TREATMENT AND REGIMEN CHANGE IN A COHORT OF HIV POSITIVE PATIENTS ON ANTI-RETROVIRAL TREATMENT AT TSHEPANG WELLNESS CLINIC,

DR GEORGE MUKHARI HOSPITAL

BY

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RESEARCH DISSERTATION SUBMITTED IN FULFILLMENT OF THE REQUIREMENTS OF THE DEGREE OF

MASTER OF PUBLIC HEALTH AT THE SCHOOL OF PUBLIC HEALTH, FACULTY OF HEALTH SCIENCES,

UNIVERSITY OF LIMPOPO.

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2010

DECLARATION

I N.M.Moeketsi declare that **Treatment and regimen change in a cohort of HIV positive patients on anti-retroviral treatment at Tshepang wellness clinic, Dr George Mukhari Hospital**' hereby submitted to the University of Limpopo for the degree of Master of Public Health has not previously been submitted by me for a degree at this or any other university; that is my work in design and in execution, and that all material contained herein has been duly acknowledged.

N.M.Moeketsi

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Signature of candidate

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DEDICATION

With this dissertation I would like to thank our Almighty God for His grace, strength and protection. Even though there were challenges in my journey from the beginning until now, he showed me that he was always there for me. I would once more like to thank my wonderful family for being there for me with their understanding and unconditional support during my studies. I know sometimes it was tough for them to put up with me but still they were always there for me. I will always be grateful for that because I wouldn't have achieved this without them.

ACKNOWLEDGEMENTS

I sincerely thank my supervisor Prof Supa Pengpid for her continuous guidance, and support throughout the period of conducting this research. I would also like to acknowledge contribution made by Ms Madiba on my studies and all the lectures from the School of Public Health, University of Limpopo, at Medunsa campus.

I wish to extend my deepest gratitude to Mr. Dungu, CEO of Dr George Mukhari Hospital and Project Manager of Tshepang Wellness Clinic and support from the clinic staff for making my life easy during data collection of my study.

Finally, I would like to thank my wonderful husband and my family for their unconditional support throughout my studies. They have been my pillar of strength and they made it possible for me to face challenges that come with being a student, a mother to my children and a wife to my husband.

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LIST OF ACRONOMY AND ABBREVIATION

MNPC - Medunsa National Pharmacovigilance Centre

ARV - Antiretroviral

ADR - Adverse drug reaction

OTC - Over the counter

LFT - Liver function test

NRTI -Non nucleoside reverse transcriptase inhibitor

d4t - Stavudine

ddi - didanosine

PIs - Protease inhibitors

NNRT -Non nucleoside reverse transcriptase inhibitor

NVP -Nevarapine

PLWHA - People living with HIV and AIDS

WHO –World Health Organization

AIDS –A cquired Immune Deficiency Syndrome

ART -Antiretroviral therapy

AZT -Zidovudine

EFV - Efavirenz

HAART -Highly active antiretroviral therapy

HIV - Human Immunodeficiency Virus

PLWHA - People living with HIV/AIDS

PMTCT -Prevention of mother-to-child transmission

RTV -Ritonavir

STI -Sexually Transmitted Infection

TB -Tuberculosis

VL -Viral Load

DEFINITION OF TERMS

- Pharmacovigilance - is a science relating to detection, assessment, understanding, and prevention of adverse effects. http://www.en.wikipedia.org/wiki/Pharmacovigilance

- Retrospective – backwards looking review of the characteristics of a group of individual in relation to morbidity. Martin A. et.al.(Fifth Edition) Oxford Concise Medical Dictionary

- Prospective – a study in which the subjects are identified and then followed forward in time. http://www.medterms.com/script/main/art.asp?articlekey=24050

- Toxicities – degree of which something is poisonous.

  Martin A. et.al (Fifth Edition) Oxford Concise Medical Dictionary

- Peripheral Neuropathy – a problem with the functioning of the nerves outside the spinal cord, symptoms may include numbness, weakness, burning pain and loss of reflex. http://www.medterms.com/script/main/art.asp?articlekey=4838

- Lipodystophy – Any disturbance of fat metabolism or any distribution of fat in the body. Martin A. et.al (Fifth Edition) Oxford Concise Medical Dictionary

- Lipoatrophy – loss of subcutaneous fat.
  http://www.en.wikipedia.org/wiki/Lipoatrophy

- Lactic Acidosis – a compound that form in the cells as the end products of glucose metabolism in the absence of oxygen.

  Martin A. et.al (Fifth Edition) Oxford Concise Medical Dictionary

- Mylosuppression – a condition in which bone marrow activity is decreased, resulting in fewer red blood cells, white blood cells and platelets.
  http://www.medical-dictionary.thefreedictionary.com/myelosuppressive

- Hypersensitivity – extreme and abnormal sensitivity

  www.answers.com/topic/hypersensitivity

- Hepatotoxicity – damaging or destroying liver cells. Martin A. et.al (Fifth Edition) Oxford Concise Medical Dictionary

ABSTRACT

Background: Antiretroviral therapy led to a revolution in care of patients with HIV/AIDS in a developed world. Treatment is not a cure but it also presented with new challenges of side effects, drug resistance and it also dramatically reduces rate of mortality and morbidity and it also improves quality of life to people living with HIV/AIDS, and it also now considered as manageable chronic diseases. **Aim:** Aim of the study is to establish and describe reasons for treatment and regimen change in a cohort of HIV positive patients on ART enrolled in the pharmaco-epidemiological survey at Tshepang wellness clinic. **Objectives:** is to determine reasons for treatment and regimen change, types of treatment and regimen change among patients on ART who are enrolled in pharmaco-epidemiological survey at Tshepang wellness clinic. **Design and Methods:** Study is a retrospective cohort study, and sample size of 301 medical records of a cohort of HIV positive patients on ARVs enrolled in a longitudinal pharmaco-epidemiological survey from November 2006-May 2007 reviewed. Data extraction tool used to collect data and software called SPSS 17.0 used to analyze data and relevant themes were extracted to determine distribution of variables.

Results: Results of this study indicated that 91 (85%) were males and (87.8%) 191 were females. Age was grouped as teenagers (15-25yrs), young adults (26-49yrs) and adults (50-70yrs). Results also shows reasons of treatment and regimen change of which majority of patients 134(44.8%) changed due toxicity followed by 16 (5.4%) who changed because of pregnancy, and the other 4(1.3%) changed because of resistance, and the last 2(0.7%) which are regarded as minorities change because of T.B.

Conclusion and Recommendations: Results shows that majority of pharmacovigilance patients were initiated Regimen 1 compared to other regimens. Toxicity appear as the main reason of treatment and regimen change on this study as 140(46.4%) reported toxicities (peripheral neuropathy, lactic acidosis, lipodystrophy and lipoatrophy). Implementation of monitoring of adherence needed for prevention of resistance and virological failure.

CHAPTER I

INTRODUCTION AND BACKGROUND

1.1 **Introduction**

According to WHO/UNAIDS/UNICEF (2009) each year around 2.7 million more people become infected with HIV and 2 million die of AIDS. Statistics for the end of 2008 indicate that around 33 million people are living with HIV, the virus that causes AIDS.

Although HIV and AIDS are found in all parts of the world, some areas are more infected than others. The worst affected regions are Sub Saharan Africa, where in a few countries more than one in five adults is infected with HIV. The epidemic is spreading most rapidly in Eastern Europe and Central Asia, where the number of people living with HIV increased to 67% between 2001 and 2008 (WHO/UNAIDS/ UNICEF, 2009).

When AIDS first emerge, no one could have predicted how the epidemic would spread across the world and how many millions of lives would change. AIDS can devastate families, communities and whole continents. We have seen the epidemic shock decades off countries national development, widen the gulf between rich and poor nations and push already stigmatized group closer to margins of society. We are living in an international society, and HIV became the first truly international epidemic, easily crossing oceans and boarders.

More than twenty five million people around the world have died of AIDS related disease. In 2008, 2.7 million people were newly infected with HIV, and 2 million men, women and children lost their lives. Thirty-three million people around the world are now living with HIV. It is disappointing that the global numbers of people infected with HIV continue to rise, despite the fact that effective prevention strategies already exit (WHO/UNAIDS/ UNICEF, 2009).

It is in Africa, in some of the poorest countries in the world, that the impact of the virus has been most severe. At the end of 2007, there were 9 countries in Africa where more than one tenth of the adult population aged 15-49 yrs was infected with HIV. In three countries, all in the southern corner of the continent, at least one adult in five is living with virus. In Botswana, a shocking 23.9% of adults are now infected with HIV, while in South Africa, 18.1% are infected. With a total of around 5.7 million infected, South Africa has more people living with HIV than any other country (WHO/UNAIDS/UNICEF, 2009).

Rates of HIV infection are still extremely high in sub Saharan Africa, and an estimated 1.9 million people in this region became newly infected in 2007. This means that there are now an estimated 22 million Africans living with HIV/AIDS. In this part of the world, particularly, women are disproportionately at risk. As the rate of HIV infection in general population raises, the same patterns of sexual risk results in more new infections simply because the chances of encountering an infected partner became higher (WHO/UNAIDS/UNICEF, 2009).

According to AIDS foundation of South Africa (2008), a change of leadership finally saw the tide turning towards provision of anti-retroviral therapy (ART) for people living with HIV in 2008. The South African Government first embarked upon an Operational Plan to provide to people with HIV through the public health sector in November 2003. This was achieved only after years of intensive lobbying, driven largely by the treatment Action Campaign and supported by trade unions, civil society, including American Foreign Service Association (AFSA) and international activists and agencies. The plan was rolled out slowly, obstructed both by the Health Minister and by provincial leaders. The criteria for access to ART included that a persons CD4 count (which measures the number of disease fighting cells in the blood) should be below 200. This means that many people were sick by the time they qualified for ART and many died waiting to start the medication. By early 2005 according to AIDS Foundation of South Africa (2008) only some 30 000 patients were receiving treatment through the state programme. By end of 2008, fewer than 600 000 people were being treated. However, the year 2008 saw a turnaround in the

government commitment to dealing effectively with the HIV and AIDS epidemic. A new minister of Health was appointed who pledged to implement a National Strategic Plan (NSP) that included a target of providing 80% of all people in need of antiretroviral (ARV) drugs with treatment by 2011(AIDS Foundation of South Africa, 2008).

Undoubtedly the most significant recent development in the HIV/AIDS struggle in South Africa was the decision taken by Government in 2003(AIDS Foundation South Africa, 2008) to provide antiretroviral (ARV) therapy in the public health sector as part of the Operational Plan for Comprehensive HIV and AIDS Care, Management and Treatment for South Africa.

This decision gives new hope to thousands of people who require this treatment to reduce morbidity levels and defer premature death. However this decision brings with it a new set of challenges, these included overcoming capacity constraints within the public health sector and issues of treatment literacy for patients to ensure treatment compliance and avoidance of the emergence and spread of drug resistance strains of the virus (AIDS Foundation South Africa, 2008).

Patient adherence in taking their medication is the key to success of this programme: (AIDS Foundation South Africa, 2008), patients are required to take three types of tablets twice a day at the same time each day for the rest of their lives. Treatment preparedness and support for patients commencing ARV therapy is therefore imperative.

As ARV therapy is a life time commitment it is vital that patients in the earlier stages of HIV be educated on wellness management and encouraged to keep themselves healthy for as long as possible so that their CD4 counts remain high and referring the need to commence ARV therapy. The office of the national manager of the ARV programme released the national patient numbers by province and site for the first time in January 2005 (AIDS Foundation South Africa, 2008). The statistics of AIDS Foundation South Africa showed that about 29 000 people were on ARV treatment

and more than 113 public sector facilities by that time. The figure for KwaZulu-Natal was 8467; Gauteng had nearly 10 000 patients on ARVs, Northern Cape 515 and North West nearly 2800. Mpumalanga had almost 1000 patients on ARVs by the end of December, Free State 945 and Limpopo just 729, the Western Cape nearly 6 200 (AIDS Foundation South Africa, 2008).

The discovery of highly active antiretroviral(ARV) therapy(ART) and its introduction in the developed countries is considered by many to be one of the greatest success stories of modern medicine, and despite still critical concern regarding toxicity, adherence and widespread development of viral resistance. These concerns can not negate the dramatic reduction in HIV associated morbidity and mortality that have resulted from the widespread introduction of triple combination ART in the mid 1990s. According to World Health Organization (WHO) today ARV treated patients can generally anticipate survival as their prognosis leading a good quality life for many years (WHO, 2005).

The provision of safe, effective ART to the millions of individuals in need of resource constrained settings likewise expected to dramatically reduce HIV/AIDS related morbidity and mortality, improve quality of life, and increase social and political stability (WHO, 2005). The challenge is great, as HIV/AIDS has progressed largely unchecked in many parts of the world where the epidemic has been underestimated and shrouded in denial and stigma. About forty million people worldwide infected with HIV, an estimated 6 million people are in need of immediate, life sustaining ART. Yet only around 400,000 (WHO, 2005) people in low and middle income countries have access to such treatment. Most HIV infected individuals live in severely resource constrained settings, where the HIV epidemic continues to grow at a rate of 5 million infections per year (WHO, 2005).

The event of potent antiretroviral therapy (ART) in 1996 led to a revolution in the care of patients with HIV/AIDS in the developed world. Although the treatments are not a cure and present new challenges with respect to side effects and drug resistance, they have dramatically reduced rates of mortality and morbidity, have improved the

quality of life of people living with HIV/AIDS and HIV/AIDS is now perceived as a manageable chronic illness rather than plague (WHO, 2004).

Considerable progress has been made in providing global access to antiretroviral therapy, with three million people currently on antiretroviral drugs around the world (WHO, 2004). However the effectiveness of treatment programs, particularly in low and middle income countries, risks being compromised by problems related to toxicity, intolerance and drug-drug interactions. These adverse events, be the acute or chronic, mild or severe, are relatively common phenomena affecting both individual patients and public health, but are being only intermittently identified and scarcely systematically reported in low and middle income settings (WHO, 2004). Adverse reaction related to use of antiretroviral drugs may severely jeopardize confidence in the safety of these medicines and alter patient adherence to antiretroviral therapy, not only reducing the treatment efficacy with increased morbidity and mortality, but also reducing treatment programme effectiveness and increasing the risk of emergence of secondary drug resistance. New adverse events and toxicities are identified, as people live longer on ART. For these reasons there is an agent need to strengthen the science of pharmacovigilance for antiretroviral drugs.-by WHO Department of HIV and Medicine Policy (WHO, 2004).

1.2 Background and Rationale

Pharmacovigilance programme is an integral part of antiretroviral programme and globally the reporting of adverse drug reaction for all the medicine that has been poor, and remains limited in the case of antiretroviral agents (WHO, 2004). Health care professionals are more likely to identify and report adverse drug reaction if they have sufficient knowledge and ability to identify, manage and prevent such reaction, and this is what our pharmacovigilance trainer do to health care professionals especially to the sites that we are working with, so that they must not ignore adverse drug reaction.

According to Fischer (2004) long term ARV toxicity is recognized as a major threat to long term life prognosis and immediate quality of life of ARV patients. Health

authorities and healthcare providers rely on the pharmacovigilance system to obtain the required epidemiological data and manage insights required to deal with long term toxicity.

The Medunsa National Pharmacovigilance Centre (MNPC) is collaboration between the National Department of Health and the Medunsa Campus of the University of Limpopo, with a primary function of monitoring the safety of antiretrovirals (ARVs) used by adults HIV/AIDS patients countrywide. The pharmacovigilance centre started in September 2004 to improve patients' wellbeing through ensuring the safe and effective use of ARVs and other medicine used in HIV/AIDS patients. The MNPC liaise with 5 roll out sites or what is currently called wellness clinics in four provinces which includes Gauteng (Tshepang and Kalafong), Limpopo (Mankweng), North West (Rustenburg) and Mpumalanga (Witbank) with the aim to expand to 27 sites with 3 sites per province.

At the beginning, MNPC used to enroll up to 30 patients per week per site excluding Kalafong, which was only concentrated on the prospective follow up, and at the beginning most of the patients were changing from regimen 1a to 1d. But now according to Tshepang clinic (2008) statistics more than 10 000 enrolled in the clinic, and most of them are changing regimens from regimen 1a up to 1d and even regimen 2, but the most dominant regimen with majority of patients is regimen 1c. Based on these regimens my study will be concentrating on why HIV positive patients at Tshepang wellness clinic are changing treatment from one regimen to another, (reasons for treatment change).

A National Adverse Drug Reaction reporting database (NADR) which is compatible with the WHO Pharmacovigilance database was developed in 1974 known as Pharmaceutical Information and Pharmacovigilance Association. Adverse Drug Reaction (ADRs) reported from all centers are fed into an International Pharmacovigilance database, however the reporting of ADR globally for all the medicine has been poor, and remain limited in the case of antiretroviral agents. Health

professionals are more likely to identify and report adverse drug reaction if they have sufficient knowledge and ability to identify, manage and prevent such reaction. The training of health care professionals is a role that the MNPC has adopted and executed over the years the centre has been existence Fischer (2004). My study is concentrating on the identified adverse drug reaction documented on the patients' files by the health care staff, and then explanation will be given on how ADR (Adverse Drug Reaction) interact with a specific treatment, while pharmacovigilance concern is adverse drug reaction that should be reported, and the study main aim is to describe reasons of treatment and regimen change. During data collection all the adverse drug reaction reported by patients, most of them lead to treatment and regimen change (e.g. peripheral neuropathy, lactic acidosis etc), and those adverse effects/ reaction will automatically be my reasons for treatment and regimen change.

1.3 Problem statement

Tshepang wellness clinic receives accreditation to roll out ART in July 2004-and about 4000 patients are currently on ART according to statistics of Tshepang updated by data capture of the clinic- 23 September 2007.

ARVs suppress HIV replication and consequently delaying diseases progression, and also prolong and enhance the quality of life of people living with HIV and AIDS (PLWHA).Though the roll out of ARVs was a breakthrough for the people of South Africa, it brought with it a different challenge of dealing with numerous side effects of the drugs which may vary from one person to the next and range from mild and manageable to severe side effects. It has been documented that most patients experience minor side effects which are tolerated as patients continue to take drugs while other patients may experience severe and life threatening side effects requiring medication adjustment or complete discontinuation and change to a completely different drug regimen. The key to managing side effects is to know what to watch out for, and having a plan in place to respond if problems occur (Kocholla et al. 2007).

Tshepang wellness clinic is one of the largest and busiest ARV roll out centers in Gauteng province, the management of a large group of patients on ARVs was daunting task for the health professionals working in the same centre. It was crucial that a system to manage and monitor ARV side effects and morbidity be put in place and Tshepang wellness clinic and the MNPC developed the pharmaco-epidemiological survey. During November 2006 a cohort patients on ARVs was enrolled in a longitudinal pharmaco-epidemiological survey conducted by (Gaeme, 2006) to ensure drug safety standards are being performed.

About 500 patients were enrolled and retrospective reviews of their medical records were conducted to document side effects that are not identified during the trials of the drugs. From 2006 to March 2007 the cohort was then followed up prospectively and for each visit, and interview was conducted with the patient and medical record reviewed. Tshepang wellness clinic faces many challenges in the management and treatment of patients on ARVs, and concern during the survey was the high prevalence side effects among cohort, which included toxicities, pregnancies, poor adherence, resistance and treatment failure documented. Treatment failure was identified as one of the key challenges and one of the most prevalent in the cohort. ARV data- medication and dose, start date, stop date or change and if stopped or change reason must be indicated, and same applies to concomitant medication. During our Retrospective survey (500 selected patients) we noticed challenges of ARV's at Tshepang which are toxicities, pregnancies, poor adherence, resistance and treatment failure.

1.4 Aim

The aim of the study is to establish and describe reasons for treatment and regimen change in a cohort of HIV positive patients on ART enrolled in the pharmaco-epidemiological survey at Tshepang wellness clinic.

1.5 Re search questions

The research questions of this study are:

- What are the reasons for treatment change among patients on ART who are enrolled in the pharmaco-epidemiological survey at Tshepang clinic?
- What are the reasons for and types of treatment and regimen change among the study population?
- Is there a relationship between the patient's socio-demographic characteristics and treatment or regimen change?

1.6 Study objectives

The objectives of this study are:

1.6.1 To determine treatment and regimen change among patients on ART who are enrolled in pharmaco-epidemiological survey at Tshepang wellness clinic

1.6.2 To determine the types of treatment and regimen change among cohort of HIV positive patients on antiretroviral treatment at Tshepang Wellness Clinic Dr George Mukhari Hospital.

1.6.3 1.6.3 To determine reasons for treatment and regimen change among cohort of HIV positive patients on antiretroviral treatment at Tshepang Wellness Clinic Dr George Mukhari Hospital.

CHAPTER II
LITERATURE REVIEW

2.1. Introduction

This chapter discusses critically the review of some studies that describes reasons of treatment and regimen change of ARVs in HIV positive patients. Toxicity, resistance, treatment failure and adherence are some of the reasons for treatment change. Finally treatment interruption and drug interaction also highlighted as it also causes treatment or regimen change. This chapter is divided into 4 sections, of which first section highlight overview of treatment and regimen change, the second section provides information about reasons of treatment and regimen change, third section highlight treatment interruption and last section is about drug interaction.

Types of regimes according to National Antiretroviral treatment Guideline, National Department of Health South Africa (2004)

1a d4T / 3TC / efavirenz
1b d4T / 3TC / NVP
1c AZT/3TC/efavirenz
1d AZT/3TC/NVP
2 AZT / ddI / lopinavir / ritonavir

2.2. Overview of treatment and regimen change

There are many options for first line ART, but second line therapy is necessary for persons who fail first line treatment (Makison, Moing, Kouanfack, Laurent, and Delaporte, 2008).

Toxicology

2.3.1. Toxicity Rate

Results of the studies conducted by WHO (2006) highlight that most initial regimens used in the ARV scale up since 2003 have included AZT or d4t with 3TC and NVP or EFV. The predominant toxicities have included the adverse events expected from the use of these drugs in the settings. E.g.: anemia, peripheral neuropathy, lactic acidosis, and lipodystrophy.

In a study in India between 1996 and 2004, 1443 ART naïve patients received regimens containing d4T or AZT. The most common toxicities were rash (66%), hyper toxicity (27%) and anemia (23%). According to UNICEF/UNAIDS/WHO (2009) in Abidjan, Cote d'Ivoire, 498 adults with median baseline hemoglobin of 113g/l started AZT +3TC + EFV (1b), 118 patients had grade ¾ neutropenia and 23 had great ¾ anemia. Of these patients 80% were taking Co-trimaxazole, which can cause anemia and neutropenia. In the DART study being conducted in Uganda and Zimbabwe, 219 of 3314 participants (6.6%) developed grade 4 anemia by week 48, in the same study ABC hypersensitivity reaction were reported in 2% of participants.

In Tororo Uganda, Zachariah, et al (2006), 1073 participants were treated with d4T +3TC + NVP. The participants for remaining free of severe toxicities at 6,12 and 18 months were 92%,86% and 84 % respectively where as nearly 50% of the patients experienced some form of toxicities by 18 months. Toxicity requiring a change in therapy occurred in 21% of the cohort, most commonly switches from d4T to AZT. In Nairobi Kenya 284 patients received d4T +3TC + NVP and the reported toxicities free survival rate was 21% at 18 months. In a report from Zachariah et.al (2006) Khayelisha South Africa on 1700 patients receiving ART, one agent was substituted in approximately 10 % because of toxicity. The rates were similar for d4T (8.5 %), AZT (8.7%) and NVP (8.9%) (Zachariah, et al, 2006).

2.3.2. Overlapping toxicities of HAART and ART

Dean, Edward, and Ives (2002) highlighted the problems of overlapping toxicities when they found a high incidence (54%) of adverse events in a cohort of 188 patients co infected with HIV and tuberculosis**.** One small cohort found a high incidence (55%) of peripheral neurophathy in patients receiving both stavudine and isoniazid therapies and another study found peripheral neurophathy to be the most common toxicity in a cohort patients co-infected with HIV and tuberculosis.

2.3.3. Toxicities caused by Stavudine

HAART usually consist of two nucleoside, reverse transcriptase inhibitors (NRTIs) with either a protease inhibitor (PI) boosted by ritonavir or a non-nucleoside reverse transcriptase inhibitor (NNRTI).A stavudine as an NRTI with either NNRTI or a PI are highly effective, and showing efficient virological response and strong increase in CD4 cell count (Makison, et al, 2008).

Stavudine inhibits mitochondrial polymerase of the adipocyte tissue, nerves, liver and pancreas, as may be revealed by lipoatrophy, peripheral neuropathy, hepatitis or pancreatitis Makison, et al (2008). According to Makison, et al (2008) dysfunction of mitochondria produces insufficient amounts of ATP, leading to increased lactate levels. Increase of lactate production in tissue contrasts with diminished lactate clearance and potentially explaining hyperlactaemia and lactic acidosis. Effects of stavudine are highlighted above (lipoatrophy, peripheral neuropathy, hepatitis or pancreatitis and hyperlactaemia or lactic acidosis. All this effects will be explained in details in the paragraph below.

Makison, et al (2008) highlighted that next to lamuvidine, stavudine is the most common used NRTI, because of its relatively low cost. Stavudine is the NRTI and it is also a regimen1 that is most often associated with mitochondrial toxicity, which

results in high rates of lipoatrophy, peripheral neuropathy, lactic acidosis, and pancreatitis.

2.3.4. Stavudine induced Peripheral Neuropathy (Rural Uganda)

According to prospective study by Gerald, et al (2008) from 10%-21% of persons exposed to stavudine developed peripheral neuropathy in developed countries. Although symptoms usually resolve after prompt discontinuation of stavudine therapy, persistent symptoms in a subset of patients may be problematic in developing countries, where many persons rely on physical labour for survival and usually do not have disability insurance. Cohort studies from Cameroon, India and Thailand found peripheral neuropathy rates that were similar to or, surprisingly. Lower than those in developed countries. It is hard to establish whether these lower rates reflect under ascertainment biases. However 56 % of patients in a Malawian cohort developed peripheral neurophathy (Gerald, et al, 2008).

2.3.5. Stavudine induced peripheral neuropathy (Malawi)

Based on the prospective study conducted by Beadles, et al (2009) a total of 860 adults ARV-naïve participants were initiated on d4t containing treatment regimen and 308 (35.8%) of these were reported symptoms of peripheral neuropathy within median of 28 days after ARV drug initiation. All received supportive treatment of peripheral neuropathy within a median of 28 days after ARV drug initiation. All received supportive for neuropathy and analgesics, vitamins, amitryptilline and either had a single substitution or were maintained on d4t of these 306 were seen during follow up for a median of 20.5 months after diagnosis of peripheral neuropathy. Among the 143 participants who were maintained on d4t, 77 (53, 8%) showed some improvements 58 (40.5%) remained the same and 8 (5.6%) worsened. A further 153 (50%) switched to AZT containing ART regimen because of severe (Grade 3 or 4) of persistent neuropathy. Of these 115 (75.2%) showed improvement in neuropathy grade at follow up.

2.3.6. Stavudine induced peripheral neurophathy

Peripheral Neuropathy is common in the setting of antiretroviral (ARV) programmes in resource-limited settings and posed a significant challenge in assessment and management. A retrospective analysis was undertaken of prevalence and management of PN in a cohort of 3341 patients conducted by Makison, et al (2008) were on highly active antiretroviral therapy. A first line ARV regimen containing Stavudine (D4t) is used for clinically eligible patients. Amitryptilline is prescribed for symptom relief and in case of persistent or escalating symptoms zidovudine (AZT) is substituted for d4t. Leg pain or numbness was reported in 1173 patients (35%). However, only 428(13%) were given a diagnosis of PN, 228(7%) were prescribed amitrptilline and 200(6%) were switched to AZT. A recent pharmacokinetics study in this population showed a high Cmax of d4t with the generic combination triomune (d4tmg). This could account for the high prevalence of PN. The optimum time to switch to a nonD4t contain regimen is unknown (Makison, et al, 2008).

2.3.7. Stavudine induced Peripheral neuropathy (Uganda)

Based on the results of Makison, et al. (2008) 10 to 20% of persons exposed to stavudine develop peripheral neuropathy within 48 weeks. Symptoms generally resolve with prompt discontinuation of stavudine but may persist in a subset of patients. In rural Uganda cohort of 1029 persons under stavudine/ lamivudine/ nevirapine or efavirenz, severe graded peripheral neuropathy appeared in 9% of patients (median follow up of 11.2 months). Tuberculosis treatment at baseline was associated with neuropathy despite use of pyridoxine with isoniazid. In Kenya prospective cohort of 1286 patients(94.4% under stavudine, neurophathy was the highest reported toxicity after a median follow up time of 11.6 months (20.7%) of patients.

2.3.8. Stavudine induced Lipodystrophy and metabolic complications

According to cohort study conducted by Ramnath, et al (2007) the prevalence of stavudine-associated lipodystrophy in western studies has reached as high as 50%-63%. However, many of these studies included patients who also received protease inhibitors, which independently cause lipodystrophy. The risk has been shown to be greater for those initiating HAART with low CD4 cell count and low body mass index. Because stavudine associated lipodystrophy commonly present as lipoatrophy (i.e., fat loss in the cheeks, arms and buttocks) malnutrition complicates its diagnosis. Careful assessment is needed to differentiate lipoatrophy from general wasting to prevent unnecessary modification of therapy. Some data suggest that ethnic variability affects the incidence of lipodystrophy. White race may be an independent risk factor for the development of lipodystrophy. According to study results conducted by Subbarman Ramnath, et al (2007) a small South cohort had a 3.5% rate of lopodystrophy, multiple sudsequent East Asian cohorts shows rates similar to those in western studies according to Ramnath, et al (2007). Only 17% of patients in Southern Asian cohorts developed lipodystrophy compared to 24.8% of patients in a Rwandan cohort and 46.1% in Indian cohort.

The tendency of stavudine associated lipoatrophy to affect facial features raises concerns that the widespread use of the drug in developing countries may increase stigma and decrease HAART adherence. A study of 410 patients of Chinese ethnicity in Singapore found that lipodystrophy affected social relation for 23% of the patients and mood for 36%. However 1% of the patients wanted to discontinue therapy because of this toxicity. In contrast, a smaller study suggested that 14% of Brazilian patients considered therapy discontinuation because of this adverse effect. Because toleration of lipodystrophy may be culturally specific, region specific research may help determine the variability of stavudine use in different countries. Although zidovudine sometimes causes lipodystrophy, stavudine is strongly associated with adverse effect. Therefore, one approach for reducing incidence of lipodystrophy

would be substitude zidovudine for stavudine 6-12 months after HAART initiation, when lipodystrophy may begin to develop. This allows antiretroviral roll out programs to briefly take advantage of the lower cost and better initial tolerability of stavudine. Also stavudine containing HAART is associated with resolution of anaemia in many patients within 6 months after initiation (Ramnath, et al, 2007).

Lipodystrophy and hyperlipidemia are metabolic complications less frequently been seen in HIV patients treated with abacavir, nevirapine or efevirenz plus 2NIRT. Retrospective study conducted by Subbaraman, et al (2002) cohorts of 300 cases of adult HIV positive patients who begin or continued with antiretroviral treatment based in ABA, NEVI or EFA, with 2NIRT. Two groups were done: Group 1: Treatment naïve 180 cases. Group 2: Experienced in treatment adult HIV positive who were switching to non Protease Inhibitors 120 cases. Group 1 male 90% female 10%, Group 2male 94%, female 6%. Subgroups A: Abacavir (ABA), B: Nevirapine (NEV), C: Efavirenz (EFA). Syndrome fat maldistribution including lipodystrophy or lipoatrophy were seen in only 5% in the groups of group1, but were more frequents in group 2: 15% in 2A35% in 2B, 40% in 2C and 80% in 2D p=0.05. (Subbaraman, et. al, 2002).

2.3.9. Stavudine/Zidovudine induced Lipoatrophy

Subbaraman, et al (2007) highlight that morphologic changes that may occur in HIV treated patients under HAART is referred as lipodystrophy. Lipoatrophy presents as peripheral fat loss, including hollowing of the cheeks, wasting of extremeties or flattering of the buttocks.In the randomized NOVAVIR trial, comparing stavudine/ lamuvidine/Indinavir and Zidovudine/Lamuvidine/Indinavir in 170 patients pretreated for more than 6 months with zidovudine, didanosine or Zalcitabine, the incidence at month 30 of lopoatrophy was increased in the stavudine arm versus the zidovudine arm for facial atrophy(48 versus 22%, p= 0.011), lower limbs atrophy (49 versus 22%, p=0.006) buttocks atrophy(47 versus 20%, p=0.009) and venomegaly (57 versus 24%, p=0.001). In a Rwandan setting of 409 individuals under HAART for more than

1 year (90% on stavudine), lipoatrophy or mixed forms with lipodystrophy were apparent in 29.4% of patients after a median of 16 months of treatment.

2.3.10. Stavudine induced Lactic Acidosis

Although relatively infrequent, multiple cohort studies and case reports from developing countries highlight concerns about timely diagnosis of life threatening stavudine- induced lactic acidosis, for which women may be at a higher risk. Pilot studies from Haiti and South Africa found that point of care testing with hand held devices measuring lactic acid levels facilitated timely diagnosis of hyperlactaemia and prevented unnecessary regimen modification in patients without increased serum lactate levels (Subbaraman, et al, 2007).

2.3.11. Stavudine induced Hyperlactaemia

According to cohort study conducted by Makison, et al. (2008) eight to 18% HIV patients test positive for hyperlactaemia in Western studies in which stavudine, zidovudine, lamuvidine or didanosine were the major NRTIs used. Lactic acidosis is often associated with liver enzyme increase, hepatomegaly, pancreatitis or signs of hepatic failure, with mortality rate approaching 30%.In a retrospective cohort study of 1735 patients (63% females) in Soweto, South Africa, median time (range) to lactic acidosis of 23 patients or asymptomatic hyperlactaemia of 44 patients were respectively 34 weeks and 47 weeks. Risk factors included stavudine treatment, obesity (defined by a body index> 30) and female gender (5 versus 1% for men).Results conducted by Makison, et al (2008) 23 patients had lactic acidosis, and 7 had a fatal outcome (30.4%). Similarly, in Botswana 650 patients(69.4%females) included in the Tshepo study with a median follow up time of 89.7 weeks and rate of 3.4% lost to follow up showed a higher than expected rate of lactic acidosis. Fifteen patients (2%) developed moderate to severe symptomatic hyperlactaemia (lactic level >4.4mmol/l with associated symptoms), seven (1%) had lactic acidosis and severe pancreatitis and 4 of 7 patients died. Six of the seven patients with lactic acidosis and 6 of the 8 patients with moderate to severe hyperlactaemia were receiving stavudine based combination (Makison, et al, 2008).

2.3.12. Zidovudine induced Mylosuppression.

Zidovudine falls under regimen 2 according to National Antiretroviral treatment Guideline, National Department of Health South Africa (2004). It is also used as a substitute for stavudine as they are both NRTI (Nucleoside Reverse Transcriptase Inhibitors) and stavudine is the most commonly used NRTI because of it's less expensive than zidovudine. This drug is prescribed for patients who discontinue stavudine because of toxicity (e.g. lipodystrophy, peripheral neuropathy, lactic acidosis and pancreatitis).

Mylosuppression.

Anemia is common in developing countries, particularly among HIV infected and generally worsens with disease progression. High background levels of anaemia may preclude zidovudine related anaemia usually occurs within 3 months after therapy initiation. Studies from Nigeria, Co^ te d'Ivoire, Haiti and India have found rates of Zidovudine related anaemia of 3%-12% (Daniel, Moh, and Messou, et al, 2003).

2.3.13. Nevarapine induced hypersensitivity

Nevirapine is a Nonucleoside Reverse Transcriptase Inhibitors **(NNRTIs)** that is usually prescribed for pregnant women and also prescribed for patients who can not tolerate efavirenz as they are both NNRTIs.

Hypersensitivity

Nevirapine is the most commonly used NNRTI in developing countries because of its lower cost, compared with efavirenz. According to Subbaraman, et al. (2007) hypersensitivity rash occurred in 16%-20% of patients in studies of developed countries. Two US studies that disaggregated data by ethnicity found that mostly persons of Mexican origin and some persons of South American origin were at a higher risk. Haiti, India, Thailand and Malawi found Nevirapine associated rash rates of 3%-26%. Female patients may be at an increased risk of nevirapine associated rash. Initiating patients on a lower lead in dosage of nevirapine of 200 mg once daily,

followed by escalating to the full 200mg twice daily dosage after 2 weeks, helps prevent severe rashes, such as Stevens - Johnson syndrome (Subbaraman, et al., 2007).

2.3.14. Nevirapine induced Hepatotoxicity

The incidence of drug related hepatitis in US and European trials has ranged from 1% to 10%.According to study conducted by Severe, Leger, Charles, et al (2005) cohorts from Haiti, Thailand, India, Zambia and Malawi found similar rates of nevirapine associated hepatotoxicity ranging from 1% to 7%. A South African study reported a 17% incidence of serious hepatotoxicity (i.e.,alanine aminotransferease and aspartate aminotransferase levels 5 times the upper limit than normal). Female patients with a BMI 18.5 had a 50% incidence of serious hepatotoxicity. A Thai study found that 17(18.6%) of 91 patients receiving nevipapine therapy developed serious hepatitis, which may be explained by high prevalence of hepatitis B (HBV)virus and hepatitis C(HCV) co infection in this cohort. Similar to findings in western studies, HBV infected patients in this study had a higher hepatotoxicity rate (57.4%) than did HBV uninfected patients, and patients with HCV had a hepatotoxicity rate of 72.2% (Severe, et al., 2005)

2.3.15. Efavirenz induced neuropsychiatric disorder

Neuropsychiatric disorder

Efavirenz is a Non Nucleoside Reverse Transcriptase Inhibitor (NNRTI) and is a regimen 1, who is usually prescribed to most of the patients that initiates ARVs except those with a history of psychiatric disorder and pregnant patients. For patients with psychiatry disorder, it worsens psychiatric condition and it is also not safe for pregnant women as it causes congenital abnormalities. Neuropsychiaric disorders are the most concerning adverse effects associated with efavirenz therapy with regard to tolerability and adherence. According to study conducted by Subbaraman et.al (2007) from Haiti, found that 46 (10%) of 452 patients discontinued efavirenz therapy because of persistent neurotoxicity, this rate is higher than results found in US studies.

A study from Cote d"voire also found a neurotoxicity rate (69%) after initiation of efavirenz therapy.

SECTION 2:

2.4.1. Treatment change and treatment switch

In Uganda, CDC Uganda reported that 10% f patients receiving treatment through a home based care programme developed a severe peripheral neuropathy, and side effects was vastly more frequent than any other severe side effects. Seventeen percentages (17 %) of patients switched from d4T during 18 months of follow up, compared with 4% who switched from Nevarapine due to adverse reaction (rash). Participants in the study had 73% probability of remaining on their original three drugs, first line regimen after 18 months and 16% probability of experiencing severe adverse events by this point. 2012 participants receiving one of the first line regimen (d4T, 3TC and NVP (38%)), the incident of peripheral neuropathy was greater than any other serious side effects. Patients receiving Nevarapine and d4T were more than 3 times more likely to modify treatment than patients taking AZT,3TC and Efarivenz (34 changes per 100 patients compared to 10.5 changes /100 patients years) according Were, et al (2007). In Rwanda 83% of changes reported at two health facilities were d4T, almost entirely due to peripheral neuropathy. In Kenya study conducted reported that 486 changes made to first line therapy among more than 2000 patients receiving ARV therapy.65% of changes were due to lipodystrophy and 11% were due to virologic failure of first line treatment, with peripheral neuropathy leading to treatment changes in less than 5%. Lactic acidosis, another life threatening side effect of d4T, has been observed at the unusually high frequency in women with higher body weight (>75 kg), possibly due to fat accumulation in the liver as a results of greater body weight (Were, et al, 2007).

2.4.2. Treatment change due to pregnancy

Among pregnancy reported prospectively by Matthew, et al (2004) to an ARV pregnancy registry in the United States, birth defects were observed 4 of 12 (2.8%)

live birth following exposure to EFV based regimens in the first trimester of pregnancy. The rates were similar to the prevalence of birth defects in the United States population which is (3.1%), based on surveillance data from the United States Centre for disease Control and Prevention. Three retrospective cases reports of neural tube defects with first trimester EFV exposure. Treatment with EFV should be avoided in the first trimester according to Matthew et.al (2004), which is period of organogenesis, EFV is not recommended for use among women of childbearing potential unless effective contraception can be ensured.

SECTION 3:

2.5.1. Treatment interruption

Study conducted by WHO (2006) symptomatic hyperlactemia is less common (reported in 0.2 to 0.2%) of infected adults and the syndrome of lactic acidosis is rare. In cohort of adults receiving NRTI therapy at John Hopkins University between 1989 and 1994, the incidence of lactic acidosis was 0.13%, in a more recent cohort of 964 infected adults from France followed between 1997 and 1999, the incidence of symptomatic hyperlactemia was 0.8% per year for all the patients and 1.2% for patients receiving Stavudine (d4T). Although lactic acidosis has been described in association with all NRTI drugs, particularly if treatment is over 6 months in duration therapy with Didanosine (ddi) or d4t may be more likely to be associated with this syndrome. Life threatening and fatal cases of lactic acidosis have been reported in HIV infected children, while uncommon lactic acidosis is associated with high fatality rate (33 to 57%).

2.5.2. Resistance and treatment failure

A Worldwide Surveillance Program (WATCH) conducted by WHO (2004) found the rate of resistance (to any drug) among treatment naïve individuals was 5.5% in Africa, 7.4% in East Asia, 5.7% in Southern Asia, and 6.4% in Latin America lower than in Northern America (11.4%) and Europe (10.6%) (WHO, 2004).

In a cohort study there were 305 ARV naïve patients with HIV recent infection from 12 provinces in central Thailand between 1 January 2003- 31 December 2006 according to Anekthananon, Ratanasuwan, Techasathit, Soniai, and Suwannagool (2004). The overall median age was 24 years, the median duration of known HIV infection was 3 months and there were 169 (55%) women- 130 of whom (77%) were pregnant. The majority of participants (5215, 70%) reported HIV related heterosexual risk and 23(8%) reported male to male transmission risks, the median CD4 count was 545 cells/ml (range 356-901cells/L) 115 participants (38%) reported a sexual partner with HIV infection who was receiving ART, 104 (90%) were on non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimen and 11 (10%) were on protease inhibitor (PI) based regimens. Seven patients (2%) had confirmed GPO-VIR drug resistance over the 4 year period. All reported a single sexual partner and reported no recent (24 months) sexual encounters with a commercial sex worker. Each identified sexual partner had documented GPO-VRI non adherence and GPO-VIR treatment failure (Anekthananon, et al, 2004).

Tanzania and US researchers asked 150 adults treated for at least 6 months. They defined virologic failure as a viral load above 400 copies/ml. Twenty three people (16%) reported incomplete adherence. According to De Luca, Weidler, Giambenedeti, et al (2007) among 48 people (32%) with virologic failure, self reported poor adherence more than tripled the risk of failure. According to researchers, people who disclosed their HIV status to family members or others had 90% lower risk of virologic failure (De Luca, et. al, 2007).

2.5.3. Adherence

The cross sectional study conducted by WHO (2006) in the three private clinics in Botswana between January and July 2000 reported the barriers to and level of treatment adherence in 109 patients who had at least three months on ART. Patients and health care providers (60%) were interviewed separately to obtain information on adherence. In this study, (54%) of the patients self reported adherence. Gaps in treatment is (29%) according to WHO (2006),were more frequently reported than day

to day no adherence (17%). The main reason for gaps in treatment was inadequate insurance coverage for the expensive medication (69%). For all groups the other major barriers to adherence were financial constrains (44%), stigma (15%), travel/immigrants (10%) and side effects (9%) (WHO, 2006).

CHAPTER III
METHODOLOGY

3.1. Study design

The study will employ a retrospective cohort study. The medical records of a cohort of HIV positive patients on ARVs enrolled in a longitudinal pharmaco-epidemiological survey from November 2006 to May 2007 reviewed. During this time Pharmacovigilance Department were reviewing files of selected patients from enrollment date of the clinic until the last visit, of which by then, the last visit to most of the patients were May 2007. During data collection, data collected retrospectively (from the last visit backwards) from the files identified with a green sticker.

3.2. Study setting

The study was conducted at Tshepang wellness clinic Dr George Mukhari Hospital, Gauteng Province, South Africa. The clinic consist of project manager's office, Pharmacy for ARVs only, 5 doctors consultation rooms, 4 councillors rooms, 1 Social worker consultation room, 1 dietitian room, data capture room, 2 filing rooms and waiting area. Dr George Mukhari Hospital is a 1700 beded tertiary health institution and it receives referrals from Gauteng, North West, Limpopo and Part of Mpumalanga Provinces. Tshepang is one of the credited sites to supply antiretroviral treatment (ART).This clinic receives patients referred from primary health care sites, and some of the patients are self referred.

The (MNPC) Medunsa National Pharmacovigilance Centre liaise with 5 roll out sites or what is currently called wellness clinics in four provinces which includes Gauteng and the site clinic name is Tshepang Wellness Clinic, and the primary function of this department is monitoring the safety of antiretroviral (ARVs) used by adults HIV/AIDS patients countrywide as mentioned earlier.

3.3. Study population

The study population was the records of HIV positive patients on ARVs who were enrolled in the pharmaco-epidemiological survey. These patients were randomly selected from November 2006- May 2007 by Pharmacovigilance Department out of all patients who are taking ART at Dr George Hospital, Tshepang wellness clinic. The total number of Pharmacovigilance files is 503 files, while 301 files reviewed during data collection of this study, and clinic lost other files.

3.4. Sample size

All 503 patients enrolled at Pharmacovigilance survey, of which 301 files reviewed while clinic lost other 202 pharmacovigilance files. Pharmacovigilance patients were randomly selected out of all patients attending clinic, of which all files counted from one up to 10 and every 10^{th} file selected, Pharmacovigilance department sampled only 503 files. During data collection of these study only 301 files identified as pharmacovigilance files, Filing manager said they lost other files when they move from old building to new one, sometimes other patients doesn't return files. Pharmacovigilance files were identified by green sticker, apparently most of the old files covers were replaced by new cover and when they put a new cover clinic didn't put back the sticker, and other patients who doesn't want to be part of Pharmacovigilance anymore removed that green sticker.

3.5. Data Collection tool

A data extraction tool (see Appendix A) developed by the researcher used to extract data from the medical records. The data extraction tool extracted the following:

- **Socio-demographic data** - which includes age, gender, level of education, employment status, source of income and marital status
- **Behavioral data-** includes smoking, use of alcohol, use of traditional medicine and lastly habit forming drugs
- **Treatment related data –** includes start date of ARV, which regime prescribed, reason for ARV change, reported toxicities, any treatment interruption and if so duration of treatment interruption.

3.6. Data collection method

Data collected from all files identified by green sticker, 20 files reviewed per day, meaning 10 files per researcher and her assistance. Data quality control (double checking) done daily after 20 files reviewed before files goes back for filing. Data collected from 29 February 2009 until 23 March 2009.

Problems and Barriers encountered during data collection

Problems encountered during data collection was a day before collection of data (researcher and research assistant) had to select files with a green sticker, of which some of the files doesn't have all the information needed, they looked like a new enrolled patients with a new prescription, meaning all the other information was missing (e.g. socio demographic data and behavioral data). During data collection as mentioned that files selected a day before data entry, clinic staff sometimes takes the files that are selected for the following day, of which that experience made researchers to select at least 30 files instead of 20 in case they take some of the files that were selected. While sometimes when researchers are busy with the file, clinic staff will come and take the file that they are busy working at. Researcher had to explain everything to research assistant as she was not clear with some of the

information needed, and researcher also had to go through to the file that research assistant reviewed to make sure that all the information needed is collected. The last one is every day researchers had to file back all the files that were used for that day, of which it was difficult sometimes as files were filed according to numbers and most of the time they were complaining about researchers' wrong filing.

3.7. Inclusion and Exclusion criteria.

Selection criteria used- all files identified with green sticker were selected, and new covers putted to some other files with green sticker. Files with new cover without green stickers excluded because there were no pharmaco-vigilance sign (green sticker).

Inclusion criteria

- All files with a green sticker were included during data collection.
- A file with a green sticker with all information needed included (e.g.: sociodemographic data, behavioral data and treatment related data).
- A file with a green sticker that has all the necessary information- that falls under loss to follow up or deceased included.

Exclusion criteria

- All the files with green sticker reviewed, nothing excluded.
- Some of the files removed green sticker and those excluded as the researcher assumed that there are patients that does not want to be part of pharmacovigilance anymore, as during enrollment of pharmacogigilance study, they were assured that the study is voluntary and they won't be penalized in case of withdrawal from the study.

3.8. Ethical consideration

Ethical approval was obtained from Medunsa Research and Ethics Committee prior to the execution of the study in February 2009 with Protocol no: MREC/PH/08/2009: PG (see Appendix E). Permission to conduct the study also requested and obtained from CEO of the hospital and Project Manager of the clinic (see Appendix D). There was no contact between the researcher and patients, informed consent were not necessary. Safe keeping of records maintained as data collected in one of the filing rooms at Tshepang Wellness Clinic. The researcher and her assistance together with the clinic staff were the only people that had an access to that room. Only numerical identification used as reference, confidentiality and anonymity of subject was maintained by not recording identifying details such as names or any other personal details.

3.9. Data analysis method and results presentation

The variables are shown in the table below:

Table 4.1 Variables and their description: Description of actual process

Variables	Description of variables
Gender	Coded 1 if the person is a male Coded 2 if the person is a female
Age group	Coded 1 if 15 - 25 Coded 2 if 26 - 49 Coded 3 if 50 – 70
Education group	Coded 1 if there is no schooling Coded 2 if the person had grade 1- 5 Coded 3 if the person had grade 6 - 7 Coded 4 if the person had grade 8 - 12 Coded 5 if the person had tertiary education Code 6 not documented

Employment Status	Coded 1 if the person is employed Coded 2 if the person is unemployed Coded 3 not documented
Source of income	Coded 1 if it is none Coded 2 if the person employed Coded 3 if it is disability grand Coded 4 if it is child support grand Coded 5 not documented Coded 6 if is pension
Marital status	Coded 1if the person is single Coded 2 if the person is married Coded 3 if the person is divorced Coded 4 if the person is a widower Coded 5 if the person not documented Coded 6 if the person cohabitating
Smoking	Coded 1 if it is yes Coded 2 if it is no Coded 3 if the person stopped Coded 4 if it is not documented
Use of alcohol	Coded 1 if it is yes Coded 2 if it is no Coded 3 if the person stopped Coded 4 if it is not documented
Habit forming drugs	Coded 1 if it is yes Coded 2 if it is no Coded 3 if the person stopped Coded 4 if it is not documented
Regimen	Coded 1 if it is 1a Coded 2 if it is 1b

	Coded 3 if it is 1c Coded 4 if it is 1d
Reason for ARV's change/ stopped	Coded 1 if is toxicity Coded 2 if is pregnancy Coded 3 if is weight loss Coded 4 if it is not documented Coded 5if it is TB Coded 6 if it is resistance
New ARV's prescribed	Coded 1 if it is yes Coded 2 if it is no Coded 3 if it is not documented
Which ARV's prescribed	Coded 1 if it is 1a Coded 2 if it is 1b Coded 3 if it is 1c Coded 4 if it is 1d Coded if it is regimen 2
Reported toxicities	Coded 1 if it is lipodystrophy Coded 2 if it is lipoatrophy Coded 3 if it is hyperlactaemia Coded 4 if it is peripheral neuropathy Coded 5 if it is TB Coded 6 if it is resistance
Any treatment interruption	Coded 1 if it is yes Coded 2 if it is no Coded 3 if it is not documented

3.9.1. Data Analysis

During the data cleaning phase respondents were excluded for a number of reasons: missing values, errors in the data and inconsistencies.

The results were analyzed using statistical software SPSS 17.0 computer program and relevant themes were extracted. Results are presented in a form of tables, graphs and charts. Statistical significance of the difference between treatment change and regimen change among different socio demographic characteristics was tested using Chi- square test to compare proportion and measure associations between the two variables.

3.10. Validity and Reliability

Medical records are often used in epidemiological studies to abstract data. However careful consideration should be given to quality of data because medical records are made for diagnostic and treatment purpose not for research. Therefore more complete information about exposure would be more frequently found in patients with severe disease. The difference in accuracy of medical records will tend to produce overestimation of the association under study.

Therefore validity and reliability maintained by letting two researchers to collect data from the files of the cohort, one file from one researcher to second researcher. We compared data collected daily and data was expected to be the same, where there were difference of data, we compare and rectify an error.

CHAPTER IV

PRESENTATION AND DATA ANALYSIS

4.1 Introduction

This chapter describes how data has been analyzed and which programme has been used. It consists of 13 tables and 5 figures and all with their descriptions. First paragraph is the figures followed by tables.

4.2 Data analysis

The results from the study were analyzed using SPSS 17.0 statistical software. Frequency table for all variables will be given in order to determine the distribution of variables. Cross tabulation is also done to determine the relationship between the predictor variables and the response.

Statistical significance of the difference between treatment change and regimen change among different socio demographic characteristics was tested using Chi-square test to compare proportion and measure associations between the two variables.

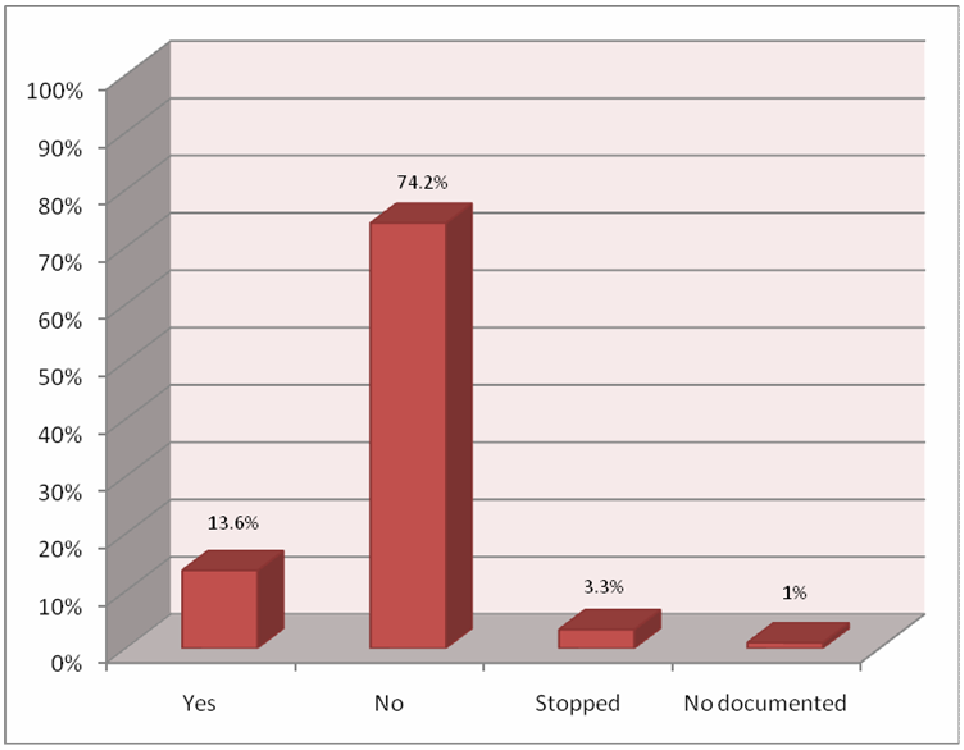

Figure 4.1 Distribution of smoking behavior among HIV positive patients on anti-retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital.

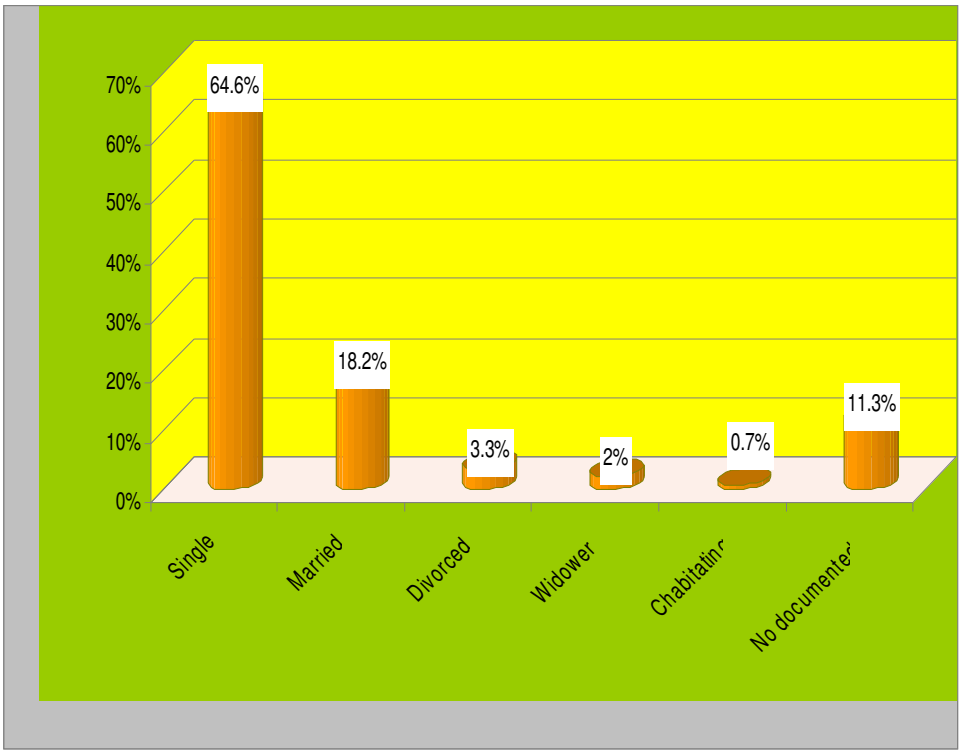

Figure 4.2. Distribution of marital status among HIV positive patients on anti-retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital

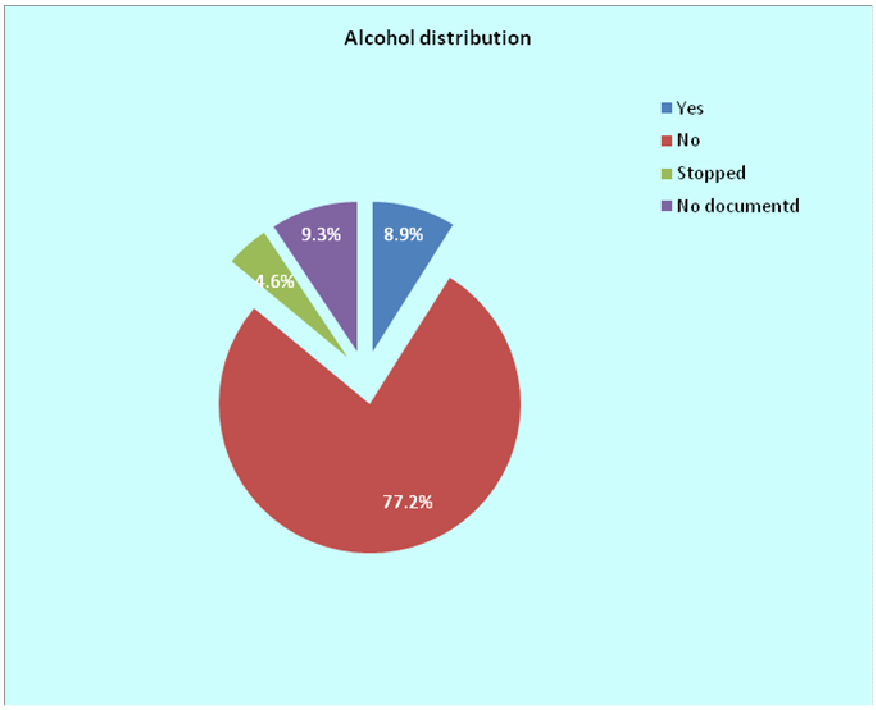

Figure 4.3. Distribution of the use of alcohol among HIV positive patients on anti-retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital

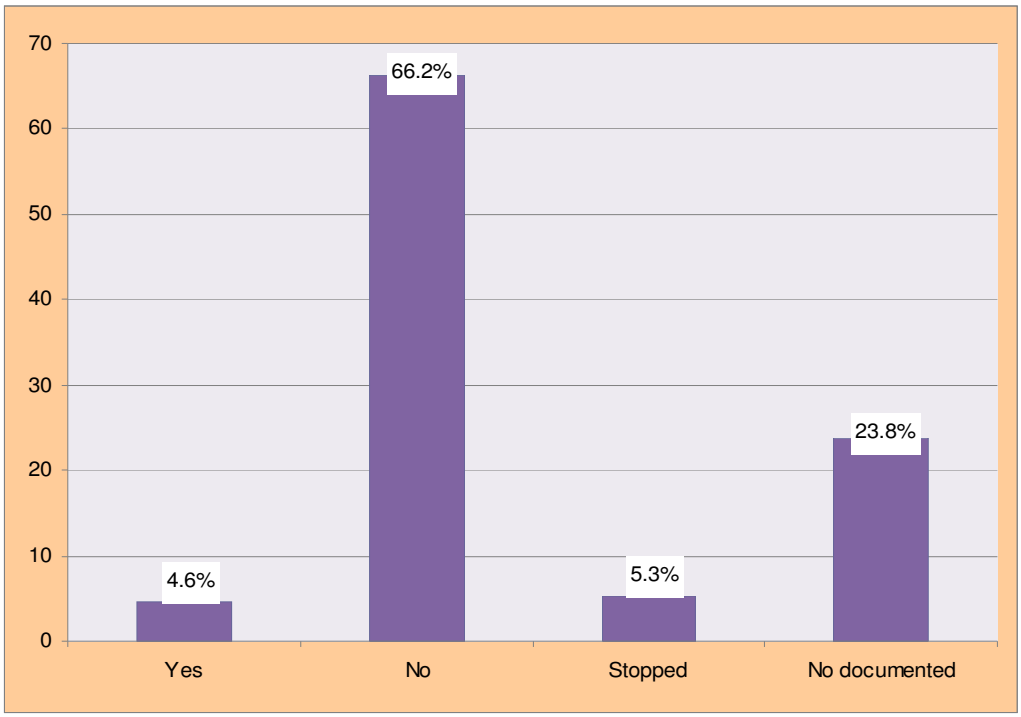

Figure 4.4 Distribution of the use of traditional medicine among HIV positive patients on anti retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital.

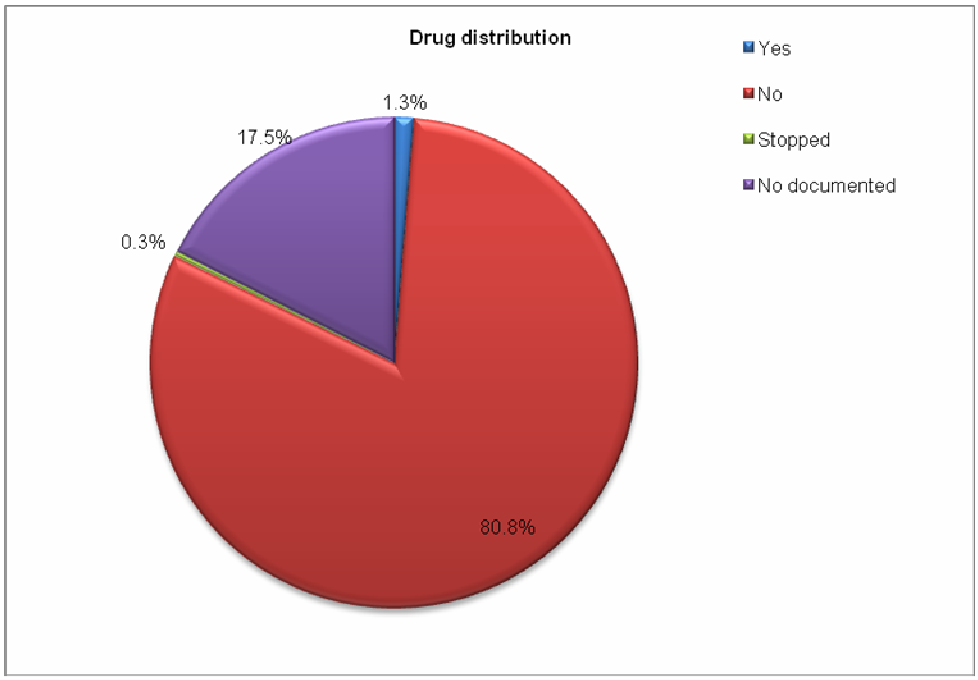

Figure 4.5. Distribution of habit forming drugs among HIV positive patients on anti-retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital.

4.3 Frequency table for variables and their description

Table 2. Demographic variables among HIV positive patients on anti retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital

Demographic variables		**Number**	**Percent**
Gender	Male	108	35.8
	Female	191	63.2
Age	15-25	23	7.6
	26-49	248	82.1
	50-70	26	8.6
	Not documented	2	0.7
Education	No schooling	16	5.3
	Grade 8-12	140	140
	Tertiary	15	15
	No schooling	59	59
Employment	Employed	51	16.9
	Unemployed	209	69.9
Income	None	90	29.8
	Employed	26	8.6
	Disability grand	57	18.9
	Child support	51	16.9

	Other	5	1.6

Table 1, Figure 4.1, 4.2, 4.3, 4.4 and 4.5 above display the frequency distribution of 301 HIV positive patients on ARVs enrolled between November 2006 to May 2007 in a longitudinal pharmaco-epidemiological survey. One hundred and eight (35.8%) of the patients were male and 191(63.2%) were female and 1% was not documented. Ages were grouped as teenagers (15 - 25 years), young adult (26-49 years) and older adults as (50-70 years). The highest age groups were young adult (26-49 years) with 248 (82.1%) followed by older adults (50-70 years) with 26 (8.6%) respondents and teenagers (15 - 25 years) with 23 (7.6%). The mean age ware 12.4 and median was 11.2 with standard deviation of 4.5. Most patients who finished grade 8-12 were 140(46.4%) followed by 15 (5.0%) who finished their tertiary level. Two hundred and nine (69.9%) patients were employed and 51(16.9%) were unemployed.

The majority of the patients started their treatment between July 2005 – December 2005 91(approximately 31.2%). Between January 2006 – December 2006 were 90 (approximately 30.3%). Followed by those who started from January 2005-June 2004 70 (23.1%) and between July 2006-December 2006 were 34 (11.4%). See table 2 below.

Table 3. Distribution of start date of ARV's among HIV positive patients on antiretroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital.

	Distribution of ARV's	Number	Percent
Year	July 2004-Decemaber 2004	13	4.0
	January 2005-June 2004	70	23.1

	July 2005-December 2005	91	31.2
	January 2006-June 2006	90	30.0
	July 2006-December 2006	34	11.4

Table 4. Number of patients in each regimen among HIV positive patients on antiretroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital

Regimen	No.	Percentages
Regimen 1a	255	85.2
Regimen 1b	17	5.7
Regimen 1c	20	6.7
Regimen 1d	2	0.7
Not documented	5	1.7
Total	299	100%

Total number of pharmacovigilance files reviewed were 299. Out of them majority of them were on Regimen 1a which are two hundred and fifty five (85.2%), then followed by those that were on Regimen 1c with twenty patients (6.7%), then Regimen 1b with seventeen patients (5.7%) , followed by the last and considered to be minority which is Regimen 1d with two patients (1.7%) and remaining five patients (1.7%) regimens are not documented.

As highlighted in table 4, majority of patients were on Regimen 1a and out 255 patients, 164 were females, and the rest 91 were males. Female patients were considered to be majority with (87.7%), followed by Regimen 1c as highlighted in the

first table. Out of this twenty, thirteen (7.0%) were females and seven (6.5%) were males.

In regimen 1b which is considered to be the next with seventeen patients, out of this seventeen, nine were males (8.4%) and females with eight patients (4.3%). The last regimen and considered to have minority of patients is regimen 1d with total number of two patients (1.1%).

Table 5. Cross table of age and gender among HIV positive patients on anti retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital.

(Percentages present by row)

Variables		**Original Regimes n (%)**			
		1a	**1b**	**1c**	**1d**
Gender	Male	91 (85.0)	9 (8.4)	7 (6.5)	Nil
	Female	164 (87.7)	8 (4.3)	13 (7.0)	2 (1.1)
Age (years)	15-25	21 (95.5)	1 (4.5)	Nil	Nil
	26-49	212 (86.9)	14 (5.7)	16 (6.6)	2 (0.8)
	50-70	20 (79.6)	2 (7.7)	4 (15.4)	Nil

Age is divided into 3 groups based on table 4, which is group A.15-25 yrs, group B. 26-49yrs and group C. 50-70yrs.Majority of patients were falling under group B 26-49yrs,as they were 212 (86.9%) and these 212 patients were all on Regimen 1a, followed by group A (15-25yrs) and twenty one patients (95.5%) are falling under this group, then followed twenty patients (79.6%) which falls under goup C (50-70yrs) and they are all receiving regimen 1a.

Regardless of age and gender majority of patients are taking regimen 1a, followed by regimen 1c. Group B (26-49yrs) with 16 patients (6.6%), then group C (50-70yrs) with four patients(15.4%), then followed by those getting Regimen 1b, based on regimen 1b, group B in terms of age is the majority because sixteen patients out of twenty falls under 26-49yrs, followed by 50-70 yrs group who has four patients(15.4%) and the last group who considered to be minority are patients receiving regimen 1d with two patients of which both of them fall under age 26-49 yrs.

Table 6. Reason for ARV's change/stopped total indicated each reasons among HIV positive patients on anti retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital.

ARV's change/stoped	Number	Percentages
Toxicity	148	49.5
Pregnancy	16	5.4
Other-(weight loss)	nil	nil
TB	4	1.3
Resistance	7	2.7
Total number of reasons change/ stoppped ARV	**175**	**58.9**

Most of patients changed/stopped treatment because of different reasons like toxicities, pregnancy, T.B and resistance. Hundred and fourty eight (49.5) change because of toxicities, then followed by pregnancy with sixteen patients (5.4%), then resistance with seven patients (2.7%) followed by last which is T.B with four patients

(1.3%). In general total number of patients that changed treatment are hundred and seventy five (58.9%).

Based on the findings, majority of patients change treatment because of toxicity. Toxicity according to the results of this study can be hyperlactaemia, peripheral neurophathy, hyperlactaemia,lipodystrophy, lipoatrophy and resistance.Results of this study shows that majority of patients were one hundred and thirty four (44.8%) reported toxicities and they had to change treatment, followed by sixteen patiets (5.4%) that changed treatment due to pregnancy and resistance also identified to four patients (1.3%), and the other two patients (0.7%) presented with T.B and they all had to change treatment due to this toxicities.

Table 7. Reasons and combined reasons of ARV's change/stopped among HIV positive patients on anti retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital.

ARV's change/stoped	Number	Percentages
Toxicity alone	134	44.8
Pregnancy alone	16	5.4
TB alone	2	0.7
Resistance alone	4	1.3
Combination of toxicity and pregnancy	2	0.7
Combination of Toxicity and TB	2	0.7
Combination of Toxicity and resistnace	4	1.3
Total number of patients who changed regimens	**165**	**55.18**

Other patients presented with combination of two toxicities, two patients (0.7%) presented with pregnancy and toxicity, and onother two (0.7%) patients presented with toxicity and T.B, while the last four patients (1.3%) presented with toxicity and resistance. To all this patients specific toxicity name of diagnose were not mentioned which means is either one of the ones that are mentioned earlier. Total number of patients that changed treatment due to toxicity are one hundred and sixty five (55.18%).

Table 8: Cross table of age and gender among HIV positive patients on anti retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital.

(Percentages presented by row)

Variables		**Reasons for changed treatments (%)**			
		Toxicity	**Pregnancy**	**TB**	**Resistance**
Gender	Male	44 (84.6)	Nil	1 91.9)	1 (1.9)
	Female	91 (86.7)	16 (5.4)	1 91.0)	3 (2.9)
Age (years)	15-25	8 (100)	Nil	Nil	Nil
	26-49	113 (83.7)	16 (5.4)	2 (1.5)	4 (3.0)
	50-70	13 (100)	Nil	Nil	Nil

Toxicity: As mantioned on the table above, majority of patients changed treatment because of toxicity, ninety one of them (86.7%) were females and fourty four were males (84.6%). One hundred and thirteen (83.7%) of this total patients were between

age 26-49yrs and thirteen (100) were between age 50-70 yrs and the last and minority were between age 15-25 yrs.

Pregnancy: Sixteen female patients (5.4%) change treatment because of pregnancy and all of this patients were between age 26-49 yrs.

T.B: Only two patients (1.5%) changed treatment because of T.B, and out of this two, one (1.9%) was a male and the other one (1.0%) was a female, and both of them were also between age 26-49 yrs.

Resistance: Four patients presented with resistance, three (2.9%) of them were females and only one was a male(1.9%), and all this four patients (3.0%) were between age 26-49 yrs.

Table 9. Distribution of treatment change among HIV positive patients on anti retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital.

Variables		Number	Percentages
New ARV's prescribe	Yes	179	59.9
Which ARV's prescribe	Regimen 1a	1	0.3
	Regimen 1b	14	4.7
	Regimen 1c	150	50.2
	Regimen 1d	3	1.0
	Regimen 2	11	3.7
	Total received new prescribe	**179**	**59.9**
Any treatment interruption	Yes	7	2.3
	No	286	95.7
	Not documented	6	2.0

Total number of 179 (59.9%) patients changed treatment from one regimen to onother even though the original treatment is not documented.One patient (0.3%) changed to regimen 1a, fourteen (4.7%) changed to regimen 1b, one hundred and fifty patients which are majority (50.2%) changed to regimen 1c, three patients changed to regimen 1d and eleven patients (3.7%) changed to regimen 2. Original treatment of all this patients are not documented. When you compare this table with the table below all the numbers are the same except regimen 1c of which there is a possibility that some other patients started with this regimen and then changed to onother regimen due to toxicity, and maybe still experience another toxicities and then changed back to this regimen 1c again.Seven patients (2.3%) had a treatment interruption and two hundred and eighty six (95.7%) did not experience any treatment interruption and nothing documented on six (2.0%) patients.

When compare this table with the first table where original treatment are documented, on the first table majority of patients were two hundred and fifty five and they were on regimen 1, but now on this table majority of patients are one hundred and fifty (50.2%) and all this patients are on regimen1c, of which there might be a possibility that patients changed from regimen 1a to regimen 1c.

Table 10: Cross table of age and gender among HIV positive patients on anti retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital.

(Percentages present by row)

Variables		**Regimes of new prescribes n (%)**				
		1a	**1b**	**1c**	**1d**	**Regime 2**
Gender	Male	Nil	4 (6.7)	52 (86.7)	2 (3.3)	2 (3.3)
	Female	1 (0.8)	10 78.4)	92 (82.4)	1(0.8)	9 (7.6)

Age (years)	15-25	Nil	Nil	8 (100)	Nil	Nil
	26-49	1 (0.6%)	14 (9.0)	128 (82.1)	3 (1.9)	10 (6.4)
	50-70	Nil	Nil	13 (92.9)	Nil	1 (7.1)

According to this table new regimens prescribed are based on age and gender. In regimen 1a according to this table and results of pharmacovigilance cohort patients, only one patient (0.8%) changed to regimen 1a and the same patient is a female who is between 26-49 yrs, then followed by regimen 1d with total number of three patients. Two of these patients were males (3.3%) and one (0.8%) of the three is a female. All of these three (1.9%) patients age between 26-49yrs. The next regimen is 1b with fourteen patients, out of these fourteen, ten (78.4%) were females and four (6.7%) were males, and all these fourteen patients fall between age 26-49 yrs. Majority of patents have changed to regimen 1c as total number of one hundred and forty four were all changed to this regimen. Females as usual are majority and they were ninety two (82.4) and males were fifty two (86.7%), one hundred and twenty eight of the patients (82.1%) receiving this regimen age between 26-49 yrs then followed by thirteen (92.9%) who age between 50-70 yrs and the last eight (100%) age between 15-25 yrs. Regimen 2 had eleven patients, and nine (7.6%) were females and two(3.3%) were males and ten out of this eleven were between age 26-49 yrs and one (7.1%) patient age between 50-70 yrs.

Table 11: The comparison of original ARV regimes and types of new treatment prescribed among HIV positive patients on anti retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital.

Original regimes	Number	%	New regimes	Number	%
Regimen 1a	255	85.2	Regimen 1a	1	0.3
Regimen 1b	17	5.7	Regimen 1b	14	4.7
Regimen 1c	20	6.7	Regimen 1c	150	50.2
Regimen 1d	2	0.7	Regimen 1d	3	1.0
			Regimen 2	11	3.7

Based on the results of the study, this table shows that majority of patients were two hundred and fifty five(85.2%), initiated with regimen 1a, and only one patient (0.3%) change from original treatment which is not indicated to regimen 1a.Only seventeen patients (5.7%) initiated with Regimen 1b, while some other patients whom their original treatment is not indicated change to this regimen. The results shows that twenty patients (6.7%) were initiated with regimen 1c, and one hundred and fifty patients (50.2) which regarded as majority changed to this regimen. Only two patients (0.7%) which regarded as minorities initiated with this regimen 1d and still, manority of three patients (1.0%) changed to this regimen.The last regimen is regimen 2 with eleven patients (3.7%) and their initial treatment is unknown, they all ended up in this regimen and the reasons of change from their initial regimen are not documented.

Table 12. Reported number of each toxicities among HIV positive patients on anti retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital

Reported toxicities	Number	Percentages
Lipodystrophy	44	14.7
Lipaotrophy	25	8.4
Hyperlacteamia	52	17.4
Peripheral neuropathy	38	12.7
TB	1	0.3
Resistance	5	1.7
Total reported toxcities	**165**	**55.2%**

Out of 299 pharmacovigilance patients, one hundred and sixty five (55.2%) reported different toxicities. Fifty two patients (17.4%) reported hyperlactaemia, followed by forty four patients (14.7%) that reported lipodystrophy, followed by thirty eight patients (12.7%) who reported peripheral neurophathy. Lipoastrophy also identified to twenty five patients (8.4%). Only few five patients (1.7%) had resistance and only one patient (0.3%) had T.B.

Table 13. Reported number of toxicities on patients and one or more toxicities reported among HIV positive patients on anti retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital.

Reported toxicities	Number	Percentages
Lipodystrophy alone	32	10.7
Lipaotrophy alone	9	3.0
Hyperlacteamia alone	33	11.0
Peripheral neuropathy alone	28	9.4
Resistance alone	2	.7
Lipodystrophy and Lipaotrophy	3	1.0
Lipodystrophy and Hyperlacteamia	3	1.0
Lipodystrophy and Peripheral neuropathy	2	.7
Lipaotrophy and Hyperlacteamia	8	2.7
Lipaotrophy and Peripheral neuropathy	1	.3
Lipaotrophy and TB	1	.3
Hyperlacteamia and Peripheral neuropathy	5	1.7
Hyperlacteamia and Resistance	2	.7
Lipodystrophy, Lipaotrophy and Peripheral neuropathy	1	.3
Hyperlacteamia, Peripheral neuropathy, and resistance	1	.3
Total patients reported toxicities	**134**	**43.8**

Reported one toxicity on each patient

Based on the findings majority of patients which are thirty three (11.0%) reported with hyperlactaemia followed by lipodystrophy with thirty two patients (10.7%), then peripheral neurophathy with 28 patients (9.4%), lipoatrophy identified on nine patients (3.0%) and the last two patients (0.7%) reported resistance.

Reported one or more toxicities on one or more patients

Other patients reported more than one toxicities, out of hundred and thirty four patients (43.8%), three out of them (1.0%) reported with both lipodystrophy and lipoatrophy, while onother three patients (1.0%) reported with both lipodystrophy and hyperlactaemia. Lipodystrophy and peripheral neurophathy reported by two patients (0.7%). Lipoatrophy and hyperlactaemia are reported by eight patients (2.7%). One patient (0.3%) reported with lipoatrophy and peripheral neurophathy while another one (0.3%) reported with lipoatrophy and T.B. Another five patients (1.7%) reported with hyperlactaemia and peripheral neurophathy and onother two (0.7%) with hyperlactaemia and resistance. One patient (0.3%) reported more than two toxicities which are lipodystrophy,lipoatrophy and peripheral neurophathy and onother one(0.7%) also reported with more than two toxicities which are hyperlactaemia, peripheral neurophathy and resistance.

Table 14: Cross table of age, gender and reported toxicities among HIV positive patients on anti retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital (Percentages present by row)

Variables		Regimes of new prescribes n (%)					
		Lipodystrophy	Lipoatrophy	Hyperlactaemia	Peripheral Neuropathy	TB	Resistance
Gender	Male	8 (18.2)	3 (36.8)	11 (25.0)	10 (22.7)	1 (2.3)	11 (25.0)
	Female	24 (27.6)	6 (6.9)	22 (25.3)	18 (20.7)	1 (1.1)	16 (18.4)
Age (years)	15-25	Nil	Nil	5 (62.5)	1 (12.5)	Nil	2 (22.5)
	26-49	31 (24.8)	9 (8.3)	23 (21.1)	22 (20.2)	2 (1.8)	22 (20.2)
	50-70	1 (7.7)	Nil	4 (30.8)	5 (38.5)	Nil	3 (21.3)

Based on the findings females regarded as majority to all toxicities, twenty two female patients reported (25.3%) hyperlactaemia and eleven males (25.0%) reported this toxicity as well. Total number of these patients is thirty three. Out of this thirty three, twenty three of them (21.1%) age between 26-49 yrs, followed by five patients who age between 15-29 yrs and the last four patients' age between 50-70 yrs.

Twenty four females (27.6%) reported lipodystrophy and only eight males (18.2%) reported the same toxicity and total number of patients reported with lipodystrophy is thirty two. Out of this thirty two, thirty one (24.8%) age between 26-49 yrs and only one patient fall under age 50-70 yrs.

Peripheral neuropathy is reported by twenty eight patients based on this findings and females are still regarded as majority as they are eighteen (20.7%) followed by males which they regarded as minority because they are only ten (22.7%). Out of this twenty eight, twenty two patients (20.2%) age between 26-49 yrs, followed by five patients (38.5%) who they age between 50-70 yrs and the last one patient (12.5%) age between 15-25 yrs.

Twenty seven patients reported with resistance and sixteen (18.4%) of them were females and eleven (25.0%) were males. Out of these twenty seven patients twenty two (20.2%) age between 26-49 yrs, followed by three patients (21.3%) who age between 50-70 yrs and the last two patients (22.5%) were age between 15-25 yrs.

Lipoatrophy is regarded as one of the toxicities and nine patients had this side effect; six patients (6.9%) were females and three (36.8%) were males and all this patients' age between 26-49 yrs. The last two patients reported T.B, only one (1.1%) is a male and the other one is a female (2.3%). Both this two patients age between 29-49 yrs. In terms of age, majority of all the patients who reported different toxicities age between 26-49 yrs.

Table 15. Proportional comparisons between different demographic characteristics, smoking and drinking and treatment change among of HIV positive patients on anti retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital

(Chi-square test: [Percentages present by row]

Variables		Changed Treatment		Chi-Square	P-value
		Yes	No		
Gender	Male	60 (55.6)	48 (44.4)	1.31	0.25
	Female	119(62.3)	71 (37.7)		
Age (years)	15-25	8 (34.8)	15 (65.2)	7.37	0.02*
	26-49	156(62.9)	92 (37.1)		
	50-70	14(53.8)	12 (46.2)		
Education	No education & primary	48 (54.5)	40 (45.5)	0.53	0.47
	Secondary & Tertiary	92 (59.4)	63 940.6)		
Employment status	Un employed	30 (58.8)	21 (41.2)	3.95	0.13
	Employed	120(47.4)	89(42.6)		
	Pensioner & social grants	29 (74.4)	10 (25.6)		
Marital status	Single, widowed, Divorced	119(56.4)	92 (43.6)	0.46	0.50
	Married, cohabitating	35 (61.4)	22 (38.6)		
Smoking	Smoker	24 (58.5)	17 941.5)	0.67	0.79
	Non smoker	142(60.7)	92 (39.3)		
Drink alcohol	Drinker	14 (51.9)	13 (48.1)	0.87	0.35
	Non drinker	151(61.1)	96 (38.9)		

*Significance at p-value < .05

Gender results: Base on the findings of table 12 majority of patients who changed treatment are females as one hundred and nineteen (62.3%) of them changed treatment from one regimen to another and the remaining seventy one female patients (37.7%) still remain on the same treatment. Total number of female patients is one hundred and ninety. Sixty males (55.6%) also changed treatment from one regimen to another and only forty eight (44.4%) did not change. Chi- square of the gender is 1.31 and P value is 0.25.

Age results: In terms of age, 156 patients (62.9%) who age between 26-49 yrs change treatment from one regimen to another and ninety two patients (37.1%) who fall under this age did not change treatment. Then followed by fourteen patients (53.8%) who age between 50-70 yrs who also change treatment and 12 patients (46.2%) of the same age did not change treatment. The last group is twenty three patients whom eight of them change treatment and the remaining fifteen did not change treatment. Total number of all this patients is two hundred and ninety seven, meaning only one patient age was not documented. Chi square of age is 7.37 and P value is 0.02.

Education: Ninety two patients (59.4%) attended school until secondary and tertiary and this patients changed treatment and sixty three (94.6%) of the same educational level did not change treatment. Total number of patients with no educational background together with those attended until primary are eighty eight and forty eight (54.5%) of them change treatment and forty (45.5%) of the same educational background did not change treatment. Chi square of education is 0.53 and P value is 0.47.

Employment status: Total number of patients who changed treatment is one hundred and seventy nine and one hundred and twenty of them (47.4%) were employed while thirty(58.8%) were unemployed and the last group who get income from pension grand and social grand were twenty nine (74.4%).

Total number of patients who did not change treatment is one hundred and twenty and eighty nine of them (42.6%) were employed, followed by unemployed group of twenty one (41.2%), and the last group who considered to be minority when compared with this group of patients who did not change treatment but who got income from pension grand and social grand are only ten patients (25.6%). Chi square of employment status is 3.95 and P value is 0.13.

Marital status: This group is divided into two, the first one is all the patients who are single, widows and those that are divorced and the second group is the ones that are married and cohabitating. Total number of the first group is two hundred and eleven and one hundred and nineteen of them (56.4%) change treatment from one regimen to another, and ninety two of them (43.6%) did not change treatment, they remained on their initial treatment.

Second group which are those who are married and cohabitating and their total number is fifty seven, and thirty five of them (61.4%) which are majority did change treatment from their initial treatment to another treatment while the remaining twenty two (38.6%) did not change. Chi square of marital status is 0.46 and P value is 0.50.

Smoking

This group is also divided into two, smokers and non smokers. Total number of smokers is forty one and twenty four of them (58.5%) did change treatment and the remaining seventeen (41.5%) did not change treatment. Total number of non smokers is two hundred and thirty four and one hundred and forty two (60.7%) of them who are majorities change treatment from their initial regimen to another and the remaining minorities of ninety two (39.3%) did not change treatment.

Alcohol: Minority of patients were drinking alcohol which were twenty seven and fourteen of them (51.9%) change treatment from the initial treatment to another one while 13(48.1%) did not change treatment.

Majority of patients were non alcohol drinker which was two hundred and forty seven and one hundred and fifty one (61.7%) of them changes treatment and minority of them which are ninety six (38.9%) did not change treatment. Chi square of alcohol drinker is 0.87 and P value is 0.35.

Table 16: based on the results of this table patients change treatment due to toxicities while others did not change treatment, but this change of treatment is highlighted in terms of gender, age, education, employment status, marital status, smoking and drinking alcohol. Majority of patients that changed treatment due to toxicity are seventy one (81.6%) females and sixteen (18.4%) of them did not change treatment and thirty three (75%) of male patients also change treatment and eleven (25.0%) of them did not experience any toxicity meaning they did not change treatment. Chi square of gender is 0.78 and P value is 0.38.

Age in years: Majority of patients age between 26-49years were eighty seven (79.8%) changed treatment because of toxicity while twenty two patients (20.2%) of the same age did not change treatment. And then followed by ten patients (76.9%) who age between 50-70yrs also change treatment and three patients (21.1%) of the same age group still remain to their initial treatment. Minority of patients who changed treatment were those aged between 15-25yrs and they were six (75.0%) and two patients (25.0%) of the same age group did not change treatment. Chi square of age is 0.15 and P value is 0.98.

Education: In terms of education most of the patients that changed treatment were fifty (75.8%) and this group studied until secondary and tertiary, and sixteen patients (24.4%) of the same age group remained to their original treatment. Thirty patients(83.3%) who some of them did not go to school at all together with those that attended until primary did change treatment and six patients of the same age

group(16.7%) did not change treatment. Chi square of education is 0.79 and P value is 0.37.

Table 16: The proportional comparisons between different demographic characteristics, smoking and drinking, treatment changed and reported toxicities among HIV positive patients on anti retroviral treatment at Tshepang wellness clinic Dr George Mukhari Hospital.

(Chi-square test: Percentages present by row)

Variables		Changed Treatment		Chi-Square	P-value
		Yes	No		
Gender	Male	33 (75.0)	11 (25.0)	0.78	0.38
	Female	71 (81.6)	16 (18.4)		
Age (years)	15-25	6 (75.0)	2 (25.0)	0.15	0.98
	26-49	87 (79.8)	22 (20.2)		
	50-70	10 (76.9)	3 (21.1)		
Education	No education & primary	30 (83.3)	6 (16.7)	0.79	0.37
	Secondary & Tertiary	50 (75.8)	16 (24.2)		
Employment status	Un employed	17 (70.8)	7 (29.2)	1.52	0.49
	Employed	70 (80.5)	17 (19.5)		
	Pensioner & social grants	17 (85.0)	3 (15.0)		
Marital status	Single, widowed, Divorced	60 (81.7)	15 (18.3)	0.94	0.33
	Married, cohabitating	22 (73.3	8 (26.7)		
Smoking	Smoker	16 (84.2)	3 (15.8)	0.33	0.57
	Non smoker	80 (78.4)	22 (21.6)		
Drink alcohol	Drinker	7 (70.8)	3 (30.3)	0.60	0.44
	Non drinker	90 (80.4)	22 (19.6)		

*Significance at p-value < .05

Employment status: Majority of seventy (80.5%) patients who changed treatment because of toxicities are those who are employed followed by seventeen (70.8%) unemployed group together with another seventeen (85.0%) who got money from pension and social grand. Another group of twenty patients did not change treatment, and out of this group seventeen (19.5%) of them who are regarded as majority are employed, followed by seven (29.2%) unemployed group and the last group which are three patients (15.0%) got money from pension and social grand. Chi square of employment is 1.52 and P value is 0.49.

Marital status: Based on the results of this marital status, group of single, widow and divorced are majority as sixty patients(81.7%) changed treatment from one regimen to another due to toxicity and minority of twenty two patients(73.3%) who were married and cohabitating also changed treatment. Another group of fifteen patients(18.3%) who are single, widow and divorced did not change treatment, followed by the last group of patients who are married and cohabitating are eight(26.7%), and they did not change treatment as well, meaning they remained on their initial treatment. When we compare these three groups based on employment status majority are those that changed treatment compared to those that did not change treatment.
Chi square of marital status is 0.94 and P value is 0.33.

Smoking: Sixteen patients (84.2%) based on this results were smokers and eighty (78.4%) patients were non smokers and this two groups have both changed treatment, and eighty of them (78.4%) were non smokers and regarded as majority. The next group is the group of patients that did not change treatment and three (15.8%) of them were smokers while another twenty two (21.6%) were non smokers. Chi square of smoking is 0.33 and P value is 0.57.

Alcohol drinker: This group is divided into two, the drinker and non drinker. Ninety patients (80.4%) who were non drinker were majority and they changed treatment

from one regimen to another and seven patients (70.8%) were alcohol drinker also changed treatment. The other group are those that did not change treatment, twenty two of them (19.6%) did not change treatment while three (30.3%) did change treatment. Chi square of smoking is 0.60 and P value is 0.44.

CHAPTER V

DISCUSSIONS, CONCLUSION AND RECOMMENDATIONS

5.1. Discussions

In this chapter, a summary of the study is provided. Details of the major findings of the study are underlined in the conclusion, and finally, recommendations emerging from the findings of this study are proposed.

5.1.1. Toxicity

According to study results of a cohort of HIV positive patients at Tshepang wellness clinic majority of patients which is 85% initiated with Regimen 1A (d4T, 3TC and EFV) and 6.7% started with Regimen 1C (AZT, 3TC and EFV). Results also shows that 58.9% patients changed treatment because of different toxicities of which 49.5% changed because of lipodystrophy, lipoatrophy, lactic acidosis or hyperlactaemia. The study results show that only 0.3% receiving Regimen 1a remains free from tocixity while the rest of the patients changed to other regimens due to toxicities.

Effects of stavudine are highlighted as lipodystrophy,peripheral neurophathy, hepatitis, pancreatitis and hyperlactaemia or lactic acidosis. Literatures highlighted that stavudine is the NRTI and is also a regimen 1, that is most often associated with mitochondrial toxicity, which results in high rate of lipoatrophy, peripheral neurophathy, lactic acidosis and pancreatitis.

Findings about toxicity-According to studies conducted by Zachariah et.al (2006) in Tororo Uganda 1073 participants were treated with d4t, 3TC and NVP. The participants of remaining free from toxicities at 6,12 and 18 months were 92%, 86% and 84% respectively where as nearly 50% of the patients experienced some form of toxicities by 18 months. Toxicity requiring change in therapy occurred in 21% of the cohort, most commonly switched from d4T to AZT. In Nairobi Kenya 284 patients received d4T, 3TC and NVP and reported toxicity free survival rate was 21% at 18 months. In a report from Zachariah et.al (2006) Khayelisha South Africa on 1700 patients receiving ART, one agent was substituted in approximately 10% because of toxicity.

5.1.2. Results about stavudine and Peripheral neuropathy

Based on results of the study conducted at Tshepang wellness clinic only 12.7% of patients diagnosed with peripheral neuropathy of which cause is not highlighted in this study, the only thing that is documented is that majority of 85.2% of patients started with Regimen 1a which includes stavudine, and again 50.2% patients changed to regimen 1c containing AZT, as it highlighted before that is the substitute of d4T, while other patients changed to other regimens.

According to prospective study conducted by Gerald et.al (2008) from 10-21% of persons exposed to stavudine developed peripheral neuropathy in developed countries. 56% patients in Malawi cohort study according to Gerald et.al (2008) developed peripheral neuropathy. Another study conducted by Beadles et.al (2008) highlighted that ARV naïve patients who initiated d4T containing treatment regimen were reported symptoms of peripheral neuropathy within 28 days after ARV drug initiation, and 50% of patients switched to AZT containing ARV regimen because of severe persistent neuropathy. According to Markison et.al(2008) in resource limited settings results shows that first line ARV containing stavudine used for clinically eligible patients and 13% of patients were given diagnose of Peripheral neuropathy and 6% switched to AZT as it is used as a substitute for d4T.

5.1.3. Results about stavudine and lipodystrophy

Results of the study conducted at Tshepang wellness clinic in a cohort of HIV positive patients shows that only 14.7% of patients diagnosed with lipodystrophy. It is highlighted in the literature review that stavudine is strongly associated with this adverse effect and it is also mentioned that for reducing incidence of lipodystrophy substitute of stavudine to zidovudine is recomended. As it mentioned before that 85.2% of patients started with regimen 1a containing d4T, and 50.2% changed to regimen 1c containing AZT.

According to cohort study conducted by Ramnath et.al (2007) the prevalence of stavudine associated lipodystrophy in western studies has reached as high as 50-63%.Results of this study shows that a small south cohort had 3.5% rate of lipodystrophy, and only 17% of patients in Southern Asian cohorts developed lipodystrophy compared with 24.8% of patients in Rwanda cohort and 46.1% in Indian cohort.

5.1.4. Results about stavudine and Lipoatrophy

Results of cohort patients at Tshepang wellness clinic shows that only 8.4% of patients diagnosed with lipoatrophy and 3 of them were males (36.8%) and majority of 6 were females (6.9%). Subbaraman et.al (2007) mentioned that in Rwadan individuals that were receiving HAART for more than a year 90% of them were on stavudine, and 29.4% of them presented with lipoatrophy or mixed form with lipodystrophy

5.1.5. Results about stavudine and hyperlactaemia

Results of cohort of HIV positive patients at Tshepang wellness clinic, shows that 33 patients out of 299 diagnosed with lactic acidosis and 22 of them were females which is (25.3%) and only 11(25%) were males. This shows that females are mostly majority diagnosed with lactic acidosis compared to men.

The major use treatment was NRTI which is stavudine and lamivudine and this treatment also used in the Western studies according to Makison et.al (2008). According to cohort study conducted by Makison et.al (2008) 8-18% of HIV positive patients test positive for hyperlactaemia in Western studies in which stavudine, lamivudine or didanosine were the major NRTIs used. Literature review highlighted that in a retrospective cohort study of 1735 patients in Soweto, South Africa (63%) were females and 23 patients presented with lactic acidosis and risk factor include stavudine. Risk factor includes stavudine treatment. In Botswana 650 patients (69.4%) were females, and Tshepo study showed a higher than expected rate of lactic acidosis while fifteen patients(2%) developed moderate to severe symptomatic hyperlactaemia.

5.1.6. Treatment change due to pregnancy

Study conducted at Tshepang wellness clinic in a cohort of HIV positive patients shows that 16patients (5.4%) change treatment due to pregnancy, but substitute of treatment is not highlighted.

According to Matthew et.al (2007) treatment with efavirenz should be avoided in the first trimester which is the period of organogenesis and again birth defects were observed in the United States following exposure to efavirenz.

5.1.7. Resistance and treatment failure.

Results of the study conducted at Tshepang wellness clinic shows that only 7 patients (2.7%) diagnosed with resistance and adherence related to resistance is not highlighted anywhere

In Tanzania study conducted by De Luca et.al (2007) 23 people (16%) reported incomplete adherence and among 48 people (32%) with virologic failure self reported poor adherence.

5.1.8. Treatment interruption

In a cohort of HIV positive patients at Tshepang wellness clinic only 7 patients had treatment interruption according to Dr's orders but reason of interruption is not documented.According to study conducted by WHO (2006) it is mentioned that treatment interrupted because of lactic acidosis is 0.13% of patients receiving NRTI at John Hopkins University.

5.2. Conclusions

5.2.1. Data collection

500 Pharmacovigilance files were supposed to be reviewed, instead 301 files reviewed, reason being the clinic lost some of the files, only 301 files were the ones with a pharmacovigilance sign, this files includes active patients(patients that are still coming for treatment), loss to follow up including those that fall under deceased. During data collection most of the files doesn't have initiation information, especially sociodemographic information and that's why there is a (not documented) as an answer.

Treatment related data was always there but to most of the files it was only recent information not information from initiated date of treatment and in this way it doesn't give us all the information or reasons of what happened to the patient to be where he/she is in terms of treatment. More or less 20 files reviewed per day as we experience d some challenges during data collection, e.g.: clinic staff will come and take files that we selected for the day and some times they will take it when you are busy with it, in that way meaning you will have to search for it again the following day.

5.2.2. Data entry and data analysis

Data entered in excel spread sheet and then imported and analyzed into software SPSS 17.0 computer program and relevant themes were extracted. During data cleaning phase respondent were excluded for reasons like missing values, errors and data inconsistence. Data described by means of tables, histograms, pie charts, cross tabulation and summary statistics. Statistical significance of the difference between treatment change and regimen change among different socio demographic characteristics was tested using Chi- square test to compare proportion and measure associations between the two variables.

5.2.3. Summary of the results

The purpose of this study is to identify reasons of treatment and regimen change in a cohort of HIV positive patients at Tshepang wellness clinic and to make appropriate recommendations to the doctors (Senior Management) of the clinic to minimize treatment and regimen change to patients if possible based on the recommendations of this study.

Based on the results of this study, conducted on the patients that were enrolled at Tshepang wellness clinic from July 2004- May 2007. Results showed that from July 2005- December 2005 91 patients (31.2 %) which are majority enrolled for pharmacovigilance study compared to other years. Again 255 patients (85.2%) were initiated Regimen 1a which are majority compared to other types of regimens, and 17 patients (5.7%) were initiated regimen 1b, 20patients (6.7%) were initiated regimen c and the last and minority 2 patients (0.7%) changed to regimen 1d.

Based on the results of reasons of treatment and regimen change, toxicity appear as the main reason of treatment and regimen change on this study because 148 patients reported toxicities 49.5% (peripheral neuropathy, lactic acidosis, lipodystrophy,

lipoatrophy etc.) . Pregnancy is the following one with 16(5.4%) patients and all of them were females. T.B and Resistance are the following reasons with 6(2.0%) patients, and on this two variables males were 2 and females were 4. In general based on the results majority of patients who changed treatment were females which are 91(86.7%) and males are minorities of 44(84.6%). Results shows that 33 patients (11.0%) changed treatment because of hyperlactaemia and these patients are majority in terms of toxicities, followed by 32 patients (10.7%) who changed because of lipodystrophy and peripheral neurophathy also noted on 28 patients (9.4%). Nine patients (3.0%) also change treatment because of lipoatrophy and the last 2(0.7%) which are regarded as minorities changed because of resistance.

Patients stopped or changed the initiated treatment, according to this results in 2005 4 patients (1.3%) changed to another regimen, 2006 only 78(5.6%) also changed, 2007- 97patients (32.2%) which are majority of pharmacovigilance out of the other years (July 2004-2007 May) also changed. The rest of the patients which are 122(40.5%) were not documented.

5.3. Recommendations

Based on the findings of this study, the following are proposed to minimize treatment and regimen change on HIV patients at Tshepang wellness clinic

- Any treatment with long term side effects needs to be closely monitored
- Suggestion is that all the Physician working at HIV clinics must be trained for HIV so that they can be able to identify or detect side effects
- If possible Stavudine should no longer prescribed instead NRTI in line with WHO recommendation for first line antiretroviral therapy
- Implementation of monitoring of adherence needed to prevent virological failure and resistance
- Suggestion is that clinic staff should start with pill count for prevention of resistance
- Obesity especially for women should be taken into consideratrion before initiation of ARVs especially stavudine to prevent hyperlactaemia
- Government can minimize adverse drug reaction by letting the primary health care clinics to open 24hrs; including holidays to accommodate everyone that works until late or on weekends with the aim of engaging more patients in long term follow up.
- Recommendation is that before initiation of treatment to anyone, our government should take into consideration socioeconomic status of the patients, instead of giving them grand they can provide them with transport to and from the clinic and give them food parcels, because not every one who is unemployed qualify for grand. By doing so it will be fair to everyone, and maybe resistance will be minimized.
- Implementation of protocols for regular clinical screening of patients will help the doctors that doesn't have HIV/AIDS speciality to detect toxicities earlier and it will also help them in terms of correct treatment initiation

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Appendix A: Data Collection Sheet (data Extraction sheet

Case No	
Hospital no	
SOCIO DEMOGRAPHICS	
Gender	
Age	
Level of Education	
Employment status	
Source of income	
Marital status	
BEHAVIORAL DATA	
Smoking	
Use of alcohol	
Use of traditional medicine	
Habit forming drugs	
TREATMENT RELATED DATA	
Start date of ARVs	
Regimen 1a,1b,1c,1d	
Regimen 2	
Stop date of reg 1a,1b,1c,1d or 2	
Reason for ARV change	
New ARVs prescribed	
Which regimen prescribed?	
1a,1b,1c,1d or 2	
Reported toxicities	
Any treatment interruption?	
If yes for how long?	

Appendix B: Estimated time table and Budget

Activities	Time
Submission to REPC, MREC	Jan-Feb 2009
Permission: Hospital CEO & HOD	Feb 2009
Collect data from hospital files & enter into database	February- April 2009
Data Analysis	June 2009
Data interpretation	July 2009
Writing-up	September 2009
Submit 1st draft	November 2009
Correction and re-submission	February 2010
Final submission	March 2010

Budget

	Costs	**Total costs**
Telephone cost and emails	For both researchers	R500.00
Copies of data collection tools	500 copies	R500.00
Transport to Hospital for data collection(both researcher) For maximum of 30 days	R50 x 30 daysx2 (researchers)	R1500x 2= R3000.00
Data analysis by statisticians	R3000,00	R3000.00
Total costs		R7000.00

APPENDIX C

FACULTY OF HEALTH SCIENCES, SCHOOL OF PUBLIC HEALTH
STUDENT RESEARCH PROJECT MANAGEMENT
DATA COLLECTION CONFIRMATION SHEET

1. Researcher declaration

Name of Researcher: NTSHEBO MOCKETSI
Title of study: Treatment and regimen change in a cohort of HIV positive patients on ARV treatment at Tshepang Wellness clinic, Dr George Mukhari Hospital.
Research project Number: MREC/PH/108/2009: PG
Period of data collection: Initiated: 29.02.2009 Completed: 23.03.2009

I hereby declare that I collected data according to the specifications of the approved proposal.
Signed: N Mocketsi

2. Research site and activities

Name of organization/institution: Tshepang Wellness clinic Dr George Mukhari Hospital

Type of organization/institution (mark with an X)				
Industry	Health facility X	Educational institution	NGO	Other (specify)

Town/Village (name)	Country
Ga-rankuwa (PRETORIA)	South AFRICA

Main data collection activities (sign against all applicable)			
Interviews	Focus groups	Record reviews X	Self-administered questionnaire

Other people involved in data collection: Salome Matarose

I, T.H. NKOSI being the OPERATIONAL MANAGER (position) of the above organization/institution, hereby confirm that the researcher named above collected data as indicated
Signature T.H. NKOSI Date: 2009/04/01

Contact details of organization/institution

Postal/Physical address: PRIVATE BAG X422 PRETORIA, 0001
Telephone: (012) 529-3342 Facsimile: (012) 5266000 ext 194
Email:

GAUTENG PROVINCIAL GOVERNMENT
DR. GEORGE MUKHARI HOSPITAL
PRIVATE BAG X422
30 MAY 2009
PRETORIA 0001
PATIENT ADMIN
GAUTENG PROVINSIALE REGERING

Official stamp of organization

APPENDIX D

DR GEORGE MUKHARI ACADEMIC HOSPITAL
OFFICE OF THE CLINICAL DIRECTOR

health for a better life

Enquiries: Dr. Ddungu MPE
Tel no: +27 12 529 3880
Fax no: +27 12 529 3851

To Ms. Ntshebo Mirriam Moeketsi
P.O. Box 29973
Sunnyside
0132

Date: 18th February 2009

RE : PERMISSION TO CONDUCT RESEARCH.

The Dr. George Mukhari Hospital hereby grants you permission to conduct research on "Treatment and regimen change in a cohort of HIV positive patients on anti-retroviral treatment at Tshepang Wellness Clinic, Dr. Goerge Mukhari Hospital."

We note that you have already obtained ethical Clearance from the Human Research Ethics Committee.

☑ This permission is granted subject to the following conditions:
That the Hospital incurs no cost in the course of your research.

☑ That access to the staff and patients at the Dr George Mukhari Hospital will not interrupt the daily provision of services.

☑ That prior to conducting the research you will liaise with the supervisors of the relevant sections to introduce yourself (with this letter) and to make arrangements with them in a manner that is convenient to the sections.

Yours sincerely

GAUTENG PROVINCIAL GOVERNMENT
DIRECTOR CLINICAL SERVICES
2009 -02- 19
PRIVATE BAG X422
PRETORIA 0001
DR GEORGE MUKHARI HOSPITAL

DR. DDUNGU M.P.E.
DIRECTOR: CLINICAL SERVICES

Please provide a copy of the Patient Information Sheet and Consent form to be used, ~~BEFORE~~ commencing.
19/02/2009.

Private Bag X422
Pretoria
0001

APPENDIX E

UNIVERSITY OF LIMPOPO

Medunsa Campus

P O Medunsa
Medunsa
0204
SOUTH AFRICA

Tel: 012 - 521 4000
Fax: 012 - 560 0086

MEDUNSA RESEARCH & ETHICS COMMITTEE

CLEARANCE CERTIFICATE

MEETING: 01/2009

PROJECT NUMBER: MREC/PH/08/2009: PG.

PROJECT :

Title:	Treatment and regimen change in a cohort of HIV positive patients on anti-retroviral treatment at Tshepang wellness clinic, Dr George Mukhari Hospital
Researcher:	NM Moeketsi
Supervisor:	Prof Supa Pengpid
Hospital Superintendent:	Mr Ramafoko (Dr George Mukhari Hospital)
Involved Departmental Head:	Tshepang Wellness Clinic (Dr George Mukhari Hospital)
Department:	HSMP
School:	Public Health
Degree:	MPH

DECISION OF THE COMMITTEE:

MREC approved the project.

DATE: 05 February 2009

RESEARCH & PARTNERSHIP
2009 -02- 05
MEDUNSA CAMPUS

PROF GA OGUNBANJO
CHAIRPERSON MREC

Note:

i) **Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee.**

ii) **The budget for the research will be considered separately from the protocol.**

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.