



Usage of central nervous system medication in HIV/AIDS patients: Longitudinal analysis (2005-2015) of prevalence and prescribing pattern changes

F Wafawanaka

 orcid.org/0000-0003-1300-7490

BPharm

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Supervisor: Prof MS Lubbe

Co-supervisor: Mrs I Kotzé

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PREFACE

This dissertation was written in the format of an article. Chapter 3 contains the results of the empirical investigation, written in the form of two manuscripts. The two manuscripts are prepared for submission to the following journals for publication:

- *The African Journal of Infectious Diseases*
- *Social Psychiatry and Psychiatric Epidemiology*

Both of the manuscripts and their references were written in accordance to the author guidelines specified by the respective journals (Annexures J and K). However, the complete reference list of the dissertation is listed according to the referencing style of the North-West University.

The dissertation is divided into four chapters. Chapter 1 provides an overview of the study and problem statement, research aims and objectives, as well as a description of the method followed to conduct the empirical investigation. Chapter 2 is a comprehensive literature review to fulfil the literature objectives stated for this study. Chapter 3 contains the two manuscripts that answer the empirical objectives. The final chapter concludes this study, providing future recommendations, study limitations and strengths. References and annexures are provided at the end of the dissertation.

The contributions of each author for both manuscripts are subsequently outlined.

AUTHORS' CONTRIBUTIONS TO MANUSCRIPT 1

The contributions of each author for manuscript 1, “Changes in the incidence and prevalence of HIV/AIDS in the South African medical schemes environment from 2005 to 2015”, were as follow:

Author	Role in study
Mr F Wafawanaka	Planning and designing and implementation Data and statistical analysis Data interpretation Writing of the manuscript and dissertation
Prof MS Lubbe (Supervisor)	Supervision of study and manuscript concept Data and statistical analysis Guidance and interpretation of the results Revising and approval of the final manuscript and dissertation
Mrs I Kotzé (Co-supervisor)	Co-supervision of study and manuscript concept Guidance and interpretation of the results Revising and approval of the final manuscript version
Mrs M Cockeran (Statistician)	Data and statistical analysis Verifying the results from the statistical analysis Revising and approval of the final manuscript version

With the following statement the co-authors confirm their role in the study and give their permission that the manuscript may form part of this dissertation.

I declare that I have approved the above mentioned manuscript and that my role in this study, as indicated above, is representative of my actual contributions and I hereby give my consent that it may be published as part of the MPharm study of F Wafawanaka.



Prof MS Lubbe



Mrs M Cockeran



Mrs I Kotzé

AUTHORS' CONTRIBUTIONS TO MANUSCRIPT 2

The contributions of each author for manuscript 2, “**Prescribing patterns of central nervous system medication in HIV/AIDS patients in the private healthcare sector in South Africa: 2005-2015**”, were as follow:

Author	Role in study
Mr F Wafawanaka	Planning, designing and implementation of the study Data and statistical analysis Data interpretation Writing of the manuscript and dissertation
Prof MS Lubbe (Supervisor)	Supervision of study and manuscript concept Data and statistical analysis Guidance and interpretation of the results Revising and approval of the final manuscript and dissertation
Mrs I Kotzé (Co-supervisor)	Co-supervision of study and manuscript concept
Mrs M Cockeran (Statistician)	Data and statistical analysis Verifying the results from the statistical analysis Revising and approval of the final manuscript version

With the following statement the co-authors confirm their role in the study and give their permission that the manuscript may form part of this dissertation.

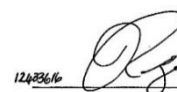
I declare that I have approved the above mentioned manuscript and that my role in this study, as indicated above, is representative of my actual contributions and I hereby give my consent that it may be published as part of the MPharm study of F Wafawanaka.



Prof MS Lubbe



Mrs M Cockeran



Mrs I Kotzé

ABSTRACT

Title: Usage of central nervous system medication in HIV/AIDS patients: Longitudinal analysis (2005-2015) of prevalence and prescribing pattern changes.

Keywords: Incidence; prevalence; HIV/AIDS; central nervous system medication, HIV/AIDS, neurological disorders, private health sector, South Africa

The treatment of HIV/AIDS and coexisting psychiatric disorders is critical to the wellbeing of patients. There is currently a dearth of information on the scope of prescribing of central nervous system (CNS) medication among HIV-infected individuals in the South African private health sector, specifically the medical scheme environment.

The general aim of the study was to determine possible changes in the prevalence and incidence rates of HIV/AIDS, and prescribing patterns of CNS medication in HIV/AIDS patients from 1 January 2005 to 31 December 2015 in the private health sector of South Africa. Retrospective medicine claims data from a pharmaceutical benefit management (PBM) company were used. The outcomes of the study will be presented in two manuscripts.

Manuscript 1 conveyed on the findings of the investigation into the trends in the incidence and prevalence rate of HIV/AIDS patients. An open cohort of all patients with a diagnosis code for HIV/AIDS (ICD-10 codes B20-B24) and who claimed antiretroviral medication was used. Both HIV/AIDS incidence and prevalence rates were measured per 1 000 medical scheme beneficiaries for each year. Data were stratified by gender, age group and province.

A total of 1 213 676 and 843 972 patients claimed medicine items in 2005 and 2015, respectively. In 2005, 0.63% ($n = 7\ 665$) of patients on the PBM database were HIV/AIDS patients and 2.10% ($n = 17\ 302$) in 2015. The prevalence rate of HIV/AIDS increased 3.3 times [6.3 (2005) to 20.5 (2015) per 1 000 medical scheme beneficiaries]. The incidence rate of HIV/AIDS also increased 2.3 times from 3.9 in 2006 to 9.1 per 1 000 medical scheme beneficiaries in 2015.

The prevalence rate of HIV/AIDS among females had increased by more than three times over the study period, with a prevalence rate of 20.4 per 1 000 medical scheme beneficiaries in 2015. During the same period, the incidence rate of HIV/AIDS in female patients doubled, from 4.0 per 1 000 female medical scheme beneficiaries in 2006 to 8.5 in 2015, whereas the incidence rate among males rose from 3.9 in 2006 to 9.9 per 1 000 medical scheme beneficiaries in 2015. The age group ≥ 40 and < 60 years had the highest HIV/AIDS prevalence rates of 14.4 in 2005 and 38.3 in 2015. This was followed by age group ≥ 60 and < 70 years. The age group ≥ 0 and < 6 years had the lowest HIV/AIDS prevalence rate. In the age group ≥ 18 and < 40 years, the HIV/AIDS

prevalence rate increased by 2.9 per 1 000 medical scheme beneficiaries between 2005 and 2015. The age group ≥ 40 and < 60 years had the highest HIV/AIDS incidence rate of eight in 2006 and 18 per 1 000 medical scheme beneficiaries in 2015.

Gauteng had the highest HIV/AIDS prevalence rate (422.4 per 1 000 medical scheme beneficiaries), followed by the Western Cape (149.4), and KwaZulu-Natal (118.4) in 2015. This study undoubtedly indicates an upward trend in the diagnosis and treatment of HIV/AIDS in the private medical scheme environment of South Africa from 2005 to 2015.

Manuscript 2 reported the findings of the investigation into the prescribing patterns of CNS medication in HIV/AIDS patients. A longitudinal research design was followed to analyse retrospective CNS medicine claims data from a closed cohort (N = 308) of HIV/AIDS patients (identified with ICD-10 codes B20-B24) obtained from a PBM company's database. Measures used to analyse CNS prescribing patterns were: i) differences between 2005 and 2015 in the prescribing of active pharmaceutical ingredients according to pharmacological and sub-pharmacological groups; ii) changes in mean number of medicine items per prescription per patient from 2010 to 2015; and iii) changes in the mean number of prescriptions per patient from 2010 to 2015, stratified per gender group.

The results indicated that 86.68% of patients, including 144 (53.93%) females and 123 (46.07%) males, claimed one or more CNS prescriptions from 2005 to 2015. No associations were found between gender and the possibility to claim a CNS medication. The mean number of items per prescription per patient increased marginally from 2005 (1.22 (0.46) [1.15-1.28]) to 2015 (1.25 (0.59) [1.16-1.33]) ($P = 0.0004$; Cohen's < 0.8). The mean number of prescriptions per patient did not change significantly from 1.56 (1.57) (1.34-1.78) in 2005 to 1.93 (2.11) [1.65-2.22] in 2015 ($P > .05$).

The majority of patients received an antidepressant during 2005 (49.68%) and 2015 (73.05%), with selective serotonin re-uptake inhibitors (15.26% vs. 25.00%) as the most prescribed antidepressant sub-pharmacological group for 2010 and 2015, respectively, followed by tricyclics (14.29% vs. 19.81%) and tetracyclic antidepressants (6.82% vs. 12.99%). Amitriptyline was the most prescribed individual active ingredient prescribed in 2015 (14.61%). The prescribing of bupropion, a tetracyclic antidepressant, had increased significantly (1.3% vs. 6.82%) from 2005 to 2015 ($P = 0.0007$). The number of patients who received a sedative hypnotic, an anxiolytic or an anti-epileptic drug also increased with 45.0%, 54.55% and 89.94%, respectively, over the study period.

This study indicates various prescribing patterns of CNS medication prescribing in privately-insured HIV/AIDS patients, for example an increase in the prescribing of antidepressants, sedative hypnotics, anxiolytics and anti-epileptic drugs that should be further investigated.

LIST OF ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
APV	Amprenavir
ART	Antiretroviral therapy
ART-CC	Antiretroviral Therapy Cohort Collaboration
ARV(s)	Antiretrovirals
ASSA	Actuarial Society of South Africa
ATV	Atazanavir
ATV/r	Atazanavir/ritonavir
AZT	Zidovudine
BBC	Global Business Council
BCG vaccine	Bacillus Calmette-Guerin vaccine
CCR5	C-C chemokine receptor type 5
CD4	Cluster of differentiation 4
CD8	Cluster of differentiation 8
CDC	Center for Diseases Control and Prevention
cDNA	Combination DNA
CHARTER	Central Nervous System HIV antiretroviral therapy effects research
CI	Confidence interval
CMS	Council of Medical Schemes
CNS	Central nervous system
COBI or c	Cobicistat
COHERE	Collaboration of Observational HIV Epidemiological Research in Europe
COPD	Chronic obstructive pulmonary disease
CrAg	Cryptococcal antigen
CXCR4	Alpha chemokine receptor
CYP	Cytochrome P450
d4T	2', 3' dideoxy- 3' dideoxythymidine (Stavudine)

List of abbreviations and acronyms (continued)

ddl	Didanosine
DDI	Drug-drug interaction
DHHS	Department of Health and Human Sciences
DLV	Delavirdine
DNA	Deoxyribonucleic acid
DRV	Darunavir
DTG	Dolutegravir
DUR	Drug utilisation review
EC	Eastern Cape
EFV	Efavirenz
EPI	Expanded programme on immunization
ETR	Etravirine
EVG	Elvitegravir
FDA	Food and Drug Administration of United States of America
FDC	Fixed dose combination
FPV	Fosamprenavir
GBD	Global burden of disease
GEE	Generalized estimating equation
GP	General practitioner
HAART	Highly active antiretroviral therapy
HAD	HIV-associated dementia
HAND	HIV-associated neurocognitive disorder
HCA	Heterocyclic antidepressant
HIV	Human immunodeficiency virus
HPTN	HIV Prevention Trials Network
HREC	Health Research Ethics Committee
HTC	HIV testing and counselling
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10 th revision
IDV	Indinavir
IL-1	Interleukin-1

List of abbreviations and acronyms (continued)

INN	Enfuvirtide
IQR	Interquartile range
IR	Incidence rate
IRIN	Integrated Regional Information Networks
JC virus	John Cunningham virus
KS	Kaposi's sarcoma
KZN	KwaZulu Natal
LMICs	Low and middle income countries
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
MAOI	Monoamine oxidase inhibitor
MDD	Major depressive disorder
MIMS®	Monthly Index of Medicines Specialties
MPR	Medicine possession ratio
MTCT	Mother to child transmission
MUSA	Medicine Usage in South Africa
MVC	Maraviroc
NAPPI	National Pharmaceutical Product Index
NDOH	National Department of Health
NFV	Nelfinavir
NGO	Non-governmental organisation
NRTI	Nucleoside/nucleotide reverse transcriptase inhibitor
NVP	Nevirapine
NWU	North West University
OI	Opportunistic infection
PBM	Pharmaceutical Benefit Management
PCR	Polymerase chain reaction
PEPFAR	The U.S. President's Emergency Plan for AIDS Relief

List of abbreviations and acronyms (continued)

PI	Protease inhibitor
PLWHIV	People living with HIV
PMB	Prescribed minimum benefit
PMTCT	Prevention of mother to child transmission
PrEP	Pre-exposure prophylaxis
PTSD	Post-traumatic stress disorder
RAL	Raltegravir
RDD	Recommended daily dose
RNA	Ribonucleic acid
RPV	Rilprvirine
RTCHS	Right to Care Health Services
RTV or r	Ritonavir
SA	South Africa
SABCOHA	South African Business Coalition on Health and AIDS
SAE	South Africa Economist
SAHPRA	South African Health Regulatory Authority
SAMF	South African Medicines Formulary
SANAC	South African National AIDS Council
SAS®	Statistical Analysis System
SD	Standard deviation
SNRI	Serotonin norepinephrine reuptake inhibitor
SQV	Saquinavir
SSRI	Selective serotonin reuptake inhibitor
START	Strategic timing of antiretroviral treatment
Stats SA	Statistics South Africa
STD	Sexually transmitted disease
STI	Sexually transmitted infection
<i>T. gondii</i>	<i>Toxoplasma gondii</i>
TAF	Tenofovir alafenamide
TB	Tuberculosis
TCA	Tricyclic antidepressant
T-cell	Thymus cell

List of abbreviations and acronyms (continued)

TDF	Tenofovir disoproxil fumarate
TEMPRANO ANRS	Trial of early antiretroviral and isoniazid preventive therapy in Africa
TNF- α	Tumor necrosis factor alpha
TPV	Tipranavir
UCSF	University of California, San Francisco
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNDP	United Nations Development Programme
UNICEF	United Nations International Children's Emergency Fund
USA	United States of America
USAID	United State Agency for International Development
UTT	Universal test and treat
VL	Viral load
WHO	World Health Organization
ZDV	Zidovudine

LIST OF DEFINITIONS

Antiretroviral drug

An antiretroviral (ARV) drug is a medication that is used to treat infection by retroviruses, primarily HIV (Institute of Medicine, 2005). There are currently 5 classes of ARV drugs (entry inhibitors, nucleoside reverse transcriptase, non-nucleoside reverse transcriptase, integrase inhibitors and protease inhibitors), each of which inhibits a specific stage in the HIV life cycle (Institute of Medicine, 2005). Each class of ARV drug acts at different stages of the HIV life cycle. A combination of certain (typically three or four) ARV drugs prescribed together is known as highly active antiretroviral therapy (HAART).

Chronic disease

Chronic diseases are also known as 'non-communicable diseases', generally progress slowly with long-lasting effects and are not contagious/transmissible (Bobrow & Ehrlich, 2014:248).

Chronic disease list (CDL) conditions

The CDL of South Africa comprises of 26 chronic/non-communicable diseases and HIV/AIDS. These are chronic conditions for which a patient's medical scheme, by law, not only has to cover the medication costs, but also the costs of physicians' consultations and tests related to the condition (Council for Medical Schemes (CMS), 2010a; CMS, 2010b).

Comorbidity

For the purposes of this study, the term 'comorbidity' describes a medical condition that is present at the time of, or after, diagnosis of an index disease (in this study HIV/AIDS), without implying that the coexisting medical condition is an outcome or the result of the index disease (Almirall & Fortin, 2013: 4).

Diagnosis

Diagnosis is a process of identifying the nature of a cause of a disease and it could be medical, clinical, differential, nursing and physical in nature (The Free dictionary, 2018).

Highly active antiretroviral therapy

Highly active antiretroviral therapy (HAART) are medication used to treat HIV infection. The HAART also known as combination antiretroviral therapy (cART) is made up of three or more antiretroviral drugs which are capable of suppressing viral replication, improve immune function and delay clinical deterioration (Institute of Medicine, 2005:).

International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10)

The International Classification of Diseases is the basis for the international standard for reporting diseases and health conditions. It is generally used for the identification of health trends and statistics regarding diseases, disorders, injuries and other related health condition. (WHO, 2016c; WHO, 2018).

Prescribed minimum benefits (PMBs)

The prescribed minimum benefits in the South African context is a “set of defined benefits to ensure that all medical scheme members have access to certain minimum health services, regardless of the benefit option they have selected” (CMS, 2010a; CMS, 2010b).

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CHAPTER 1: INTRODUCTION AND OVERVIEW

1.1 INTRODUCTION

The focus of this study is on investigating possible changes in the prevalence of Human Immunodeficiency Virus / Acquired Immunodeficiency Syndrome (HIV/AIDS), and prescribing patterns of central nervous system (CNS) medicines in HIV/AIDS patients over the study period, 2005 to 2015, in the South African private health sector.

This chapter includes the background and problem statement, research aims and objectives, research methodology applied, data source and analysis, criteria for the study population and ethical considerations applicable to this study. Chapter 1 concludes with the division of the contents of the following chapter.

1.2 BACKGROUND AND PROBLEM STATEMENT

The Human Immunodeficiency Virus (HIV) infection is a major public health problem globally. The Joint United Nations Programme on HI/AIDS (UNAIDS) has estimated that, globally, 36.7 million [30.8 million to 42.7 million] people are living with HIV and, of these infected individuals, only 53% [39-65%] receive treatment (UNAIDS, 2016:3). UNAIDS recorded 19.5 million people receiving antiretroviral treatment (ART) (UNAIDS, 2016:5). In 2016, 1.8 million [1.6 million to 2.1 million] people became newly infected with HIV and 1 million (830 000 to 1.2 million] died from AIDS-related conditions (UNAIDS, 2016:3).

Sub-Saharan Africa is the worst affected region in the world with 25.4 million (64.5%) of the HIV/AIDS infected people at the end 2015, but the region has just over 10% of the world's population (WHO, 2016b). More than 54% of individuals who have HIV do not know that they have the virus (UNAIDS, 2015b:1).

Statistics South Africa (2018:1) estimated that the total number of people living with HIV in South Africa has grown from 4.72 million in 2002 to 7.52 million in 2018. The estimated overall HIV prevalence rate is approximately 13.1% among the South African population. For 2018, an estimated 19.0% of adults aged 15 to 49 years are HIV positive. 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 alone had nearly 3.9 million people on treatment, more than any other country in the world (UNAIDS, 2017b:40).

South Africa's prevalence rate varies across all the provinces, with KwaZulu-Natal having a prevalence rate of 17%, Mpumalanga and the Free State 14.0% each, the North West 13.3%, the Western Cape 5.0%, Limpopo 9.2% and the Northern Cape 7.4% (Shisana *et al.*, 2014:36). The country's overall prevalence rate of HIV infection has increased probably due to the massive expansion of the antiretroviral treatment (ART) programme (Shisana *et al.*, 2014:124). There is no vaccine and no cure for HIV/AIDS (Ferrando *et al.*, 2003:208; Castelnovo *et al.*, 2016:5). Once HIV/AIDS takes hold within a population, its grave consequences begin to emerge. The most productive age groups are hardest hit, thereby destabilising the country's economy and leaving millions of orphaned children (UNAIDS, 2005:2).

Prevention and treatment are the two approaches that can be used to manage HIV/AIDS. Many public health programmes in developing countries have emphasised prevention measures over treatment provision primarily because they are less expensive despite the existence of highly active antiretroviral treatment (HAART) (Ferrando *et al.*, 2003:209).

Rispel and Metcalf (2009:133) reported that HIV can easily be transmitted among men who have sex with men. Major contributory factors in spreading HIV in South Africa are poverty, inequality, social unrest, sexually transmitted infections, low status of women, sexual violence, migrant labourers, limited and uneven access to medical care and a history of poor leadership in response to the epidemic (South Africa National AIDS Council, 2012).

Psychiatric disorders are common in people living with HIV (PLWHA) (Els *et al.*, 1999:994). Mathers and Loncar (2006:2022) reported a prevalence rate of 15% of all disability-adjusted-life-years to be caused by neuropsychiatric disorders. In 2010, mental, neurological and substance use disorders accounted for more than 10% of global disability adjusted life years, 2.3% of global years lost to premature mortality, and 28.5% of global years lived with disability (Whiteford *et al.*, 2015:1). The effects of neuropsychiatric disorders and HIV can cause non-adherence to AIDS treatment, and this is supported by the literature (Chandra *et al.*, 2005:451).

According to Grant (2008:33), HIV infection can affect all systems in the human body, including the central nervous system (CNS). The human brain is destroyed during the early stages of infection (An *et al.*, 1999:1156). Treatment of HIV/AIDS depends largely on the suppression of a patient's viral load (VL), because morbidity from immune destruction is directly correlated with the concentration of HIV particles (Nachega *et al.*, 2007:564). When individuals do not adhere to their treatment regimens, the drugs fail to inhibit HIV and increase the patient's VL. This incomplete suppression of HIV in non-adherent patients has several serious implications for the individual level and eventually for public health as a whole (An *et al.*, 1999:1156).

Two types of HIV strains have been identified in the early and late 1980s, such as HIV-1 (Barré-Sinoussi *et al.*, 1983:868) and HIV-2 (Clavel *et al.* 1986:343). The HIV-1 strain destroys the cluster differential four (CD4) T-lymphocytes, leading to an immune compromised individual who is prone to any infection (Gurunathan *et al.*, 2009:1997). The disease progression follows four clinical HIV-1 infection phases, namely WHO HIV clinical stage 1 (the acute phase), WHO HIV clinical stage 2 (moderate unexplained weight loss phase), WHO HIV clinical stage 3 (chronic or clinical latent phase), and WHO HIV clinical stage 4 (HIV wasting syndrome phase) (Grossman *et al.*, 2006:289; Gupta *et al.*, 2007:546; Philips, 2004:51).

While the initial stage of the disease manifests itself with symptoms similar to the common cold, i.e. headache, general body pain and weakness, rash, anorexia and diarrhoea, the HIV infection steadily grows in strength and severity (Grossman *et al.*, 2006:289). Eventually, it incapacitates the majority of CD4-positive T-cells (CD4), which are crucial to the functioning of the immune system as a whole and this stage is characterised by a rate of rapid viral multiplication (Pilcher *et al.*, 2004:1785). The findings from Grossman *et al.* (2006:289) revealed that many newly infected HIV positive people develop fever, malaise and lymphadenopathy from 15 to 90 days post-exposure.

The WHO HIV clinical stage 2 is asymptomatic. The VL ranges from undetectable to significant levels (Lyles *et al.*, 200:872). During this phase, severe opportunistic infections and neoplasms develop (Pilcher *et al.*, 2004:1785; Grossman *et al.*, 2006:289).

The WHO HIV clinical stage 3 is marked by a further deterioration of the body (Ray *et al.*, 2010:123). Mutant HIVs are produced in this phase and this makes the destruction of the virus by antiretroviral drugs (ARVs) difficult (Severe *et al.*, 2010:257). The major symptoms of this phase are severe weight loss, Kaposi's sarcoma, unexplained chronic diarrhoea, persistent fever, severe bacterial infections and anaemia; and patients in this phase are more prone to tuberculosis infection (Weeks & Alcamo 2006:81). Without ART, the VL keeps on increasing, eventually leading to death (Severe *et al.*, 2010:257).

The proper diagnosis depends on several factors, but when the CD4 cell count is less than 200 cells/ μ L, individuals are generally diagnosed with AIDS (Centre for Disease Control and Prevention (CDC), 1993:6). During the WHO HIV clinical stage 4, HIV infection progresses to AIDS and the period from initial HIV infection to AIDS is approximately 10 to 12 years (Severe *et al.*, 2010:257). Without treatment, HIV/AIDS results in death (Nachega *et al.*, 2007:564).

The five major therapeutic classes of ARVs are non-nucleotide reverse transcriptase inhibitors (NNRTI), nucleoside reverse transcriptase inhibitors (NRTI), protease inhibitors (PI), neuraminidase inhibitors and antiretroviral combinations (Rossiter, 2014:335).

The use of three or more ARV drugs from at least two of the classes is termed highly-active antiretroviral treatment (HAART) (Institute of Medicine, 2005:1). Highly-active antiretroviral treatment has transformed HIV/AIDS into a manageable chronic disease instead of an acutely lethal infection, and the number of people dying from HIV/AIDS-related deaths decreased by more than 43% in the United States of America between 1995 and 1997 (Institute of Medicine, 2005:2). Antiretroviral treatment is regarded as a reference treatment for HIV/AIDS (Rossiter, 2014:365). There is no cure for AIDS (Castelnuovo *et al.*, 2016:5), but combinations of ARV drug regimens can help to decrease the progression of the disease (Braitstein *et al.*, 2006:817). Ray *et al.* (2010:123) furthermore showed a lowering in plasma VL as well as a decrease in the incidence of tumours and deaths. However, this positive outcome of HAART did not have the same effect in reducing the death toll in many developing countries, such as sub-Saharan Africa (Nachega *et al.*, 2007:566).

The transmission of HIV occurs through the exchange of bodily fluids that harbour high enough concentrations of the virus (Tovanabutra *et al.*, 2002:275). The same study investigated the transmission of HIV between positive husbands and wives and supports the argument that higher VL increases the probability of transmission. Volmink *et al.* (2007:12) found out that mothers who were taking ARVs had a low VL and vertical transmission rates decreased from mother to child during breastfeeding. The results from another study done by Cohen *et al.* (2011:493) showed that early initiation of ART can reduce the rate of sexual transmissions of HIV. Katende-Kyenda *et al.* (2011:322) reported that if optimal adherence is maintained, the quality-of-life improves and the spread of HIV throughout the population will decrease.

Despite all the therapeutic achievements that have been recorded in the last decade, the total elimination of the HIV from the body is yet to be achieved (Cohen & Gray, 2010:85). In addition to that, Arshad *et al.* (2009:1) reported that ARVs are toxic substances.

The main goals of ARTs are:

- Maximal and durable suppression of the replication of HIV.
- Restoration and or prevention of immune function.
- Reduction of HIV-related comorbidity and mortality.

- Improvement in the quality of life.

South Africa's ART programme has linked more than 80% of all people diagnosed with HIV to access appropriate treatment, care and support between 2009 and 2011 (HSRC, 2014). According to the current guidelines, ART is given regardless of CD4 count (Rossiter, 2014:341).

According to the Research and Monitoring Unit of the South African Medical Council (2018:8), HIV/AIDS was ranked the fourth chronic condition in terms of prevalence of the chronic disease list conditions. Between 2011 and 2016, treated HIV/AIDS prevalence in the private medical schemes environment increased by approximately 156.31%, which presented an average growth rate of approximately 20.71% per year for the period under review. The treated HIV/AIDS prevalence increased from 16.40 per 1 000 beneficiaries in 2015 to 22.08 per 1 000 beneficiaries in 2016, which is mostly attributable to certain medical schemes correcting their reporting of HIV/AIDS prevalence.

More than 1.5 million were treated in the public sector and 390 000 were from the private health sector in 2013 (Kanabas, 2016). In July 2013, the fixed-dose regimen was introduced in South Africa as a first-line regimen to reduce pill burden and to improve retention and adherence of HIV-positive patients (IRIN Africa, 2012:2). The South African government is financing the ART programme in the public sector by injecting more than R15 billion annually (Maurice, 2014).

Globally, psychiatric comorbidities contribute to approximately 10% of the global burden of disease (Murray *et al.*, 2013:2197). The burden of psychiatric disorders is expected to double by 2030 (Murray *et al.*, 2013:2198). Mathers and Loncar (2006:2022) projected an increase in psychiatric disorders due to non-communicable diseases.

According to Beyenburg *et al.* (2005:166), the combination of HIV/AIDS and psychiatric disorders is common. A strong relationship linked to psychiatric disorders and HIV infection was reported by Chandra *et al.* (2005:451).

Living with HIV/AIDS can contribute to mental neurological and substance abuse (MNS), and the problem is common in many developing countries such as South Africa (Jack *et al.*, 2014:8). Psychiatric disorders can be influenced by neurocognitive disturbances, opportunistic infections, medication side effects, suboptimal treatment adherence, stigma, substance abuse and the course of HIV infection (Nebhinani *et al.*, 2011:449). The study that was done in 2000 revealed that MNS was the third major cause of death in South Africa (Norman *et al.*, 2006:3).

Unfortunately, relatively little is understood about the medicine treatment patterns of people with HIV/AIDS and psychiatric comorbidities in the South African private sector, and there are few guidelines that have been developed for clinicians to treat patients with co-morbidities.

Table 1-1 shows the mental neurological and substance abuse (MNS) disorders in the top 20 leading causes of lost life years (Williams *et al.*, 2007:845; Herman *et al.*, 2009:339; Kessler *et al.*, 2009:23).

Table 1-1: Prevalence of mental neurological and substance abuse in low- and middle-income countries

MNS disorder	Lifetime prevalence South Africa (%)	12-month prevalence South Africa (%)	Lifetime prevalence China (%)	Lifetime prevalence Nigeria (%)
Anxiety disorders	15.8	8.1	4.8	6.5
Substance use disorders	13.3	5.8	4.9	3.7
Mood disorders	9.8	4.9	3.6	3.3
Any disorder	30.3	16.5	13.2	12.0

The new onset of psychotics is common in HIV infection (Harris *et al.*, 1991:369; Chandra *et al.*, 2005:455). Delirium occurs frequently in HIV/AIDS patients and is caused by the underlying infection (Chandra *et al.*, 2005:455).

Cook *et al.* (2002:401) reported complications in the diagnosis of HIV in patients taking antidepressants. Co-existing conditions such as major depression disorder can lead to someone committing suicide (Badiee *et al.*, 2012:993). Lund *et al.* (2013:845) reported that poverty can cause depression and anxiety among people.

Antiretroviral drugs such as efavirenz (EFV) and nevirapine (NVP) were reported to cause psychiatric side effects (Wise *et al.*, 2002:879; Poulsen & Lublin, 2003:451). Maggi and Halman (2001:359) reported that valproate increased the replication of HIV-1 in vitro. The mentally ill patients have difficulties in adhering to HAART (Cook *et al.*, 2002:401; Freeman & Thom, 2006:6). The WHO (2008:3) also affirmed the vulnerability of HIV/AIDS patients with psychiatric disorders that may interfere with the ability to gain or use information about HIV/AIDS. Collins *et al.* (2006:1571) reported that depression can result in worse outcomes for HIV/AIDS patients, and those with anxiety, mood disorders and substance abuse disorders. Depression and other mental disorders can cause suboptimal treatment and adherence in HIV/AIDS patients (Cook *et al.*,

2002:401). Imipramine and fluoxetine showed efficacy with no negative effects in HIV/AIDS patients taking ARV drugs (Rabkin *et al.*, 1994:516).

The treatment of HIV/AIDS and comorbid psychiatric disorders is critical to the wellbeing of a patient. Most psychiatric drugs are tolerated in conjunction with ART. However, psychiatric drugs can interact with ARVs (Ammassari *et al.*, 2004:394). Some cognitive disorders and dementia can be caused by viral infections in the central nervous system (Cournos & Forstein, 2000:3; Milton *et al.*, 2000:4).

There is a dearth of information on the effects of CNS medication in HIV/AIDS patients and MNS conditions (Beyenburg *et al.*, 2005:166; Jack *et al.*, 2014:8). Despite the increasing prevalence rates of both MNS and HIV infection in sub-Saharan Africa, little is known about the prescribing patterns of CNS medication among HIV-infected individuals in the South African private health sector. Therefore, more relevant data need to be collected in order to suggest specific treatment regimens for psychiatric comorbidities in HIV/AIDS patients.

The findings highlighted in the searched literature are significant and thought provoking in terms of prevalence of psychiatric comorbidity issues among HIV/AIDS patients. There is also a lack of information about the use of CNS medication for psychiatric disorders co-existing with HIV/AIDS in the private health sector in South Africa. This merits further research in the private healthcare sector of South Africa.

- What is the prevalence and incidence rate of HIV/AIDS globally, in Africa and in SA?
- What is the prevalence rate of psychiatric co-morbidities in HIV/AIDS patients on national, regional and international level?
- Which CNS drugs are prescribed to HIV/AIDS patients?

1.3 RESEARCH OBJECTIVES

1.3.1 Research aim

The general aim of the study was to determine possible changes in the incidence and prevalence rates of HIV/AIDS, and prescribing patterns of CNS medications in HIV/AIDS patients from 1 January 2005 to 31 December 2015 in the private health sector of SA.

1.3.2 Specific research objectives

The research project entailed a literature review and an empirical investigation. The specific research objectives for the literature review and the empirical investigation included the following:

1.3.3 Literature review

The specific research objectives of the literature review included the following:

- To conceptualise and describe the incidence and prevalence of HIV/AIDS nationally, in Africa and globally.
- To identify and describe the prevalence and incidence of psychiatric conditions in HIV/AIDS patients.

1.3.4 Empirical investigation

The specific research objectives of the empirical investigation were the following:

- Objective 1: To determine possible changes in the prevalence and incidence of HIV/AIDS in the private health sector of SA over the study period, i.e. 2005-2015.
- Objective 2: To determine possible changes in the prescribing patterns of CNS medication in HIV/AIDS patients over the study period, i.e. 2005-2015.

1.4 RESEARCH METHODOLOGY

The research project consisted of two steps, namely a literature review and an empirical investigation.

1.4.1 Literature review

The literature review focused on the most recent publications regarding the prevalence of HIV/AIDS globally, in Africa and nationally; the prevalence of psychiatric conditions in HIV/AIDS patients; and the treatment guidelines for these patients.

The following processes were followed:

- Conducted an internet search using appropriate databases such as Scopus®, Science Direct®, EBSCOhost®, PubMed®, Medline® and Google Scholar®.
- The following keywords were used in the literature search:
 - “HIV/AIDS prevalence”;
 - “Global HIV/AIDS prevalence”;
 - “HIV/AIDS prevalence in Africa”;
 - “HIV/AIDS prevalence in SA”;
 - “ARV treatment guidelines”;
 - “Psychiatric problems in HIV/AIDS patients”;
 - “Central nervous medication in HIV/AIDS patients”;
 - “Antiretroviral treatment guidelines”;
 - “Drug-drug interactions between antiretroviral drugs and the different CNS medication”

The most appropriate literature from the results was chosen to answer the research objectives.

1.4.2 Empirical investigation

The empirical investigation will be discussed under the following headings: research design, data source, target and study population, study variables, reliability and validity of database and data analysis.

1.4.2.1 Research design

A descriptive, observational research design was implemented using retrospective medicine claims data from a national representative pharmaceutical benefit management (PBM) company for the study period 1 January 2005 to 31 December 2015. Descriptive studies attempt to find and describe the occurrence of a medical condition or problem (Waning & Montagne, 2001:46). It provides “insight data about the patterns of diseases or drug use problems in a population or group” (Waning & Montagne, 2001:46). Observation research, within the context of pharmacoepidemiology, provides evidence about disease patterns and drug use problems by means of various characteristics of persons, places and time periods (Waning & Montagne, 2001:46).

Different research designs were implemented to achieve the specific objectives:

- For the **first objective**, the analysis followed a **longitudinal or trend analysis design**. A longitudinal design can be defined as an investigation where the participant outcomes and possible treatments are collected at multiple follow-up times. The way in which variables change over time will be examined (Brink *et al.*, 2012:114).
- For the **second objective**, a **retrospective longitudinal closed cohort design** was followed. Cohort studies are characterised by the following groups or cohorts of subjects through time by analysing the development of a disease or outcome (Banerjee, 2003:86). Group allocation is defined by exposure (patients taking a specific drug) or extent of exposure (drug dosing). In an open cohort design, subjects or participants are allowed to enter or leave the cohort according to defined events, such as joining or leaving a health plan (Suriki & Chan, 2008: 230). In a retrospective longitudinal closed cohort, participants are not allowed to leave the cohort.

1.4.2.2 Data sources

In this section, the database, data fields and the reliability and validity of the data will be discussed.

1.4.2.2.1 Database

The data were obtained from a PBM company that is dedicated to the effective management of medicine benefits. This database is a real-time, electronic pharmaceutical claims processing system that manages medicine benefits by acting as a link between pharmacies/doctors and medical insurers. The PBM provides medicine management services to more than 42 medical schemes and capitation plans in South Africa. The database currently contains longitudinal medicine claims data for more than 1.8 million medical scheme beneficiaries. The PBM Company is at present linked to all South African pharmacies and 98% of all dispensing doctors.

The total database for all years (1 January 2005 to 31 December 2015), consisting of all the medicine claims data available, was used. Only data from this one PBM were used.

1.4.2.2.2 Data fields

Patient demographics (such as birth date, gender, and encrypted patient member numbers), pertinent prescription information data (such as prescription number, National Pharmaceutical Product Index (NAPPI) codes (Snyman, 2018), quantity of medicine items dispensed, active ingredient, pharmacological group, dispensing date) and medical problems (such as International Codes of Diseases or ICD 10 codes) were extracted from the PBM database for analysis (WHO, 2016c).

The date of the first observed ARV prescription for a specific patient per year was assigned as the index date. The Statistical Analysis System®, SAS 9.4 ® (SAS Institute, 2012) was used to calculate the age of a patient from the date of the first observed ARV prescription in the index year and the birth date of the patient. A patient was categorised in two patient groups (HIV-only and HIV-CNS), depending on the medicine they used during the specific year.

1.4.2.2.3 Reliability and validity

Longitudinal data from 1 January 2005 until 31 December 2015 were obtained from one medicine claims database only (one PBM), thereby limiting external validity, implying that the results can be generalised to the specific database and study population only. This study was conducted from the viewpoint that all data obtained from the PBM database are correct and accurate. However, data were cleaned by deleting all duplicate claims and incomplete patient information. The datasets were verified after each cleaning process by performing random data checks.

The PBM has certain validation processes in place to ensure the integrity, validity and reliability of the data, such as data integrity validation, eligibility management, medicine utilisation and clinical management, fully integrated pre-authorisation services, including exception management; management of medicines for the chronic disease list conditions, prescribed minimum benefits (PMB) and other conditions; medicine management in capitation environments; on-line medicine expenditure reporting; and supplementary services, which include network management, development and implementation of reference price lists, formulary management, and price and product file management.

For security purposes, the PBM is not identified by name. Furthermore, as per confidentiality agreement with the PBM, all identifying information about beneficiaries, medical schemes, health plans, service providers and prescribers were encrypted or removed by the PBM before releasing the data for analysis.

1.4.2.3 Target population

The target population included all HIV/AIDS patients belonging to a medical scheme from 1 January 2005 to 31 December 2015 in the private health sector in South Africa.

1.4.2.4 Study population

This section entailed the rationale for selecting the study population, as well as the processes followed in selecting these patients. The study populations were different for the different objectives.

1.4.2.4.1 Inclusion criteria for Objective 1

All patients who meet the inclusion criteria were selected, and the data were filtered by means of the application of the exclusion criteria.

Table 1-2: Inclusion criteria for Objective 1

Criteria	Information
Study period	1 Jan 2005 to 31 Dec 2015
Diagnose	All patients with a diagnosis code for HIV/AIDS (ICD-10 code B20-B24).

Table 1-3: Exclusion criteria for Objective 1

Criteria	Information
Unknown information	Unknown gender and date of birth

1.4.2.4.2 Inclusion criteria for Objectives 2

Table 1-4: Inclusion criteria for Objectives 2

Criteria	Information
Study period	1 Jan 2005 to 31 Dec 2015 (Objective 2)
Diagnosis	All patients with a diagnosis code for HIV/AIDS (ICD-10 code B20-B24).
Treatment period	Only patients who were on the database for at least a 10-year period (preferably) continuously.
Medication	All CNS medication (MIMS® classification system, Pharmacological Group 1) claimed for above-mentioned patients.

Table 1-5: Exclusion criteria for Objectives 2

Criteria	Information
Unknown information	Unknown gender and date of birth

The following steps were followed in the process of obtaining data for the study:

- Data were obtained from the PMB's central database.
- Data were cleaned by the application of exclusion criteria on all study years from 2005 to 2015, respectively.
- Applied the inclusion criteria to obtain individual data subsets for each study year from 2005 to 2015.

The study population included all HIV/AIDS patients, and was divided into the following groups:

- All HIV/AIDS patients who had received one or more CNS medication (CNS stimulants, sedative hypnotics, anxiolytics, antidepressants, antipsychotics and anti-epileptics) during the study period.
- All HIV/AIDS patients who did not have any CNS medication during the study period.

The Monthly Index of Medical Specialties (MIMS®) classification system and the National Approved Product Pricing Index (NAPPI) code were used to identify all the CNS medicines.

1.4.2.5 Study variables

The study variables included both independent- and dependent variables. According to Brink *et al.* (2012:90), an independent variable is “a variable that influences other variables”, and a dependent variable is the “outcome variable”. Depending on the type of analysis, a variable acts as a dependent or as an independent variable.

1.4.2.5.1 Age

According to Pugh (2000:34), age is defined as a period of time that has passed since the time of birth.

Patient age was determined at time of the first dispensing of the antiretroviral drug in the index year (2005) and divided into the following age groups: group 1: >0 and <6 years; group 2: ≥6 and <12 years, group 3: ≥12 and <18 years; group 4: ≥18 and <40 years; group 5: ≥40 and <60 years; group 6: ≥60 and <70 years; group 7: ≥70 years. Costello *et al.* (2007:2) define children as the age range between 2 and 12 years and adolescents in the age range from ≥12 and ≤18 years and adults as above 18 years.

1.4.2.5.2 Gender

Gender is defined as “the physical and social condition of being male or female” (Cambridge Dictionaries Online, 2012). For the purpose of this study, participants were divided into two categories, namely female and male. Patients, for whom gender was not indicated, were excluded to ensure the quality of the data.

1.4.2.5.3 Time period

The total database was divided into different periods of time (per year).

1.4.2.5.4 Active ingredient of drug

The pharmacological classification of the CNS medications (CNS stimulants, sedative hypnotics, anxiolytics, antidepressants, antipsychotics and anti-epileptics) was done by using the MIMS[®] classification system, where medication is listed according to active pharmaceutical ingredients and registered generic names (Snyman, 2018). All medication listed under the MIMS[®] classification system, Pharmacological Group 1, was used to identify the CNS medication. Individual products could also be identified using NAPPI codes. NAPPI codes are unique nine-digit product codes that incorporate the product name, pack size, strength and manufacturer’s

name (Snyman, 2018). This method was specifically used to identify the individual CNS medication.

1.4.2.5.5 Province

The Statistical Analysis System®, SAS 9.4® (SAS Institute Inc., 2009) programme was to group all prescriber practice addresses according to province, district council, municipality and main place (specific town) level. This information allowed the researchers to investigate differences in the prevalence of HIV/AIDS in a section of the private health sector according to the different geographical areas in South Africa.

1.4.2.5.6 Number of prescriptions per patient per year

According to the Mosby's Dictionary (2009a), prescriptions are an *"order for medication, therapy, or therapeutic device given by a properly authorized person"*. The mean number of CNS prescriptions per patient per year was calculated and used as a measure of the medicine usage.

1.4.2.5.7 Number of medicine items per prescription per patient

According to the Mosby's Dictionary (2009b), *"medicine is a drug or a remedy for illness"*. The Medicines and Related Substances Control Act (101/1965) of SA defines medicine as *"any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man"*. Total number of medicine items as well as the average number of medicine items per prescription dispensed per patient per year for CNS medication was calculated, and was used as a measure of medicine usage.

1.4.2.5.8 Incidence and prevalence rate

Both HIV/AIDS incidence and prevalence rate were calculated per 1 000 medical scheme beneficiaries for that specific year.

The prevalence rate of treated HIV/AIDS was calculated per 1 000 medical scheme beneficiaries per year as follows (CDC, 2018a):

$$\text{Prevalence rate} = \frac{\text{All new and pre-existing cases during a given time period}}{\text{Population during the same time period}} (X 10^n)$$

$$n = 3$$

The incidence rate was calculated as follows (CDC, 2018b):

$$\text{Incidence rate:} = \frac{\text{Number of new cases of disease in a specified period}}{\text{Size of population at start of the specified period}} (X 10^n)$$

$$n = 3$$

Incidence was used to determine the proportion of patients who were newly treated for HIV/AIDS per year in the population covered by medical schemes during the study period (2005-2015) without taking into account when participants were diagnosed (CDC, 2018a). Each participant was tracked from the first time that he/she was identified on the PMB central database. Participants who cancelled their membership with a medical scheme administered by the PBM during the study period did not contribute to the year's denominator whereas new members of medical schemes contributed to the denominator.

1.5 STATISTICAL ANALYSIS

The Statistical Analysis System®, SAS 9.4® software (SAS Institute Inc., 2002-2012) and Statistical Package for the Social Sciences (IBM SPSS® 22) was used to analyse the data for the empirical investigation.

A *P*-value of 0.05 or less was considered statistically significant at a two-sided α -level. The practical significance of results was computed when the *P*-value was statistically significant.

1.5.1 Descriptive statistics

Variables were expressed using descriptive statistics, which include number (*n*) and proportions presented as percentages (%), arithmetic means, standard deviations (SD) and 95% confidence intervals (CI).

1.5.2 Inferential statistics

The following inferential statistics were applied:

- Differences in the mean number of prescriptions per patient per year between the different gender groups were compared by using a two-sample *t*-test (Steyn, 1999). Cohen's *d*-value was used to evaluate the effect size between means [34]. For practical significance, the following were considered: 0.2 a small effect, with no significant difference, > 0.2 and ≤0.8 a medium effect with an observable significance, > 0.8 a large effect and significant difference. (Steyn, 1999; Swanepoel *et al.*, 2010:262)

- The one-way analysis of variance (ANOVA) was used to test for significant differences between the mean numbers of CNS prescriptions per HIV/AIDS patient for the different years and the mean number of CNS medicine items per prescription per patient for the different years (Kao & Green, 2008: 158-170). We will only present the results of this analysis between the study years 2005 and 2015. If a difference was detected, *post-hoc* tests were used to determine where the differences lie. (Kao & Green, 2008: 158-170).
- The McNemar's test was used to determine whether there was a statistically significant change in the proportions of HIV/AIDS patients who received a specific CNS medication according to pharmacological group and active pharmaceutical ingredient in 2005 versus 2015 (Adedokun & Burgess, 2012:25).

1.6 ETHICAL CONSIDERATIONS

The study commenced after it was granted ethics approval by the Health Research Ethics Committee (HREC) (certificate number NWU-00179-14-A1) of the Faculty of Health Sciences of the North-West University. Permission to conduct the study was also obtained from the PBM's board of directors via the contract between the research entity MUSA and the PBM. The researcher, study leaders and statistical consultant all signed a confidentiality agreement (Annexure I).

Anonymity and confidentiality were maintained at all times; and information on identity of the beneficiaries, medical schemes, service providers and prescribers was removed by the PBM before data were received and analysed.

1.7 CHAPTER SUMMARY

This chapter included the background and problem statement, research aims and objectives, research methodology applied, data source and analysis, criteria for the study population and ethical considerations applicable to this study. The following chapter entails a comprehensive literature review with regard to the objectives of the literature study.

CHAPTER 2: LITERATURE REVIEW

2.1 INTRODUCTION

This chapter focuses on the reviewing the most recent literature regarding the prevalence of human immunodeficiency virus / acquired immune deficiency syndrome (HIV/AIDS) globally, in Africa and nationally; the prevalence of central nervous system (CNS) disorders in people living with human immunodeficiency virus (HIV) (PLWHIV); HIV/AIDS treatment guidelines and prevalence of CNS medication prescribed with antiretroviral (ARV) drugs in PLWHIV.

2.2 HUMAN IMMUNODEFICIENCY VIRUS

The HIV is a retrovirus that causes a medical condition known as acquired immune deficiency syndrome (AIDS) (Juan *et al.*, 2016:1836). HIV/AIDS is a disease that is characterised by the destruction of the human immune system (WHO, 2010). When the human defence system is weakened, opportunistic infections occur and this results in the death of an HIV-infected person (UNAIDS, 2009:14). The HIV belongs to a family of retroviruses, a member of the genus of lentiviruses that have a long period of incubation and are characterised by their ability to incorporate viral deoxyribonucleic acid (DNA) into a host cell's genome (Waki & Freed, 2010:1603). Each viral particle consists of two identical ribonucleic acid (RNA) strands that are tightly bound to the viral nucleocapsid protein (Mims *et al.*, 2004:49).

There are many sub-types of the HIV, and HIV-1 sub-type C is the most predominant variant in Southern Africa (Arien *et al.*, 2007:150). The HIV-1 sub-type C is less virulent than HIV-1 sub-types A and D (Tebit & Arts, 2011:55). Unfortunately, symptoms of HIV-1 sub-type C remain undiagnosed for a long time between the seroconversion and AIDS stage compared to the other variants (Venner *et al.*, 2016:312).

Human immune virus is primarily transmitted through unprotected sexual intercourse, from mother to child during pregnancy or breastfeeding, through needle sharing for medical purposes or injecting drugs, and blood transfusions with infected blood (Chakraborty, 2008:496; Plante & Lemon, 2010:9). In sub-Saharan Africa, the majority of new HIV infections in adults are caused by unsafe sexual intercourse in heterosexual couples, while many infected mothers spread their infections to their unborn babies through mother-to-child transmission in utero (Cohen *et al.*, 2011:493). Rispel and Metcalf (2009:133) reported that HIV could also be easily transmitted among men who have sex with men. According to SANAC (2012b:1), the major contributory factors in spreading HIV in Africa are poverty, inequality, social unrest, sexually transmitted

infections (STIs), low status of women, sexual violence, migrant labourers, limited and uneven access to medical care, and a history of poor leadership in response to the epidemic.

2.3 PATHOGENESIS OF HUMAN IMMUNE VIRUS

The immune system's main function is to protect the body from infinite pathogenic microbes, toxicities and allergens that have the ability to threaten normal homeostasis within the body (Chaplin, 2010:3). Pathogens that breach the anatomic barriers, known as the body's first-line of defence (e.g. skin, cornea, respiratory and gastrointestinal tract mucosa), can trigger either one of the immune responses (Delves, 2017a). Antigens include viruses, bacteria, and a foreign protein/pathogen that is capable of inducing an immune response that is followed by lymphocyte activation and antibody production (Mellors, 2006). A capsid is an envelope made up of approximately 1 300 identical proteins with a total of 4 million atoms that are arranged in a form of hexagon and pentagon structures (Campbell & Hope, 2015:471). The HIV capsid plays important roles in viral chemical pathways (Juan *et al.*, 2016:836). The lifecycle of HIV can be divided into six steps, namely binding, reverse transcription, integration, transcription, translation and viral assembly (Freed, 2015:484). The HIV infection happens when the viral particles are transferred from one individual to another by sexual or parenteral routes. When the HIV is inside the body, it is then transported to the lymph nodes (Freed, 2015:484).

According to Campbell and Hope (2015:471), the HIV-1 Gag polyprotein is responsible for virus assembly and release. The HIV-1 binds to the CD4 activated cell receptors such as T-helper cells, monocytes, co-receptors CCR5 (macrophages dendritic cells and T cells), CXCR4 (T cells only) and microglia, which are all important to the immune system of the host (Gallo & Montagnier, 2003:2282). The viral glycoprotein gp120 envelope binds to the activated CD4 receptors (Cohen *et al.*, 2011:496). The interaction of HIV with host cell co-receptors on the cell surfaces helps to anchor the viral particles to the CD4 cell receptors (Arthos *et al.*, 2008:307). According to Miyauchi *et al.* (2009:433), HIV-1 enters the cells by endocytosis and fusion. The virus would inject its ribonucleic acid (RNA) into the CD4 cell leaving its protein capsid outside (Freed, 2015:484). Shortly after entering the host cell, the transcription process will start (Votteler & Sundquist, 2013:232). The HIV-1 directs the host's cells to make RNA, which then converts viral RNA into combination deoxyribonucleic acid (cDNA) (Waki & Freed, 2010:1605). The messenger RNA helps to make new copies of the viral proteins (Votteler & Sundquist, 2013:232). The protease enzyme is responsible for new viral proteins maturation inside the lymph nodes (Annemarie *et al.*, 2010:59; Marchand *et al.*, 2009:1016). The DNA transcription mechanism of the host cell then makes new viral RNA strands, which are assembled and released by the cell to infect other CD4

positive cells (Freed, 2015:484). The protective mechanism within the human body cells detects the infection in response and the cells eventually go into apoptosis (Doitsh, 2014:800).

2.3.1 Pathogenesis of human immune virus

The HIV infection process in non-treated patients follows a set of stages with three distinct phases, namely 1) acute/asymptomatic, 2) symptomatic/chronic HIV infection, and 3) AIDS. The progression of the disease from initial infection to full-blown AIDS varies from one person to another. The progression of the infection can be divided into distinct stages, called HIV infection, window period, sero-conversion, asymptomatic, HIV-related illness and AIDS (AIDS Group, 2011:231).

Acute HIV infection is the first stage of HIV infection. It develops in two to four weeks when the virus is introduced in the body and there are no symptoms. The next stage is called the window period, which is the time between infection and production of antibodies and it is estimated to be three to six months after infection (UNAIDS, 2009:24). During this phase, an infected person may test negative (false negative) for HIV infection and there are no symptoms. Sero-conversion represents the point in time when a person changes his or her status from being HIV negative to HIV positive and this usually happens six to 12 weeks after being infected, when the window period ends (Gottlieb *et al.*, 2002:905). The infected person can test positive for HIV and at least one in three persons can suffer from fever, swollen lymph nodes, headache, night sweat, rash and cough (UNAIDS, 2009:25). The acute stage ranges from six to eight years (Xiumin *et al.*, 2015:245). In the acute stage, HIV multiplies very fast and spreads throughout the body. The period when the person is HIV infected and has no symptoms of AIDS is called the asymptomatic stage (Gottlieb *et al.*, 2002:905). The incubation period can range from 10 to 15 years or more (WHO, 2013a; WHO, 2013b).

The HIV-infected person has no symptoms during the asymptomatic stage. During this stage, most people are not aware that they are infected. Some people can remain HIV positive for many years having swollen lymph nodes without showing symptoms, while others may develop the disease and die shortly thereafter. The infected person will have relatively low viral concentrations in blood plasma and recovering CD4 cells; viral replication continues at high rates (Weiss 1993:1274). The symptoms of this stage are fever, throat infection, headache, fatigue, muscle and joint pains, swelling of lymph nodes, rash, oral ulcers and weight loss (NDOH, 2014a:232).

The second stage of HIV infection is called asymptomatic/clinical latency/chronic HIV infection. The HIV will continue replicating inside the CD4+ lymphocytes and monocytes leading to the destruction of CD4+ lymphocytes and impaired immunity (NDOH, 2014a:232). The symptomatic

stage is characterised by high VLs and a decrease in concentration of CD4 cell counts in the blood plasma of the infected individual (Oyefu *et al.*, 2007:2180). The PLWHIV may or may not shows signs of symptoms of HIV infection. However, symptoms tend to increase due to high levels of HIV in the body, which lead to destruction of the human immune system. The PLWHIV may develop opportunistic infections coupled with prolonged fever, chronic diarrhoea, pulmonary tuberculosis and weight loss (Lodi *et al.*, 2011:823). The HIV directly kills CD4 cells by inducing apoptosis (Grossman *et al.*, 2006:289). The major symptom noticed during this stage is the swollen gland on the infected person. Lymph tissues become burnt out, and also, HIV mutates and becomes more pathogenic (WHO, 2010a; WHO, 2010b). Without treatment with HAART, the asymptomatic stage usually advances to AIDS in 10 or more years (CDC, 2018c).

The AIDS (stage 3) stage is the terminal stage of the HIV infection. During the AIDS stage, the CD4 cell count has dropped to between 200 and 350 cells/ μ L (WHO, 2010a; WHO, 2010b). In the absence of treatment, the infected person could die (CDC, 2018c). Major characteristics of the AIDS defining stage are HIV wasting syndrome, severe lung and eye infections, oral or throat or vaginal fungal infections, and cancer (Grossman *et al.*, 2006:289). A couple of studies have reported that the average survival time after HIV infection in the absence of ART was 10 years (Grossman *et al.*, 2006:289; Gupta *et al.*, 2007:546). This is consistent with results of other studies and nearly equal to the 11 years assumed in the modelling study done by Granich *et al.* (2009:48). The symptoms associated with AIDS are extra-pulmonary TB, recurrent cold sores, recurrent herpes zoster, persistent oral and vaginal thrush infections, oesophageal candida, bacterial skin infections and rashes, pneumonia, Kaposi sarcoma, *Pneumocystis carinii pneumonia*, oral hairy leucoplakia, persistent cough, weight loss, diarrhoea, fever for more than four weeks, cytomegalovirus, *Cryptococcal meningitis* and peripheral neuropathies (CDC, 2018c; Grossman *et al.*, 2006:289).

2.3.2 Opportunistic infections

Opportunistic infections (OIs) are common in PLWHIV. Pneumonia is capable of causing HIV/AIDS complications (CDC, 2018c). Human herpes virus type 8 is associated with Kaposi sarcoma (WHO, 2013a; WHO, 2013b). Cryptococcal meningitis is prevalent in 5% of PLWHIV globally and without treatment the life expectancy could be less than one month in PLWHIV (UNAIDS, 2009:27). Other common opportunistic infections associated with HIV/AIDS are candidiasis (of throat, mouth, and vagina), herpes simplex and herpes zoster infections, tuberculosis (in more than 70% of PLWHIV), cryptosporidiosis, Kaposi sarcoma, leishmaniosis and *Pneumocystis carinii* (CDC, 2018c). Factors such as stress, nutrition, individual lifestyle and ageing could significantly contribute to the development of AIDS (Somarriba *et al.*, 2010:191). In

the absence of HAART, the VL would increase rapidly, whereas treatment increases CD4 cell count (Doitsh, 2014:800).

2.4 GLOBAL HUMAN IMMUNE VIRUS EPIDEMIOLOGY

According to the UNAIDS (2016) report on the global HIV/AIDS epidemic, there were more than 42 million PLWHIV globally in 2015. In general, HIV/AIDS prevalence rates are increasing, whereas HIV/AIDS-related deaths are decreasing globally due to HAART (Kharsany & Karim, 2016:34). More than 37 million (90%) of the total HIV/AIDS cases are found in Africa (UNAIDS, 2016:1).

It was estimated that there were 2.5 million new HIV infections in 2005 and the number decreased to 2.1 million worldwide (1.9 million adults and 240 000 < 15 years) in 2015 (UNAIDS, 2016). The global HIV incidence rate has stayed relatively constant at approximately 2.6 million new cases per year since 2005, after a period of fast decline between 1997 and 2005 (UNAIDS, 2008). The HAART also helped to reduce HIV/AIDS mortality rates globally (Nsanzimana *et al.*, 2015:169).

Tables 2-1 and 2-2 show the overall global declines in new HIV infections between 2005 and 2015 around the world (UNAIDS, 2016:1). Although the overall incidence of HIV infection has dropped, the number of people living with HIV/AIDS has increased steadily at approximately 2.5 million per year between 2005 and 2015 globally (GBD 2015 HIV Collaborators, 2016:365).

Table 2-1: Global trends in HIV incidence rates from 2005 to 2015

	2005	2010	2011	2012	2013	2014	2015
Incidence of HIV (total)	2.5 million	2.2 million	2.2 million	2.2 million	2.1 million	2.1 million	2.1 million
HIV incidence in > 15 years	2.1 million	1.9 million	1.9 million	1.9 million	1.9 million	1.9 million	1.9 million
HIV incidence in 0-14 years	450 000	290 000	270 000	230 000	200 000	160 000	150 000

Globally, the HIV incidence increased from 1.98 million in 2010 to 2.1 million in 2015 (UNAIDS, 2016:1). Significant declines in incidence rates were recorded between 2010 and 2015 in Eastern and Southern Africa, whereas Eastern Europe combined with Central Asia reported increases of above 57% (UNAIDS, 2016:1).

Table 2-2: Global changes of new HIV infections in adults in between 2010 and 2015

Year	Global total	Western & Central Europe and North America	Eastern Europe & Central Asia	Asia Pacific	Latin America	Middle East & North Africa	West & Central Africa	Eastern & Southern Africa
2010	1.98	0.91	0.12	0.32	0.1	0.19	0.46	1.2
2015	2.1	0.90	0.19	0.3	0.1	0.21	0.41	0.96
Change	6% up	1% down	57% up	5% down	0%	4% up	8% down	14% down

2.5 PREVALENCE RATES OF HIV/AIDS

Prevalence rate is defined as the number of individuals in a population who are affected by a particular disease at a point in time (Waning & Montagne, 2001:108). It is influenced by the number of new cases as well as by the number of deaths. Prevalence increases if the time that a person is infected and survives is long.

Acquired immune deficiency syndrome was first described in 1981 in the United States of America among healthy men who had sex with other men who developed *Pneumocystis carinii pneumonia* and later died (Stine, 2009:1). All the victims developed severe immunodeficiency, which led to the development of opportunistic infection with *Pneumocystis carinii*. A few years later, a group of healthcare workers in Zaire noted a new fatal disease that was causing severe weight loss and diarrhoea in people who had it and the disease was known as the 'Slims disease' (Serwadda *et al.*, 1985:849). The Slims disease was mostly found in heterosexual couples and their body immune systems were suppressed (Serwadda *et al.*, 1985:849). In 1983, scientists isolated the HIV and identified that the virus caused AIDS (Broder & Gallo, 1984). Two types of HIV strains were identified more than 30 years ago, and these are the HIV-1 strain (Barré-Sinoussi *et al.*, 1983:868) and HIV-2 strain (Clavel *et al.*, 1986:343). Between 1985 and 1987, HIV/AIDS was discovered in more than 26 countries (WHO, 2010e). Both types HIV-1 and HIV-2 cause AIDS. The HIV-1 is most prevalent in Southern Africa, whereas HIV-2 is common in West Africa (Council for Medical Schemes (CMS), 2017:1).

Since 1980, more than 80 million people have been infected by the HIV and approximately 35 million people have died of HIV/AIDS (WHO, 2015b). However, the introduction of HAART has helped to improve morbidity and quality of life among people living with HIV/AIDS (Nakagawa *et al.*, 2013:20). Current data show a steadily decrease in prevalence since 2004 due to different factors, including the increase in availability of antiretroviral therapy (ART) (WHO, 2015b). In high income countries such as in North America and Western and Central Europe, deaths due to AIDS declined by huge margins soon after HAART was introduced in the late 1990s (WHO, 2011). One study showed that PLWHIV who were on treatment in USA and Canada have a life expectancy approaching that of the general population (Samji *et al.*, 2013). The antiretroviral Therapy Cohort Collaboration (ART-CC) expanded these findings over a longer timeframe using retrospective data from one of the largest collaborations in Europe and North America (ART-CC, 2017). The ART-CC study also reported mortality reduction and increased life expectancy in people living with HIV/AIDS on ART.

Although life expectancy has improved in PLWHIV, life expectancy at age 20 remains lower by 13 years compared to the non-infected general population (Marcus *et al.*, 2016). This gap could be large especially in LMICs where data from population studies are scarce. In sub-Saharan Africa, mortality and morbidity in PLWHIV are still high compared to high income countries (WHO, 2015b). However, HAART had shown benefits among individuals receiving treatment to levels similar to those described in high income countries (Boulle *et al.*, 2014). Furthermore, one empirical study's data support that PLWHIV in LMICs can have a near-normal life expectancy, assuming they start ART when their CD4 count is still >200 CD4 cells/ μ L (Johnson *et al.*, 2013).

2.5.1 Prevalence of HIV/AIDS in children

According to the UNAIDS (2016), there were more than 3.2 million children globally under 15 years of age who were living with HIV/AIDS in 2015. SA has a high prevalence of HIV infection in the reproductive age group of women (15-49 years), and this will continue to impact on the causes of morbidity and mortality in children (UNAIDS, 2013). In 2013, the overall prevalence in women at antenatal clinics was 29.7% (NDOH, 2013c:22). According to the UNAIDS (2010), 69% of HIV incidence cases in 2009 were from children living in Africa. The same report highlighted that HIV infected children could progress to AIDS faster than adults and would die within the first two years of their lives.

The main route of transmitting HIV to a child is through vertical transmissions from an infected mother (Stine, 2009:169). It is estimated that one in 10 babies contract HIV from their infected mothers during the breastfeeding period (Chakraborty, 2008:496). A woman living with HIV/AIDS

and not on treatment is capable of transmitting the HIV to her baby at birth when the baby is in contact with her vaginal secretions in the birth canal (NDOH, 2010).

Children have no political power or economic power, no vote and no money. They are left at the mercy of the adults and many times they are forgotten. This discrepancy is evident in the fact that many caregivers of children always forget to give medication, and some think the child has recovered (Buchanan *et al.*, 2012:1244). When infected individuals do not adhere to treatment, the progression to AIDS diseases is fast. According to NDOH (2013c:9), the coverage of ART among children and adolescents is still very low in SA.

The Joint Review of HIV, TB and PMTCT programmes in SA reported that vertical transmissions at six weeks has been significantly reduced to 2.7% and the MTCT rate at 18 months is not known (NDOH, 2013c:9). Post-partum follow-up of the mother-baby pair is suboptimal, and retention in care presents a challenge. According to NDOH Consolidated Guidelines (2015b:14), South Africa's PMTCT programme of HIV is 98% successful. The PMTCT programme significantly helped to bring down child mortality due to HIV/AIDS. Treatment developments have improved the prognosis of paediatric HIV infection, and consequently the quality of life of many HIV infected children also improved (Cotton *et al.*, 2009:35).

However, with this background of inequalities between children and adults, as well as the threat of the HIV pandemic to humankind, there is a need to evaluate the impact of HIV/AIDS on children and adults in terms availability of required drugs and for the management of HIV/AIDS and related conditions. This information is vital in the formulation of short-term and long-term policies on healthcare and equitable resource allocation in the face of the HIV/AIDS pandemic.

Table 2-3 presents the global changes in HIV/AIDS prevalence, antiretroviral treatment and AIDS-related deaths from 2005 to 2015 (UNAIDS, 2016:6). There were nearly 32 million PLWHIV in 2005 and the number steadily increased to 37 million in 2016 (UNAIDS, 2016:6)

Table 2-3: The global changes in HIV/AIDS prevalence, antiretroviral treatment and AIDS-related deaths from 2005 to 2015

	2005	2010	2011	2012	2013	2014	2016
Global total prevalence of HIV/AIDS infected	31.8 million	33.3 million	33.9 million	34.5 million	35.2 million	35.9 million	36.7 million
Number of HIV infected people accessing treatment	2.2 million	7.5 million	9.1 million	11 million	13 million	15 million	18.2 million
HIV/AIDS-related deaths	2 million	1.5 million	1.4 million	1.4 million	1.3 million	1.2 million	1.1 million

2.5.2 Incidence and prevalence of HIV/AIDS in America, Europe and Asia

The profile of HIV infected people in developed countries continues to represent predominantly the marginalised groups in society. These groups include men who have sex with men, ethnic minorities, migrants from the developing countries, refugees, the homeless and often mentally ill people and the poor (Green *et al.*, 2004). Results from the HIV Prevention Trials Network (HPTN) 052 study have clearly proven the efficacy of ART for the prevention of HIV transmission (Cohen *et al.*, 2011:493), while the Trial of Early Antiretroviral and Isoniazid Preventive Therapy in Africa (TEMPRANO ANRS 12136) and Strategic Timing of Antiretroviral Treatment (START) studies have shown that early ART initiation reduces the risk of serious clinical conditions, the development of AIDS and death (Daniel *et al.*, 2015:808; Lundgren *et al.*, 2015:795).

There was approximately 1.6 million PLWHIV, 94 000 new HIV infections and more than 47 000 HIV/AIDS related deaths in the Caribbean region in 2013 (WHO, 2015b). The region had a low prevalence rate of HIV/AIDS of 0.4% in adults in 2012 (WHO, 2013b). Brazil, Colombia, Mexico and Venezuela contributed more than three quarters of the Caribbean and South American region's total HIV/AIDS cases in 2014 (WHO, 2015b). Table 2-4 indicates the prevalence estimates of HIV/AIDS on the American continent as describe by the GBD (Global burden of disease) HIV Collaborators (2016:362).

Table 2-4: Estimates of prevalence of HIV/AIDS on the American continent

	North America	Southern & Latin America	Latin America & Caribbean	Central Latin America	Tropical America	Andean Latin America	Caribbean
People living with HIV/AIDSs	882 600	85 450	1 322 070	394 060	571 240	49 310	307 450
HIV/AIDS-related deaths	7 890	2 230	46 810	12 310	21 410	1 810	11 280
% ART coverage	69.86	63.83	45.10	40.01	48.93	34.59	46.11

In Western and Central Europe, approximately 2.4 million people were living with HIV/AIDS in 2014 (GDB HIV Collaborators, 2016:361). The HIV/AIDS prevalence rate in the adult population was 0.3% and more than 27 000 people died of HIV/AIDS-related illnesses in 2015 (AVERT, 2016). France had a prevalence rate of 8%, Spain 6%, the United Kingdom 5% and Italy 5% of the total number of people living with HIV/AIDS 2013 in this region. The GDB HIV Collaborators (2016:361) estimates of prevalence of HIV/AIDS in Europe are presented in Table 2-5.

Table 2-5: Estimates of prevalence of HIV/AIDS in Europe

	Western Europe	Eastern Europe	Central Europe
People living with HIV/AIDSs	651 380	864 890	19 790
HIV/AIDS-related deaths	3 420	26 090	420
% ART coverage	63.81	18.69	46.47

More than 5 million people were PLWHIV in Asia and the Pacific regions in 2015 (AVERT, 2016). China, India and Indonesia contributed more than 75% of the total number of PLWHIV in the region (UNAIDS 2015). In this region, the HIV/AIDS statistics in 2015 were as follows: prevalence rate was 0.2% and 180 000 HIV/AIDS-related deaths in 2014, approximately 41% of HIV/AIDS patients were on HAART and more than 34% of people on treatment achieved viral suppression (UNAIDS, 2015). Table 2-6 presents the prevalence of HIV/AIDS in Asia, Oceania, North Africa and the Middle East as indicated by the GDB HIV Collaborators (2016:362).

Table 2-6: Prevalence of HIV/AIDS in Asia, Oceania, North Africa and the Middle East

	East Asia	Southeast Asia	Oceania	Central Asia	Pacific Asia	North Africa & Middle East	Australasia
People living with HIV/AIDS	796 140	1 510 910	28 850	561 900	22 060	137 940	18 690
HIV/AIDS-related deaths	42 740	57 900	990	1 870	320	7 540	100
% ART coverage	17.90	29.77	52.65	30.50	49.98	19.07	62.24

2.5.3 Incidence and prevalence of HIV/AIDS in Africa

The profile of HIV-infected people in Africa and in other LMICs is much broader when compared to high income countries. All social groups are affected, although HIV/AIDS mostly affects the poor and disadvantaged people who are the majority in these countries (WHO, 2005a). Economic status is associated with contracting HIV. The research done by Evian *et al.* (2004:129) concluded that contract, unskilled and semi-skilled workers were more likely to be infected by HIV than the managers and skilled forces. Women are more affected than men because of their biological vulnerability, as well as social and economic disempowerment in many LMICs (Pettifor, 2013:155). Both HIV/AIDS prevalence rates and the numbers of people dying from HIV/AIDS vary greatly in Africa. Therefore, the prevalence rates range from less than 0.1% in northern Africa compared to 26.5% in southern Africa (WHO, 2013b).

In general, HIV incidence rates significantly dropped in Southern Africa. During 2008, the UNAIDS (2008:30) reported high prevalence of HIV infections in LMICs, of which most of them are in Africa, with sub-Saharan accounting for 67% of all people living with HIV/AIDS and with 75% of HIV/AIDS deaths in 2007 (UNAIDS, 2008:30). The HIV incidence rates dropped by more than 50% between 2005 and 2015 in SA (UNAIDS, 2016:1). Table 2-7 shows the estimates of HIV incidence, prevalence, deaths and ART coverage in 2015 in Northern Africa (UNAIDS, 2016:1).

Table 2-7: Estimates of HIV incidence, prevalence, deaths and ART coverage in 2015 in Northern Africa

	Egypt	Libya	Morocco	Tunisia
New HIV infections (in thousands)	950	230	670	280
Prevalence of HIV/AIDS	680	243	862	262
HIV/AIDS deaths (in thousands)	210	110	360	90
ART coverage/100 people living with HIV/AIDS (%)	17.68	19.73	24.58	23.64

The HIV epidemic is severe in southern Africa, with countries such as Botswana having a prevalence rate of more than 20% (WHO, 2015b:7). There were more than 6.5 million PLWHIV in Western and Central Africa and 230 000 in North Africa and the Middle East (UNAIDS, 2016). Refer to Table 2-8 for the estimated of prevalence of HIV/AIDS in sub-Saharan Africa (UNAIDS, 2016).

Table 2-8: Estimates of prevalence of HIV/AIDS in sub-Saharan Africa

	Southern sub-Saharan Africa	Western sub-Saharan Africa	Eastern sub-Saharan Africa	Central sub-Saharan Africa
People living with HIV/AIDS	11 408 430	6 417 100	10 437 570	1 176 440
AIDS-related deaths	228 940	249 300	318 680	62 080
% ART coverage	51.04	29.09	42.82	26.41

Sub-Saharan Africa is divided into four parts, namely southern sub-Saharan Africa (6 countries), western sub-Saharan Africa (19 countries), eastern sub-Saharan Africa (15 countries) and central sub-Saharan Africa (6 countries) (UNAIDS, 2015). The prevalence of HIV/AIDS in sub-Saharan Africa was 4.7% in the adult population in 2014 (UNAIDS, 2015). Countries such as Botswana, Lesotho, Namibia, SA, Swaziland and Zimbabwe make up sub-Saharan Africa (UNAIDS, 2015). Botswana and Swaziland have HIV/AIDS prevalence rates in the adult population of 20% and 25%, respectively (UNAIDS, 2016). One study estimated that there are 3 million adolescents and young adults between the ages of 15 years and 24 years living with HIV/AIDS in sub-Saharan Africa in 2016 (Molars *et al.*, 2017:762). Refer to Table 2.9 for the Incidence and HIV/AIDS prevalence rates, HIV/AIDS-related deaths and ART coverage in 2015 in the sub-Saharan Africa (UNAIDS, 2016:1)

Table 2-9: Incidence and HIV/AIDS prevalence rates, HIV/AIDS-related deaths and ART coverage in 2015 in the sub-Saharan Africa

	Botswana	Lesotho	Namibia	SA	Swaziland	Zimbabwe
New HIV infections	23 510	24 750	14 050	529 670	13 910	104 200
Prevalence of HIV/AIDS	431 890	354 360	253410	8 409 550	263 040	1 696 170
HIV/AIDS deaths	8 070	12 570	5 090	155 190	5 890	42 120

Although HIV incidence has declined, the sub-Saharan Africa region continues to be severely affected by the HIV/AIDS epidemic, and SA continues to occupy the epicentre of the HIV/AIDS pandemic (NDOH, 2013a).

The Joint United Nations Programme on HIV/AIDS reported that Eastern and Southern Africa had the highest number of PLWHIV in Africa, followed by Western and Central Africa, Asia and the Pacific region (UNAIDS 2012). The Global AIDS Update shows that Western and Central Europe, North America, Latin America, Caribbean, Eastern Europe, Central Asia, Middle East and North Africa reported lower prevalence numbers (UNAIDS, 2016).

2.5.4 Incidence and prevalence of HIV/AIDS in provinces in South Africa

The HIV/AIDS has spread to all provinces in SA, including remote settlements (NDOH, 2015b). The HIV/AIDS prevalence is not the same within provinces and it also varies according to the age, sex, and the place where one stays. KwaZulu-Natal (KZN) and Mpumalanga recorded the highest prevalence rates of 17% and 14%, respectively, compared to the Western Cape with the lowest rate of 5.0% (Nel, 2012; Shisana *et al.*, 2014:36). Table 2-10 shows the estimates of HIV/AIDS prevalence rates in the provinces of South Africa (Stats SA, 2014; Shisana *et al.*, 2014:37)

Table 2-10: 2014 Mid-year population and HIV/AIDS estimates in South Africa

Province	Mid-year population estimates (Stats SA, 2014)	% of total population	HIV prevalence (HRSC population survey 2012 data) %	% of people living with HIV/ADS	% share of HIV + people in SA	Antenatal HIV prevalence % (2012 survey)
Eastern Cape	6 786 900	12.57	11.60	787 280	12.67	29.10
Free State	2 786 800	5.16	14.00	390 152	6.28	32.00
Gauteng	12 914 800	23.92	12.40	1 601 435	25.77	29.90
KwaZulu-Natal	10 614 400	19.80	16.90	1 807 354	29.09	37.40
Limpopo	5 630 500	10.43	9.20	518 006	8.34	22.30
Mpumalanga	4 229 300	7.83	14.10	596 331	9.60	35.60
Northern Cape	1 166 700	2.16	7.40	86 336	1.39	17.80
North West	3 676 300	6.81	13.30	121 318	1.95	29.70
Western Cape	6 116 300	11.33	5.00	305 815	4.92	16.90
TOTAL	54 002 000	100.00%		6 214 027	100.00%	
Province	Mid-year population estimates (Stats SA, 2014)	% of total population	HIV prevalence (HRSC population survey 2012 data) %	% of people living with HIV/ADS	% share of HIV + people in SA	Antenatal HIV prevalence % (2012 survey)

2.5.5 Incidence and prevalence of HIV/AIDS by age groups in South Africa

The HIV/AIDS statistics have shown a variation in prevalence rate between men and women in SA (Stats SA, 2015a:3). The incidence of HIV infections in females aged 14 to 49 years was 18.42% in 2011 and it increased to 19% in 2015 (Stats SA, 2015a:3). Table 2-11 presents the Incidence and HIV/AIDS prevalence rates by age groups in South Africa from 2005-2015 (Stats SA, 2015a:8).

Table 2-11: Incidence and HIV/AIDS prevalence rates by age groups in South Africa from 2005-2015

Year	% Prevalence	% Incidence in 15-49 years	Total HIV/AIDS population	Year	% Prevalence	% Incidence in 15-49 years
	Women 15-49 years	Adults 15-49 years	Youth 15-49 years		Women 15-49 years	Adults 15-49 years
2005	17.01	14.65	5.91	2005	17.01	14.65
2006	17.22	14.82	5.82	2006	17.22	14.82
2007	17.52	15.10	5.76	2007	17.52	15.10
2008	17.81	15.39	5.71	2008	17.81	15.39
2009	18.09	15.66	5.69	2009	18.09	15.66
2010	18.29	15.87	5.70	2010	18.29	15.87
2011	18.42	16.01	5.64	2011	18.42	16.01
2012	18.53	16.29	5.60	2012	18.53	16.29
2013	18.67	16.29	5.60	2013	18.67	16.29
2014	18.85	16.46	5.59	2014	18.85	16.46
2015	18.99	16.59	5.59	2015	18.99	16.59

The HIV infection rate was approximately 2 000 people/day in 2010 in SA (UNAIDS, 2011). There were more than 330 000 new HIV infections at national population level in 2014 in SA (UNAIDS, 2015). These results show a gradual decrease in the number of new HIV infections across the country. A number of strategies (promotion and effective distribution of condoms, HIV counselling and testing, implementation of HIV prevention strategies in sexual risky populations, medical male circumcision, sexual education in schools and community-based prevention programmes and HAART) contributed to the decline of HIV incidence in SA (NDOH, 2015b:4).

The HIV/AIDS prevalence rate in children has decreased since 2005 (SANAC 2015:9). The University of Carolina, San Francisco, conducted a behavioural survey among female sex workers between 2013 and 2014 in SA. The study revealed that the prevalence rate of HIV/AIDS has dropped from 10.3% in 2005 to 7.1% in 2012 in the 15 to 49 years age group, whereas the prevalence rate has increased in the 15 to 49 years age group by 2.4 % during the same period. The HIV/AIDS prevalence rate also increased by more than 4% in the age groups 25 years of age and above from 2002 to 2012 according to the same report. Barnighausen *et al.* (2008) measured the incidence rate at population level in rural KZN and his team found an incidence rate of 3.8% among women aged 15 to 49 years, and 2.4% in men aged 15 to 54 years. A higher HIV incidence of nearly 15.0 per 100 person years was reported in sexually active women aged 18 to 35 years by Nel *et al.* (2012). The number of people living with HIV/AIDS in SA increased by 900 000 between 2008 and 2014 (UNAIDS, 2014).

2.5.6 Incidence and prevalence of HIV/AIDS by gender in South Africa

Young women continue to be at the epicentre of HIV epidemic in SA (Shisana *et al.*, 2014:35). In 2012, more than 30% of young women, aged 20 to 34 years, were infected by HIV (HSRC, 2015; Pettifor *et al.*, 2013:158). African women from the ages of 20 to 34 years had the highest HIV incidence rate of 4.5% compared to other races in SA (Shisana *et al.*, 2014:35). The HIV/AIDS disproportionately affects women (Stats SA, 2015a:3). Approximately one in five SA women in their reproductive age was HIV positive in 2014 (NDOH, 2015b). In general, a higher HIV/AIDS prevalence was reported among women between 15 and 49 years compared to men of the same age group (Stats SA, 2015a:3).

The incidence rate among females aged 15 to 24 years was 22% compared to the incidence rate of 5% in males of the same age in 2015 (SANAC, 2015). The HIV incidence dropped by 41% between 2001 and 2011 among the younger age groups (Rehle *et al.*, 2010). According to Rehle *et al.* (2010), the incidence declined in women aged 15 to 24 years from 2.8% between 2002 and 2005 to 0.5% for the period of 2005 to 2008.

The incidence of new HIV infections in females aged between the ages of 14 and 49 years rose by 5% from 2011 to 2015 (SANAC, 2015:23). In 2015, females aged 45 to 49 years had a 15% incidence rate compared to approximately 10% of the males of the same age group (Nursing HIV, 2016:2). The incidence of males and females aged 50 to 54 years was the same (10%) in 2015. Among the adult population, the incidence dropped from 1.26% in 2002 to 0.85% in 2013 (Stats SA, 2013). According to SANAC (2014):

- New infections dropped by 39% between 2005 and 2013.
- Incidence dropped in children older than two years with girls having 1.4% compared to 0.7% among boys.
- Females aged 15 to 24 years had an incidence rate of 2.5%, and the incidence in males of the same age group was 0.5%.
- HIV incidence among females 15 to 49 years was 2.25% and 1.2% in males of the same age group.

In another study (HRSC, 2012 Survey), the HIV/AIDS prevalence rate was 6.7% in 2008 and dropped to 5.6% among women aged between 15 and 19 years, compared to 2.5% (2008) and the prevalence dropped to 0.7% (2012) among men of the same age group (Shisana *et al.*, 2014:35). Females between 20 and 24 years had prevalence rates of 21.1% (2008) and 17.4% (2012) compared to men of the same age group with 5.1% (no change in HIV/AIDS prevalence between 2008 and 2012) (Shisana *et al.*, 2014:35). The HRSC survey reported an increase in HIV/AIDS prevalence to 32.7% in 2008 and the prevalence declined to 28.4% in 2012 among females aged 25 to 29 years. The same report showed that the prevalence in men of the same age group was 17.3% (2008) and 15.7% in 2012.

Females in the 30 to 34 years age group had a prevalence rate of 10% more than males of the same age group and the figures were 29.1% in 2008 and 36% in females compared to men with a prevalence rate of 25.8% in 2008 and 25.6% in 2012. The HIV/AIDS prevalence was 28.4% (2008), 31.6% (2012) in females compared to 18.5% (2008) and 28.8% among males in the 35 to 39 years age group (UNAIDS, 2016). The prevalence in the 40 to 44 years age group was 16.3% in females versus 19.2% in males in 2008, compared to 28% in females and 15.8% in males. The prevalence increased by 5.6% (from 14.1% in 2008) in women aged between 45 and 49 years, whereas an increase of 5% (8.4% in 2008 to 13.4% in 2012) was reported among men of the same age group.

However, men aged older than 50 years had a prevalence rate higher than females of the same age group in 2012 (Shisana *et al.*, 2015:35). The number of men in the age group 50 to 54 years living with HIV/AIDS increased from 10.4% in 2008 to 15.5% in 2012, whereas the prevalence rates in women of the same age were 10.2% (2008) and 14.8% in 2012 during the same period. Females in the age group 55 to 59 years had prevalence rates of 7.7% and 9.7% in 2008 and 2012, respectively, whereas men of the same age had 5.5% and 6.2%, respectively, during the same period. The lowest prevalence rate was reported in the age group above 60 years (1.8%

and 2.4% in women in 2008 and 2012, respectively) and 3.5% and 4.6% in men in 2008 and 2012, respectively.

According to SANAC (2015), the HIV/AIDS prevalence rates were higher among men who have sex with men (MSM) and women sex workers compared to heterosexual partners (SANAC, 2015). Pary *et al.* (2008:45) also reported a higher prevalence of HIV/AIDS among MSM. The prevalence of HIV/AIDS in MSM increased by 10% between 2008 and 2012 and the figures were 22% in Cape Town and 48% in Durban (University of California San Francisco (UCSF), 2015). The SA Health Monitoring Survey found that four out of five females sex workers of ages between 30 and 35 years who were living in major cities such as Durban and Johannesburg were living with the virus (SA Health Monitoring Survey, 2014). The same report found that two out of five female sex workers were living with HIV/AIDS in Cape Town. More than 29% of pregnant women who attended antenatal clinics were living with HIV/AIDS in 2012 (NDOH, 2015b).

2.5.7 Incidence and prevalence of HIV/AIDS in children in South Africa

The MTCT rate at eight weeks has dramatically decreased to approximately 2.6/2.7% in 2011/12 (NDOH, 2013a:26). This is largely due to PMTCT. Coverage of testing pregnant women was 100% and treatment of HIV positive women was approximately 90% (NDOH, 2015b). The PMTCT programme helped to decrease infant and under-5 mortality rates, and the decrease of HIV prevalence among children aged two to 14 (3.1 %). The percentage of HIV-positive pregnant women receiving ARVs to reduce the risk of MTCT was reported to be 83% in 2009, 87.3% in 2010, and 87.1% in 2011 (NDOH, 2012).

The gains in preventing peri-partum transmission should be supported by efforts to prevent transmission from breastfeeding. According to the 2010 PMTCT survey, only 20% of HIV-positive women were exclusively breastfeeding, 62% were formula feeding and 18% were practising high-risk mixed feeding, suggesting a need for increased attention to infant feeding (Goga *et al.*, 2012). Therefore, the MTCT rate at 18 months could be considerably higher than the rate at eight weeks. The PMTCT survey showed that more than 90% of women in 2010 received ARV treatment or prophylaxis (Goga *et al.*, 2012).

2.5.8 The HIV/AIDS-related mortality in South Africa

Combination ART serves an important role in public health in reducing deaths among people living with HIV/AIDS. The highest numbers of HIV/AIDS-related deaths were reported in 2005 (WHO, 2005a). More than 365 000 HIV/AIDS-related deaths were recorded in 2005 (WHO, 2006b). Life expectancy at birth significantly dropped in SA between 2002 and 2005 (Stats SA, 2015a:5). According to the Actuarial Society of South Africa (ASSA, 2013), the annual number of AIDS-related deaths decreased from 257 000 in 2005 to 194 000 in 2010. This decline was attributed to the expansion of the ART programme. Life expectancy at birth increased, whereas adult, children under five years and infant mortality decreased (Johnson *et al*, 2013; Stats SA, 2015a:6). Approximately 780 000 deaths have been averted between 2003 and 2012 (NDOH, 2013a). The number of women aged 15 to 29 years who have died of HIV/AIDS-related illnesses was more than men in the same age group who died (Stats SA, 2015a:6). However, the same report highlighted that from ages above 35 years, there were more deaths in men compared to females. Deaths among adolescents dying from HIV/AIDs doubled in 2013, when 120 000 adolescents died (Stats SA, 2015a:5). Adolescents aged 15 to 24 years living with HIV/AIDS had the lowest proportion of ART treatment exposure (SANAC, 2015). The ART exposure in the HIV/AIDS positive population aged 15 to 49 years was 28.9% in 2014 (Stats SA, 2015a:4).

Immediate ART initiation helped to reduce the risk of severe bacterial infections in asymptomatic HIV-positive people with high CD4 cell counts above 500 cells/ μ L by 61% (O' Connor, 2017:110). However, the success of the PMTCT and the massive roll-out of ART programmes helped to raise the life expectancy in SA since 2005. After the introduction of HAART in 2004, many children under the age of five years have survived since 2005 (Stats SA, 2015a:5). The infant mortality rate dropped from 52 per 1 000 births in 2005 to 34 per 1 000 births in 2015 (Stats SA, 2015a:5). In 2015, life expectancy for males at birth was 60.6 years and 64.3 years for females (Stats SA, 2015a:5). The number of HIV/AIDS-related deaths declined from 51% in 2005 to 34% in 2009 and this was attributed to the roll-out of ART (Stats SA, 2015a:3). The deaths toll dropped from 345 000 in 2005 to 162 000 in 2015 (Stats SA, 2016:3). The number of AIDS deaths increased in 2010 and 2011 by 0.3% and 2%, respectively, thereafter dropping by more than 7% in 2015 (NDOH, 2016a). Table 2-12 shows the changes in HIV/AIDS-related deaths between 2005 and 2015 in SA (Stats SA, 2015a:6).

Table 2-12: Changes in HIV/AIDS-related deaths between 2005 and 2015 in South Africa

Year	HIV/AIDS-related deaths	Total number of deaths	% HIV related deaths
2005	345 607	682 059	50.7
2006	89 321	625 210	46.3
2007	228 384	564 663	40.4
2008	195 835	564 663	36.1
2009	179 461	528 342	34.0
2010	183 465	535 396	34.3
2011	200 654	556 087	36.1
2012	197 090	555 021	35.5
2013	177 624	539 880	32.9
2014	151 040	516 929	29.2
2015	162 445	531 965	30.5

South Africa is still yet to achieve its National Strategic Plan (2012-2016) of initiating at least 80% of the eligible people on ART by having more than 75% alive on treatment five years after initiation (WHO, 2014b).

2.6 HISTORY OF ANTIRETROVIRAL THERAPY

One of the major advances in the treatment of HIV infection has been the introduction of antiretroviral drugs (ARVs). ARVs have an incredible capacity to reduce HIV/AIDS-related deaths when patients take the medication regularly (Bor *et al.*, 2013:961). The drug called zidovudine (AZT) was approved by the Food and Drug Administration (FDA) of the United States of America in 1987 as a cancer drug and was the first antiretroviral drug (Herschhorn *et al.*, 2010:2717). The drug AZT is a nucleoside reverse transcriptase inhibitor (NRTI) that targets viral reverse transcriptase, thereby inhibiting the process of making DNA from RNA (Institute of Medicine, 2005:43). Zidovudine helped to slow down the HIV/AIDS progression in the early 1980s and 1990s, and it gave a glimpse of hope to individuals who were infected with the HIV (CDC, 1992).

A few years later, researchers noted that AZT did not overall increase the survival rate of the infected individuals and its ability to suppress the virus was low (Institute of Medicine, 2005:43). Erice *et al.* (1993:1663) reported that AZT failed to completely suppress the reverse transcriptase enzyme of HIV. Richman *et al.* (1991:1079) found out that a mutation at position 215 of the reverse

transcriptase enzyme was linked to AZT resistance. According to Manasa *et al.* (2013), many people who were infected with HIV did not respond well to many first-line drug monotherapy; therefore, the drug resistance was prevalent. Therefore, better drugs were urgently needed to suppress the virus, and HAART was introduced to address the weaknesses of treating HIV/AIDS using one drug (WHO, 2010d). The protease inhibitors (PIs) are another class of ARV that also interferes with the HIV replication (Zhengtong *et al.*, 2015:95), and this was followed by fusion inhibitors that are capable of blocking the fusion of the viral envelope and the entrance of the virus into the cell membrane (Briz *et al.*, 2006:619). The integrase inhibitors impeach the insertion of the proviral DNA to host cell chromosomes (Pommier *et al.*, 2005:236). By 2011, the FDA had approved more than 35 ARVs (Perno, 2011:41). The use of HAART has changed the pattern of morbidity and mortality associated with HIV infection in countries where such drugs are available for infected patients (UNAIDS, 2015).

Highly-active antiretroviral therapy is a triple drug (or more) therapy that is the current recommended therapy for HIV/AIDS infection and is able to suppress viral replication, improve immune function and delay clinical deterioration (Institute of Medicine, 2005:1). The HAART works by inhibiting the three main HIV enzymes, namely the reverse transcriptase, protease and integrase enzymes of HIV (Cotton *et al.*, 2009:39). There are six classes of ARVs that are used to treat HIV/AIDS. According to Meintjes *et al.* (2014:122), these are:

- Nucleoside reverse transcriptase inhibitors
- Non-nucleoside reverse transcriptase inhibitors
- Protease inhibitors
- Integrase inhibitors
- Fusion inhibitors
- Entry inhibitors

The nucleoside reverse transcriptase inhibitors (NRTIs) stop the process of RNA elongation performed by the enzyme, called reverse transcriptase (Stine, 2009:72). The reverse transcriptase enables HIV RNA to be converted to DNA. The mode of action of NRTIs is to resemble a nucleoside in every aspect, except the portion that couples with the next nucleoside in sequence. Their mechanism of action is that they are first phosphorylated by viral thymidine kinase and the second and third phosphorylation processes are done by host cell kinases. The triphosphate is then incorporated into the viral DNA causing premature chain termination, and

therefore, if reverse transcriptase incorporates a NRTI into its DNA copy, the reaction stops, leaving the enzymes blocked and DNA synthesis unfinished (Stine, 2009:72). All NRTIs are prodrugs (Guitierrez, 2008:501), and examples include efavirenz, etravirine and nevirapine.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs) form the second group of reverse transcriptase (RT) inhibitors. These are small molecules that inhibit the RT by binding to a hydrophobic pocket in the proximity of the active site of the enzyme (Stine, 2009:74). The NNRTIs directly react with HIV reverse transcriptase and inhibit its activity of reverse transcription of RNA to DNA (Owen *et al.*, 2013). Resistance to NNRTIs is caused by mutations that reduce the affinity of the inhibitor to the protein. According to Erice *et al.* (1993:1164), one mutation caused by NNRTI is enough to confer complete resistance to all compounds of the same ART class. Examples of drugs include abacavir, combination of emtricitabine-tenofovir (Truvada[®]) and lamivudine-zidovudine (Combivir[®]).

Protease inhibitors (PIs) stop the process of forming new viral particles (Palmier *et al.*, 2005:236). The viral enzyme responsible for virion maturation is protease. The PIs are small molecules that bind to the active site of the protease enzyme, and therefore competing with its natural substrates. The PIs mimic the structure of the viral peptide and act by inhibiting the HIV protease enzyme that cleaves precursor proteins (McFarland, 2009:1119). Protease inhibitors helps in making the protein necessary for building new HIV copies (Owen *et al.*, 2013). The examples of PIs include atazanavir, darunavir, fosamprenavir and indinavir.

Integrase inhibitors prevent the protease enzyme from integrating the viral DNA into the host chromosome. Integrase inhibitors disable integrase, a protein that HIV uses to insert its genetic material into CD4 cells (Hazuda *et al.*, 2000:649). Successful inhibition of integration processes leaves the viral DNA in the nucleus, where it is re-circularised by the host repair enzymes, and therefore the HIV lifecycle is disrupted. Examples of drugs include raltegravir, elvitegravir and dolutegravir.

The last group of antiretroviral drugs is the fusion inhibitors (FIs), which stop HIV before it can enter and infect the host cells. The FIs block the interaction between the virus and the CD4 receptors of the host cells. The first FIs were approved by the FDA in 2003 and are only reserved for patients in whom other treatments have failed (Institute of Medicine, 2005:3). Examples include enfuvirtide (Fuzeon[®]) and maraviroc (Selzentry[®]).

2.7 EVOLUTION OF HIV TREATMENT GUIDELINES

The HIV/AIDS antiretroviral therapy treatment guidelines have steadily improved globally since they were introduced in the late 1990s. The HAART is given to help people live longer, but people still remain HIV positive (Bruner *et al.*, 2015:192). The HIV hides inside the DNA of healthy T cells, a place where current medicine is unable to reach. While most CD4 cells die shortly after becoming infected, a small portion of T cells containing instructions for creating the virus remain dormant (Bruner *et al.*, 2015:192). This means that even if the virus is completely eliminated from the body at any time, the instructions for creating the virus could be activated and start the process all over again. However, potent ART is highly effective at preventing HIV transmission, improves lifestyle and prevents several bacterial opportunistic infections (Cohen *et al.*, 2011:500).

In 2002, WHO HIV treatment guidelines recommended initiation of ART in HIV positive people who have reached the WHO clinical stage IV (HIV disease) with CD4 cell counts of ≤ 200 cells/ μ L or less advanced disease with total lymphocyte counts of ≤ 1200 cells/ μ L (WHO, 2002a). These initial WHO HIV guidelines recognised the increased mortality of HIV/AIDS patients associated with low CD4 cell counts or low total lymphocyte counts.

In 2003, the WHO initiated the “3 by 5” programme, which aimed to have 3 million people in developing countries receiving ARVs by the end of 2005 (WHO, 2007a). However, this target was not reached, but many African countries made progress under the scheme. A few years later, the WHO set another target called “All by 2010”, which aimed to provide universal access to HIV treatment by 2010 (WHO, 2006a). Under the programme, considerable progress was made in Africa to fight against HIV/AIDS.

In November 2009, new treatment guidelines of HIV/AIDS were introduced that required early initiation of HAART for infected individuals. The revised HIV treatment guidelines stated that ART should be initiated when the CD4 cell count was ≤ 350 cells/ μ L to improve the quality of life of infected persons (WHO, 2010b).

South Africa changed its HIV treatment eligibility criteria in April 2010 to include all HIV infected pregnant and breastfeeding women and all HIV positive patients with TB co-infection and for adults to include those with CD4 cell counts between 200 and ≤ 350 cells/ μ L (WHO, 2010b). The WHO recommended that the first line of HIV/AIDS treatment should consist of an NNRTI plus two NRTIs, one of which should be AZT or TDF. Severe *et al.* (2010:257) reported that when ART is initiated early, it can delay AIDS progression and lead to reduced morbidity and mortality. The scientific evidence emerging from this study and other studies made the WHO to revise its HIV treatment guidelines. The revised guidelines were implemented gradually in all countries due to

the country's capability and availability of resources (WHO, 2010d). Children are more vulnerable to HIV than adults are, and without treatment, mortality is 50% at two years and 80% by five years (UNAIDS, 2016). In 2016, approximately 2.1 million children were in need of HAART globally and only 23% were receiving treatment compared to 48% adults (UNAIDS, 2016:7).

In 2013, the WHO further revised its HIV/AIDS treatment guidelines. The revised HIV treatment guidelines have increased the number of people eligible for ART. The WHO new guidelines recommended that the following patients should receive ART: 1) all HIV positive individuals with a CD4 cell count <500 cells/ μ L; 2) HIV infected pregnant and breastfeeding women irrespective of CD4 cell count or WHO clinical stage; and 3) HIV positive people with TB and hepatitis B co-infections irrespective of CD4 cell count or WHO clinical stage (WHO, 2013a).

The 2013 WHO guidelines reflect changes in HIV treatment. The changes were new technologies, CD4 point of care services, HIV testing and treatment and treatment monitoring, simple and safer regimens, fixed-dose combinations, PMTCT, and triple regimens (WHO, 2013a). The WHO (2013a) reported that liver disease is emerging as a leading cause of death in HIV-hepatitis B co-infected individuals and some ARVs also treat hepatitis B virus. The revised HIV treatment guidelines from the WHO recommend that ART should be given for life to HIV infected persons irrespective of their CD4 cell count. According to Doherty *et al.* (2013:528), the main changes were as follows:

- The WHO guidelines recommend reducing the use of d4T in first-line therapy because of its toxicity.
- The second-line regimens should contain a ritonavir boosted PI plus two NRTIs, either AZT or TDF, based on what was used in the first-line therapy. Ritonavir boosted, Atazanavir (ATV/r) or lopinavir (LPV/r) are the preferred PIs.
- All patients should have access to CD4 cell count testing in order to optimise pre-ART care and ART management (Patients with CD4 counts <350 cells/mm³ or with WHO stage 3 or 4 irrespective of CD4 cell count).
- Patients co-infected with drug sensitive or drug resistant HIV who should be initiated with ART irrespective of CD4 cell count.
- Pregnant women with CD4 <350 cells/ μ L for lifelong ART and CD4 > 350 cells/mm³ for prophylaxis.
- Perform VL to confirm suspected treatment failure.

- Monitor drug toxicities based on symptoms.

The current WHO HIV/AIDS treatment guidelines recommend that all HIV positive persons should be on ART regardless of the HIV staging, viral load or CD4 cell count (WHO, 2013a). The 2013 HIV/AIDS treatment guidelines from WHO no longer recommend Option A to initiate ART in pregnant and breastfeeding women, which was based on 2010 guidelines (WHO, 2013a).

2.7.1 Treatment gaps of human immune virus

Many studies have conducted intensive research on treatment of HIV/AIDS; however, a cure for HIV infection remains elusive. The HAART is used as a standard treatment for HIV infection (WHO, 2010b). Antiretroviral drugs are also used by those who are at risk of exposure to HIV for prevention, often referred to as pre-exposure prophylaxis. Individuals are able to protect themselves against HIV infection as demonstrated by many clinical studies (Galae *et al.*, 2011:256; Mailjaars *et al.*, 2017:712). Research studies have constantly shown that 20 to 30% of medication prescriptions are never filled, and that approximately 50% of medications for chronic conditions are not taken as prescribed (Kirkner, 2014:1). Many people do not manage to take their medications regularly and 23% of non-adherence is due to behavioural issues such as procrastination or forgetfulness. Often subjects are found to have drug levels in their blood that are much lower than expected if they were taking their pills as prescribed (Express Scripts, 2014:32). Another challenge that is faced by individuals taking HAART is that the medication should be taken for life in order to suppress the VL beyond detectable levels.

The UNAIDS 90-90-90 targets aim to achieve at least 90% of the infected persons should know their status, 90% of those knowing their status should be receiving ART and 90% of those on treatment should achieve complete viral suppression, which no country has yet achieved (WHO, 2016a). However, funding for HIV/AIDS programmes has dwindled in the last five years; therefore, many LMICs might not achieve this goal due to limited resources (Dieleman *et al.*, 2016). The potent HAART regimens have managed to change the deadly condition into a chronically manageable illness with infected patients generally living longer (UNAIDS, 2016).

Even though HAART is available in many countries, not everyone who is infected by HIV is on treatment (WHO, 2016a). In 2015, only 41% of people living with HIV/AIDS globally were on treatment (WHO, 2016b). According to the UNAIDS (2016) global report on HIV/AIDS, there were approximately 2.2 million people who were receiving HIV treatment in 2005. By the end of 2015, an estimated 18.2 million people were receiving HAART globally (UNAIDS, 2016:2).

In 2015, approximately 55% of people living with HIV/AIDS were on treatment in Latin America and the Caribbean; Eastern Europe and central Asia had 21%, and Asia and the Pacific had 41% treatment coverage (WHO, 2016b). The HAART helped to reduce the death toll to 1.3 million globally in 2015 (WHO, 2016b).

In Africa, there were 21.2 million people who were eligible for HAART in 2013 and only 15 million people received treatment (WHO, 2015b). At least 25% of the infected HIV individuals in sub-Saharan Africa achieved complete suppression in 2014 (WHO, 2015b). According to UNAIDS (2015), more than 50% of HIV-infected people in sub-Saharan Africa do not know their HIV status and are not on treatment.

2.7.2 HIV treatment guidelines in South Africa

There are two parallel healthcare systems in SA, namely the private health sector and the public health sectors. According to the Council of Medical Aid Schemes (CMS) report (2015), approximately 15% of the total population in SA sought treatment in the private medical aid schemes healthcare environment in 2015. The distribution of resources among the two systems is not equal and more resources are available in the private healthcare sector (CMS, 2014).

The treatment guidelines for HIV/AIDS are the same in both the public and the private health sectors (Johnson *et al.*, 2013:155). However, the private health sector uses both the National Department of Health treatment guidelines and the Southern Africa HIV Clinicians Association HIV treatment guidelines (2015).

2.7.3 Treatment of HIV/AIDS in the South Africa public health sector

Antiretroviral treatment became available in the public sector in South Africa in March 2004, and treatment was provided only at HIV/AIDS clinics in all districts in the country (Pembrey *et al.*, 2007). Statistics indicated that, by the end of 2006, approximately 200 000 people were on HIV/AIDS treatment in South Africa, of whom more than 100 000 received treatment in the private health sector and non-government organisations (NGOs) (Johnson & McLeod, 2007; WHO, 2007b).

By December 2007, South Africa had the biggest ART programme in the world, with more than 424 000 people on ART (Simelela & Venter, 2014:250). By 2008, there were 568 000 people on ART compared to 40 000 in 2004 (Simelela & Venter, 2014:250). The percentage of eligible adults and children receiving ART rose from 58.3% in 2011 to 75.3% in 2015 (NDOH, 2015a).

In 2009, there were more than 900 000 patients on ART in South Africa (NDOH, 2014b). South Africa launched the biggest HIV testing and counselling initiative in the same year. As part of the HIV testing and counselling campaign, the former president of SA, Mr Jacob Zuma, publicly tested for HIV and more than 20 million South Africans were tested for HIV between 2009 and 2011 (Simelela & Venter, 2014:250). The NDOH reported that approximately nine million people were tested for HIV between 2012 and 2013 (Shisana *et al.*, 2014). The number of pregnant women on ART rose from 87.3% in 2011 to 99% in 2012 (NDOH, 2015b). By 2015, SA had made substantial progress in stopping the spread of HIV/AIDS, with over 66% infected people knowing their HIV statuses and 80% of eligible patients on ART (Stats SA, 2015a).

The number of people on treatment in South Africa kept on increasing during the past decade. According to the UNAIDS report (2014), there were more than 3.4 million people who were receiving HIV/AIDS treatment in South Africa. The HAART has helped to reduce the number of HIV/AIDS associated deaths in all provinces of South Africa (Lessells *et al.*, 2014:17), and life expectancy in PLWHIV on treatment has significantly improved to almost normal (70 years) (Bor *et al.*, 2013:961). Tanser *et al.* (2013:966) reported that the HIV infection incidence rate has declined in SA due to HAART. Early initiation of HAART could improve the quality of life among PLWHIV (Doherty *et al.*, 2013:528).

A voluntary medical male circumcision programme was introduced around 2009 in the country as a means of reducing HIV infections, with KZN being the first to roll out the at a large scale, although the process was hampered by controversy that the procedure was not safe. By the end of 2010, approximately 131 117 men were circumcised (Simelela & Venter, 2014:250). Approximately 47 000 voluntary medical male circumcisions were performed between October 2011 and April 2013, and new infections were expected to drop by 60% (NDOH, 2014). The WHO, in conjunction with NDOH, recommended voluntary medical male circumcision as an HIV prevention strategy in South Africa in 2013 (NDOH, 2014b). This was based on scientific evidence that male circumcision could reduce the risk of contracting HIV and sexually transmitted infections, and protects women from cervical cancer (WHO, 2014a).

In 2010, the South Africa ART guidelines were launched, which prioritised HIV ARVs for a much wider group of HIV positive people and the guidelines were aligned to WHO HIV treatment guidelines (NDOH, 2014b). However, the main challenge for the government was the implementation of the programme. The 2010 WHO Guidelines on ARVs for PMTCT recommended ART for women who were eligible for one of the two prophylaxis regimen options (Options A and B), and women were put on lifelong ART. In 2011, all HIV positive adults became eligible when their CD4 cell count dropped to ≤ 350 cells/ μ L (WHO, 2015a). Initially, the South

Africa treatment guidelines had provided for ARV treatment to be started at a lower level than that recommended by the WHO. However, in 2011, the country's guidelines were brought in line with the 2010 WHO recommendations for the first time. Early in 2012, the guidance was that all patients should be initiated on ART if their CD4 cell count was less than 350 cells/ μ L.

In 2010, the ART programme in SA was decentralised through the roll-out of nurse-initiated and -managed ART in the public health sector (NDOH, 2014a). The HIV treatment initiation was performed by doctors who were rotating between primary healthcare clinics, while the professional nurses and HIV counsellors performed follow-up visits. SA government changed its guidelines to also allow nurse-initiated ART in 2010 (Sanne *et al.*, 2010:33). Approximately 1.8 million South Africans living with HIV/AIDS received ART in 2010 (WHO, 2011). Out of these, approximately 1.5 million were on treatment in the public sector, 190 000 from the private health sector and 78 000 from non-government organisations.

The country's ART programme has managed to link more than 80% of all people diagnosed with HIV to access appropriate treatment, care and support between 2009 and 2011 (HSRC, 2014; WHO, 2012). In 2014, the ART coverage was 46% in the population above 15 years and 66% between the ages zero to 14 years, and this could be attributed to favourable policies and legislation (NDOH, 2014b). The country has managed to embrace new developments in policies based on available local and international scientific evidence. The country also adopted the UNAIDS 90-90-90 target in order to strengthen the efforts for increasing ART uptake beyond 2015 (NDOH, 2016b).

2.7.4 South Africa's private health sector treatment guidelines

In the history of SA, the private sector has played a crucial role in fighting HIV/AIDS. The ARVs were mainly provided by the private sector and NGOs before 2004 (Johnson & McLeod, 2007). The private health sector started to treat HIV/AIDS in 2006 under HIV disease management programmes through medical schemes (Regensberg & Makiwane, 2009:6). Approximately 50% of the national health expenditure is spent in the private healthcare sector (Econex, 213:1). This underscores the importance of the private medical aid schemes in the healthcare environment in SA.

The private health sector serves approximately 9.2 million people (17% of the total population) (CMS, 2015a). According to the Council of Medical Schemes in South Africa, the private health sector had more than four million principal members and five million beneficiaries belonging to medical aid schemes in 2013 (CMS, 2014). The private health sector is made up of open medical aid schemes (schemes that are open to the general public; therefore, anybody can become a

member of the scheme) or closed schemes (one has to be working in a certain sector of industry, have specific academic qualifications or belong to certain trade union or professional association in order to belong to a restricted medical aid), administrators and brokers, unregulated insurance products, private hospitals and several independent hospitals, specialists, general practitioners and dentists, pharmaceutical companies, medical device manufacturers and suppliers, wholesalers; distributors and retailers, logistics providers and regulators (CMS, 2014). Healthcare professionals provide their services on private basis, and are usually funded by the subscriptions of individuals to medical aid schemes (Econex, 2013:1). Private healthcare practitioners also provide services through private hospitals. (Bassat, 2009).

2.7.4.1 Council for Medical Schemes

In December 2015, the Council for Medical Schemes (CMS) annual report reported that there were 83 medical aid schemes (23 open and 60 restricted) registered in terms of Medical Schemes Act in South Africa in 2016 (CMS, 2015/2016:123). There were more than 4.9 million beneficiaries in the open medical aid scheme market and more than 3.8 million beneficiaries in the restricted market by December 2014 (CMS, 2016a:123). Statistical data show a drop of 0.06% of medical aid schemes in 2014 compared to the total number of medical aid schemes in 2015 (CMS, 2016:125).

The Medical Scheme Act (131 of 1998), through the SA Parliament, formed the CMS, which is a board responsible for the supervision of the medical schemes in South Africa (CMS, 2009). The Medical Schemes Act (131 of 1998) was first implemented in 1999 in order to control the escalating costs of healthcare in South Africa. Regulation 8 of the Medical Schemes Act (131/1998) requires all medical schemes to fund the diagnosis, treatment and care costs of the conditions listed in the prescribed minimum benefit (PMB) list in the law.

Section 7 of the Medical Schemes Act (131 of 1998) describes the functions of the Council for Medical Schemes, which include the following:

- Protection of the interests of the medical scheme's beneficiaries at all times.
- Control and coordinate the functioning of medical schemes.
- Make recommendations to the Minister of Health on criteria for the measurement of quality and outcomes of the relevant health services provided for by medical schemes.
- Investigate complaints and settle disputes in relation to the affairs of medical schemes as provided for in the Act.

- Collect and disseminate information about private healthcare.
- Make rules, consistent with the provisions of this Act, for the purpose of the performance of its functions and the exercise of its powers.
- Advise the Minister of Health on any matter concerning medical schemes.
- Perform any other functions conferred on the Council by the Minister of Health, or by the Act.

The HIV/AIDS prescribed minimum benefit (PMB) offered some form of relief to PLWHIV after the amendment of the Medical Schemes Act of 1998 (131 of 1998) (da Silva & Wayburne, 2008:40). The PMBs are a set of defined benefits to ensure that all medical aid scheme members have access to certain minimum health services regardless of the benefit option they have selected. The PMBs also provide medical aid scheme members with continuous care to improve their health and wellbeing and to make healthcare more affordable to many (Erasmus, 2005:1). Most of the PMBs cover an additional 270 medical conditions (diagnostic treatment pairs), which are primarily offered by hospitals and 26 life threatening chronic conditions under their disease management programmes (CMS, 2015a:4; McLeod, 2005:151). This means that HIV/AIDS treatment will be covered even when normal chronic benefits have run out (Erasmus, 2005:1).

The first PMB for HIV/AIDS was implemented by some medical aid schemes in 2007 (Erasmus, 2005:1). Prescribed minimum benefits on HIV/AIDS are only given to members who have declared their HIV positive status to their medical schemes. Erasmus (2005:2) indicated that the following costs are funded by medical aid schemes according to the PMB regulations:

- Networks of professionals for pre-and post-testing counselling.
- Networks of doctors and specialists who are experts in the management and treatment of HIV/AIDS.
- Specific interventions at specific intervals, such as pathology tests, necessary to monitor both the HIV treatment and progress of the disease.
- Sending reminders to members to go for tests and consultations.
- Networks of hospitals for the treatment of HIV/AIDS-related illnesses.
- Provision of ART and other treatments, for example opportunistic infections, according to the scheme's formulary.

- The HIV/AIDS-specific call centres, mostly operated by registered nurses, for assistance with benefit queries, disease education and any additional information regarding aspects of the disease, such as diagnosis, treatment side effects, and caregiver support.
- Pain management.
- PMTCT of HIV.
- Post-exposure prophylaxis following sexual assault.
- Screening and preventive therapy for TB.

The CMS circular 73 of 2016 was aligned with the new HIV treatment guidelines as starting from September 2016 (CMS, 2016a). The circular recommended that PLHWA should be put on HIV treatment for the rest of their lives, should treat all HIV positive individuals regardless of their ages and CD4 cell counts, should give priority to those with CD4 \leq 350 cells/ μ L, consider patients in the pre-ART and wellness programme for Universal Test and Treat (UTT), assessing patients' willingness and readiness to start and those who are not ready for treatment should be kept in the wellness programme and offering continuous counselling at every visit on the importance of early treatment. The baseline monitoring of CD4 count will still be carried out as it is the key factor in determining the need to initiate opportunistic infection prophylaxis at CD4 \leq 200 cells/ μ L, identifying patients who are eligible for Cryptococci antigen (CrAg) at CD4 \leq 100, prioritisation at CD4 \leq 350 cells/ μ L and fast tracking at CD4 \leq 200 cells/ μ L (CMS, 2017:2). The CMS in line with the requirements of the PMB regulations has adopted the current national HIV treatment guidelines. The medical schemes should therefore fund the diagnosis, treatment and care of HIV according to the recently adopted national guidelines.

The HIV/AIDS is ranked fifth by prevalence compared to other chronic disease list conditions (CMS, 2016a). HIV/AIDS had a prevalence rate of 38 per 1 000 beneficiaries in 2014 and the prevalence increased to 40 per 1 000 beneficiaries in 2015 (CMS, 2016a:136). The expenditure on HIV was around R4 000.00 per beneficiary per month in 2014 and it increased to R5 000.00 per beneficiary per month in 2015 (CMS, 2016a:136). The same report stated that HIV/ AIDS is the best managed CDL condition in the industry with coverage ratios as high as 60%. The proportion of HIV beneficiaries receiving ART was 67.4% in 2015, up from 61.9% in 2014 (CMS, 2016a:138). The coverage of HIV monitoring tests has also increased significantly with increases from 53% in 2014 to 59% in 2015 for both VL tests and the CD4 counts (CMS, 2016a:139).

The costs of healthcare services in the private sector are constantly increasing due to the weak rand against major currencies on imports (NDOH, 2015a). A significant number South Africans do not have healthcare insurance; therefore, it comes as no surprise that many are attended to in the public health sector. Before HIV/AIDS was a PMB, some medical schemes covered only needed HAART treatment and stopped providing treatment when funds were exhausted. The high prevalence of people living with HIV/AIDS pushed the demand of HIV/AIDS care and services up and the cost of services also increased. The high cost of providing service means losses to medical schemes. HIV/AIDS PMB covers hospitalisation of patients, opportunistic infections, and patients do not pay co-payments (CMS, 2013). However, all chronic medications on PMB lists are regulated by the government. This list includes ARVs.

Private hospitals form a major part of the healthcare system in SA. Most private hospitals are tertiary and specialist health services (NDOH, 2008:50). Access to private hospitals was mostly limited to only the members of medical schemes.

2.7.4.2 Sources of funding HIV/AIDS in the private sector

The impact of HIV/AIDS on businesses and businesses' response to the pandemic are important. Many companies responded to the HIV/AIDS problem by implementing interventions that aimed to eliminate the disease. Some of the strategies taken by businesses included (NDOH, 2008):

- Promoting prevention and education (targeting prevention of new HIV infections).
- Improving workplace policies to ensure rights for employees such as access to healthcare and counselling.
- Giving grants to AIDS service organisations.
- Encouraging other businesses to get involved.
- Businesses have also carried out broad programmes to reach out to customers and local communities through cause-related marketing and social investment initiatives.

Public-private partnerships are a common source of funding HIV/AIDS in the private sector in South Africa (CMS, 2013). The public-private workplace partnership model is a partnership between the provincial TB programmes and mining companies and it operates by reimbursing the employers or receives TB drugs and ARVs for free for each patient treated at their clinic.

In order to meet the ever-increasing demand for HIV/AIDS care from for more than seven million people who are living with HIV/AIDS, the South Africa Government made strategic partnerships with a number of international donors and local nongovernmental organisations (NGOs) between 2004 and 2015 (United States President's Emergency Plan for AIDS Relief (PEPFAR), 2010). The PEPFAR partnered with the South Africa Government in supporting HIV prevention, care, and treatment services since 2004 (Josef *et al.*, 2014:1). The PEPFAR supported many NGOs and private health sector general practitioners (GPs) who were focusing on HIV/AIDS treatment.

Rite-To-Care Health Services (RTCHS) is a private company that specialises in providing workplace HIV outreach services to large companies in South Africa. The RTCHS covers more than 80 000 employees (Josef *et al.*, 2014:11). The RTCHS has delivered HIV/AIDS care and treatment using the following three models, namely the Direct AIDS Intervention, Thusong and down referral (Josef, *et al.*, 2014:11).

The Direct AIDS Intervention model was started in 2004 and the programme was financed through medical aid and employer sponsored insurance. This model is an example of a contracting out arrangement between the private sector agents, insurance companies or employers.

The Thusong model was financed by PEPFAR and it targeted unemployed people who were living with HIV/AIDS or low-income workers without coverage through medical aid or insurance schemes. The Thusong model was implemented between 2005 and 2012 and a total of 6 000 HIV/AIDS patients received HIV care and treatment. The Thusong model was part of PEPFAR's broader national effort to involve South Africa's private sector GPs in HIV care in order to relieve overburdened public and private not-for-profit health facilities.

The third model was called the down referral model and started in 2012 at the time that the Thusong model was phased out. The programme is financed by PEPFAR and the SA government. In response to overcrowding at public hospitals for HIV/AIDS care, this model tested the cost-effectiveness of transferring stable HIV patients to RTCHS-managed South Africa (GP). The SA government planned to finance the cost of running the down referral model using revenues generated from the proposed national health insurance programme. One example of the down referral mode is the GP-model, which admits HIV/AIDS patients who are already on ART for three to six months from the public health sector and who do not have private medical health insurance. The GP-model was started in the North West Province by the NDOH to provide treatment through selected private South Africa. (Igumbor *et al.*, 2014:2). The NDOH provides ART and laboratory services through their district pharmacy and National Health Laboratory Services, respectively. All GPs were trained on HIV/AIDS and TB management. The GPs charge

a negotiated fee, and adherence and treatment support services are provided by a private health solution company called BroadReach Healthcare® Company. The office set-up costs at selected public healthcare clinics are covered by BroadReach Healthcare® Company. The key component of the model is a patient care information management system. The costs of services charged to the patients are competitive by harnessing public sector regulations and experience and on the other hand private sectors human resources and infrastructure. Cost is a major barrier to receive treatment in many LMICs. Weiser *et al.* (2003:281) found the cost of ARVs in Botswana to be a major barrier to ART uptake and the adherence among patients dropped to 44%.

Tuberculosis and HIV/AIDS are treated in the SA mining industry but they do not provide HIV/AIDS services to outsiders. The mining industry of SA was not spared from HIV/AIDS. Companies were negatively affected due to increased mortality and morbidity among workers (SA Business Coalition on HIV & AIDS (SABCOHA), 2003). Workers were absent so long due to sicknesses (SABCOHA, 2003) and some workers died as a result of HIV/AIDS. Replacing employees is not easy since it involves hiring and training; the time taken to replace a lost employee can be longer than one month if the person is skilled. Therefore, many mining companies have HIV/AIDS programmes (SABCOHA, 2003). These programmes focus on offering HIV treatment to employees and surrounding areas, especially female sex workers. The Anglo Coal Company in SA partnered with trade unions and neighbouring communities on HIV/AIDS programmes (Daly, 2000). In 2000, the company had more than 10 500 employees and those who were infected by HIV were treated at company premises. The company gave condoms, and used videos and theatres to educate its employees on HIV/AIDS and sexually transmitted diseases (STDs). The company also formed a partnership with the local government authorities in providing mobile STD clinics, as well as safety, life and better food. Anglo Coal Company also partnered with Eskom, Ingwe Coal, and the University of Zimbabwe on the Kriel Project to educate sex workers and their customers in practising safe sex (Daly, 2000).

The Harmony Gold Mining Company limited (SA) partnered with NGO Family Health International in 1997 to set up the Lesedi HIV/AIDS Prevention Project (UNAIDS, 2000). The company had approximately 4 000 workers, mostly migrant workers from neighbouring countries such as Zimbabwe, Zambia and Malawi, by then. Many of its workers had HIV/AIDS and were always sick. Harmony Gold Mining Company started by focusing on its employees by educating them about HIV/AIDS and distributing condoms, but the company failed to change the sexual behaviour of its workers. Later, the company targeted female sex workers from the surrounding communities and encouraged them to visit Harmony hospital. Outreach activities also included women. The programme was later joined by two other mining companies (Gold Fields Limited and Joe Mine) (UNAIDS, 2000).

Eskom is one of the first companies in SA to have an HIV/AIDS strategic plan for its workers in 1998. The company set a strategic committee to monitor HIV by testing its employees anonymously. The committee also oversees HIV/AIDS prevention and education campaigns. In 2013, Eskom had more than 46 000 employees (Eskom SOC Holdings limited presentation, 2013:5). The company provides HIV/AIDS counselling and treatment for its infected workers. Eskom also funds NGOs working on AIDS prevention and vaccine research. It also works with the government on HIV/AIDS public campaigns and makes regular broadcasts on national radio and television stations.

Elsewhere, the business sector responded to HIV reflection positively. Thailand's American International Assurance gave donations to NGOs and public health organisations and medical schemes promoting HIV/AIDS prevention. The company partnered with an NGO called CARE on preventing HIV among factory workers (Daly, 2000).

The Northlines Airlines[®], a USA company, established a partnership with the Paediatric AIDS Foundation that had and created a programme called "Air Cares" (Steckel *et al.*, 1999). The airline used in-flight videos, magazines and bonus miles for passengers to raise money. In a year, the airline's campaign on HIV reached more than 40 million of its own passengers, and the raised money was donated to the Foundation.

Tata Iron and Steel Company[®] Limited in India had an HIV/AIDS programme for its employees (UNAIDS, 1999). The company focused on its employees as well as the public. In the community, the company works with community groups to distribute condoms and information pamphlets on HIV/AIDS. The company also installed vending machines in places where more people visit. The HIV/AIDS patients were admitted to its hospital without discrimination. The company also works with the National AIDS Control Organization and NGOs in India.

The Actuarial Society of SA (2005) predicted the prevalence of HIV in medical aid schemes to be 10% of people living with HIV/AIDS in SA who are covered by medical aid schemes. According to Stevens *et al.* (2008:202), the HIV/AIDS PMB served more than 100 000 people living with the virus in the private health sector.

There were 390 000 HIV/AIDS patients who received HIV care in the private health sector in 2013 (AVERT, 2016). HIV/AIDS is covered by the medical schemes in terms of the Medical Schemes Act (131 of 1998) under PMBs related to HIV infection (McLeod *et al.*, 2003:77).

Currently, there is limited data on the prevalence of HIV/AIDS and the prescribing patterns of ART in the private health sector of SA. Data on treatment of HIV/AIDS co-morbid mental disorders in

the private sector are also limited. It is against this background that the study attempted to determine the prevalence of HIV/AIDS and co-morbidities, prescribing patterns of ARVs and CNS medications as well as drug-drug interactions in AIDS patients accessing treatment in the private health sector in SA.

2.7.4.3 HIV treatment guidelines in the private health sector

Eligibility criteria for ART initiation have evolved progressively over time. From programme inception until early 2010, adults were eligible for ART initiation when their CD4 cell count was 200 cells/ μ L and less, or if they were in WHO clinical Stage 4. In early 2010, all infants, pregnant women and patients co-infected with TB became eligible for ART with a CD4 count of \leq 350 cells/ μ L. In late 2011, all HIV-infected adults became eligible when their CD4 count was 350 cells/ μ L and below. Scientific evidence showed that HAART medication has decreased the morbidity and mortality from the HIV/AIDS disease worldwide (Abbas *et al.*, 2006). In rural settings of SA, such as in KZN, the massive HAART roll-out programme resulted in a decline of HIV/AIDS-related deaths by 22% in men and 29% in women (Herbst *et al.*, 2009:754).

HIV/AIDS has no cure, but it can be treated by HAART (Mills *et al.*, 2011:853). The HAART inhibits HIV replication. Each type of ARV drug in the regimen targets different parts of the HIV lifecycle to maximise the benefit. Successful HIV suppression slows the disease progression and therefore increases the survival of the infected person (Cohen *et al.*, 2011:1953; Herbst *et al.*, 2011:760). Anglemyer *et al.* (2011) reported that HAART can reduce HIV transmission in HIV-discordant couples.

In line with latest WHO HIV treatment guidelines (the consolidated clinical guidelines on ART were recommended in 2013 (WHO, 2013), SA, with the help of SANAC, NDOH, and development partners again updated its treatment guideline in April 2015 to ensure compliance with international standard treatment for HIV/AIDS. The standard treatment guidelines and essential medicines list for SA primary healthcare recommends that diagnosis of HIV infection should meet the following criteria (NDOH, 2014a):

- The patient is offered pre- and post-test counselling.
- Patient's confidentiality is ensured.
- HIV test in adults must be confirmed with a second test (either two rapid tests, using kits from different manufacturers, or with one rapid test and one laboratory test, usually ELISA).
- HIV antibodies are not detected during the first few weeks in primary infection.

2.7.4.4 HIV testing and counselling

The guiding principles adhere to the five C's, namely consent, confidentiality, counselling, correct test results and connections to care, treatment and prevention services (WHO, 2016a:68). The guidelines state that:

- All people receiving HIV testing and counselling must give informed consent (verbal consent is sufficient and written consent is not required).
- HIV testing and counselling services are confidential.
- Always offer pre- and post-HIV testing and counselling services and give high quality information.
- Must be accompanied by appropriate and high quality pre-test information and post-test counselling.
- Providers should provide high-quality testing services, and quality assurance mechanisms should be in place to ensure the provision of correct test results.
- Link patient to prevention, care and treatment services.

2.7.4.5 World Health Organization HIV staging

The WHO staging system for HIV infection and disease in adults and adolescents has four clinical stages, and the details for each stage are highlighted (refer to Annexure E). The WHO clinical staging of HIV/AIDS is important in terms of prognosis and the initiation of therapy and it consists of four clinical stages (Regensberg & Makiwane, 2009:8).

2.7.4.6 Universal test and treat

South Africa formally adopted new recommendations from the WHO, the Universal Test and Treat (UTT), in accordance with the WHO new guidelines on HIV treatment in 2015 (WHO, 2015a). The UTT directly supports UNAIDS's 90-90-90 targets of ensuring that 90% of all people living with HIV know their HIV status, 90% of people with diagnosed HIV infection receive sustained ART and 90% of all people receiving ART have viral suppression (Granich *et al.*, 2009:54). SA embraced UTT and key changes made by NDOH to the national treatment guidelines for PMTCT and management of HIV in children, adolescents and adults were on the following items (European AIDS Clinical Society, 2015; WHO, 2015a).

2.7.5 World Health Organization HIV treatment guidelines

South Africa has revised its HIV treatment guidelines and the changes made are aligned with the WHO HIV treatment guidelines (WHO, 2013a). The most recent changes in the SA HIV/AIDS treatment guidelines are: all pregnant women and TB co-infected patients became eligible for ART irrespective of their CD4 cell count, although pregnant women with a CD4 count above 350 cells/ μ L when initiating ART were expected to interrupt ART on cessation of breastfeeding, until their CD4 count was at the 350 cells/ μ L or less threshold (SANAC, 2014). The PMTCT of HIV in the country resulted in reductions in vertical HIV transmissions from 14% in 2004 to less than 3% in 2011 (Goga *et al.*, 2012). Volmink *et al.* (2007:12) found that mothers who were taking ARVs had low VLs and the vertical transmission rates decreased from mother to child during breastfeeding. The current threshold for ART initiation is CD4 <500 cells/ μ L, with Option B+ being to test and treat children younger than five years. ART guidelines are regularly aligned with global policies, and include phased replacement of the multiple drug regimens with FDCs, which are simpler in relation to adherence. The country changed from triple drug therapy to FDCs, which are cost effective and the country saved R2.2 billion between 2013 and 2014 (NDOH, 2013c).

The new recommendations made the following changes (European AIDS Clinical Society, 2015; WHO, 2015a):

Changes specific to pregnant/breastfeeding women

- All HIV positive women who are pregnant or breastfeeding to be initiated on ART regardless of their CD4 cell counts.
- EFV is the recommended first-line regimen regardless of the gestation period.
- Use of HAART for the rest of life.
- Testing VL for women on HAART for more than three months at confirmation of their pregnancies.
- Repeat the HIV tests for women who initially tested HIV negative after every three months during pregnancy, at labour, at six weeks expanded programme on immunisation (EPI) visit, and after every three months during breastfeeding; then, routinely during antenatal care, postnatal care and EPI.
- Close monitoring of women with contraindications to fixed dose combinations.

- Provision of birth HIV polymerase chain reaction (PCR) for all HIV exposed neonates.
- Utilisation of extended 12-week NVP or dual post-exposure prophylaxis with NVP and AZT for infants where maternal VL suppression is absent.

Changes specific to infants and early adolescents (European AIDS Clinical Society, 2015; WHO, 2013a; WHO, 2015a) are as follows:

- Providing HAART to all children under the age of five years regardless of their CD4 count or clinical HIV staging.
- Initiating HAART to children to children ≥ 5 years starting at CD4 cell count ≤ 500 cells/ μ L regardless of the HIV clinical staging.
- Immediate initiation of infant ART with first positive HIV polymerase chain reaction (PCR), while waiting for confirmatory HIV test results.
- Use of second HIV/PCR test as a confirmation for positive HIV PCR test.
- Viral load is no longer recommended as part of baseline assessment for ART initiation in children.
- Birth PCR HIV testing of all HIV-exposed neonates, repeated at 10 weeks and rapid HIV test at 18 months. For neonates on extended 12-week NVP, the PCR test should be repeated at 18 weeks and a rapid HIV test at 18 months.

The European AIDS Clinical Society (2015) made specific changes to treat adolescents and adults by initiating early ART at CD4 cell count ≤ 500 cells/ μ L. The changes were:

- Provision of ART for those with Hepatitis B co-infection, regardless of their CD4 cell count or clinical staging.
- Harmonised ART regimen across populations, mainly in pregnant and breastfeeding women, adolescents and adults.
- Initiate ART for all HIV/TB co-infected individuals.
- Inclusion of guidance on HIV for key populations.
- Use of simplified fixed-dose combinations for ART.

- Use of VL for monitoring treatment success and early identification of treatment failure.
- Routine Cryptococci infection screening for all HIV-infected patients with CD4<100 cells/ μ L.
- Use Tuberculin sensitivity tests as part of screening for isoniazid preventive therapy (IPT).
- Use third-line drugs for patients falling second-line regimens.

The management of HAART depends on monitoring both the CD4 cell count and VL (WHO, 2016a). The CD4 cell counts inform decisions for when to start initiation of ART, whereas VL measurement is considered the gold standard for monitoring the effectiveness of combined ART and detecting early adherence problems in people living with HIV/AIDS (Ford *et al.*, 2015:1128). In developed countries, the effectiveness of the HAART regimen is determined using both VL and CD4 cell count measurements, which are generally carried out at least every six months. There is a concerted effort to increase access to VL testing in developing countries and most national guidelines recommend either targeted or routine VL monitoring. These changes are reflected in the WHO HIV treatment guidelines, which recommend that VL is the preferred approach to monitoring treatment efficacy and detecting adherence problems and CD4 cell count for HIV staging (WHO, 2013a; WHO, 2014a; Ford *et al.*, 2015:1128). Many countries have adopted the WHO guidelines to monitor ART effectiveness using both CD4 cell count and VL.

2.7.5.1 First-line ART regimen for adults

The recommended revised 2013 WHO HIV treatment guidelines are: First-line ART should consist of two NRTIs plus NNRTI (Lessells *et al.*, 2014:17; WHO, 2015a):

- TDF + 3TC (or FTC) + EFV as a fixed-dose combination is recommended as the preferred option to initiate ART.

If TDF + 3TC (or FTC) + EFV is contraindicated or not available, the options recommended are:

- AZT + 3TC + EFV
- AZT + 3TC + NVP
- TDF + 3TC (or FTC) + NVP
- Countries should discontinue d4T use in first-line regimens because of its metabolic toxicities.

- Special circumstances prescribers should use regimens containing ABC, d4T and boosted PIs.

However, the standard ART in SA consists of the use of at least three medications to maximally suppress HIV and stop the progression of the HIV disease. ARTs commonly used are: NRTIs inhibitors such as AZT, 3TC, TDF and FTC, NNRTIs such as NVP and EFV, and PIs such as LPV/ (WHO, 2013a)

2.7.5.2 First-line ART for pregnant, breastfeeding women and their infants

Once daily FDC of TDF + 3TC or FTC + EFV is the WHO recommended first-line ART in pregnant and breastfeeding women (WHO, 2013a:116; European AIDS Clinical Society, 2015; WHO, 2015a). The other guidelines included (WHO, 2013a:116; European AIDS Clinical Society, 2015; WHO, 2015a):

- Fixed-dose combination of TDF + 3TC (or FTC) + EFV (once/daily) is recommended as first-line ART in pregnant and breastfeeding women, including pregnant women in the first trimester of pregnancy and women of childbearing age. The recommendation applies both to lifelong treatment and to ART initiated for PMTCT.
- Infants of mothers who are receiving ART and are breastfeeding should receive six weeks of infant prophylaxis with daily NVP.
- If infants are receiving replacement feeding, they should be given four to six weeks of infant prophylaxis with daily NVP (or twice-daily AZT). Infant prophylaxis should begin at birth or when HIV exposure is recognised postpartum.

Table 2-13 presents the infant prophylaxis guidelines (European AIDS Clinical Society, 2015; WHO, 2015a).

Table 2-13: Infant prophylaxis

Infant age	Daily dosage NVP
Birth to 6 weeks	
Birth weight 2 000-1 499 grams	10 mg once daily
Birth weight ≥ 2 500 grams	15 mg once daily
> 6 weeks to 6 months	20 mg once daily
>6 months to 9 months	30 mg once daily
>9 months until breastfeeding ends	40 mg once daily

Simplified infant prophylaxis dosing recommendations: AZT simplified infant prophylaxis dosing recommendations; only recommended in settings with replacement feeding: AZT

- Birth to 6 weeks (birth weight 2 000-2 499 grams), recommended dosage: 10 mg two times daily.
- Birth to 6 weeks (birth weight >2 500 grams); recommended dosage: 15 mg two times daily.

The first-line ART for children younger than three years of age are as follows (European AIDS Clinical Society, 2015; WHO, 2015a):

- Preferred regimens ABC or AZT + 3TC + LPV/r.
- Alternative regimens ABC or AZT + 3TC + NVP.
- Special circumstances d4Td + 3TC + LPV/r or d4T + 3TC + NVP based on the general principle of using non-thymidine analogues in first-line regimens.

Table 2-14: First-line ART for children three years and older (including adolescents)

	Children 3<10 years and adolescents>35 kg	Adolescents (10-19 years ≥35 kg)
Preferred	ABC + 3TC + EFV	TDF + 3TC (or FTC) + EFV
Alternative	ABC + 3TC + NVP AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + EFV TDF + 3TC (or FTC) + NVP	AZT + 3TC + EFV AZT + 3TC + NVP TDF + 3TC (or FTC) + NVP
Special circumstances	d4T + 3TC + EFV d4T + 3TC + NVP	ABC + 3TC + EFV ABC + 3TC + NVP

2.7.5.3 Tuberculosis co-treatment in children with HIV

Tuberculosis comorbid HIV/AIDS is a major problem globally. Approximately 2.4 million out of 38 million PLWHIV worldwide had TB in 2015 (UNAIDS, 2016). In 2010, there were 350 000 HIV/AIDS associated TB deaths globally (UNAIDS, 2016). One study proved that early initiation of HAART medication could reduce bacterial infections such as TB by more than 77% (Daniel, *et al.*, 2015:111).

New recommended regimens for children and adolescents who need TB treatment are as follows (European AIDS Clinical Society, 2015; WHO, 2015a):

- Younger than 3 years: Recommended 2 NRTIs + NVP, ensuring that dose is 200 mg/m² or Triple NRTI (AZT + 3TC + ABC).
- Three years and older: Recommended 2NRTIs + EFV or Triple NRTI (AZT + 3TC + ABC).

Recommended regimens for children and infants initiating TB treatment while receiving ART (children on standard NNRTI-based regimen) (2 NRTIs plus EFV or NVP) (WHO, 2013a:116; European AIDS Clinical Society, 2015; WHO, 2015a):

- Younger than 3 years: Continue NVP, ensuring that dose is 200 mg/m² or Triple NRTI (AZT + 3TC + ABC).
- Three years and older: If the child is receiving EFV, continue the same regimen. If the child is receiving NVP, substitute with EFV or Triple NRTIs (AZT + 3TC + ABC).

Recommended regimen for children and infants initiating TB treatment while receiving ART (child on standard PI- based regimen) (2 NRTIs plus LPV/r) (WHO, 2013a:116; European AIDS Clinical Society, 2015; WHO, 2015a):

- Younger than 3 years: Triple NRTIs (AZT + 3TC + ABC) or substitute NVP for LPV/r, ensuring that dose is 200 mg/m² or continue LPV/r; consider adding RTV to achieve the full therapeutic dose.
- Three years and older: If the child has no history of failure of an NNRTI-based regimen: substitute with EFV or Triple NRTI (AZT + 3TC + ABC) or continue LPV/r; consider adding RTV to achieve the full therapeutic dose.

- Three years and older: If the child has a history of failure of an NNRTI-based regimen: Triple NRTI (AZT + 3TC + ABC) or continue LPV/r; consider adding RTV to achieve the full therapeutic dose. Consider consultation with experts to construct a second-line regimen.

2.7.5.4 Monitoring the response to ART and the diagnosis of treatment failure

The new recommendations are (WHO, 2013a:116; European AIDS Clinical Society, 2015; WHO, 2015a):

- Viral load is recommended as the preferred monitoring approach to diagnose and confirm ARV treatment failure.
- If VL is not routinely available, CD4 count and clinical monitoring should be used to diagnose treatment failure.

2.7.5.5 Preferred second ARV regimens for adults, adolescents, pregnant women and children

Using a boosted PI + 2NRTI combination is recommended as the preferred strategy for second-line ART for adults, adolescents and also for children when NNRTI-containing regimens were used in first-line ART (WHO, 2013a:116; European AIDS Clinical Society, 2015; WHO, 2015a):

- Adults and adolescents (≥ 10 years), including pregnant and breastfeeding women: Preferred: AZT + 3TC + LPV/r AZT + 3TC + ATV/r.
- Alternative: TDF + 3TC (or FTC) + ATV/r TDF + 3TC (or FTC) + LPV/r.
- Children: If an NNRTI-based first-line regimen was used: preferred regimen is ABC + 3TC + LPV/r.
- Alternative regimens are: ABC + 3TC + LPV/r TDF + 3TC (or FTC) + LPV/r.
- Children younger than 3 years: If a PI-based first-line regimen was used: Preferred regimen: No change from first-line regimen in use.
- Alternative regimen: AZT (or ABC) + 3TC + NVP.
- Children older than 3 years and younger than 10 years: If a PI-based first-line regimen was used: Preferred: AZT (or ABC) + 3TC + EFV.
- Alternative regimen: ABC (or TDF) + 3TC + NVP.

2.7.5.6 Second-line ART regimen for adults and adolescents

Second-line ART for adults should consist of two NRTIs plus a ritonavir-boosted PI (WHO, 2013a:116; European AIDS Clinical Society, 2015; WHO, 2015a):

- Adults and adolescents (≥ 10 years): If d4T or AZT was used in first-line ART, use TDF + 3TC (or FTC) + ATV/r or LPV/r.
- Adults and adolescents (≥ 10 years): If TDF was used in first-line ART, use AZT + 3TC + ATV/r or LPV/r.
- Pregnant women (same regimens recommended for adults and adolescents): If rifabutin is available, use a standard PI-containing regimen as recommended for adults and adolescents.
- Pregnant women with HIV and TB co-infection (same regimens recommended for adults and adolescents): If rifabutin is not available, use same NRTI backbones as recommended for adults and adolescents plus double-dose LPV/r (that is, LPV/r 800mg/200mg twice daily) or standard LPV dose with an adjusted dose of RTV (that is, LPV/r 400mg/400mg twice daily).
- Pregnant women with HIV co-infection: preferred is AZT + TDF + 3TC (or FTC) + (ATV/r or LPV/r).

2.7.5.7 Third-line ART regimen

- New consolidated guideline recommendations (conditional) (WHO, 2013a:116; European AIDS Clinical Society, 2015; WHO, 2015a):
- Developed by national programmes; should develop policies for third-line ART.
- Third-line regimens should include new drugs with minimal risk of cross-resistance to previously used regimens, such as integrase inhibitors and second-generation NNRTIs and PIs.
- Patients on a failing second-line regimen with no new ARV options should continue with a tolerated regimen.

2.7.5.8 HIV/AIDS intervention strategies

The HIV incidence rate remains high in SA despite some developments in prevention strategies. The SA government has made some inroads in implementing a number of programmes to reduce and prevent transmission of HIV, including the PMTCT programmes, supplying free ARVs, and HIV voluntary counselling and testing (NDOH, 2015b:14). The evidence rate from the HIV Prevention Trials Network (HPTN) 052 study supports treatment as prevention for HIV and *Tuberculosis Bacillus* (TB) mortality, transmission and morbidity. The HPTN 052 trial showed a 96% reduction in HIV transmission and of the trial participants completely adhering to treatment, which is unlikely in large-scale interventions (Cohen *et al.*, 2011:497). The same study suggested that HIV transmission is very minimal when the VL is below 1500 copies/mm³.

Treatment as prevention is an intervention that was first tested in randomised trials (Brunell *et al.*, 2006:91; Donnell, 2010; Quinn *et al.*, 2000:927; Tovanabutra *et al.*, 2002:282). Early initiation on ART could reduce viral replication and transmission. Granich *et al.* (2009:53) suggested a 99.4% reduction in infectiousness of those on ART. The ARVS could reduce HIV transmission among people taking treatment and this was reported by Anglemyer *et al.* (2011) in a trial where the HIV transmission rate was reduced by 86%. In addition to that, the ongoing treatment roll-out, according to WHO HIV guidelines of ART at CD4 cell count of $\leq 350\mu\text{L}$, has a profound impact on the HIV epidemic (Hontelez *et al.*, 2011).

Other strategies included promoting condom use, and providing education to disadvantaged groups, especially women, by making sure that girls attend school at least 80% of each term (Beksinska *et al.*, 2012:51). Although extensive efforts to curb the epidemic made by the government and the civic society may have resulted in a decline of HIV incidence among youth in the past few years, incidence levels remained high (Johnson *et al.*, 2012:1551). Commitment to achieve universal coverage gives a glimpse of hope that HAART can be used to prevent onwards transmission (Cohen *et al.*, 2011:497).

The timing of treatment initiation for people living with HIV/AIDS is important. Once initiated on combined ART, an infected individual should continue with HAART for the rest of his/her life in order to maximise viral suppression and reduce drug resistance (Lessells *et al.*, 2014:17). Human immune virus statistics have shown that infected people can live for many years without any symptoms, and treating these people will produce more benefits compared to those with HIV/AIDS (Bor *et al.*, 2013:961).

Effective programmes such as voluntary medical male circumcision and PrEP with ARVs, and post-exposure prophylaxis can reduce HIV transmission without changing sexual behaviour

(Auvert, 2005:298; Murnane *et al.*, 2013:2155). Post-exposure prophylaxis is a short-term ART used to reduce chances of acquiring HIV (WHO, 2013b). In SA, the duration of post-exposure prophylaxis is 28 days, and first dose should be taken in less than 72 hours after HIV exposure (NDOH, 2014a).

The treatment of sexually transmitted diseases is also important in reducing HIV transmissions. The opportunistic infections (OIs) could cause substantial morbidity, which might result in hospitalisation, necessitate toxic and expensive therapies, and shorten survival of people with HIV infection. The HAART could reduce Hepatitis B virus (HBV) co-infections among HIV positive people and this reduces mortality rates in severe chronic liver disease (Hoffmann *et al.*, 2009:1881). According to the World Bank (1994) and Gumede (1997), their reports provided estimates from Tanzania that showed that an adult on average suffers 17 episodes of HIV/AIDS-related illnesses before death, while a child suffers 6.5 episodes. This means that for people living with HIV/AIDS, occasionally they require admission to secondary and tertiary facilities, and a lack of or poor availability of essential drugs is one of the major constraints to the safe and effective treatment of opportunistic infections (Gumede, 1997). For the health service to meet such challenges and the increase in demand for drugs for management of HIV/AIDS and related cases, proper planning and implementation in drug selection procurement and distribution is vital to avert drug shortages. According to the United Nations AIDS report on the global AIDS epidemic (2013), many people unfortunately died prematurely due to a lack of essential drugs for OIs. The same report highlighted that OIs were the ultimate cause of death in HIV positive people and could be prevented, treated or managed with cost effective essential drugs. However, many people, especially in resource poor nations, do not have regular access to these essential drugs, including those for OIs in HIV/AIDS (Quick *et al.*, 1997).

While HAART remains the most effective strategy for reducing morbidity and mortality related to opportunistic infections, antibiotic prophylaxis has emerged as important preventive measure. For instance, co-trimoxazole prophylaxis is widely used in sub-Saharan Africa to prevent multiple infections. In two randomised controlled trials in Cote d'Ivoire, co-trimoxazole prophylaxis compared to placebos resulted in fewer hospitalisations and fewer cases of enteritis, pneumonia, non-typical salmonella and septicaemia (Wiktor, 1999). The therapy of OIs has changed substantially during the AIDS epidemic. More information on efficacy, toxicity, and interaction of drugs to treat and prevent OIs has emerged, and management strategies have evolved. New drugs have also become available that occupy important roles in our therapeutic armamentarium (NDOH, 2016a).

2.7.5.9 Antiretroviral therapy in South Africa

South Africa's treatment HIV/AIDS guidelines were revised in 2013 to align with current WHO treatment guidelines (NDOH, 2015b). According to NDOH (2015b) standard treatment guidelines, care-related activities for people living with HIV/AIDS include the following: treatment of common HIV-related infections including pneumonia, candidiasis, herpes simplex virus, tuberculosis, diarrhoea diseases, varicella zoster virus infections and other fungal infections; prophylaxis against OIs; access to high quality primary and reproductive healthcare; access to sexually transmitted infections (STIs) care; detection and treatment of HIV-related OIs; detection and treatment of HIV-related cancers, including Kaposi Sarcoma, lymphoma, and cervical cancer; detection and treatment of neurological problems and mental illnesses complicating HIV infection; HAART; psychological support; and counselling.

Between 2015 and 2016, SA had adopted the recommended WHO universal ART for all people living with HIV/AIDS (WHO, 2015a). All HIV infected persons are eligible for ART medication, regardless of their CD4 cell count, VL count or WHO HIV staging. Nevertheless, HIV/AIDS cannot be completely destroyed with the ARV drugs that are currently available and the long-term use of HAART might have side effects that are severe to health (Gandhi *et al.*, 2010). Even when the VL is undetectable in plasma, some viral particles are still present in the host cells that are not reached by current HAART, and these may provide a source of viral rebound if treatment is stopped (Bruner *et al.*, 2015:192; Hermankova *et al.*, 2003:7388). The NDOH recommended the following ARVs to treat HIV/AIDS in SA (NDOH, 2014a). Table 2-15 presents the antiretroviral drugs for the treatment of HIV/AIDS available in SA (Rossiter, 2014:339-352).

Table 2-15: Antiretroviral drugs for the treatment of HIV/AIDS available in SA

ACTIVE INGREDIENT	ARVs available in SA
NRTIs	
Abacavir	Ziagen® GlaxoSmithKline; Aspen Abacavir®; Cipla-Abacavir® <i>tablets</i> 300 mg; <i>oral solution</i> 20 mg/mL oral (as sulphate)
	Adco-Abacavir®; Invertron® Norvagen; Sonke Abacavir® <i>tablets</i> 300 mg Auro-Abacavir® Novagen <i>oral solution</i> 20 mg/mL (as sulphate) Kavimun® Paed Mylan <i>tablets</i> 60 mg

ACTIVE INGREDIENT	ARVs available in SA
Didanosine (ddl)	<p>Videx® BM Squibb EC <i>capsules</i> 250 mg, 400 mg Aspen Didanosine® <i>tablets</i>, 25 mg, 50 mg, 100 mg, 150 mg Deladex® Novagen® <i>capsules</i> 250 mg, 400 mg Sonke Didanosine® <i>tablets</i> 25 mg, 50 mg, 100 mg, <i>capsules</i> 250 mg, 400 mg</p>
Emtricitabine (FTC)	<p><i>Tenofovir/emtricitabine fixed dose combination:</i> Truvada® Aspen Pharmacare, Adco-Emtevir® Al Pharm; Didivir® Cipla Medpro; Tyricten® Aurobindo <i>tablets</i> tenofovir disoproxil fumarate/emtricitabine 300/200 mg <i>Emtricitabine/tenofovir/efavirenz fixed dose combination:</i> Atripla® MSD; Atroiza® Mylan; Citenvir® Novagen Pharma; Odimune® Cipla Medpro; Tribuss® Aspen Pharmacare; <i>tablets</i> emtricitabine/tenofovir/disoproxil fumarate/efavirenz 200/300/600 mg</p>
Lamivudine (3TC)	<p>3TC® GlaxoSmithKline; Aspen Lamivudine®; Legram® Novagen Pharma <i>tablets</i> 150 mg; oral solution 10mg/mL (contains 3 g sucrose /15 mL) Adco-Lamivudine® <i>tablets</i> 150 mg; <i>oral solution</i> 50 mg/5 mL Cipla-Lamivudine® <i>tablets</i> 150 mg, 300 mg <i>oral solution</i> 50 mg/5mL Lazena® Mylan <i>tablets</i> 150mg, 300 mg, Sonke-Lamivudine® <i>tablets</i> 150 mg Pharma-Q Lamivudine® <i>syrup</i> 10 mg/mL <i>Zidovudine/lamivudine combination:</i> Aspen Lamzid®; Cipla Duovir®; Combivir® Glaxo-SmithKline; Lodiz® Novagen Pharma, Sonke Lamivudine + Zidovudine® <i>tablets</i> zidovudine/lamivudine 300/150 mg Retrovir®/3TC Post-HIV Exposure Prophylaxis Starter pack GlaxoSmithKline Retrovir® 18 <i>capsules</i>, zidovudine 100 mg plus 3TC® 6 <i>tablets</i>, lamivudine 150 mg (3-day starter pack) <i>Zidovudine/lamivudine plus efavirenz</i> Cipla-Duovir®/Cipla Efavirenz® co-pack Cipla Medpro Cipla-Duovir® <i>tablets</i>, zidovudine/lamivudine 300/150 mg plus Cipla-Efavirenz® <i>tablets</i>, efavirenz 600 mg <i>Zidovudine/lamivudine/ abacavir</i> Trizivar® GlaxoSmithKline; Sonke Abaciamizia® <i>tablets</i> zidovudine/lamivudine/abacavir 300/150/300 mg <i>Zidovudine/lamivudine/nevirapine</i></p>

ACTIVE INGREDIENT	ARVs available in SA
	Triplavar® Cipla Medpro <i>tablets</i> zidovudine/lamivudine/nevirapine 300/150/200 mg <i>Lamivudine/abacavir</i> Kivexa® GlaxoSmithKline <i>tablets</i> lamivudine/abacavir 300/600 mg <i>Stavudine/lamivudine/nevirapine</i> Triomune-30® Cipla Medpro, SonkeLamNevStav® Ranbaxy Be-Tabs; Virtrium® Aspen Pharmacare stavudine/lamivudine/nevirapine 30/150/200 mg
Stavudine (d4T)	Zerit® BM Squibb <i>capsules</i> 15 mg, 20 mg, 30 mg, 40 mg Aspen Stavudine® <i>capsules</i> 15 mg, 20 mg, 30 mg Sonke Stavudine® <i>capsules</i> 30 mg, 40 mg Combination preparations see above
Tenofovir (TDF)	Viread® Aspen care; Aspen Tenofovir®; Cipla Tenofovir®; Ricovir® Mylan; Sonke Tenofovir®; Zefin® Novagen <i>tablets</i> tenofovir disoproxil fumarate 300 mg Combinations preparations see above
Zidovudine (AZT)	Retrovir® GlaxoSmithKline <i>capsules</i> 100mg, 250 mg; <i>syrup</i> 50mg/5mL; <i>IV infusion</i> 200mg/20mL Adco-Zidovudine® <i>tablets</i> 300 mg; <i>oral solution</i> 50 mg/5mL Aspen Zidovudine® <i>tablets</i> 300 mg; <i>capsules</i> 100 mg, 250 mg; <i>syrup</i> 50 mg/5mL Dozra® Novagen Pharma; Cipla-Zidovudine® <i>tablets</i> 300 mg; <i>capsules</i> 100 mg; <i>oral solution</i> 50 mg/5mL Pharma-Q Zidovudine® <i>syrup</i> 50 mg/5mL Sonke Zidovudine® <i>tablets</i> 300 mg Zidomat® <i>tablets</i> 100 mg, 300 mg Combination preparations see above
NNRTIs	
Efavirenz	Stocrin® MSD; Arrow Efavirenz® Watson Pharma; Aspen Efavirenz®; Cipla Efavirenz® <i>tablets</i> 600 mg Adco-Efavirenz®; Erige® Novagen Pharma <i>capsules</i> 50 mg, 200mg; <i>tablets</i> 600 mg Sonke Efavirenz® <i>capsules</i> 200mg; <i>tablets</i> 600 mg Combination preparations see above
Etravirine	Intelence® Aspen Pharma care <i>tablets</i> 100 mg

ACTIVE INGREDIENT	ARVs available in SA
Nevirapine	Viramune® Ingelheim; Aspen Nevirapine®; Viropan® Novagen; Cipla-Nevirapine® <i>tablets</i> 200 mg; <i>suspension</i> 30 mg/5mL Adco-Nevirapine®; Sonke Nevirapine® <i>tablets</i> 200 mg <i>Combination</i> preparations see above
PIs	
Atazanavir	Reyataz® BM Squibb; Aspen Atazanavir® <i>capsules</i> 150 mg, 200 mg (as sulphate)
Darunavir	Prezista® Aspen <i>tablets</i> 300 mg (as ethanolate)
Fosamprenavir	Telzir® GlaxoSmithKline <i>tablets</i> 700 mg
Indinavir	Crixivan® MSD <i>capsules</i> 200mg, 400 mg (as sulphate)
Ritonavir	Norvir® Abbott SEC <i>soft capsules</i> 100 mg; <i>oral solution</i> 80mg/ML
Lopinavir/ritonavir	Aluvia® Abbott <i>tablets</i> 100/25 mg, 200/50 mg Kaletra® Abbott <i>oral solution</i> lopinavir/ritonavir 80/20 mg/mL
Saquinavir	Invi-rase® Roche <i>capsules</i> 200 mg (as mesylate)
OTHER ANTIRETROVIRALS	
Raltegravir	ISENTRESS® MSD <i>tablets</i> 400 mg(as potassium salts)

2.8 PREVALENCE OF CO-MORBIDITIES IN HIV/AIDS

Comorbidity in HIV/AIDS is defined as any disease condition outside the scope of HIV/AIDS-defining illnesses (Lorenc *et al.*, 2014:84). HIV/AIDS is associated with many comorbidities. The most common comorbidities associated with HIV/AIDS are chronic conditions such as cardiovascular diseases, chronic obstructive pulmonary disease, diabetes, obesity, metabolic syndromes and disruption of cognitive function (Guaraldi *et al.*, 2015; Narayan *et al.*, 2014:2). These comorbidities are prevalent among the elderly PLWHIV and they face serious health challenges such as psychiatric disorders (mood, dementia, psychosis) as a result of HIV infection, non-communicable diseases (cancer, chronic kidney disease, hypertension, diabetes, hepatic disorders) and opportunistic infections caused by *Cryptococcus neoformans*, *Toxoplasma gondii*, *Tuberculosis mycobacterium* (Guaraldi *et al.*, 2011:1120; Guaraldi *et al.*, 2015; Narayan *et al.*, 2014:2).

Across the lifespan of the infected individual, Hepatic C co-infections (Hernandez & Sherman, 2011:478) and metabolic disorders (McCutchan *et al.*, 2012:485) are risk factors and these could lead to serious neurocognitive disorders (Hinkin *et al.*, 2008:11). Archer (2016:1) reported that

HIV is associated with high rates of CNS disorders among PLWHIV. The CNS complications could be caused by long-term severe HIV infection or as a result of social determinants of health, HAART or ageing (CDC, 2008). However, HAART could help to increase the life expectancy of PLWHIV and help to decrease the number of people progressing to HAND (Watkins & Treisman, 2015:37). The HIV-1 infection targets the CNS in the subcortical brain areas and results in a high prevalence of delirium, depression, opportunistic CNS infections and dementia (Luma *et al.*, 2013). The HIV-1 could multiply in the brain in astrocytes and microglia, allowing the virus to hide from HAART and later compromise the neuronal function. Many PLWHIV could die from Hepatitis B and Hepatitis C co-infections (Thorn *et al.*, 2017:2525).

The WHO HIV treatment guidelines have no specific recommendations on screening and treatment for mental disorders among people living with HIV/AIDS (WHO, 2013a). The Mental Health Gap Action Programme (mhGAP) intervention guide for mental, neurological and substance use disorders can be used for people living with HIV/AIDS (WHO, 2010c). Some studies have reported that the prevalence of CNS disorders is increasing among people living with HIV/AIDS, including those taking medication (Luma *et al.*, 2013; Weiss *et al.*, 2010:39). Data are limited regarding treating HIV/AIDS associated with CNS disorders in LMICs. This study's main focus was identifying the prevalence rate of CNS usage in HIV/AIDS patients in the private healthcare sector of SA, and potential changes that have occurred in HIV/AIDS treatment guidelines from 2005 to 2015. Some complications of HIV/AIDS are shown in Table 2-16 (Chu & Selwyn, 2011:398; Goulet *et al.* 2007:1593; Weiss *et al.* 2010:39).

Table 2-16: Major complications in people living with HIV/AIDS

Body systems	Direct effect of HIV infection	Complications	Associated pathogens	HAART-related adverse reactions
Cardiovascular	HIV-associated cardiomyopathy, atherosclerosis	Heart disease, endocarditis	Cytomegalovirus, invasive fungi, Mycobacterium species, TB, Toxoplasma gondii T. gondii): Myocarditis, pericarditis	ABC causes cardiotoxicity*; PIs cause dyslipidaemia
Pulmonary	HIV-associated hypertension, emphysema*, pneumonitis	COPD, lung cancer (including Kaposi sarcoma & lymphoma	Pulmonary TB, cytomegalovirus, invasive fungi, Pneumocystis jiroveci, T, gondii, Mycobacterium tuberculosis: Pneumonia, pneumonitis	
Digestive	HIV-induced enteropathy, non-alcoholic fatty liver disease*	Lymphoma, Kaposi sarcoma, human papilloma virus related malignancies, viral hepatitis.	Protozoa, candida species, herpes simplex virus, cytomegalovirus	NRTIs: pancreatitis, PIs: diarrhoea, fatty liver*
Neck & head	HIV-associated retinopathy	Dental & gland disease, gingivitis	Cytomegalovirus, T. gondii, Human simplex virus, varicella zoster virus: Acute retinal necrosis & progressive outer retinal necrosis: Retinitis Invasive fungi: Otitis, Sinusitis	
Neuropsychiatric (Refer to Table 2.8.2)	HIV-associated neurocognitive disorders, myelopathy, neuropathy, radiculopathy	Primary CNS lymphoma Chronic psychiatric disorders	Cytomegalovirus, JC virus Cryptococcus neoformans, T. gondii	EFV: vivid dreams, sedation NRTIs: peripheral neuropathy
Renal	HIV-associated nephropathy	Chronic kidney disease not caused by HIV-associated nephropathy	STIs such as Chlamydia trachomatis	PIs: nephrolithiasis Tenofovir: nephrotoxicity

Body systems	Direct effect of HIV infection	Complications	Associated pathogens	HAART-related adverse reactions
Musculoskeletal	Myopathy, myositis	Osteopenia, osteoporosis, osteonecrosis		NRTI or NNRTIs: Osteomalacia* PIs with statin: myopathy
Endocrine	Impaired lipid & glucose metabolism HIV-associated wasting lipodystrophy Hypogonadism* , premature ovarian failure		Cytomegalovirus, invasive fungi, mycobacterium species: Adrenal gland infiltration	PIs: glucose or lipid disorders, lipodystrophy
Hematologic or oncologic	Coagulation disorders* Anaemia of chronic disease	Multiple myeloma, lymphoma	Invasive fungi, cytomegalovirus, mycobacterium species: Bone marrow infiltration leading to pancytopenia	AZT & trimethoprim/sulfamethoxazole: anaemia
Dermatologic	Eosinophilic folliculitis*	Kaposi sarcoma, molluscum contagiosum, eczema, Seborrheic dermatitis, psoriasis	Varicella zoster virus, fungal dermatoses	

2.8.1 Neuropsychiatric system

Complications of ARVs and complications of HIV infection usually overlap in HIV/AIDS patients. The complications might lead to psychiatric problems such as mania and substance abuse (Sullivan *et al.*, 2008:6). The HIV infection could cause a range of antiviral responses in the body, including the production of virus-specific antibodies, but the major response is in the cell-mediated immunity (Overbaugh & Morris, 2012:6).

Natural killer cells are vital to host a defence system against infections. The HIV infection could cause dysregulation of many aspects of immune responses, such as defective antibody and T-cell responses to new antigens and decreased natural killer cell response (Mavilio *et al.*, 2003:15011). As a result of damage to cells involved in cell-mediated immunity, toxins were released that, in turn, damaged the immune cells both systemically and within the CNS (Bolokadze *et al.*, 2008:34). The HIV infection could induce chronic inflammation in the brain and this resulted in infected cells producing IFN IL-1 and TNF- α and MDD (Krishnadas & Cavanagh,

2012:492). In another study, HIV invaded the subcortical areas and destroyed the basal ganglia, thalamus and temper limbic structures leading to new-onset depression, mania or psychosis (Nebhinani & Matoo, 2013:47). Without the support of glial cells and with the release of neurotoxins, neurons could be damaged or destroyed (Bolokadze *et al.*, 2008:34; Mavilio *et al.*, 2003:15011).

2.8.2 Central nervous system HIV infection complications

The HIV/AIDS and HAART are associated with many neurological complications such as HIV-mediated neurotoxicity, myelopathy, pain, changes in cognition, dementia, and psychiatric complications such as MDD, schizophrenia, substance abuse and dependence, and mania (Ellis *et al.*, 2010). Lack of treatment of these conditions could cause HIV/AIDS patients not to adhere to their treatment regimens (WHO, 2016a:171).

When HIV enters the human body, the first organ to be destroyed is the CNS (An *et al.*, 1999:1160). Once the CNS is infected, several neurological and psychiatric complications could follow (Bhaskaran *et al.*, 2008:213). People living with HIV/AIDS have a higher probability of suffering from one mental disorder in their lifetime than HIV negative people (Freeman *et al.*, 2008:498). According to Bolokadze *et al.* (2008:34), TB meningitis is a most common neurological complication and it affects more than 34% of PLWHIV. It was estimated that one in two PLWHIV suffered from chronic mental disorders (Bing *et al.*, 2001:721). Some mental disorders associated with HIV/AIDS can be categorised as brain diseases, personality and temperament disorders, social determinants of health, and behaviour disorders (Prince *et al.*, 2007:871). Pre-existing mental disorders are risk factors of contracting HIV as a result of irrational behaviour (Angelino & Treisman, 2008:100; Rabkin *et al.*, 2004:47).

It is estimated that more than 40% of PWHIV could develop neurological complications of the central and peripheral nervous systems (Rani *et al.*, 2015). According to Chipimo and Fylkesnes (2010:9), HIV/AIDS is capable of affecting all organs of the human body. The CNS was reported by Lind *et al.* (2010:294) as the second-most commonly affected organ in HIV infected individuals. Therefore, it is not surprising that series of mental disorders could occur after HIV infection (Bhaskaran *et al.*, 2008:213). The study done by Letendre *et al.* (2009:46) highlighted a high prevalence rate (7%) of CMV encephalitis among HIV/AIDS patients.

2.8.2.1 Neurological complications due to HIV/AIDS

Neurological complications due to HIV/AIDS can be divided into two major categories, namely the primary and secondary disorders. Primary CNS complications due to HIV infections include HIV-associated CNS lymphomas, progressive multifocal leukoencephalopathy, toxoplasmosis, cytomegalovirus encephalitis, cerebrovascular diseases, neurocognitive disorders, vacuolar myelopathy and certain peripheral neuropathies (McDaniel *et al.*, 1997:311). Secondary neoplastic complications due to HIV infection could be caused by autoimmune, Kaposi's sarcoma, *Tuberculosis meningitis*, and fungal infections (*Penicillium mameffeii* encephalitis and *Cryptococcal meningitis*) (Gurunathan *et al.*, 2009:1997; McDaniel *et al.*, 1997:311). The HIV infection could also lead to opportunistic infections of CNS (Kaplan *et al.*, 2005:69).

2.8.2.1.1 Peripheral neuropathy

Peripheral neuropathy is a condition that affects the nerves, which may affect normal functions such as sensation, locomotion, gland or organ function, or other aspects of health, depending on the type of nerve affected (England *et al.*, 2005:199). Some of the common causes of peripheral neuropathies include HIV infection, genetics, CNS diseases, systemic diseases, hyperglycaemia-induced glycation, vitamin deficiency, chemotherapy, radiation therapy, medication, traumatic injury, radiation therapy, excessive alcohol consumption, and coeliac diseases (England *et al.*, 2005:200). Peripheral neuropathy is prevalent in 15 to 50% of PLWHIV (Yadav & Collman 2009:445). When HIV infected monocytes cross the blood brain barrier and enters the CNS cells, it could lead to HIV/AIDS associated neurocognitive disorder (HAND) (Ances & Ellis, 2007:90).

2.8.2.1.2 HIV/AIDS associated neurocognitive disorder

The HIV/AIDS associated neurocognitive disorder (HAND) is an AIDS defining stage that affects the cognitive function and neurobehavioral function (Bolduc *et al.*, 2016:31). Bolokadze *et al.* (2008:34) estimated that more than 24% of PLWHIV are likely to suffer from HAND. According to Valcour *et al.* (2012:280), approximately 40 to 50% of PLWHIV were suffering from HAND, and cognitive decline, impairment in attention, learning and executive function were being associated with increased rates of mood disorders. Letendre (2011:137) classified HAND as asymptomatic neurocognitive disorders, mild neurocognitive disorders or HIV associated dementia (HAD). However, a couple of studies have reported that the prevalence rate of HAND in HIV/AIDS is declining due to HAART (Cross *et al.*, 2013:1114; Gougeon *et al.*, 2016:1619).

The HIV infected monocytes and CD4 cells could infect the CNS cells and produce neurotoxic host and viral factors, pro-inflammatory chemokines and cytokines such as tumour necrosis factor (TNF α) and IL-1 β (Yadav & Collman 2009:445). High levels of cytokines found in HIV/AIDS patients caused brain inflammation by entering the brain from the blood (Tiraboschi *et al.*, 2015:390). The HAART could completely suppress VL, but it has failed to suppress TNF α (Zhou *et al.*, 2017:1133).

2.8.2.1.3 Distal sensory polyneuropathy

Distal sensory polyneuropathy is a result of damage to the peripheral nerves often causing weakness, pain, and numbness in the affected organs (England *et al.*, 2005:199). The condition is characterised by a slow progressive or static toe and distal foot neurotic pain (England *et al.*, 2005:199). Distal sensory polyneuropathy affects more than 70% of PLWHIV globally (Simpson *et al.*, 2006:1679). Pettersen (2006:816) reported that distal sensory polyneuropathy was caused by indinavir. In another study, ARVs caused distal sensory polyneuropathy that was associated with mitochondrial DNA damage (Moyle (2005:47). The same study also reported other peripheral neurological disorders, such as mononeuropathy simplex, plexopathies and acute demyelination polyneuropathy, which are caused by HIV/AIDS.

2.8.2.1.4 Drug induced psychosis

Psychosis is a clinical term that describes a severe mental disorder in which thought and emotions are so impaired that contact is lost with external reality (Ham *et al.*, 2017:11). Psychosis can be caused by genetic or environmental vulnerability factors, or a combination of both. Psychosis is prevalent among PLWHIV. Prescribed medication can cause psychosis (Ham *et al.*, 2017:11). Some antiretroviral drugs are associated with psychosis. Efavirenz and nevirapine could cause drug-induced psychosis (Wise *et al.*, 2002:879; Poulsen & Lublin, 2003:452). Symptoms of drug-induced psychosis are similar to symptoms caused by schizophrenia, and it is difficult to distinguish between them (Ham *et al.*, 2017:11). Drugs' adverse reactions, including symptoms such as paraesthesia, dysesthesia, back pain, loss of sensation of the lower limbs, bowel and bladder malfunctions, are common among PLWHIV (Chu & Selwyn, 2011:397).

Sacktor (2002:115) defined HIV-associated dementia (HAD) as a progressive subcortical dementia condition. The incidence rate of HAD ranges from 4 to 7% globally, and the accumulative prevalence rate is estimated to be 15% (Arthur *et al.*, 1993:2245). The incidence of HAD in people living with HIV/AIDS who are not on HIV treatment is estimated to be 35 per 1 000 person years (Joska *et al.*, 2011:1197). Sacktor (2006:311) reported a decrease in the prevalence of HAD to be associated with HAART and an increase in the prevalence of HIV-1 minor cognitive

disorder. Known risk factors of HAD include old age, loss of weight, persistent physical symptoms, immune activation, HIV subtypes and drug resistance (Letendre, 2011:137). Symptoms of HAD include slowing of motor and mental function with memory loss and language deficit (Resnick *et al.*, 1988:9).

2.8.2.1.5 Myelopathy

Myelopathy is a condition that results from a serious impairment of the spinal cord (Narayan *et al.*, 2014:2). Main causes of myelopathy include spinal stenosis, spinal trauma and spinal infections, as well as autoimmune, oncological, neurological and congenital disorders. The HAART has managed to significantly reduce vacuolar myelopathy, but it remains the most common chronic myelopathy associated with HIV. Vacuolar myelopathy occurs when AIDS is full blown, when CD4⁺lymphocyte concentrations are very low, often comorbid with AIDS dementia complex, peripheral neuropathies, and opportunistic infections or malignancies of the CNS or peripheral nervous system such as cytomegalovirus, progressive multifocal leukoencephalopathy, lymphoma (Narayan *et al.*, 2014:2). Human T-cell lymphotropic virus-1 (HTLV-1) was reported to co-occur with HIV infection (Simpson & Olney, 1992:708). High prevalence rates of co-infections of HIV and HTLV-1 were reported in SA among people living with HIV/AIDS (Bhigjee *et al.*, 2001:348). Schutte *et al.* (2013:1) reported that more than 50% of HIV/HTLV-I myopathies were seen at Steve Biko Academic Hospital and 33% were attended to in KZN. The HIV-associated myelopathies caused vacuoles in the lateral and posterior of the thoracic spinal cord, and mostly affected the lower extremities (Schutte *et al.*, 2013:1). Symptoms of myelopathy include weakness, changes in sensation and spasms (Chu & Selwyn, 2011:397).

2.8.2.1.6 Delirium

Delirium is a generic name for a common mental state with multiple aetiologies, such as sepsis, hypoxemia, anaemia, CNS infections, HAART, opioids, and HIV infection (Hogan & Wilkins, 2011:571). The condition is characterised by changes in cognition and an inability to concentrate or process external stimuli. According to Sammond and Bairy (2007), more than one in three PLWHIV suffer from delirium globally. The prevalence rate of delirium in PLWHIV is estimated to range from 43 to 65% in late-stage AIDS (Hogan & Wilkins, 2011: 571). Nevirapine and efavirenz are both associated with potentially significant neuropsychiatric impairments (Emilio *et al.*, 2008:485) The prevalence of schizophrenia among people living with HIV/AIDS has steadily increased since the 1980s (Carey *et al.*, 1995:262).

2.8.2.1.7 Mental disorders as a reaction to HIV infection

Recent data have showed that mood disorders are common among HIV/AIDS patients (Slabbert *et al.*, 2015:3). The prevalence rate of new psychiatric conditions in HIV positive people ranges from 0.2 to 15% globally (Joska *et al.*, 2008:213). Some researchers have suggested that PLWHIV are more distressed and could develop dementia, mood, and psychiatric disorders as a result of HIV infection or OIs (Owe-Larsson *et al.*, 2009:115). However, psychiatric disorders comorbid with HIV/AIDS are commonly under-detected in many LMICs.

The prevalence rate of HIV/AIDS comorbid serious mental disorders ranges from 1 to 24% globally (De Hert *et al.*, 2011:138). The co-morbidities in HIV infection are multifactorial and could occasionally contribute to poor quality of life, adherence, treatment outcomes, diagnosis and poor quality of care. The sub-Saharan Africa region has a high prevalence rate (60%) of severe mental disorders among people living with HIV/AIDS (Joska *et al.*, 2008:213).

The HIV infection could lead to depression, anxiety, severe loss of cognition, sleeplessness and pain (Archer, 2016:2; Costa *et al.*, 2016:3209; Mohamed *et al.*, 2015:760). One study highlighted serious complications of HAART and complications of HIV/AIDS overlapping significantly (Chandra *et al.*, 2005:464). HIV/AIDS increases the risks of mental disorders, including major depression disorder (MDD), bipolar disorder, anxiety, and substance use (Vance *et al.*, 2011: 17). According to the WHO global report (2016:2) projections, it is estimated that depression alone will be the leading cause of disease burden worldwide by 2030. More than 350 million people are currently suffering from MDD globally.

2.8.2.1.8 Major depressive disorders

Depression is also known as major depressive disorder (MDD) or clinical depression. It is a common mood disorder in which, according to Miners *et al.* (2014:32), and Moore *et al.* (2016:589) can be caused by genetic, biological, environmental and psychological factors. Forms of depression include dysthymia (persistent depressive disorder), postpartum depression, psychotic depression and seasonal affective disorder (Miners *et al.*, 2014:32). However, MDD is a big problem in countries with higher prevalence rates of HIV/AIDS (Lipine & Bairy, 2011:2; Moore *et al.*, 2016:589).

According to Marwick and Kaaya (2010:417), the prevalence rate of MDD in PLWHIV ranges between 19% and 43% globally. The prevalence of MDD in PLWHIV in Africa ranges from 3% to 54% (Kiyanda 2011:12). Sin and DiMatteo (2014:568) reported that PLWHIV had twice the incidence rate of MDD compared to HIV negative people. The MDD was found to be seven times

more in HIV/AIDS patients than in the general population in Ghana (Nakimuli-Mpungu *et al.*, 2011:160). Chipimo and Fylkesnes (2009:298) reported a 13% prevalence rate of mental disorders in the general Zambian population, with a high 2.0 odds ratio among people living with HIV/AIDS. According to Chibanda *et al.* (2016), almost 60% of PLWHIV also suffered from depression. Wittchen *et al.* (2011:668) estimated that more than 38.2% (164.7 million people) of the total European population suffered from a mental disorder in 2011.

People living with HIV/AIDS in SA experience higher rates of depression and poorer quality of life compared to HIV negative individuals (Brandt, 2009:123). Freeman *et al.* (2008:489) found that people who were living with HIV/AIDS in SA had a prevalence rate of mental disorders of 43% compared to 16.5% observed in HIV/AIDS negative individuals, which complicates the treatment and management of AIDS and mental disorders. In a six-month follow-up study in HIV/AIDS-infected patients in SA, scientists reported that more than 34% of the patients were suffering from depression and 26% had PTSD (Olley *et al.*, 2006:479).

In SA, between 26% and 38% of HIV/AIDS patients suffered from a common mental disorder versus 12.6% in the general population, whereas 20 to 60% of HIV infected individuals also suffered from psychiatric disorders (Jonsson *et al.*, 2013:159). The same report highlighted that approximately 25% of HIV infected persons suffer from some form of depression and approximately 10% of patients suffer from MDD. Nakimuli-Mpungu *et al.* (2011:166) reported anxiety, sadness, age and stress as some factors associated with depression in rural Uganda. Levinson (2006) examined the pathophysiology of MDD and found a complex interaction that existed between genetic factors and psychosocial stressors, which resulted in functional and structural changes in the areas of the brain responsible for mood regulation and emotions.

In SA, prevalence rates of depression, anxiety, substance use disorders in people living with HIV/AIDS are increasing (Jonsson *et al.*, 2013:155). Age and gender are thought to play a role in increasing the risk for depressive disorders. Olley *et al.* (2006:482) reported that female gender, negative life events and disability were associated with MDD.

Major depressive disorder is a risk factor of HIV transmission (Tsai *et al.*, 2013:2765). Depression can negatively affect the ability to make decisions, and therefore many people living with HIV/AIDS end up taking illicit drugs (Watkins & Treisman, 2012:277). According to Himelhoch *et al.* (2009:1735), MDD could interfere with ARV regimens. Researchers reported that patients who were suffering from MDD experienced higher rates of mortality, and that the rate of HIV/AIDS disease progression was higher compared to the general population. The MDD was associated

with neuropsychological impairments of the executive function of HIV/AIDS patients (Snyder, 2013:81).

Untreated MDD might result in severe emotional, behavioural and health problems (CMS, 2016b:1). Common complications associated with MDD include weight increase or obesity (can cause various heart-related diseases and diabetes), unhealthy weight loss, physical pain and illness, alcohol or substance abuse, anxiety, conflict with others, social isolation, suicidal feelings, self-mutilation such as cutting, and premature death from other medical conditions (CMS, 2016b:1).. South Africa has the 8th largest suicide rate in the world and this might be caused by HIV/AIDS (CMS, 2016b:1). The prevalence rate of maniac disorder coexisting with cognitive deficit in people living with HIV/AIDs is lower than MDD (Subedi *et al.*, 2013:8).

2.8.2.1.9 Bipolar disorder

Bipolar disorder is different from depression. Bipolar disorder includes episodes of extremely low moods that are similar to major depression (called bipolar depression), extreme high (euphoric or irritable) moods called mania, or a less severe form called hypomania. Bipolar disorder comorbid with HIV/AIDS is prevalent. It is estimated that more than 2.6% of HIV/AIDS patients also suffer from bipolar depression (Beyer *et al.*, 2007:36). In 2015, more than 182 000 HIV/AIDS patients were suffering from bipolar depression in SA (Stats SA, 2015a:1), and the evidence underscored the critical need for mental disorder care for PLWHIV in SA considering that the country has the biggest proportion of HIV infected population in the world (Lund *et al.*, 2013:915).

2.8.2.1.10 Anxiety disorder

Anxiety disorders are a group of mental illnesses that cause distress to someone who wants function in a normal way (Moore *et al.*, 2016:589). Examples of anxiety disorders include panic disorder, social anxiety disorders, phobias, and generalised anxiety disorder. Like other forms of mental disorders, they can be caused by changes in the brain, genetics and environmental stress. In another study, high levels of anxiety were found to be significantly associated with HIV/AIDS (Tesfaw *et al.*, 2016:6).

HIV is a common cause of post-traumatic disorders (PTSD) among PLWHIV (Gaynes *et al.*, 2008:505). The PTSD is a major contributor of mental illness in SA, contributing at least 23% among the age group 16 to 64 years (Hirschowitz, 1997:1; Williams *et al.*, 2007:850). Risk factors for PTSD in HIV/AIDS include physical symptoms, pre-HIV trauma, less perceived social support, perceived stigma, and negative life events (Katz & Nevid, 2005:118). In SA, death from external causes and especially trauma are known to be a large burden to the health system (Hardcastle

& Brysiewicz 2013). For instance, in KZN, trauma represents approximately 27% of emergency room visits (Lutge *et al.*, 2016). There are also known disparities in trauma care and access to care, especially in relation to ambulatory or pre-hospital care and the dichotomy of private and public healthcare provision (Goosen *et al.*, 2003:704).

2.8.2.1.11 Stigma

According to the Webster's New World Dictionary, the short definition of stigma is a mark of disgrace or reproach (Gates, 2008). Berger *et al.* (2001:518) defined stigma as a perceived negative attribute that causes someone to devalue or think less of the whole person. Information on the impact of stigma and discrimination around HIV/AIDS in SA is limited. Since the 1980s when HIV was discovered, stigma associated with HIV/AIDS has been a major barrier to HIV prevention and treatment efforts (Stein, 2003). The UNAIDS (2005) defines stigma as the branding or labelling of a person or a group of persons as being unworthy of inclusion in human community, resulting in discrimination and ostracism. Focus on stigma has steadily gained momentum during the past 30 years. Despite this attention, stigma among PLWHIV continues to be a major barrier to seeking appropriate healthcare among PLWHIV for nearly 30 years after the start of the epidemic.

Stigma is associated with HIV/AIDS because of the mode of its transmission, and infected individuals may find it difficult to get support in their times of need (Simbayi *et al.*, 2007:1823). Stigma could also challenge intimate relationships with issues of fidelity and trust that lie at the heart of such relationships. The results might be loss of relationships and even domestic violence (Simbayi *et al.*, 2007:1823). Because sexuality and death are such taboo subjects in most SA cultures, it is difficult for infected individuals and families to address the issues with openness and honesty. In a study by Murphy *et al.* (2006:19), the researchers highlighted strong correlations between stigma and depression among women living with HIV. Other researchers have highlighted a strong link between stigma and non-adherence to antiretroviral treatment (Watkins & Treisman, 2015:39). However, stigma experienced by PLWHIV varies among infected people and different populations. Among African Americans living with HIV, factors including increased social support from friends and higher educational level predicted lower perceived HIV-related stigma. Mental disorders such as PTSD could indirectly cause poor adherence to medication in PLWHIV (Cook *et al.*, 2002).

2.8.2.1.12 Substance abuse

Substance abuse is defined as a pattern of harmful use of any substance for mood-altering purposes (Buddy, 2018). People can abuse substances such as alcohol, tobacco and other illegal drugs such as marijuana, methamphetamine, ketamine, cocaine, hallucinogens, ecstasy, or heroin, or legal drugs, such as Viagra, caffeine, prescription medication, as well as some substances that are not drugs (bath salts, anabolic steroids) (Buddy, 2018). Abuse might occur when one uses a substance in a way that is not intended or recommended, or using more than the prescribed quantity. The use of marijuana has been associated with complications of mental and neurological substance use disorders in 20 to 73% of PLWHIV since the beginning of the epidemic (Gallego, 2000). Substance abuse has been a major problem in many LMICs, including SA, with alcohol and cocaine on the top of the list among PLWHIV (Gaynes *et al.*, 2008:505). Howard *et al.* (2002:2175) clearly showed that alcohol abuse was associated with poor adherence to ARVs. Alcohol was associated with risky sexual behaviour, which could result in one having many sexual partners and failure to wear condoms (Baingana *et al.*, 2005). Serious CNS damage experienced by PLWHIV due to alcohol abuse has been reported by Whiteford *et al.* (2010:1).

Studies on cocaine use are rare in literature. Tucker *et al.* (2003:573) reported that users of cocaine interfered with treatment regimens leading to poor adherence. Therefore, poor adherence to drugs could lead to poor treatment outcomes and development of treatment resistant HIV strains. Other drugs that caused people living with HIV/AIDS to stop HAART regimens were ecstasy, inhalant nitrates, ketamine and hallucinogens (Halkitis *et al.*, 2002).

2.8.2.1.13 Psychosis disorders

Psychoses in HIV/AIDS can be classified as primary or secondary psychosis disorders (Matcheri & Yoshio, 2013:4). Primary psychoses are those where the virus is both necessary and sufficient and the disorders are common in HIV negative people with acute metabolic dysfunctions, whereas secondary psychoses are associated with OIs that take advantage of the progressive immune deficiency as a result of injuries of spinal cord and brain, metabolic encephalopathy associated with renal, hepatic, pulmonary and endocrine failures (Alciati *et al.*, 2001:229; Ronald *et al.*, 2009:144).

Sexual abuse, job, partner violence, education, homelessness, medication and substance abuse in conjunction with HIV infection contribute to the development of psychosis (Subedi *et al.*, 2013:9). The HIV infection could induce psychosis directly or indirectly (Subedi *et al.*, 2013). Symptoms of psychosis in HIV/AIDS include delirium, dementia or organic brain disorders (Sall *et al.*, 2009:206). People living with HIV/AIDS usually suffer from severe neuropsychological

disorders and often have higher rates of substance abuse and higher mortality rates (Van Tieu *et al.*, 2009:314)

2.8.2.1.14 Infectious and oncologic complications due to HIV infection

Oncologic complications in HIV/AIDS are malignancies as a result of the viral infection (Rodger *et al.*, 2013:973). Before the HIV epidemic was discovered in the early 1980s, AIDS-defining cancers such as Kaposi Sarcoma (KS), Hodgkin lymphoma, cervical cancer and primary CNS lymphoma were rare disorders. The KS incidence rate significantly increased between 1987 and 2002 (Elton *et al.*, 2002:1204). Some lymphomas are associated with HIV infection and examples are Burkett's Lymphoma, Burkett's-like lymphoma, diffuse large B cell lymphoma, peripheral lymphoma, and primary effusion body cavity lymphoma, plasmablastic lymphoma of the oral cavity, polymorphic B cell lymphoma and Hodgkin lymphoma (Rubinstein *et al.*, 2014:455). The incidence rate of AIDS defining cancers declined by 70% due to HAART (Shiels *et al.*, 2011:753). However, HAART has failed to eliminate AIDS-defining cancers and these malignancies currently account for 15 to 19% of all deaths in PLWHV in the USA (Rodger *et al.*, 2013:973). The CNS malignancies are prevalent among PLWHIV (Lee *et al.*, 2010:149; Watkins & Treisman, 2015:39).

The incidences of opportunistic infections (OIs) in comorbid with HIV infection have generally decreased globally due to the introduction of HAART. The treatment of OIs in HIV infected individuals with co-morbidities and HIV non-infected patients is similar. According to Guaraldi *et al.* (2016:1633), HIV/AIDS could be a risk factor of OIs of the CNS.

The HIV infection could lead to OIs in the CNS (Narayan *et al.*, 2014:2). Most common OIs associated with depressive disorders are toxoplasmosis, cryptococcal meningitis, herpes zoster and varicella virus infections, herpes simplex, hepatitis C co-infection as well as its treatment with Interferon-gamma (Jones *et al.*, 2004). Neurosyphilis is prevalent in HIV/AIDS patients (Watkins & Treisman., 2015:39). Meningitis was the main cause of mortality and morbidity in HIV positive individuals in sub-Saharan Africa in 2013 (Velmtan *et al.*, 2014:19191). The main symptoms of meningitis are fever, pain in the neck or stiffness and seizure (Chu & Selwyn, 2011:397). The TEMPRANO ANRS 12136 Study Group (2015:820) conducted a randomised controlled trial of early ARVs and isoniazid preventive therapy in Africa. The results of the trial showed that early initiation of HAART prevented HIV positive patients from contracting tuberculosis and other invasive bacterial infections. The OIs of the CNS in PLWHIV are shown in Table 2-17 (Chu & Selwyn (2011:398).

Table 2-17: Infectious and oncologic complications of the CNS in HIV/AIDS patients

Complication*	Signs and symptoms	Typical CD4 cell count
Cerebral toxoplasmosis	Seizure/coma with progressive disease, headache, confusion, occasional fever, focal neurological deficits	< 50/mm ³
Cryptococcal meningoencephalitis or cryptococcal	Altered mental status, headache, fever, confusion	< 50/mm ³
Viral meningoencephalitis	Fever, headache, focal deficits, lethargy, confusion, occasional seizure (virus specific listed below)	-
Cytomegalovirus	Deteriorating focal deficits	< 50/mm ³
Herpes simplex virus	Memory, personal and behavioural changes	< 200/mm ³
Varicella zoster virus	Vasculitis leading to stroke syndromes	Risk increases with lower CD4 cell count
Progressive multifocal leukoencephalopathy	Progressive focal deficits (such as declining cognition, cranial nerve palsy, aphasia, ataxia, sensory loss/weakness), may lead to coma	< 200/mm ³
Neurosyphilis	Multiple symptoms such as delirium, dementia, focal deficits, stroke syndromes associated with arteritis, ocular & auditory changes, meningitis, behavioural & psychological changes, myelitis	< 350/mm ³
Primary CNS lymphoma	Headache, blurred vision, motor difficulties, change in cognition and personality, focal deficits, confusion	Risk increases with lower CD4 cell count

2.8.3 Non-adherence

Globally, non-adherence to medication is a complex and multifaceted healthcare problem. Hugtenburg *et al.* (2013:675) defined non-adherence as an act of failure of patients to follow the recommendations for prescribed treatments. Causes of non-adherence include treatment, patient's behaviour, age of patient, poor outcome expectancies regarding benefits of following the treatment, and healthcare service providers (Hugtenburg *et al.*, 2013:675). Non-adhering patients do not usually benefit from treatment and this might result in increased morbidity and death rates as well as increased costs (Halpern *et al.*, 2011:25).

Non-adherence to medication is prevalent among PLWHIV (Subedi *et al.*, 2013:8). According to Slabbert *et al.* (2015), medication compliance is very low in PLWHIV. The neuropsychiatric disorders in HIV/AIDS patients caused non-adherence to AIDS treatment and this is supported by Chandra *et al.* (2005:451). Tucker *et al.* (2003), in their report on HIV/AIDS cost and services utilisation, showed that HIV-seropositive patients with depression, generalised anxiety disorder and panic disorder were more likely to be non-adherent than those without a psychiatric disorder. When individuals do not adhere to their treatment regimens, the drugs failed to inhibit HIV and failed to reduce the patient's VL (An *et al.*, 1999:1156). People living with HIV/AIDS who failed to comply with their treatment had twice the chance of risking relapses and were likely to experience severe antidepressant syndromes (Nerenberg, 2001:20).

2.8.4 Drug-drug interactions

Drug-drug interaction (DDI) is a modification of the effect of a drug when administered with another drug (Prueksaritanont *et al.*, 2013:629). The effect may be an increase or a decrease in the action of either substance, or lethal in some situations (Huang *et al.*, 2008:662). The particular interaction may be the result of a chemical-physical incompatibility of the two drugs or a change in the rate of absorption or the quantity absorbed in the body, the binding ability of either drug, or an alteration in the ability of receptor sites and cell membranes to bind either drug (Prueksaritanont *et al.*, 2013:629). Most adverse drug-drug interactions are either pharmacodynamics or pharmacokinetic in nature and the interactions prevent drugs from performing as expected.

The knowledge of treating HIV/AIDS and CNS co-morbidities as compared to those with HIV alone will help us to improve the HIV/AIDS treatment and care in SA and this might lead to reduced drug resistance and HIV transmission rates. However, treatment of HIV/AIDS with comorbid CNS disorders is complicated due to some drug-drug interactions as well as cost implications to patient treatment programmes. Polypharmacy is a major problem in patients taking both the HAART and other CNS medications. It is estimated that approximately 10 to 15% of potential drug-drug interactions (DDIs) are common in people taking more than three drugs (Hamilton, 1998:1112). The incidence rate of potential DDIs could range from 13% for two drugs to 82% for at least seven drugs (Goldberg *et al.*, 1996:448). The DDIs could be serious, and therefore some of them could affect the absorption, distribution, metabolism, or excretion of drugs, and they might interact in a synergistic or antagonist fashion, thereby altering their pharmacodynamics (Young, 2005:286).

Most of the ARV drugs are metabolised by cytochrome P450 in the liver and intestine (Southern African HIV Clinicians Society, 2014:130). However, NNRTIs are not used in the second-line regimen due to their increased risk of failing to suppress HIV (Hill *et al.*, 2013:83). The Department of Health and Human Services Panel (2013) in USA recommended that ART guidelines for adults and adolescents should include a minimum of three ARV drugs from two different classes of ARVs and some regimens are made up of up to six different drugs. Sharma and Kadhiravan (2008:170) described HAART as a combination of at least two NRTIs and in combination with either a PI or NNRTI.

Some DDIs could be life threatening. People living with HIV/AIDS are faced with the challenge of taking more than one drug and this could result in potential DDIs (Tseng & Foisy, 1999:461). There is evidence suggesting that some ARVs caused the development of neuropsychiatric syndromes such as psychosis, mania and depressive disorders (Angellino & Treisman, 2008:100). Zidovudine (AZT), didanosine and efavirenz (EFV), clonidine, corticosteroids and muscle relaxants have been cited to cause depression among PLWHIV (Angellino & Treisman, 2008:100; Dolder *et al.*, 2004:41). AZT has some health outcome benefits. Higher doses of AZT penetrated the blood brain barrier and were seen to be effective in slowing down HAD (Dolder *et al.*, 2004:41). However, AZT was associated with causing confusion, agitation, headaches, myalgia and insomnia in 5% of PLWHIV (Rachlis & Fanning, 1993:312). Manic episodes were common in patients who were treated with AZT (Wright *et al.*, 1989, 339). In another study, AZT was associated with myelopathy in the thoracic spine of more than half of PLWHIV (Dal Pan & McArthur, 1996:339). According to Guitierrez (2008:496), most NRTIs could cause hypersensitivity in PLWHIV.

The EFV has a lower increased risk of teratogenicity during the first trimester of pregnancy (Rossiter, 2014:340). Nevirapine is preferred when combined with rifampicin-based TB treatment (Rossiter, 2014:339). The drugs d4T and 3TC were once used as the first-line NRTIs of choice for both children and adults (NDOH, 2014a). However, better combinations of ARVs became available and current recommendations favour 3TC and ABC in children and 3TC or FTC combined with TDF in adults (NDOH, 2014a). The NRTIs such as 3TC, FTC and TDF are effective against hepatitis B, making them the ideal choice for co-infections (WHO, 2014a). Treatment with stavudine, zalcitabine and dideoxynucleosides didanosine could trigger HIV/AIDS associated neurotoxicity and inflammation (Bacellar *et al.*, 1994:1892). Lopinavir/ritonavir altered rosuvastatin plasma concentrations in health volunteers (Kisser *et al.*, 2008:470)).

Interferon could cause neuropathic pain and weakness in some individuals (Glenn *et al.*, 2002:1204). The combination of delavirdine and NVP was reported to cause adverse drug

reactions in the CNS (Clifford *et al.*, 2005:714). Known CNS negative effects caused by EFV include headache, confusion, stupor, dizziness, agitation, insomnia, impaired concentration and hallucinations (Clifford *et al.*, 2005:714). Approximately one in two PLWHIV taking EFV might end up suffering from depression, anxiety and suicidal ideations (Moyle, 2005:47). Co-administration of PIs with statins, antiepileptic drugs and calcium channel blockers could cause myopathy, rhabdomyolysis and heart failure (DHHS, 2009).

The PIs, when combined with other ARVs, helped to decrease the VL and opportunistic infections and as a result HIV/AIDS-related deaths have decreased significantly (WHO, 2014a:1). Many PIs were cited to cause CNS complications in HIV/AIDS patients (Pettersen *et al.*, 2006:823). The major side effects caused by PIs were diarrhoea, constipation, abdominal cramps, flatulence, nausea and vomiting (Guitierrez, 2008:505). Phenobarbital and other barbiturates increased the PIs' metabolism (Baxter, 2008:785). Ribavirin might react with AZT leading to increased anaemia and hepatic decompensation (WHO, 2013a:143).

Neutrophils are an important part in the non-specific immune system response to bacterial infections. Neutrophils confine the pathogens to a local site, thereby preventing the spreading of the bacterial disease (Elliot *et al.*, 2015:3104). O'Connor *et al.* (2017:105) found that immediate ART initiation could reduce bacterial infections by 61% in asymptomatic HIV/AIDS patients with a CD4 cell count above 500 cells/ μ L (Daniel *et al.*, 2015:808). The Strategic Timing of Antiretroviral Treatment (STAT) trial study reported a 57% reduction in risk of HIV/AIDS and non-AIDS morbidity and deaths in people who were taking HAART compared to those who deferred the treatment (O'Connor, 2017:105). People living with HIV/AIDS who are not on treatment were more prone to severe malaria than HIV negative people (Kamya *et al.*, 2012:706).

A large number of HAART regimens and neuropsychotropic drugs are metabolised by cytochrome P450 enzymes (Glenn *et al.*, 2002:1208). The cytochrome P450 enzymes of drugs could be induced or inhibited, and therefore it is difficult to predict drug-drug interactions in most cases. Ritonavir showed the greatest inhibitory effects on the cytochrome 3A4 pathway (Glenn *et al.*, 2002:2018). Drug-drug interactions between anticonvulsant drugs and ARVs are not well understood (Honda *et al.*, 1999:302).

According to Heelon and Meade (1999:471), patients on methadone treatment experienced withdrawal symptoms following the introduction of NVP. In the same study, the concentration of methadone was reduced in the presence of NVP and these findings suggest the need to carefully monitor patients on methadone and NNRTIs. Methadone metabolism is idiosyncratic and it involves cytochrome P450 enzymes. These interactions may also occur through effects on renal

clearance and glucuronidation. McCance-Katz *et al.* (1998:435) examined methadone effects on AZT. The researchers found that the levels of methadone in blood plasma did not change after initiating AZT, but the AZT levels in blood were affected by methadone. The same study reported that high levels of AZT were found in the blood – enough to cause side effects and toxicity.

The potential DDIs between antidepressants and HAART are shown in Table 2.18. (Jonsson *et al.* 2013:159-161; Foy *et al.*, 2014: 212-222).

Table 2-18: Potential drug-drug interactions between antidepressants and antiretroviral drugs

Antidepressant class and drug	Daily dosage	Possible side effects	Possible drug-drug interactions
SSRIs			
Fluoxetine	20-60 mg	Headache, nausea, vomiting, irritability, (initially), sexual dysfunction	EFV: potential increase levels. Monitor for worsening on neuropsychiatric illness.
Citalopram/ Escitalopram	10-20 or 5-10 mg	Headache, nausea, vomiting, irritability, (initially) sexual dysfunction	Generally, no clinically significant drug-drug interactions. PIs: Potentially for decreased citalopram dose.
Sertraline	50-100 mg	Headache, nausea, vomiting, irritability, (initially) sexual dysfunction	Generally, no clinically significant drug-drug interactions; however, EFV may decrease dose of sertraline.
TCA's			
Amitriptyline	25-100 mg nocte	Sedation, anticholinergic side effects for example urinary retention, worsening confusion in older patients, constipation. Fatal in overdose	Amitriptyline and PIs may increase the concentration of acetylcholine, Amitriptyline: Potential cardiac arrhythmia abnormalities due to increased dose of amitriptyline.

Antidepressant class and drug	Daily dosage	Possible side effects	Possible drug-drug interactions
SNRIs			
Venlafaxine	75-225 mg	Potential for withdrawal syndrome if stopped quickly. Initial irritability and gastrointestinal side effects. Sexual side effects	EFV and NVP may decrease venlafaxine concentration. PIs may increase venlafaxine concentration.
Tetracyclic antidepressants			
Mirtazapine	15-45 mg nocte	Sedation, weight gain	NVP and EFV potentially increase mirtazapine clearance.
Trazadone	50-150 mg	Sedation	Important interaction: PI/r may increase trazadone dramatically.
Not inhibitors			
Bupropion XL	150-300 mg	Irritability, anxiety, tremulousness, paraesthesia, insomnia, seizures	EFV and PIs potential for decreasing the dose of Bupropion XL.

Antidepressant class and drug	Daily dosage	Possible side effects	Possible drug-drug interactions
Antipsychotics			
First-generation antipsychotics			
Haloperidol	0.5-5mg nocte	Extra pyramidal side effects (dystonia, tremor, akathisia, cog wheeling, bradykinesia)	PI/r may increase haloperidol concentration. EFV may decrease haloperidol concentration.
Chlorpromazine	25-200mg in divided doses	Sedation, anticholinergic side-effects, NMS	PI/r may increase chlorpromazine concentrations.
Second-generation antipsychotics			
Risperidone	0.5-4 mg	Extra-pyramidal side effects, sedation	Risperidone levels may increase with PIs. EFV and NVP may decrease risperidone concentration. Monitor extra-pyramidal side effects and neuroleptic malignant syndrome.
Quetiapine	25-600 mg	Sedation, cardiac issues (Quetiapine prolongation is rare)	Pi/r: potentially increased levels of quetiapine with increased sedation. EFV and NVP may decrease levels of quetiapine.

Antidepressant class and drug	Daily dosage	Possible side effects	Possible drug-drug interactions
Olanzapine	5-20 mg	Sedation, metabolic syndrome-recommended lipogram if available	Probable interactions with PIs. PIs: decreased concentrations of olanzapine may need to increase dose or choose alternative agent.
Aripiprazole	5-30 mg	Akathisia, sedation	PI/r could potentially increase aripiprazole concentration. EFV and NVP could decrease aripiprazole concentration.
Clozapine	25-250 mg	Neutropenia Best to avoid without specialist support	Probable interaction with PIs. Possible increased concentration with PIs and possible increased risk of sedation and seizures.
Mood stabilisers			
Lithium	400-800 mg	Lithium toxicity may be life threatening. Monitor levels regularly once steady state is reached	Relative contraindication to avoid with TDF. Potential risk for increased acute kidney problems.
Sodium valproate	200-800 mg	Sedation, thrombocytopenia, toxic valproate levels if not monitored regularly	Interaction with AZT (increased AZT and PI/r may decrease valproate and increased levels). Monitor closely.
Lamotrigine	25-200 mg	Stevens Johnson syndrome	

Antidepressant class and drug	Daily dosage	Possible side effects	Possible drug-drug interactions
Carbamazepine	100-200 mg take one tablet twice daily	Sedation, syndrome of inappropriate ADH, skin rash, cognitive dulling, decreased white cell count	NVP and EFV: decreased carbamazepine. PI/: Increased carbamazepine decrease EFV.
Benzodiazepines			
Alprazolam	1-2 mg/daily	Sedation, dependence	PIs increase concentration of alprazolam.
Diazepam	Sedation, respiratory depression and ataxia	Sedation, respiratory depression and ataxia	PIs increase diazepam

2.8.5 Treatment of CNS complications due to HIV infection

Major depressive disorder (MDD) is a treatable condition with psychotherapy and antidepressants (CMS, 2016b:2). Psychotherapy is often used to treat MDD when one opens up and shares with others about his condition, moods, feelings, thoughts and behaviour.

The treatment of MDD as specified in the prescribed minimum benefits (PMB) regulations is very limited. Currently, the treatment options of MDD, which are funded by medical schemes, include hospital-based management up to three weeks per year (including inpatient electro-convulsive therapy and inpatient psychotherapy) or outpatient psychotherapy of up to 15 contacts (CMS, 2016b:2). The PMB level of care covers only three weeks when one is admitted to a hospital (in-hospital treatment), which includes all consultations with psychiatrists, psychologists, all psychotherapy that is provided, occupational therapy, all group therapy sessions and medicine. Antidepressants are not covered by the PMB when one is discharged from the hospital (CMS, 2016b:3). The PMB fully funds the diagnosis of MDD. The following tests are covered by the medical aid schemes as part of the diagnosis of MDD (unipolar and bipolar disorders): complete blood cell count, thyroid stimulating hormone, vitamin B12 and vitamin D, rapid plasma regain (RPR) to screen for syphilis, HIV test, electrolytes (calcium, magnesium and phosphate concentrations) and creatinine to test kidney function, liver function tests, blood alcohol level, as well as blood and urine toxicology screen to test for drug use (CMS, 2016b:5). The PMB also covers cases where the doctor suspects brain injury (organic brain syndrome) or decreased function of the pituitary gland (to test the hormones that control the thyroid gland, adrenal glands, ovaries, and testes), and brain scans. These scans may include a computed tomography scan or magnetic resonance imaging scan (CMS, 2016b:3).

Little is known about the current prescribing patterns of CNS medications and HAART in patients suffering from HIV/AIDS and mental disorders in the private health sector in SA. The treatment guidelines for the initial treatment of HIV infection recommend the use of at least three ARVs (Bartlett *et al.*, 2006:2051). Drug-drug interactions associated with HIV medications and antidepressants could alter the pharmacokinetics or pharmacodynamics (Seden *et al.*, 2009:5). The antidepressants could cause general adverse events such as nausea, vomiting, abdominal pain, dizziness, diarrhoea and peripheral neuropathy (NDOH, 2015b:79).

The current guidelines for the treatment of mental illnesses such as MDD are less clear and more variable as to how long the first-line regimens should be tried before switching to second-line

agents (Furukawa *et al.*, 2013:916). Depression alone is complicated to treat (Ogasawara & Ozaki, 2012:1159).

Cognitive impairment HAD and peripheral neuropathy could be directly caused by HIV infection (Chandra *et al.*, 2005:451). The use of HAART could prevent HAD disorders (Sacktor, 2006:311). The PIs have limited abilities to penetrate the CNS, and therefore their use to treat HIV/AIDS was thought to be limited (Sacktor, 2006:311). However, the PIs in combination with other ARVs can be used to treat many CNS complications (Glenn *et al.*, 2002:1206).

HIV infection could delay cognition in children (Potterton *et al.*, 2009:55; Van Rie *et al.*, 2009:641). In general, HAART improved the health of patients by decreasing encephalopathy (Patel *et al.*, 2009:1899). Chiriboga (2005:406) found that 72% of children on HAART medication had neurological improvements.

Lamotrigine treats epilepsy and is also effective in treating neuropathic pain in PLWHIV, but the drug could also cause severe rash (Simpson *et al.*, 2000:2115). Selegiline improved HIV-associated cognitive disorders (Schifitto *et al.*, 2009:1975). Antidepressants were reported to be effective medication in treating depression and anxiety in people with several co-morbidities (Akena *et al.*, 2012:2802; Watkins *et al.*, 2011:623). Clomipramine and imipramine protected the neurological damages in the CNS and were thought to have anti-inflammatory effects (Hareziak *et al.*, 2011:625). However, tricyclic antidepressants are anticholinergic and can interact with HAART (Watkins & Treisman, 2015:39).

Clozapine proved to be effective in treating HIV associated psychosis in HIV patients who developed drug-induced Parkinson disease; however, the drug caused bone marrow toxicity and aplastic anaemia (Lera & Zirulnik, 1999:128).

2.8.6 Toxicities of HAART

Toxicity refers to the total adverse reactions or the degree of danger posed by a substance to living organisms (Rodrigue-Novoa *et al.*, 2006:234). People living with HIV/AIDS can experience side effects due to differences in the genetic makeup of individuals, metabolism due to gender, concomitant medications and incomplete adherence to medication (Rodrigue-Novoa *et al.*, 2006:234). According to the WHO consolidated guidelines (2013a:138), the following are some of the common drug toxicities with antiretroviral drugs observed in HIV/AIDS patients:

- Stavudine and didanosine can cause fat redistribution syndrome among people living with HIV/AIDS. The symptoms are enlarged breasts in women, buffalo humps, loss of subcutaneous fat and facial wasting.
- Tenofovir can reduce bone density.
- Tenofovir can cause renal failure (renal tubular dysfunction).
- Abacavir-related hypersensitivity can develop in 5% of Caucasian HIV/AIDS patients. The reaction develops within a few days after taking the drug. Hypersensitivity is rare in black African HIV/AIDS patients (NDOH, 2014a).
- Stavudine and PIs are associated with hyperlipidaemia in young adults with HIV/AIDS (WHO, 2013a:138).
- Efavirenz is associated with breast enlargement in both adolescent boys and girls (NDOH, 2014a).
- Lactic acidosis is prevalent in children (1-20 months after initiation) due to NNRTIs and NRTIs. The main culprits are didanosine and stavudine (WHO, 2013a:139).
- Some Bacille Calmette-Guerin (BCG) adverse events (abscess on site of injection, osteitis, supportive lymphadenopathy, and skin and eye reactions) (WHO, 2013a:138).
- Vascular inflammation is associated with lipid changes as a result of HIV infection and HAART. Abacavir could cause cardiotoxicity (Justman *et al.*, 2003:298).

For common side effects of drug-sensitive TB therapy and ART, refer to Annexure D, and for common drug toxicities and side effects of ARV drugs, refer to Annexure E.

Many illicit drugs are metabolised via cytochrome P450 pathways. Ritonavir has shown to interact with methylenedioxymethamphetamine, which is metabolised via P450 2D6 (Mirken, 1997). In another study, the combination of ritonavir or saquinavir and gamma-hydroxybutyrate prolonged the effects of methylenedioxymethamphetamine and the recipe is fatal (Harrington *et al.*, 1999:2221).

People with psychiatric disorders often have low rates of adherence to ARV therapy and conversely the treatment for psychiatric disorders improves adherence (Slabbert *et al.*, 2015:1).

Appropriate screening, prevention and treatment of psychiatric disorders prior to or concurrent with HAART can enhance patient compliance. However, HIV/AIDS and its treatment have shown to cause neurological and psychiatric consequences. Among barriers of successful treatment are mental disorders that have contributed to the spread of HIV infection by influencing high risk behaviours and compromised adherence to the ART. (Slabbert *et al.*, 2015:1).

2.9 CHAPTER SUMMARY

This chapter covered the incidence and prevalence of HIV/AIDS globally and nationally, and the World Health Organization treatment guidelines of HIV/AIDS and the prevalence of co-morbidities in HIV/AIDS.

The following chapter contains the results and a discussion of how the objectives stated for the empirical phase of this investigation were met.

CHAPTER 3: RESULTS AND DISCUSSION

3.1 INTRODUCTION

This chapter contains two manuscripts that present the results and discussions of this study's empirical investigation presented in article format. Each manuscript conformed to the guidelines for authors per requirement for each journal.

3.2 MANUSCRIPT 1

Objective one from the empirical investigation is addressed in manuscript 1:

- Objective 1: To determine possible changes in the prevalence and incidence of HIV/AIDS in the private health sector of SA over the study period, i.e. 2005-2015.

Manuscript 1 is prepared and will be submitted to the journal '*The African journal of infectious diseases*'. Refer to Annexure G for the specific author guidelines of the journal.

CHANGES IN THE INCIDENCE AND PREVALENCE OF HIV/AIDS IN THE SOUTH AFRICAN MEDICAL SCHEMES ENVIRONMENT: 2005 TO 2015

Authors

Floidy Wafawanaka¹ Martie S Lubbe¹, Irma Kotze¹, Marike Cockeran²

Affiliations

¹ North-West University, Medicine Usage in South Africa, Faculty of Health Sciences, Potchefstroom Campus, South Africa

² Statistics, School of Computer, Statistical and Mathematical Sciences, North-West University, Potchefstroom Campus, Potchefstroom

Corresponding author

Martie S Lubbe, Medicine Usage in South Africa (MUSA), North-West University, Potchefstroom, 2520, South Africa. Website: www.nwu.ac.za. Martie Lubbe (Martie.Lubbe@nwu.ac.za).

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Abstract

Background: The private medical scheme environment in South Africa is profoundly influenced by the human immune virus/acquired immune deficiency syndrome (HIV/AIDS) pandemic. We aimed to determine changes in the incidence and prevalence rate of HIV/AIDS in the private medical schemes environment from 2005 to 2015 in South Africa.

Materials and methods: Retrospective medicine claims data from an open cohort of HIV/AIDS patients were obtained from a database of a pharmaceutical benefit management (PBM) company from 1 January 2005 to 31 December 2015. Both HIV/AIDS incidence and prevalence rates were measured per 1 000 medical scheme beneficiaries for each year. Data were stratified by gender, age group and province.

Study population: The cohort included all patients with a diagnosis code for HIV/AIDS (ICD-10 codes B20-B24) and who claimed antiretroviral medication.

Results: The proportion of HIV/AIDS patients increased from 0.63% (2005) to 2.10% (2015). The prevalence rate of HIV/AIDS patients per 1 000 medical scheme beneficiaries increased from 6.3 (2005) to 20.5 (2015) per 1 000 medical scheme beneficiaries. The incidence rate of HIV/AIDS also increased 2.3 times from 2005 to 2015. In 2015, both the prevalence and incidence rates of HIV/AIDS were higher in males than in females. Gauteng had the highest HIV/AIDS prevalence rate (422.4 per 1 000 medical scheme beneficiaries), followed by the Western Cape (149.4), and KwaZulu-Natal (118.4) in 2015.

Conclusions: There is an increased trend in the treatment of HIV/AIDS patients under the prescribed minimum benefits of medical schemes. This may be due to improved data management systems of medical schemes and administrators, and increased beneficiary awareness of rights, as well as changes in care-seeking behaviour.

Keywords: Incidence; prevalence; HIV/AIDS; medical schemes; South Africa

Abbreviations:

AIDS	Acquired immune deficiency syndrome
ARV	Antiretroviral drug
CDC	Centres for Disease Control and Prevention
CMS	Council of Medical Schemes
HAART	Highly active antiretrotherapy
HIV	Human immune virus
ICD-10	International Statistical Classification of Disease Related Health Problems, 10 th Revision
NAPPI	National Pharmaceutical Product Index
NDOH	National Department of Health
NWU	North West University
PBM	Pharmaceutical benefit management
PLWHIV	People living with HIV/AIDS
STATS SA	Department of Statistics South Africa
UNAIDS	The Joint United Nations Programme on HIV/AIDS
WHO	World Health Organization

Introduction

The human immune virus/acquired immunodeficiency syndrome (HIV/AIDS) is a global challenge, a primary cause of deaths in Africa, and the fourth largest cause of death worldwide (WHO, 2014). Globally, it was estimated that more than 42 million people, mainly among the age group 15 to 44 years, were living with HIV/AIDS (PLWHIV) in 2015 (The Joint United Nations Programme on AIDS/HIV (UNAIDS), 2016). The sub-Saharan Africa region has the highest number of PLWHIV, contributing more than 70% to the global total of the HIV-infected population (UNAIDS, 2015). In the region, approximately 4 000 people are infected daily by HIV, particularly among adolescents and young adults (Kharsany & Karim, 2016).

South Africa carries the highest burden of the HIV/AIDS disease, contributing to more than 33% of all new HIV infections in sub-Saharan Africa in 2015 (UNAIDS, 2016). It is estimated that 19% (8.2 million) of the global number of PLWHIV live in South Africa, with approximately 15% of new HIV cases (270 000) in 2015 (UNAIDS, 2016). In South Africa, the prevalence rate of HIV/AIDS in the general population is estimated to be more than 11% (Statistics South Africa (STATS SA), 2015). Women aged 15 to 24 years were more vulnerable to HIV infection than their male counterparts in rural South Africa (Abdool et al, 2015). Apart from having the largest HIV/AIDS treatment programme in the world, with 4.3 million people on treatment, South Africa is one of the countries with the highest HIV/AIDS-related deaths in the world with approximately 11% (110 000 people died in 2015) (Lessells et al, 2014; UNAIDS, 2016).

The introduction of antiretroviral drugs (ARVs) helped to reduce the number of new HIV infections globally and increased the survival of PLWHIV (Tanser et al, 2013). People living with HIV/AIDS who are on highly active antiretroviral therapy (HAART) have been noted to have improved HIV treatment and care (Hong and Banks, 2015). Following the introduction of HAART, the number of PLWHIV has steadily increased between 2005 and 2015 (Lessells et al, 2014). Current data show that new HIV infections are declining globally, probably due to HAART (UNAIDS, 2017). It was estimated that there were 270 000 new HIV infections in South Africa in 2015 (UNAIDS, 2017). The country has also recorded a significant decline in vertical transmissions of HIV from mothers to their unborn babies, and the rate declined from 14% in 2004 to less than 2% in 2015 (National Department of Health (NDOH), 2015a). The number of PLWHIV in South Africa among the age group 15 to 24 years has decreased from 7.3% in 2002 to 4.6% in 2017 (STATS SA, 2017). The overall prevalence rate among antenatal women was 30.2% in 2010, and declined to 29.7% in 2013 in the country (NDOH, 2015b).

The success of HAART dramatically changed the treatment of HIV/AIDS globally. The HAART has managed to improve both the survival rates and the quality of lives among PLWHIV globally (Bor et al,

2013; UNAIDS, 2016). Since HAART was introduced in South Africa, its benefits are widely recognised, the survival rates of those infected with HIV had significantly improved and also life expectancy has increased (Bor et al, 2013). This shift could result in HIV-infected people living longer and the country will continue to face a growing HIV/AIDS prevalence rate (Castelnuovo et al, 2016). The increase in the HIV/AIDS prevalence rate is particularly prominent in South Africa with more than 8.2 million PLWHIV in 2015 (STATS SA, 2015). Overall, 19% of the South African population were PLWHIV in 2014, with more women being infected (21.3%) than men (11.6%) (Rehle et al, 2010; STATS SA, 2015).

Since 2004, South Africa has had the biggest antiretroviral therapy programme in the world, with more than 3.4 million (42%) PLWHIV on treatment in 2014 (NDOH, 2015a; UNAIDS, 2015). Many types of antiretroviral drug ARV combinations were used to treat HIV/AIDS between 2005 and 2015 (NDOH, 2015b). Initial treatment of HIV/AIDS included triple nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors, and protease inhibitors regimens, which only provided a glimpse of hope for a short time (Car et al, 1998). The HIV/AIDS treatment guidelines have evolved fast and today fixed dose combinations, which include more tolerable drugs, are available (McKinnell et al, 2010). Highly active antiretroviral drugs are the standard treatment of HIV/AIDS since 1996 and they have dramatically changed HIV infections from acute to treatable chronic conditions (Council of Medical Schemes (CMS), 2015).

The numbers of PLWHIV treated reported in the above paragraph do not include figures from the private medical scheme sector. This translates to a high HIV/AIDS treatment gap that is noticeable in South Africa. Therefore, increasing the capacity to treat HIV/AIDS is a respectable call in South Africa given the scale of the epidemic and scarce public healthcare infrastructure (Leisegang et al, 2013). One way to increase the number of people on antiretroviral treatment and to improve retention within HAART care for HIV-positive patients is to utilise medical schemes in the private healthcare sector. Contracting private doctors to initiate HAART and follow up public sector patients in their private rooms according to the public sector guidelines has been successfully implemented in South Africa and in other low- and middle-income countries (Montgomery, 2016). The influence of HIV/AIDS treatment in the private medical schemes environment is potentially important, but understudied. HIV/AIDS is treated as a prescribed minimum benefit in the private medical scheme healthcare sector regardless of the benefit option medical aid members have selected (CMS, 2017).

According to the 2015 CMS report, HIV/AIDS is the best managed chronic condition in the medical schemes environment in South Africa. HIV/AIDS was ranked the fourth among the top 10 chronic conditions in the population covered by medical aid schemes in 2015 (CMS, 2016). The prevalence rate of

treated HIV/AIDS in both open and closed medical aid schemes increased from 15.36 per 1 000 medical scheme beneficiaries in 2011 to 17.31 per 1 000 medical aid beneficiaries in 2015 and this because of the corrections made by some medical schemes in reporting the prevalence of HIV/AIDS (Research and Monitoring Unit of the Council for Medical Schemes, 2015). However, the prevalence of HIV/AIDS for both females and males in the medical schemes environment is increasing year by year (CMS, 2016). From 2010 to 2015, the prevalence rate of treated HIV/AIDS in the medical schemes environment has increased by more than 125%. Approximately 8 700 000 people were registered members of 83 medical aid schemes in 2015 (CMS, 2017).

Despite the enormity of HIV/AIDS, the magnitude of both the incidence and the prevalence rates in the medical schemes environment in South Africa remain largely undocumented. HIV/AIDS continues to affect many people in South Africa despite the availability of HAART in the country. Against this background, this study sought to determine the possible changes in the incidence and prevalence rates of treated HIV/AIDS in the population covered by medical schemes from 2005 to 2015 in South Africa.

Methods

Study design and setting

A longitudinal research design was implemented using retrospective data from an open cohort of patients living with HIV/AIDS. Data, from 1 January 2005 to 31 December 2015, were obtained from the database of a pharmaceutical benefit management (PBM) company. The cohort included all patients with diagnosis codes for HIV/AIDS (ICD-10 codes B20-B24) and who claimed antiretroviral medication.

Data source

The PBM company currently manages the medicine benefits of more than 1.8 million beneficiaries on behalf of 42 medical schemes and capitation plans in South Africa. Several automated validation processes were applied by the PBM company to ensure the quality of data. External validity was limited because the data were obtained from one PBM company; therefore, the results could be used only for those medical scheme beneficiaries and medical schemes managed by the specific PBM.

The dataset consisted of the following fields: Patient's demographic information (date of birth, gender), a unique code for the medical scheme member and beneficiary, prescription number, date of dispensing of the prescription, trade name of medication, National Pharmaceutical Product Index (NAPPI) code of each medicine, the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (Selfmed Medical Scheme, 2016) and in which provinces each antiretroviral item was dispensed.

Study variables and measurements

The number of HIV/AIDS patients on the database was stratified by year, gender, age group and province. Patient age was determined at time of the first dispensing in the index year (2005) and divided into the following age groups: Age group 1: >0 and <6 years; Age group 2: ≥6 and <12 years, Age group 3: ≥12 and <18 years; Age group 4: ≥18 and <40 years; Age group 5: ≥40 and <60 years; Age group 6: ≥60 and <70 years; Age group 7: ≥70 years. In addition to that, patients were grouped into two categories according to their gender (male and female) and province.

In this study, the prevalence rate of treated HIV/AIDS patients was calculated per 1 000 medical scheme beneficiaries per year, as follows (CDC, 2018a):

$$\text{Prevalence rate} = \frac{\text{All new and pre-existing cases during a given time period}}{\text{Population during the same time period}} (X 10^n)$$

$$n = 3$$

The population in the equation includes the total population or the population of the specific gender or age group on the database.

The incidence was used to determine the proportion of the study participants who have newly registered their HIV/AIDS status with their medical schemes during the study period (2005-2015) without taking into account when participants developed the disease. Each participant was followed from the time he/she was registered with the PMB central database. Participants who cancelled their membership with a specific medical scheme did not contribute to the year's denominator, whereas new members contributed to the denominator.

The HIV/AIDS incidence rate was calculated as per 1 000 medical scheme beneficiaries for that specific year. The incidence rate was calculated as follows (CDC, 2018b):

$$\text{Incidence rate:} = \frac{\text{Number of new cases of a disease in a specified period}}{\text{Size of population at start of the specified period}} (X 10^n)$$

$$n = 3$$

The population in the equation includes the total population or the population of the specific gender or age group on the database.

Data analysis

The Statistical Analysis System® (SAS 9.4®) software (SAS Institute Inc., 2002-2012) was used to analyse the data. Variables were expressed using descriptive statistics, which include numbers (n) and proportions presented as percentages (%), arithmetic means, standard deviations (SD) and 95% confidence intervals (CI).

Ethical considerations

This study was approved by the Health Research Ethics Committee of the North-West University (NWU-00179-14-A1-01), and goodwill permission to perform the study was obtained from the board of directors of the PBM company.

Results

Patients on the PBM database and the study population were stratified by gender and age group in Table 1. A total of 1 213 676 and 843 972 patients claimed medicine items in 2005 and 2015, respectively. In 2005, approximately 0.63% (n = 7 665) of patients on the PBM database were HIV/AIDS patients and 2.10% (n = 17 302) in 2015.

In 2005, there were 675 812 females and 537 864 males, of which 4 395 females and 3 270 males were living with HIV/AIDS. In 2015, female HIV/AIDS patients were 445 626, and 398 166 males of which 9 092 females and 8 250 males were PLWHIV.

Table 1: Demographics of HIV/AIDS patients on PBM database from 2005-2015

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Total number of patients on PBM database											
Total number of patients (N)	1 213 676	1 256 886	910 023	758 497	1 033 039	968 131	864 958	815 789	809 833	838 617	843 972
Male	537 864 (44.32%)	558 414 (44.43%)	407 955 (44.83%)	343 169 (45.24%)	473 809 (45.87%)	446 744 (46.14%)	402 488 (46.53%)	384 159 (46.89%)	379 756 (46.89%)	392 235 (46.77%)	398 166 (47.20%)
Female	675 812 (55.68%)	698 472 (55.57%)	502 068 (55.17%)	415 328 (54.76%)	559 230 (54.13%)	521 387 (53.86%)	462 470 (53.47%)	431 630 (53.11%)	430 077 (53.11%)	446 382 (53.23%)	445 626 (52.80%)
Total number of HIV/AIDS patients											
Total HIV/AIDS patients (n)	7 665 (0.63%)	10 177 (0.81%)	10 094 (1.11%)	11 687 (1.54%)	16 035 (1.55%)	19 209 (1.98%)	18 851 (2.18%)	16 075 (1.97%)	16 407 (2.10%)	15 964 (1.90%)	17 302 (2.10%)
Male	3 270 (42.7%)	4 338 (42.6)	4 149 (41.1%)	5 093 (46.1%)	7 105 (44.30)	10 152 (52.90%)	10 300 (54.60%)	8 221 (51.10%)	8 187 (49.90%)	7 537 (47.20%)	8 250 (47.70%)
Female	4 395 (57.3%)	5 839 (57.4)	5 945 (58.9%)	6 594 (57.9%)	8 930 (55.70%)	9 057 (47.10%)	8 551 (45.40%)	7 854 (48.90%)	8 220 (50.10%)	8 427 (52.80%)	9 062 (52.30%)
Classification by age groups of HIV/AIDS patients											
≥0 and <6 years	53 (0.69%)	50 (0.49%)	29 (0.29%)	3 (0.03%)	39 (0.24%)	21 (0.11%)	21 (0.11%)	23 (0.14%)	32 (0.20%)	28 (0.18%)	39 (0.22%)
≥6 and <12 years	349 (4.55%)	448 (4.40%)	436 (4.32%)	424 (3.63%)	473 (2.95%)	446 (2.32%)	380 (2.02%)	340 (2.12%)	347 (2.11%)	329 (2.06%)	326 (1.88%)
≥12 and <18 years	39 (0.51%)	84 (0.83%)	90 (0.89%)	121 (1.04%)	162 (1.01%)	186 (0.97%)	197 (1.05%)	214 (1.33%)	252 (1.54%)	307 (1.92)	309 (1.79%)
≥18 and <40 years	229 (2.99%)	293 (2.87%)	240 (2.38%)	225 (1.93%)	341 (2.13%)	328 (1.71%)	277 (1.47%)	263 (1.64%)	293 (1.79%)	279 (1.75%)	314 (1.81%)
≥40 and <60 years	5 199 (67.83%)	6 670 (65.64%)	6 395 (63.35%)	7 066 (60.46%)	9 830 (61.30%)	10 187 (53.03%)	9 821 (52.10%)	9 070 (56.42%)	9 084 (55.37%)	8 745 (54.79)	9 742 (56.31%)
≥60 and <70 years	1 716 (22.39%)	2 555 (25.11%)	2 831 (28.05%)	3 764 (32.21%)	5 085 (31.71%)	5 896 (30.69%)	6 002 (31.84%)	5 973 (37.16%)	6 165 (37.58%)	6 035 (37.80%)	6 307 (36.45%)
≥70 years	80 (1.04%)	77 (0.76%)	73 (0.72%)	84 (0.72%)	105 (0.65%)	135 (0.70%)	142 (0.75%)	192 (1.94%)	234 (1.43%)	241 (1.51%)	265 (1.53%)

The results in Figure 1 below show the prevalence rate of HIV/AIDS patients per 1 000 medical scheme beneficiaries, which had increased from 6.3 in 2005 to 20.5 per 1 000 medical scheme beneficiaries in 2015.

The prevalence rate per 1 000 medical scheme beneficiaries of female HIV/AIDS patients was 6.5 in 2005, and increased to 20.4 by the end of 2015. Among males, the prevalence rate of HIV/AIDS increased from 6.0 (2005) to 21.7 (2015) per 1 000 medical schemes beneficiaries (Figure 1).



Figure 1: Prevalence rate of HIV/AIDS patients per 1 000 medical scheme beneficiaries by gender from 2005 to 2015

Figure 2 demonstrates the HIV/AIDS changes in incidence rate per 1 000 medical scheme beneficiaries from 2005 to 2015. For HIV/AIDS, the combined incidence rate has increased from 3.9 in 2006 to 9.1 per 1 000 medical scheme beneficiaries in 2015. The HIV/AIDS incidence rate among females increased from 4.0 per 1 000 medical scheme beneficiaries in 2006 to 8.5 in 2015, whereas the incidence rate among males rose from 3.9 in 2006 to 9.9 per 1 000 medical scheme beneficiaries in 2015 (Figure 2).

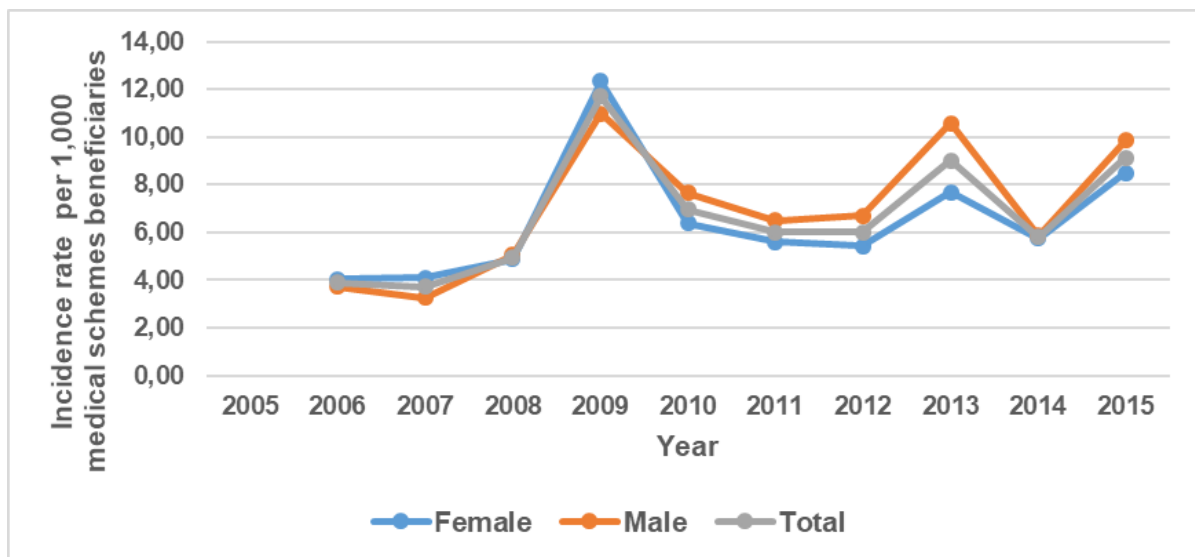


Figure 2: HIV/AIDS incidence rate per 1 000 medical scheme beneficiaries by gender in the medical schemes environment in South Africa between 2005 and 2015

Age is an important variable in evaluating the impact of HIV/AIDS within a specific population group. The prevalence and incidence rates of HIV/AIDS patients per 1 000 medical scheme beneficiaries by age group are illustrated in Figures 3 and 4, respectively. Age group ≥ 40 and < 60 years had the highest HIV/AIDS prevalence rates of 14.4 in 2005 and 38.3 in 2015. This was followed by age group ≥ 60 and < 70 years. The age group ≥ 0 and < 6 years had the lowest HIV/AIDS prevalence rate and was followed by age group ≥ 6 and < 12 years with prevalence rates of 2.1 and 2.6 per 1 000 medical scheme beneficiaries for 2005 and 2015, respectively. In the age group ≥ 18 and < 40 years, the HIV/AIDS prevalence rate increased by 2.9 per 1 000 medical scheme beneficiaries between 2005 and 2015. The prevalence rate in age group ≥ 70 years was 2.7 per 1 000 medical scheme beneficiaries in 2015, which is an increase of 2.1 from 2005.

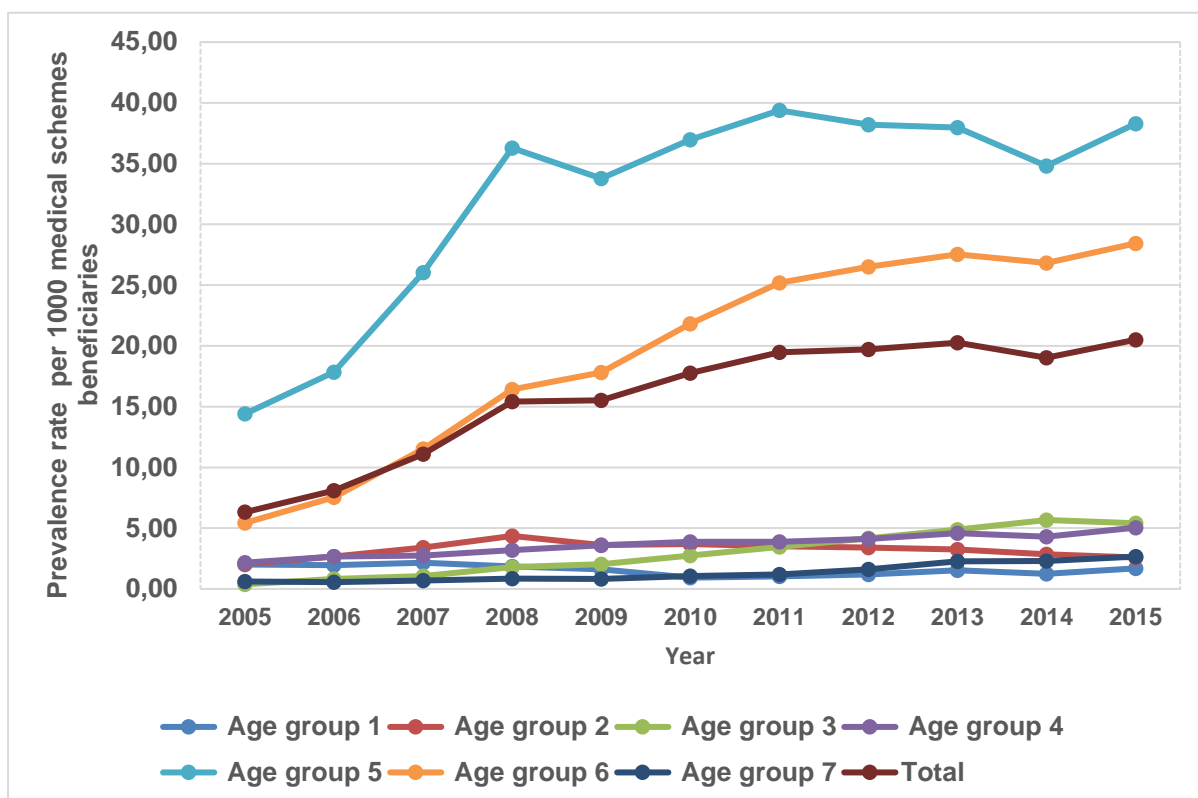


Figure 3: Prevalence rate of HIV/AIDS patients per 1 000 medical scheme beneficiaries by age group from 2005 to 2015

The HIV/AIDS incidence rate among the ≥ 0 and < 6 years declined from 1.71 in 2006 to 1.51 per 1 000 medical scheme beneficiaries in 2015 (Figure. 4). Age group ≥ 6 and < 12 years had a HIV/AIDS incidence rate of less than 1 per 1 000 medical scheme beneficiaries in 2006 and 1.1 in 2015. The HIV/AIDS incidence rate among the ≥ 12 and < 18 years was less than 1 per 1 000 medical scheme beneficiaries by the end of 2006 and the incidence rate increased to 2 in 2015. Between 2006 and 2015, the HIV/AIDS incidence rate increased by 1 per 1 000 medical scheme beneficiaries in the age group ≥ 18 and < 40 years. However, the age group ≥ 40 and < 60 years had the highest HIV/AIDS incidence rate of 8 in 2006 and the number increased to 18 per 1 000 medical scheme beneficiaries in 2015. The HIV incidence rate was 4 per 1 000 medical scheme beneficiaries in 2006 among the ≥ 60 and < 70 years, and it had increased to 11 in 2015. The age group ≥ 70 years recorded the lowest HIV/AIDS incidence rate of less than 1 per 1 000 medical scheme beneficiaries in 2006 and 2015.

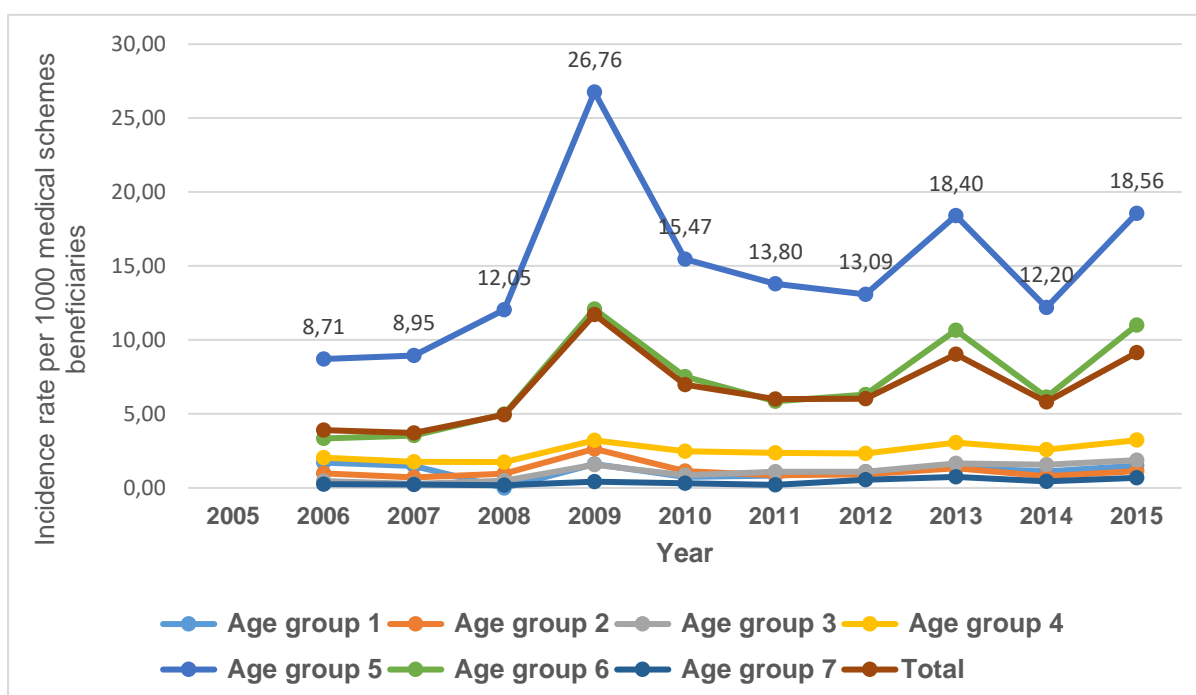


Figure 4: Incidence rate of HIV/AIDS per 1 000 medical scheme beneficiaries by age group from 2005-2015

Data on the HIV/AIDS prevalence rate of per 1 000 medical scheme beneficiaries according to province are presented in Figure 5. The highest HIV/AIDS prevalence rate was noticed in Gauteng at 372.9 per 1 000 medical scheme beneficiaries in 2005, compared to 422.4 per 1 000 medical scheme beneficiaries in 2015. The Western Cape had 152.9 HIV/AIDS patients per 1 000 medical scheme beneficiaries in 2005, and it decreased to 149.4 in 2015. The HIV/AIDS prevalence rate declined from 140.4 per 1 000 medical scheme beneficiaries in 2005 to less than 118.4 in 2015 in KwaZulu-Natal. The Northern Cape had an HIV/AIDS prevalence of 15.9 per 1 000 medical scheme beneficiaries in 2005, compared to 23.5 in 2015. The Free State reported a lower HIV/AIDS prevalence rate at 42.6 per 1 000 medical scheme beneficiaries in 2005 and 65.5 in 2015. Four provinces had HIV/AIDS prevalence rates between 48 and 83 per 1 000 medical scheme beneficiaries during the study period, with Mpumalanga having 48.4, the North West 55.0, Limpopo 63.9 and the Eastern Cape 69.2 rate per 1 000 medical scheme beneficiaries in 2005. However, in 2015, there were 53.6, 46.4, 38.8 and 62.6 HIV/AIDS patients per 1 000 medical scheme beneficiaries for Mpumalanga, the North West, Limpopo and the Eastern Cape, respectively.

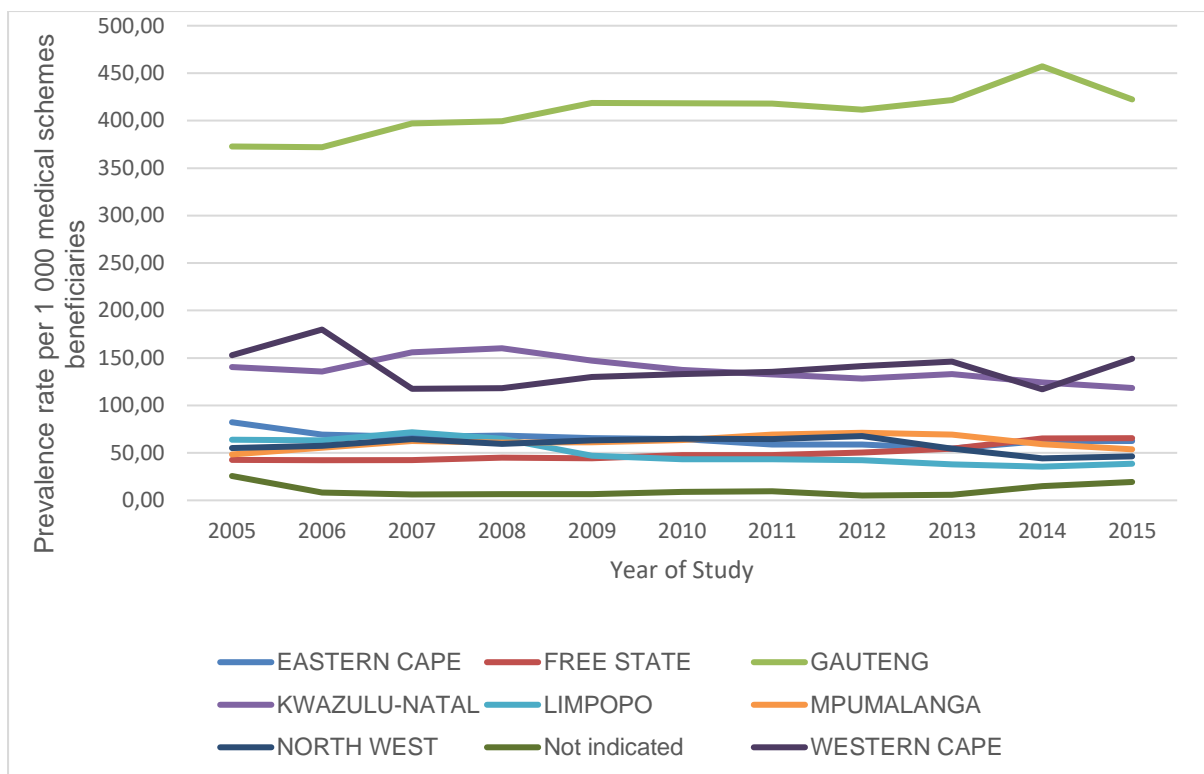


Figure 5: Prevalence rate of HIV/AIDS patients per 1 000 medical scheme beneficiaries by province in South Africa from 2005-2015

Discussion

The aim of the study was to determine changes in the HIV/AIDS incidence and prevalence rates in a population that was covered by private medical schemes in South Africa between 2005 and 2015.

Studies determining both the incidence and prevalence rates of HIV/AIDS in the medical schemes environment are limited, particularly in South Africa. However, few studies were done in developed countries that focused on the prescribing patterns of antiretroviral drugs in treating HIV/AIDS, but most of studies did not recruit participants from the private medical scheme environment (McManus et al, 2015; Williams et al, 2014).

From the results, it is evident that both the incidence and prevalence rates of HIV/AIDS patients who claimed antiretroviral drugs through the PBM increased from 2005 to 2015. The prevalence rate of HIV/AIDS increased 3.3 times and the incidence rate increased 2.3 times from 2005 to 2015. These increases in the prevalence rate were probably due to changes that were made by medical aid schemes in reporting their disease data between 2010 and 2015 (Research and Monitoring Unit of the Council for Medical Schemes, 2015, CMS, 2016, CMS, 2017). Other contributing factors can be the worsening disease profile, increased beneficiary awareness of their rights, and changes in care-seeking behaviour (CMS, 2017).

It was also observed that women were unreasonably affected by HIV/AIDS, particularly among the 15 to 40 years' group (NDOH, 2015b). According to Delva and Karim (2014), women are eight times more exposed to the risk of HIV infections than males of the same age are. Our results showed that the prevalence rate of HIV/AIDS among females had increased by more than three times between 2005 and 2015, with a prevalence rate of 20.4 per 1 000 medical scheme beneficiaries by the end of 2015. During the same period, the incidence rate of HIV/AIDS in female patients doubled. Women are more likely to be screened for HIV during pregnancy as part of the prevention of mother-to-child HIV transmission programme (NDOH, 2015a). Another possible reason is that HIV/AIDS is successfully treated as a prescribed minimum benefit. Medical schemes are increasingly geared towards giving people living with HIV/AIDS that much-needed extra bit of support for a healthy and productive life. All care for any exposure to HIV/AIDS is covered under the PMB enshrined in the Medical Schemes Act 131 of 1998 (CMS, 1998). In April 2010, the PMB guidelines with regard to HIV/AIDS were changed significantly to combat some of the concerns that have arisen over time. From 2010, the PMBs included HIV testing. Our study showed that slightly more females than males were treated between 2005 and 2009 and the trend was reversed from 2011 to 2014.

Age was an important variable in this study. Our results on the prevalence rate of HIV/AIDS among the adolescent age groups on the PBM database were similar to those found by the Council Medical Schemes (Research and Monitoring Unit of the Council for Medical Schemes, 2015). Results from our study also showed that adults aged ≥ 40 and < 60 years were affected by HIV/AIDS more than the rest of the other age groups on the PBM database. The National Department of Health (2015b) reported a high HIV/AIDS prevalence rate in the public sector among the age group ≥ 40 and < 60 years. The age group ≥ 0 and < 6 years had the lowest HIV/AIDS prevalence rate of 1.68 per 1 000 medical schemes beneficiaries in 2015. The observed decline in the prevalence rate of age group ≥ 0 and < 6 years may be attributed to the successful implementation of the prevention of mother-to-child transmission (NDOH, 2015b). Our study showed a similar trend.

Further investigations were done to determine the HIV/AIDS prevalence rate in the provinces of South Africa. The province with the highest HIV/AIDS prevalence rate was Gauteng at 372.9 in 2005 and 422.4 per 1 000 medical scheme beneficiaries in 2015. The increase in Gauteng may be attributed to a larger proportion of working class, and the presence of large corporate organisations that are members of medical aid schemes. According to the CMS (2017) annual report, the highest number of health service providers, health visits and beneficiaries are found in Gauteng, followed by the Western Cape. Mpumalanga, the Northern Cape, Western Cape and Limpopo consistently have lower proportions.

In general, the demand for healthcare service is estimated to be 10 000 medical scheme beneficiaries per healthcare provider (CMS, 2017). The level of healthcare provider demand is significantly higher in Gauteng than the other provinces. Some of the provinces may have higher levels of healthcare

providers, yet much lower utilisation demand and these provinces include KwaZulu-Natal, the Free State and the Western Cape (CMS, 2016). Mpumalanga, the Northern Cape, Limpopo and the North West have relatively lower demand. All these trends may be more associated with the size of medical scheme beneficiaries per province than healthcare demand. In some provinces, this phenomenon may be linked to the inequalities across the respective provinces (CMS, 2016). In the latter case, greater effort in engaging the private sector may be required. The level of physician density ratios at national level is relatively lower compared to the global level. The level of physicians in the public sector may have contributed to pulling the physician density ratio down. The private sector could augment health resource capacity for rolling-out the National Health Insurance (NHI). The White Paper on the NHI recommends engagement with the private sector to implement the NHI (CMS, 2017). However, all other provinces had HIV/AIDS prevalence rates of less than 180 per 1 000 medical scheme beneficiaries throughout the study period (Figure 3). The Western Cape was second with a high prevalence rate of 150 per 1 000 medical scheme beneficiaries in 2015. KwaZulu-Natal was in the third position with a prevalence rate of 118 HIV/AIDS patients per 1 000 medical scheme beneficiaries in 2015. The prevalence rate of HIV/AIDS in the medical scheme environment in KwaZulu-Natal started to decline steadily from 2008. The HIV/AIDS prevalence rates per 1 000 medical scheme beneficiaries of four provinces were in the range of 48 to 83 in 2015. Two of the provinces, Limpopo and the North West, showed a declining trend of the HIV/AIDS prevalence rates in this medical scheme population. The prevalence rate of HIV/AIDS in Limpopo decreased by more than 60% (from 64 in 2005 to 39 per 1 000 medical scheme beneficiaries in 2015). The same trend was observed in the North West, where the prevalence rate declined by 19%, from 55 in 2005 to 46 per 1 000 medical scheme beneficiaries in 2015.

Lastly, results from our study highlighted that HIV/AIDS is treated as a prescribed minimum benefit and this could increase the prevalence rate, since many PLWHIV will live longer due to HAART; this concurs with the observations made by Bor et al (2013). Between 2005 and 2015, the HIV/AIDS incidence rate decreased to less than 2 per 1 000 medical scheme beneficiaries in the age groups ≥ 0 and < 12 years. This could be because of the successful implementation of the PMTCT programme. In the age group ≥ 12 and < 18 years, the HIV/AIDS incidence rate has steadily increased from 2007 to 2015 (Figure 4) with a value of 5 per 1 000 medical scheme beneficiaries in 2015. The age group ≥ 18 and < 40 years had reported a slight increase in the HIV/AIDS incidence rate from 2 (2005) to 3.2 per 1 000 medical scheme beneficiaries in 2015. An incidence rate of 0.67 per 1 000 was noticeable in the age group ≥ 70 years, probably because elderly people are less sexually active than before. In general, our study showed an increase in the HIV/AIDS incidence rate for all age groups from 6 to 21 per 1 000 medical scheme beneficiaries in 2005 and 2015, respectively.

Study strengths and limitations

An important limitation of this study was that data were obtained from only one of the PMBs in South Africa; generalisability and external validation of the data are therefore limited. The study sought to determine possible changes in the incidence and prevalence rate of HIV/AIDS in the medical schemes environment in the private healthcare sector of South Africa. The numbers of HIV/AIDS patients registered with PMBs and disease management programmes have increased significantly during the last decade and this is one of the strengths of PBMs, which has highlighted the positive effect in the treatment of HIV/AIDS in South Africa.

Conclusion

Our study clearly indicates an upward trend in the diagnosis and treatment of HIV/AIDS in the private medical scheme environment of South Africa from 2005 to 2015. Our findings showed that, if fully implemented, the HIV prescribed minimum benefit could avert millions of deaths and prevent new HIV infections in South Africa. Data from CMS (2015) revealed that HIV/AIDS is the best managed chronic condition in the private healthcare sector in South Africa. In conclusion, not all PLWHIV are on treatment in South Africa, regardless of the tremendous achievement the country has achieved during last 10 years. Achieving universal treatment is still far from reality due to the cost of treating HIV/AIDS.

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Author contributions

F Wafawanaka: For writing the manuscript, analysing the data and interpreting the results. All authors read and agreed on the final version of the paper.

MS Lubbe: For conceptualising the study, analysing the data, interpreting the study and results as well as supervising the study.

I Kotze: For supervising the study, providing guidance in writing and data analysis.

M Cockeran: For conceptualising the study, analysing the data, interpreting the study and results

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Conflict of interest

The authors declare no conflict of interest with regard to the research, authorship and/or publication of this manuscript.

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3.3 MANUSCRIPT 2

Objective two from the empirical investigation is addressed in manuscript 2:

- Objective 2: To determine possible changes in the prescribing patterns of CNS medication in HIV/AIDS patients over the study period, i.e. 2005-2015.

Manuscript 1 is prepared and will be submitted to the journal '*Social Psychiatry and Psychiatric Epidemiolog*'. Refer to Annexure G for the specific author guidelines of the journal.

Prescribing patterns of central nervous system medication in HIV/AIDS patients in the private healthcare sector in South Africa: 2005-2015

Authors

Floidy Wafawanaka¹ Irma Kotze¹ Marike Cockeran² Martha Susanna Lubbe¹

Affiliations

¹ Medicine Usage in South Africa, Faculty of Health Sciences, North-West University, Potchefstroom, South Africa

² Statistics, School of Computer, Statistical and Mathematical Sciences, North-West University, Potchefstroom, South Africa

Corresponding author

Martie Lubbe (Martie.Lubbe@nwu.ac.za). North-West University, Medicine Usage in South Africa, School of Pharmacy, Faculty of Health Sciences, Potchefstroom, South Africa. Website: www.nwu.ac.za. Martie Lubbe (Martie.Lubbe@nwu.ac.za). Telephone: 0027 18 299 2287.

Short title: Central nervous system medication in HIV/AIDS patients

Abstract

Purpose: To determine, over an 11-year period, possible changes in the prescribing patterns of CNS medication in HIV/AIDS patients.

Methods: A longitudinal research design was followed to analyse retrospective medicine claims data from a closed cohort (N = 308) of HIV/AIDS patients (identified with ICD-10 codes B20-B24) obtained from a South African pharmaceutical benefit management (PBM) company's database. The study period was 11 years, from 1 Jan. 2005 to 31 Dec. 2015. Measurements included: i) different types of active pharmaceutical ingredients according to pharmacological groups; ii) number of medicine items per prescription; and iii) number of prescriptions per patient.

Results

In this study, 86.68% (n = 267) of HIV/AIDS patients claimed one or more CNS prescriptions during the study period. The mean number of items per prescription per patient increased marginally from 2005 (1.22(0.46) [1.15-1.28] to 2015 (1.25(0.59) [1.16-1.33]) ($P = 0.0004$; Cohen's d -value < 0.8). The mean number of prescriptions per patient did not change significantly from 1.56 (1.57) (1.34-1.78] in 2005 to 1.93 (2.11) [1.65-2.22] in 2015 ($P > .05$). The majority of patients received an antidepressant during 2005 (49.68%) and 2015 (73.05%). The number of patients who received a sedative hypnotic, an anxiolytic or an anti-epileptic drug increased with 45.0%, 54.55% and 89.94%, respectively, over the study period.

Conclusions

Major changes took place in CNS medication prescribing in privately-insured HIV/AIDS patients. The increase in the prescribing of antidepressants, sedative hypnotics, anxiolytics and anti-epileptic drugs should be further investigated.

Keywords: CNS medication, HIV/AIDS, neurological disorders, private health sector, South Africa

Introduction

Human immune virus/acquired immune deficiency syndrome (HIV/AIDS) is a global health problem, with different prevalence rates between countries and regions, and is the number one leading cause of death in many low- and middle-income countries (LMICs) [1]. Central nervous system (CNS) disorders comorbid HIV/AIDS is prevalent in many LMICs, and this presents major challenges to governments and infected individuals [2]. Some studies from different LMICs have reported a high prevalence of HIV/AIDS comorbid neurological disorders [3, 4]. The global prevalence rate of neurocognitive disorders is estimated to range from 25 to 40% among people living with HIV/AIDS (PLWHIV) before they die [5]. In many countries, risk factors form the driving force of HIV/AIDS comorbid CNS disorders. The most common risk factors for developing CNS impairments include HIV infection and antiretroviral drugs, Hepatitis B and C infections, opportunistic infections, diabetes, cardiovascular diseases, substance abuse and ageing [6, 5, 7].

Nightingale et al. [6] reported that HIV infection could result in neurological and neuropsychiatric disorders. The HIV is capable of infecting the CNS, particularly the brain, within a few days after entering the body [8]. The virus is capable of crossing the blood brain barrier and damage neurons, eventually leading to serious cognitive impairment [9]. The prevalence of HIV-associated dementia in PLWHIV ranges between 20 and 85% [10]. A couple of studies have estimated the prevalence of HIV-associated dementia to be more than 50% [11, 12]. HIV infection was identified as a risk factor of dementia in people who were not on treatment [13]. Many deaths have been reported as a result of HIV/AIDS comorbid CNS disorders [12, 14]. A further complicated factor is the weakened immune system of PLWHIV, which made them more prone to many kinds of opportunistic infections [15]. A great emphasis was placed on opportunistic infections comorbid HIV/AIDS and the co-infections that could lead to HIV/AIDS-related CNS cancers [6]. In another study, it was reported that HIV infection was, *inter alia*, linked to the development of brain tumours, tuberculosis, pneumonia, *Salmonella* infection, candidiasis, toxoplasmosis and *Streptococcus meningitides* [16].

Highly active antiretroviral therapy (HAART) is the standard treatment for HIV/AIDS [17, 18]. In many countries, the introduction of HAART has managed to reduce the high HIV/AIDS-related mortality and morbidity, thereby transforming HIV/AIDS into a manageable chronic condition [19, 20, 21]. In the era of HAART, the prevalence rates of neurological complications due to co-infections and comorbidities are increasing among PLWHIV [22, 23, 24]. Some researchers have suggested that antiretroviral drugs have managed to decrease the incidence of opportunistic infections and AIDS-defining cancers of the CNS [22, 23]. However, one research study emphasised that the incidence rate of HIV-dementia has increased due to HAART and the survival benefits conferred by HAART [25]. There is evidence to suggest neurocognitive disorders were prevalent before treatment with antiretroviral drugs [26].

Treatment of CNS disorders with CNS medication in PLWHIV has proven to be effective in reversing some of the neurocognitive disorders [27]. Due to the high prevalence rate of HIV/AIDS in South Africa, it is most common that HIV/AIDS comorbid with some of the major CNS disorders [2]. However, data on the usage of CNS medication and their prescribing patterns in PLWHIV in the private health sector in South Africa is scarce. Consequently, the aim of this study was to determine the prescribing patterns of CNS medication in HIV/AIDS patients in the private medical scheme environment in South Africa.

Methods

Study design

A longitudinal research design was followed using retrospective medicine claims data from a closed cohort of HIV/AIDS patients obtained from a South African pharmaceutical benefit management (PBM) company's database. The study period covered 11 years, from 1 Jan. 2005 to 31 Dec. 2015.

Study population

The study population included all patients (N = 308) on the database with an International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnosis code for HIV/AIDS (ICD-10 codes B20-B24) [28, 29] and who were on the database from 1 Jan. 2005 to 31 Dec. 2015. These patients could continuously claim CNS medication during the study period.

In the index year (2005), the study population was divided into two groups: i) HIV/AIDS patients who did not receive any CNS medication during the study period; and ii) HIV/AIDS patients who had received one or more CNS medication during the study period.

Data source

Data were obtained from a large independent privately-owned pharmaceutical benefit management (PBM) company's database. The PBM company administers and manages a variety of medicine benefit categories and capitation plans on behalf of medical schemes in South Africa. The medicine benefit allocation is based on medicine claims processing rules and authorisations; therefore, the claiming provider cannot manipulate the allocation of these benefits. Benefit allocation is ultimately the result of the benefit design and rules implemented by each medical scheme. Several automated validation processes were applied by the PBM company to ensure the validity and quality of the data.

The dataset consisted of patient demographics, and medication- and disease-related information. Patient demographics included the gender and date of birth, together with an encrypted medical scheme membership number that was used to follow-up patients' prescriptions over the 11-year period. Information on the dispensed medication included the prescription number and date, the National Pharmaceutical Product Index (NAPPI) code [30, 31] of each medication, and the active pharmaceutical ingredient. HIV/AIDS patients were identified using the International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) code, B20-B24 [28, 29].

Study variables

Independent variables for the study included the patient's gender and age. Patients' age was calculated on the date of dispensing of the first antiretroviral prescription in the index year (2005) in line with the patient's date of birth. Patients with unknown gender and date of birth were excluded. The study population was categorised by gender and divided into seven age groups: >0 and <6 years; ≥6 and <12 years, ≥12 and <18 years; ≥18 and <40 years; ≥40 and <60 years; ≥60 and <70 years; ≥70 years. Because of the low prevalence of patients in certain age groups, we did not stratify any medicine prescribing measures into age groups. Only the numbers of items per prescription per patient and the numbers of prescriptions per patient for the different years were stratified per age group.

Dependent variables consisted of the medicine prescribing measures. In this study, the CNS medication was identified according to the active pharmaceutical ingredient using the MIMS Desk Reference (MDR) and the National Pharmaceutical Product Interface (NAPPI) codes [30, 31]. We used the Monthly Index of Medical Specialities (MIMS[®]) classification system to classify the CNS medication according to the following pharmacological and sub-pharmacological groups [31]:

Central nervous system stimulants

- Sedative hypnotics
- Anxiolytics
- Antidepressants
- Antipsychotics
- Anti-epileptics
- Anti-Parkinson agents
- Antivertigo and anti-emetic agents
- Antimigraine agents
- Alzheimer's disease medication

Prescribing of CNS medication was assessed by measuring changes over the study period or between 2010 and 2015 in the: i) different types of active pharmaceutical ingredients according to pharmacological and sub-pharmacological groups; ii) mean number of medicine items per prescription per patient per year; and iii) mean number of prescriptions per patient per year, stratified per gender group. In South Africa, a prescription can contain one or more medicine items; and a patient can receive more than one prescription in a month.

Statistical analysis

The Statistical Analysis System[®] (SAS 9.4[®]) software [32] was used to analyse the data. Variables were expressed using descriptive statistics, which include numbers (n) and proportions presented as percentages (%), arithmetic means, standard deviations (SD) and 95% confidence intervals (CI). A *P*-value of 0.05 or less was considered statistically significant at a two-sided α -level. Practical significance of results was calculated when the *P*-value was statistically significant.

A two-sample *t*-test was used to compare the number of prescriptions per patient per year between the different gender groups [33]. Cohen's *d*-value was used to evaluate the effect size between means [34]. For

practical significance, the following were considered: 0.2 a small effect, with no significant difference, > 0.2 and ≤0.8 a medium effect with an observable significance, > 0.8 a large effect and significant difference.

The one-way analysis of variance (ANOVA) was used to test for significant differences between the mean numbers of CNS prescriptions per HIV/AIDS patient for the different years and the mean number of CNS medicine items per prescription per patient for the different years [35]. We will only present the results of this analysis between the study years 2005 and 2015. If a difference was detected, *post-hoc* tests were used to determine where the differences lie. [36].

The McNemar's test was used to determine whether there was a statistically significant change in the proportions of HIV/AIDS patients who received a specific CNS medication in 2005 versus 2015 [37].

Ethical considerations

This study was approved by the Health Research Ethics Committee of the North-West University (NWU-00179-14-A1-01), and goodwill permission to perform the study was obtained from the board of directors of the PBM company.

Results

Table 1 depicts the demographic characteristics of the study population (HIV/AIDS cohort). The cohort consisted of 308 HIV/AIDS patients. A total of 267 (86.68%) patients, including 144 (53.93%) females and 123 (46.07%) males claimed one or more CNS prescriptions during the study period of 11 years. Forty-one (13.32%) HIV/AIDS patients did not claim any CNS medication during the study period, and represented 11.11% (n = 18) of the females (N= 162) and 15.75% (n = 13) of the males (N= 146). No statistically significant differences were found between the mean age of patients who claimed CNS medication and those who did not claim. The mean age of female patients in the HIV/AIDS cohort was 36.77 (9.92) years (95% CI: 35.23-38.31) and male patients 39.60 (11.79) years (95% CI: 37.67-41.53 years) ($P = .0241$, Cohen's d -value = 0.2).

The majority of patients (73.41%) who claimed CNS medication belonged to the age group ≥ 40 and < 60 years, followed by age group ≥ 60 and < 70 years (20.97%). The mean age of female patients who claimed CNS medication was 37.12(9.25) years (95% CI: 35.69-38.65), and male patients 40.32(10.72) years (95% CI: 38.41-42.26 years) ($P = 0093$, Cohen's d -value = 0.3).

Table 1: Characteristics of study population (HIV/AIDS cohort)

	HIV/AIDS cohort					Total (N)		P-value
	Received CNS medication		No CNS medication					
	n	%	n	%				
Cohort	267	86.69	41	13.31	308			
Gender					N	%		
Female	144	53.93	18	43.90	162	52.60	0.2311 [†]	
Male	123	46.07	23	56.10	146	47.40		
Age (years)	38.59(10.06)		34.96(15.19)		38.11(10.92)		0.1449 [‡]	
Mean(SD)[95% CI]	[37.39-39.80]		[30.17-39.76]		[36.88-39.34]			
Female	37.12(9.25)		33.95(14.20)		36.77 (9.92)		0.3677 [‡]	
	[35.69-38.65]		[26.89-41.01]		[35.23-38.31]			
Male	40.32(10.72)		35.75(16.19)		39.60(11.79)		0.2046 [‡]	
	[38.41-42.26]		[28.75-42.75]		[37.67-41.53]			
P-value[‡]	0.0093		0.7073		0.0241			
	.3				.2			
Age groups (years)	n	%	n	%	N	%		
≥0 and <6	3	1.12	2	4.88	5	1.62	0.0985 [†]	
≥6 and <12	6	2.25	4	9.76	10	3.25		
≥12 and <18	1	0.37	0	0.00	1	0.32		
≥18 and <40	2	0.75	0	0.00	2	0.65		
≥40 and <60	196	73.41	26	63.41	222	72.08		
≥60 and <70	56	20.97	9	21.95	65	21.10		
≥70	3	1.12	0	0.00	3	0.97		

[†] Chi-square (χ^2) test

[‡] Two-sample *t*-test, Cohen's *d*-value

SD: Standard deviation; CI: Confidence interval

Table 2 illustrates the CNS items and prescription information prescribed to HIV/AIDS patients from 2005 to 2015. The results indicate that the number of items per prescription per patient increased statistically significantly from 2005 (1.22(0.46) [1.15-1.28]) to 2015 (1.25(0.59) [1.16-1.33]), although it is not of practical significance ($P = 0.0004$; Cohen's *d*-value < 0.8). There was no statistical significant increase in the mean number of prescriptions per patient over the study period from 1.56 (1.57) (1.34-1.78) in 2005 to 1.93 (2.11) [1.65-2.22] in 2015 ($P > .05$). The same trend was experienced with the mean number of prescriptions per patient over the study period for male and female patients ($P > .05$).

Table 2: Number of CNS medicine items and prescriptions prescribed to HIV/AIDS patients: 2005-2015

		2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	P-value†	
Patients receiving CNS medication	N _{Patients} (%)	198(64.29)	200(64.94)	175(56.82)	177(57.46)	186(60.39)	195(63.31)	214(69.48)	202(65.58)	200(65.94)	255(82.79)	208(67.53)		
	N _{Items}	381	361	380	448	500	476	456	496	498	539	517		
Items per prescription per patient	Mean(SD)	1.22(0.46)	1.33(0.67)	1.2(0.53)	1.35(0.76)	1.33(0.62)	1.22(0.44)	1.23(0.50)	1.27(0.62)	1.28(0.55)	1.11(0.69)	1.25(0.59)	0.0004§	
	95% CI	[1.15,1.28]	[1.24,1.42]	[1.21,1.28]	[1.24,1.46]	[1.24,1.42]	[1.15,1.28]	[1.17,1.30]	[1.19,1.36]	[1.20,1.36]	[1.01,1.18]	[1.16,1.33]		
Prescriptions per patient	N _{Prescriptions}	309	325	301	315	393	391	377	390	381	456	402		
	Mean(SD)	1.56(1.57)	1.63(1.89)	1.72(1.91)	1.78(2.15)	2.11(2.31)	2.01(2.14)	1.76(1.72)	1.93(2.02)	1.91(2.22)	1.79(2.10)	1.93(2.11)	0.2254	
	95% CI	[1.34,1.78]	[1.36,1.89]	[1.43,2.01]	[1.46,2.11]	[1.78,2.45]	[1.70,2.31]	[1.53,1.99]	[1.65,2.21]	[1.61,2.21]	[1.53,2.05]	[1.65,2.22]		
Variables														
Gender	Male	n _{Prescriptions}	188	170	163	183	249	228	215	220	200	230	192	
		Mean(SD) 95% CI	1.81(1.90)[1.44,2.18]	2.07(2.66)[1.49,2.66]	2.14(2.51)[1.57,2.72]	2.01(2.40)[1.51,2.51]	2.65(2.78)[2.08,3.22]	2.60(2.49)[2.06,3.12]	1.92(1.78)[1.59,2.25]	2.2(1.93)[1.82,2.58]	2.04(2.14)[1.61,2.47]	2.05(2.33)[1.62,2.49]	2.23(2.27)[1.75,2.72]	0.2729
	Female	n _{Prescriptions}	121	155	138	132	144	163	162	170	181	226	210	
		Mean(SD) 95% CI	1.29(1.02)[1.08,1.51]	1.31(0.97)[1.14,1.49]	1.39(1.21)[1.15,1.64]	1.53(1.82)[1.44,1.92]	1.57(1.54)[1.25,1.88]	1.52(1.66)[1.20,1.84]	1.59(1.64)[1.27,1.91]	1.67(2.07)[1.26,2.07]	1.77(2.29)[1.33,2.23]	1.58(1.88)[1.27,1.90]	1.72(1.94)[1.37,2.07]	0.5336
		P-value‡	0.0191	0.0048	0.0096	0.1406	0.0012	0.0005	0.1593	0.0603	0.3979	0.0747	0.0831	

† ANOVA

§ ANOVA, Tukey multiple comparison test, Cohen's *d*-value < .8 for all possible combinations

‡ Two-sample *t*-test, Cohen's *d*-value

SD: Standard deviation; CI: Confidence interval

Table 3: Central nervous system medication prescribed to HIV/AIDS patients according to pharmacological and sub-pharmacological group: 2005 versus 2015

Pharmacological/sub-pharmacological group	Number of patients(N = 308)				P-value [†]
	2005		2015		
	n	%	n	%	
Central nervous system stimulants	0	0.00	0	0.00	
Sedative hypnotics	60	19.48	87	28.25	0.0262
Anxiolytics	55	17.86	85	27.60	0.0112
Benzodiazepines	33	10.71	76	24.68	<0.0001
Others	22	7.14	9	2.92	0.0916
Antidepressants	153	49.68	225	73.05	0.0002
Tricyclic	44	14.29	61	19.81	0.0971
Non-tricyclic	10	3.25	7	2.27	0.4669
Selective serotonin re-uptake inhibitors	47	15.26	77	25.00	0.0071
Serotonin and noradrenaline re-uptake inhibitors	22	7.14	23	7.47	0.8815
Noradrenaline (and dopamine re-uptake inhibitors)	9	2.92	13	4.22	0.3938
Tetracyclic	21	6.82	40	12.99	0.015
Lithium	9	2.92	13	4.22	0.3938
Others	0	0.00	4	1.30	
Antipsychotics	7	2.27	10	3.25	0.4669
Phenothiazines	0	0.00	1	0.32	
Butyrophenones	1	0.32	4	1.30	0.1797
Atypical antipsychotics	6	1.95	5	1.62	0.763
Anti-epileptics	19	6.17	36	11.69	0.0219
Anti-Parkinson agents	1	0.32	2	0.65	0.5637
Dopaminergics	0	0.00	2	0.65	
Anticholinergics	1	0.32	0	0.00	
Antivertigo and anti-emetics agents	81	26.30	66	21.43	0.216
Antimigraine agents	5	1.62	6	1.95	0.763
Alzheimer's disease medication	0	0.00	0	0.00	

[†]McNemar test

Table 3 indicates the different CNS medication prescribed to HIV/AIDS patients according to their pharmacological and sub-pharmacological groups in 2010 versus 2015. Table 4 depicts the top 80% of CNS medication prescribed to HIV/AIDS patients according to active pharmaceutical ingredients in 2010 vs. 2015.

The results in Table 3 confirmed that the majority of HIV/AIDS patients received antidepressants during 2005 (49.68%) and 2015 (73.05%), which indicates an increase of 47.06% in the number of HIV/AIDS patients who received an antidepressant. In 2005, the antidepressants were followed by the antivertigo and anti-emetics agents (26.30%), and in 2015, by sedative hypnotics (28.25%) and anxiolytics (27.60%). The McNemar's test confirmed a significant difference, with an increasing trend in the proportion of patients who were treated antidepressants ($P < .0002$), sedative hypnotics ($P = .0262$), anxiolytics ($P = .0112$) and anti-epileptic drugs ($P = .0219$). The number of patients who received a sedative hypnotic or an anxiolytic or an anti-epileptic drug increased with 45.0%, 54.55% and 89.94%, respectively, over the 11-year study period. The proportion of HIV/AIDS patients who received antivertigo and anti-emetics agents decreased insignificantly from 26.30% in 2005 to 21.42% in 2015 ($P = 0.216$).

The most prescribed antidepressants for both 2005 and 2015 were the selective serotonin re-uptake inhibitors (15.26% vs. 25.00%), followed by tricyclics (14.29% vs. 19.81%) and tetracyclic (6.82% vs. 12.99%), respectively (Table 3). A significant change was found in the proportion of HIV/AIDS patients who received antidepressants from the pharmacological groups, selective serotonin re-uptake inhibitors ($P = .0071$) and tetracyclic antidepressants ($P = .015$). The proportion of HIV/AIDS patients who received the selective serotonin re-uptake inhibitor, escitalopram, increased significantly from 2005 to 2015 ($P = .0001$), as well as citalopram (Table 4). The tricyclic antidepressant, amitriptyline ($P = .0466$), and the tetracyclic antidepressant, bupropion ($P = .0007$), reveal the same trends. Amitriptyline was the most prescribed individual active ingredient prescribed in 2015 (14.61%).

Sedative hypnotics were the second most prescribed CNS medication (19.48% vs. 28.25%) to HIV/AIDS patients during 2005 and 2015 (Table 3). The results in Table 4 show that the individual sedative hypnotics, zolpidem and zopiclone, were prescribed to a constant proportion of patients in 2005 and 2015 ($P > 0.05$).

The number of HIV/AIDS patients who received anxiolytics increased with 55% from 2005 and 2015, with significant change in the proportion of patients who received benzodiazepines (e.g. alprazolam, bromazepam, clobazam, diazepam, lorazepam, oxazepam) ($P < .0001$) from 2005 and 2015. A significant change in the proportion of HIV/AIDS who received diazepam in 2015 compare to 2005 was found ($P = .0163$).

The results in Table 3 indicated that the proportion of HIV/AIDS patients who received anti-epileptic drugs increased significantly from 2005 to 2015 ($P = 0.0219$). The only antiepileptic drugs prevalent in the top 80% of active pharmaceutical ingredients used in 2005 and 2015 were carbamazepine and pregabalin. Pregabalin was only prescribed in 2015. The proportion of patients who received carbamazepine in 2005 did not change significantly in 2015 ($P = .1779$). The increase in anti-epileptic drugs may be the result of an increase in the prescribing of pregabalin in 2015 and the prescribing of carbamazepine.

According to the results in Table 4, metoclopramide was the most prescribed individual CNS active ingredient in 2005. The proportion of patients who received it in 2015 decreased, but the change was not statistically significant ($P = .1585$)

Table 4: Top 80% central nervous system medication prescribed to HIV/AIDS patients according to active pharmaceutical ingredient: 2005 versus 2015

Active pharmaceutical ingredient	Number of patients(N = 308)				P-value [†]
	2005		2015		
	N	%	N	%	
Metoclopramide	49	15.91	36	11.69	0.1585
Fluoxetine	31	10.06	23	7.47	0.2763
Amitriptyline	28	9.09	45	14.61	0.0466
Zolpidem	26	8.44	36	11.69	0.2041
Zopiclone	23	7.47	18	5.84	0.4349
Duloxetine	20	6.49	16	5.19	0.505
Mirtazapine	17	5.52	17	5.52	1
Carbamazepine	17	5.52	10	3.25	0.1779
Citalopram	13	4.22	24	7.79	0.0705
Cyclizine	13	4.22	9	2.92	0.3938
Diazepam	12	3.90	27	8.77	0.0163
Alprazolam	12	3.90	21	6.82	0.1172
Dothiepin	12	3.90	13	4.22	0.8415
Mianserin	10	3.25	7	2.27	0.4669
Lithium	9	2.92	13	4.22	0.3938
Bromazepam	5	1.62	11	3.57	0.1336
Cinnarazine	5	1.62	9	2.92	0.285
Bupropion	4	1.30	21	6.82	0.0007
Nitrazepam	2	0.65	12	3.90	0.0075
Escitalopram	1	0.32	24	7.79	<0.0001
Pregabalin	0	0.00	19	6.17	
Clobazam	0	0.00	15	4.87	

[†]McNemar test

Discussion

The aim of the study was to determine, from 2005 to 2015, the prescribing patterns of CNS medication in HIV/AIDS patients in the medical scheme environment (private health sector) of South Africa. Prescribing of CNS medication was measured by focusing on the following: i) difference between 2005 and 2015 in the prescribing of active pharmaceutical ingredients according to pharmacological and sub-pharmacological groups; ii) changes in mean number of medicine items per prescription per patient from 2005 to 2015; and iii) changes in the mean number of

prescriptions per patient from 2005 to 2015, stratified per gender group. The study population consisted of a closed cohort of 308 HIV/AIDS patients.

Patients living with HIV/AIDS have a higher risk of developing CNS comorbidities [38]. In this study, 86.68% of patients, including 144 (53.93%) females and 123 (46.07%) males, claimed one or more CNS prescriptions during the study period of 11 years. No associations were found between gender and the possibility to claim a CNS medication. The majority of patients (73.41%) who claimed CNS medication during the study period belonged to the age group ≥ 40 and < 60 years, followed by age group ≥ 60 and < 70 years (20.97%).

This study indicates a statistically significant, but not practically significant, increase in the mean number of items per prescription per patient from 2005 (1.22 (0.46) [1.15-1.28]) to 2015 (1.25 (0.59) [1.16-1.33]) ($P = 0.0004$; Cohen's d value < 0.8). There was no statistically significant increase in the mean number of prescriptions per patient over the study period from 1.56 (1.57) (1.34-1.78) in 2005 to 1.93 (2.11) [1.65-2.22] in 2015 ($P > .05$). Gender did not have an influence on the mean number of prescriptions per patient over the study period ($P > .05$).

Patients living with HIV/AIDS have a higher rate of neurological disorders [22]. Depression and anxiety are the most common neurological disorders in HIV/AIDS [39]. The current study confirmed that the majority of HIV/AIDS patients received antidepressants during 2005 (49.68%) and 2015 (73.05%), which indicates an increase of 47.06% in the number of HIV/AIDS patients who received antidepressants. These results may be an indication that most of our study population suffered from depression and anxiety disorders.

This study indicated that the most prescribed antidepressants for both 2005 and 2015 were the selective serotonin re-uptake inhibitors (e.g. escitalopram, citalopram and fluoxetine) (15.26% vs. 25.00%, respectively), which is indicated for major depression, followed by tricyclics (e.g. amitriptyline and dothiepin) (14.29% vs. 19.81%) and tetracyclic (6.82% vs. 12.99%). These results are supported by other studies that confirmed associations between antidepressant usage and HIV/AIDS [22, 39,40,41,42].

The tricyclic antidepressant, amitriptyline, was the most individually prescribed active ingredient in 2015 (14.61%). This may be based on long-term experience with the use of tricyclic antidepressants [39]. The side effects of tricyclic antidepressants, namely the anticholinergic effects, can also be used by physicians to treat diarrhoea, stomach upset and depression in the HIV/AIDS patient [43]. The prescribing of bupropion, a tetracyclic antidepressant, had increased significantly (1.3% vs. 6.82%) from 2005 to 2015 ($P = 0.0007$). Bupropion is normally used to treat depression and for smoking cessation. Bupropion could interact with ritonavir, efavirenz [44], can cause agitation, anxiety, insomnia, seizures and headache [31], but does not have sexual side effects.

The number of HIV/AIDS patients who received anxiolytics increased with 54.55% from 2005 to 2015, with significant changes in the proportion of patients who received benzodiazepines (e.g. alprazolam, bromazepam, clobazam, diazepam, lorazepam, oxazepam, nitrazepam) ($P < .0001$) from 2005 to 2015. The use of anxiolytics such as alprazolam, bromazepam, clobazam and diazepam could be suggesting that HIV/AIDS patients also suffer from anxiety.

Sedative hypnotics (e.g. zolpidem, zopiclone) were the second most prescribed CNS medication (19.48% vs. 28.25%) to HIV/AIDS patients during 2005 and 2015. Zolpidem and zopiclone are non-benzodiazepine and are safer for long-term use, because they cannot cause drug dependence and daytime sedation that may result from benzodiazepines [43]. Anxiolytics could stop anxiety, panic disorders, and alcohol withdrawal and promote sleep [31, 43].

The results indicated that the proportion of HIV/AIDS patients who received anti-epileptic drugs increased significantly from 2005 to 2015 ($P = 0.0219$), which was mainly the result of the prescribing of carbamazepine and pregabalin. Pregabalin was only prescribed in 2015 and the proportion of patients who received carbamazepine in 2005 did not change significantly in 2015 ($P = 0.1779$). The prescribing of lamotrigine and valproate acid in this population was very low and did not appear in the top 80% of active pharmaceutical ingredients prescribed in this study. Valproic acid does not appear to exhibit significant CYP-based drug interactions with antiretrovirals, but may impair zidovudine metabolism through the inhibition of glucuronidation, but there is no evidence of the clinical importance thereof [45]. Lamotrigine is indicated for the treatment of bipolar disorder and is not metabolised through the CYP system. Lamotrigine is well known for its life-threatening skin rashes, such as Stevens-Johnson syndrome. Its concentration can also decrease when used in combination with ritonavir (without any clinical implications) [45].

In this study, the prescribing of lithium did not increase significantly from 2005 to 2015 (2.22% vs. 4.22%) ($P = .3938$).

Metoclopramide declined from 15.91% in 2005 to 11.69% in 2015. The drug is indicated for gastrointestinal motility disorders and nausea [31]. However, metoclopramide is associated with headache, dyskinesia in the elderly, agitation and depression, and this could be one of the reasons why it was prescribed less in 2015 [31].

The main strength of this study was that all HIV/AIDS patients who were enrolled into the study were diagnosed with HIV/AIDS by a medical practitioner and registered by their medical scheme as an HIV/AIDS patient. It was possible to follow 308 HIV/AIDS patients for 11 years, and therefore the duration of the study was long enough to eliminate seasonal variations and also provide an opportunity to identify small changes in prescribing patterns, which might have occurred between 2005 and 2015. Furthermore, the reliability and validity of the data were ensured by the PBM company's internal validation processes, such as gate-keeping services, eligibility services, utilisation management services, clinical management services and pricing management along with real-time benefit management. This ensured that information received for this study, and subsequently its results, was sufficiently accurate.

Our study has a number of limitations, which should be taken into account by the reader. First and foremost, this study included only private-insured HIV/AIDS patients enrolled for 11 years in a nationally-representative medicine claims database that was acquired from a South African PBM company. Therefore, the findings cannot be generalised to HIV/AIDS patients who received their medication from public health facilities in South Africa or private patients who are responsible for their own medical expenses. There is also a small possibility that patients may be taking medication that was not claimed through their medical scheme, and therefore not included in the database. Secondly, we could not identify the indication for the use of the CNS medication because of incomplete ICD-10 diagnose codes for the CNS medication and additional clinical information.

Despite the limitations outlined, our findings suggest a number of important trends in the CNS medication in private-insured HIV/AIDS patients in South Africa. The increase in the use of antidepressant, anxiolytics and sedative hypnotics should be further investigated in the medical scheme environment in South Africa.

Ethical considerations

This study was approved by the Health Research Ethics Committee of the North-West University (NWU-00179-14-A1-01), and goodwill permission to perform the study was obtained from the board of directors of the PBM company. A specific patient could not be identified; therefore, confidentiality of information was maintained throughout the study.

All procedures performed in this study were in accordance with the ethical standards of our institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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Conflict of interest

The authors declare no conflict of interest with regard to the research, authorship and/or publication of this manuscript.

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3.4 CHAPTER SUMMARY

Chapter three fulfilled the objectives of the empirical phase of this study by means of the results that were presented in the form of two manuscripts.

The following chapter concludes the content of this dissertation with the final conclusions based on the objectives, limitations, strengths, and recommendations for the purpose of future research.

CHAPTER 4: CONCLUSIONS AND RECOMMENDATIONS

4.1 INTRODUCTION

The purpose of this chapter is to review how the research objectives, as outlined in Chapter 1, were met, as well as to discuss the results that were reported in two manuscripts in Chapter 3. Finally, it identifies the limitations and strengths of the study and also provides recommendations for future research studies.

4.2 CONCLUSIONS DERIVED FROM THE LITERATURE STUDY

The specific research objectives of the literature review included the following:

- Conceptualise and describe the incidence and prevalence of HIV/AIDS nationally, in Africa and globally..
- Identify and describe the prevalence of psychiatric co-morbidities in HIV/AIDS patients.

The conclusions that were drawn after meeting the above objectives are discussed in the following paragraphs.

4.2.1 To conceptualise and describe the incidence and prevalence of HIV/AIDS nationally, in Africa and globally

The Human Immunodeficiency Virus (HIV) is a retrovirus that causes a medical condition known as Acquired Immune Deficiency Syndrome (AIDS) (Juan *et al.*, 2016:1836). The HIV/AIDS is a disease that is characterised by the destruction of the human immune system (WHO, 2010b:6). When the human defence system is weakened, opportunistic infections occur and this results in causing the death of an infected person. The HIV belongs to a family of retroviruses, a member of the genus of lentiviruses, which have a long period of incubation and are characterised by their ability to incorporate viral DNA into a host cell's genome (Waki & Freed, 2010:604). Each viral particle consists of two identical RNA strands that are tightly bound to the viral nucleocapsid protein (Mims *et al.*, 2004). There are many sub-types of the HIV, and HIV-1 sub-type C is the most predominant variant in southern Africa (Arien *et al.*, 2007:150). The HIV-1 sub-type C is less virulent than HIV-1 sub-types A and D (Tebit & Arts, 2011:55).

The global prevalence of HIV/AIDS estimated that 36.9 million (31.1 million to 43.9 million) globally were living with the virus in 2016, of whom more than 29.7 million (70%) were living in sub-Saharan Africa (UNAIDS, 2016). It was estimated that that nearly 21.7 million (59%) PLWHIV accessed antiretroviral therapy in 2017 globally (UNAIDS, 2017a; UNAIDS, 2017b). The Joint United Nations Programme on HI/AIDS (UNAIDS) estimated that between 44 and 73% of PLWHIV were older than 15 years and 37 and 70% of children under the age of 14 years were on treatment in 2017 (UNAIDS, 2017a; UNAIDS, 2017b). In 2017, 61 to 95% of pregnant women living with HIV/AIDS were on treatment and this helped to prevent transmission of HIV to their babies (UNAIDS, 2017a; UNAIDS, 2017b).

The incidence of HIV infections is declining globally (UNAIDS, 2016). Globally, the HIV/AIDS epidemics have decreased over the last two decades, from 3.7 million new infections since the peak in 1996 to 1.8 million in 2016 (UNAIDS, 2016). In the same report, UNAIDS reports that between 2010 and 2016, HIV infection incidence rates among adults have significantly decreased by almost by 16% globally, from 1.9 million to 1.6 million. In children, the incidences went down by at least 35%, from 270 000 to 180 000 between 1995 and 2015 (UNAIDS, 2016). The same trend was reported by Tanser *et al.* (2013:966), and their study showed that HAART has managed to reduce new infections from 2.2 million in 2005 to 1.5 million in 2013 worldwide.

The increased coverage of highly-active antiretroviral treatment (HAART) in southern Africa has also reduced the number of people dying from HIV/AIDS by an estimated 40% between 2005 and 2013 (UNAIDS, 2014). Despite the benefits of HAART, in sub-Saharan Africa, HIV/AIDS still remains the main killer disease, accounting for more than 75% of deaths within the region (UNAIDS, 2014).

South Africa has the largest number of people living with HIV (PLWHIV) in the world (STATS SA, 2015a:6). The same report highlighted that there were more than 4 million PLWHIV in 2005 and the number increased to 7.1 million in 2015. Shisana *et al.* (2014) estimated the overall HIV-prevalence rate to be approximately 11.0% and 18.8% among adults. Females aged 12 to 18 years have a higher risk (5-7 times) of contracting HIV than their male counterparts of the same age (de Oliveira *et al.*, 2017:41). KwaZulu-Natal is the epicentre of HIV/AIDS in South Africa (STATS SA, 2013:6). The prevalence of HIV/AIDS among pregnant women in rural KwaZulu-Natal was more than 40% (NDOH, 2013a). Treatment coverage of HAART in SA is more than 50% (STATS SA, 2013).

4.2.2 To conceptualise and describe the prevalence of psychiatric co-morbidities in HIV/AIDS patients

Lorenc *et al.* (2014:84) defined a comorbidity as any disease condition outside the scope of HIV/AIDS-defining illnesses. Long exposure to HIV has resulted in other health problems such as cancers and opportunistic infections (Guaraldi *et al.*, 2015).

The increase in life expectancies of PLWHIV could be associated with risks of developing other conditions such as cardiovascular diseases, chronic obstructive pulmonary disease, diabetes, obesity, metabolic syndromes and disruption of cognitive function (Guaraldi *et al.*, 2015, Narayan *et al.*, 2014:2; Watkins & Treisman, 2015:37). The HIV/AIDS is associated with many neurological complications, such as HIV-mediated neurotoxicity, myelopathy, pain, changes in cognition, dementia, and psychiatric complications such as major depressive disorders, schizophrenia, substance abuse, dependence and mania (Ellis *et al.*, 2010; Wilson *et al.*, 2010). The virus is also capable of destroying all the organs in the body, including the CNS (Lind *et al.*, 2010:294). The majority of neurological and psychiatric complications could follow after HIV infection (Bhaskaran *et al.*, 2008:213). The HIV-1 infection targets the CNS in the subcortical brain areas and results in a high prevalence of delirium, depression, opportunistic CNS infections and dementia (Luma *et al.*, 2013). The HIV-1 could multiply in the brain in astrocytes and microglia, allowing the virus to hide from HAART and later compromise the neuronal function. *Tuberculosis meningitis* is a most common AIDS-defining opportunistic infection (Mouna *et al.*, 2016). Other opportunistic infections in HIV/AIDS are caused by *Cryptococcus neoformans*, *Toxoplasma gondii*, and *Tuberculosis mycobacterium* (Guaraldi *et al.*, 2015; Narayan *et al.*, 2014:1).

High prevalence of mental disorders among PLWHIV is an example of comorbidities in HIV/AIDS (Luma *et al.*, 2013; Weiss *et al.*, 2010:39). One study reported neurological complications of the central and peripheral nervous systems were 40% among PLWHIV (Rani *et al.*, 2015). The prevalence of CMV encephalitis is approximately 7% among HIV/AIDS patients (Letendre *et al.*, 2009:46). Other comorbidities also associated with HIV/AIDS might include psychiatric disorders (mood, dementia, psychosis) as a result of HIV infection, as well as non-communicable diseases (cancer, chronic kidney disease, hypertension, diabetes, hepatic disorders).

Across the life span of the infected individual, Hepatic C co-infections and metabolic disorders (Hernandez & Sherman, 2011:478; McCutchan *et al.*, 2012:485) are risk factors and these could lead to serious neurocognitive disorders (Hinkin *et al.*, 2008:11). Archer (2016:1) reported that

HIV is associated with high rates of CNS disorders among PLWHIV. The CNS complications could be caused by long-term severe HIV infection or as a result of HAART or ageing (CDC, 2008).

The WHO HIV-treatment guidelines have no specific recommendations on screening and treatment for psychiatric disorders among people living with HIV/AIDS. The Mental Health Gap Action Programme (mhGAP) intervention guide for mental, neurological and substance use disorders can be used in people living with HIV/AIDS (WHO, 2010c).

Managing symptoms of CNS disorders in PLWHIV who are on treatment is an important step that might help to improve the clinical outcome of the patient. Examples of symptoms in HIV/AIDS include fatigue, neuropathy, nausea, vomiting, anxiety, anorexia, fear, coughing, rashes, headaches, diarrhoea, insomnia, depression, vivid horrible dreams, pain and numbness (Sousa *et al.*, 2006:333). Some studies reported depression (Peltzer *et al.*, 2016:60), anxiety (Moore *et al.*, 2016:589) and neuropathy (Kaku & Simpson, 2014. 522). Despite the high prevalence of symptoms being experienced by HIV-infected individuals, data are limited regarding treating HIV/AIDS-associated symptoms in the private healthcare sector of South Africa. Symptoms are often not diagnosed properly by doctors and remain untreated in many LMICs (Peltzer *et al.*, 2016).

4.3 CONCLUSIONS DERIVED FROM THE EMPIRICAL STUDY

The objectives of the empirical study, written in the format of two manuscripts, were to:

- Determine possible changes in the incidence and prevalence of HIV/AIDS in the private health sector of SA over the study period, i.e. 2005 to 2015.
- Determine possible changes in the prescribing patterns of CNS medication in HIV/AIDS patients over the study period, i.e. 2005 to 2015.

The conclusions derived from the empirical investigation are discussed in the following paragraphs.

4.3.1 Incidence and prevalence of HIV/AIDS as indicated by the medical aid schemes claims database

The empirical objective to determine possible changes in the incidence and prevalence of HIV/AIDS in the private health sector of SA over the study period, i.e. from 1 January 2005 to 31 December 2015, was achieved and reported in manuscript 1, titled, “**Changes in the incidence and prevalence of HIV/AIDS in the South African medical schemes environment from 2005 to 2015**”. Manuscript 1 is prepared for and will be submitted to *African journal of infectious diseases*. Refer to Annexure J. for the author guidelines of the journal.

Studies determining both the incidence and prevalence rates of HIV/AIDS in the medical schemes environment are limited, particularly in South Africa. We aimed to determine changes in the incidence and prevalence rate of HIV/AIDS in the private medical schemes environment from 2005 to 2015 in South Africa.

Retrospective medicine claims data from an open cohort of HIV/AIDS patients were obtained from a database of a pharmaceutical benefit management (PBM) company from 1 January 2005 to 31 December 2015. The cohort included all patients with a diagnosis code for HIV/AIDS (ICD-10 codes B20-B24) and who claimed antiretroviral medication. Both HIV/AIDS incidence and prevalence rates were measured per 1 000 medical scheme beneficiaries for each year. Data were stratified by gender, age group and province.

A total of 1 213 676 and 843 972 patients claimed medicine items in 2005 and 2015, respectively. In 2005, approximately 0.63% (n = 7 665) of patients on the PBM database were HIV/AIDS patients and 2.10% (n = 17 302) in 2015.

The main findings of this study were the following:

- Both the incidence and prevalence rates of HIV/AIDS patients who claimed antiretroviral drugs through the PBM increased from 2005 to 2015. The prevalence rate of HIV/AIDS increased 3.3 times and the incidence rate increased 2.3 times from 2005 to 2015. The prevalence rate of HIV/AIDS patients per 1 000 medical scheme beneficiaries was 6.3 in 2005 and 20.5 per 1 000 medical scheme beneficiaries in 2015. The incidence rate has increased from 3.9 in 2006 to 9.1 per 1 000 medical scheme beneficiaries in 2015. This increase in the prevalence rate was probably influenced due to changes that were made by medical aid schemes in reporting their disease data between 2010 and 2015 (CMS, 2016, and 2017). Other

contributing factors can be the worsening disease profile, increased beneficiary awareness of their rights, and changes in care-seeking behaviour (CMS, 2017).

- The prevalence rate per 1 000 medical scheme beneficiaries of female HIV/AIDS patients was 6.5 in 2005, and increased to 20.4 by the end of 2015. Among males, the prevalence rate of HIV/AIDS increased from 6.0 (2005) to 21.7 (2015) per 1 000 medical scheme beneficiaries. In 2015, both the prevalence and incidence rates of HIV/AIDS were higher in males than in females.
- The HIV/AIDS incidence rate among females increased from 4.0 per 1 000 medical scheme beneficiaries in 2006 to 8.5 in 2015, whereas the incidence rate among males rose from 3.9 in 2006 to 9.9 per 1 000 medical scheme beneficiaries in 2015.
- The age group ≥ 40 and < 60 years had the highest HIV/AIDS prevalence rates of 14.4 in 2005 and 38.3 in 2015. This was followed by age group ≥ 60 and < 70 years.
- The age group ≥ 0 and < 6 years had the lowest HIV/AIDS prevalence rate and was followed by age group ≥ 6 and < 12 years with prevalence rates of 2.1 and 2.6 per 1 000 medical scheme beneficiaries for 2005 and 2015, respectively.
- The highest HIV/AIDS prevalence rate was noticed in Gauteng at 372.9 per 1 000 medical scheme beneficiaries in 2005, compared to 422.4 per 1 000 medical scheme beneficiaries in 2015. The increase in Gauteng may be attributed to a larger proportion of working class, and the presence of large corporate organisations that are members of medical aid schemes. According to the CMS (2017) annual report, the highest numbers of health service providers, health visits and beneficiaries are found in Gauteng, followed by the Western Cape. Mpumalanga, the Northern Cape, Western Cape and Limpopo consistently have lower proportions.
- The Western Cape was second with a prevalence rate of 152.9 HIV/AIDS patients per 1 000 medical scheme beneficiaries in 2005, and it decreased to 149.4 in 2015.
- KwaZulu-Natal was in the third position with a declining HIV/AIDS prevalence rate from 140.4 per 1 000 medical scheme beneficiaries in 2005 to less than 118.4 in 2015 in KwaZulu-Natal.

This study undoubtedly indicates an upward trend in the diagnosis and treatment of HIV/AIDS in the private medical scheme environment of South Africa from 2005 to 2015.

Concisely, this study has met the first objective of the empirical investigation, which pertained to the changes in the incidence and prevalence of HIV/AIDS in the medical schemes environment in South Africa.

4.3.2 Possible changes in the prescribing patterns of CNS medication prescribing in HIV/AIDS patients over the study period, i.e. 1 January 2005 to 31 December 2015

The empirical objective to determine the prescribing patterns of the CNS medication in HIV/AIDS patients in the private health sector in South Africa was achieved and reported on in manuscript two, titled: **“Prescribing patterns of central nervous system medication in HIV/AIDS patients in the private healthcare sector in South Africa: 2005-2015.”** Manuscript 2 is prepared for and will be submitted to the journal *Social Psychiatry and Psychiatric Epidemiology Journal* (refer to Annexure K).

The aim of the study was to determine, from 2005 to 2015, the prescribing patterns of CNS medication in HIV/AIDS patients in the medical scheme environment (private health sector) of South Africa. A longitudinal research design was followed to analyse retrospective medicine claims data from a closed cohort (N = 308) of HIV/AIDS patients (identified with ICD-10 codes B20-B24) obtained from a PBM company’s database. Prescribing of CNS medication was measured by focusing on the following: i) differences between 2005 and 2015 in the prescribing of active pharmaceutical ingredients according to pharmacological and sub-pharmacological groups; ii) changes in mean number of medicine items per prescription per patient from 2010 to 2015; and iii) changes in the mean number of prescriptions per patient from 2010 to 2015, stratified per gender group.

The main findings of this study were the following:

- In this study, 86.68% of patients, including 144 (53.93%) females and 123 (46.07%) males, claimed one or more CNS prescriptions from 2005 to 2015.
- No associations were found between gender and the possibility to claim a CNS medication.

- The majority of patients (73.41%) who claimed CNS medication during the study period belonged to the age group ≥ 40 and < 60 years, followed by age group ≥ 60 and < 70 years (20.97%).
- No practically significant increases in the mean number of items per prescription per patient from 2005 (1.22 (0.46) [1.15-1.28]) to 2015 (1.25 (0.59) [1.16-1.33]) ($P = 0.0004$; Cohen's < 0.8) were found.
- The mean number of prescriptions per patient did not change over the study period from 1.56 (1.57) (1.34-1.78) in 2005 to 1.93 (2.11) [1.65-2.22] in 2015 ($P > .05$). Gender did not have an influence on the mean number of prescriptions per patient over the study period ($P > .05$).
- The majority of patients received an antidepressant during 2005 (49.68%) and 2015 (73.05%). The number of patients who received a sedative hypnotic, an anxiolytic or an anti-epileptic drug increased with 45.0%, 54.55% and 89.94%, respectively, over the study period.
- The most prescribed antidepressants for both 2010 and 2015 were the selective serotonin re-uptake inhibitors (15.26% vs. 25.00%), followed by tricyclics (14.29% vs. 19.81%) and tetracyclic (6.82% vs. 12.99%), respectively. Amitriptyline was the most prescribed individual active ingredient prescribed in 2015 (14.61%). The prescribing of bupropion, a tetracyclic antidepressant, had increased significantly (1.3% vs. 6.82%) from 2005 to 2015 ($P = 0.0007$).
- Sedative hypnotics were the second most prescribed CNS medication (19.48% vs. 28.25%) in 2005 and 2015. The sedative hypnotics, zolpidem and zopiclone, were prescribed to a constant proportion of patients in 2005 and 2015 ($P > 0.05$).
- The number of HIV/AIDS patients who received anxiolytics increased with 55% from 2005 and 2015, with significant changes in the proportion of patients who received benzodiazepines (e.g. alprazolam, bromazepam, clobazam, diazepam, lorazepam, oxazepam) ($P > .0001$).
- The proportion of HIV/AIDS patients who received anti-epileptic drugs increased significantly from 2005 to 2015 ($P = 0.0219$). The only antiepileptic drugs prevalent in the top 80% of active pharmaceutical ingredients used in 2005 and 2010 were carbamazepine and pregabalin.
- The proportion of HIV/AIDS patients who received anti-vertigo and anti-emetic agents decreased insignificantly from 26.30% in 2010 to 21.42% in 2015 ($P = 0.216$).

In its summary of the relevant findings, this study has met the second objective of the empirical investigation, which pertained to the use of CNS medication in HIV/AIDS patients in the medical schemes healthcare environment.

4.4 STRENGTHS AND LIMITATIONS OF THE STUDY

The empirical study has a number of limitations, which should be taken into account by the reader

- An important limitation of this study was that data were obtained from only one of the PMBs in South Africa; generalisability and external validation of the data are therefore limited.
- This study included only private-insured HIV/AIDS patients enrolled for 11 years in a nationally-representative medicine claims database that was acquired from a South African PBM company. Therefore, the findings cannot be generalised to HIV/AIDS patients who received their medication from public health facilities in South Africa or private patients who are responsible for their own medical expenses.
- There is also a small possibility that patients may be taking medication that was not claimed through their medical scheme, and therefore not included in the database.
- The indication for the use of the CNS medication could not be identified because of incomplete ICD-10 diagnose codes and additional clinical information.

The study had its own strengths.

- The main strength of this study was that all HIV/AIDS patients who were enrolled into the study were diagnosed with HIV/AIDS by a medical practitioner and registered by their medical scheme as an HIV/AIDS patient.
- It was possible to follow 308 HIV/AIDS patients for 11 years, and therefore the duration of the study was long enough to eliminate seasonal variations and also provide an opportunity to identify small changes in prescribing patterns, which might have happened between 2005 and 2015.
- The reliability and validity of the data were ensured by the PBM company's internal validation processes, such as gate-keeping services, eligibility services, utilisation management services, clinical management services and pricing management along with real-time benefit

management. This ensured that information received for this study, and subsequently its results, was sufficiently accurate.

- A number of important trends regarding the prescribing of CNS medication in private-insured HIV/AIDS patients in South Africa were found. This study highlighted the incidence and prevalence of HIV/AIDS and the changes in the prescribing patterns of CNS medication in HIV/AIDS patients in a medical aid schemes environment in South Africa. As such, it helps to determine both the burden of HIV/AIDS and potential CNS comorbidities in HIV/AIDS in the private health sector of South Africa.

4.5 RECOMMENDATIONS

The following recommendations are proposed from the study:

Further research should be conducted, which should include, *inter alia*, the following analyses:

- The increase in the use of antidepressants, anxiolytics and sedative hypnotics in the HIV/AIDS patient should be further investigated.
- The prescribed daily doses of the CNS active pharmaceutical ingredients and its influence on changes of therapy should be further investigated.
- Studies to determine actual costs incurred by patients in treating HIV/ADS and its comorbidities should be conducted.
- Prospective studies on the use of CNS medication in HIV/AIDS should be conducted.

4.6 CHAPTER SUMMARY

This chapter summarised and concluded the specific objectives of the study as highlighted in the literature review and empirical investigation. In addition to that, strengths and limitations of the study were identified and discussed, and recommendations for future research were made.

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ANNEXURE A: WHO CLINICAL STAGING OF HIV/AIDS FOR ADULTS AND ADOLESCENTS

Clinical Stage	Clinical Conditions or Symptoms
Primary HIV infection	<ul style="list-style-type: none"> Asymptomatic Acute retroviral syndrome
Clinical stage 1	<ul style="list-style-type: none"> Asymptomatic Persistent generalized lymphadenopathy
Clinical stage 2	<ul style="list-style-type: none"> Moderate unexplained weight loss (<10% of presumed or measured body weight) Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) Herpes zoster Angular cheilitis Recurrent oral ulceration Pruritic Papular eruptions Seborrheic dermatitis Fungal nail infections
Clinical stage 3	<ul style="list-style-type: none"> Inexplicable severe weight loss (>10% of presumed or measured body weight) Unexplained chronic diarrhoea for >1 month Unexplained persistent fever for >1 month (>37.6°C, intermittent or constant) Persistent oral candidiasis (thrush) Oral hairy leukoplakia Pulmonary tuberculosis (current) Severe presumed bacterial infections (e.g., pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteremia) Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis Inexplicable anaemia (haemoglobin <8 g/dL) Neutropenia (neutrophils <500 cells/μL) Chronic thrombocytopenia (platelets <50,000 cells/μL)
Clinical stage 4	<ul style="list-style-type: none"> HIV wasting syndrome, as defined by the CDC (see Table 1, above) Pneumocystis pneumonia Recurrent severe bacterial pneumonia Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site) Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) Extra-pulmonary tuberculosis Kaposi sarcoma

Clinical Stage	Clinical Conditions or Symptoms
	<ul style="list-style-type: none"> • Cytomegalovirus infection (retinitis or infection of other organs) • Central nervous system toxoplasmosis • HIV encephalopathy • Cryptococcosis, extra-pulmonary (including meningitis) • Disseminated non-tuberculosis mycobacteria infection • Progressive multifocal leukoencephalopathy • Candida of the trachea, bronchi, or lungs • Chronic cryptosporidiosis (with diarrhea) • Chronic isosporiasis • Disseminated mycosis (e.g., histoplasmosis, coccidioidomycosis, penicilliosis) • Recurrent non-typhoidal <i>Salmonella</i> bacteremia • Lymphoma (cerebral or B-cell non-Hodgkin) • Invasive cervical carcinoma • Atypical disseminated leishmaniasis • Symptomatic HIV-associated nephropathy • Symptomatic HIV-associated cardiomyopathy • Reactivation of American trypanosomiasis (meningoencephalitis or myocarditis)

Source: WHO(2007a)

ANNEXURE B: SOUTH AFRICAN NATIONAL GUIDELINES FOR COMMENCING ANTIRETROVIRAL THERAPY

ELIGIBILITY CRITERIA
CD4 count \leq 350 cells/microliter regardless of stage or symptoms*
WHO stage 3 or 4 or other serious morbidity regardless of CD4 count (Cryptococcal meningitis - defer ART for 4-6 weeks).
TB regardless of CD4 count (TB meningitis -defer ART for 4-6 weeks).

*The WHO has moved the threshold for ART initiation to 500 cells/microliter. Source: (Rossiter, 2014:341).

ANNEXURE C: CLASSIFICATION OF ANTIRETROVIRAL DRUGS

Antiretroviral drug class	Comments
Nucleoside/nucleotide reverse transcriptase inhibitors	No significant interaction. Triple NRTI combination may be considered as ART regimen in exceptional circumstances
Non-nucleoside reverse transcriptase inhibitors	<p>Efavirenz is the preferred NNRTI for use with TB treatment.</p> <p>There is a moderate reduction in nevirapine concentrations.</p> <p>Leading-in dosing should be omitted. Monthly ALT monitoring is recommended.</p>
Protease inhibitors	<p>Dramatic reduction of concentrations of all PIs and none can be used without dose adjustment.</p> <p>In adults, limited evidence supports dose adjustments from the following agents (regular ALT monitoring essential):</p> <p>Doubling the dose of lopinavir/ritonavir. Dose should be titrated up over 2 weeks to improve tolerability. The final dose is lopinavir 800 mg 12 hourly ritonavir 200 mg 12 hourly.</p> <p>Saquinavir 400 mg 12 hourly + ritonavir 400 mg 12 hourly.</p> <p>In children:</p> <p>Add ritonavir to match the lopinavir dose. Doubling the dose of lopinavir/ritonavir is not recommended as it results in sub therapeutic lopinavir concentrations</p>

ANNEXURE D: CLASSIFICATION: COMMON SIDE EFFECTS OF DRUG SENSITIVE TB THERAPY AND ART

SIDE EFFECT	ARVs	TB TREATMENT
Nausea	AZT; PIs	Pyrazinamide
Peripheral neuropathy	d4T, ddi	INH
Hepatitis	NVP, EFV, PIs	Pyrazinamide, Rifampicin, INH
Rash	NVP, EFV	Rifampicin, INH, Pyrazinamide

Source: NDOH, 2015:84.

ANNEXURE E: COMMON DRUG TOXICITIES AND SIDE EFFECTS OF ARV DRUGS

DRUG	SIDE EFFECTS	RISK FACTORS	SUGGESTED MANAGEMENT
Abacavir	Hypersensitivity reaction	Presence of HLAB*5701 gene	If ABC is being used in first-line ART, substitute with TDF or AZT If ABC is being used in second-line ART, substitute with TDF
Atazanavir	Indirect hyperbilirubinaemia (clinical jaundice)	Underlying hepatitis disease HBV & HCV c0-infection Concomitant use of hepatotoxic drugs	LPV/r or DRV/r, if boosted PIs are contraindicated & NNRTIs have failed in first-line ART, consider integrase inhibitors
	Electrocardiographic abnormalities (PR interval prolongation)	Pre-existing condition disease Concomitant use of other drugs that may prolong the PR interval	
Emitricitabine	Severe skin rash & hypersensitivity reactions Hyperpigmentation of palms & soles	Unknown	Limited options are available
Zidovudine (AZT)	Anaemia, neutropenia, myopathy, lipoatrophy, or lipodystrophy	Baseline anaemia & neutropenia	If AZT is being used in first-line substitute with TDF or ABC
	Lactic acidosis or severe hepatomegaly with steatosis	BMI>25 (or body weight > 75kg) Prolonged exposure to nucleoside analogues	
Lamivudine (3TC)	Headache, dry mouth		AE very rare
Nevirapine (NVP)	Hepatotoxicity	Underlying hepatic disease HBV & HCV co-infection Concomitant use of hepatotoxic drug	If the person cannot tolerate either NNRTI, use PIs
	Hypersensitivity reaction, Steven-Johnson syndrome Convulsions	Risk factors unknown History of seizures	

DRUG	SIDE EFFECTS	RISK FACTORS	SUGGESTED MANAGEMENT
Efavirenz (EFV)	Persistent CNS toxicity (such as abnormal dreams, depression or mental confusion)	Depression or other mental disorder (previously or at baseline)	Daytime dosing
Tenofovir (TDF)	Flatulence, nausea, diarrhoea, abnormal discomfort Asthenia Acute renal insufficiency, Fanconi syndrome Chronic renal insufficiency		Active against hepatitis B but not FDA approved for treatment of hepatitis B. in patients with HIV and hepatitis B co-infection, hepatitis may flare upon discontinuation of TDF Gastrointestinal symptoms may be worse in lactose-intolerant patients; TDF is formulated with lactose Adjust dosage for renal insufficiency or failure
Lopinavir/ritonavir	Diarrhoea, nausea, vomiting Dyslipidaemia Elevation in liver function tests Taste pervasion		Available in tablets or oral solution. Tablets do not require refrigeration Oral solution contains 42% alcohol Avoid combining oral solution with Metronidazole or Disulfiram. Alcohol in Disulfiram-like reaction
Rotinavir	Nausea, vomiting, diarrhoea, abdominal pain Elevation in liver function tests Fatigue Circumoral or peripheral numbness Taste pervasion hyperuricemia		Capsule are stable at room temperature for up to 30 days Avoid combining oral solution with Metronidazole or Disulfiram. Alcohol in oral solution may cause Disulfiram-like reaction Has significant interactions with many medications

Source: NDOH, 2015:85-86.

ANNEXURE F: VALIDATION PROCESSES TO ENSURE THE VALIDITY AND RELIABILITY OF DATA EMPLOYED BY THE PBM

Validation processes: Examples	Validation processes: Examples
Data integrity validation and eligibility management	<ul style="list-style-type: none"> • Claim field format checks • Provider validation checks • Member validation checks • Verify dependant code • Waiting period check • Duplicate check
Medicine utilisation management (checked at active ingredient level against patient history)	<ul style="list-style-type: none"> • Refill limits (e.g. 12 fills per year for chronic medication) • Fill limitations per period (e.g. 1 fill per 26 days) • Product quantity limits (e.g. 200 analgesics/365 days) • Products requiring pre-authorisation (e.g. immune-modulating agents) • Patient specific exclusions (e.g. for pre-existing conditions and general waiting periods) • Pre-existing conditions (e.g. patient specific as advised by scheme) • Drug to gender limitations (e.g. hormone replacement therapy in women) • Invalid prescriber specialty (e.g. Diane™ prescribed by dermatologists) • Broad category exclusions (e.g. soaps/shampoos excluded) • Specific products excluded (e.g. urinary antiseptics) • Waiting periods (e.g. patient specific as advised by scheme)
Clinical management	<ul style="list-style-type: none"> • Ingredient duplication • Maximum daily dose exceeded • Therapeutic duplication • Drug-drug interactions • Drug-allergy interactions • Drug-age interactions • Drug-gender interactions • Drug-disease interactions • Drug-inferred health state interactions

Validation processes: Examples	Validation processes: Examples
Pricing management	<ul style="list-style-type: none"> • Continuous price file maintenance • Apply reference pricing, e.g. generic reference pricing and therapeutic reference pricing (i.e. formulary based pricing for chronic diseases)
Formulary management	<ul style="list-style-type: none"> • Management of chronic disease List prescribed minimum benefits and non-chronic disease list conditions • Daily real-time benefit validation

ANNEXURE G: PHARMACOLOGICAL CLASSIFICATION

Pharmaceutical classification (MIMS®):	
1.1. Central nervous system stimulants	1.1.1. Central analeptics 1.1.2. Respiratory stimulants 1.1.3. Others (excluding methylphenidate and atomoxetine)
1.2. Sedative hypnotics	1.2.1. Benzodiazepines 1.2.2. Barbiturates 1.2.3. Others
1.3. Anxiolytics	1.3.1. Benzodiazepines 1.3.2. Others
1.4. Antidepressants	1.4.1. Tricyclic 1.4.2. Non-tricyclic 1.4.3. Mono-amine oxidase inhibitors 1.4.3.1. Non-selective mono-amine oxidase inhibitors 1.4.3.2. Selective mono-amine oxidase inhibitors 1.4.4. Selective serotonin re-uptake inhibitors 1.4.5. Serotonin and noradrenaline re-uptake inhibitors 1.4.6. Lithium 1.4.7. Tetracyclic 1.4.8. Melatonergic specific 1.4.9. Lithium 1.4.10. Others
1.5. Antipsychotics	1.5.1. Phenothiazine 1.5.2. Butyrophenone 1.5.3. Atypical antipsychosis 1.5.4. Others
1.6. Anti-epileptics	1.6 Anti-epileptics
1.7. Anti-Parkinsonism	1.7.1 Dopaminergesics 1.7.2. Anticholinergics 1.7.3. Others
1.8. Anti-vertigo and anti-emetic agents	1.8 Antivertigo and anti-emetic agents
1.9. Anti-migraine	1.9 Antimigraine
1.10. Alzheimer's disease	1.10 Alzheimer's disease

Source: MIMS® 2015.

ANNEXURE H: CHRONIC DISEASES LIST OF SOUTH AFRICA

The CMS (2015) in South Africa indicate the 26 chronic conditions and HIV/Aids that are covered in a section of the PMBs and are listed below.

Addison's Disease

Asthma

Bipolar Mood Disorder

Bronchiectasis

Cardiomyopathy

Chronic Renal Failure

Chronic Obstructive Pulmonary Disease

Congestive Heart Failure

Coronary Artery Disease

Crohn's Disease

Diabetes Insipidus

Diabetes Mellitus Type 1

Diabetes Mellitus Type 2

Dysrhythmia

Epilepsy

Glaucoma

Haemophilia

HIV/AIDS

Hyperlipidaemia

Hypertension

Hypothyroidism

Multiple Sclerosis

Parkinson's Disease

Rheumatoid Arthritis

Schizophrenia

Systemic Lupus

Ulcerative Colitis

ANNEXURE I: CERTIFICATE OF ETHICAL APPROVAL



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Institutional Research Ethics Regulatory Committee

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ETHICS APPROVAL CERTIFICATE OF STUDY

Based on approval by Health Research Ethics Committee (HREC) on 01/12/2016 after being reviewed at the meeting held on 15/09/2016, the North-West University Institutional Research Ethics Regulatory Committee (NWU-IRERC) hereby approves your study as indicated below. This implies that the NWU-IRERC 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: Medicine prescribing patterns in a section of the private health sector utilising data from a Pharmaceutical Benefit Management company in South Africa.																														
Sub-study title: Usage of central nervous system medication in HIV/AIDS patients: Longitudinal analysis (2005-2015) of prevalence and prescribing pattern changes.																														
Study Leader/Supervisor: Prof MS Lubbe																														
Student: F Wafawanaka																														
Ethics number: <table border="1"><tr><td>N</td><td>W</td><td>U</td><td>-</td><td>0</td><td>0</td><td>1</td><td>7</td><td>9</td><td>-</td><td>1</td><td>4</td><td>-</td><td>A</td><td>1</td></tr><tr><td colspan="3">Institution</td><td colspan="5">Study Number</td><td colspan="2">Year</td><td colspan="5">Status</td></tr></table> <small>Status: S = Submission; R = Re-Submission; P = Provisional Authorisation; A = Authorisation</small>	N	W	U	-	0	0	1	7	9	-	1	4	-	A	1	Institution			Study Number					Year		Status				
N	W	U	-	0	0	1	7	9	-	1	4	-	A	1																
Institution			Study Number					Year		Status																				
Application Type: Sub-study																														
Commencement date: 2016-12-01																														
Risk: <table border="1"><tr><td>Minimal</td></tr></table>	Minimal																													
Minimal																														
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 up to a maximum period of three years.																														

Special conditions of the approval (if applicable):

- Translation of the Informed consent document to the languages applicable to the study participants should be submitted to the HREC (if applicable).
- Any research at governmental or private institutions, permission must still be obtained from relevant authorities and provided to the HREC. Ethics approval is required BEFORE approval can be obtained from these authorities.

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-IRERC 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. Would 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. Would there be 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-IRERC 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 IRERC 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 IRERC or HREC for any further enquiries or requests for assistance.

Yours sincerely

Linda du Plessis

Digitally signed by Linda du Plessis
DN: cn=Linda du Plessis, o=NWU,
ou=Vaal Triangle Campus,
email=linda.duplessis@nwu.ac.za,
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Prof Linda du Plessis

Chair NWU Institutional Research Ethics Regulatory Committee (IRERC)

ANNEXURE K: AUTHOR GUIDELINES MANUSCRIPT 2

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- ⌘ Commentaries should not contain more than 10,000 characters and less than 10 references. Please do not include an abstract or keywords
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- Methods
- Results
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LaTeX macro package (zip, 182 kB)

Headings

Please use no more than three levels of displayed headings.

Abbreviations

Abbreviations should be defined at first mention and used consistently thereafter.

Footnotes

Footnotes can be used to give additional information, which may include the citation of a reference included in the reference list. They should not consist solely of a reference citation, and they should never include the bibliographic details of a reference. They should also not contain any figures or tables.

Footnotes to the text are numbered consecutively; those to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data). Footnotes to the title or the authors of the article are not given reference symbols.

Always use footnotes instead of endnotes.

Acknowledgments

Acknowledgments of people, grants, funds, etc. should be placed in a separate section on the title page. The names of funding organizations should be written in full.

REFERENCES

Citation

Reference citations in the text should be identified by numbers in square brackets. Some examples:

1. Negotiation research spans many disciplines [3].
2. This result was later contradicted by Becker and Seligman [5].
3. This effect has been widely studied [1-3, 7].

Reference list

The list of references should only include works that are cited in the text and that have been published or accepted for publication. Personal communications and unpublished works should only be mentioned in the text. Do not use footnotes or endnotes as a substitute for a reference list.

The entries in the list should be numbered consecutively.

#: Journal article

Gamelin FX, Baquet G, Berthoin S, Thevenet D, Nourry C, Nottin S, Bosquet L (2009) Effect of high intensity intermittent training on heart rate variability in prepubescent children. *Eur J Appl Physiol* 105:731-738.
<https://doi.org/10.1007/s00421-008-0955-8>

Ideally, the names of all authors should be provided, but the usage of "et al" in long author lists will also be accepted:

Smith J, Jones M Jr, Houghton L et al (1999) Future of health insurance. *N Engl J Med* 341:325-329

#: Article by DOI

Slifka MK, Whitton JL (2000) Clinical implications of dysregulated cytokine production. *J Mol Med*. <https://doi.org/10.1007/s001090000086>

#: Book

South J, Blass B (2001) *The future of modern genomics*. Blackwell, London

#: Book chapter

Brown B, Aaron M (2001) The politics of nature. In: Smith J (ed) *The rise of modern genomics*, 3rd edn. Wiley, New York, pp 230-257

#: Online document

Cartwright J (2007) Big stars have weather too. IOP Publishing PhysicsWeb. <http://physicsweb.org/articles/news/11/6/16/1>. Accessed 26 June 2007

#: Dissertation

Trent JW (1975) *Experimental acute renal failure*. Dissertation, University of California

Always use the standard abbreviation of a journal's name according to the ISSN List of Title Word Abbreviations, see

ISSN.org LTWA

If you are unsure, please use the full journal title.

For authors using EndNote, Springer provides an output style that supports the formatting of in-text citations and reference list.

EndNote style (zip, 2 kB)

Authors preparing their manuscript in LaTeX can use the bibtex file spbasic.bst which is included in Springer's LaTeX macro package.

TABLES

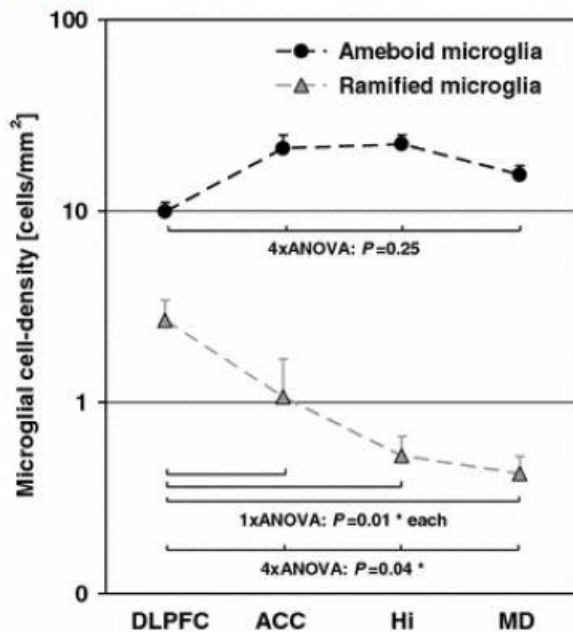
- ⌘ All tables are to be numbered using Arabic numerals.
- ⌘ Tables should always be cited in text in consecutive numerical order.
- ⌘ For each table, please supply a table caption (title) explaining the components of the table.
- ⌘ Identify any previously published material by giving the original source in the form of a reference at the end of the table caption.
- ⌘ Footnotes to tables should be indicated by superscript lower-case letters (or asterisks for significance values and other statistical data) and included beneath the table body.

ARTWORK AND ILLUSTRATIONS GUIDELINES

Electronic Figure Submission

- ⌘ Supply all figures electronically.
- ⌘ Indicate what graphics program was used to create the artwork.
- ⌘ For vector graphics, the preferred format is EPS; for halftones, please use TIFF format. MSOffice files are also acceptable.
- ⌘ Vector graphics containing fonts must have the fonts embedded in the files.
- ⌘ Name your figure files with "Fig" and the figure number, e.g., Fig1.eps.

Line Art



- ⌘ Definition: Black and white graphic with no shading.
- ⌘ Do not use faint lines and/or lettering and check that all lines and lettering within the figures are legible at final size.
- ⌘ All lines should be at least 0.1 mm (0.3 pt) wide.
- ⌘ Scanned line drawings and line drawings in bitmap format should have a minimum resolution of 1200 dpi.
- ⌘ Vector graphics containing fonts must have the fonts embedded in the files.

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Definition: Photographs, drawings, or paintings with fine shading, etc.

If any magnification is used in the photographs, indicate this by using scale bars within the figures themselves.

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- All figures have descriptive captions (blind users could then use a text-to-speech software or a text-to-Braille hardware)

- Patterns are used instead of or in addition to colors for conveying information (colorblind users would then be able to distinguish the visual elements)

- Any figure lettering has a contrast ratio of at least 4.5:1

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- Aspect ratio: 16:9 or 4:3

- Maximum file size: 25 GB

ANNEXURE L: PROOF OF LANGUAGE EDITING

To whom it may concern

Cecile van Zyl
Language editing and translation
Cell: 072 389 3450
Email: Cecile.vanZyl@nwu.ac.za

20 November 2018

Dear Mr / Ms

**Re: Language editing of dissertation (Prescribing patterns of central nervous system medication
in HIV/AIDS patients in the private healthcare sector in South Africa: 2005-2015)**

I hereby declare that I language edited the above-mentioned thesis by Mr Floidy Wafawanaka (student number: 28374307).

Please feel free to contact me should you have any enquiries.

Kind regards



Cecile van Zyl
Language practitioner
BA (PU for CHE); BA honours (NWU); MA (NWU)
SATI number: 1002391

ANNEXURE M: PROOF OF TECHNICAL EDITING

TO WHOM IT MAY CONCERN

I hereby declare that the dissertation titled:

Usage of central nervous system medication in HIV/AIDS patients: Longitudinal analysis (2005-2015) of prevalence and prescribing pattern changes

by

F Wafawanaka
26374307

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

E Oosthuizen
February 2019
