Quantification, Fate and Hazard Assessment of HIV-ARVs in Water Resources

Volume 2
Social aspects

Report to the
Water Research Commission

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EXECUTIVE SUMMARY

BACKGROUND

Since 1981, the world has struggled to cope with the extraordinary dimensions of a particular disease – HIV/AIDS. In 2006 South Africa had the highest number of AIDS related deaths – more than 345 000 (Statistics South Africa, 2017). However, this number has rapidly decreased to just under 127 000 AIDS-related deaths in 2017. This is for the most part attributed to modern-day innovations and the increase in the rollout of antiretroviral treatment. It is estimated that more than seven million South Africans were living with HIV/AIDS (Statistics South Africa, 2016). Just under four million South Africans are receiving treatment, more than any other country (UNAIDS, 2017c). Even more so, this number only accounts for the 53% of individuals eligible for treatment.

South Africa still has one of the highest HIV incidence rates in the world, the largest treatment programme, and therefore the greatest consumption of antiretroviral drugs per capita (Wood et al., 2014), with prescribed amounts of up to several tons per year (Swanepoel et al., 2015). The national rollout of antiretrovirals began in 2005 with the objective of one service point in each of the 53 districts of South Africa. Since then, it has improved the quality of life and the historical pattern of mortality in South Africa. However, there may be subtle, yet unquantified effects and processes that need to be better understood. These include environmental concentrations of the drugs, secondary human exposures, effects on aquatic life, and social considerations. These interactions are the subject of this Water Research Commission report.

Certain antiretroviral compounds can be excreted largely unchanged after consumption (e.g. acyclovir didanosine and tenofovir) whereas other compounds undergo extensive biotransformation prior to elimination from the body (Galasso et al., 2002; Al-Rajab et al., 2010). Up to 90% of orally consumed pharmaceutical drugs reach wastewater in one form or another (Halling-Sørensen, 1998). Research also suggests that compounds such as emtricitabine, ganciclovir, and lamivudine are metabolized only to a small extent in the human body (10-30%), whereas abacavir and zidovudine are primarily metabolized to their glucuronide-adducts (Funke et al., 2016).

Swanepoel et al. (2015) documented the presence of various antiretrovirals (nevirapine, didanosine, stavudine, tenofovir, nelfinavir, nevirapine, and saquinavir) in drinking- and groundwater samples. So also has the presence of antiretrovirals in South African waters been investigated by Schoeman et al. (2015), Wood et al. (2015) and Robson et al. (2017). It is therefore known that these pharmaceutical compounds are found in water resources, but knowledge of the implications and consequences thereof is exceptionally deficient.

The high prevalence and vast volume of antiviral drugs being consumed and excreted via various pathways into the natural environment poses an ever-increasing risk of pharmaceutical pollution. Many of the biological, economic, and social concerns of these highly bioactive compounds are unknown; endeavours to mount an effective solution are to date fragmented and vastly under-resourced. Subsequently, as result of previous research and an increasing demand to fulfil the many gaps in knowledge about this particular subject, the North-West University project team set about to complete a thorough risk assessment, quantification, and fate of HIV-ARVs in the water resources of South Africa. The project team consisted of specialists in social and health systems associated with this multidisciplinary topic, as well as the required partnerships and technology to conduct comprehensive research. Accordingly, the project contained many objectives and components as described below.

Towards a social and health perspective

A very important aspect associated with this study is the social and health perspective that includes release pathways of antiretrovirals, the usage of other medication with HIV/AIDS, and the state of the people living with HIV/AIDS (PLWHA) in South Africa. The incentive thereof was to increase cognizance of the fact that

HIV/AIDS is a multifaceted subject, affecting various fields and disciplines. The preservation of health in itself is a very complex subject and must be protected against the general social determinants of what is being constituted as health. Hence, from a health and social perspective, HIV and AIDS are approached as a biopsychosocial reality within this study. Since its inception, originally based on a mainly biological and ecological assessment, this project evolved to approach HIV from a holistic perspective (environmental, social, and health).

The HIV/AIDS disease affects all aspects of humanity, not just PLWHA, but relationships, cultures, communities, societies, and the supporting environment as a whole. This is meaningful because the social aspects influence people's help-seeking behaviour, it might restrain people from being tested, to commence with treatment, and to prevent spreading of the disease. Information on antiretrovirals in water could also then impact on PLWHA and people close to them, health professionals and health systems, and towards appropriate and constructive discarding practices of antiretrovirals and surplus pharmaceuticals in general. This study therefore describes the antiretroviral pathways from human consumption through the biopsychosocial determinants of health, and defines the disruptive link between antiretroviral consumption, challenged health systems, and the environment.

As stated by Grant (2008), all systems in the human body, including the central nervous system, can be affected by HIV. The human brain, for example, is affected during the early stages of the infection. However, the incomplete suppression of HIV by non-adherent PLWHA can also have serious consequences on an individual level and ultimately to public health (An et al., 1999). Living with HIV can contribute to mental neurological and substance abuse – a common problem in developing countries (Jack et al., 2014). This project investigates the possible changes in the prevalence of HIV, and prescribing patterns of central nervous system medications in PLWHA from 1 January 2005 to 31 December 2015 in the private health sector of South Africa.

According to Nebhinani et al. (2011), PLWHA with psychiatric disorders can be affected by neurocognitive disturbances, opportunistic infections, medication side effects, suboptimal treatment adherence, stigma, substance abuse, and the course of HIV infection. Antiretroviral drugs such as efavirenz and nevirapine cause psychiatric side effects in some (Wise et al., 2002; Poulsen and Lublin, 2003). High et al. (2006) also reported that long-term use of highly active antiretroviral therapy may be associated with cognitive impairment and can subsequently lead to dementia in older PLWHA. This is a serious concern, especially when taking into account that several tons of pharmaceutically active ingredients are released into South African waters each year.

Alas, little is known about the pharmaceutical treatment patterns of PLWHA and psychiatric comorbidities in the South African private sector, with limited guidelines developed for clinicians to treat such comorbidities. This substantiated the need to investigate other possible co-existing conditions in PLWHA, which can in turn be used to generate specific treatment regimens of psychiatric comorbidities in PLWHA. Knowledge of the different aspects of HIV/AIDS in the private health sector will also contribute to improving the burden of this disease in South Africa. Accordingly, this project aimed to compile a demographic-, clinical- and medicine claims profile of patients with HIV in the private healthcare sector of South Africa.

Public health embraces physical, psychological, social, and community health. According to Tzoulas et al. (2007), if green infrastructure and ecosystem health are improved, it presents the environmental setting of public health. Therefore, it could be said that a healthy environment, with a healthy supply of water, supports the health of the public. Knowledge about the value of water quality would be more significant to the public if modelled changes presented the risks associated with recreational opportunities and drinking water. These risks include the direct and indirect consequences of pharmaceutical exposures in surface and drinking water, which can in turn affect the value of aquatic ecosystem services. This study therefore also incorporates an investigation into the valuation of ecosystem services and disservices at health clinic gardens in South Africa and the link between ecosystem services and public health.

Contextual- and capacity development activities

In addition, the present study also included contextual and capacity development activities. This comprised of excursions to the different community health centres in Ikageng, Potchefstroom, which included the Boiki Tlhapi, Promosa, and Steve Tshwete Community Health Centre. In order to gain a better perspective on the everyday struggles accompanying HIV/AIDS, attention was given to adherence to complex antiretroviral treatment regimens and stigmas affecting the behaviour and relationships of people living in the communities. A review on the stockpiling of ARVs in rural households is also included.

Other activities comprised of attending the reporting seminar on the NWU Project for HIV and AIDS in the curriculum (2014-2017), funded by HEAIDS and DHET-NSF. The project aimed to assist in the understanding of how assumptions about HIV and AIDS are entrenched in the intersectionality that runs through specific sexual, socio-economic, gender and racial relationships. The seminar brought to light that, although there have been significant advances in medical interventions for HIV and AIDS, HIV discrimination and stigma continues to demean those infected and affected by the disease. This gap is to be addressed so that guidelines and recommendations can be made to aid developers of higher education programmes to successfully alter the curriculum in order to make it more applicable to students who live in a country with a high prevalence of HIV and AIDS.

On 29 and 30 November 2018, the, North-West University (NWU), Potchefstroom campus held an 'Emerging and Persistent Contaminants / Pathogens: Risk assessment, quantification and fate of HIV ARVs in Water Resources' policy brief writing workshop. The workshop was presented by a communications strategist along with researchers from the NWU, free-of-charge, to delegates from different government departments and other selected stakeholders. One of the objectives of the workshop being to capacitate government officials regarding the skill of writing policy briefs. During the two-day workshop, the delegates were guided towards translating the results from this project into a one-page policy brief and infographic aimed at specific stakeholders. The draft of the policy brief directed at the ministers of different government departments noting HIV-ARVs in water resources is included in Appendix J (Figure 22), and the draft infographic directed at specific professions councils on responsible discarding practices is included in Appendix K (Figure 23). The delegates effectively summarised, gave context, and described causes and effects of the current complexities of HIV-ARVs in water. They concluded with important recommendations to improve the current social and environmental situation. So also, did they effectively illustrate a call onto all health practitioners towards awareness, engagement, and advocacy of responsible discarding practices, regarding medication in efforts towards a healthier environment. Subsequently, delegates gained essential skills in knowledge translation.

AIMS

The primary aim of this study was to offer an overview of the sources, travel pathways, behaviour, fate, and impact of antiretrovirals within the environment, which is compiled in volume 1 of this report. From the environmental perspective, it was clear that the social perspective played an equally important role in understanding the fate and consequences of antiretrovirals in South Africa. Subsequently, through the biopsychosocial determinants of health, the antiretroviral pathways from human consumption were to be proposed and discussed from a health perspective. The disruptive link between antiretroviral consumption, challenged health systems, and the environment was also to be described. This is followed by recommendations for action and supplementary studies.

MATERIALS AND METHODS

The health perspective on antiretroviral pathways (CHAPTER 2:) involved an integrated literature review. Here the antiretroviral pathways from human consumption through the biopsychosocial determinants of health were proposed and discussed. The disruptive link between antiretroviral consumption, health systems, and the natural environment were also reviewed.

In addition, two complementary studies are included. These studies were added as a natural evolution of this project when additional complementary activities on this subject were discovered at the NWU. These expanded on the social aspects and health systems associated with HIV/AIDS since it pertains to how medication is used, pathways on how the compounds may enter the environment, and possible targets for interventions on all levels. The complementary studies are not yet completed as they started later, but further information will become available.

- CHAPTER 3:Usage of central nervous system medication in patients with HIV;
- CHAPTER 4:The profile of South African patients with HIV in a medical scheme environment;

CHAPTER 3: of the complementary studies included the component concerning the usage of central nervous system medication in HIV/AIDS patients. This study comprised of a literature review and an empirical investigation to determine the possible changes in the prevalence of HIV/AIDS, and prescribing patterns of central nervous system medications in HIV/AIDS patients over the study period (2005-2015), in the South African private health sector.

The profile of South African PLWHA in a medical scheme environment (CHAPTER 4:) entailed a literature review and empirical investigation. With the intention of determining the demographic-, clinical-, and medicine claims profile of PLWHA in the private healthcare sector of South Africa by using medicine claims data attained from a pharmaceutical benefit management company. A literature review was done on publications regarding the impact of HIV/AIDS in South Africa and internationally. The burden will be conceptualised from a clinical and an economic perspective, prevalence rate, co-existing chronic disease list conditions, and treatment methods are to be investigated. The empirical investigation included a cross-sectional, observational and quantitative research design implemented using retrospective medicine claims data from a pharmaceutical benefit management company.

RESULTS AND DISCUSSION

Health perspectives

The First Pathway: ARVs entering the South African health systems

HIV incidence and prevalence were investigated and found not to be representative of the society and requires further investigation. However, according to the CMS (2015a), HIV was the chronic disease that had grown the most from 2008 to 2013 (21.4%). In relation to the overburdened primary health care and failing health systems, South Africa's antiretroviral tender processes were found to be the largest in the world, funded predominantly by the Global Fund, and competitive enough to increase antiretroviral affordability (Sauls, 2015). It is therefore understandable that the administration of highly active antiretroviral therapy presents a complex value chain from production to consumption, based on the principles of primary health care. Yet, the Gauteng health system has been described in 2014 as a system in crisis marked by medicine shortages, disintegrating infrastructure, broken equipment, staff shortages and fund mismanagement. Reasons raised for a systemic failure and resource shortages are poor supply chain management, ineffective management, and poor financial management. Delivery of sufficient antiretrovirals to primary health care clinics requires functioning value chains and sufficient process compliance.

Specially trained health professionals need to follow the standardised national antiretroviral treatment regimens for adults and adolescents directed by the Essential Drug List (DoH, 2014). Antiretroviral and treatment regimens accessible in South African health systems according to the Essential Drug List are presented in Table 7and Table 8.

The first pathway also conducted research on the antiretroviral value chain in a typical Gauteng Primary Health Care clinic. The financial and human resources needed to realise the value chain within Gauteng's provincial medicine depot to sub-depots and several municipal depots, are astronomical. The National Department of Health (DoH, 2010), therefore noted that the value chain could be simplified to one distribution system. Entry of antiretrovirals into primary health care facilities indicated dissatisfactory inventory management in overburdened and understaffed clinics. In addition to the provision of ARVs from provincial depots to consumers, the DoH (2010) aimed to decentralise chronic disease medication by extending the value chain beyond primary health care facilities. The Gauteng Department of Health 2015/2016 reported also on the status of the Centralised Chronic Medicine Dispensing and Distribution (CCMDD). The CCMDD programme decrease waiting times at clinics and the out-patient departments of hospital pharmacies, and is aimed to increase affordable and timely delivery of essential medicine within resource-limited health system impacted by high disease burdens.

Examination of the challenges of antiretroviral adherence indicated that a 95% adherence to antiretroviral treatment is required to maintain viral load suppression and to prevent viral mutations. However, antiretroviral treatment adherence at the Kwa-Thema clinic (Ekurhuleni) for example, only had a 77% adherence. Subsequently, South Africa is dependent on the PEPFAR and UNAIDS 90-90-90 strategy in order to improve HIV/AIDS management and quality of life.

Insufficient evidence was obtained about antiretroviral discarding practices within the context of South Africa. However, the discarding practices of unwanted medications were reviewed (WHO 1999 guidelines). Despite the WHO guidelines, it was determined that South Africa should firstly be responsible to adhering its own policies and regulations. In general, the best environmental solution for pharmaceutical destruction is a purpose-built, high temperature incineration with adequate flue gas cleaning, although other methodologies may also be applicable. An international perspective of medicine discarding practices in general indicated that there is reason for concern for the disposal practices by the public as well as pharmaceutical waste on different levels of service delivery, as these could leak to the environment.

The Second Pathway: ARV processes through the biological pathways

The first aspect of this pathway entailed investigating antiretroviral elimination and excretion routes. The results were compiled, predominantly indicating renal and faecal elimination with only lamivudine being excreted via breast milk. When the contributing factors in HIV transmissions were investigated, it was noted that political and economic instability have an impact on HIV health promotion, for the reason that it complicates the activation and institution of behavioural change programmes. These include HIV screening and testing, antiretroviral treatment aimed to decrease viral load and transmission risks, treatment of sexually transmitted infections, and promotion of condom use. Another factor identified within this pathway was poor infrastructure and environmental health risks in informal settlements. Generic characteristics of informal settlements are: illegality and informality; inappropriate locations; restricted public and private sector investment; social stress; poverty and vulnerability. Over-crowding and high density living with poor services and poor environmental conditions are a detriment to promote health and improve quality of life. Typical challenges faced in informal settlements are overloaded sewerage systems that would pose a leakage point of pharmaceuticals to the environment. Subsequently, informal settlements are very vulnerable to pollutants and exposures in water systems. Concerning the procedures of the dead or dying, washing of corpses and burial practices, insufficient literature was obtained to describe the actual cultural actions surrounding these practices.

The Third Pathway: ARV's realities within psychosocial pathways

This pathway identified that although HIV transmissions follow a biological route, the impact transcends into a psychosocial and spiritual dimension. It was discovered that the lack of adherence to antiretroviral regimes are generally caused by substance abuse such as alcohol. Poverty, unemployment, crime, and fragmented social structures were investigated, and the social dynamics applied to antiretroviral pathways were summarised (Table 10). The study also revealed the impacts of HIV stigma. Concerning healthcare, HIV stigma is detrimental to antiretroviral adherence and prevents disclosure practices. HIV-related stigma effects psychosocial wellbeing of PLWHA and limits access to various facilities, including health systems. The outcome of HIV-stigma investigation revealed that it hampers effective disclosure management and requires the health system to conduct continuous risk-benefit analysis between economies of scale to care for such large patient corps against risking stigma. Antiretroviral related crime and corruption was also investigated within this pathway. Some examples of antiretroviral-related crime and corruption occurring within South Africa were reviewed and identified.

The Fourth Pathway: ARV impact on natural resources

This pathway identified the dominant risks of unwanted medications infiltrating the environment as follows: contamination of drinking water, especially through improper landfills; disposal of anti-neoplastics, disinfectants and non-biodegradable antibiotics into sewage systems; the release of toxic pollutants into the air due to low temperatures or open containers; scavenging in insecure and unprotected landfills; and the risk that expired unwanted medications re-enter the market for general public consumption. It was also determined that safe discarding practices should be promoted to health professionals and the public. Moreover, it should be done under national and governmental regulation and guidance with minimal financial and environmental cost. This report concluded that neither antiretrovirals, nor HIV, nor water is isolated from each other. These aspects should be addressed fundamentally across scientific, cultural, geographic, and organizational boundaries.

Complementary studies

1) Usage of CNS medication by medical scheme beneficiaries

A total of 1 213 676 and 843 972 patients claimed HIV-related 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. Both the incidence and prevalence rates of HIV/AIDS patients who claimed ARV 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 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. 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 scheme environment in South Africa.

2) Profiles of SA patients with HIV in a medical scheme environment

A total of 16 763 HIV/AIDs patients claimed antiretroviral medication in 2016, with an average age of 42,1 years. The highest HIV/AIDS prevalence was noticed in Gauteng (31.1%) followed by Western Cape (18.4%) and KwaZulu-Natal (14.2%) in 2016. 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 maximum number of HIV/AIDS patients per province were in the following districts: Buffalo City Metropolitan, Lejweleputswa, eThekwini, City of Johannesburg, City of Tshwane, Capricorn, Nkangala, Bojanala, Frances Baard and Overberg. The top three highest distribution of ARV drugs were: efavirenz/emtricitabine (19.65%); Emtricitabine/tenofovir (18.21%); and efavirenz (10.27%).

Although these studies began out of phase and are not yet complete, their results will become available with completion.

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SUMMARISED RECOMMENDATIONS

Health perspective on antiretroviral pathways

The following recommendations are proposed for the health perspective on antiretroviral pathways: (CHAPTER 2:):

- Reassess all discarding practices.
- Develop different sustainable discarding practices.
- Enforce the implementation of different sustainable disposal practices through legislation.
- Develop different measurement and evaluation systems to assess the effectiveness and efficiency of sustainable disposal practices such as landfills.
- Improve wastewater treatment plants to reduce the releases of antiretrovirals to water, thereby reducing human exposure and impacts on ecosystems.

Usage of central nervous systems medication (CNS) in patients with HIV/AIDS

The following recommendations are proposed for monitoring the usage of central nervous systems medication (CNS) in patients with HIV/AIDS (CHAPTER 3:):

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

- 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.

Profiling South African human immunodeficiency virus and acquired immune deficiency syndrome patients in the medical scheme environment in the private health sector of South Africa.

The following recommendations are proposed regarding profiling (CHAPTER 4:):

- Maintain and update the established demographic profile of HIV/AIDS patients regarding age and gender, geographical location as well as the type of prescribers of the ARV medication, so that any changes can be documented.
- Continue monitoring the clinical profile by identifying co-existing CDL list conditions, ARV treatment patterns and the adherence of patients toward ARV medication so that the effect of new developments and changes can be documented.
- Continue monitoring changes in the medicine claims profile of general medicine prescribing patterns, the type of medicine providers, and the direct medicine costs.
- This information will inform changes in patterns from well-informed databases, and indicate where interventions are required to reduce releases to the environment.

CONCLUSIONS

The absence of an effective cure to combat HIV/AIDS, ensures the continued usage of strong therapeutic drugs to suppress and alleviate symptoms. This in turn ensures ART and thereby the foundation of ARV pollution. However, this research has highlighted that the intersectionality of HIV expands into natural resources and that ARV pollution co-exists with numerous other social and health consequences. The dearth of a cure therefore places research focus on environmental relief and sustainability. This study has brought to light that by understanding and improving the social and health implications of ARVs in South Africa, researchers might be able to improve environmental conditions as well.

However, solely relying on statements regarding end-of-pipe solutions that are often obvious and easy to hide behind are simplistic and not reflecting holistic reality. We demonstrated the critical intersections between the need to consume pharmaceuticals by PLWHA, the need to protect their dignity and confidentiality, the onus placed on PLWHA to adhere to prescriptions, the need to supply them adequately and timely with medication and health services, better understand the various social, psychological, psychiatric, and household constraints faced by PLWHA, reduce accumulation and the discard and waste, reduce off-label use, and to strengthen the understanding of ecosystem services at a scale wider than clinics.

An already stressed environment, inadequate waste management (solid and wastewater), social practices, and a strained health system, forced by the relentless need to distribute and adhere to antiretroviral therapy, all contribute towards environmental pollution, poverty and social tensions (including stigma, crime, and corruption). Consequently, the combination of these factors most likely burdens society, infrastructure, environment, and slows the alleviation of poverty.

It is a moral and historic obligation to the more than 39 million people who have died from this disease to relieve as far as possible the burdens placed on PLWHA (another 39 million), their families, and communities, and to reduce transmission to those not yet affected, from the hard lessons we have learned. South Africa have subscribed to the UNAIDS 90-90-90 strategy to improve HIV/AIDS management and quality of life. To reiterate;

- By 2020, 90% of all people living with HIV will know their HIV status.
- By 2020, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy.
- By 2020, 90% of all people receiving antiretroviral therapy will have viral suppression.

It is inevitable that environmental considerations be accorded a lesser importance than poverty alleviation and disease prevention and management when dealing with emergencies. However, with this project we have now illustrated the links between the strategies employed to combat and manage the disease with a

healthy, safe, and functioning ecosystem and her services. The protection of the environment, the management of the disease, and the moral obligations we have towards people living with HIV and AIDS, are irrevocably linked. Current and future health management should therefore mainstream the environment in strategy, planning, execution, and monitoring for optimal welfare for all.

FINAL RECOMMENDATIONS

- The NWU research team have developed methods and knowledge on how the characterise the insidious problematics concerning HIV antiretrovirals on a regional scale for a specific disease. We have learned many lessons and gained tremendous experience. However, HIV antiretrovirals and the disease condition are not the only pharmaceutical and disease combinations that will result in environmental pollution. Although some of what we report is generic to the entire pharmaceutical spectrum, there are many situations that we do not know and understand, especially within a South African and African context. More studies are being published on the environmental side of pharmaceutical pollution in Africa. However, an integrated assessment as we have undertaken has nowhere been done. We therefore suggest that a much larger study, based on the experience and expertise developed by the current study would be appropriate for South Africa.

- The science of pharmaceuticals in the environment is developing at a rapid pace. New findings on, inter alia, health and environmental impacts, risk assessments, analytical techniques, and mitigation measures are published almost daily. It is also likely that guideline values for concentrations of pharmaceuticals in water and food will be developed soon, and implemented or negotiated by authorities and international agencies. It would be incumbent for South Africa and the Water Research Commission to keep abreast of these developments and thereby provide guidance to local, regional, and national authorities, as well as water supply companies. This may be achieved by commissioning an annual summary report.

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ACRONYMS and ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
ADD	Average daily dose
ADI	Acceptable daily intake
AhR	Aryl hydrocarbon receptor
AIDS	Acquired immune deficiency syndrome
ANC	African National Congress
ART	Antiretroviral therapy
ARV	Antiretroviral
ATV	Atazanavir
AUTHeR	Africa Unit for Transdisciplinary Health Research
AZT	Zidovudine
BG	Baragwanath
cART	Combination antiretroviral therapy
CCMDD	Centralised chronic medicine dispensing and distribution
CCMT	Continuous care and monitoring of treatment
CCR5	Chemokine receptor antagonists
CD_4	Cluster of differentiation 4
CDC	Centres for Diseases Control and Prevention
CDL	Chronic disease list
CE	Collision energies
CHW	Community health workers
CI	Confidence interval
CMS	Council of Medical Schemes
CNS	Central nervous system
COPC	Community-oriented primary care
CWP	Community Works Programme
d4T	2', 3' didehydro- 2', 3' dideoxythymine (Stavudine)
ddC	Zalcitabine
ddI	Didanosine
DNA	Deoxyribonucleic acid

DRE	Dioxin response element
DUR	Drug utilisation review
EDL	Essential drug list
EFV	Efavirenz
ETR	Etravirine
FDC	Fixed dose combination
FI	Fusion inhibitor
FRNA	F-specific RNA bacteriophages
FTC	Emtricitabine
GDP	Gross Domestic Product
GEE	Generalised estimating equations
GP	General practitioner
GR	Glucocorticoid receptor
HAART	Highly active antiretroviral therapy
HLB	Hydrophilic-lipophilic balance
HLB-L	Hydrophilic-lipophilic balance low
HI	Health index
HIV	Human immunodeficiency virus
HIV-ARV	HIV-antiretroviral therapy
HREC	Health Research Ethics Committee
HQ	Hazard quotient
ICD	International Disease Code 10
IQR	Interquartile range
IS	Fluconazole-d4
ISO	International Organization for Standardization
LAR	Luciferase assay reagent
LGBTI	Lesbian, gay, bisexual, transgender, and intersex
LMICs	Low- and middle-income countries
LPV/r	Lopinavir/ritonavir
MEA	Millennium Ecosystem Assessment
MEC	Member of Executive Council
MIMS	Medicine Monthly Index Specialities
MNS	Mental neurological substance use
MPharm	Master of Pharmacy

MPR	Medicine possession ratio
MTD	Minimum therapeutic dose
MTT	2-(4,5-dimethylthiazol-2-yl)-2,5 diphenyltetrazolium bromide
MUSA	Medicine Usage in South Africa
NAPPI	National Approved Product Pricing Index
NC	North Carolina
NFV	Nelfinavir
NHI	National Health Insurance
NHRPL	National Health Reference Price Listing
NMISA	National Metrology Instrument of South Africa
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NSP	National strategic plan
NVP	Nevirapine
NWU	North-West University
OR	Odds ratio
PBM	Pharmaceutical benefit management
PCDL	Personal compound database and library
PDD	Prescribed daily dose
PEPFAR	Presidents Emergency Plan for AIDS Relief
PHC	Primary health care
PI	Protein inhibitor
PLC	People living close
PLWHA	People living with HIV/AIDS
PMB	Prescribed minimum benefits
PMTCT	Prevention of mother-to-child-transmission
PPCPs	Pharmaceuticals and personal care products
PrEP	Pre-exposure prophylaxis
RAL	Raltegravir
RDD	Recommended daily dose
REP	Relative effects potency
RfD	Reference dose
RNA	Ribonucleic acid
RPV	Rilprivirine

RTV	Ritonavir
SAMF	South African Medicines Formulary
SAPC	South African Pharmacy Council
SAS®	Statistical Analysis System®, SAS 9.4® (SAS Institute Inc., 2002-2012)
SC	Solvent control
SCG	Single-cell gel
SD	Standard deviation
SD	Single dose
SQV	Lopinavir
STG	Standard Treatment Guideline
STI	Sexually transmitted infection
TB	Tuberculosis
TDF	tenofovir
UMs	Unwanted medications
UNAIDS	United Nations AIDS
USA	United States of America
UTT	Universal test and treat
WHO	World Health Organisation
WTP	Willingness to pay
WWTP	Wastewater treatment plant

GLOSSARY

AIDS. A fatal disease caused by HIV in which there is a severe loss of the body's cellular immunity, greatly lowering the resistance to infection and malignancy.

Antiretrovirals. Antiretroviral drugs inhibit the reproduction of retroviruses (viruses composed of RNA rather than DNA) to aid in the treatment of HIV infections.

Authorised pharmacist prescriber. Pharmacists who may prescribe schedule 1-4 medication for essential primary care as defined in the essential drug list guidelines and are registered to practise in this manner according to Pharmacy Act (53 of 1974).

Clinical profile. In terms of this study the clinical profile of the HIV/AIDS patient includes the coexisting chronic disease list conditions, antiretroviral treatment patterns and the adherence of the patient towards anti drugs by using the medicine procession rate as a proxy for adherence.

Demographic profile. In terms of this study the demographic profile portrays the age, gender, geographical location based on the postal code of the prescriber as well as the type of prescribers of the antiretroviral drugs.

Designated service provider. The prescribed minimum benefits (PMB) should be delivered by a designated service provider that is specified in the medical scheme rules to avoid co-payments and to have access to unlimited benefits. These service providers include doctors, pharmacies and hospitals, group of doctors or clinics.

Geographic location. The geographical location in terms of this study is based on the geographic location of the prescriber practise and will be determined by the postal code of the practice of the prescriber of the ARV drugs. It will be determined at provincial- and district level. The postal code of the prescriber will be used as a proxy for the geographical location of the patient.

HAART. Refers to very potent ART regimen which almost invariably inhibits viral replication to undetectable levels in the blood. It comprises of a combination of antiretroviral drugs.

HIV. Human immunodeficiency virus is a sexually transmitted virus, which left untreated, can lead to the fatal disease AIDS. HIV infection leads to low levels of $CD4^+$ T cells through a number of mechanisms. When $CD4^+$ T cell numbers decline below a critical level, cell-mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections.

Incidence. The HIV incidence is the number of new HIV infections in a population during a certain time period.

Intersectionality. The interconnected nature of social classifications such as race, gender, and class as they apply to a given individual or group, regarded as creating interdependent and overlapping systems of discrimination or disadvantage.

Medicine claims profile. In terms of this study the medicine claims profile of the HIV/AIDS patient includes the general medicine usage patterns, the type of medicine provider and a direct medicine cost analysis.

Prescribed minimum benefits (PMB). Prescribed minimum benefits are 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.

Prevalence. HIV prevalence is the percentage of people that are HIV+ in the population out of the total population at a given point in time.

Stigma. UNAIDS (2003), defines HIV-related stigma and discrimination as: "... a 'process of devaluation' of people either living with or associated with HIV and AIDS... Discrimination follows stigma and is the unfair and unjust treatment of an individual based on his or her real or perceived HIV status."

Woonga. Is a drug common in South African slum. It is a concoction of various substances such as rat poison, soap powder, etc. The main ingredient is ARVs. Whoonga is distributed as a fine white powder which is added to marijuana and/or tobacco. It is one of the most lethal drugs in the world.

Xenophobia. A dislike of or prejudice against people from other countries.

CHAPTER 1: INTRODUCTION

1.1 RATIONALE

South Africa (SA) has the largest HIV epidemic globally, with about 12,6% HIV prevalence and an estimated 7,06 million people living with HIV (PLWH) in 2017. The reality of the South African health system is that in 2016, 56% PLWH in SA accessed antiretroviral therapy (ART), benchmarked as the largest global ART treatment programme to 20% of PLWH worldwide. One of South Africa's strategies is to have 90% of PLWH receiving sustained ART by 2022. Having scaled-up access to ART through decentralised uninterrupted antiretroviral drugs (ARVs) supplies leading to large quantities of ARVs in resource-poor communities. It is evident that a predominantly pathological approach, resulting in potential environmental impacts, is being followed and that a more holistic perspective is necessitated. Increased consumption of ARVs in these resource-poor communities may lead to increased environmental challenges.

Some unintended environmental impacts include detrimental ARV contamination as active pharmaceutical ingredients are ubiquitous environmental contaminants. ARVs present as emerging contaminants (environmental unregulated compounds) amid limited knowledge of environmental toxicity and actions, risking adverse effects on ecosystems and viral resistance. Recent SA studies detected various ARVs in many water sources country-wide where current water treatment systems are unable to successfully remove ARVs from contaminated water. Environmental ARV release is a concern due to potential ecosystem alterations and viral resistance from multigenerational chronic exposure to trace levels of multiple ARVs, requiring environmental stewardship. A move in perspective where the presence of ARVs in water is viewed in relation to the complexities of HIV and AIDS may be of invaluable insight regarding improved means to address the concerns and challenges being faced.

1.2 PROJECT AIMS

The main aim of this study was to provide an overview of the sources, travel pathways, behaviour, fate and impact of antiretrovirals within the environment. Which is achieved by means of the following objectives:

1. To determine and document in a concise manner, the current use patterns and amounts of HIV-ARVs, as well as predict, from historic data, possible future scenarios.
2. To improve the sampling, extraction and analytical procedures, as well as implement a QA/QC scheme that will be done independently.
3. To determine potential major metabolites that may need additional attention through co-analysis for the parent compounds.
4. To determine spatial and temporal patterns of ARVs in wastewater, treated effluent, natural water, and drinking water.
5. To determine potential impacts in the environment using cell-based bio-assays, exposing freshwater snails, and investigating potential impacts on bacteriophages.
6. To conduct a human health risk assessment, based on the data generated.
7. To propose ARV pathways from human consumption through the biopsychosocial determinants of health, discussed from a health perspective.
8. To describe the disruptive link between ARV consumption, challenged health systems and the

environment.

9. To generate recommendations for action and/or supplementary studies.

Aims 2-6 are compiled in Quantification, fate and hazard assessment of HIV-ARVs in water resources: Volume 1 – Analytical and biological aspects.

1.3 SCOPE AND LIMITATIONS

Table 1: Limitations associated with each research component.

RESEARCH COMPONENT	LIMITATIONS
A health perspective on ARV pathways	● This is a fluid situation and changes and new insights should be monitored.
Usage of central nervous system medication in HIV/AIDS patients: longitudinal analysis (2005-2015) of prevalence and prescribing pattern changes	● There is no clinical information available regarding the CD4 counts and viral loads in patients' records in the database. ● Databases are restricted; incomplete information (including data on severity of illness). ● Coding is often inaccurate/incomplete (limited space for secondary diagnoses). ● Can only find events for existing codes; the database may not include the entire population.
Profile of South African HIV/AIDS patients in a medical scheme environment	● The postal code of the prescriber used to identify the geographical area might be limited as not all patients reside in the same area as their prescriber. ● Not all medical practitioners include the ICD-10 code on prescriptions or might note the wrong ICD 10 code. It is therefore not possible to determine the scope of this list limitation. ● Patient on HIV treatment for preventive reasons include but may not be limited to the prevention of mother-to-child-transmission, needle pricks, and post-exposure prevention, sexual partner diagnosed and treated. These treatments cannot be identified from the database and will be considered as a limitation for the purpose of this study. ● The medicine possession ratio will be used to indicate non-adherence and medicine oversupply but is merely an indication of possession of medication and cannot determine if the patient is actually taking the medication and will therefore be considered as a limitation to the study.

1.4 SUMMARY OF WORK TO DATE

Table 2 and Table 3 summarise the work to date, revised due dates and deliverables submitted thus far.

Table 2: Work completed to date.

No.	Task	Summary of work to date
1.	Human risk assessment	An integrated literature review has been completed to provide a critical synthesis of HIV and AIDS from a health perspective into the realities were environmental- and health sciences can and should collaborate towards a transdisciplinary outcome. The four ARV pathways have been investigated and discussed.
2.	AUTHeR *activity 1-3*	Conducted a systematic review for publication in an international journal on end user medication discarding practices. Too little information within literature existed regarding medication discarding practices, and it is recommended that research need to be initiated to investigate this topic. Policy brief training workshop presented to identified government departments and other stakeholders. Towards training government officials in the skill of writing a policy brief, and creating co-ownership of HIV-ARVs in water between the university and government. Two policy briefs were compiled. Implementation of a take-back HIV-ARVs disposal strategy with the Department of Health. Approved and awaiting the release of funds. .
3.	Usage of CNS medication	Literature study has been completed and research methods included.
4.	Profile of South African HIV/AIDS patients in a medical scheme environment	Development of research proposal. Approval of research proposal by Scientific Committee of research entity was obtained. Approval by Health Research Ethics Committee was obtained. Background and research method were included.

Table 3: Deliverable due dates and deliverables submitted to date.

No.	Deliverable	Status	Due date
1	Initial request.	Completed	30/05/2016
2	Detailed plan HIV-ARV use patterns, status quo regarding current use and predictions.	Completed	18/07/2016
3	Research progress report of components completed during past 12 months.	Completed	10/04/2017
4	Research progress report of the components completed during the past 24 months.	Completed	30/04/2018
5	Final report.	Completed	31/05/2019

BACKGROUND

1.5 HIV-AIDS

1.5.1 The origins of HIV-AIDS

The first recognised cases of AIDS (acquired immune deficiency syndrome) were reported in the summer of 1981 in the USA. The virus, which caused AIDS in the proportion of those infected was only discovered in 1983 and is now known as the human immunodeficiency virus (HIV).

The HIV epidemic arose after zoonotic infections with simian immunodeficiency viruses from African primates. One obstacle posed by HIV is that it has a high genetic variability. Subsequently, HIV can be divided into two major types, namely HIV-1 and HIV-2. According to Maartens et al. (2014), HIV-1 was most likely transmitted from apes and HIV-2 from sooty mangabey monkeys. The apparent genetic diversity of HIV-1 is a repercussion of the error-prone function of its reverse transcriptase, causing a high mutation rate. HIV-2 is predominantly confined to West Africa and causes an equivalent illness to HIV-1. However, the immunodeficiency progresses are more gradual and the HIV-2 is less transmissible (Sharp and Hahn, 2011).

Four groups of HIV-1 have been documented and embody three distinct transmission events from chimpanzees and one from gorillas. M, N, and O represent the chimpanzee transmission events and P the gorilla transmission events. In contrast to group M, groups N, O, and P are restricted to West Africa. Whereas group M is by far the most common type of HIV with more than 90% of HIV/AIDS cases deriving from HIV-1, group M, thereby also responsible for causing the global HIV pandemic. Nine subtypes (A-D, F-H, J, and K) subsists within group M. Subtype B predominates in western Europe, Australia and in America, while subtype C predominates in India and Africa which also accounted for 48% of HIV-1 cases worldwide in the year 2007 (Hemelaar et al. as cited by Maartens et al., 2014).

According to Satriano et al. (2005), the life expectancy at that time for an individual diagnosed with AIDS was but a mere six months. More than thirty years later, together with the introduction of combination antiretroviral therapy (cART), the clinical picture of HIV has shifted from a fatal illness to a chronic, manageable condition. An ageing cohort is now seen in developed countries where cART has been accessible from its inception and individuals diagnosed with HIV are living almost normal life expectancies. Subsequently, this has led to challenges of managing the comorbidities associated with age and with the long-standing consequences associated with cART. Despite this, HIV continues to exhort a massive economic and public health burden.

1.5.2 HIV/AIDS – a global perspective

Since the 1980's, this infectious disease has become a worldwide public health problem. It is estimated that globally, 36.7 million [30.8-42.7 million] people are living with the HIV of which 53% [39-65%] receives treatment (UNAIDS, 2016a). 19.5 million people was the estimated number receiving antiretroviral treatment (ART) in 2016 (UNAIDS, 2016a). In 2016, 1.8 million [1.6-2.1 million] people became newly infected with HIV, and 1 million [830 000-1.2 million] died from AIDS-related conditions (UNAIDS, 2016a).

1.5.3 HIV/AIDS in Africa

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 of year 2015, even though the region has just over 10% of the world's population (WHO, 2016). More than 54% of individuals who have HIV, are unaware that they are positive carriers of the virus (UNAIDS, 2015). The rapid increase of ART for HIV in sub-Saharan Africa over the past decade, is a unique achievement in the global fight against HIV. Due to large investments from sources such as the Global Fund to Fight AIDS, tuberculosis, and malaria; the Presidents Emergency Plan for AIDS Relief (PEPFAR); and bilateral donors, the number of HIV-infected people receiving life-saving treatment in sub-Saharan Africa increased from just 300,000 in 2004, to 6 million in 2015 (PEPFAR, 2016; UNAIDS, 2016a; UNAIDS, 2016b). Consequently, HIV-related morbidity and mortality have decreased dramatically in this region (UNAIDS, 2016a).

1.5.4 HIV/AIDS in South Africa

Statistics South Africa (2016), estimated that the total number of PLWHA in South Africa has grown from 4.72 million in 2002 to 7.03 million people in 2016. In 2013, it was reported that HIV/AIDs was responsible for more than 300 000 deaths in South Africa (UNAIDS, 2014). UNAIDS (2017b), documented an increase in the number of PLWHA from 5.1 million in 2005 to 7.1 million in 2017. The number of newly infected people in South Africa decreased from 500 000 [470 000-30 000] patients in 2005 to 270 000 [240 000-290 000] in 2016 (UNAIDS, 2017b). South Africa alone had nearly 3.9 million people on treatment, more than any other country in the world (UNAIDS, 2017c).

HIV/AIDS can only be prevented by reducing the risk of exposure, as there is no cure for HIV/AIDS. Subsequently, the virus can only be controlled by the use of ART (UNAIDS, 2016b; WHO, 2016). For these reasons, the supply of ART internationally and in South Africa, is vital to achieve the goal set by UNAIDS to reduce HIV/AIDS (UNAIDS, 2014; UNAIDS, 2016b; WHO, 2016). UNAIDS (2016b), chose a new strategy at the end of 2015 to eliminate HIV and AIDS as a global threat by the year 2030. Many countries including South Africa have adopted this strategy together with the objective known as the 90-90-90 strategy. Which entails that by 2020, 90% of PLWHA should be aware of their status; 90% of those diagnosed should receive ART; and 90% of those receiving ART should illustrate imperceptible levels of the virus (DoH, 2016; PEPFAR, 2016).

1.5.4.1 Prevalence

The Council of Medical Schemes (CMS) (2015) annual report 2013/2014, indicated that HIV prevalence among medical scheme members in the private healthcare sector has grown from 6.6% in 2008 to 17.4% in 2013. According to the CMS (2015), HIV was the chronic disease that had grown the most (21.4%) from 2008 to 2013. The latest Annual Report of the CMS (2016) indicated that the number of PLWHA in the medical scheme environment of South Africa increased from 27.7 per 1000 members in 2014, to 30.7 per 1000 members in 2015.

According to the Shisana et al. (2012) survey, the prevalence of HIV/AIDS differs from one province to the next. Kwa-Zulu Natal has a prevalence rate of 17%, 14% for the Free State, and 14% for Mpumalanga. The Western Cape has the lowest HIV/AIDS prevalence rate of 5%, whereas the prevalence in the Northern Cape is currently 7.4%, and 13.3% in the North-West. This survey shows that the prevalence rate of HIV/AIDS is substantially different from one province to another, between patients' age groups and gender (Shisana et al., 2012).

In accordance with UNAIDS (2014), South Africa's prevalence rate of adult PLWHA was estimated to be 19.1%. With the province of KwaZulu-Natal, seemingly functioning as the epicentre of the epidemic, research suggest that within certain communities a 15-year-old girl has an 80% probability of being infected with HIV within her lifespan (Hontelez et al., 2011; Nordling, 2016). Shisana et al. (2014), argued that the

country's overall prevalence rate of HIV infection had increased conceivably due to the massive expansion of the ART programme from 2007 to 2011.

The UNAIDS (2016a), has adopted a life-cycle approach by identifying key population groups in order to ensure optimal solutions that may be obtained through their entire lifetime. The prevention starts from mother-to-child transition, and intervention takes place from the birth of the child through to adulthood. Therefore, the WHO has support techniques in place for pregnant women and children (Luo et al., 2017). Key populations identified by UNAIDS (2016a), are sex workers, men having sex with men (MSM), people dependent on injectable drugs, migrants, and convicts. As indicated in the UNAIDS life cycle approach, the prevalence of PLWHA according to age and gender perspective are important factors in fighting HIV/AIDS (UNAIDS, 2016a).

1.5.4.2 Treatment

Presently, the most extensive ART programme in the world is contributed by roughly 7 million of South Africa's PLWHA and receiving ART. Increased access to ART is largely accountable for the rise in South Africa's average life expectancy at birth from 53.4 years (2004) to 62.5 years in 2015 (Nordling, 2016). Concurrently, infant mortality was reduced from 54 per 1000 births to less than 30 per 1000 births, and maternal mortality declined from 190 per 100 000 births to 155 per 100 000 births. Most of this was achieved by the increased use of antiretrovirals (Gray and McIntyre 2016), where 3.9 million people have received ARVs (UNAIDS, 2017c). When considering the amount of ARV consumption, it is to no incredulity that the Department of Health's report of HIV, AIDS, TB, and STIs in 2015 reported that an ART unit cost of R2 550 per patient per annum in Gauteng. This represents the massive financial burden of ARV management on South Africa. To add further strain, the most productive demographic age group is often affected the gravest, subsequently destabilising the economy and leaving many orphaned children (UNAIDS, 2006). The scientific contributions made in South Africa, will therefore have an unprecedented effect on the HIV epidemic worldwide.

1.5.5 Introductory notes on HIV and AIDS as a medical condition

For clarification, this report presents HIV and AIDS as two manageable conditions, as stipulated and regulated by the South African Essential Drug List (EDL) (DoH, 2014). HIV and AIDS represent more than a virus infection with biomedical signs, symptoms, and related treatment. As HIV replicates in the cluster differential four (CD4) positive monocytes and lymphocytes, it leads to the advanced destruction of these CD4+ lymphocytes causing a compromised immunity. Initially, the primary HIV infection presents with glandular fever-type illness, a maculopapular rash, and small orogenital ulcers (DoH, 2014). From this primary infection, an infected person can remain asymptomatic for many years besides generalised lymphadenopathy. Diagnosing HIV is another complexity. The progress from HIV infection to AIDS is organised by the World Health Organisation (WHO in Essential Drug List, 2014) according to a four stage system, applicable to adults and adolescents. This system presents a disease with multiple phases and faces, thereby complicating diagnosis (system is summarised in appendix A).

Therefore, PLWHA can present with increased frequency of minor infections and inflammatory skin conditions, followed by more severe infections, weight loss, or chronic diarrhoea. Tuberculosis is a severe infection going hand-in-hand with HIV. Finally, HIV-associated cancers and severe opportunistic infections leading to AIDS. The diagnosis of HIV starts in South Africa through pre- and post-test counselling and the provision of patient confidentiality. Rapid tests are available and can be followed by the ELISA (Enzyme linked immune-sorbent assays) test, although there is a window period after the first weeks of the primary infection when HIV antibodies are not detectable. This window period causes a risk for re-infection (DoH, 2014). The determined treatment for HIV is ART, used to suppress viral replication, increases the CD4+ count that reduces HIV-associated diseases and concomitant death. ART is guided by strict national guidelines (DoH, 2014).

The world has progressed positively and negatively in the response to HIV and AIDS. Today we see a stronger proactive approach with the universal test and treat (UTT) principle of HIV. UTT enables any HIV-positive person to access ART irrespective of a CD4-count and supports the 90-90-90 strategy. South Africa adopted the UTT policy from the WHO on 1 September 2016 (Pillay, 2016). Since then, all HIV-positive children, adolescents, and adults could start with lifelong ART irrespective of their CD4-counts, while PLWHA with CD4+ counts equal to or less than 350 were prioritized. All PLWHA in the pre-ART and wellness programmes could also enrol for UTT. CD4+ count remains the baseline monitoring mechanism to initiate and monitor ARVs. ART however, still requires the positive consent from the person living with HIV/AIDs.

In addition, there is the development of the pre-exposure prophylaxis (PrEP), which gives people the choice to decrease their risk for infection. It is a daily single oral consumption of Truvada (containing both tenofovir and emtricitabine) and when taken consistently, can reduce the risk of HIV infection up to 92% (CDC, 2016). It strengthens health-seeking behaviour and is advocated especially to people in the high-risk cluster to contract HIV, such as commercial sex workers and MSM.

1.5.5.1 The four clinical stages of HIV

As mentioned before, the disease progression follows four clinical HIV-1 infection phases namely HIV clinical stage 1 (the acute phase), HIV clinical stage 2 (moderate unexplained weight loss phase), HIV clinical stage 3 (chronic or clinical latent phase), and HIV clinical stage 4 (HIV wasting syndrome phase) (Philips, 2004; Grossman et al., 2006; Gupta et al., 2007).

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

The HIV clinical stage 2 is asymptomatic. The viral load (VL) ranges from undetectable to significant levels (Lyles et al., 2000). During this phase, severe opportunistic infections and neoplasms develop (Pilcher et al., 2004; Grossman et al., 2006).

The HIV clinical stage 3 is marked by a further deterioration of the body (Ray et al., 2010). Mutant HIVs are produced within this phase, increasing the difficulty of virus destruction faced by ARVs (Severe et al., 2010). The major symptoms of this phase include severe weight loss, Kaposi's sarcoma, unexplained chronic diarrhoea, persistent fever, severe bacterial infections, and anaemia. In addition, PLWHA in this phase are more susceptible and prone to tuberculosis infection (Weeks and Alcamo, 2006).

The proper diagnosis depends on several factors. Nonetheless, when the CD4+ cell count is less than 200 cells/ µL, individuals are generally diagnosed with AIDS (CDC, 1993). During the 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). Without ART, the VL keeps on increasing and HIV/AIDS eventually leads to the death of the patient (Severe et al., 2010).

1.6 THE GENESIS OF ANTIRETROVIRAL THERAPY

In 1987 the pharmaceutical compound, zidovudine, was approved which lead to the era of the antiretroviral treatment. Zidovudine is a thymidine nucleoside analogue that affects the reverse transcriptase enzyme required for HIV replication. Shortly thereafter, the clinical benefit of retrovir (AZT) was revealed in a placebo-controlled trail, which presented significant short-term clinical and survival improvement in patients with advanced stages of the disease (van Sighem et al., 1999; Karim and Karim, 2010). Subsequently,

additional nucleoside reverse transcriptase inhibitors (NRTI) were developed in the late 1980's. However, succeeding reports on monotherapy with AZT and other NRTIs failed to display significant survival advantages when therapy was commenced at earlier stages of HIV infection. As the availability of various drug classes increased, triple combination therapy showed greater and more resilient benefits than either mono- or dual therapy.

Observation of the benefits of ARV therapy on both the late and earlier asymptomatic phase of HIV infection was made possible by the development of surrogate markers of HIV disease progression, with CD4+T-cell counts functioning as the first reliable markers for disease progression (Karim and Karim, 2010). The development of protease inhibitors (PI) in 1996 initiated the era of highly active antiretroviral therapy (HAART). A new class of antiretrovirals, together with a commercial polymerase-chain-reaction-based assay, allowed for accurate monitoring of viral response to pungent therapy. Developments in the latest molecular quantitative viral assays have furthermore allowed circulating plasma HIV to be quantified to a lower threshold of only 50 copies of HIV RNA/mL.

The increase of CD4+T-cells together with the increase in the percentage of patients attaining viral suppression below 50 copies/mL, are now standard endpoints of ART trials (Karim and Karim, 2010). A third class of ARVs was developed shortly after the first PIs became obtainable, known as the non-nucleoside reverse transcriptase inhibitors (NNRTIs). Drug combinations from these classes of ARVs now represent the standard of care for ART (Esté and Cihlar, 2010). Although dual NRTIs constitute the orthodox foundation of ART, dual nucleoside therapy alone is not recommended any longer due to viral suppression being sub-optimal which can lead to increased drug resistance.

1.6.1 Objectives of antiretroviral therapy

The main objective of ART is to prevent or postpone the inevitable progression towards AIDS and consequential death. Effective ART does not completely avert clinical events and the initiation of therapy in advanced HIV cases with CD4+T-cell counts <50 cells/mL, can lead to new AIDS diagnoses in 10-15% of the individuals regardless of virological suppression (Saag and Kilby, 1999). However, auspicious responses to therapy generally include a decrease in plasma HIV-1 RNA together with an increase in CD4+T-cell counts. Subsequently, much of the clinical benefit of therapy is accounted for by the reduction in plasma viremia due to ART. Furthermore, the sustained suppression of plasma viral loads has become the most imperative quantifiable objective of therapy, generally associated with an increase in CD4+T-cell counts (Auvert et al*.,* 2004).

In addition, long-term cohort research studies and national death registers have confirmed the continued benefits of ART (Karim and Karim, 2010). The main objective of ART is to prevent or postpone the preordained progression towards AIDS and the consequential death of HIV infected patients. Effective ART does not completely avert clinical events and the initiation of therapy in advanced HIV cases with CD4+T-cell counts <50 cells/mL, can lead to new AIDS diagnoses in 10-15% of the individuals regardless of virological suppression (Saag and Kilby, 1999). However, auspicious responses to therapy generally include a decrease in plasma HIV-1 RNA together with an increase in CD4+T-cell counts. Subsequently, much of the clinical benefit of therapy is accounted for by the reduction in plasma viraemia due to ART. Furthermore, the sustained suppression of plasma viral loads has become the most imperative quantifiable objective of therapy and is generally associated with an increase in CD4+T-cell counts (Auvert et al*.,* 2004). In addition, long-term cohort research studies and national death registers have confirmed the continual benefits of ART (Karim and Karim, 2010).

1.6.2 Constraints of antiretroviral therapy

As mentioned before, ART is effective in regulating viral replication but is incapable of eradicating latent HIV-1, which persists in the host by incorporation into the genomes of metabolically inactive yet long-lived memory CD4+T-cells. According to Karim and Karim (2010), this reservoir of latently infected cells permits the reappearance of viremia when therapy is discontinued, thereby necessitating life-long therapy.

Successful ART increases naïve and memory CD4+T-cells and the partial restoration of immunity to certain opportunistic infections. Nevertheless, ART is unable to restore HIV-1 specific immune responses (Kushnir and Lewis, 2011). The capacity to restore immune response is reduced when therapy is commenced late in the clinical course of the disease as well as the capacity of the adult thymus to repopulate the immune repertoire also deteriorates with an increase in age (Crum et al., 2006; Karim and Karim, 2010). Increasing recognition of the adverse effects related to long-term drug use, including mitochondrial and metabolic toxicities, has subsequently led to more conservative approaches reflected in the evolution of treatment guidelines.

Metabolic abnormalities of the glucose and lipid metabolism include insulin resistance, hyperlipidaemia, and diabetes mellitus (Carr et al., 1998). With an increase in the life expectancy of patients on ART, so has an increase in the temporal exposure to metabolic toxicity caused an increase in the risk of cardiovascular events. Alterations in body habitus have also been increasingly documented in patients receiving ART, which is associated with changes in lipid and glucose metabolism (Karim and Karim, 2010). Both wasting of the peripheral fat of the limbs, face, and buttocks and augmented fat deposition in the abdomen and other subcutaneous areas, including submental and retroauricular regions constitute of the lipodystrophy syndrome (Azu, 2010).

These long-term metabolic problems were first thought to be limited to patients receiving PIs, but has now been indicated to be related to all of the presently licensed drug classes. Although NRTIs predominantly target the reverse transcriptase enzymes of HIV, they also have diverse affinities for associated human mitochondrial enzymes (DNA polymerase gamma) encoding for the mitochondrial structural sub-unit essential for the oxidative phosphorylation pathway. The inhibition of this enzyme, due to the dideoxy of the NRTI drugs (ddC, d4T and ddI), accounts for mitochondrial dysfunction. Mitochondrial toxicity has protean indicators, including asymptomatic lactic acidaemia, life threatening lactic acidosis, chronic myopathy, or peripheral neuropathy (Soriano et al., 2008). The acknowledgment of the deleterious impact of these toxicities on the tolerability thereof has led to the innovation of additional drugs within each class, which consist of improved metabolic profiles and tolerabilities (Karim and Karim, 2010).

1.6.3 HIV-ARV compounds as used in South Africa

As mentioned in Volume 1, an arsenal of over 30 Food and Drug Administration (FDA) approved drugs are accessible for the treatment of HIV-1 infections (Arts and Hazuda, 2012), of which various combinations are accessible or approved in different countries. ART regimes are constantly changing due to new insights and product development. At the commencement of this project, various literature studies were considered in order to determine the most prevalent and utilized ARV compounds within South Africa on which the focus was to be drawn. The latest information available on which HIV-ARVs are generally used in South Africa, are contained in the Notice from the National Department of Health (appendix B), reproduced, and explained in a poster as found in appendix C. Even though, there are numerous bioactive compounds, this project set about to analyse the antiretrovirals as presented in Table 4. This is supported by its vast consumption in South Africa, prescription quantities, availability of obtaining active ingredients as well as its occurrence and detection in the natural environment such as found in subsequent literature (refer to Table 5).

Table 4: ARV classes and compounds analysed within this study.

Drug class	ARV generic name	Abbreviation	CAS no	FDA approval date
Nucleoside reverse transcriptase inhibitors	didanosine	ddI	69655-05-6	9 Oct 1991
	lamivudine	3TC	134978-17-4	17 Nov 1995
	stavudine	d4T	3056-17-5	24 Jun 1994
	zidovudine	ZDV/AZT	30516-87-1	19 Mar 1987
Non-nucleoside reverse transcriptase inhibitors	efavirenz	EFV	154598-52-4	17 Sep 1998
	nevirapine	NVP	129618-40-2	21 Jun 1996
Protein inhibitors	lopinavir	LVP	192725-17-0	15 Sep 2000
	ritonavir	RTV	155213-67-5	1 Mar 1987

Table 5: Antiretroviral drugs quantified in South African water bodies.

Compound	Sample	Maximum concentration (µg/L)	Reference
Atazanavir	Effluent	0.740	Abafe et al., 2018
Didanosine	Surface water	0.054	Wood et al., 2015
	Groundwater	0.003	Swanepoel et al., 2015
	Drinking water	0.003	Swanepoel et al., 2015
Darunavir	Effluent	17.000	Abafe et al., 2018
Efavirenz	Influent	17.4	Schoeman et al., 2015
	Effluent	7.1	Schoeman et al., 2015
	Influent	0.010	Robson et al., 2017
	Surface water	0.005	Robson et al., 2017
	Effluent	4.000	Schoeman et al., 2017
	Influent	34.000	Abafe et al., 2018
	Effluent	34.000	Abafe et al.., 2018
	Dam water	0.082	Rimayi et al., 2018
	River water	0.354	Rimayi et al., 2018
	Groundwater	0.005	Rimayi et al., 2018
Emtricitabine	River water	0.013	Rimayi et al., 2018
Indinavir	Effluent	0.042	Abafe et al., 2018
Lamivudine	Surface water	0.24	Wood et al., 2015
	Surface water	5.4	Schoeman et al., 2015
	Influent	2.200	Abafe et al., 2018
	Effluent	0.130	Abafe et al., 2018
Lopinavir	Surface water	0.31	Wood et al., 2015
	Surface water	0.001	Swanepoel et al., 2015
	Effluent	3.800	Abafe et al., 2018
Nevirapine	Surface water	1.48	Wood et al., 2015

Compound	Sample	Maximum concentration (µg/L)
	Surface water	4.9	Schoeman et al., 2015
	Influent	2.1	Schoeman et al., 2015
	Effluent	0.35	Schoeman et al., 2015
	Effluent	0.004	Swanepoel et al., 2015
	Drinking water	0.003	Swanepoel et al., 2015
	Groundwater	0.005	Swanepoel et al., 2015
	Effluent	0.473	Schoeman et al., 2017
	Influent	2.800	Abafe et al., 2018
	Effluent	1.900	Abafe et al., 2018
	Dam water	0.055	Rimayi et al., 2018
	River water	0.071	Rimayi et al., 2018
	Groundwater	0.013	Rimayi et al., 2018
Maraviroc	Effluent	0.039	Abafe et al., 2018
Raltegravir	Effluent	3.500	Abafe et al., 2018
Ritonavir	Effluent	1.500	Abafe et al., 2018
Rimantadine	Surface water	0.02	Wood et al., 2015
Stavudine	Surface water	0.78	Wood et al., 2015
	Drinking water	0.001	Swanepoel et al., 2015
Tenofovir	Surface water	0.24	Wood et al., 2015
	Effluent	0.002	Swanepoel et al., 2015
Zalcitabine	Surface water	0.07	Wood et al., 2015
Zidovudine	Surface water	0.97	Wood et al., 2015
	Effluent	0.003	Swanepoel et al., 2015
	Drinking water	0.002	Swanepoel et al., 2015
	Influent	53.000	Abafe et al., 2018
	Effluent	0.500	Abafe et al., 2018

1.7 HEALTH SERVICES IN SOUTH AFRICA

Under the leadership of the African National Congress (ANC), South Africa has transformed from a curative and hospital-centric to a primary health care (PHC) philosophy in 1994. A PHC philosophy is based on the development and participation of the community in planning, provisioning, controlling, and monitoring of services (Cullinan, 2006). It is aimed to make comprehensive health services affordable, equitable, accessible and of quality and was implemented to echo Clause 27.1 of the Constitution of South Africa:

27. (1) Everyone has the right to have access to –
(a) health care services, including reproductive health care;
(b) sufficient food and water; and
(c) social security, including, if they are unable to support themselves and their dependants, appropriate social assistance.

(2) The state must take reasonable legislative and other measures, within its available resources, to achieve the progressive realisation of each of these rights.
(3) No one may be refused emergency medical treatment.

As PHC takes comprehensive care into communities, local clinics and community health centres are said to be the first level of South African health services and by norm a patients' ideal first point of entry concerning health care (Cullinan, 2006). These facilities treat "ambulatory patients", which refers to those patients that are capable of walking to the facility and are not confined to a bed (Cullinan, 2006).

A clinic refers to a facility that provides a variety of PHC services, which is usually open eight hours a day (Cullinan, 2006). Concerning emergencies, some staff members may be required to sleep near or at the clinic (Cullinan, 2006). A community health centre provides a variety of PHC services as well as 24-hour maternity and emergency service and contains up to 30 beds where patients can be observed for up to 48 h (Cullinan, 2006). Furthermore, it contains no operating theatre (only a procedure room), patients will only be given general anaesthetics if necessary, and patients will not be admitted as inpatients (Cullinan, 2006).

It was stated in an article published in Critical Health 1983 (Anon, 1983) that community-based services are usually staffed with two types of personnel, including community health workers who are usually trained state-employees, and voluntary health workers with limited training. These personnel were tasked with promoting improved habits and encouraging vegetable gardening, attendance at immunisation clinics, purification of water, and sanitation (Anon, 1983).

The Pholela Health Centre, located in rural KwaZulu-Natal, was an ideal PHC model that was operational from 1940 to 1970 (Kautzky and Tollman, 2008). It was among the first demonstrations used to inform and define the practice of PHC (Kautzky and Tollman, 2008). The Pholela health centre was intended to provide comprehensive preventive and curative services as to serve as a model upon which other rural and urban health clinic centres would be developed (Kautzky and Tollman, 2008). Pholela was concerned with the provision of holistic health care, rather than only medical care, which provided one of the first working models of community-oriented primary care (COPC) in practice (Kautzky and Tollman, 2008). COPC according to Dhlomo (2015) "is a continuous process by which PHC is provided to a defined community on the basis of its assessed health needs, by the planned integration of primary care practice and public health".

Pholela health centre focused on the health of families and the community, rather than on individuals alone, by seeking to identify and addressing the social conditions and determinants that influence population health broadly (Kautzky and Tollman, 2008). Target areas included hygiene and sanitation, nutrition, water, housing conditions and occupational threats. Pholela health centre also addressed the health needs of vulnerable and high-risk groups, such as women and children (Kautzky and Tollman, 2008). This included mandatory immunisations, school feeding schemes, the establishment of household and community food gardens, child growth monitoring, breastfeeding and baby food supplementation, communal childcare services, and family planning. The use of vegetable gardens was used to address malnutrition (Dhlomo, 2015). Ultimately, mainly due to politics, the progress South Africa made over 20 years of innovative community-based research, training and health systems development was lost (Kautzky and Tollman, 2008).

According to Robinson (2015), many public PHC clinics provide excellent services, although there are no standards that the clinics should meet, nor are there means to implement and maintain standards. Robinson (2015), also stated that "initiatives, inspiration, motivation and dedication of the facility managers" lead to the clinics being well-run, "rather than national, provincial or district office efforts or systems". According to Robinson (2015), a shift to standardise clinics is necessary. This can be achieved by implementing business principles used in the franchising concept (Robinson, 2015).

CHAPTER 2: HEALTH PERSPECTIVE ON ARV PATHWAYS: INTEGRATED LITERATURE REVIEW

2.1 INTRODUCTION

Since 1987 the World Health Organisation urges stakeholders that the world is losing its battle against the disease burden of modern life. The Ottawa Charter for Health Promotion (WHO, 1986) was then declared whereby 148 participating WHO countries declared that health should be promoted and protected against the backdrop realities of the social determinants of health. Biology, genetics, gender, race, and age are but one cluster of biological determinants. It is taking a person's relationships, household, and lifestyle into consideration, that the preservation of health becomes very complex. From a health perspective, therefore, the HIV and AIDS are approached as a bio-psychosocial reality, referred to as the social determinants of health. What complicates matters more, are the essential elements to consider even before one acts towards the promotion and protection of health. The Ottawa Charter refers here to the fundamentals for health listed as shelter, income, education, equity, sustainable eco-systems, peace, and absence of war to be addressed in the run towards health (WHO, 1986).

The intersectionality of HIV within the boundaries of a paradoxical country such as South Africa, brings about a kaleidoscope of complexities. HIV cannot be viewed nor understood from a single discipline nor a single paradigm. It is this deliberate attempt to approach HIV from a holistic perspective that directs this review. HIV infiltrates all spheres of reality and integrates all the pathways of humanity. HIV is not a simple virus and the exploration thereof opens a field of complex dynamics within and between individuals, relationships, households, cultures, communities, and societies. Yet, these dynamic interactions impact on people's help seeking behaviour, might limit people to get tested, to start with treatment, to suppress the VL and to prevent further spreading. Knowledge of ARVs in water could therefore contribute to PLWHA and people living close (PLC) as well as health professionals and health systems towards approved and constructive discard practices of ARVs and unwanted medications (UMs) in general.

2.1.1 Aims and objectives

The aim of this integrated literature review is to provide a critical synthesis of HIV and AIDS from a health perspective into the realities where environmental- and health sciences can and should collaborate towards transdisciplinary outcome. It strengthens the argument that ARVs in water are complex and part of real-life challenges, best understood from a holistic approach. The objectives are to propose ARV pathways from human consumption through the biopsychosocial determinants of health, discussed from a health perspective and to describe the disruptive link between ARV consumption, challenged health systems, and the environment.

2.1.2 Setting

The ARV pathways within a South African context are presented within the daily life challenges within a Gauteng-based informal settlement. According to the 2014 Annual Report of Gauteng (2014), there is an increase in informal settlements over the past two decades, leading to definite spatial and environmental changes. This context was selected because ARVs represents a science of exactness, of regularity and precision occurring within uncontrolled and unpredicted settings, from ARV procuring challenges within overburdened systems to illiterate and unemployed consumers with basic needs. South Africa has become an example of the upscaling of ARV treatment, infiltrating public health systems towards a point that ARVs have become a chronic disease.

Accommodating more than 22% of the South African population, Gauteng is the most populated province. By 2013 Gauteng housed an estimated population of 12 728 4386 people (Statistics South Africa, 2013). It is anticipated that Gauteng might house 15.6 million people by 2020 as this province saw an increase in population from 2001-2011 of 2.9 million people. Gauteng has to cater for the largest complement of migration from neighbouring cities, towns, villages as well as other countries. When referring to Gauteng, it encapsulates six districts, namely Johannesburg Metro (catering for almost 37% of the Gauteng population), Tshwane, Ekurhuleni, West Rand, Sedibeng and Metsweding, presents 33 hospitals in total within all six districts. The two tertiary hospitals within Gauteng is the Charlotte Maxeke Johannesburg Academic hospital (1 018 beds) and Chris Hani Baragwanath Academic Hospital (2 888 beds). Yet, the heartbeat for health care in Gauteng lies within the clinics rendering PHC to not only the Gauteng population, but also across provincial boundaries. The age distribution of Gauteng presents a typical migration society with a lower proportion of 10 to 14-year olds and a higher proportion of people 15 to 29 years old.

Despite heroic attempts to increase health systems access, the need for health care in South Africa is growing. According to the 2015 South Africa yearbook, there are a total of 4 200 public health facilities catering for 13 718 people per clinic against the WHO guidelines of 10 000 people per clinic. PHC clinics therefore presents a continuous fight against overburdened health systems whilst having to treat the largest population on ARVs, globally. Approximately 82.6% of all South Africans are fully dependent on the state health systems and this is also congruent in Gauteng. The sustainability of the dichotomous public-private rhetoric in South Africa is even more alarming when considering that whilst less than 17,4% of the South African population is medically insured, there were 88 different medical schemes in South Africa in 2015 (South Africa yearbook) with only 8 469 784 beneficiaries and a total contribution of R84,9 billion per annum.

2.2 MATERIALS AND METHODS

A qualitative, explorative, descriptive, and contextual design was followed through an integrated literature review. Data collection included scientific and non-scientific information collected between February and March 2017. Scientific literature was obtained through a strategic search process on EBSCOhost, Emerald Insight Journals, ScienceDirect and Google Scholar databases. For grey literature, a general literature search was conducted also in Google. Search strings were linked to each pathway and Boolean searches were conducted. An all-inclusive sample was used and the only exclusion criterium being literature dated older than ten years. All available national and international literature were critically analysed per pathway and synthesised for reporting purposes. Literature was first screened by title and abstract for suitability, where after the final selection was conducted. The sample size was captured in Table 6.

Table 6: Search strategy and sample size.

Search theme, search string	Data selected	Actual data used
ARV prevalence and/or incidence	4	2
ARV consumption and/or adherence	16	10
ARV value chain* and/or Gauteng and/or primary health care and/or PHC clinic*	8	3
HIV and/or AIDS and bodily fluids	11	3
ARV secretion and/or excretion and/or metabolism and/or elimination	16	3
Informal settlements or squatter camps or slums	26	18
Rural living condition* and/or water and/or sewerage and/or house*	32	12

Search theme, search string	Data selected	Actual data used
Medic* disposal practices and/or discarding practices and/or destroy and/or unwanted medic*	20	1
ARV and alcohol use and/or informal settlement* and/or drug use	5	4
	N=138	**n=56**

Four major pathways are presented (Figure 1). The first pathway presents the entering of ARVs into the South African health systems. This pathway explains ARV value chain within the public health system and ensures ARVs availability to align with the principles of PHC, namely making ARV as part of an integrated chronic disease, accessible, affordable, and available. The second pathway presents the biological perspectives of ARV from consumption to excretion. It presents the complexities for environmental health within the limited services of life in an informal settlement. The third pathway presents ARVs within the psychosocial realities of living in an informal settlement. It moves HIV and ARVs beyond known and visible boundaries and challenges the intersectionality thereof. The fourth pathway serves as the conclusion of this process, considering the risks that improper ARV disposal practices might lead to the entering of ARVs into the natural resources surrounding a typical Gauteng-based informal settlement.

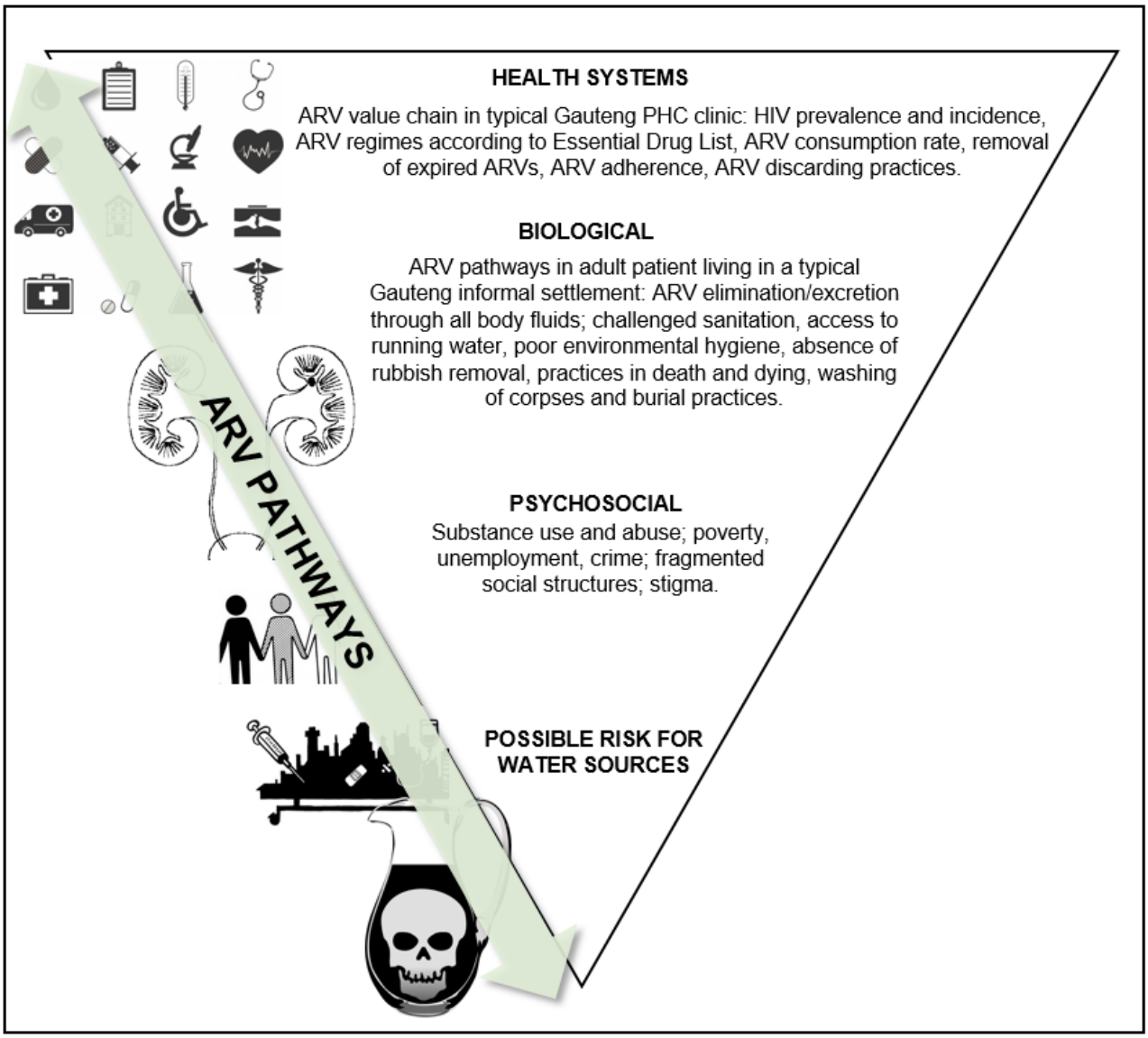

Figure 1: Conceptual framework on ARV pathways from a health perspective.

2.3 RESULTS

Expounded from the comprehensive report, to address objectives 7, 8 and 9, the following activities conducted by the Africa Unit for Transdisciplinary Health Research (Table 6):

Table 6: Activities conducted by the Africa Unit for Transdisciplinary Health Research.

Activity	Date
1st activity: Conduct a systematic review for publication in an international journal on end user medication discarding practices	
Get team together and plan	15-Apr
Do Systematic Review	01-May
Write manuscript	07-Jul
Review manuscript	01-Sep
Submit manuscript	15-Nov
2nd activity: Policy brief training to appropriate government departments	
Invite members (Approximately 20 people, 2 days on campus)	15-Mar
Two days training on campus (accommodation, travel, sustenance)	11-Jun
Finalisation of policy briefs (AUTHeR team)	12-Jun
Present policy briefs for WRC (Prof Bouwman)	15-Aug
Send policy briefs to stakeholders (AUTHeR Team)	20-Aug
3rd activity: Water training workshop	
Get team together and plan	10-Apr
Develop training material	10-Apr
Graphic design by Anelia Marais	24-Apr
Implement training at Promosa dam	09-May
Refine training material (AUTHeR team)	09-May
Disseminate training event and package for WRC	20-May
4th activity: Medication discarding initiatives with containers initiative (a larger AUTHeR project to strengthen public health systems in rural communities)	
Get team together and plan	09-Jul
Submit abstract on systematic review	09-Jul
Present SR at conference	23-Nov

2.4 DISCUSSION

2.4.1 1ST Pathway: ARVs entering the South African health systems

South African health systems accommodate a quadruple disease burden. The combination of disease associated with chronic diseases, including HIV and TB, poverty and crime as well as conditions associated with mothers and children necessitates comprehensive PHC services.

2.4.1.1 HIV prevalence and incidence

HIV is a chronic and non-notifiable, predominantly sexually transmitted disease of which an accurate HIV prevalence is difficult. South African statistics base HIV prevalence on health information obtained at antenatal clinics (ANCs) is not representative of society. The HIV prevalence of the total number of people in South Africa with HIV (Statistics South Africa, 2016) from 2002 to 2015 increased from 4,02 million (2002) to 6,19 million (2015) with an estimated 11.2% of the South African population being HIV-positive by 2015. When considering that one-fifth of all the reproductive, South African women are HIV-positive, then the estimated prevalence of 16,6% of adult South Africans in the age groups 15-49 years being HIV-positive, becomes realistic.

2.4.1.2 Overburdened Primary Health Care and failing health systems

South African health systems is built from a PHC philosophy (African National Congress, 1997). This system is free of charge, nurse-driven and based on quality and comprehensive healthcare that are also affordable, accessible and equal. Since 2011, South Africa presented re-engineering of PHC, aimed to improve access through ward-based outreach teams, improved school health running hand-in-hand with the National Health Insurance (NHI) systems. Since 1994, healthcare focus was on access and equity, but shifted since 2011 also to quality. PHC services have therefore become nodes of super-specialised care rendered within relatively basic conditions. In Gauteng alone, there are 411 PHC clinics which presented in 2016, 153 440 PLWHA newly initiated on ARVs; 533 093 households were visited, and 100 ward-based outreach teams were activated (Gauteng Department of Health Annual report 2016).

In 2014, the Operation Phakisa 2: Scaling up Ideal Clinic Realisation and Maintenance Programme was activated as the most recent programme to upgrade and transform all public clinics into ideal clinics (PHC clinics and community health centres) based on the principles of social franchising. South Africa's ARV tender processes are according to Sauls (2015), the largest, funded predominantly by the Global Fund and competitive enough to increase ARV affordability. It is therefore comprehensible that HAART presents a complex value chain from production to consumption based on the principles of PHC. Yet, the Gauteng health system has been described by SECTION27 in 2014 as a system in crisis marked by medicine shortages, disintegrating infrastructure, broken equipment, staff shortages and fund mismanagement. Reasons raised for a systemic failure and resource shortages are poor supply chain management, ineffective management and poor financial management. Delivery of sufficient ARVs to PHC clinics require functioning value chains and sufficient process compliance.

2.4.1.3 ARV regimes according to the Essential Drug List

In South Africa, the National Strategic Plan for HIV, STIs and TB 2012-2016 (NSP) serves as an authoritative strategic framework directing the management of HIV nationally. ARV initiation, adherence and retention on a PHC level is essential to prevent hospital admissions as Long et al. (2016), concluded that inpatient care of hospitalised patients associated with HIV and AIDS burden hospital care, despite of PHC facilities. As already mentioned, the activation of ART is complex. Specially trained health professionals need to follow the standardised national ART regimen for adults and adolescents directed by the EDL (DoH, 2014). The following ARVs are available according to the EDL (DoH, 2014) (Table 7):

Table 7: ARVs presented in South African health systems according to the Essential Drug List.

Class	Medicine	Dosage
NRTI	Zidovudine (AZT)	300 mg, 12 hourly
NRTI	Lamivudine (3TCA)	150 mg 12 hourly or 300 mg daily
NRTI	Abacavir (ABC)	600 mg daily
NRTI	Tenofovir (TDF)	300 mg daily
NRTI	Emtricitabine (FTC)	200 mg daily
NNRTI	Nevirapine (NVP)	200 mg daily for 14 days, then 200 mg 12 hourly
NNRTI	Efavirenz (EFV)	600 mg nocte
PI	Atazanavir (ATV)	300 mg and ritonavir 100 mg daily
PI	Lopinavir/ritonavir (LPV/r)	400/100 mg 12 hourly

It presents three progressive regimens of ART. Supply chains further entails enough ARV stock for different ART regimens. These regimens are summarised as follow (Table 8):

Table 8: Three progressive ART regimens followed within South African health systems.

1st line ART regime	
All new patients, including pregnant women.	TDF + FTC (or 3TC) + EFF. FDC preferred.
Contra-indication to EFV.	TDF + FTC (or 3TC) + NVP
Contra-indication to TDF.	ABC + 3TC + EFV (or NVP)
Contra-indication to TDF and ABC.	AZT + 3TC+ EFV (or NVP)
2nd line ART regime	
Management of virological failure	
Failing on a TDF based 1st line regimen	AZT+3TC+ LPV/r
Failing on an ABC based 1st line regimen	AZT+3TC (or FTC) and LPV/r
Dyslipidaemia or diarrhoea associated with LPV/r	with LPV/r Switch LPV/r to ATV/r
3rd line ART regime	
Failing 2nd line regimen for > 1 year and good adherence documented (e.g. by pharmacy refills on time for the last 6 months).	Only patients with resistance to LPV/r (or ATV/r) qualify for 3rd line. Regimen will be determined by an expert committee based on the pattern of resistant mutations and the prior history of antiretroviral exposure.

2.4.1.4 ARV value chain in a typical Gauteng Primary Health Care clinic

The information expounded above presents the complexity of ART to be managed in a comprehensive and efficient manner. On a PHC level ARVs require efficient, effective and rigid management in ART (Mahoro, 2013) to maintain adherence, VL suppression and prolong survival. There is also no true substitution to ARVs. Therefore, an uninterrupted supply flow of ARVs is essential.

The typical value chain for ARVs start with a tender process. The ARVs in Gauteng is predominantly funded by the Global Fund and administered by both the national and provincial departments of health. ARV suppliers deliver ARVs to provincial depots from where it is distributed to district depots to hospitals and clinics. Gauteng presents with two sub-depots and the metropolitan municipalities of Johannesburg,

Ekurhuleni, and Tshwane function also from at least one municipal depot (DoH, 2010). The majority of South African depots utilise the services of private contractors to supply ARVs to provincial facilities. Fragmentation of pharmaceutical services are a reality as medicine depots are accountable to facilities and not only limited to pharmaceutical services (DoH, 2010). This is also the case for Gauteng. The financial and human resources needed to realise the value chain within Gauteng's provincial medicine depot to sub-depots and several municipal depots, are astronomical and the DoH (2010), noted that the value chain can be simplified to one distribution system.

The entry of ARVs into PHC facilities presents a new Pandora's Box as inventory management is often secondary to patient care in overburdened and understaffed clinics. Challenged and problematic ARV inventory management as with various other medicines has been reported (Tayob, 2012; Mahoro, 2013). Stock outs and stock losses are reported in various South African health facilities, also in PHC clinics. Poor inventory management implies also (Mahoro, 2013) poor quality record keeping, insufficient space allocation and general organisation in medicine storerooms. Due to staff shortages and limited space, there might not be an allocated community pharmacist or pharmacy assistant to receive ARV stock and to monitor the flow thereof. Staff is inadequately trained for stock management at this large scale and direct monitoring, evaluation and supervision by district pharmacy pharmacists exaggerates the situation (Tayob, 2012).

In addition to the provision of ARVs from provincial depots to consumers, the continuous care and monitoring of treatment (CCMT) is driven by the National Department of Health (DoH, 2010), aimed to decentralise chronic disease medication, extends the value chain now beyond PHC facilities. The Gauteng Department of Health 2015/2016 reported also on the status of the Centralised Chronic Medicine Dispensing and Distribution (CCMDD). The CCMDD programme decrease PLWHA waiting times and clinics and the out-patient departments of hospital pharmacies and is aimed to increase affordable and essential medicine within resource-limited health system impacted by high disease burdens. Through CCMDD, PLWHA can collect their ARVs at their nearest accredited medicine pick-up point and visit the clinic every six months for a follow-up monitoring. Between 2015 and 2016 the Gauteng Department of Health enrolled 114 926 patients on the CCMDD programme.

Distribution and dispensing of ARVs within the CCMDD are provided by private service providers. Gauteng had by end of 2016, 171 pick-up points of which 51% were within the public sector. Examples of the CCMDD are separate quick service ques at clinics and adherence clubs. In 2016 to 2017, the Part Station Dis-Chem pick-up point was activated at the Park Station. The Park Station is used by an estimated two million commuters that can now collect their ARVs as well as other chronic medicine, at the Park Station on their way to and from work without taking off working hrs. The CCMDD programme is context specific. For example, in Tshwane, 40% of patients collect their chronic medication at pharmacies within the private sector (Gauteng Department of Health, 2016).

2.4.1.5 The challenges of ARV adherence

ARV adherence of 95% is necessary to maintain VL suppression and to prevent viral mutations. According to Eyassu et al. (2016), ART adherence at a Kwa-Thema clinic in Ekurhuleni presented with only 77%. South Africa is dependent on the PEPFAR (United States president's emergency plan for AIDS relief) funding to provide comprehensive treatment to PLWHA and PLCs. In 2015, the Joint United Nations Programme on HIV/AIDS (UNAIDS) presented a FastTrack strategy with 90-90-90 targets in HIV management by 2020. This strategy states the baseline for the initiation of ARV, suppress viral loads, and improve health outcomes. The 90-90-90 strategy as mentioned before implies to actively target that 90% of all PLHWA know their status; for 90% of PLWHA adhere to ART and that 90% of PLWHA on ART presents with sufficient viral suppression and therefore improve HIV and AIDS management and improved quality of life to more than 73% of PLWHA globally.

2.4.1.6 ARV discarding practices

Insufficient evidence was obtained about ARV discarding practices within the context of South Africa. There the reader is immediately directed to discarding practices of unwanted medications (UMs). The WHO stipulated the management of unwanted medications in an original 1999 recommendation. These guidelines stipulate that UMs should be considered as pharmaceutical wastes and managed in accordance. UMs can be activated for healthcare and/or household activities. Typical reasons for UMs are non-compliance practices of consumers, dispensing practices or prescribing patterns of medical practitioners.

It is worth noting that the original WHO 1999 guidelines for safe disposal practices were directed to countries experiencing a crisis status such as a post war, although these guidelines can also be generalised to emerging economies with challenged health systems. Despite the WHO guidelines, South Africa is first responsible to adhere to its own policies and regulations. In general, the best environmental solution for pharmaceutical destruction is a purpose-built, high temperature incineration with adequate flue gas cleaning, although other methods are also possible. A first consideration is the proper administration when writing-off UMs from procurement to donated drugs (WHO, 1999).

An international perspective of medicine discarding practices in general, indicates that there is reason for concern for the disposal practices by the public as well as pharmaceutical waste on different levels of service delivery. The European Union directive that member states should ensure appropriate collection systems (Directive 2001/83/EC and 2004/27/EC) are followed by these member states. The Swedish pharmacy chain (Apoteket AB) where UMs are returned to pharmacies to be eventually incinerated and the ash thereof cleaned before the steam is released which led to increased awareness of UMs and the impact thereof on the environment. There are no official UM disposal guidelines in New Zealand. Abahussain et al. (2012), reported these concerns in a study conducted amongst pharmacists in Kuwait.

In general, the public tends to discard medicine by flushing it down the drain or disposing it in the garbage. This causes pharmaceutical waste to enter the ecosystem and ultimately impact on the environment and on human health. It was interesting when Abahussain et al. (2012), concluded that although pharmacists were aware of their inappropriate discarding practices, they were aware and informed of their responsibilities to protect the environment and urged proper monitoring processes. Gaps in responsible disposal practices of UMs were identified in Kabul, Afghanistan (Bahaar et al., 2017), fortifying again the need for standardised pharmaceutical waste management practices for the general public.

In South India, in accordance to Lagishetty et al. (2014), 85% of patients sampled from a tertiary hospital weren't aware of the risks of improper UM discarding practices and 63.5% of the participants disposed medication into the trash and dustbins and didn't follow eco-friendly routes of disposing. The AID for AIDS (2017) recycling programme in New York, United States of America has a functioning HIV medicine recycling program for the gathering, sorting, storing of unused medicine as well as discarding, redistributing and discarding practices.

2.4.2 2ND Pathway: ARV processes through the biological pathways

The second pathway describes the ARV process from a biological perspective.

2.4.2.1 ARV elimination

Within a typical Gauteng informal settlement, one should first consider the ARV elimination and excretion route. According to Ansari (2011), the most prominent route of ARV elimination is summarised in Table 9:

Table 9: ARV elimination route (Ansari, 2011).

Medicine	Elimination route
Zidovudine (AZT)	Renal
Lamivudine (3TCA)	Renal, breast milk
Abacavir (ABC)	Hepatic
Tenofovir (TDF)	Renal
Emtricitabine (FTC)	Renal
Nevirapine (NVP)	Renal
Efavirenz (EFV)	Renal
Atazanavir (ATV)	Faecal, renal
Lopinavir/ritonavir (LPV/r)	Faecal, renal

Understanding the elimination routes of ARVs is the starting block of the pathways thereof within the context of an informal settlement. This elimination runs predominantly through urine and faeces with some limited elimination in breast milk. These excrements however enter the water, sanitation, and sewerage systems already compromised within informal settlements.

2.4.2.2 Contributing factors in HIV transmission

According to Klatt (2015), the following factors promote heterosexual transmission of HIV: economic and political instability within the community; multiple sexual partners; unprotected sexual intercourse with lack of barrier precautions; frequent change in sexual partners; lack of male circumcision; socially vulnerable women and young people; presence of additional sexual transmitted infections. Political and economic instability impacts on HIV health promotion because it complicates the activation and institution of behavioural change programmes; which include HIV screening and testing, ARV aimed to decrease VL and transmission risks, treatment of STIs, promotion of condom use.

HIV transmission via blood exposure is particularly high amongst injection drug users sharing needles and include specifically crack cocaine users due to broken epithelial barriers and methamphetamine users (Klatt, 2015). Traditional methods to reduce HIV transmission rates are (according to Klatt, 2015) to treat HIV as an illness, not a social stigma; reduce levels of poverty that leads to increased risk of drug abuse and promiscuity; provide sufficient HIV testing and counselling to strengthen screening services; educational programmes aimed to prevent STIs developed for adults and children; access to male circumcision; access to clean needles for drug users; sexual barrier precautions amongst high risk groups such as commercial sex workers and clients; sustainable provision of ARVs to all HIV-positive including pregnant women; pre-exposure prophylaxis.

2.4.2.3 Poor infrastructure and environmental health risks in informal settlements

An informal settlement is according to the National Department of Human Settlements ‘an unplanned settlement no land which has not been surveyed or proclaimed as residential, consisting mainly of informal dwellings (shacks)’ (HDA, 2013). Generic characteristics of informal settlements are illegality and informality; inappropriate locations; restricted public and private sector investment; social stress; poverty and vulnerability. By 2011, 76% of Gauteng households were informal residential, lived in shacks not in backyards (HDA, 2013). There has been an increase of 7.4% per annum of shacks in backyards in Gauteng from 192 568 households in 2001 to 305 683 by 2011.

The increase in shacks and informal settles ran hand in hand with stagnated or declined access to piped water, sanitation services and electricity (although sanitation and electricity access improved within the City

of Johannesburg) (HDA, 2013). 30% of households in Gauteng functioned as one-person households who lived in shacks not in backyards of which 71% were male headed in 2011 (HDA, 2013). Female-headed households were significantly larger in more-than-one-person households in Gauteng. Informal settlements are the 'arrival cities' for those seeking an entry into the labour market and is therefore closely linked to unemployment. In general, the mean income of R800 per household per month was reported by 2011.

Take the township of Alexandra as an example (Report on the interactive planning workshop for Johannesburg of 2000 presented by the World Bank, 2001). Established in 1912, the original settlement was designed for 70 000 inhabitants, but today easily houses 750 000 people. There are today an estimated 20 000 shacks of which 7 000 are within backyards. The significant increase of unplanned population growth in Alexandra overloads the water and sewerage infrastructure. Over-crowding and high density living with poor services and poor environmental conditions are detriment to promote health and improve quality of life. Typical challenges faced in informal settlements are overloaded sewerage systems. For example, in Alexandra, there are four times more people utilising the waterborne sewerage system leading to frequent blockages and surcharges. Poor access to sewer lines makes maintenance impossible and poor sanitation facilities.

More challenges typical to informal settlements are low water pressures and dangerous electrical connections. By 2008, Gauteng had 85 informal settlements formalised, by 2009 36 informal settlements were eradicated (Anon, 2011). By 2011, Gauteng's municipalities delivered sanitation to 167 014 households and provided potable water to 228 046. The infrastructure budget spent by 2011 exceeded R5 billion. Regarding solid waste management, Gauteng municipalities focused on improved waste management, which included waste recycling and solid waste removal. A total of 44 projects on landfill management were implemented. Gauteng provides free basic electricity ranging from 50kWh to 100kWh per month. In the areas supplied by Eskom, 98% of poverty-stricken households received by 2011 free basic electricity. There has been progress in formal refuse removal practices also in informal settlements in Gauteng.

2.4.2.4 Practices in death and dying, washing of corpses and burial practices

In handling a corpse for burial preparation and autopsies, support universal precaution mechanisms such as protective masks and eyewear; laboratory gowns, gloves, routine standard infection control practices, detergent to clean bloody or soiled work surfaces and use of disinfectants. There is a minimal risk for funeral directors to be exposed to HIV when they stick to proper precautions: wear protective waterproof gown or apron, mask and protective eyewear and disposable gloves. Discard sharps and needles into puncture-proof containers. Transport bodies in waterproof, lead proof shroud/body bag (Klatt, 2015). Insufficient literature was obtained to describe the actual cultural actions surrounding the practices of death and dying, of washing of corpses and burial practices.

2.4.3 3RD Pathway: ARV's realities within psychosocial pathways

The psychosocial pathways of HIV and AIDS are best described according to the intersectionality thereof. It forces one to recognise ARV transmission beyond the typical heterosexual modes. Although HIV transmission follows a biological route, HIV impact transcends into the psychosocial and spiritual dimensions of man.

2.4.3.1 ARVs and substance use

Schneider et al. (2012), presents alcohol as a reality impacting on all the spheres (transmission, acquisition, stages of disease) of HIV and AIDS. High alcohol utilisation is associated with high risk sexual behaviour (for example decrease in condom use) leading to super-infection (re-infection) and a higher risk for other STIs, making alcohol a key determinant in HIV transmission. Complacency towards ARV and treatment regimens intensifies in the presence of alcohol use. Viral resistance risks increase in poor ARV adherence

(below 95%) and possible spreading drug resistant HIV mutations. Caregivers that are alcohol users make compromise the treatment regime of children taking ARVs. The impact of alcohol consumption on the immune system alters the pathogenesis of HIV.

There is a direct link between alcohol consumption and liver diseases complicating the metabolising of ARVs. Both the NNRTIs and PIs are prone to increased liver metabolism because of the effect of alcohol on the CYP3A4 enzyme system. Because HIV runs hand-in-hand with comorbidities and the management of opportunistic infections (including homeopathic and herbal remedies; analgesics and anti-inflammatories; recreational drugs; certain psychopharmacologies) the person with HIV consume various drugs simultaneously. This, when consumed with alcohol can have adverse health outcomes. The use of traditional herbal medicines and ARVs consumed simultaneously are possibly exacerbated by alcohol consumption. Don't stop ARVs during binge drinking.

On a study focusing on a comprehensive treatment programme for people with Tuberculosis (TB), irrespective of their HIV status, stated that an inclusive programme is necessary addressing alcohol and tobacco use and abuse, psychosocial counselling and poverty, participating the health sector, government sector and social sectors (Naidoo et al., 2013). The link between ART non-adherence and alcohol use necessitates ART adherence interventions that are alcohol-focused (Kekwaletswe and Morojele, 2014). ARVs enter also the broader drug-abuse scenario with drugs such as whoonga and nyaope. Whoonga-users (whoonga is a street drug mixture of heroin, cocaine and dagga) are also directly associated with criminal activity whilst stealing ARVs from people in essential need thereof. In 2016 the City of Johannesburg declared an intensified war against drug abuse, referring specifically to nyaope and other drugs destructing the Gauteng youth, families and communities (Dlamini, 2016).

2.4.3.2 Poverty, unemployment, crime and fragmented social structures

It can be argued that poverty, unemployment and crime run parallel causing toxic social dynamics. The realities of social disintegration in a typical Gauteng informal settlement and how it can affect ARV pathways, are summarised in Table 10. This content is an application from the Gauteng Annual Report of 2015.

Table 10: Social dynamics within Gauteng applied to ARV pathways.

Social dynamic within Gauteng	Linked to ARV pathway
There is a gradual shift towards lower household income and continuous racialized income disparities. By 2011, 39% of Gauteng residents viewed themselves as poor (against 33% in 2009); 30% as working class (against 34% in 2009); 27% as middle class (against 24% in 2009) and 2% as upper class (against 3% in 2009).	Underprivileged communities will have a larger dependence on state provided free healthcare and access to ARVs through PHC and CCMDD. The gradual decline in household income implies an indirect increase of state dependence. There is no indication of a decrease in ARV in the near South African future. Racialized income disparities imply a stronger dependence on PHC.
Child-headed households in Gauteng increased by 7.8% from 3,053 (2002) to 3,293 (2010). The household headed child cannot seek employment, has limited access to basic needs, and lives in severe poverty.	Child-headed households can be seen as a direct outcome of HIV and AIDS. The ARV UTT available to all citizens have diminished disappearance of a generation of parents, whose children are now orphaned. Orphaned and child-headed households strengthen the bio-psychosocial and community vulnerability of children in a high-risk age group.
Gender-based violence in the form of rape, sexual assault, femicide and domestic violence are realities in Gauteng. Gender-based violence remains under-reported. There were 12 419	Without stereotyping, ARV pathways cannot ignore the lack of social cohesion amongst Gauteng citizens. Gender-based violence is a risk for STIs and HIV transmission and the under-

Social dynamic within Gauteng	Linked to ARV pathway
such crimes reported in 2011-2012 against 18 176 sexual crimes reported in 2008-2009. The reason for a decline is unknown. Gender-based violence was more acceptable to Gauteng inhabitants earning between R1 601 and R12 800/month.	reporting thereof. ARVs become sensitive when both partners haven't disclosed their status. In return, the very present of ARVs might trigger violence and abuse.
Although, Gauteng presents safe spaces for being gay, lesbian, bisexual, transgender, and intersex (LGBTI), there are also reports of homophobia and discrimination leading to violence, rape and murder. Verbal abuse, physical abuse, and sexual violence do occur against the LGBTI in various formats and an increase in hate-crimes such as corrective rapes.	When managing ARVs and the associated stigma, this situation is intensified when PLWHA have to keep their sexual orientation a secret. Undisclosed HIV status impact directly on the 90-90-90 strategy.
Although, women are today more homeowners, women within Gauteng remains unwillingly unemployed or stuck within low paid insecure employment.	Unemployed, incapacitated, and poor women with children might turn to commercialised sex work to earn an income. Placing them in a risk group.
HIV and AIDS discrimination still occurs within the workplace throughout South Africa.	Discrimination and stigma in the workplace have a direct impact in health seeking behaviour of PLWHA and might cause poor ARV adherence.
Gauteng is one of the most diverse provinces in South Africa. It is a contradictory story of racism and xenophobia on the one side against social cohesion, identity, and non-racialism on the other side. Transcending differences are still obstacles by race, gender, class, religion, sexuality, and unique life experiences. By 2011, 54% of the Gauteng population in general were born in Gauteng and 35% of inhabitants came from external areas, nationally and internationally. Gauteng is therefore a pressure cooker of ethnic, linguistic, and cultural diversity.	Communities that lack social cohesion and negates identity, cannot provide the necessary support to PLWHA and PLC. Diversity, racism, and xenophobia risk a traditional view of HIV from a pure biomedical perspective. Managing ARVs from a biomedical perspective disregard the personal values of PLWHA and PLC and complicates the pathway towards responsible ARV disposal practices.
55% of Gauteng residents recalled a faith-based organisation or activity where they participated as part of civil society.	Faith-based organisations play a significant role in communities and might play a stronger role in ARV pathways towards responsible ARV disposal practices.

2.4.3.3 HIV stigma

Stigma is best understood by the definition of Alonzo and Reynolds (1995), defined over a decade ago as *"*…the stigmatized are a category of people (HIV) who are pejoratively regarded by the broader society as devalued, shunned or otherwise lessened in their life chances and in access to the humanizing benefit of free and unfettered social intercourse". It is linked to disrespect and discrediting behaviour (Sultana, 2014), inequality, fear and prejudice (DoH, 2015). HIV stigma directly on the access to healthcare, is detrimental to ARV adherence and prevents disclosure practices. In 2012, Grut et al. reported that poor access to health systems in informal and poverty-stricken communities remain a reality in South Africa in general.

HIV related stigma is an old phenomenon that surfaced since the beginning of the initial HIV pandemic (Poindexter, 2013) and rampant in sub-Saharan Africa (Tsai, 2015).

The very same health systems directed to render comprehensive care in HIV and AIDS management, are dominant causes for stigma. HIV-related stigma presents in PLWHA's own communities, personal environments, financial environments, educational institutions, the workplace, healthcare settings, and religious institutions (Varaz-Diaz et al., 2013; Stutterheim et al., 2014). Health systems stigmatise PLWHA intentionally and unintentionally. Finally, HIV-related stigma impacts on the PLWHA's psychosocial wellbeing and limits access to various facilities, including health systems. The final outcome of HIV-stigma hampers effective disclosure management and requires the health system towards a continuous risk-benefit analysis between economies of scale to care for such large patient corps against risking stigma.

2.4.3.4 ARV crime and corruption

ARV might be a free service within South Africa but represents also an illegal industry to others. In 2014, two health officials were arrested selling ARVs to patients in Hillbrow, Gauteng (Anon, 2017). In this event patients visited the clinic, were informed that the ARVs were out of stock, but should meet a health worker in a nearby park to buy their ARVs at R50-R100 per bottle. The Bhekisisa Report (2016), reported the unlawful theft of ARVs dedicated for South Africa, sold on the open market to Zambia. Shaick reported in 2016, of a 38-year old woman participating in an ARV theft syndicate within the Empangeni region, having on the day of the sting operation ARVs to the value of R300 000.

Of the retrieved ARV bottles, names of South African PHC facilities were visible, linking ARV theft to health care workers linked into the syndicate. This specific incident aimed to present ARVs to the drug dealer market to manufacture whoonga. These are only some examples of ARV-related crime and corruption occurring within South Africa. In 2017, Thamela reported of a cleaner working in a PHC clinic in Soweto caught with stolen ARVs aimed to be sold (Thamela, 2017). The alleged clinic employee had 4 kilograms of lamivudine (179 bottles) and some vitamins in his private possession. According to Tsuyuki, et al. (2015), the following motivations were given in a qualitative research study in Florida (United States of America) for PLWHA to buy ARVs on the illicit market:

- Replace ruined or lost ARVs.
- Buy a back-up ARV stock.
- Due to limited access or poor-quality healthcare.
- Repurchase ARVs after selling ARVs for money or drugs.

2.4.4 4TH Pathway: ARV impact on natural resources

The WHO's 1999 guideline for pharmaceutical disposal practices, warned about the consequences of improper disposal practices of UMs in general (WHO, 1999). Improper disposal practices compromise the environment if it leads to contamination of water supplies, wildlife and water sources nearby communities. Improper landfill practices of UMs can lead to children and scavengers. The dominant risks for UM infiltration into the environment are listed as:

- Contamination of drinking water especially through improper landfills.
- When anti-neoplastics, disinfectants and non-biodegradable antibiotics are disposed into sewage systems.
- Releasing toxic pollutants into the air due to low temperatures or open containers.
- Scavenging in insecure and unprotected landfills.
- The risk that expired UMs re-enter the market for general public consumption.

Safe ARV discarding practices are everybody's responsibility. Health professionals and the public should all be informed of safe disposal practices. The challenges are that ARV disposal should occur at a minimum

financial cost and without risking the public's health and the environment. Therefore, UM disposal practices should be done under national and governmental regulation and not be dependent on individuals. Facilitative public relations are essential to disseminate information of UM disposal as UM disposals can easily be sensationalised and politicised. As part of this studies outcomes, see briefing note of HIV-ARVs in water resources (Appendix J) and Responsible discarding infographic – HSPCA (Appendix K).

From a biomedical perspective, ARVs in water are viewed within a limited, pathological approach. Yet, through a holistic perspective, ARVs in water becomes integrated into the complexities of HIV and AIDS referred to as the ARV pathways. The objectives of this report were to propose the ARV pathways from human consumptions towards the challenges thereof on the environment. The aim was to propose that transdisciplinary approach to ARVs in water can present a unique view to get a deeper understanding of this complex phenomenon. It positioned ARVs in water into the larger realities of South African health systems and South African diversity. This report concludes that not ARVs nor HIV nor water resources are isolated and should be addressed over scientific boundaries.

2.5 RECOMMENDATIONS

Summary of recommendations

The following recommendations are proposed for the health perspective on antiretroviral pathways – integrated literature review:

- Reassess all discarding practices.
- Develop different sustainable discarding practices.
- Enforce the implementation of different sustainable disposal practices through legislation.
- Develop different measurement and evaluation systems to assess the effectiveness and efficiency of sustainable disposal practices such as landfills.
- Improve wastewater treatment plants to reduce the releases of antiretrovirals to water, thereby reducing human exposure and impacts on ecosystems.

CHAPTER 3: USAGE OF CENTRAL NERVOUS SYSTEM MEDICATION IN HIV/AIDS PATIENTS: LONGITUDINAL ANALYSIS (2005-2015) OF PREVALENCE AND PRESCRIBING PATTERN CHANGES

3.1 INTRODUCTION

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

3.1.1 Background and problem statement

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 HAART (Ferrando et al., 2003). Major contributory factors in spreading HIV in South 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 (South Africa National AIDS Council, 2012).

Psychiatric disorders are common in PLWHA (Els et al*.,* 1999). Mathers and Loncar (2006), 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 year lived with disability (Whiteford et al., 2015). The effects of neuropsychiatric disorders and HIV can cause the lack of adherence to ART which is supported by the literature (Chandra et al., 2005).

According to Grant (2008), HIV infection can affect all systems in the human body including the CNS. The human brain is destroyed during the early stages of infection (An et al., 1999). Treatment of HIV/AIDS depends largely on the suppression of a patient's VL, because morbidity from immune destruction is directly correlated with the concentration of HIV particles (Nachega et al., 2007). 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).

As mentioned before, two types of HIV strains have been identified in the early and late 1980's, such as HIV-1 (Barré-Sinoussi et al., 1983) and HIV-2 (Clavel et al., 1986). The HIV-1 strain destroys the CD_4 T-lymphocytes leading to an immune compromised individual who is prone to any infection (Gurunathan et al*.*, 2009). 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 and Gray, 2010). In addition to that, Arshad et al. (2009) also reported that ARVs are toxic substances.

As mentioned before, the main goals of ART 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 (UNAIDS, 2012; Human Science Research Council, 2014). According to the current guidelines, ART is given regardless of CD_4 count (Rossiter, 2014).

In 2007, the South African government implemented prescribed minimum benefits (PMB) for HIV/AIDS in the private health sector (Erasmus, 2007). According to the Research and Monitoring Unit of the South African Medical Council (2018), 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). 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). The burden of psychiatric disorders is expected to double by 2030 (Murray et al., 2013). Mathers and Loncar (2006) projected an increase in psychiatric disorders due to non-communicable diseases. According to Beyenburg et al. (2005) 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). Depression, alcohol abuse, injuries and other neurological disorders accounts for a larger percentage of lost disability-adjusted-life-years than cardiovascular diseases (UNAIDS, 2007).

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). 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). The study that was done in 2000 revealed that MNS was the third major cause of death in South Africa (Norman et al., 2006).

Unfortunately, relatively little is understood about the pharmaceutical 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 comorbidities.

Table 11: The prevalence of mental neurological and substance abuse in low- and middle-income countries.

MNS disorder	Lifetime prevalence South Africa (%)	12 months 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; Chandra et al., 2005). Delirium occurs frequently in HIV patients and is caused by the underlying infection (Chandra et al., 2005).

Cook et al. (2002), 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). Lund et al. (2013), reported that poverty can cause depression and anxiety amongst people.

Antiretroviral drugs such as efavirenz and nevirapine were reported to cause psychiatric side effects (Wise et al., 2002; Poulsen and Lublin, 2003). Maggi and Halman (2001), 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; Freeman and Thom, 2006). WHO (2008), also affirmed the vulnerability of HIV/AIDS patients with psychiatric disorders that may interfere with the ability to gain or use information about HIV. Collins et al. (2006), reported that depression can result in worse outcomes for HIV patients, and those with anxiety, mood disorders and substance abuse disorders. Depression and other mental disorders can cause suboptimal treatment and adherence in HIV patients (Cook et al., 2002). Imipramine and fluoxetine showed efficacy with no negative effects in HIV patients taking ARV drugs (Rabkin et al., 1994).

The treatment of HIV 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). Some cognitive disorders and dementia can be caused by viral infections in the CNS (Cournos and Forstein, 2000; Milton et al., 2000).

There is a dearth of information on the effects of CNS medication in HIV/AIDS patients and MNS conditions (Beyenburg et al., 2005; Jack et al., 2014). 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 needs to be collected in order to suggest specific treatment regimens of 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-exiting with HIV/AIDS in the private health sector in South Africa. Further research in the private health care sector of South Africa.

This research study will try to answer the following questions:

- What is the prevalence of HIV/AIDS globally, in Africa and in South Africa?
- What is the prevalence of psychiatric comorbidities in HIV/AIDS patients on both a national and international level?
- Which CNS drugs are prescribed to HIV/AIDS patients?

3.1.2 Research aim and objectives

3.1.2.1 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.

3.1.2.2 Specific research objectives

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.

3.2 MATERIALS AND METHODS

3.2.1 Research methodology

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

3.2.1.1 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.

Different research designs were implemented to achieve the specific objectives:

- For the first objective, the analysis followed a longitudinal or trend analysis design.
- For the second objective, a retrospective longitudinal closed cohort design was followed

3.2.1.2 Database

The data was 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 40 medical schemes and capitation plans in South Africa. The database currently contains longitudinal medicine claims data for more than 1.6 million medical scheme beneficiaries. The PBM is at present linked to all of South African pharmacies and 98% of all dispensing doctors. The total database for all years (1 January 2005 to 31 December 2015), consists of all the medicine claims data available, was used. Only data from this PBM was used.

3.2.1.3 Data fields

Patient demographics (such as birth date, gender, diagnosis, and encrypted patient member numbers), pertinent prescription information data (such as prescription number, NAPPI codes, NAPPI code description-trade name, days' supply, quantity of medicine items dispensed, active ingredient, pharmacological group, dispensing date) and medical problems (such as International Codes of Diseases or ICD 10 codes) was extracted from the PBM database for analysis.

The Statistical Analysis System®, SAS 9.4 ® (SAS Institute, 2012) was used to calculate the age of a patient from 1 January of the year following the date that the prescription was dispensed. The date of the first observed ARV prescription for a specific patient per year was assigned as the index date. A patient could be categorised for the different years in two patient groups (HIV-only and HIV-CNS), depending on the medicine they used during the specific year.

3.2.1.4 Reliability and validity

Longitudinal data from 1 January 2005 until 31 December 2015 was 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 was 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 (CDL), 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 confidentiality 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.

3.2.1.5 Target population

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

3.2.1.6 Study population

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

3.2.1.6.1 *Inclusion and exclusion criteria for objective 1*

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

Table 12: Inclusion criteria for objective 1.

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

Table 13: Exclusion criteria for objective 1.

Criteria	**Information**
Unknown information	Unknown gender and date of birth

3.2.1.6.2 *Inclusion and exclusion criteria for objective 2*

Table 14: Inclusion criteria for objectives 2 and 3.

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).
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) claim for above-mentioned patients.

Table 15: Exclusion criteria for objective 2.

Criteria	Information
Unknown information	Unknown gender and date of birth

3.2.1.7 The following steps were followed in the process of obtaining data to the selection of 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 was used to identify all the ARV and CNS medicine.

3.2.1.8 Study variables

The study variables will include both independent- and dependent variables. According to Brink et al. (2012b), 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 will act as a dependent or as an independent variable.

3.2.1.8.1 *Age*

According to Pugh (2000), 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), 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.

3.2.1.8.2 *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 is not indicated, were excluded to ensure the quality of the data.

3.2.1.8.3 *Time period*

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

3.2.1.8.4 *Active ingredient of drug*

The pharmacological classification of 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 pharmacological active ingredients and registered generic names (Snyman, 2011). 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 which incorporate the product name, pack size, strength and manufacturer's name (Snyman, 2018). This method will specifically be used to identify the CNS medication.

3.2.1.8.5 *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.

3.2.1.8.6 *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.

3.2.1.8.7 *Number of medicine items dispensed per prescription per patient*

According to the Mosby's Dictionary (Harrison et al., 2009), "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.

3.2.1.8.8 *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):

$$\text{Prevalence rate : } = \frac{All\ new\ and\ pre{-}exiting\ cases\ during\ a\ given\ time\ period}{Population\ during\ the\ same\ time\ period}(X\ 10^n)$$
$$n = 3$$

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

$$\text{Incidence rate: } = \frac{Number\ of\ \ new\ cases\ of\ disease\ in\ a\ specified\ period}{Size\ of\ population\ at\ start\ of\ the\ specified\ period}\ (X\ 10^n)$$
$$n = 3$$

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.

3.2.2 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.

3.2.2.1 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).

3.2.2.2 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. 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).

- 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 and Green, 2008). 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 and Green, 2008).

- 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 and Burgess, 2012).

3.2.3 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.

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

3.3 RESULTS, DISCUSSION AND CONCLUSIONS

3.3.1 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 an applicable journal.

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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 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 (refer to Table 16).

Table 16: 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%)

	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
≥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%)

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) (refer to Figure 2 and Figure 3).

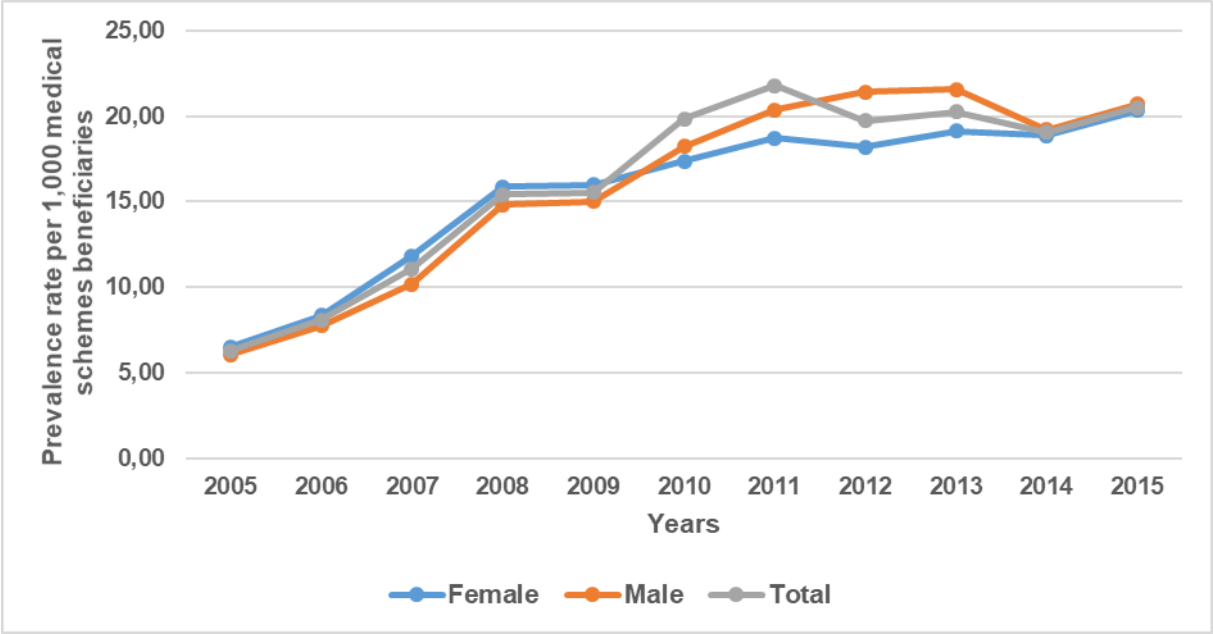

Figure 2: Prevalence rate of HIV/AIDS patients per 1000 medical scheme beneficiaries by gender from 2005 to 2015.

Figure 3: HIV/AIDS incidence rate per 1000 medical scheme beneficiaries by gender in the medical schemes environment in South Africa between 2005-2015.

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 scheme beneficiaries. In 2015, both the prevalence and incidence rates of HIV/AIDS were higher in males than in females (refer to Figure 2 and Figure 3).

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.

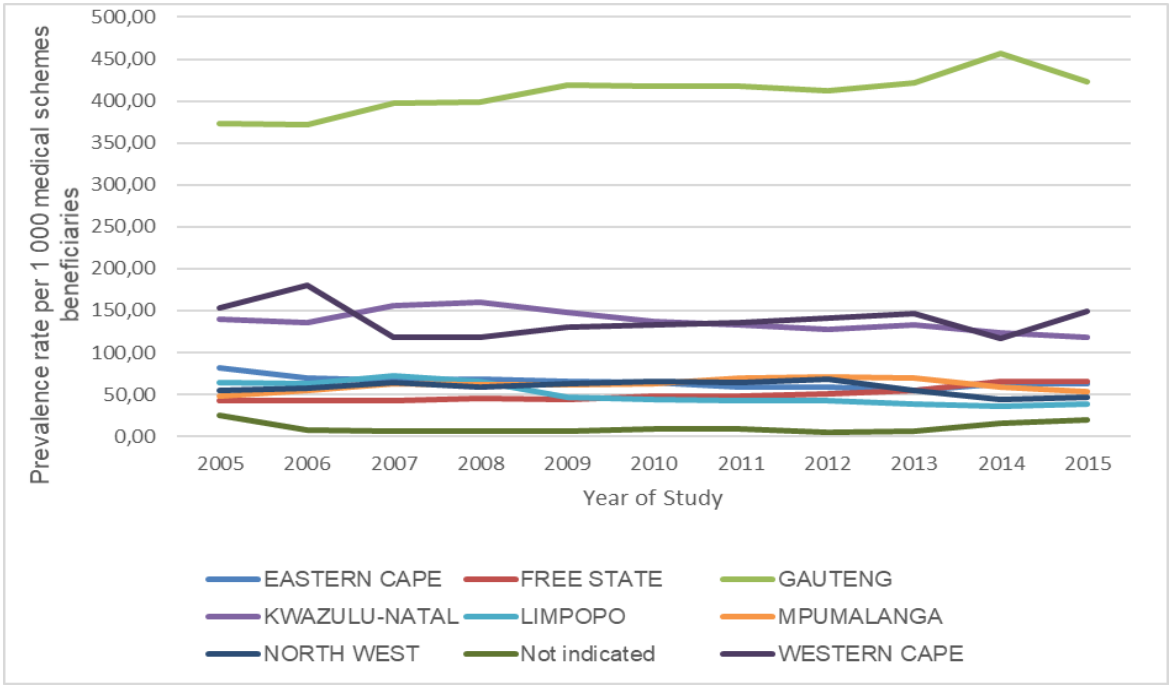

Figure 4: Prevalence rate of HIV/AIDS patients per 1 000 medical scheme beneficiaries by province in South Africa from 2005-2015.

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 organizations 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 found 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 scheme environment in South Africa.

3.3.2 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 an applicable journal.

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 scheme healthcare environment.

3.4 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 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.

3.5 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.

CHAPTER 4: PROFILE OF SOUTH AFRICAN PATIENTS WITH HIV IN A MEDICAL SCHEME ENVIRONMENT

4.1 INTRODUCTION

This study focuses on profiling South African Human Immunodeficiency Virus and Acquired Immune Deficiency Syndrome patients in the medical scheme environment in the private health sector of South Africa.

4.1.1 Background and problem statement

Since 1996, the public sector accepted the Standard Treatment Guideline (STG) and Essential Drug List guidelines as the standard prescribers to be compliant with (South Africa, 1996). Although, the private healthcare sector prescribers are encouraged to use the same STG (South Africa, 1996), there is no legislation that enforces these guidelines. The CMS (2016), reported that HIV is the 5th highest prevalent chronic disease when including chronic diseases such as hypertension, hyperthyroidism, hyperlipidaemia, diabetes myelitis type 2 and asthma. In 2007, the South African government made HIV part of the 270 PMB medical conditions list that demands to be covered in full without any exclusion, which drives the costs of medical schemes higher (CMS, 2017a). The government also negotiated reduced prices for ART from tenders for more affordable HAART for patients in both the public and private healthcare sector (Wayburne and Da Silva, 2007).

HIV affects the whole body of those infected, including the central nervous system (Grant, 2008). High et al. (2006), indicated that long-term use of HAART may be associated with cognitive impairment and as a result can lead to dementia in older patients. A study done by Ovbiagele and Nath (2011), also indicated the higher incidence of ischemic stroke with co-existing HIV infection. Rodriguez-Penney et al. (2013), found that there is a relationship between older patient with HIV and the prevalence of other co-existing chronic diseases such as diabetes (17.8%), syndromic neurocognitive impairment (15.4%), and malignancy (12.2%). Langebeek et al. (2017), reported that older patients with co-morbidities and HIV-positive status were significantly and independently associated with worse physical and mental health related quality of life than those individuals without co-morbidities. This substantiated the need to investigate other possible co-existing conditions in patients with HIV.

HIV is a unique chronic disease as it is the only chronic disease that has an adherence-resistance relationship (Bangsberg et al., 2004). Failure of the patient to comply with the treatment dose as prescribed leads to increased viral replication and selective resistance to specific ARV treatment (Kleeberger et al., 2001). A Link between the disease itself and adherence obstacles faced by PLWHA has also been documented. Slabbert et al. (2015), e.g., indicated that patients with HIV have a higher possibility to develop major depression, decreasing adherence to ARV treatment. The progression of the disease and eventual death are highly related to the adherence of ART and the prescribed regimens (Bangsberg et al., 2004). Adherence barriers to ART leads to less resistance, complications, and treatment cost (Kleeberger et al., 2001; Martin et al., 2005; Cramer et al., 2008).

Understanding the different aspects of HIV in the private health sector of South Africa, will assist in developing methods to improve the burden of HIV. Despite the increasing prevalence rate of patients with HIV in the South African medical scheme environment, little is known about the profile of these individuals. There is a lack of information about the chronic medication treatment patterns of CDL conditions, co-exiting with HIV and the direct medicine treatment cost involved. The more chronic diseases a patient is registered for, the lower the mental and physical health of the HIV positive patients (Langebeek et al., 2017).

In 2014, CMS reported that 27 beneficiaries per 1000 were registered for HIV at the chronic disease management programme, which increased to 30 beneficiaries per 1000 in 2015 (CMS, 2016; CMS, 2017b). The average growth rate in chronic diseases as reported by the CMS are: hypertension at 7,7%; diabetes mellitus type 2 at 11,1%; and HIV treated patients at 16,8% (CMS, 2017b). There is a lack of research about the prevalence of multiple CDL conditions in patients living with HIV in the private sector of South Africa. Therefore, more relevant information is required for decision-making purposes to manage this health and economic burden of HIV in the private health sector of South Africa.

The focus of this study was to compile a profile of the patients with HIV in the medical scheme environment of the South African private health sector, using a medicine claims database of a PBM company.

4.1.2 Research aims

The aim of the study was to determine the demographic-, clinical-, and medicine claims profile of patients with HIV in the private healthcare sector of South Africa, using medicine claims data obtained from a PBM company.
The demographic profile included the demography of patients such as age, gender, geographic location.

4.1.3 Specific empirical research objectives

The specific research objectives of the empirical study included the following objectives pertaining to the HIV/AIDS patient in the private healthcare patient:

- Establish a demographic profile of HIV/AIDS patients by focussing on the age and gender of the patient, geographical location[1] as well as the type of prescribers of the ARV medication.
- Determine the clinical profile by identifying co-existing CDL list conditions, ARV treatment patterns and the adherence[2] of patients toward ARV medication.
- To investigate the medicine claims profile by investigating the general medicine prescribing patterns, the type of medicine provider and a direct medicine cost analysis of ARV treatment.

The study variables are divided under the different categories as listed in Table 17:

Table 17: Study variables categorised according to relevant profiles.

Demographical profile	Clinical Profile	Medicine claims profile
Age	Co-existing CDL conditions: (Using the ICD 10-codes) (not included in this report).	Type of medicine claimed: identifying the acute, oncology, chronic and PMB medicine usage (not included in this report).
Gender	Prescribing patterns of ARV medication	General medicine usage patterns of patients (not included in this report).
Geographical location	Adherence to ARV drugs (not included in this report).	Medicine provider
Prescriber type		Direct medicine cost analysis (not included in this report).

[1] Geographical location will be determined using the postal codes of the prescriber as proxy.
[2] The medicine procession ratio as a proxy to determine adherence.

4.2 MATERIALS AND METHODS

4.2.1 Research method

The research method includes a literature review and an empirical study.

4.2.1.1 Empirical study

4.2.1.1.1 *Study design*

A cross-sectional, observational and quantitative research design was implemented using retrospective medicine claims data from a PBM company.

In a cross-sectional design the prevalence of the different variables is studied at a specific point in time (a day, month, year for example) (from Jan 2016 to Dec 2016 for the purposes of this study) (Kholmatova et al., 2016). Therefore, only one years' data can be used, and it does not require an increase in the number of years, since patient profiles (demographic-, clinical-, and medicine claims profile) may be duplicated. Only one year of data is required to achieve the empirical research objectives, the aim is not to investigate changes over time.

No interventions were done during the study; therefore the study design can be classified as observational (Brink et al., 2012a). In the study design both numerical and inferential statistics are used to provide descriptive results (Brink et al., 2012a; Kholmatova et al., 2016).

Retrospective data are data of a chronological clinical register where the healthcare register is kept. Data sources may be the copies of prescriptions dispensed, treatment records kept at prescribers and/or patient information records kept at healthcare facilities (WHO, 1993). According to the WHO (1993), retrospective data enables the researcher to obtain less biased data as it supplies data for a period longer than a year. A limitation of retrospective data is that patients' information may be incomplete (WHO,1993) therefore, for the purpose of this study all the data from 1 January 2016 to 31 December 2016 that meet the inclusion and exclusion criteria in Table 18 was used. The data obtained is verified by the PBM company using the techniques listed in Appendix I (refer to paragraph 4.2.1).

4.2.1.1.2 *Study and target population*

The target population consists of all patients with HIV treated in the private health sector in South Africa in the year 2016.

The study population includes all patients with HIV treated with ARV medication in the private health sector of South Africa. The patients must be members or dependants of members of medical schemes whose administration is handled by this specific PBM. Patients were selected according to the subsequent inclusion and exclusion criteria as per Table 18.

Table 18: Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
Study period: 1 Jan 2016 to 31 Dec 2016. Ages: All ages. Gender: Both gender groups male and female were included in this study. Diagnosis code: ICD-code B20-B24[3] Medication: Antiretroviral drugs	All incomplete data fields for age, gender, diagnoses code and postal code of the provider (needed for geographical location).

No sampling was necessary in this study as the information of all patients who meet the inclusion criteria were selected for this study.

4.2.1.1.3 *Data source and data fields*

The medicine claims database of a PBM company of South Africa was used as data source to conduct the empirical study. For confidentiality reasons the name of this company will not be revealed. Medical schemes are an important funder for health services and medicine in the private health sector. The medicine claims database of the PBM Company includes data of 41 medical schemes and gives access to data of around 1.6 million beneficiaries.

The PBM Company is a real-time electronic management system that manages patients' benefits and acts as a mediator between the healthcare provider and medical scheme for all medicine claims submitted. MUSA is a research entity that has a contractual agreement with the PBM Company to obtain data for research purposes.

4.2.1.2 Validity and reliability of the data source

The data used in this study was obtained from the medicine claims database as agreed between MUSA and the PBM Company. As the data was obtained from only one database, it leads to limited external validity as the data is specific to this database and study population only. For the purpose of this study it was assumed that all information is correct and accurate. Duplicate claims and incomplete patient information was not included in the data analysis. Random data checks were performed to verify the datasets.

The PBM Company performs internal validation processes such as gate-keeping services, eligibility services, medicine utilisation management services, fully integrated pre-authorization program, management of medicines for the CDL conditions, management of PMB and other conditions, clinical management services, pricing management as well as real-time benefit management. There are supplementary networks that also include network management, reference pricing that is being applied and formulary of medication management.

As per confidentiality agreement with PBM Company all identifiable information about medical schemes, patients, and prescribers was encrypted or deleted by the PBM Company before providing data for analysis.

[3] B20 Human immunodeficiency virus [HIV] disease resulting in infectious and parasitic diseases
B21 Human immunodeficiency virus [HIV] disease resulting in malignant neoplasms
B22 Human immunodeficiency virus [HIV] disease resulting in other specified diseases
B23 Human immunodeficiency virus [HIV] disease resulting in other conditions
B24 Unspecified human immunodeficiency virus [HIV] disease (WHO, 2016)

4.2.1.3 Data fields used in this study

The following data fields were extracted from the database:

- Date of birth of the patient
- Gender indicated as male or female
- Postal code of the healthcare provider
- Type of prescriber
- Type of medicine provider
- Trade name of the drugs
- NAPPI-code[4](National Approved Product Pricing Index codes) of the drugs
- Dispensing date of the prescription
- The number of days the medication is supplied for
- ICD-10 codes (International Classification of Diseases and Health-Related Problems) for PMB (Prescribed minimum benefits) CDL conditions (Chronic disease list conditions)
- The amount paid by the medical scheme and patient

These data fields were used in different statistical calculations to provide information in consultation with a statistical analyst employed by NWU Potchefstroom campus.

4.2.2 Study variables

The study includes the mentioned variables as categorised in Table 55.

4.2.2.1 Demographic profile variables

Demographic variables include age, gender group, as well as the prescriber of the ARV and geographical location[5] of the patients.

4.2.2.1.1 *Age*

The age of the person was calculated from 1 January of the year following the date that the prescription was dispensed by making use of the Statistical Analysis System®, SAS 9.4® (SAS Institute Inc., 2002-2012) programme. Patients were then categorised into the age groups according to the UNAIDS' strategy 2016-2021 (UNAIDS, 2016c).

4.2.2.1.2 *Gender*

For the purpose of this study, gender was divided into two categories, namely female and male. Patients for whom gender was not indicated was excluded from the study to ensure that the quality of the data is maintained.

4.2.2.1.3 *Geographical location*

The postal code of the prescriber of the ARV drugs was used as a proxy for geographical location of patients. Data was analysed at provincial and district levels. According to the Municipal Demarcation Board Act 1998, the municipal demarcation board is allowed to determine boundaries in South Africa by its own initiative or at the request of the Minister of Provincial and Local Government, the Member of Executive Council (MEC) responsible for local government in a province, or a municipality. The nine different

[4]The NAPPI-code is a unique nine-digit long product codes introduced to facilitate electronic transactions. Each code is unique for each medicine product name, registration, pack size, strength, manufacturer of the product, and dosage (Medikredit, 2003)

[5] The geographical location of the patient will be determined by using the postal code of the prescriber's practice as a proxy.

provinces and 52 districts in South Africa currently determined by the Municipal Demarcation Board (1998) are attached in appendix H (South Africa, 1998b).

4.2.2.1.4 *Prescriber type*

The PBM's data are also divided according to prescriber type (i.e. person writing the prescription). The prescribers were divided into the following five categories:

- General medical practitioners: This group includes all the medical providers who are registered with the South African Health Professional Council as a general medical practitioners (South Africa, 1974).
- Authorised pharmacist prescriber: This group consists of all the authorised pharmacist prescribers who are registered with the South African Pharmacy Council as a qualified pharmacist with an additional qualification permitting him/her to provide primary health services (South Africa, 1974).
- Pharmacies: This group includes all the pharmacies' qualified personnel who are registered with the South African Pharmacy Council (SAPC). Pharmacies as prescribers include all the registered pharmacists, pharmacist technicians[6], pharmacist assistants and pharmacist interns excluding pharmacotherapists (South Africa, 1974; SAPC, 2010).
- Other: This group includes all of the following prescribers: day clinics, specialised prescribers, general dental practices, community health, general dental practices, homeopaths, group practices, group hospitals, community dentistry, private hospital (tariffs A and B), provincial hospitals-, and operating theatres.
- The specialised prescribers include anaesthesiology, cardiology, clinical haematology, dermatology, diagnostic radiology, gastroenterology, neurology, nuclear medicine, obstetrics/ gynaecology, oncology, ophthalmology, oral pathology, orthodontics, orthopaedics, otorhinolaryngology, paediatrics, pathology, periodontics, urology, surgery (including paediatric surgery), psychiatry, physical medicine, plastic and reconstructive surgery, prosthodontics, pulmonology, radiography, rheumatology, thoracic surgery, physicians/ immunologist/ rheumatology/ nephrology/ endocrinology.

4.2.2.2 Clinical profile variables

The clinical profile variables include: identifying co-existing CDL conditions; type of medicine (acute, chronic, prescribed minimum benefits, oncology) (Not included in this report); ARV treatment prescribing patterns; and the adherence of patients in terms of ARV drugs by using the medicine possession ratio as a proxy for adherence (Cramer et al., 2008) (not included in this report).

4.2.2.2.1 *Prescribing patterns of ARV medication*

The data source was used to identify the prescribing patterns[7] of the ARV medication by using the active ingredients and combination of active ingredients claimed per patient. These prescribing patterns of the ARV medication were compared with the STG suggested by the WHO (WHO, 2015) and the regimes included in the EDL implemented by the DoH (2014), to determine whether the prescribing patterns in the private healthcare sector of South Africa have any relation to these regimes. Table 19 includes the medication available in South Africa for treatment of HIV that is available on the market until February 2017 (SAMF, 2012; MIMS, 2017).

[6] Pharmacist technicians may also prescribe schedule 1 and schedule 2 drugs without the supervision of a pharmacist according to amended Pharmacy Act (53 of 1974).

[7] Prescribing patterns include the most prevalent drug(s) and regimens, percentage of fixed dosage combinations and type of medication (e.g. generic or original drugs).

Table 19: HIV medicine on the market 2017 per active ingredient, tradename in South Africa.

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

Active ingredient(s)	Trade name(s)	Single dose (SD)/ Fixed dose combinations (FDC)
	Sonk Efvarirenz®	
Etravirine (ETR)	Intelence®	Single dose
Nevirapine (NVP)	Viramune® Aspen Nevirapine® Auro Nevirapine® Cipla Nevirapine® Adco Nevirapine® Sonke Nevirapine®	Single dose
Combined NRTIs/NNRTIs		
AZT/3TC	Combivir® Aspen Lamzid® Auro Lamizido® Cipla Douvir® Sonke Lamivudine + Zidovudine®	FDC
AZT/3TC/ABC	Trizivar® Sonke Abaclamzid®	FDC
3TC/ABC	Kivexa® Dumiva®	FDC
d4T/3TC/NVP	Triomune-30® Nevasta® Virtrium® Sonke-LamNevStav® Triomune-40®	FDC
TDF/FTC	Truvada® Adco Emtevir® Aspen Tenofovir and Emtricitabine® Didivir® Tencitab® Tenemine® Tyricten®	FDC
FTC/TDF/EFV	Atripla® Atenef® Atreslawin® Atroiza®	FDC

Active ingredient(s)	Trade name(s)	Single dose (SD)/ Fixed dose combinations (FDC)
	Odimue® Tribuss® Trivenz®	
TDF/3TC/EFV	Eflaten® Tenarenz®	FDC
Dolutegravir/ABC/3TC	Trelavue®	FDC
3TC/AZT/NVP	Triplavar®	FDC
Protease inhibitors		
Atazanavir	Reyataz® Atazor® Aspen Atazanavir®	Single dose
Darunavir	Prezista®	Single dose
Fosamprenavir	Telzir®	Single dose
Indinavir	Crixivan®	Single dose
Nelfinavir (NFV)	Vira-cept®	Single dose
Ritonavir (RTV/r)	Norvir®	Single dose
Lopinavir-ritonavir (LPV/r)	Aluvia® Kaletra®	FDC
Saquinavir (SQV)	Invir-rase®	Single dose
Other ARV		
Raltegravir	Isentress®	Single dose
Dolutegravir	Tivicay®	Single dose
Rilpivirine	Edurant®	Single dose

The DoH (2012), published standard treatment guidelines which are based on the WHO guidelines. The preferred regimes represented by the DoH, South Africa and the WHO guidelines are included in Table 20 (DoH, 2012; MIC, 2015; WHO, 2015).

Table 20: Regimens of first line and second line treatment according to the DoH and the WHO.

Regimen Choice	Combination of regimen	Regimen no.	Regimen choice	Combination of regimen	Regimen no.
First line treatment according to Department of Health			**First line treatment according to Department of Health**		
Stavudine based	d4T + 3TC + EFV d4T + 3TC + NVP	Regimen 1-1 Regimen 1-2	Fixed dose combination based	TDF + FTC+ EFV TDF + 3TC+ EFV	Regimen 1-7 Regimen 1-8
Tenofovir based	TDF + 3TC+ EFV	Regimen 1-3 Regimen 1-4	Alternative options	AZT+ 3TC + EFV	Regimen 1-1 Regimen 1-2

Regimen Choice	Combination of regimen	Regimen no.	Regimen choice	Combination of regimen	Regimen no.
	TDF + 3TC+ NVP			AZT + 3TC + NVP	
Zidovudine based	AZT + 3TC+ EFV AZT + 3TC+ NVP	Regimen 1-5 Regimen 1-6		TDF + 3TC+ NVP TDF + FTC+ NVP	Regimen 1-4 Regimen 1-9
Fixed dose combination	TDF + FTC + EFV	Regimen 1-7		TDF+ 3TC/FTC+ DTG	Regimen 1-10
Second line treatment			**Second line treatment**		
Failure of d4T or AZT base	TDF+ 3TC+ LPV/r	Regimen 2-1	Should include 2 NRTIs and a protease inhibitor		Regimen 2-1 and 2-2
Failure of TDF base	AZT+ 3TC+ LPV/r	Regimen 2-2	Alternative options	2 NRTIs + DRV/r LPV/r+ RAL	Regimen 2-3 Regimen 2-4
Third line treatment includes a referral to the specialist where the specific genotype must be tested, and specific resistance must be identified with the help of a specialist.			Third line treatment includes a referral to the specialist where the specific genotype must be tested, and specific resistance must be identified with the help of a specialist.		

The ARV drugs were also categorized according to their 'generic status indicator'. The PBM also assign a 'generic status indicator' to all medicine products on their database. Status was categorized as: i) an original medication with generic equivalent(s); ii) original medication with no generic equivalent(s); or iii) as generic medication.

4.2.2.3 Statistical analysis

The Statistical Analysis System, SAS 9.4® (SAS Institute, 2002-2017) was used to analyse the data according to the research objectives of the empirical study. The statistical analysis was performed in consultation with Statistical Consultation Services of NWU University (Potchefstroom Campus).

4.2.3 Ethical considerations

The study commenced after it was granted ethics approval by the Health Research Ethics Committee (HREC) (certificate number NWU-00179-14-A1-07) 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.

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

4.3 RESULTS AND DISCUSSION

A total of 16 763 HIV/AIDs patients claimed antiretroviral medication in 2016, with an average age of 42,1 (SD=11.6) year. Figure 5 presents the gender distribution of the study population.

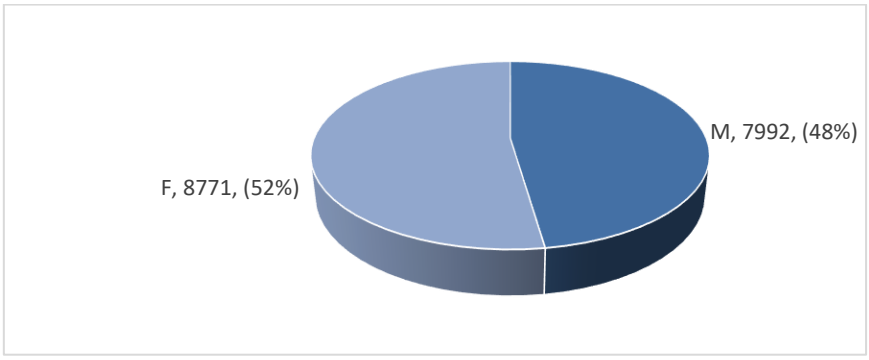

Figure 5: Gender distribution of study population.

Table 21: Age group and gender distribution of HIV/AIDS patients.

Gender	Age group (years)							Total
	< 2.0	>= 2.0 and < 12.0	>= 12.0 and <18.0	>= 18.0 and <25.0	>= 25.0 and <45.0	>= 45.0 and <65.0	>= 65.0	
Female	17	140	170	222	5662	2440	120	8771
	(0.19%)	(1.60%)	(1.94%)	(2.53%)	(64.55%)	(27.82%)	(1.37%)	(52.32%)
Male	20	144	166	108	3660	3706	188	7992
	(0.12%)	(0.86%)	(0.99%)	(0.64%)	(21.83%)	(22.11%)	(1.12%)	(47.68%)
Total	37	284	336	330	9322	6146	308	16763
	(0.22%)	(1.69%)	(2.00%)	(1.97%)	(55.61%)	(36.66%)	(1.84%)	(100.00)

Table 22: Distribution of HIV/AIDS patients per province.

Province	n	%
Western Cape	3077	18,4
Northern Cape	274	1,6
North West	1407	8,4
Mpumalanga	1472	8,8
Limpopo	638	3,8
KwaZulu-Natal	2374	14,2
Gauteng	5209	31,1
Free State	1388	8,3
Eastern Cape	924	5,5
Total	16763	100,0

The highest HIV/AIDS prevalence was noticed in Gauteng (31.1%) followed by Western Cape (18.4%) and KwaZulu-Natal (14.2%) in 2016. 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.

Figure 20 to Figure 14 indicate the prevalence of HIV/AIDS according to the districts per province. The maximum number of HIV/AIDS patients per province where in the following districts:

- Buffalo City Metropolitan
- Lejweleputswa
- eThekwini
- City of Johannesburg
- City of Tshwane
- Capricorn
- Nkangala
- Bojanala
- Frances Baard
- Overberg

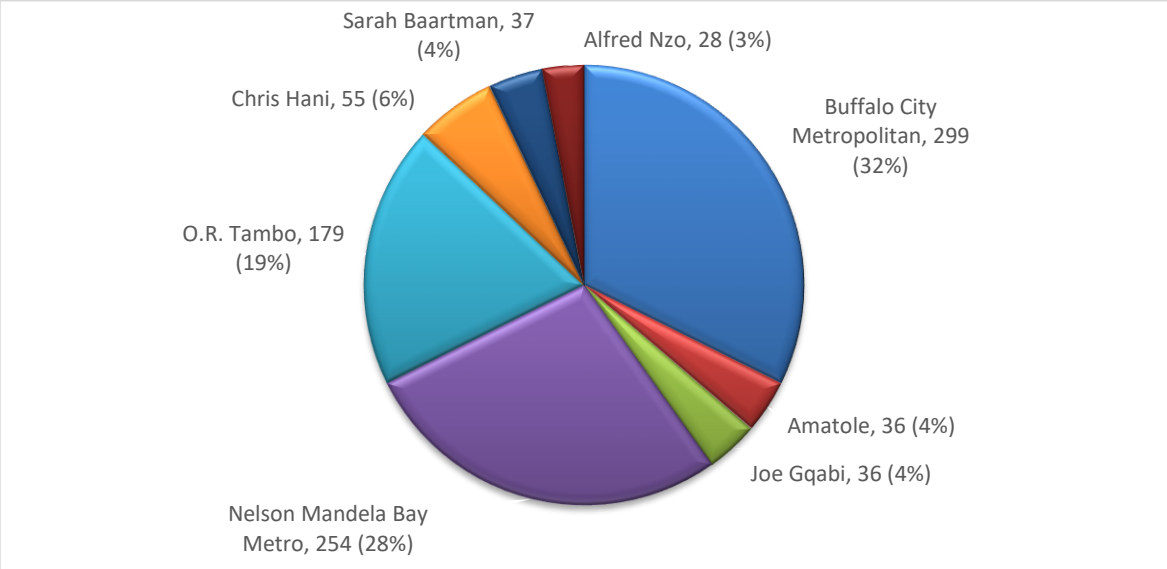

Figure 6: Number of HIV/AIDS patients per district in Eastern Cape.

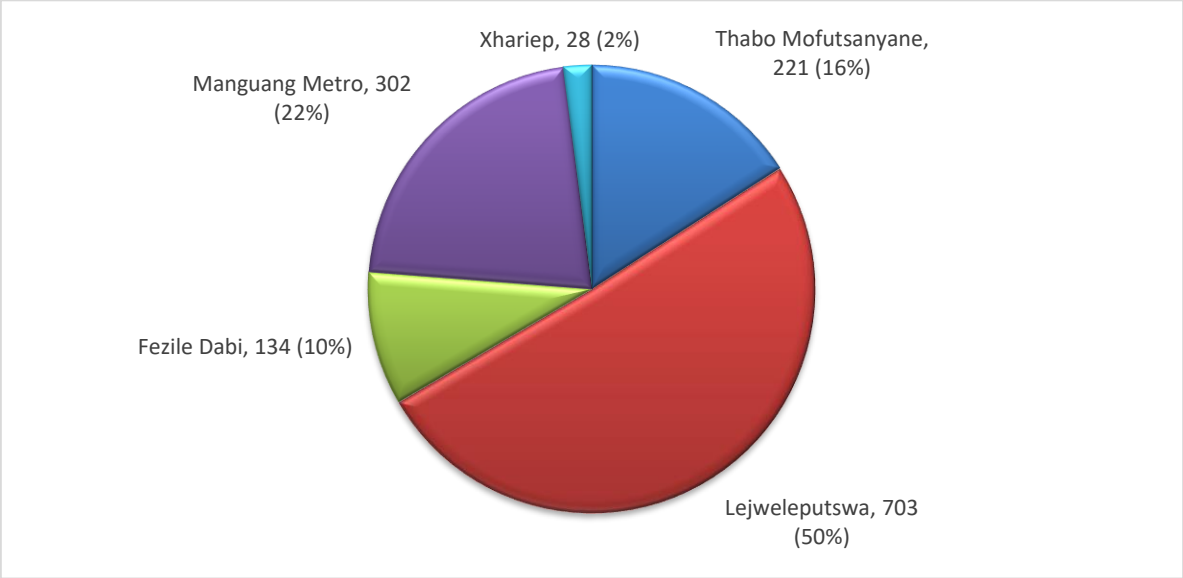

Figure 7: Number of HIV/AIDS patients per district in the Free State.

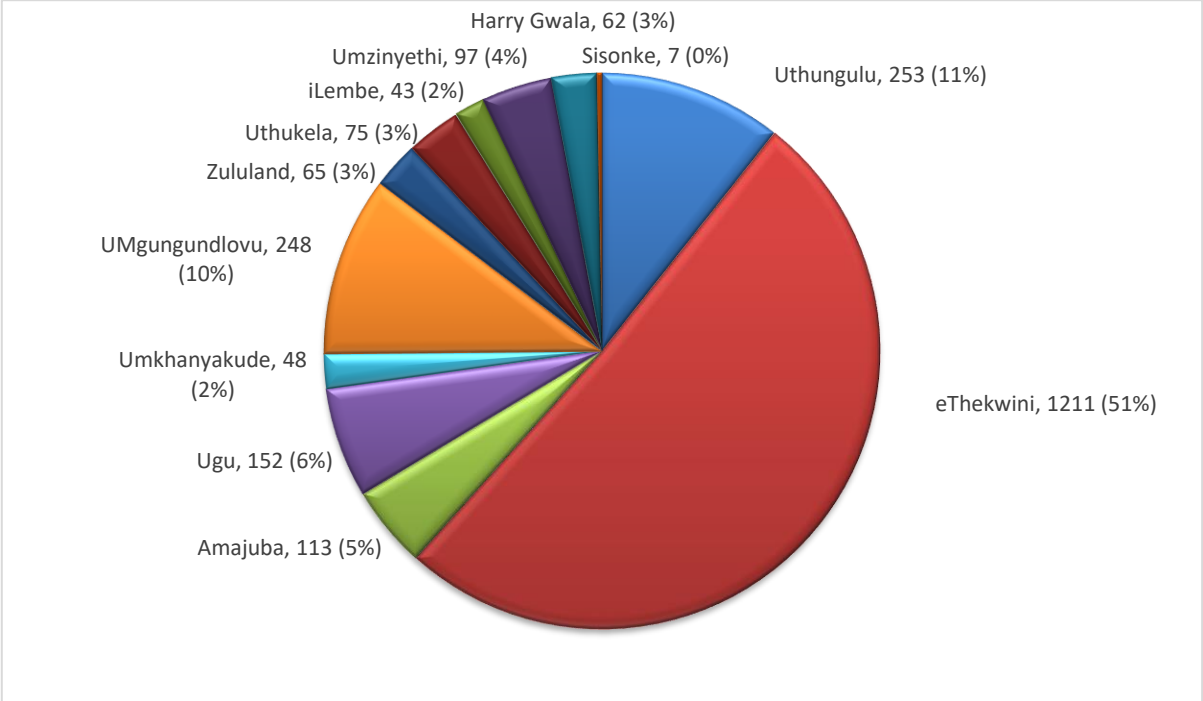

Figure 8: Number of HIV/AIDS patients per district in KwaZulu-Natal.

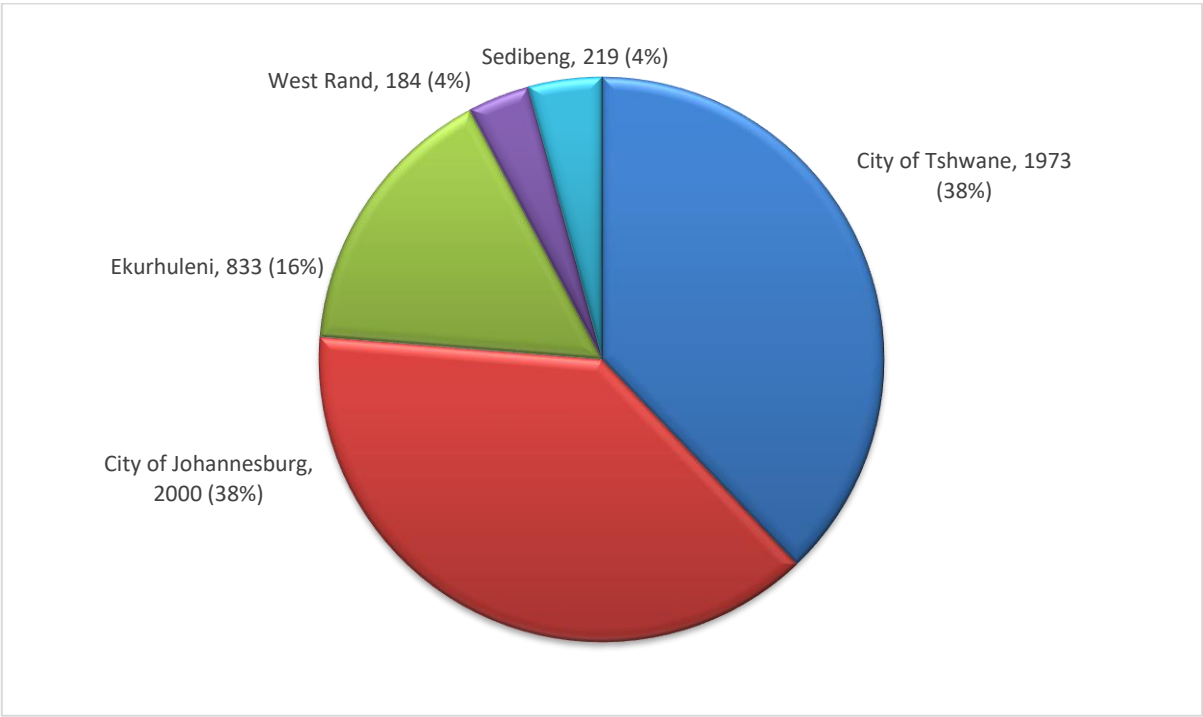

Figure 9: Number of HIV/AIDS patients per district in Gauteng.

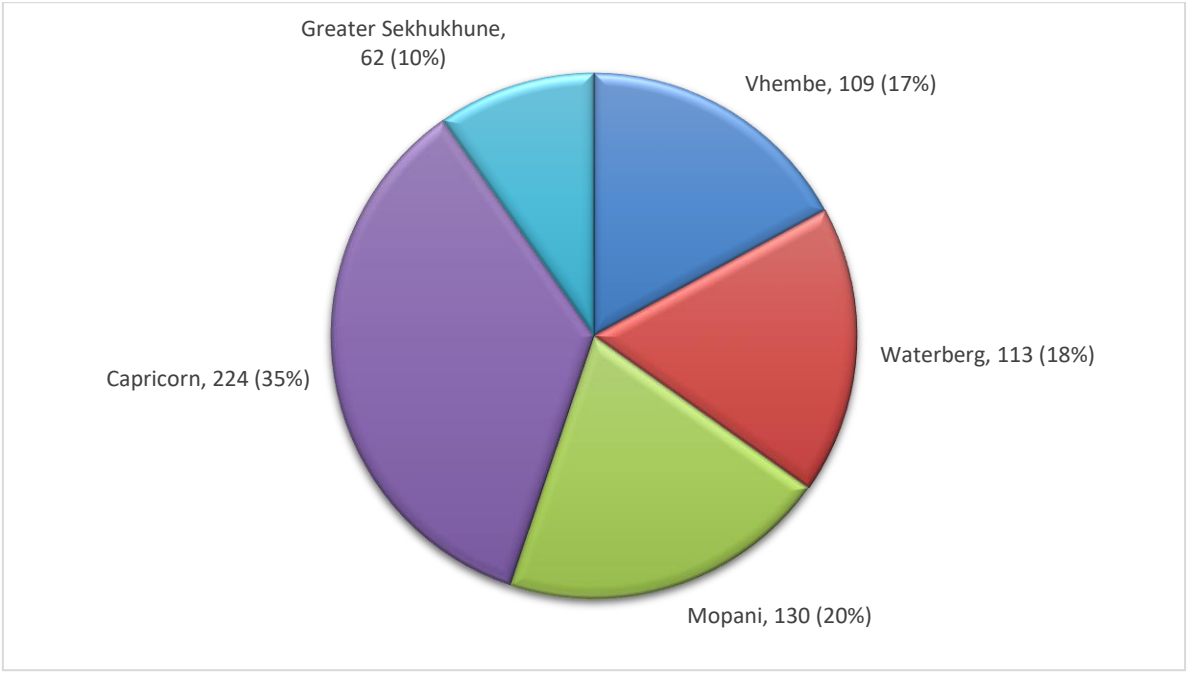

Figure 10: Number of HIV/AIDS patients per district in Limpopo.

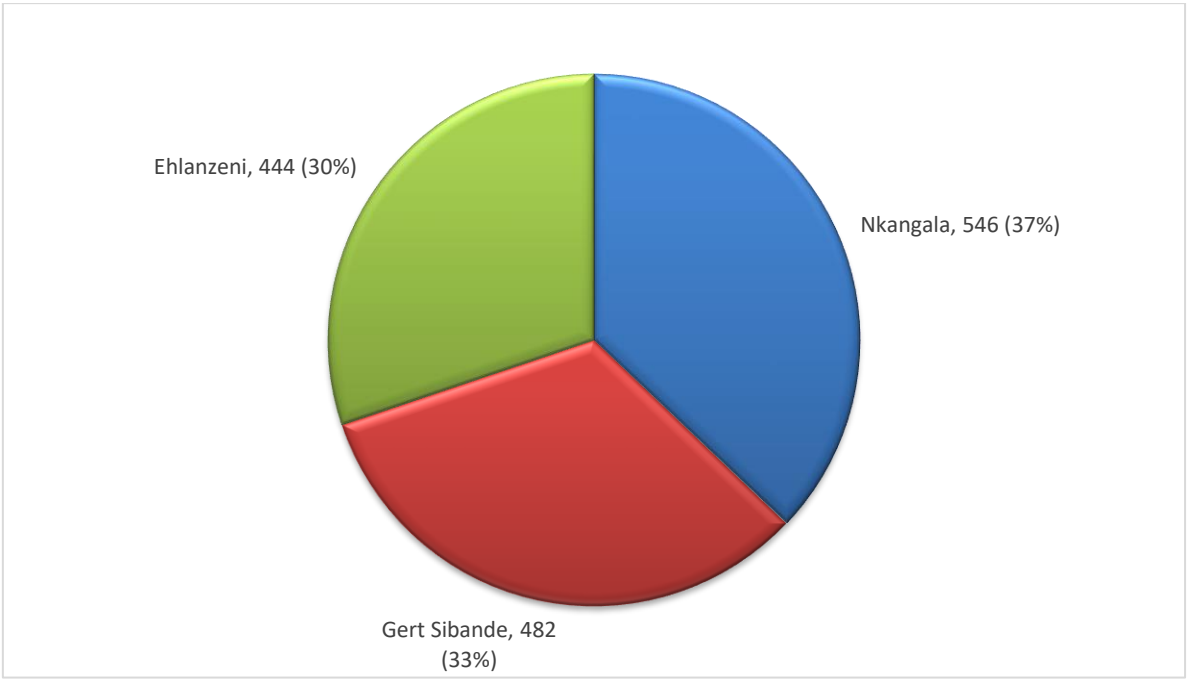

Figure 11: Number of HIV/AIDS patients per district in Mpumalanga.

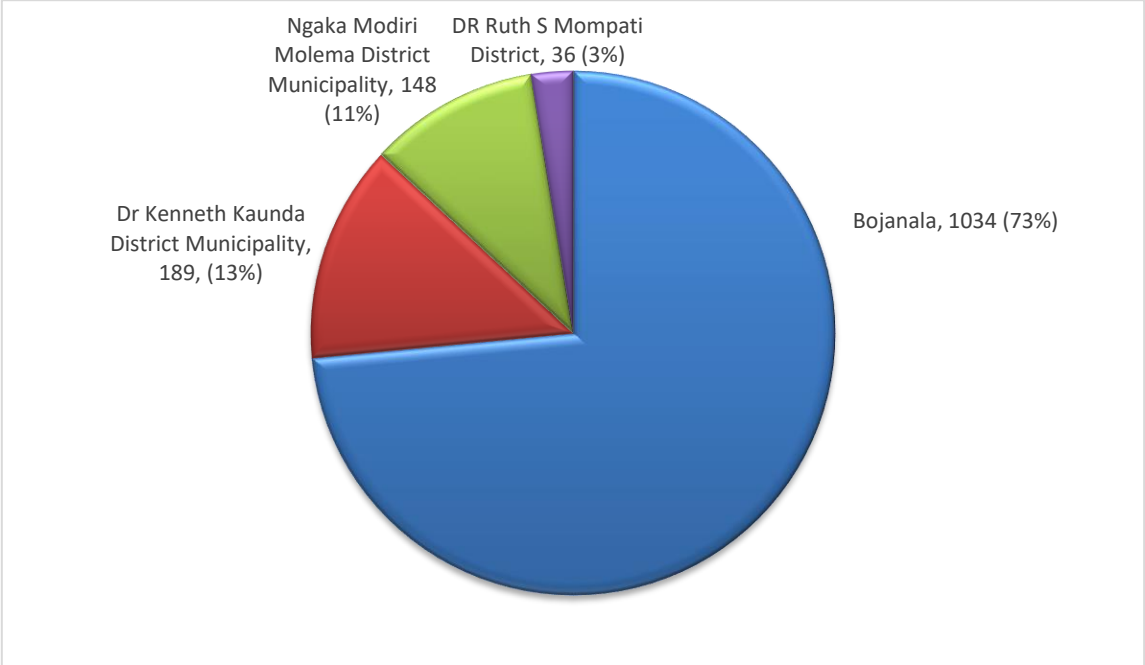

Figure 12: Number of HIV/AIDS patients per district in the North West province.

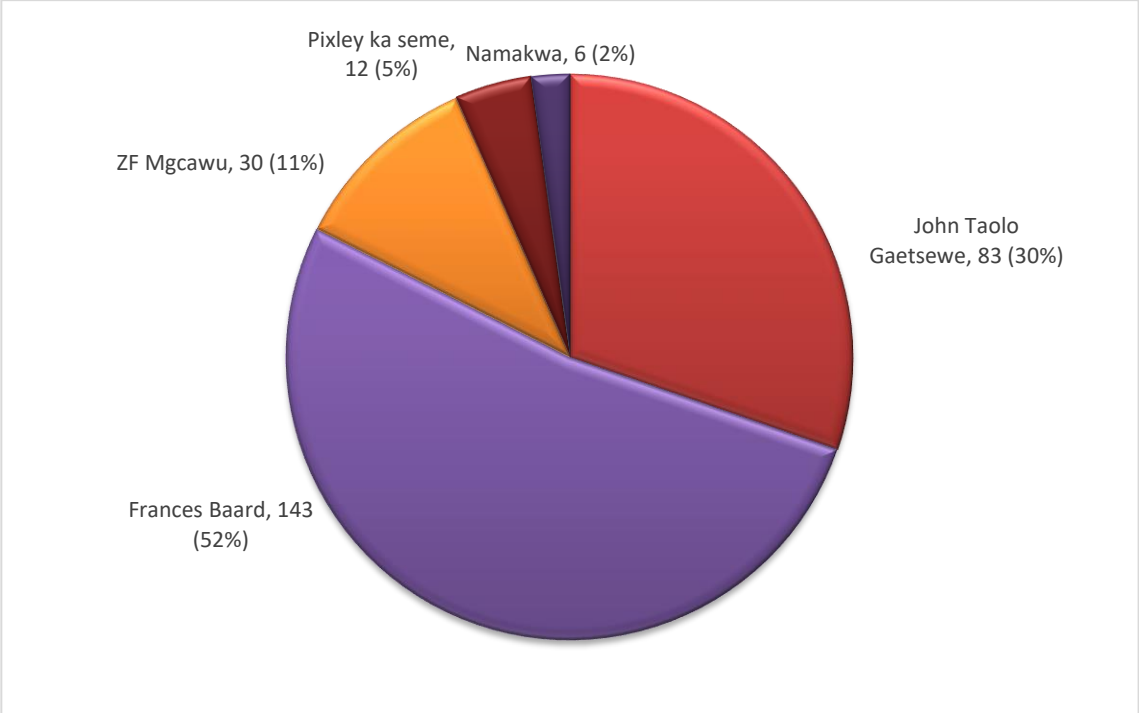

Figure 13: Number of HIV/AIDS patients per district in the Northern Cape.

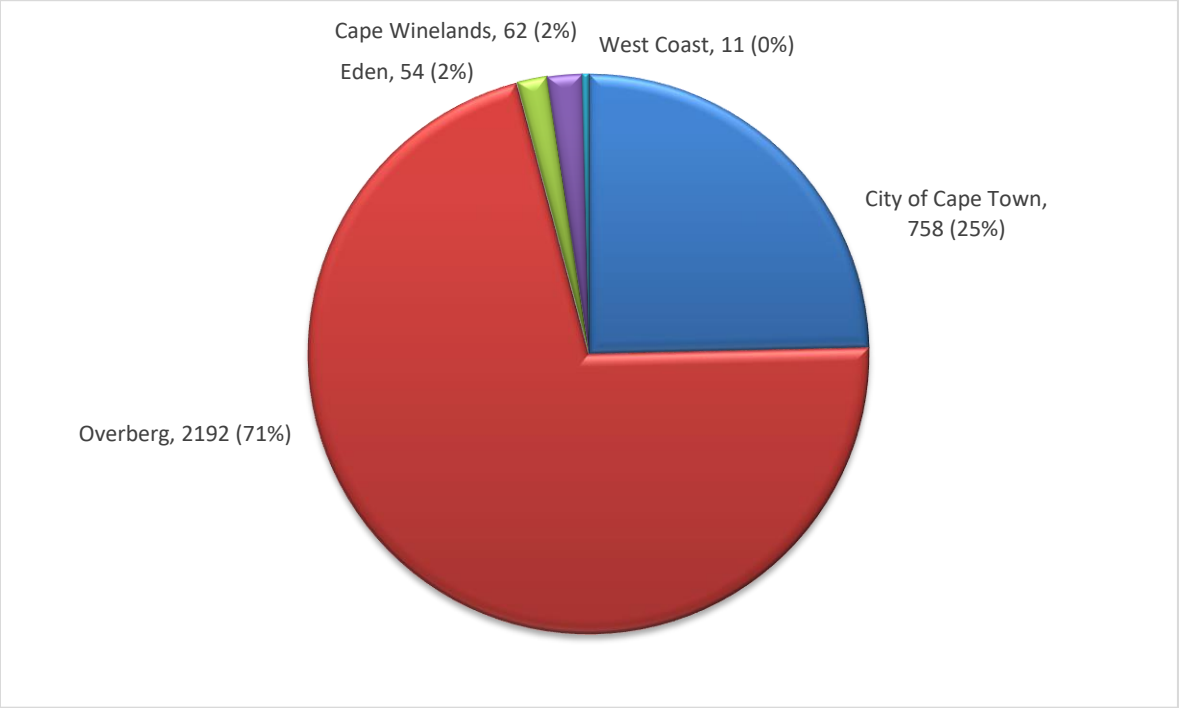

Figure 14: Number of HIV/AIDS patients per district in the Western Cape.

Table 23 indicates the different ARV drugs that were prescribed to the HIV/AIDS patients.

Table 23: Distribution of ARV drugs claimed to HIV/AIDS patients.

Antiretroviral drug	n	%
Efavirenz/emtricitabine	34021	19.65
Emtricitabine/tenofovir	31531	18.21
Efavirenz	17773	10.27
Lopinavir/ritonavir	14899	8.61
Lamivudine/zidovudine	13329	7.70
Emtricitabine	7272	4.20
Ritonavir	6355	3.67
Lamivudine	5098	2.94
Tenofovir/emtricitabine	4984	2.88
Atazanavir	4803	2.77
Nevirapine	4749	2.74
Abacavir/lamivudine	4621	2.67
Tenofovir	4600	2.66
Tenofovir/lamivudine/e	3563	2.06
Abacavir	3358	1.94
Lamizido	3174	1.83
Rilpivirine	2778	1.60
Zidovudine	1335	0.77
Raltegravir	1006	0.58

Antiretroviral drug	n	%
Stavudine	709	0.41
Darunavir	638	0.37
Tenofovir/efavirenz/la	625	0.36
Lamivudine/nevirapine/	486	0.28
Didanosine	427	0.25
Efavirenz/lamivudine/t	406	0.23
Etravirine	231	0.13
Dolutegravir	155	0.09
Saquinavir	140	0.08
Lamivudine/tenofovir	24	0.01
Indinavir	14	0.01
Abacavir/lamivudine/	9	0.01
Dolutegravir/abacavir/	8	0.00
Lamivudine/zidovudine/	6	0.00
Fosamprenavir	2	0.00
Lamivudine	1	0.00
Saquinavir mesylate	1	0.00

4.4 LIMITATIONS AND STRENGTHS

The empirical study had several limitations:

- Data was obtained from only one of the PMBs in South Africa; generalisability and external validation of the data is therefore limited.
- This study included only private-insured HIV/AIDS patients enrolled for 2016 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.
- The postal code of the prescriber used to identify the geographical area might be limited as not all patients reside in the same area as their prescriber.
- Not all medical practitioners were included the ICD-10 code on prescriptions or might note the wrong ICD 10 code. It is therefore not possible to determine the scope of this list limitation.
- 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.
- 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.

Table 24: Statistical analysis system.

Objectives	Measurements	Variables		Statistical analysis		
		Independent	**Dependant**	**Descriptive**	**Inferential**	**Practical significance**
To determine the demographical profile of the patient with HIV	Total number of patients with HIV on the database		Number of patients with HIV on the database			
	Age group distribution of the patients with HIV	Age group	Number of patients with HIV on the database			
	Gender distribution of the HIV patients	Gender	Number of patients with HIV on the database			
	Geographical location (determined on district and provincial levels) of the HIV patients	The geographical location of the HIV patient (determined on district and provincial levels)	Number of patients with HIV on the database			
	To determine the prescriber, type responsible for issuing prescriptions	Prescriber type: General medical practitioners, pharmacotherapists, pharmacies, specialists and other prescribers.	Number of patients with HIV on the database			
	Difference in the mean age of patients taking ARV treatment stratified according to gender	Gender	Age	If the mean ± SD, 95% CI. If skew distributed, Median, IQR	*t*-test	*d*-value
	Difference in the mean age of patients taking ARV treatment stratified according to geographical location	Geographical location	Age	If the mean ±SD, 95% CI. If skew distributed, Median, IQR	ANOVA	*p*-value < 0.05 *d*-value

	To determine the geographical distributions of patients with HIV stratified by age group and gender	Geographical distribution on provincial and district level	Age group Gender	Frequency (%)	Chi-square	*p*-value < 0.05 Cramér's V
	Number of CDL conditions per patients with HIV	Gender Age group	Number of CDL conditions per patient	Mean (SD) 95% CI or median, IQR depending on distribution	*t-t*est ANOVA	*p*-value < 0.05 *d*-value
To determine the clinical profile of the patients with HIV	Acute medicine usage Chronic and prescribed minimum benefit medicine usage Oncology medicine usage	Type of acute medication claimed Type of chronic and prescribed minimum benefit medicine Type of oncology medicine usage	Number of patients with HIV	Frequency (%)		
	Acute medicine usage Chronic and prescribed minimum benefit medicine usage Oncology medicine usage	Gender Age group	Number of acute medication claimed Number of chronic and prescribed minimum benefit medicine claimed Number of oncology medicine usage	Mean (SD) 95% CL or median, IQR depending on distribution	*t-t*est ANOVA	*p*-value < 0.05 *d*-value
	Prescribing patterns of ARV medication	Active ingredients ART regimen	Number of patients with HIV	Frequency (%)		

		Fixed dosage regimen Type of medicine (generic, original, etc.)				
	Prescribing patterns of ARV medication	Gender Age group	Active ingredients ART regimen Fixed dosage regimen Type of medicine (generic. original, etc.)	Frequency (%)	Chi-square	*p*-value < 0.05 Cramér's V
	Adherence to ARV medication	Gender Types of active ingredients Age group Number of co-existing conditions	MPR	Mean (SD) 95% CI or median, IQR depending on distribution	*t-t*est ANOVA	*p*-value < 0.05 *d*-value
	General medicine prescribing patterns	Gender Age group	Acute medicine usage Chronic and prescribed minimum benefit medicine usage Oncology medicine usage	Prevalence	Chi-square	*p*-value < 0.05 Cramér's V
	General medicine prescribing patterns	Average number of prescriptions per patient Average number of items per prescriptions per patient	Acute medicine usage Chronic and prescribed minimum benefit medicine usage Oncology medicine usage	Mean (SD) 95% CI or median, IQR depending on distribution	ANOVA	*p*-value < 0.05 *d*-value

To determine the medicine claims profile of the patient with HIV	Medicine provider: general practitioner, dispensing doctors, specialists, courier pharmacies, retail pharmacies and other providers.	Medicine provider	Number of patients	Prevalence		
	Cost analysis of disease: Total amount prescription amount, amount paid by medical schemes and total amount liable by the patient.	Active ingredients (ARVs) ART	Cost analysis: Total amount, amount paid by medical scheme, amount paid by the patient.	Average cost/ Mean (SD) 95% CI median, IQR	ANOVA	*p*-value < 0.05 *d*-value

CHAPTER 5: CONTEXTUAL- AND CAPACITY DEVELOPMENT ACTIVITIES OF THE PROJECT

5.1 INTRODUCTION

5.2 COMMUNITY HEALTH CENTRES IKAGENG

On the 13th of October 2016 the research team set about to get an insight view on what it means to live in a world characterised with HIV and AIDS. The day started off with a general introductory presentation form Dr P. Bester, Africa Unit for Transdisciplinary Health Research (AUTHeR) at the North-West University (NWU), regarding certain healthcare statistics and present-day stigma's found amongst South Africans (Figure 15).

Figure 15: Captured moment of HIV-ARV research team members engaged in introductory presentation.

The team then undertook an excursion to the different community health centres in Ikageng, Potchefstroom, which included the Boiki Tlhapi, Promosa and Steve Tshwete Community Health Centre. The majority of time was spent at the Boiki Tlhapi Community Health Centre where a new perspective was obtained for the everyday struggles of health care workers and PLWHA. Here the senior health care staff explained that Boiki Tlhapi is a primary health care facility providing AIDS, HIV and TB-associated therapy, care and support services (Figure 16).

Figure 16: Boiki Tlhapi Community Health Centre staff engaging with HIV-ARV research team members.

The centre therefore has a community oriented primary health care programme which strives to monitor and work proactively towards the improved health and well-being of community members within the area. The facility provides HIV counselling and testing in addition to running a support group dedicated to PLWHA and those around them. Boiki Tlhapi is also an accredited ART initiation and constant treatment site for thousands of community members passing through their doors each month (Figure 17). Centre pharmacists gave a descriptive account of the several antiretroviral compounds used in treatment and how it is generally distributed amongst patients and the implications associated with it. Once again it was emphasised how problematic it is to get community members to understand and adhere to complex antiretroviral treatment regimes, when many are bound to stigma's and inadequate levels of education.

Figure 17: Prescribed antiretroviral medication for treatment of HIV-positive community members**.**

5.3 HEAIDS: HIV AND AIDS IN THE CURRICULUM

On the 31st of March 2017 various members of the project team attended the reporting seminar on the NWU Project for HIV and AIDS in the curriculum (2014-2017), funded by HEAIDS and DHET-NSF, held in the Institutional Office, Potchefstroom. There the Deputy Vice-chancellor: teaching and learning, Prof Martin Oosthuizen, gave a word of welcome followed by Prof Lesley Wood (Research Professor, Faculty of Education Science, NWU) who gave an overview of the project, after which the various team members of the NWU project then imparted the knowledge produced within their individual projects in relation to how an intersectional approach to HIV education can be utilised to promote information and address issues pertinent to curriculum transformation.

The project aimed to assist in the understanding of how assumptions about HIV and AIDS are entrenched in the intersectionality that runs through specific sexual, socio-economic, gender and racial relationships. The seminar brought to light that, although there have been significant advances in medical interventions for HIV and AIDS, HIV discrimination and stigma continues to demean those infected and affected by the disease. This gap is to be addressed so that guidelines and recommendations can be made to aid developers of higher education programmes to successfully alter the curriculum in order to make it more applicable to students who live in a country identified by HIV and AIDS. Prof. Oosthuizen also argued that students should be deliberately equipped with the critical literacies to comprehend disparities in social construct that are often embedded in particular identity constructs, power relations and ideological presumptions.

Contributions made and the knowledge already obtained from the Risk assessment of HIV-ARVs in water resources lead to the teams' invitation to the HEAIDS congress that was held in Durban the 9-11th of June 2017. By completing cutting-edge research, the HIV-ARV team aims to benefit the society through knowledge about the environmental implications related to ART, which can potentially form part of future education programs.

5.4 STOCKPILING OF ARVS IN RURAL HOUSEHOLDS

During 2017, Dr Rina Muller from the School of Nursing Science shared the realities of medication stockpiling in homes as one mechanism of improper handling of ARVs (Figure 50). These home visits are part of the community nursing curriculum, where community-based training is used to equip nursing students with the realities and circumstances in rural areas and how to deal with these particular challenges (Figure 51). Student nurses conduct a multi-generation home visit in remote rural areas.

A lecturer/preceptor/clinical accompanist escorts 2-3 students to conduct a home visit, arranged via a gatekeeper of the area, e.g. a community health worker. The community health worker also accompanies the group to the home and assists with language barriers (provides translation services for those who do not understand Setswana). The aim of the visit is to earn the trust of the residents, to explore and describe the problems experienced in the household, to compile a plan of action and to conduct a follow-up visit discussing the problems identified. During the follow-up visit the household members should discuss their predicaments, their opinion will be asked on what they should do to deal with the particular problems, and information is provided on available resources within the community that can provide assistance. Referral letters are presented if necessary.

The students receive detailed information on what can be expected from a theoretical aspect and ethical or practical challenges they might come across. During such a home visit permission is obtained from the person deemed to be the head of the household. Usually the grandmother gives consent during daytime. Consent makes it possible for the lecturer and students to go through a home and inspect the fridge, kitchen and cupboards in order to determine if there is enough nourishment and if there is electricity in the house.

Unintentional stockpiling of medicine, especially ARVs, were found in homes. The change agent is the grandmother or mother of the household, who disposes of unused medications by dumping it in the garbage when “spring cleaning”. Medication was stored in the fridges and cupboards usually in a big container. Concerningly, even mixed antibiotic regimes were not completed, it was used up to a point where a child showed no more visible symptoms and then left to be used for future illnesses.

The community was unaware that mixed antibiotics and other pharmaceuticals lost their efficiency after reaching the expiration date. Stockpiling of pharmaceuticals and disposal thereof in household garbage systems is a big problem in developing and underdeveloped countries. Those residents who have the privilege of a toilet, flush unused medications down the toilet. The improper disposal of unused medications has the potential to harm the environment, wildlife, and humans. Thus, this information need to be incorporated in education systems and greater awareness must be made at community health care centres.

Figure 18: Dr Rina Muller, carrying out home visits investigating the handling and discarding of unused ARVs in rural households in the North West province.

Figure 19: Student nurse educates community health workers on the handling of medication. This information can then be translated back to community members during home visits.

5.5 POLICY WORKSHOP

On the 29th and 30th November 2018, the AUTHeR and NWU held an 'Emerging and Persistent Contaminants / Pathogens: Risk assessment, quantification and fate of HIV ARVs in Water Resources' policy brief writing workshop. The workshop was presented by a communications strategist and researchers from the NWU, free-of-charge, for delegates from government departments and selected stakeholders on how to summarise research results into a policy brief. A policy brief is a very specific summary of the crucial empirical research results and is aimed at government policymakers and others that influence and help formulate the policy. During the two-day workshop, the delegates were able to translate the results from the 'Emerging and Persistent Contaminants / Pathogens: Risk assessment, quantification and fate of HIV ARVs in Water Resources' project into a one-page policy brief.

The delegates therefore effectively summarised, gave context, causes and effects of the current problem of HIV-ARVs in water resources, and concluded with important recommendations to improve the current social and environmental situation. So also, did they effectively illustrate a call onto all health practitioners towards awareness, engagement and advocacy of responsible discarding practices, regarding medication in efforts towards a healthier environment, which formed part of the outcomes of CHAPTER 2:. Subsequently, delegates gained an essential skill in knowledge translation.

CHAPTER 6: CONCLUSION

The absence of an effective cure to combat HIV/AIDS ensures the continued usage of strong therapeutic drugs to suppress and alleviate symptoms. This in turn ensures ART and thereby the foundation of ARV pollution. However, this research has highlighted that the intersectionality of HIV expands into natural resources and that ARV pollution co-exists with numerous other social and health consequences. The dearth of a cure therefore places research focus on environmental relief and sustainability. This study has brought to light that by understanding and improving the social and health implications of ARVs in South Africa, researchers might be able to improve environmental conditions as well.

However, solely relying on statements regarding end-of-pipe solutions that are often obvious and easy to hide behind are simplistic and not reflecting holistic reality. We demonstrated the critical intersections between the need to consume pharmaceuticals by PLWHA, the need to protect their dignity and confidentiality, the onus placed on PLWHA to adhere to prescriptions, the need to supply them adequately and timely with medication and health services, better understand the various social, psychological, psychiatric, and household constraints faced by PLWHA, reduce accumulation and the discard and waste, reduce off-label use, and to strengthen the understanding of ecosystem services at a scale wider than clinics.

An already stressed environment, inadequate waste management (solid and wastewater), social practices, and a strained health system, forced by the relentless need to distribute and adhere to antiretroviral therapy, all contribute towards environmental pollution, poverty and social tensions (including stigma, crime, and corruption). Consequently, the combination of these factors most likely burdens society, infrastructure, environment, and slows the alleviation of poverty.

It is a moral and historic obligation to the more than 39 million people who have died from this disease to relieve as far as possible the burdens placed on PLWHA (another 39 million), their families, and communities, and to reduce transmission to those not yet affected, from the hard lessons we have learned. South Africa have subscribed to the UNAIDS 90-90-90 strategy to improve HIV/AIDS management and quality of life. To reiterate;

- By 2020, 90% of all people living with HIV will know their HIV status.
- By 2020, 90% of all people with diagnosed HIV infection will receive sustained antiretroviral therapy.
- By 2020, 90% of all people receiving antiretroviral therapy will have viral suppression.

It is inevitable that environmental considerations be accorded a lesser importance than poverty alleviation and disease prevention and management when dealing with emergencies. However, with this project we have now illustrated the links between the strategies employed to combat and manage the disease with a healthy, safe, and functioning ecosystem and other services. The protection of the environment, the management of the disease, and the moral obligations we have towards people living with HIV and AIDS, are irrevocably linked. Current and future health management should therefore mainstream the environment in strategy, planning, execution, and monitoring for optimal welfare for all.

6.1 FINAL RECOMMENDATION

- The NWU research team have developed methods and knowledge on how the characterise the insidious problematics concerning HIV antiretrovirals on a regional scale for a specific disease. We have learned many lessons and gained tremendous experience. However, HIV antiretrovirals and the disease condition are not the only pharmaceutical and disease combinations that will result in environmental pollution. Although some of what we report is generic to the entire pharmaceutical

spectrum, there are many situations that we do not know and understand, especially within a South African and African context. More studies are being published on the environmental side of pharmaceutical pollution in Africa. However, an integrated assessment as we have undertaken has nowhere been done. We therefore suggest that a much larger study, based on the experience and expertise developed by the current study would be appropriate for South Africa.

- The science of pharmaceuticals in the environment is developing at a rapid pace. New findings on, inter alia, health and environmental impacts, risk assessments, analytical techniques, and mitigation measures are published almost daily. It is also likely that guideline values for concentrations of pharmaceuticals in water and food will be developed soon and implemented or negotiated by authorities and international agencies. It would be incumbent for South Africa and the Water Research Commission to keep abreast of these developments and thereby provide guidance to local, regional, and national authorities, as well as water supply companies. This may be achieved by commissioning an annual summary report.

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APPENDIX A: CLINICAL STAGES OF HIV AND AIDS

Table 25: Clinical stages of HIV/AIDS as defined by WHO (2007).

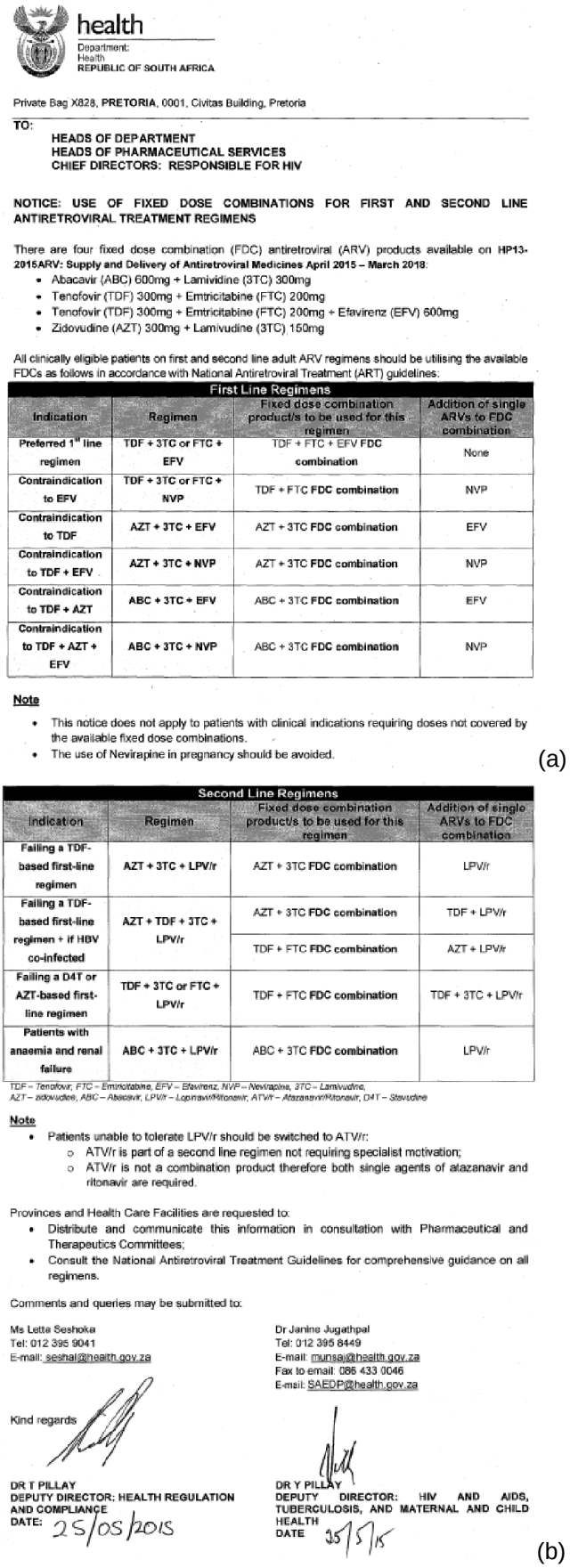
WHO Clinical Staging of HIV/AIDS for Adults and Adolescents

Clinical Stage	Clinical conditions or symptoms
Primary HIV infection	Asymptomatic Acute retroviral syndrome
Clinical stage 1	Asymptomatic Persistent generalised lymphadenopathy
Clinical stage 2	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	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	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 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 *Salmonella* 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: World Health Organization. 2007. WHO Case Definitions of HIV for Surveillance and Revised Clinical Staging and Immunological Classification of HIV-Related Disease in Adults and Children.

APPENDIX B: ART REGIMES SOUTH AFRICA.



health
Department:
Health
REPUBLIC OF SOUTH AFRICA

Private Bag X828, **PRETORIA**, 0001, Civitas Building, Pretoria

TO:
HEADS OF DEPARTMENT
HEADS OF PHARMACEUTICAL SERVICES
CHIEF DIRECTORS: RESPONSIBLE FOR HIV

NOTICE: USE OF FIXED DOSE COMBINATIONS FOR FIRST AND SECOND LINE ANTIRETROVIRAL TREATMENT REGIMENS

There are four fixed dose combination (FDC) antiretroviral (ARV) products available on **HP13-2015ARV: Supply and Delivery of Antiretroviral Medicines April 2015 – March 2018**:

- Abacavir (ABC) 600mg + Lamividine (3TC) 300mg
- Tenofovir (TDF) 300mg + Emtricitabine (FTC) 200mg
- Tenofovir (TDF) 300mg + Emtricitabine (FTC) 200mg + Efavirenz (EFV) 600mg
- Zidovudine (AZT) 300mg + Lamivudine (3TC) 150mg

All clinically eligible patients on first and second line adult ARV regimens should be utilising the available FDCs as follows in accordance with National Antiretroviral Treatment (ART) guidelines:

First Line Regimens

Indication	Regimen	Fixed dose combination product/s to be used for this regimen	Addition of single ARVs to FDC combination
Preferred 1st line regimen	**TDF + 3TC or FTC + EFV**	TDF + FTC + EFV **FDC combination**	None
Contraindication to EFV	**TDF + 3TC or FTC + NVP**	TDF + FTC **FDC combination**	NVP
Contraindication to TDF	**AZT + 3TC + EFV**	AZT + 3TC **FDC combination**	EFV
Contraindication to TDF + EFV	**AZT + 3TC + NVP**	AZT + 3TC **FDC combination**	NVP
Contraindication to TDF + AZT	**ABC + 3TC + EFV**	ABC + 3TC **FDC combination**	EFV
Contraindication to TDF + AZT + EFV	**ABC + 3TC + NVP**	ABC + 3TC **FDC combination**	NVP

Note

- This notice does not apply to patients with clinical indications requiring doses not covered by the available fixed dose combinations.
- The use of Nevirapine in pregnancy should be avoided.

(a)

Second Line Regimens

Indication	Regimen	Fixed dose combination product/s to be used for this regimen	Addition of single ARVs to FDC combination
Failing a TDF-based first-line regimen	**AZT + 3TC + LPV/r**	AZT + 3TC **FDC combination**	LPV/r
Failing a TDF-based first-line regimen + if HBV co-infected	**AZT + TDF + 3TC + LPV/r**	AZT + 3TC **FDC combination**	TDF + LPV/r
		TDF + FTC **FDC combination**	AZT + LPV/r
Failing a D4T or AZT-based first-line regimen	**TDF + 3TC or FTC + LPV/r**	TDF + FTC **FDC combination**	TDF + 3TC + LPV/r
Patients with anaemia and renal failure	**ABC + 3TC + LPV/r**	ABC + 3TC **FDC combination**	LPV/r

TDF – Tenofovir, FTC – Emtricitabine, EFV – Efavirenz, NVP – Nevirapine, 3TC – Lamivudine, AZT – zidovudine, ABC – Abacavir, LPV/r – Lopinavir/Ritonavir, ATV/r – Atazanavir/Ritonavir, D4T – Stavudine

Note

- Patients unable to tolerate LPV/r should be switched to ATV/r:
  - ATV/r is part of a second line regimen not requiring specialist motivation;
  - ATV/r is not a combination product therefore both single agents of atazanavir and ritonavir are required.

Provinces and Health Care Facilities are requested to:

- Distribute and communicate this information in consultation with Pharmaceutical and Therapeutics Committees;
- Consult the National Antiretroviral Treatment Guidelines for comprehensive guidance on all regimens.

Comments and queries may be submitted to:

Ms Letta Seshoka
Tel: 012 395 9041
E-mail: seshal@health.gov.za

Dr Janine Jugathpal
Tel: 012 395 8449
E-mail: munsaj@health.gov.za
Fax to email: 086 433 0046
E-mail: SAEDP@health.gov.za

Kind regards

DR T PILLAY
DEPUTY DIRECTOR: HEALTH REGULATION AND COMPLIANCE
DATE: 25/05/2015

DR Y PILLAY
DEPUTY DIRECTOR: HIV AND AIDS, TUBERCULOSIS, AND MATERNAL AND CHILD HEALTH
DATE 25/5/15

(b)

Figure 20: Notice from the National Department of Health regarding the use of fixed dose combinations for first- and second-line antiretroviral treatment regimes.

APPENDIX C: ART GUIDELINES SOUTH AFRICA.

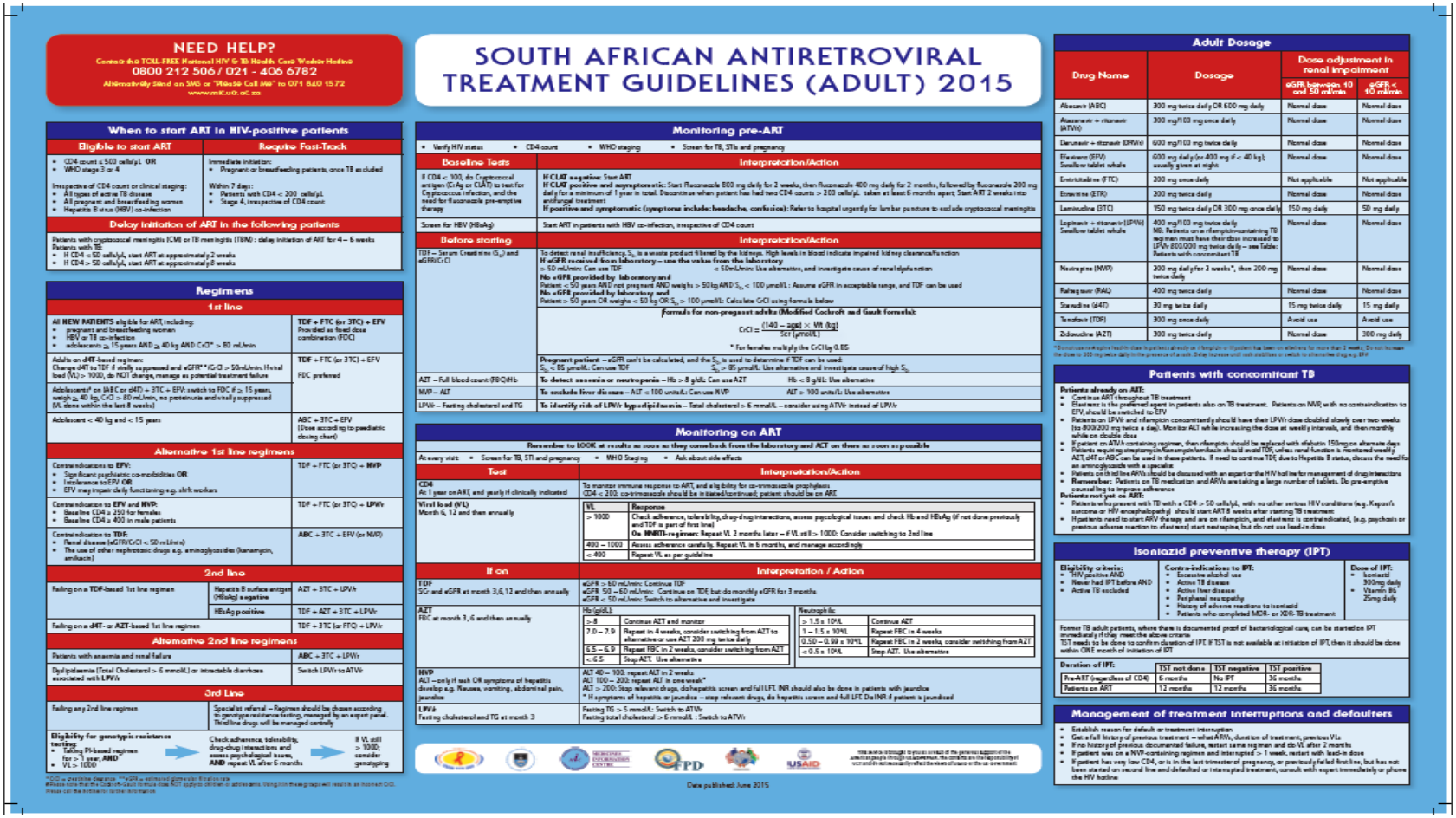


Figure 21: Antiretroviral treatment guidelines for adults in South Africa 2015.

APPENDIX D: SOUTH AFRICAN NATIONAL GUIDELINES FOR COMMENCING ANTIRETROVIRAL THERAPY.

Table 26: Eligibility criteria fir commencing ARVT in SA (Rossiter, 2014).

ELIGIBILITY CRITERIA
CD_4 count ≤350 cells/microliter regardless of stage or symptoms*
WHO stage 3 or 4 or other serious morbidity regardless of CD_4 count (Cryptococcal meningitis – defer ART for 4-6 weeks).
TB regardless of CD_4 count (TB meningitis-defer ART for 4-6 weeks).

*The WHO has moved the threshold for ART initiation to 500 cells/microliter.

APPENDIX E: CLASSIFICATION OF ANTIRETROVIRAL DRUGS.

Table 27: Classification and commentary of various ARV drug classes.

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	Efavirenz is the preferred NNRTI for use with TB treatment. There is a moderate reduction in nevirapine concentrations. Leading-in dosing should be omitted. Monthly ALT monitoring is recommended.
Protease inhibitors	Dramatic reduction of concentrations of all PIs and none can be used without dose adjustment. In adults, limited evidence supports dose adjustments from the following agents (regular ALT monitoring essential: ● 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. ● Saquinavir 400 mg 12 hourly + ritonavir 400 mg 12 hourly. In children: ● Add ritonavir to match the lopinavir dose. Doubling the dose of lopinavir/ritonavir is not recommended as it results in sub therapeutic lopinavir concentrations

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

Table 28: 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.	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).	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. DianeTM 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	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
Pricing management	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	Management of chronic disease List prescribed minimum benefits and non-chronic disease list conditions Daily real-time benefit validation

APPENDIX G: PHARMACEUTICAL CLASSIFICATION

Table 29: Classification of various pharmaceuticals.

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. Others
1.5. Antipsychotics	1.5.1. Phenothiazines 1.5.2. Butyrophenones 1.5.3. Others
1.6. Anti-epileptics	

APPENDIX H: LIST OF PROVINCES AND DISTRICTS

Table 30: List of the different provinces and districts.

Province	Name of district
Eastern Cape	Alfred Nzo district
	Amatole district
	Chris Hani district
	Joe Gqabi district
	OR Tambo district
	Sarah Baartman district
Free State	Fezile Dabi district
	Lejweleputswa district
	Mangaung Metropolitan municipality
	Thabo Mofutsanyana district
	Xhariep district
Gauteng	City of Ekurhuleni
	City of Johannesburg
	City of Tshwane
	Sedibeng district
	West Rand district
KwaZulu-Natal	eThekwini district
	Harry Gwala district
	iLembe district
	Ugu district
	uMgungundlovu district
	uMkhanyakude district
	uMzinyathi district
	Uthukela district
	uThungulu district
	Zululand district
Limpopo	Capricorn district
	Mopani district
	Sekhukhune district
	Vhembe district
	Waterberg district

Mpumalanga	Ehlanzeni district Gert Sibande district Nkangala district
Northern Cape	Frances Baard district John Taolo Gaetwewe district Namakwa district Pixeykasema district ZF Mgcawu district
North-West	Bojanala Platinum district Ngakamodiri Moleme district Dr Kenneth Kaunda district Dr Ruth Segomotsi Mompati district
Western Cape	West Coast district Cape Winelands district Overberg district Eden district Central Karoo district

APPENDIX I: VALIDATION PROCESS TO ENSURE THE VALIDITY AND RELIABILITY OF DATA EMPLOYED BY THE PBM COMPANY

Table 31: Validation process to ensure the validity and reliability of data employed by the PBM Company.

Validation process	Examples
Clinical management	Ingredient duplication Maximum daily dose exceeded Therapeutic duplication Drug-drug interactions Drug-allergy interactions Drug-age interactions Drug-gender interaction Drug inferred health state interactions
Data integrity validation and eligibility management	Claim field format checks Duplicate check Provider validation checks Member validation checks Verify dependent code Waiting period check
Formulary management	Managing PMB, CDL and non-chronic disease list conditions Daily real-time benefit validation

Medicine utilisation management – checked at active ingredient level against the patient history)	Fill limitations (e.g. one fill per 26 days for chronic medication.) Refill limitations (e.g. only twelve fills per year for chronic medication) Product quantity limits (e.g. 200 analgesics in 365 days cycle) Product pre-authorizations (e.g. anti-retroviral 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. birth-control tablets limited to females only.) Invalid prescriber speciality (e.g. Diane TM prescribed by dermatologist) Board category exclusions (e.g. soaps/shampoos are excluded) Specific product excluded (e.g. urinary antiseptics) Waiting periods (e.g. as advised by scheme, specific to patient)
Pricing management	Apply reference pricing (e.g. therapeutic- and generic reference pricing was applied, i.e. formulary-based pricing for chronic diseases.)

APPENDIX J: BRIEFING NOTE OF HIV-ARVS IN WATER RESOURCES

NWU®

WATER RESEARCH COMMISSION

MINISTERIAL BRIEF

BRIEFING NOTE ON HIV-ARVs IN WATER RESOURCES TO THE MINISTERS OF WATER AND SANITATION, ENVIRONMENTAL AFFAIRS & HEALTH

Departments of Water and Sanitation, Environmental Affairs and Health

His honourable Mr. Guglie Nkwinti, Her Honourable Ms. Nomvula Mokonyane, and His Honourable Dr. Pakishe Aaron Motsoaledi

Purpose

The purpose of this brief is to inform the Ministers about an ongoing study titled: *Risk assessment, quantification, and fate of HIV-ARVs in water resources*. *HIV-ARVs* belong to the group known as Contaminants of Emerging Concern (CECs), which are compounds that currently do not have regulation associated with them and therefore are not monitored. However, due to their continuous production, lack of appropriate disposal, constant input into the environment and presence in water resources albeit in small concentrations, there is sufficient imperative to understand the possible negative effects on the environment and human health. CECs also p[illegible]e chal[illegible]ut across both water, environment an[illegible]ealth sphe[illegible]s and[illegible]ghlight the[illegible]cessary integration in those three s[illegible]eres in ord[illegible]o d[illegible]gn relevan[illegible]olicy fo[illegible] their effective management

Current situation

By July 2019 the *Risk assessment, quantification, and fate of HIV-ARVs in water* resources report will be published by the Water Research Commission. It is anticipated that the media will focus on the following findings in this report:

- Levels of ARVs in water sources.
- ARV drug resistance and compliance.
- (Im)proper ARV discarding compliance.
- Insufficient wastewater treatment.

Background

The therapeutic benefits of antiretroviral therapy (ART) against the human immunodeficiency virus (HIV), as well as its side effects, has been well researched and documented. However, a more recent public health concern that is presenting itself for urgent attention and research is the possibility of large amounts of antiretroviral drugs (ARVs) that enters water resources through surface runoff as well as wastewater treatment plant effluents.

South Africa (SA) has one of the largest HIV epidemics globally (about 18.8% adult HIV prevalence; 7.2 million people living with HIV (PLWH) in 2017). SA supports 90% of PLWH to receive sustained ART by 2022. This implies scaled-up access to ART through decentralised uninterrupted antiretroviral (ARV) supplies, supplying large quantities to resource-poor communities.

The South African programme has been benchmarked as the largest global ART treatment programme, providing ART to 20% of the global population of PLWH. It is expected that the vastness and success of these programs will increase in the years to come, due to the fact that the World Health Organization (WHO) recommends that any person diagnosed with HIV be put on an ART regime, immediately, regardless of their CD4 count. Furthermore, UNAIDS has proposed the 90x90x90 strategy/goal for 2020. This goal aims to ensure that 90% of all PLWH will:

I) know their status;
II) are receiving sustained ART; and,
III) those who are receiving therapy, will have a viral suppression.

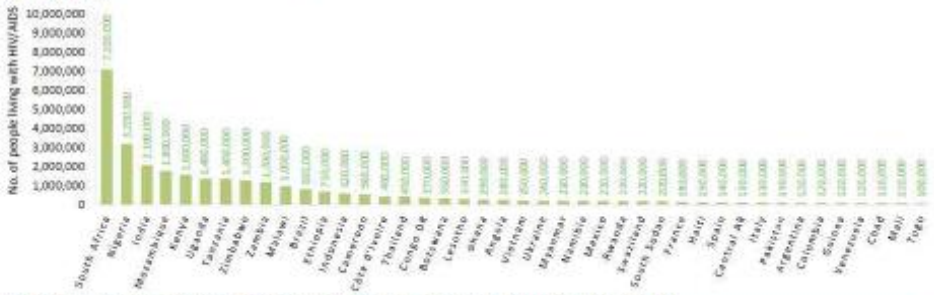


Figure 1 Countries ranked in terms of the number of people living with HIV/AIDS in 2016.

Due to South Africa's large ART programme, it is estimated that the number of ARVs consumed by PLWH in South Africa could easily reach 4.32 tons per day, amounting to approximately 1.1 - 1.4 million kilograms per annum. Bioavailability values indicate that none of the current ARVs is 100% absorbed within the bloodstream and that ARVs are excreted unchanged with only a small number converted to metabolites. Hence, it is estimated that roughly one-third of the consumed ARVs are released into the environment on an annual basis, via human excretion (urine and faeces). This estimation can be even higher if taking into consideration the improper disposal of unused or expired medication, which is often seen in these communities, due to a lack of take-back policies for medication.

Unintended environmental impact with harmful ARV contamination as active pharmaceutical ingredients was detected during the *Risk assessment, quantification and fate of HIV-ARVs in water resources study* in water sources countrywide. ARVs are evolving contaminants (environmental unregulated compounds). At present there remains limited knowledge of environmental toxicity, risking adverse effects on ecosystems and viral re[illegible]hese co[illegible]rrent water treatment systems are [illegible]able to re[illegible]ve A[illegible]/s from c[illegible]aminate water successfully. Since [illegible]vironmenta[illegible]RV r[illegible]ase conce[illegible] potenti ecosystem alterations and [illegible]ral resistanc[illegible]rom [illegible]nal chro[illegible] exposure to trace levels [illegible] multiple AR[illegible], en[illegible]vironmen[illegible]steward and appropriate ARV disc[illegible]ding practi[illegible] are [illegible]tivated.

Methods

The HIV-ARV II Research Group investigates the sources, pathways, behaviour, fate, and impact of antiretrovirals (ARVs) within the environment, as well as relevant sociological and health aspects. Therefore, nine objectives were purposed to fulfill this aim. The first was to ascertain and document in a concise manner the present usage patterns and quantities of antiretrovirals, as well as to predict from historic data, potential impending scenarios. Next was to improve the sampling, extraction, and analytical practices to determine spatial and temporal patterns of antiretrovirals in natural and drinking water. Possible biological impacts are also investigated using cell-based bio-assays, and exposure testing with bacteriophages and freshwater snails. Furthermore, a human health risk assessment is conducted based on the data generated. Through the biopsychosocial determinants of health, the antiretroviral pathways from human consumption were developed and assessed within a health perspective. Finally, the disruptive link between antiretroviral consumption challenges to health systems is investigated.

Results and Conclusion

The Research Group has developed analytical methods with which the presence, concentrations, and spatial and temporal changes have been elucidated. Almost all ARVs have been found in natural and some in drinking water, but none in fish. The group also found effects on freshwater snails and viruses. This research highlighted that the intersectionality of HIV expands also into natural resources and that scale-up of ARVs through t[illegible]e-back strategies a[illegible]surrence is essential.

Rec[illegible]mendations

Th[illegible]llo[illegible]ng recommendation[illegible]re made regarding the results:

- Reassess all pharmaceutical discarding practices.
- Develop different sustainable discarding practices.
- Enforce the implementation of different sustainable disposal practices through legislation.
- Develop different measurement and evaluation systems to assess the effectiveness and efficiency of sustainable disposal practices.
- Improve wastewater treatment plants to reduce the releases of ARVs to water, thereby reducing human exposure and impacts on ecosystems.

For more information:
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Compiled and prepared by the Africa Unit for Transdisciplinary Health Research (AUTHeR), a research entity in the Faculty of Health Sciences, North-West University (NWU); and the Water Research Commission (WRC).

http://health-sciences.nwu.ac.za/auther

References: https://goo.gl/4H5s2v

Yours sincerely,
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Figure 22: Briefing note on HIV-ARVs in water resources to the ministers of water and sanitation, environmental affairs and health (draft).

APPENDIX K: RESPONSIBLE DISCARDING INFOGRAPHIC HSPCA

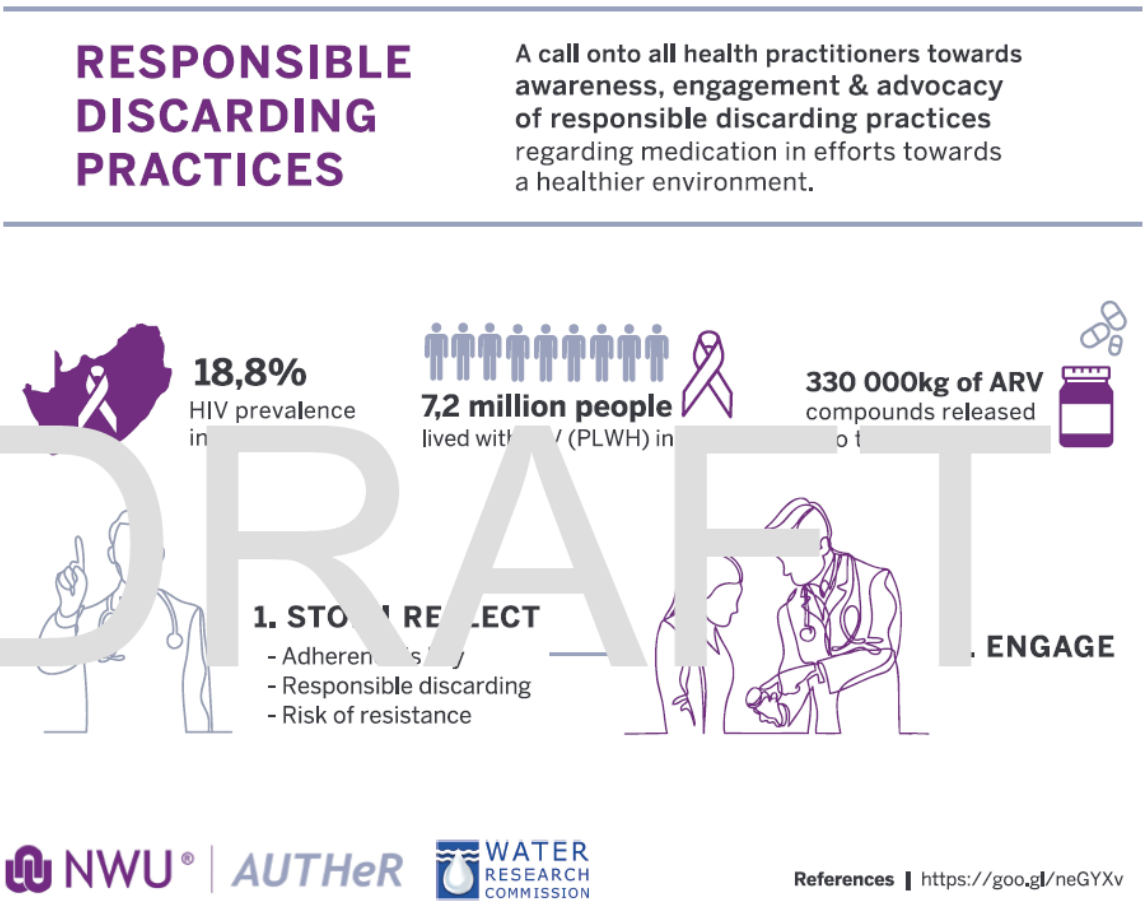

Figure 23: Policy draft of responsible discarding infographic.

END VOLUME 2