIs should be prescribed with a PI to serve as alternatives in the case of failure or if first-line treatment is contra-indicated. The DOH (2016:11.1-11.26) guidelines specify that if a tenofovir-based first-line treatment is contra-indicated, treatment should be replaced by AZT, 3TC and EFV or NVP combination

(DOH, 2016:11.1-11.26; WHO, 2016c). This study found that EFV, AZT and 3TC were among the top five single active ingredient ARV items with the highest claims, suggesting that the medical professionals prescribed the alternative suggested according to first- and second-line regimen guidelines (DOH, 2016:11.1-11.26; WHO, 2016c). The study results indicated that medical professionals were more likely to follow first- and second-line regimens suggested as per the STG of the DOH (2016:11.1-11.26) and WHO (2016c) compared to the three- and four-item regimens indicated in Table 4 of Manuscript 2.

Patient characteristics such as age and gender influence their risk of acquiring HIV and/or co-existing diseases (Langebreek *et al*., 2017:1480-1481; UNAIDS, 2016c). Co-existing diseases in PLWHA may lead to drug-drug or drug-disease interactions that impact these patients' treatment (MIC, 2016:64). Even though 86.1% of PLWHA in the study population were not diagnosed with any CDL condition, the type of co-existing CDL condition prevalent in the PLWHA was dependent on age group and gender ($p < 0.05$). Women with HIV infection were more likely to be diagnosed with hypertension, whereas men had a higher probability of being diagnosed with hyperlipidaemia or a combination of hypertension and hyperlipidaemia. PLWHA aged ≥ 18 years had a higher tendency to be diagnosed with hypertension, hyperlipidaemia or both. Asthma and epilepsy were more prevalent among PLWHA younger < 18 years than those ≥ 18 years.

It was found that using the type of co-existing diseases and treatment patterns to profile PLWHA can help healthcare providers personalise future treatment plans according to characteristics such as age, gender and probability of co-existing CDL conditions.

4.4 Strengths and limitations of the study

Limiting factors that apply to either the literature review or the empirical investigation of the present study are listed below:

- Only medical aid schemes administered by one PBM company were presented in the study, limiting external validity. The results can only be generalised to the private healthcare sector and not to the entire South African population.
- Data from the public health sector were not available on the PBM company database.
- The database used ICD-10-codes and NAPPI-codes to determine diagnoses and medicine use, and it did not provide comprehensive clinical data regarding disease management.

- Deviation from ART treatment patterns could not be determined as it was not within the scope of data.

- The co-existing chronic diseases were limited to the 26 CDL conditions identified by ICD-10 codes. Other chronic co-existing diseases were excluded because their ICD-10 codes are not always indicated.

- The use of the postal codes of the prescriber's practice as a proxy for geographic location may not be accurate as the practice may be situated in a different location from the beneficiaries' resident address. Some medical scheme options encourage beneficiaries to use specific doctors, specialists, or other medical professionals to impact the geographic location data further.

The major strengths of the study were:

- The research showed that PBMs positively affect the treatment of HIV/AIDS in South Africa as disease management programmes are providing comprehensive HIV/AIDS treatment.

- The PBM company ensured the data's validity and reliability; therefore, the assumption was made that the data were correct. The data were also checked for outliers and duplications.

- The study population can be seen as an accurate representation of the entire database, considering that it is mandatory to specify the ICD-10 codes accurately when claiming reimbursement for CDL conditions, including HIV/AIDS.

4.5 Recommendations

The following recommendations for future research are suggested based on this study:

- To investigate how the number and type of CDL conditions impact medical schemes' risk profile.

- To investigate how ARV treatment patterns are impacted by specific CDL conditions such as hypertension and/or hyperlipidaemia.

- To investigate if the incidence of epilepsy in PLWHA younger than 18 years are aggregated by specific ARV medication.

- To investigate the possibility to develop an FDC treatment option for children to simplify the dosing schedule.

4.6 Chapter summary

The study objectives for both the literature review and empirical investigation were stated in this chapter. Conclusions from both the literature and empirical review were highlighted, followed by limitations of the study and recommendations for future studies.

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ANNEXURE A: ETHICS CERTIFICATE

Private Bag X6001, Potchefstroom,
South Africa, 2520

Tel: (018) 299-4900
Faks: (018) 299-4910
Web: http://www.nwu.ac.za

Research Ethics Regulatory Committee

Tel: +27 18 299 4849

Email : Ethics@nwu.ac.za

ETHICS APPROVAL CERTIFICATE OF STUDY

Based on approval by **Health Research Ethics Committee (HREC)** on **27/11/2017**, the North-West University Research Ethics Regulatory Committee (NWU-RERC) hereby **approves** your study as indicated below. This implies that the NWU-RERC grants its permission that provided the special conditions specified below are met and pending any other authorisation that may be necessary, the study may be initiated, using the ethics number below.

Study title: Profile of South African HIV/AIDS patients in a medical scheme environment

Study Leader/Supervisor: Prof MS Lubbe
Student: T Erasmus-21975310
Ethics number:

N	W	U	-	0	0	1	7	9	-	1	4	-	A	1	-	0	7
Institution				Study Number						Year			Status				

Status: S = Submission; R = Re-Submission; P = Provisional Authorisation; A = Authorisation

Application Type: Sub-study

Commencement date: 24/11/2017 **Risk:** Minimal

Approval of the study is initially provided for a year, after which continuation of the study is dependent on receipt of the annual (or as otherwise stipulated) monitoring report and the concomitant issuing of a letter of continuation.

General conditions:

While this ethics approval is subject to all declarations, undertakings and agreements incorporated and signed in the application form, please note the following:

- *The study leader (principle investigator) must report in the prescribed format to the NWU-RERC via HREC:*
  - *annually (or as otherwise requested) on the monitoring of the study, and upon completion of the study*
  - *without any delay in case of any adverse event or incident (or any matter that interrupts sound ethical principles) during the course of the study.*
- *Annually a number of studies may be randomly selected for an external audit.*
- *The approval applies strictly to the proposal as stipulated in the application form. Should any changes to the proposal be deemed necessary during the course of the study, the study leader must apply for approval of these amendments at the HREC, prior to implementation. Should there be any deviations from the study proposal without the necessary approval of such amendments, the ethics approval is immediately and automatically forfeited.*
- *The date of approval indicates the first date that the study may be started.*
- *In the interest of ethical responsibility the NWU-RERC and HREC retains the right to:*
  - *request access to any information or data at any time during the course or after completion of the study;*
  - *to ask further questions, seek additional information, require further modification or monitor the conduct of your research or the informed consent process.*
  - *withdraw or postpone approval if:*
    - *any unethical principles or practices of the study are revealed or suspected,*
    - *it becomes apparent that any relevant information was withheld from the HREC or that information has been false or misrepresented,*
    - *the required amendments, annual (or otherwise stipulated) report and reporting of adverse events or incidents was not done in a timely manner and accurately,*
    - *new institutional rules, national legislation or international conventions deem it necessary.*
- *HREC can be contacted for further information or any report templates via Ethics-HRECApply@nwu.ac.za or 018 299 1206.*

The RERC would like to remain at your service as scientist and researcher, and wishes you well with your study. Please do not hesitate to contact the RERC or HREC for any further enquiries or requests for assistance.

Yours sincerely

Prof. Refilwe Phaswana-Mafuya
Chair NWU Research Ethics Regulatory Committee (RERC)

ANNEXURE B: AUTHOR GUIDELINES FOR SOUTHERN AFRICAN JOURNAL OF HIV MEDICINE

Overview

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

Original Research Article

An original article provides an overview of innovative research in a particular field within or related to the focus and scope of the journal, presented according to a clear and well-structured format.

Word limit	3500-5500 words (excluding the structured abstract and references)
Structured abstract	250 words to cover a Background, Objectives, Method, Results and Conclusion
References	60 or less
Tables/Figures	no more than 7 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate

Editorial

Editorials are by invitation only and are intended to provide expert comment on relevant topics within the focus and scope of the journal.

Word limit	800 words
References	10 or less

Case Report

A venue to document their experience with testing, diagnosis and treatment of a patient, animal or group. This can include the diagnosis and treatment of a patient, or a potential description of the implementation of an educational programme or healthcare-related intervention towards the improvement of human development

Word limit	500-800 words (excluding the structured abstract and references)
Structured abstract	250 words to cover a Introduction, Patient presentation, Management and outcome, and Conclusion
References	15 or less
Tables/Figures	no more than 4 Tables/Figure
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate

Clinical Images

The aim is to show a classic, rare or unusual manifestation of HIV or HIV-related conditions. The text should very briefly summarise the case and also include a brief description/discussion of the visual image itself.

Word limit	150 words (excluding references)
Title	8 words
Authors	Max 2
References	2 or less
Figures	High quality image in one of the following formats: PDF, GIF, JPEG, TIFF, BMP More than 1 panel is permitted in the image. If the image contains more than 1 panel, submit two images, one original and one with the panels labelled.
Ethical statement	should be included in the manuscript
Compulsory supplementary file	ethical clearance letter/certificate

Review Article

Review articles provide a comprehensive summary of research on a certain topic, and a perspective on the state of the field and where it is heading. These articles are often meta-analyses comparing and combining findings of previously published studies.

Word limit	2500-4000 words (excluding the abstract and references)
References	15 or less
Structured abstract	250 words to include a Background, Objectives, Method, Results and Conclusion
Tables/Figures	data in the text should not be repeated extensively in tables or figures

Scientific Letter

Original research that is limited in scope can be submitted as a scientific letter rather than a full original research article.

Word limit	1500 words
References	6 or less
Tables/Figures	no more than 1 Table/Figure

Guidelines

A guideline provides evidence-based recommendations that will influence clinical research and practice. These can be consensus-based statements of reporting standards or clinical practice guidelines.

Word limit	1 000 words

Obituaries

Is a news article that reports the recent passing of a person, typically along with an account of the person's work achievement and life.

Word limit	400 words
Photo	a photograph of the deceased

Opinion Papers

Short opinion pieces or personal perspectives (not research papers) that takes on a personal viewpoint of HIV and/or AIDS treatment, prevention and related topics relevant to clinical and public health practice as to provide a contextual and holistic view of practices across the continent. With rare exceptions, these essays are meant to express a personal viewpoint and should have no more than two authors.

Word limit	2000 words (excluding the structured abstract and references)
Unstructured abstract	250 words
References	15 or less
Tables/Figures	no more than 2 Tables/Figure
Ethical statement	should be included in the manuscript, if applicable

Cover Letter

The authorship, disclosure statements, copyright, and license agreement form is our compulsory cover letter which needs to form part of your submission. Kindly download and complete, in English, the provided **form**.

Anyone that has made a significant contribution to the research and the paper must be listed as an author in your cover letter. Contributions that fall short of meeting the criteria as stipulated in our policy should rather be mentioned in the 'Acknowledgements' section of the manuscript. Read our **authorship** guidelines and **author contribution** statement policies.

Original Research Article full structure

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

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

Background: Why do we care about the problem? State the context and purpose of the study. (What practical, scientific or theoretical gap is your research filling?)

Objectives: What problem are you trying to solve? What is the scope of your work (e.g. is it a generalised approach or for a specific situation)? Be careful not to use too much jargon.

Method: How did you go about solving or making progress on the problem**?** State how the study was performed and which statistical tests were used. (What did you actually do to get the results?) Clearly express the basic design of the study; name or briefly describe the basic methodology used without going into excessive detail. Be sure to indicate the key techniques used.

Results: What is the answer**?** Present the main findings (that is, as a result of completing the procedure or study, state what you have learnt, invented or created). Identify trends, relative change or differences on answers to questions.

Conclusion: What are the implications of your answer**?** Briefly summarise any potential implications. (What are the larger implications of your findings, especially for the problem or gap identified in your motivation?)

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

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

Social value: The first part of the introduction should make a clear and logical argument for the importance or relevance of the study. Your argument should be supported by use of evidence from the literature.

Scientific value: The second part of the introduction should make a clear and logical argument for the originality of the study. This should include a summary of what is already known about the research question or specific topic, and should clarify the knowledge gap that this study will address. Your argument should be supported by use of evidence from the literature.

Conceptual framework: In some research articles it will also be important to describe the underlying theoretical basis for the research and how these theories are linked together in a conceptual framework. The theoretical evidence used to construct the conceptual framework should be referenced from the literature.

Aim and objectives: The introduction should conclude with a clear summary of the aim and objectives of this study.

Research methods and design: This must address the following:

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

Setting: A description of the setting for the study; for example, the type of community from which the participants came or the nature of the health system and services in which the study is conducted.

Study population and sampling strategy: Describe the study population and any inclusion or exclusion criteria. Describe the intended sample size and your sample size calculation or justification. Describe the sampling strategy used. Describe in practical terms how this was implemented.

Intervention (if appropriate): If there were intervention and comparison groups, describe the intervention in detail and what happened to the comparison groups.

Data collection: Define the data collection tools that were used and their validity. Describe in practical terms how data were collected and any key issues involved, e.g. language barriers.

Data analysis: Describe how data were captured, checked and cleaned. Describe the analysis process, for example, the statistical tests used or steps followed in qualitative data analysis.

Ethical considerations: Approval must have been obtained for all studies from the author's institution or other relevant ethics committee and the institution's name and permit numbers should be stated here.

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

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

Key findings: Summarise the key findings without reiterating details of the results.

Discussion of key findings: Explain how the key findings relate to previous research or to existing knowledge, practice or policy.

Strengths and limitations: Describe the strengths and limitations of your methods and what the reader should take into account when interpreting your results.

Implications or recommendations: State the implications of your study or recommendations for future research (questions that remain unanswered), policy or practice. Make sure that the recommendations flow directly from your findings.

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

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

Also provide the following, each under their own heading:

Competing interests: This section should list specific competing interests associated with any of the authors. If authors declare that no competing interests exist, the article will include a statement to this effect: The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article. **Read our policy on competing interests.**

Author contributions: All authors must meet the criteria for authorship as outlined in the **authorship** policy and **author contribution** statement policies.

Funding: Provide information on funding if relevant

Data availability: All research articles are encouraged to have a data availability statement.

Disclaimer: A statement that the views expressed in the submitted article are his or her own and not an official position of the institution or funder.

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

Case Report full structure

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

Abstract: The abstract should be no longer than 250 words and must be written in the past tense. The abstract should give a concise account of the Introduction, Patient presentation, Management and outcome and significance of the matter. The abstract can be structured and should consist of four paragraphs labelled Introduction, Patient presentation, Management and outcome, and Conclusion.

Introduction: Describe the context and the reason for publishing this patient study.

Patient presentation: Describe your 3-stage assessment of the patient.

Management and outcome: Describe the management plan, progress and final outcome.

Conclusion: Summarise the lessons learnt and key implications or recommendations.

Introduction: Convey clearly what is particularly interesting about the patient that you want to describe to the reader. It is useful to begin by placing the study in a historical or social context. If similar cases have been reported previously, please describe them briefly. Clarify your aim or objectives in publishing this patient study.

Ethical considerations: Papers based on a case study that involves the treatment of humans must adhere to the Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects. Specify the recognised ethics committee from which approval for the case study was obtained; also state the serial number of the ethical clearance. Case studies must have the consent of the patient(s) or waiver of consent approved by an ethics committee.

Patient presentation: Describe your patient in detail with consideration of the following aspects:

Describe the information that was gathered on the patient's medical problem(s) from the consultation, physical examination and results of any investigations.

Describe the information that was gathered on the patient's perspective of their illness (loss of function, ideas, beliefs, concerns, expectations, or feelings)

Describe the information that was gathered on the patient's context (family structure and function, occupational issues, environment)

Provide a 3-stage assessment of the patient's clinical, individual and contextual issues.

Management and outcome: In this section, you should clearly describe the plan for care, as well as the care that was actually provided, how the patient's condition progressed over time and the final outcome.

Discussion: Summarise the key points, lessons learnt and discuss these in relation to the literature. Clarify the implications or recommendations that arise from this patient study.

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Example 3	A.B. developed the theoretical formalism, performed the analytic calculations and performed the numerical simulations. Both A.B and B.C. contributed to the final version of the manuscript. B.C. supervised the project.
Example 4	A.B., B.C., C.D., D.E., E.F., F.G., and G.H. conceived and planned the experiments. A.B., B.C., C.D. and D.E. carried out the experiments. A.B., F.G. and E.F. planned and carried out the simulations. J.K., K.L., A.B., B.C., D.E., C.D., F.J., and F.G. contributed to sample preparation. A.B., B.C., C.D., D.E., FJ, E.F., F.G. and G.H. contributed to the interpretation of the results. A.B. took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.
Example 5	A.B. and B.C. designed the model and the computational framework and analysed the data. A.B. and C.D. carried out the implementation. A.B. performed the calculations. A.B. and B.C. wrote the manuscript with input from all authors. D.E. and E.F. conceived the study and were in charge of overall direction and planning.
Example 6	A.B. designed and performed the experiments, derived the models and analysed the data. B.C. assisted with XYZ measurements and C.D. helped carry out the XYZ simulations. A.B. and D.E. wrote the manuscript in consultation with C.D., B.C. and E.F..
Example 7	A.B. devised the project, the main conceptual ideas and proof outline. B.C. worked out almost all of the technical details, and performed the numerical calculations for the suggested experiment. C.D. worked out the bound for

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Example 8	A.B., B.C. and C.D. designed the study. A.B., D.E. and E.F. performed the XYZ experiments. F.G. and G.H. performed XYZ simulations. I.H. and M.C. expressed and purified all proteins. A.B., H.J., B.C. and C.D. analysed the data. A.B., B.C. and C.D. wrote the paper with input from all authors.
Example 9	A.B. and B.C. designed and directed the project; C.D., D.E., A.B. and B.C. performed the experiments; C.D. and B.C. analysed spectra; A.B. and E.F. made the simulations; B.C. developed the theoretical framework; C.D., A.B. and B.C. wrote the article.
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Example 2	A.B. and B.C. carried out the experiment. A.B. wrote the manuscript with support from C.D.. D.E. and E.F. fabricated the XYZ sample. F.G. and G.H. helped supervise the project. G.H. and H.I. conceived the original idea. H.I. supervised the project.
Example 3	A.B. developed the theoretical formalism, performed the analytic calculations and performed the numerical simulations. Both A.B and B.C. authors contributed to the final version of the manuscript. B.C. supervised the project.
Example 4	A.B., B.C., C.D., D.E., E.F., F.G., and G.H. conceived and planned the experiments. A.B., B.C., C.D. and D.E. carried out the experiments. A.B., F.G. and E.F. planned and carried out the simulations. J.K., K.L., A.B., B.C., D.E., C.D., F.J., and F.G. contributed to sample preparation. A.B., B.C., C.D., D.E., FJ, E.F., F.G. and G.H. contributed to the interpretation of the results. A.B. took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.
Example 5	A.B. and B.C. designed the model and the computational framework and analysed the data. A.B. and C.D. carried out the implementation. A.B. performed the calculations. A.B. and B.C. wrote the manuscript with input from all authors. D.E. and E.F. conceived the study and were in charge of overall direction and planning.
Example 6	A.B. designed and performed the experiments, derived the models and analysed the data. B.C. assisted with XYZ measurements and C.D. helped carry out the XYZ simulations. A.B. and D.E. wrote the manuscript in consultation with C.D., B.C. and E.F..
Example 7	A.B. devised the project, the main conceptual ideas and proof outline. B.C. worked out almost all of the technical details, and performed the numerical calculations for the suggested experiment. C.D. worked out the bound for quantum mechanics, with help from D.E.. E.F. verified the numerical results of the xyz by an independent implementation. F.G. and G.H. proposed the xyz experiment in discussions with A.B.. B.C., C.D., G.H. and A.B. wrote the manuscript.
Example 8	A.B., B.C. and C.D. designed the study. A.B., D.E. and E.F. performed the xyz experiments. F.G. and G.H. performed XYZ simulations. I.H. and M.C. expressed and purified all proteins. A.B., H.J.., B.C. and C.D. analysed the data. A.B., B.C. and C.D. wrote the paper with input from all authors.
Example 9	A.B. and B.C. designed and directed the project; C.D., D.E., A.B. and B.C. performed the experiments; C.D. and B.C. analysed spectra; A.B. and E.F. made the simulations; B.C. developed the theoretical framework; C.D., A.B. and B.C. wrote the article.

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Data openly available in a public repository that does not issue DOIs	The data that support the findings of this study are openly available in [repository name] at [URL], reference number [reference number].
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Author Guidelines

General

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The maximum word-length for reports of original research is 3000 words excluding tables, figures, references and summary. We encourage submission of additional supporting material

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Format

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Journal article:

1**.** King VM, Armstrong DM, Apps R, Trott JR. Numerical aspects of pontine, lateral reticular, and inferior olivary projections to two paravermal cortical zones of the cat cerebellum. J Comp Neurol 1998;390:537-551.

Book:

2. Voet D, Voet JG. Biochemistry. New York: John Wiley & Sons; 1990. 1223 p.

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AMA (American Medical Association) Reference Style

In-Text Examples:

Diabetes mellitus is associated with a high risk of foot ulcers.[1-3]

Several interventions have been successful at increasing compliance.[11,14-16]

The data of Smith et al[18] is further evidence of this effect.

As reported previously,[1,3-6]

The results were as follows[4]:

Reference List Examples:

Journal article (1-6 authors):

1. Hu P, Reuben DB. Effects of managed care on the length of time that elderly patients spend with physicians during ambulatory visits. *Med Care.* 2002;40(7):606-613.

Journal article with more than 6 authors:

2. Geller AC, Venna S, Prout M, et al. Should the skin cancer examination be taught in medical school? **Arch Dermatol**. 2002;138(9):1201-1203.

Journal article with no named author or group name:

3. Centers for Disease Control and Prevention (CDC). Licensure of a meningococcal conjugate vaccine (Menveo) and guidance for use--Advisory Committee on Immunization Practices (ACIP), 2010. **MMWR Morb Mortal Wkly Rep**. 2010;59(9):273.

Electronic Journal article:

If you have a doi (preferred):

4. Gage BF, Fihn SD, White RH. Management and dosing of warfarin therapy. **Am J Med**. 2000;109(6):481-488. doi:10.1016/S0002-9343(00)00545-3.

If you do not have a doi:

5. Aggleton JP. Understanding anterograde amnesia: disconnections and hidden lesions. **Q J Exp Psychol**. 2008;61(10):1441-1471. http://search.ebscohost.com/login.aspx?direct=true&db=pbh&AN=34168185&site=ehost-live. Accessed March 18, 2010.

Journal article published online ahead of print:

6. Chau NG, Haddad RI. Antiangiogenic agents in head and neck squamous cell carcinoma: tired of going solo [published online ahead of print September 20, 2016]. *Cancer*. doi: 10.1002/cncr.30352.

Entire Book:

6. McKenzie BC. Medicine and the Internet: Introducing Online Resources and Terminology. 2nd ed. New York, NY: Oxford University Press; 1997.

Book Chapter:

7. Guyton JL, Crockarell JR. Fractures of acetabulum and pelvis. In: Canale ST, ed. *Campbell's Operative Orthopaedics*. 10th ed. Philadelphia, PA: Mosby, Inc; 2003:2939-2984.

Electronic Book:

8. Rudolph CD, Rudolph AM. *Rudolph's Pediatrics.* 21st ed. New York, NY: McGraw-Hill Companies; 2002. http://online.statref.com/Document/Document.aspx?DocID=1&StartDoc=1&EndDoc=1882&FxID=13&offset=7&SessionId=A3F279FQVVFXFSXQ . Accessed August 22, 2007.

Internet Document:

9. American Cancer Society. Cancer Facts & Figures 2003. http://www.cancer.org/downloads/STT/CAFF2003PWSecured.pdf. Accessed March 3, 2003.

NOTES:

- If there are more than 6 author names in a reference, the first 3 author names are retained with “et al” (set in roman).
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- Colon is used between the volume number and the page range.
- Full page range is used.
- End period at the end of a reference.
- Place of publication is given first followed by publisher name.
- Colon is used between the publisher location and the publisher name.
- Year of publication is given after the publisher name, separated by a semicolon.
- Chapter title is set in roman and sentence case.
- Book title is set in italics and title case.
- Query is raised for page range if it is not given.
- Date of last access is required for Web site citations.

ANNEXURE D: LANGUAGE EDITING

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Editing & translating – English/Afrikaans

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5 March 2021

To Whom It Might Concern

CONFIRMATION OF LANGUAGE EDITING

I hereby confirm that I, Elzet Blaauw, have edited the following sections of Tiffany Erasmus' MPharm dissertation: Acknowledgements, Preface, Authors' Contributions to Manuscript 1 and 2, Abstract, List of Abbreviations and Acronyms, List of Definitions, Chapter 1, Chapter 2, Manuscript 1 in Chapter 3 and Chapter 4.

All changes and suggestions were done with the MS Word track changes function and can be requested if necessary.

I confirm that I am a professional language practitioner. I have obtained an MPhil degree in Translation and Editing (cum laude, 2012) from Stellenbosch University, and I am a member of the Professional Editors' Guild (www.editors.org.za). I have nine years' experience editing academic research documents.

Please do not hesitate to contact me with any further queries.

Kind regards



Elzet Blaauw

ANNEXURE E: TECHNICAL EDITING

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Phone: 0834755363

5 March 2021

TO WHOM IT MAY CONCERN

I hereby declare that the proposal titled:

Profile of South African HIV/AIDS patients in a medical scheme environment

by

T Erasmus

21975310

has been technically edited by myself, which includes all tables and figures as well as the layout of the document's contents.

E Oosthuizen

March 2021