EXTENT AND REASONS FOR SUBSTITUTING AND SWITCHING HIGHLY ACTIVE ANTIRETROVIRAL THERAPY AT THE KATUTURA INTERMEDIATE HOSPITAL IN WINDHOEK, NAMIBIA

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KEYWORDS

HIV/AIDS, antiretroviral, HAART, switch, substitute, toxicity, adverse effects, resource poor country, developing country, Sub-Saharan Africa.

ACRONYMS

ABC	Abacavir (antiretroviral medicine)
AIDS	Acquired Immuno-Deficiency Syndrome
ARV	Antiretroviral
ART	Antiretroviral Therapy
AZT/3TC	Zidovudine and Lamivudine (antiretroviral medicine)
BMI	Body Mass Index
CD4	CD4 T-cells (T-lymphocytes bearing CD4 receptor)
ddI	Didanosine (antiretroviral medicine)
DNA	Deoxyribonucleic Acid
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immuno-Deficiency Virus
IDV	Indinavir (antiretroviral medicine)
IDV/r	Indinavir + Ritonavir (antiretroviral medicine)
KIH	Katutura Intermediate Hospital
LPV	Lopinavir (anti retroviral medicine)
LPV/r	Lopinavir + Ritonavir (antiretroviral medicine)
MoHSS	Ministry of Health and Social Services
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NtRTI	Nucleotide Reverse Transcriptase Inhibitor
NVP	Nevirapine (antiretroviral medicine)
PI	Protease Inhibitor (antiretroviral medicine)
IQR	Inter Quartile Range
RNA	Ribonucleic Acid

RTV	Ritonavir (antiretroviral medicine)
TDF	Tenofovir (antiretroviral medicine)
UNAIDS	Joint United Nations Programme on HIV and AIDS
WHO	World Health Organisation

ABSTRACT

Background: Namibia is one of the Southern African countries hardest hit by the HIV epidemic, with an estimated one out of every five people infected (MoHSS, 2004). Approximately 80,000 of the infected population currently require antiretroviral treatment (ART). In order to prevent the progression of the HIV infection to AIDS, patients are required to take antiretroviral medicines lifelong. This lifelong use exposes patients to toxicities of these medicines and the only available options of managing the toxicities of ARVs are to treat the toxicity or substitute or switch the offending medicines.

Aim: The current study aimed to describe the extent and reasons for substituting and switching HAART at the Katutura Intermediate Hospital in Windhoek, Namibia.

Methodology: A descriptive retrospective case series study, in which medical records were reviewed to determine the extent and reasons for substituting and switching HAART was conducted. Random sampling was used to draw a sample of 500 from 3477 adult HAART patients who commenced treatment between 1 January 2002 and 31 December 2006. A pre-piloted data collection tool was used to collect the data. The following information was collected: baseline CD4 count, weight, initial ARVs, first and second ARV substitutions, ART switch and the reasons for substituting ARVs or switching ART during the indicated period. Epi Info version 6 was used to analyse frequencies, means and medians of all important variables in the data set.

Results: The sample was made up of 500 HAART patients; 60% were females. The median age of the sample was 34 years (Inter-quartile range (IQR) 30 – 40) and the median CD4 cell count was 153 cells/mm^3 (IQR 96 – 212) at initiation of therapy. The median time on

treatment before first substitution was 28 months (IQR 24 – 34), whereas the median time before second substitution was 10 months (IQR 6 – 15) from the time of the first substitution. The median time before switching was 31 months (IQR 24 - 39). A total of 31% of the study subjects underwent a substitution once, whereas 1.8% underwent a second substitution. Only six (1.2%) patients switched to a second line treatment after the modification of the treatment. The most commonly recorded reason for the first substitution was toxicity (19%). As in other studies, stavudine (D4T), nevirapine (NVP) and efavirenz (EFV) were the ARVs associated with most of the recorded toxicities. High viral load (50%) was the most reported reason for switching. In almost half of the substitution cases the reasons for substitution were not stated, and in a third of the switch cases the reasons for switching were not stated.

Conclusion: The rate of substitution at 31% was similar to that found in other resource poor settings, however, the rate of switching (1.2%) was much lower than was found in similar settings. The main reason stated for substituting antiretrovirals was “toxicity”.

DECLARATION

I declare that "Extent and reasons for substituting and switching Highly Active Antiretroviral Therapy at the Katutura Intermediate Hospital in Windhoek, Namibia" is my own work that it has not been submitted for any degree or examination in any other university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Full Name: Johannes Gaeseb **Date: 20 November, 2008**

Signed:

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CHAPTER 1: INTRODUCTION

1.1 Introduction

The 2008 report on the global Acquired Immuno-Deficiency Syndrome (AIDS) epidemic from the Joint United Nations Programme on HIV/AIDS (UNAIDS) indicated that there was a total of 33.2 million people living with the Human Immunodeficiency Virus (HIV) in the year 2007 (UNAIDS, 2008). There were 2.5 million new infections and 2.1 million people died of AIDS in 2007. In Sub-Saharan Africa there were 1.7 million new infections with a total of 22.5 million infections, which represent 67%, or two thirds, of the global total. Globally, 50% of those that are HIV positive are women, whereas in Sub-Saharan Africa women make up 60% of the HIV positive population (UNAIDS, 2008).

Southern Africa is the epicentre of this epidemic, with 35% of the global HIV infected people living in this region while it is only home to about 10% of the world's population (UNAIDS, 2008; SADC, 2006). Namibia is one of the Southern African countries hardest hit by the HIV epidemic with an estimated 230,000 people infected (MoHSS, 2004). Approximately 80,000 of these infected people require antiretroviral treatment (ART) (MoHSS, 2007).

In recognition of the above-mentioned, and the advances made in treating HIV infected people in other parts of the world, Namibia started providing Highly Active Antiretroviral Therapy (HAART) in 2002, as a pilot project at Katutura and Oshakati Intermediate Hospitals. HAART is characterised by the provision of at least three antiretroviral medicines (ARVs) to a HIV infected person (MoHSS, 2003). Based on the lessons learned from this pilot project, Namibia developed national guidelines for the use of antiretrovirals (ARVs). (MoHSS, 2003)

ARVs are divided in three major classes, based on their action on the HI-virus, namely:

- Nucleoside Reverse Transcriptase Inhibitors (NRTIs);
- Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIs); and
- Protease Inhibitors (PIs).

The Namibian HAART is based on the backbone of NRTIs with a NNRTI and/or a PI. HAART consists of at least three ARVs made up of 2 NRTI and 1 NNRTI and/or 1 PI. Treatment regimens without a PI are classified as first line, whereas the ones that contain a PI are classified as second line (MoHSS, 2003).

According to the Namibian ART guidelines, patients must meet the criteria indicated in the guidelines to qualify for HAART (MoHSS, 2003). These criteria are put in place to ensure that the patients are committed to lifelong treatment with ARVs, thereby reducing the number of defaulters and consequently the development of drug resistance. According to the 2003 guideline, patients would be started on HAART if they had the following: WHO stage IV HIV disease (clinical AIDS), irrespective of CD4 cell count; or WHO stages I, II and III HIV disease, with a CD4 cell count of below 200 cells/mm^3. In addition, before a patient is put on treatment, the patient must meet the following criteria: have lived at a fixed address for the past three months; have ready access to a designated treatment centre; have identified someone to serve as treatment supporter; and must be committed to long term treatment.

In response to the WHO's 3x5 strategy, which was aimed at getting 3 million HIV infected people in middle and lower income countries on antiretroviral therapy by the year 2005, Namibia rolled out the ART programme to all state hospitals country wide in 2003. By the end of 2007 approximately 38,046 (66%) people were on HAART (MoHSS, 2008).

The effectiveness of HAART in reducing morbidity and mortality has been shown in both industrialised (Palella et al., 1998; Berry et al., 2001) and resource limited settings (Wester, et al., 2005; Ivers, Kendrick and Doucette, 2005). Several studies have demonstrated, especially in clinical trials in industrialised countries, that long time exposure to ARVs is associated with adverse reactions or toxicities (Moyle, 1999; Kimm et al., 2007; Murphy, 2007). A South African study assessing the adverse drug reactions in adult medical inpatients, in a hospital serving a community with high HIV/AIDS prevalence, found that antiretrovirals were the commonest class of drugs causing adverse reactions (Metha et al., 2007). Other studies in resource poor settings such as Malawi, Senegal and South Africa, also found that toxicities were the commonest reason for treatment modification (Jahn et al., 2008; Etard et al., 2006; Suleman and Ramkissoon, 2008). Studies have also indicated that such toxicities, coupled with inconveniences, such as high pill burden, dosing and dietary restrictions, affect adherence to these effective drugs and thus may render them ineffective (Moyle, 2003; Clayden, 2006).

In order to address such negative effects, clinicians and their patients are required to modify such therapies in order to reduce or eliminate the offending medicines (Wilken, Glesby, and Gulick, 2006). Substitution means the changing of one or two medicines within the first or second line regimen, whereas switching refers to the changing from a first line regimen to a second line regimen. Understanding the extent and reasons for substituting and switching ARVs, and which toxicity is associated with which antiretroviral could allow providers to target those toxicities, or be cautious with the use of toxicity-associated antiretrovirals to reduce interruption or discontinuation of antiretroviral therapy.

In Namibia the number of people on antiretrovirals has increased with the scaling up of antiretroviral therapy services. When the scaling up process started in 2003 less than 3% of the people requiring treatment were on treatment. By the end 2007, 66% (38,046) were on antiretroviral treatment (MoHSS, 2008). It is further projected that by the end of 2013, 80% of those requiring treatment (84,000) will be on antiretroviral treatment. These figures indicate that large numbers of people will be exposed to ARVs. The Katutura Intermediate Hospital (KIH) is one of the three intermediate hospitals in the country, and being situated in the capital city, Windhoek, it receives referrals from the other two intermediate hospitals as well as the district hospitals. As one of the ART pilot sites, the Katutura Intermediate Hospital has one of the highest numbers (12%) of people on antiretrovirals compared to all other sites. This study intended to describe the extent and reasons for substituting and switching Highly Active Antiretroviral Therapy at the Katutura Intermediate Hospital.

1.2. Aim and objectives

1.2.1. Aim

To describe the extent and reasons for substituting and switching highly active antiretroviral therapy at the Katutura Intermediate Hospital (KIH) in Windhoek, Namibia.

1.2.2. Objectives

1. To measure the extent of substitution of antiretrovirals in the provision of HAART at KIH.
2. To measure the extent of switching from the first line ARVs to second line ARVs in the provision of HAART at KIH.
3. To describe the stated reasons for substituting and switching ARVs in the provision of HAART at KIH.

CHAPTER 2: LITERATURE REVIEW

This chapter will consist of two sections. The first section will clarify terms and concept used, whereas the second section will highlight relevant literature on the subject matter.

2.1. Definition of terms and concepts

Antiretroviral drugs

These are medications that are used in the treatment of infections caused by Human Immunodeficiency Virus. There are different classes of antiretroviral drugs and they act at different stages of the Human Immunodeficiency Virus life cycle (WHO 2006a:24). (See Table 2)

HAART regimen

HAART stands for highly active antiretroviral therapy, which refers to the taking of three or more antiretroviral drugs for the treatment of HIV infection.

1st line treatment regimens

REGIMEN (ART guideline 2003)	REGIMEN (ART guideline 2007)
NVP/D4T/3TC; NVP/AZT/3TC; NVP/AZT/ddI; (NVP/D4T/ddI)	NVP/D4T/3TC; NVP/AZT/3TC
EFV/D4T/3TC; EFV/AZT/3TC; EFV/AZT/ddI; (EFV/D4T/ddI)	EFV/D4T/3TC; EFV/AZT/3TC

2nd line treatment regimens

REGIMEN (ART guideline 2003)	REGIMEN (ART guideline 2007)
IDV/r/D4T/3TC; IDV/r/AZT/3TC; IDV/r/AZT/ddI; (IDV/r/D4T/ddI)	
LPV/r/D4T/3TC; LPV/r/AZT/3TC; LPV/r/AZT/ddI; (LPV/r/D4T/ddI)	LPV/r/AZT/TDF/3TC; LPV/r/AZT/3TC/ddI; LPV/r/ABC/ddI

CD4+ T-cell (T-lymphocytes bearing the CD4 receptor) count

This is one of the useful and reliable methods to assess if a Human Immunodeficiency Virus positive patient should start antiretroviral therapy, as well as assessing the effectiveness of antiretroviral therapy. According to the Namibian antiretroviral therapy guideline of 2003 (as well as the guideline for 2007) treatment is started once a patient's CD4 cell count is ≤200 cells/mm^3.

Modification

Modification is defined as substituting antiretrovirals or switching antiretroviral therapy

Substitution

Substitution is defined as replacing one antiretroviral medicine in antiretroviral therapy with another antiretroviral medicine of the same class, e.g. replacing one Nucleoside Reverse Transcriptase Inhibitor antiretroviral with another Nucleoside Reverse Transcriptase Inhibitor antiretroviral.

Switching

Switching is defined as replacing first line antiretroviral medicines with second line antiretroviral medicines.

Viral load

Viral load is a measure of the severity of a viral infection, and can be calculated by estimating the plasma level (quantity) of human immunodeficiency virus (HIV) ribonucleic acid (RNA). It is measured as RNA copies/ml of blood plasma.

2.2. Relevant literature

The human immunodeficiency virus (HIV), the virus that causes acquired immunodeficiency syndrome (AIDS), replicates continuously in CD4 cells causing their depletion and predisposing the patient to opportunistic infections and tumours. There is currently no cure for HIV infection, only ways to control it and attempt to keep it from progressing into AIDS. A key strategy in fighting the global epidemic of HIV/AIDS has been the development of antiretroviral medicines. Antiretrovirals act by slowing down the reproduction rate of the human immuno-deficiency virus. There are three classes of antiretrovirals named after their mechanism of action, as indicated in Table 1 below.

Table 1: Classes of antiretroviral (adapted from MoHSS, 2003)

Antiretroviral class	Antiretroviral
Nucleoside reverse transcriptase inhibitors (NRTI)	zidovudine, stavudine, didanosine, zalcitabine, lamivudine, abacavir, emtricitabine
Non-nucleoside reverse transcriptase inhibitors (NNRTI)	nevirapine, efavirenz

Protease inhibitors (PI)	saquinavir, indinavir, ritonavir, amprenavir, lopinavir-ritonavir, atazanavir

**underlined antiretrovirals are in the MoHSS guidelines for antiretroviral therapy of 2003*

Nucleoside reverse transcriptase inhibitors work by halting the multiplication of the virus by stopping the elongation of the new DNA chain. Non-nucleoside reverse transcriptase inhibitors bind directly to the reverse transcriptase enzyme, thereby interfering with its activity. The difference between the mechanism of action of NNRTIs and NRTIs is that NRTIs competes with the naturally occurring deoxynucleotides needed to synthesize the viral DNA, whereas NNRTIs binds at a different site on the enzyme and thereby inhibits the movement of protein domains needed to carry out the process of DNA synthesis. Protease inhibitors block the enzyme protease which is necessary for final processing and thereby prevents maturation into an infectious virus.

Highly Active Antiretroviral Therapy (HAART), which is the combined use of antiretrovirals, prevents the HIV from spreading in the body at different stages of its development process and thereby avoids development of resistant viral strains, delays clinical progression and diminishes mortality (Carpenter et al., 2000). HAART consist of at least three antiretrovirals of at least two different classes (MoHSS, 2007). There are first line and second line treatment regimens of HAART in terms of the guidelines for antiretroviral treatment (MoHSS, 2003). The second line treatment regimens contain protease inhibitors and are mainly reserved for those patients that fail or do not respond well to first line treatment regimens. In 2007 Namibia introduced a second edition of the National Guidelines for Antiretroviral Therapy. The second edition was necessitated by experiences from the first editions and new developments in clinical practise of antiretroviral therapy provision. The second edition of the guideline have several changes such as the introduction of new

antiretrovirals, e. g. tenofovir, abacavir, to increase the number of treatment options available to clinicians. Another change is the increased baseline level of CD4 cell count, from 200 to 250 cells/mm^3, for pregnant women to start ART.

2.2.1. Improved survival with antiretrovirals

The advent of ARVs has reduced the rate of morbidity and mortality in people infected with HIV in both developed and developing countries (Palella et al., 1998; Hogg et al., 1998; Nkhoma et al., 2008). In their study Palella et al found that the rate of mortality was reduced, even for patients with a low CD4 count (≤50 mm^3), with the increase in intensity of ART (the use of a combination ARVs). A Botswana study also found that the rate of survival of HIV infected patients increased with the use of ART (Wester et al., 2005). A study by Emery et al., (2008) that compared two groups of patients, those who were either ART naïve or did not receive ART for at least 6 months and those who were continuously on ART, found that the risk of opportunistic diseases and progression to AIDS was reduced by early ART use rather than deferred ART use. This was further confirmed by Berry et al., (2001) that indicated that initiation of combination antiretroviral therapy at the diagnosis of HIV produced significant virologic, immunologic and clinic benefits to patients. Dragsted et al., (2004) also found that the risk of immunological failure, in patients that respond well on their HAART treatment, diminished the longer they stayed on an effective treatment.

In many resource poor countries, ART is only started once the CD4 cell count ≤200 cells/mm^3 in asymptomatic patients. However, several studies (Sterling et al., 2003; Lau, Gange and Moore, 2007) have indicated that the chances of survival were increased if ART was started earlier, i.e. at CD4 cell counts of >200 cells/mm^3. In their study Sterling et al (2003) found that the risk of clinical disease progression was high among patients who

initiate therapy at CD4 cell count <200 cells/mm^3. In a Botswana study it was found that the risk of mortality was 3.2 times more for those patients who started ART with a CD4 count ≤50 mm^3 than those who started with a CD4 count >50 mm^3. Stringer et al., (2006) in Zambia, further confirmed that starting ART at CD4 count >200 mm^3 increases the chances of survival as compared to starting with lower CD4 cell count.

Starting treatment at CD4 cell counts >200 mm^3 would have implications for patients, as they would be required to start antiretroviral therapy earlier. It would expose patients that are put on toxic antiretrovirals to the effects of these antiretrovirals very early and for much longer times, compared to if they had waited for the CD4 cell count to drop. Governments in resource poor settings would also be stretched for resources. If patients should start at higher CD4 cell counts than what is in the current guidelines (≤200 cells/mm^3), then this would mean more patients would be on treatment and this would require more human and financial resources (including facilities) to manage the antiretroviral treatment programme.

Evidence from studies indicates that there is a need to control opportunistic diseases in order to improve prognosis of HIV infected patients (Pallela et al., 1998; Lau, Gange and Moore, 2007). Pallela et al., found that there is a corresponding decline in morbidity, especially of the most common opportunistic diseases such as P. carinii pneumonia, M. avium complex disease and cytomegalovirus retinitis, with the increased intensity of the ART. These findings further confirmed that viral load is inversely proportional to ART intensity, with patients on no ART having the highest viral load and those on combination ART containing a PI having the lowest viral load (Pallela et al., 1998). In their study that compared risk of non-AIDS related mortality to that of AIDS related mortality, Lau, Gange and Moore (2007), found that AIDS related mortality was much higher than non-AIDS related mortality in patients with

CD4 counts equal to or less than 200 cells/mm^3. However, this study also found that the overall AIDS-related mortality decreased with the increased use of HAART.

2.2.2. Adherence to antiretrovirals

The provision of ARVs by means of HAART reduces the viral load and thereby reduces the progression of HIV infection into AIDS (WHO, 2003). In order to prevent progression of the disease, patients must maintain an undetectable level of the virus, which requires them to maintain a very high adherence level. Adherence to ARV medicines is a key determinant of the success of HAART (MoHSS, 2007). Poor adherence may lead to virological failure, development of resistance to the medicines with the resulting poor clinical outcome of the treatment. In order to be able to suppress the viral load to levels less than 400 copies/ml, the patients must be more than 95% adherent to their ARV medications (Chesney, 2003). A study by Brigido et al., (2001), in Brazil, found that the risk of both development and death to AIDS increased with lower adherence levels. The less adherent the patient was on the medications, the greater the inability to suppress the viral replication.

Adherence to antiretrovirals is one of the many challenges patients face in maintaining successful antiretroviral therapy. In addition, antiretrovirals can also cause adverse effects that in turn may affect patients' adherence in the long term. Therefore, there is need to prepare patients for the implications of being on HAART before they are started on treatment.

2.2.3. Antiretroviral toxicities

Aniretrovirals, like any other drugs, are not without potential toxicities. Some toxicities are mild and easily manageable, while some warrant stopping therapy. Since there is no cure for HIV infection, patients need to take their HAART treatment lifelong. This long term

exposure of patients to ARVs may have a negative effect on the patient, that is, the patient gets exposed to adverse effects of the antiretroviral medicines (Moyle, 2003). There are class-wide side effects for NRTIs, NNRTI and PIs as indicated in Table 2 (Powderly, 2002; Shibuyama et al., 2006).

Table 2: Class-wide toxicities of antiretrovirals (adapted from Shibuyama et al., 2006)

Class of antiretroviral	Toxicities
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTI)	Anaemia, neutropenia, lactic acidosis, hepatic toxicity, pancreatitis, peripheral neuropathy, lipoatrophy, myopathy, metabolic side effects
Non-nucleoside transcriptase inhibitors (NNRTI)	Rash (hypersensitivity), hepatic toxicity, central nervous system reactions
Protease inhibitors (PI)	Lipid and glucose abnormalities, nephrolithiasis, skin changes

The negative effect of long term use of antiretrovirals has been shown in clinical trials and general clinical practise in both developing and developed country settings. In a Uganda study by Forna et al., (2007), in which patients were treated with stavudine, lamivudine and nevirapine or efaverenz, toxicities developed in 40% of the patients; 36% of the patients developed peripheral neuropathy, of which 9% was severe. The other toxicities reported included rash (6%), of which 2% was severe; hypersensitivity reaction (2%); acute hepatitis, anaemia, acute pancreatitis, and lactic acidosis all of which constituted less than 0.5%. An Italian cohort study by Monforte et al., (2000), found that 36.2% of the patients discontinued

their initial HAART regimen. The reasons cited for these discontinuations were toxicity (21.1%), regimen failure (5.1%), non-adherence (7.1%) and other reasons (2.9%) (Monforte et al., 2000). According to Calza, Manfredi and Chiodo (2003), protease inhibitor (PI) containing treatments are associated with a rapid increase in plasma lipid concentrations in 70% to 80% of the patients. PI regimens are also associated with fat redistribution and lipodystrophy syndrome. Patients on HAART containing the PIs indinavir and ritonavir were more likely to discontinue treatment compared to those with regimens containing the PI, saquinavir.

An Indian study that assessed the clinically significant toxicities of long term, fixed dose generic HAART, found that rash (15.2%) and peripheral neuropathy (9%) were the most common toxicities (Kumarasamy et al., 2008). Other clinically significant toxicities were anaemia (5.4%) and hepatitis (3.5%). In this study women were more likely to experience lactic acidosis, whereas the incidence of immune reconstitution syndrome was higher in men. Hawkins et al., (2007) in their study of an urban Kenyan population found that 26.5% of the patients experienced ART-related toxicities. Neuropathy was the highest reported toxicity at 20.7% of the observed toxicities. Schramm et al., (2008) reported that 97% of patients in their study were diagnosed with ARV related toxicities of which 19% were severe. The most frequent diagnoses were: lipodystrophy (63%), hypertriglyceridemia (41%), asthenia (32%) and increased liver enzymes (27%). Suleman and Ramkissoon (2008) in their public sector antiretroviral services study in South Africa found that the most common side effects for patients on first line HAART was peripheral neuropathy (36%). However a study by Arenas-Pinto et al., (2008) has shown that peripheral neuropathy is experienced shortly after ART exposure. This could indicate that the development of peripheral neuropathy with long term use of ART is limited to subgroups rather than being generalised.

Although there are class-wide toxicities associated with ARVs, particular ARVs are associated with a higher incidence of a particular toxicity compared to others in the same class (WHO, 2008; MoHSS, 2008), as indicated in the Table 3 below.

Table 3: Toxicities mostly associated with specific antiretrovirals (adapted from Shibuyama et al., 2006)

Class	Antiretroviral	Toxicities
Nucleoside/nucleotide reverse transcriptase inhibitors (NRTI)	zidovudine (AZT)	Anaemia, neutropenia, myopathy
	stavudine (D4T)	Peripheral neuropathy, lipoatrophy, lactic acidosis
	didonasine (ddI)	Pacreatitis, peripheral neuropathy
Non-nucleoside transcriptase inhibitors (NNRTI)	nevirapine (NVP)	Rash (hypersensitivity), hepatic toxicity
	efavirenz (EFV)	Central nervous system reactions, possible teratogenecity
Protease inhibitors (PI)	indinavir (IDV)	Nephrolithiasis, skin changes
	ritonavir (RTV)	Lipid and glucose abnormalities

A study by Law et al., (2003) found that nevirapine was associated with a higher incidence of severe hepatoxicity in patients receiving NNRTI containing regimens. A Spanish study also found that 9% of the patients discontinued nevirapine because of either rash or hepatotoxicity (Martinez et al., 2001). A study assessing the antiretroviral-associated toxicity in Mozambican pregnant women found that severe hepatoxicity was more common in those receiving a nevirapine-containing HAART and a CD4 cell count of ≥250 cells/mm^3 (Jamisse et al., 2007). Several studies also found that Hepatitis virus B and C co-infection, female

gender and high CD4 cell count are risk factors for NNRTI associated toxicities, which are mainly rash and hepato-toxicity (van Leth et al., 2005; Kappelhoff et al., 2005; van Schalkwyk et al., 2008).

Brinkman et al., (1998) indicated that nucleoside analogues cause mitochondrial DNA toxicity, which in turn result in the clinically observed symptoms and signs of these ARVs. According to Brinkman et al. (1998), long term use of AZT is associated with myopathy and bone-marrow toxicity (anaemia), whereas long term use of D4T is associated with neuropathy, pancreatitis, hepatic steatosis and lactic acidosis. Murphy et al., (2007) further confirmed that mitochondrial toxicity is responsible for the earlier mentioned adverse effects as well as lipodystrophy caused by NRTIs such as D4T and DDI.

Some studies have indicated that exposure to D4T, female gender and body mass index (BMI) greater than 25 are risk factors for lactic acidosis (John et al., 2001; Wester et al., 2007; Geddes et al., 2006). It was further shown that replacing the offending ARVs with less potent mitochondrial inhibitors reduces or even reverses the adverse effect (Lonergan, Barber and Mathews, 2003).

A Rwandan study found that the prevalence of lipodystrophy was more than three times higher in D4T containing regimen compared to AZT containing regimen. Other studies also found that long term use of D4T is a risk factor for lipodystrophy (van Griensven et al., 2007; Mauss et al., 2002; Saint-Marc et al., 1999; Joly et al., 2002; Chariylertsak et al., 2008). McComsey et al., (2008) have shown that the mitochondrial RNA and DNA alterations in subcutaneous fat tissue of HIV positive subjects with lipoatrophy are linked to ART and not HIV infection. This was confirmed by the fact that the adverse effect improved when the

offending ARV was replaced by less mitochondrial toxic antiretrovirals (Domingo et al., 2004; Garcia-Benayas et al., 2003; McComsey et al., 2005; Llibre et al., 2006; Martinez et al., 2008).

Several studies also showed that long term use of D4T is associated with high prevalence of peripheral neuropathy (Konchalard and Wangphonpattanasiri, 2007; Scarsella et al., 2002; Laurent et al., 2008; Canestri et al., 2007). As with all mitochondrial toxic ARVs the adverse event is reduced or reverse once mitochondrial toxic ARV is substituted with a mitochondrial less toxic ARV (Makinson et al., 2008).

In most of the studies toxicities did not necessitate the termination of the treatment, toxicities were managed by substituting the offending medicine or by treating the toxicity. In general, the rate of discontinuation due to toxicities reduced the longer the patients were on the treatment (Monforte et al., 2000).

2.2.4. Modifying Antiretrovirals

There are several options available for clinicians to manage antiretroviral (ARV) toxicities, these include substituting an offending drug with another within the same group, switching to a second line regimen, treating the toxicity, interrupting the treatment for certain periods - so called “treatment holidays” or discontinuing the treatment. In terms of the 2003 Namibian Antiretroviral therapy guideline, antiretroviral therapy (ART) may be changed due to toxicity or treatment failure. In the case of a toxicity associated with an ARV, the offending ARV must be replaced with another ARV that does not have the toxicity or is less toxic.

2.2.4.1. Substitution

Substitution is one of the strategies available to clinician to manage antiretroviral toxicities. It is defined as replacing one antiretroviral medicine in antiretroviral therapy with another antiretroviral medicine of the same class, e.g. replacing one nucleoside reverse transcriptase inhibitor antiretroviral with another nucleoside reverse transcriptase inhibitor antiretroviral.

A Botswana study assessing the response to Highly Active Antiretroviral Therapy (HAART), found that there was a 32.2% rate of switching due to toxicities to drugs (Wester et al., 2005). In a clinical trial analysis of an United Kingdom study by Mocroft et al., (2001), 64.4% of the patients modified (defined as stopping at least one of the ARVs in the regimen) their HAART due to toxicities or patient choice. Mocroft et al., further found that patients that started more than three ARVs were more likely to modify their regimen, as were those that had regimens containing ritonavir (Mocroft et al., 2001). In an Indian study, 20% of the patients modified (defined as any alteration of one or more components of the regimen) their first line regimen. The reasons for modification were adverse effects (64%), cost (19%) and treatment failure (14%) (Kumarasamy et al., 2006).

A Zambian study assessing the effectiveness of their ART programme, found that there was a 40% switching of ARVs due to toxicities (Stringer et al., 2006). An urban outpatient cohort study in the United States of America found that 61% of the patients changed or discontinued their initial treatment, primarily because of adverse events (24%) (O'Brien et al., 2003). Cesar et al., (2008) in their study in the Caribbean and Latin America found that 36% of the patients switched ARVs and in 58% of the cases the given reason was toxicities. In a Cape Town based South African study by Boulle et al., (2007) up to 28% of the patients had at least one ARV substitution in a period of 3 years. A Malawian survey found that 2.9% patients substituted at least one antiretroviral (ARV) of their first line treatment. The recorded reasons for these substitutions were skin rashes (45.6%) and peripheral neuropathy (44%).

The decision to substitute an antiretroviral depends on the ability of the clinician to associate the toxicity with a particular antiretroviral as well as the severity of the toxicity. In general mild toxicities do not require substitution, but can be managed symptomatically. Mild toxicities are those that do not have symptoms causing an inability to perform usual social and functional activities (Sabundayo et al., 2006).

2.2.4.2. Switching

Switching is an option available to clinicians to "rescue" a patient from a failing regimen. It is defined as modifying a treatment from a first line regimen to second line regimen. According to WHO, determining treatment failure can be done in three ways: 1) clinically, by disease progression and WHO staging; 2) immunologically, using CD4 cell counts over time and 3) virologically, by measuring plasma viral loads (WHO, 2006). In resource poor settings laboratory equipment required for immunological and virological assessment are not usually available due to cost. Therefore, clinicians in resource poor settings mainly rely on disease progression and WHO staging, which might be "too late" for the patient. WHO in its 2006 revision of the antiretroviral therapy recommendations indicated that the timing of switching is critical; if made too early it depletes available options and alternatively if it is made too late the prognosis of the patient is affected negatively.

The TREAT Asia HIV Observational Database (TAHOD) study found that 39% of the patients changed their first line treatment and from those 6% changed to second line treatments (Srasuebkul et al., 2007). In a South African study looking at the cost-effectiveness of ART in Khayelistsha, it was found that no patients changed their regimen during the first six months on treatment. However, at 48 months 16% had switched (Clearly,

McIntyre and Boulle, 2006). Coetzee et al., (2004) found that at 24 months follow-up 8.7% of the patients of their Khayelitsha (South Africa) study have changed to a second line regimen. Coetzee et al., (2004) further found that 15.1% of patients changed their treatment due to toxicities or contraindications, and 8.4% due to toxicities alone.

2.2.4.3. Discontinuation

Although discontinuing the ART is not desirable, it has been reported to occur mainly due to drug toxicities. Discontinuation is defined as stopping all antiretrovirals at once. If the toxicity is life-threatening there is a need to discontinue antiretroviral therapy until the patient has stabilised (WHO, 2006). However, there are concerns with this strategy because NNRTIs have a longer half life compared to NRTIs and so this may result in patients receiving mono-therapy for a period of time, which in turn may result in development of resistance to NNRTIs. However, WHO recommends discontinuation because benefits outweigh the risk of resistance development to NNRTIs. In a clinical trial analysis of an United Kingdom study by Mocroft et al., (2001), 26% discontinued (defined as simultaneously stopping all ARVs) their HAART regimen within the first year of therapy. In a Ugandan study assessing the discontinuation and modification of HAART, 13.7% patients discontinued their initial treatment (Kiguba et al., 2007).

The rate of modification, in the first year of treatment, is in general much lower in studies in resource poor settings compared to studies in developed countries. The reason for the low rate of substitutions could be that in resource poor settings the clinicians are working with a limited formulary, as alternatives within the same drug classes may not be available due to cost. The reason for the low rate of switching in resource poor setting could be that the health professionals in these settings are trying to preserve the available second line therapies.

Therefore, they try to keep the patients on the first line treatment as long as possible (WHO, 2006).

Apart from aforementioned differences all studies indicated adverse reactions as the main reason for changing therapy. This was followed by treatment failure in studies in the developed country setting, whereas cost was the second cause of change in the some resource poor settings. In developed countries ART is generally provided free of charge or covered by private insurance, but in many resource-poor setting patients have to pay for their antiretroviral therapy medicines out of their pockets. This is prohibitive for those in resource poor settings, especially with regard to the high prices of newer and less toxic ARVs. However, the new move to assist with rolling out of ART services in resource poor settings has lead to reduction of ARV prices and donor funding of some antiretrovirals. Although these factors have increased the uptake of antiretroviral therapy, other factors such as stigma, lack of availability of qualified health personnel, infrastructure and laboratory monitoring still negatively impact on access to HAART in resource poor settings (Stringer et al., 2006; Carmody et al., 2003).

The WHO report in its "Towards Universal Access" strategy indicated that a large number of patients have been put on antiretrovirals (ARVs), especially in resource poor countries (WHO, 2008). According to this reports there were 2 million people on ARVs at the start of this strategy in 2005, this figure has increased to about 3 million people on ARV treatment at the end of 2007. These figures indicate that many more people will be exposed to ARVs. Namibia has also scaled up the provision of antiretroviral therapy considerably and by the end of 2007 there were approximately 37,000 people on antiretroviral therapy, compared to less than 10,000 in 2005. As more Namibian patients are put on HAART, there is need to

determine the effect of long term antiretroviral drug use on these patients, so that clinicians can optimally manage their patients on HAART.

CHAPTER 3: METHODOLOGY

3.1. Study Design

A descriptive retrospective case series study was chosen in which medical records were reviewed to determine the extent and reasons for substituting and switching HAART. The researcher chose this method, because the required information was readily available and it involved minimal resources. The researcher did not have any sponsors and had also work commitments. Therefore, this method suited the researcher as it enabled him to meet his work commitments and also do the research.

3.2. Study Setting

This study was carried at an urban intermediate hospital in Namibia. The Katutura Intermediate Hospital is an 800 bed hospital that serves as a referral hospital. In addition to the general services available at other district hospitals, it also offers specialist services such as gynaecology, urology, ophthalmology, orthopaedics and ENT. This intermediate hospital commenced the provision of antiretroviral therapy (ART) as one of the pilot centres in Namibia in 2002 and ART was later rolled out country wide from 2004, based on lessons learned from the pilot programme. The number of people put on antiretrovirals increased with the scaling up of antiretroviral therapy services. When the scaling up process started in 2003 less than 3% of the people requiring treatment were on treatment. By the end 2007, 66% (38,046) were on antiretroviral treatment (MoHSS, 2008). Of these patients about 12% are receiving their treatment at KIH. It is further projected that by the end of 2013, 80% of those requiring treatment (84,000) will be on antiretroviral treatment.

3.3. Study Population

The study population was all adults (18 years and above) that started on Highly Active Antiretroviral Therapy (HAART) between 1st January 2002 – 31st December 2006 at the KIH. The only inclusion criterion was that the patients must have had at least one follow-up visit subsequent to commencing HAART.

3.4. Study Sample

The KIH has an enrolment rate of approximately 60 patients per month on HAART and it was found that 3477 patients were enrolled on ART between 1 January 2002 and 31 December 2006. The sample size was calculated with the assistance of Epi Info version 6 using the following assumptions:

- There are several variables that will be measured and thus the researcher will use the extent of switching from 1st line to 2nd ART as the determining variable, because it has the lowest expected rate of 15% (Clearly, McIntyre and Boulle, 2006).
- The researcher would prefer the range of the true value to be ±3% from the expected value.
- 95% confidence interval

The calculated sample size for the population of 3477 was 471, but the researcher used the sample size of 500 to accommodate for records that were incomplete and would require skipping/disregarding certain selected files. The researcher randomly selected 500 records of the adult patients that enrolled for ART during the period of 2002 – 2006. Simple random sampling was used to get the study sample for this research project. Since the inception of the ART programme, patient files have been kept for all the patients enrolled for treatment. These files were allocated unique patient numbers, which were in chronological order that were used throughout the health system and not the patient names. The researcher used these

numbers and fed them in the Moonstat® software to generate the random numbers for the defined sample size. The selected files were then numbered serially, and these numbers were then used for research purposes. The researcher was unable to get the required sample size with the first run of the random numbers and thus had to repeat this exercise three times. At the end of the third cycle the researcher had 535 records. The first 500 hundred records were then enter into Epi Info version 6 (2005) and checked for duplicate numbers. Sixteen (16) duplicate numbers were found and replaced with non-duplicate numbers from the remaining 35 records.

3.5. Data Collection

A pre-piloted data collection tool (Appendix A) was used to collect the data. The following information was collected: baseline CD4 count, weight, initial ARVs, first and second ARV substitutions, first ART switch and the reasons for substituting ARVs or switching ART during the indicated period. A pilot of 15 patient files was carried out at the Windhoek Central Hospital. Windhoek Central Hospital is a similar type of hospital to that of Katutura Intermediate Hospital (KIH) making it a suitable setting for piloting the data collection tool. Both the Windhoek Central Hospital and KIH are higher level health facilities compared to district hospitals. At higher level facilities, specialists and consultants, as well as laboratory equipment, are readily available. Therefore, piloting the data collection tool at such a facility was appropriate. Minor adjustments were made to the data collection tool after the pilot to collect data that was not included initially in the tool, such as the latest weight, latest CD4 and time on treatment.

The ART clinic of KIH retains all the patient files in a locked filing room. The files were stored in locked metal cabinets that are chronologically numbered. Each file had records of

one patient that consisted of prescription book, clinician's note booklet and all laboratory results of the patient. Access to the files was restricted to data clerks and nurses based at the ART clinic. The researcher accessed the patient files with the permission of the Senior Medical Superintendent of the hospital. This permission was granted once the research study protocol was accepted by the Ministry of Health and Social Services (MoHSS), which also included permission to conduct the study by the Permanent secretary of the MoHSS. The researcher collected the data himself, thus there was no need to train data collectors. However, two data clerks that were used to counter-check the collected data were trained on what information to look for in the patient file to check the correctness of the collected data in the data collection tool. This was done by simulation, where the researcher would collect data from the patient files and the data clerks would counter-check the collected data from the file from where it was collected in the presence of the researcher. Only when the clerks were able to ensure a 100% counter check were the clerks "recruited" to do the counter checking. The data was collected between the 30th May 2008 and 30th June 2008.

3.6. Data Management and Analysis

The researcher collected the data himself by transcribing what the clinicians had written in the patient's file to the data collection tool. The researcher made use of two data clerks, responsible for the filing of these files, to do a counter-check on 10% of the files, at a minimum of three intervals during the data collection. In other words, once the researcher had finished 100 data collection records, for example, then the clerk would randomly pick 10% of the completed data collection records, which is ten data collection records in this case. The clerk would then counter-check the data collected with the specific patient file for each data collection record. The collected data was kept in the researcher's office in a locked cabinet. When the researcher was not in his office, both the office and the cabinet were locked and the

keys always in possession of the researcher. The collected data was entered into the computer for analysis, using Epi Info version 6. Data entry was checked by a colleague who is a Master of Public Health (MPH) student. The data was entered directly into Epi Info and when required the researcher would export the data to Windows Excel to perform certain analyses. The computer was password protected to ensure confidentiality of the data. Once entered into Epi Info the data was cleaned by running frequencies of the reference numbers to ensure that there were no double entries and scrutinized for invalid values.

The data was analysed using Epi Info version 6. Since it was a case series study the results are presented by means of simple descriptive statistics such as frequencies, proportions, means (or medians where distribution is not normal) for all important variables in the data set.

3.7. Validity and Reliability

The issues of validity and reliability in the study were addressed in a number of ways. The most accurate measurements are obtained by measuring the entire population. However, due to lack of time, financial and material resources it was not possible to study the entire population. Therefore, a representative sample was drawn from the study population. Simple random sampling was used to draw a representative sample from the population. This ensured that all possible samples have an equal probability of being selected and addressed the issue of selection bias (De Vos, 2002).

Measurement bias was addressed by the researcher collecting all the data himself and by transcribing directly what the medical doctor had written in the patient's file onto the data collection tool. The pre-piloted data collection tool was designed to collect only the data required for the study. When collecting the data the researcher made use of the two trained

data clerks, responsible for the filing of these files, to do a counter check on 10% of the files, at a minimum of three intervals of data collection. During data entry the researcher requested a colleague, who is also a MPH student, to counter check the entered data. Data was also cleaned by examining frequencies to ensure that there were no duplicate or erroneous entries.

3.8. Generalisability

As the sampling method ensured that the study sample was representative of the study population, that is, patients who commenced HAART at KIH between 1 January 2002 and 31 December 2006, the results may be generalisable to this study population. However, they are not generalisable to the wider population on HAART throughout Namibia.

3.9. Limitations

One of the major limitations of the study was that in many cases either the reasons for modification of ART were not recorded in the patients' files ('missing'), or that the reasons were given in broad terms, such as 'toxicity'. This made proper quantification of these parameters difficult. The study will not be able to determine causality, but might be able to find association. The study also excluded HAART patients who did not have a follow up visit recorded in their notes. Inclusion of these patients may have given a false indication that more patients stay on their initial therapy without any modification.

3.10. Ethical considerations

This study did not involve contact with human subjects. All the required data was collected from secondary data sources, that is, medical records. Ethical approval was obtained from the University of the Western Cape Ethics Committee and the Ministry of Health and Social

Services (Appendix B). Approval was also obtained from the Senior Medical Superintendent of the Katutura Intermediate Hospital for access to the patient files. As only already available information was transcribed from the files there was no need for clinical staff or patients to be present. The process of transcription of information was done mainly over the weekends and at other suitable times that did not adversely influence the patient flow and the work of the clinical staff. Confidentiality was invested in the research and no names appeared on the data collection tool and the researcher used patient codes to identify the patient files. The data was kept in a locked steel cupboard in a locked office, if not in use. The computer that was used for data entry and analysis was pass word protected. No names or any means of identification was used in the final report. The results of the study will be made available to KIH ART Clinic clinical staff, the management of KIH and the management of MoHSS.

CHAPTER 4: RESULTS

This section describes the results of the study. This includes the demographic data, baseline data and other variables such as frequency of substitution and switching of antiretrovirals and the reported toxicities associated with the use of specific antiretrovirals.

4.1. Baseline characteristics of HAART patients

Table 4: Baseline characteristics of HAART patients (N= 500)

Gender, n (%)	
Male	200 (40%)
Female	300 (60%)
Age (years), median (IQR)	**34 (30 – 40)**
Male	38 (34 – 44)
Female	32 (29 – 37)
Treatment supporter, n (%)	
Yes	463 (93%)
No	37 (7%)
Weight (kg), median (IQR)	**57 (50 – 65)**
CD4 cell count (cells/ml), median (IQR)	**153 (96 – 212)**
First treatment combination, n (%)	
First line treatment	*455 (91%)*
1. D4T/3TC/NVP	219 (48%)
2. D4T/3TC/EFV	108 (24%)
3. AZT/3TC/NVP	91 (20%)
4. AZT/3TC/EFV	37 (8%)
Second line treatment	*31 (6%)*
1. LPV/r/3TC/D4T	13 (42%)
2. LPV/r/3TC/AZT	18 (58%)
Other	*14 (3%)*
TDF/3TC/EFV	14 (3%)

The baseline characteristics describe the health profile of the patients, who commenced on HAART between January 2002 and December 2006, as recorded in the patient notes when the patient started anti-retroviral therapy. The baseline characteristics of the study sample are

summarised in Table 4. The sample was made up of 500 patients, of which 300 (60%) were female. The median age of the sample was 34 years (IQR 30 – 40) with the mean age being 36 years. However, the median age of the females was lower than that of the males, being 32 years and 38 years, respectively. The median CD4 cell count at initiation of therapy was 153 cell/mm^3 (IQR 96 – 212). More than two thirds of the patients, 359 (72%), started ART with a CD4 cell count of ≤200 cells/mm^3 and 206 (58%) of these were females. Almost all the patients, 463 (93%), had treatment supporters. Overall, the median time that the individuals in the study sample were on treatment was 37 months with an IQR of 28 – 43 months.

Most of the patients in the study sample, 91% (455), were started on one of the four first line antiretroviral treatment regimens as indicated in Table 4. Six percent (31) patients were started on a second line regimen and the remaining 3% (14) commenced on a treatment regimen not included in the Namibian ART treatment guideline of 2003.

4.2. First substitution

Table 5: Characteristics of HAART patients at first substitution (N=157)

Gender, n (%)	
Male	63 (40%)
Female	94 (60%)
Treatment supporter, n (%)	
Yes	150 (96%)
No	7 (4%)
Time to 1st substitution (months), median (IQR)	28 (24 – 34)
CD4 cell count (cells/ml), median (IQR)	409 (287 – 562)

Almost one third, 31% (157), of the patients in the sample underwent a first substitution of one or more antiretrovirals and out of these 157 patients, 60% (94) were female (See Table

5). The median time on treatment before substitution was 28 months (IQR 24 – 34). The median CD4 count at the time of first substitution was 409 cells/ml (IQR 287 – 562).

Table 6: Treatment changes at first substitution (N=157)

Initial treatment	Treatment after first substitution	
First line treatment (149)	***First line treatment (140)***	***Other (9)***
D4T/3TC/NVP (89)	AZT/3TC/NVP (69)	TDF/3TC/EFV (1)
	D4T/3TC/EFV (9)	TDF/3TC/NVP (1)
	AZT/3TC/EFV (9)	
D4T/3TC/EFV (48)	AZT/3TC/EFV (37)	TDF/3TC/EFV (5)
	AZT/3TC/NVP (3)	
	D4T/3TC/NVP (3)	
AZT/3TC/NVP (9)	AZT/3TC/EFV (8)	TDF/3TC/NVP (1)
AZT/3TC/EFV (3)	D4T/3TC/EFV (1)	TDF/3TC/EFV (1)
	AZT/3TC/NVP (1)	
Second line treatment (8)	***First line treatment (5)***	***Second line treatment (3)***
LPV/r/D4T/3TC (6)	D4T/3TC/NVP (1)	LPV/r/AZT/3TC (3)
	D4T/3TC/EFV (1)	
	AZT/3TC/EFV (1)	
LPV/r/AZT/3TC (2)	AZT/3TC/EFV (1)	
	D4T/3TC/EFV (1)	

Out of the 89 (20%) patients on first line treatment of D4T/3TC/NVP, 87 remained on first line treatment and two changed to treatment not in the guideline. Of the patients on the D4T/3TC/EFV treatment (48), only five changed to treatment not on the guideline while the rest remained on first line treatment. Of the six patients on the second line treatment of LPV/r/D4T/3TC, three were moved back to first line treatment and the remainder were still on second line treatment (LPV/r/AZT/3TC).

A total of 145 (92%), out of the 157 HAART patients who underwent substitution, were on first line antiretroviral treatment after substitution. Of those who were on first line treatment 50% were on AZT/3TC/NVP, 39% on AZT/3TC/EFV, 8% on D4T/3TC/EFV and 3% on

D4T/3TC/NVP. Two percent of those who underwent first substitution were on second line treatment and the remaining 6% were on treatments not indicated in the ART guideline.

Table 7: Number of times antiretroviral substituted at 1st substitution (N=157)

Antiretroviral	Times substituted	%
D4T	130	75%
NVP	27	16%
EFV	7	4%
AZT	4	2%
LPV/r	5	3%

Note: Some patients substituted more than one antiretroviral at a time, therefore the actual substitutions are more than N

Table 8: Substituted antiretrovirals and adverse events or toxicities at 1st substitution (N= 157)

Adverse Event/Toxicity	Incidence of adverse events/toxicities					TOTAL
	D4T	NVP	EFV	AZT	LPV/r	
Toxicity (unspecified)	30				1	31 (18%)
More than 2yrs on D4T	13					13 (8%)
Peripheral neuropathy	11	1				12 (7%)
Lipo-dystrophy	4				1	5 (3%)
PTB	2	10	1	1	1	15 (9%)
Lipoatrophy	2					2 (1%)
Gynaecomastia	2					2 (1%)
Lactic Acidosis	1					1 (0.5%)
Impotence	1	1				2 (1%)
Pregnancy	1		1			2 (1%)
Bone marrow depression		1		1		2 (1%)
NVP hypersensitivity		1				1 (0.5%)
Jaundice		1				1 (0.5%)
Anaemia				1		1 (0.5%)
Others	7	1				8 (5%)
Missing	56	11	5	1	2	75 (43%)
TOTAL	**130**	**27**	**7**	**4**	**5**	**173**

D4T was the antiretroviral that was mostly substituted at 130 (75%) of the substitutions, followed by NVP 27 (16%), EFV 7 (4%) and AZT 4 (2%) respectively (Table 7). Some of

the patients (12) substituted more than one ARV at a time, which made the substitutions more than the number of patients. The most commonly reported reasons for first substitution were toxicities (unspecified) at 18% the highest as indicated in Table 8 (which indicates the number of times a toxicity was reported). Toxicity refers to any adverse advent that has not been specified by the clinician. The total toxicities, including unspecified toxicities, were 98 after first substitution. In almost half, 75 (43%), of the cases reasons for substitution were not indicated.

4.3. Second substitution

Table 9: Characteristics of HAART patients at second substitution (N=9)

Gender, n (%)	
Male	5 (56%)
Female	4 (44%)
Treatment supporter, n (%)	
Yes	9 (100%)
Time to 2nd substitution (months), median (IQR)	10 (6 – 15)
CD4 cell count (cells/ml) at 2nd substitution, median (IQR)	375 (264 – 411)

A total of 9 (2%) patients in the study sample underwent a second substitution. This group consisted of 5 (56%) males and all had treatment supporters. The median time to second substitution from the first substitution was 10 months (IQR 6 – 15) and the median CD4 cell count at second substitution was 375cells/ml (IQR 264 – 411).

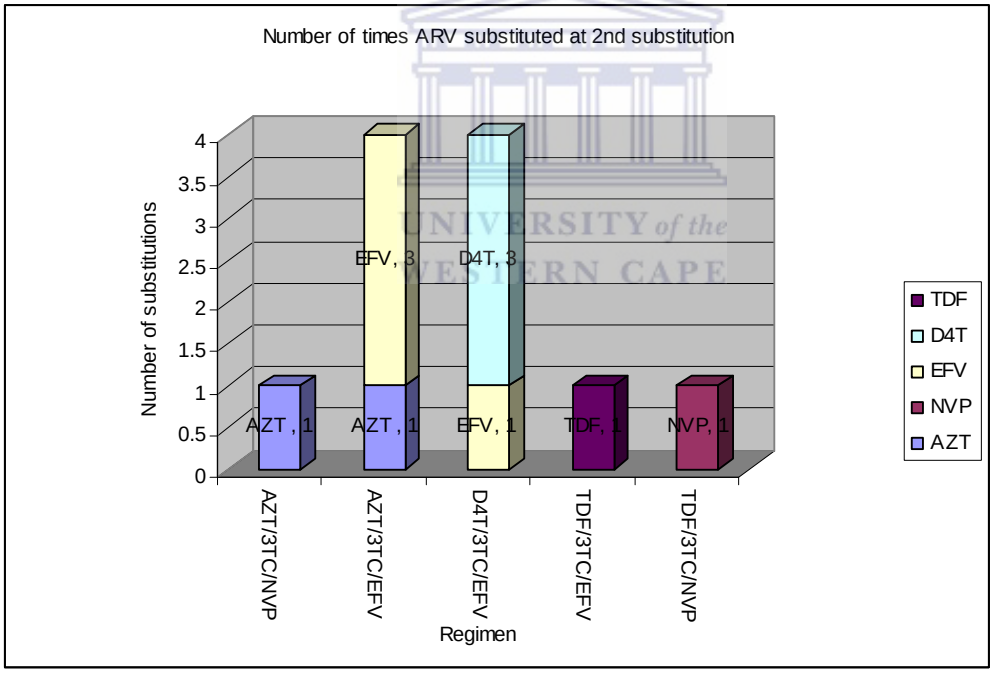
Of those who underwent a second substitution, 7 (78%) were on first line treatment after the second substitution and two (22%) of the patients were on treatments not listed on the ART guideline of 2003, namely TDF/3TC/NVP and TDF/3TC/EFV, respectively.

Table 10: Treatment changes at second substitution (N=9)

Initial treatment	Treatment at 1st substation	Treatment at 2nd substitution
D4T/3TC/NVP (5)	AZT/3TC/EFV (1)	*TDF/3TC/EFV (1)**
	D4T/3TC/EFV (3)	AZT/3TC/NVP (1)
		AZT/3TC/EFV (2)
	AZT/3TC/NVP (1)	D4T/3TC/NVP (1)
D4T/3TC/EFV (2)	AZT/3TC/EFV (1)	AZT/3TC/NVP (1)
	TDF/3TC/EFV (1)	AZT/3TC/EFV (1)
AZT/3TC/NVP (2)	AZT/3TC/EFV (1)	AZT/3TC/NVP (1)
	TDF/3TC/NVP (1)	*TDF/3TC/EFV (1)**

**Treatment not on treatment guideline*

Figure 1: Number of times ARV substituted at 2nd substitution (N=9)



The antiretroviral that was substituted most frequently at the second substitution was EFV, with four patients (36%) as indicated in Figure 1.

The reasons recorded for the second substitutions included anaemia, TB, myopathy and general toxicities, however the reason was not recorded in more than a third (37%) of the

reported cases. D4T and EFV were the antiretrovirals associated with most recorded incidence of toxicities for second substitutions.

4.4. Switching

Table 11: Characteristics of HAART patients at time of switch (N=6)

Gender, n (%)	
- Male	4 (67%)
- Female	2 (33%)
Treatment supporter, n (%)	
- Yes	6 (100%)
Time to switch (months), median (IQR)	36 (28 – 39)
CD4 cell count (cells/ml) at switch, median (IQR)	182 (178 – 242)

Only six patients in the study sample switched treatment and two-thirds, 67%, were males. The median time to switch was 31 months (IQR 24 – 39) and the median CD4 cell count at switching was 214 cells/ml (IQR 178 – 440).

Table 12: Treatment changes at switch (N=6)

Initial treatment	Treatment after switch	
First line treatment (6)	***Second line treatment (1)***	***Other (5)***
D4T/3TC/NVP (1)		LPV/r/TDF/3TC/AZT (1)
D4T/3TC/EFV (2)	LPV/r/3TC/AZT (1)	LPV/r/TDF/3TC/AZT (1)
AZT/3TC/NVP (2)		LPV/r/TDF/3TC/AZT (2)
AZT/3TC/EFV (1)		LPV/r/IDV/r/TDF (1)

A total of 6 (1.2%) patients in the study sample switched from first line to second line treatment. Of those who switched to second line only one (17%) switched to treatments on the 2003 guidelines, which is LPV/r/AZT/3TC, whereas five (83%) switched to treatments not listed in the guideline.

The most commonly reported reasons for patients switching ART was a high viral load, in three patients (50%). In two (33%) of the cases the reasons were not stated, whereas one patient (17%) was switched due to lipomastitis.

In conclusion, this section highlighted the main results of this study. The results provided useful information on the extent and reasons for substituting and switching in this sample of HAART patients at the Katutura Intermediate Hospital.

CHAPTER 5: DISCUSSION

This study analysed a sample of 500 patients that started anti-retroviral therapy (ART) between 1 January 2002 and 31 December 2006 at the Katutura Intermediate Hospital (KIH). It is the first study to assess the toxicities associated with antiretroviral use in Namibia. In this study 97% of the study subjects were started on treatments according to the Namibian antiretroviral therapy guidelines of 2003 (MoHSS, 2003), which was based on the WHO resource-limited settings guidelines of 2002 (WHO, 2006). Those started on treatments that were not specified by the 2003 ART guideline, were on treatments containing TDF instead of AZT or D4T. In this study 337 (67%) of the patients remained on their initial treatment for a median follow-up period of 37 months (IQR 28 – 43 months). This is comparable to other findings in resource poor settings (Schramm et al., 2008; Jahn et al., 2008).

A total of 359 (72%) of the patients were started on ART with a CD4 cell count of ≤200 cells/mm^3. This was in line with the Nambian ART guidelines and WHO recommendations in similar resource poor settings (WHO, 2006). Several studies (Sterling et al., 2003; Lau, Gange and Moore, 2007; Stringer et al., 2006) have shown that people do poorly when starting at low CD4 cell count. However, this study sample did not show a similar trend, as although more than two thirds of the sample started art at CD4 cell count of ≤200 cells/mm^3, only about 24 (5%) patients were recorded to have virologic failure (virologic failure is defined as a follow-up CD4 cell count that is lower than the baseline CD4 cell count). This study could not determine any apparent reasons for the good prognosis of HAART patients at low CD4 cell count level, and it is contrary to what was found in other studies.

5.1. Substitution

The rate of first ART substitution at 31% (157 patients) is similar to what was found in studies in other resource poor settings. A Botswana study found a rate of 32.2% (Wester et al., 2005), whereas a TREAT Asia Observational Database (TAHOD) study found a rate of 39% (Srasuebkul et al., 2007). The rates in resource poor settings are much lower at 32% and 39%, compared to what has been observed in developed countries (45%) (Mocroft et al., 2001; Vo et al., 2008; Abgrall et al., 2006). In this study, females (60%), were more likely to substitute ARVs compared to their male counterparts. The higher rate for female ARV substitution could be due to pregnancies, since EFV is contra-indicated in pregnancy due to its possible teratogenocity (MoHSS, 2003). Some studies have also shown that female-gender is a risk factor for lactic acidosis and hepato-toxicity (Garcia-Benayas et al., 2003; John et al., 2001; van Leth et al., 2005). However, this study could not verify this finding due to high numbers of missing data and the reporting of toxicities that were unspecified.

The median time before first substitution was 28 months. This was much longer than was reported in other studies in similar settings, a Malawian study (2008) reported 5 months and a South African study (2004) reported 42 days. In an Indian study, patients modified treatment, by substituting one or more antiretrovirals in their initial treatment within 40 days of treatment (Kumarasamy et al., 2006). Mocroft et al., (2001) reported that patients modified their treatment by six months. However, in this sample only 12 (2.4%) of the patients substituted antiretrovirals within the first six months. This much lower than what was found in the Indian study over the same period (Kumarasamy, 2006).

The reason for this long duration and lower rates could be that clinicians want to preserve available treatments as long as possible for future use because the formulary is limited in

resource poor settings such as Namibia. It could also be that the patients in this sample have a better tolerance of the antiretrovirals in use. The reasons for the good tolerance to treatment of the patients in this sample were beyond the scope of this study and would require a separate study to explore this further.

A total of nine (1.8%) of the patients underwent a second substitution. About equal male and female patients substituted ARVs for second time. The rate of second substitution is much lower than the 62% reported by Kirstein et al., 2002, in their United States study. As reported by Kistein et al., the median time (10 months) for moving from the second regimen to a third regimen is much shorter than moving from the first regimen to the second regimen (28 months). ARV toxicities were the main reason for the second substitutions, with D4T and EFV being associated with the most adverse events. However, it must be noted that the sample size (N=9) was very small and this makes interpretation difficult.

The most cited reason for first substitution was toxicities 98, both specified and unspecified toxicities. Unspecified toxicities constituted 18% (31), which is the highest reason for substituting antiretroviral medicines. This was similar to other studies in both the developing and developed world, where toxicities were the principle reasons for substituting ART medications (Mocroft et al., 2001; Kumarasamy et al., 2006; Wester et al., 2005). Being more than two years on D4T, 13 (8%), was the second reason for substituting ARVs. The 'more than two years on D4T' can also be cited as clinician's choice as the patients' treatments were modified because of the clinicians' perceived possible toxicity due to D4T. This perception is justified because of the latest available literature on this medicine (D4T), and even the new Namibian ART guideline (2007) indicates the substitution of D4T when required (MoHSS, 2007). Pulmonary Tuberculosis (PTB) was the third most commonly reported reason for

ARV substitutions at 7% (12). The modification due to PTB is due to the interaction of nevirapine with PTB regimen, especially rifampicin (MoHSS, 2003). Nevertheless, the findings are similar with findings in other studies that toxicities are the main reasons for modifying ART.

5.2. Toxicities

The most reported specified toxicities were peripheral neuropathy 7% (12), lipo-dystrophy 3% (5) and lipo-atrophy 1% (2). These toxicities were similar to those indicated in other studies in resource poor settings, although the rates were not similar. In the TAHOD study lipo-atrophy was leading toxicity of ART change, whereas it was peripheral neuropathy in this study. A Ugandan study by Forna et al., (2007) found peripheral neuropathy as the leading reason for modifying ART, which was similar to the finding of this study.

D4T was the ARV with most reported toxicities (130), followed by NVP (27). This corresponded to finding in other studies (Brinkman et al., 1998; Murphy et al., 2002) that NRTI are mitochondrial DNA toxic, resulting in several adverse effects. The fact that D4T, a NRTI, was found to be associated with more adverse events such as peripheral neuropathy, lipo-dystrophy and lipoatrophy confirm the mitochondrial toxicity of this ARV in the patients of this study. NVP was associated with the second highest toxicities after D4T, namely peripheral neuropathy, impotence, bone marrow depression, jaundice and NVP hypersensitivity. The high number of PTB that is record with NVP is due to interaction of NVP with PTB medicines such as rifampicin (MoHSS, 2008), as stated earlier. In order avoid this drug interaction, ART patients that are started on NVP containing antiretroviral therapy replace the nevirapine with efavirenz (MoHSS, 2008).

However, one of the major limitations of this study was the high number of unspecified toxicities. Out of a total of 57 reported toxicities, 30 (53%) were not specified and simply indicated as 'toxicity'. This is probably due to the design of the form that the clinicians were using when they were having consultations with patients. This form did not make provision for writing a specific toxicity or did not list the specific toxicities but only provided a tick box for 'toxicity'. It is worth noting that in 75 (43%) of the substitutions the reasons were not indicated. This could be an indication that there is need for training clinicians in recording and reporting suspected adverse drug reactions.

5.3. Switching

The rate of switching from a first line to second line ART was only 1.2% (six patients), which is much lower than what was found in other studies. A South African study found that 8.7% of the patients changed to a second line (Coetzee et al., 2004) and the TAHOD study found that 6% changed to second line (Srasuebkul et al., 2007). The reason for these low rates could again be that the clinicians have limited choices and thus are trying to preserve treatment options for future use, as pointed out in the TAHOD study. The median time to switch treatment was found to be 31 months with an inter-quartile range (24 – 39 months), which is similar to findings in other studies (Clearly, McIntyre and Boulle, 2006; Coetzee et al., 2004) in resource poor settings that indicate that changes take longer to occur in these settings. In developed countries up to 62% of the patients switched to second line within 12 months of starting their antiretroviral therapy (Kistein et al., 2002; Vo et al., 2008). This could be because of the availability of a larger number of treatment options available to clinicians, should the patients experience problems with their current regimens. In addition, the clinicians in these settings have better access to laboratory tests for closer monitoring of their patients' condition.

In three of the six patients, the reason recorded for switching to second line ART was a high viral load, which is an indication of treatment failure. This finding was similar to that reported by other studies in that patients' switched to second line ART due to treatment failure (Kumarasamy et al., 2006; Pujades-Rodrigues et al., 2008). Of these three patients who had high viral load, two patients (67%) started ART with CD4 cell count that was <200 cells/mm^3 and one (33%) had a CD4 count that was less than the baseline CD4 count at the time of switch. It is reported that if a follow-up CD4 cell count is lower than the initial CD4 cell count that it was a possible predictor of treatment failure. This finding indicated that CD4 count was not a sensitive enough predictor of treatment failure. CD4 cell count might be relatively high (higher than the initial CD4 cell count), but the viral load might be increasing due to ineffective treatment. However, because of the unavailability of viral load test, which is a more reliable determinant of treatment failure, clinicians in resource poor settings are compelled to rely on the reduction of CD4 cell counts to make their clinical decisions, especially in asymptomatic patients.

One patient was switched due to toxicity. This is interesting as toxicities are mainly taken care of by substituting the offending drug. It is not clear from the available data whether the patient had exhausted all the available options and thus the clinician was left with no option than to switch to a second line therapy. The sample size was also very small and the results should be interpreted cautiously.

Another interesting observation in this study sample was that those who started on second line ART, five (16%) were moved back to first line ART, that is, ART without a PI. The main reason for this reversal was indicated as toxicity, with LPV/r being the ARV associated with

the toxicity. However, some clinicians that made this modification questioned the appropriateness of starting these patients on a second line therapy in the first place. The patient records also did not indicate the reason for this initial decision. In the absence of proper notes to inform the clinicians of the initial decision, they had no other option but to put the patients back on first line treatment. The rationale of putting these patients on first line treatment would probably be to preserve the PI treatment for the patients' future use. However, it could be limiting to the clinicians if the first line treatment failed, the clinicians would not have alternatives as the PI-based second line treatments would be 'toxic' to the patients. This requires an expansion of the currently available formulary to include treatments that do use the same or similar mechanism to the ones currently available.

5.4. Clinical records and reporting

An issue that was highlighted by this study was poor record keeping in patients clinical notes. This was evidenced by clinicians not specifying details of reasons for substituting or switching antiretroviral therapy. In addition, on many occasions clinicians did not give the specific toxicities for substituting antiretrovirals. This made interpretation of their decisions to substitute or switch ARVs difficult. It is critical that full details of all patients' treatments are documented in clinical notes, and this is particularly important for monitoring new treatments such as HAART which are complex and utilise new, potent and potentially toxic drugs. These findings point to the need to ensure that clinicians' record detailed patient notes and to educate them to report all adverse drug reactions to the newly established Therapeutic Information and Pharmacovigilance Centre, in Windhoek. This will ensure that critical information on the antiretroviral therapy programme will be more readily available to programme managers and the Ministry of Health and Social Services.

CHAPTER 6: CONCLUSIONS AND RECOMMENDATIONS

6.1. Conclusions

In this study it was found that the Namibian clinicians closely followed the ART guideline, as 93% of the patients were started on treatments according to the guideline. Two thirds (337) of the patients remained on their initial treatment for median period of 37 months.

The rate of substitution of 31% is similar to that found in other resource poor settings and the most reported reason for modifying ART was toxicity. The most reported toxicities for substituting ARV were peripheral neuropathy (7%), followed by lipodystrophy (3%). These toxicities are similar to those reported in similar settings. D4T and NVP were the antiretrovirals mostly associated with toxicities, and again this is similar to findings in other resource poor settings, as well as in developed countries.

The rate of switching, at 1.2%, was much lower than is found in other resource poor settings. This could be due to several reasons, including that clinicians were trying to preserve treatment as long as possible because of the limited formulary available to them. Alternatively, Namibian patients may tolerate the first line treatments well, although it was beyond the scope of this study to investigate this aspect. High viral load was identified as the principle reason for switching ART.

It must be noted that in 75 (43%) and 2 (33%) of the cases the reasons for substituting and switching, respectively, were not stated. Additionally, in 31 (18%) of the cases of first substitution and 2 (22%) of the cases of second substitution the reason was given broadly as "toxicity". This made it difficult to reliably quantify the reasons for modification of ART. It indicated that steps must be taken to ensure clinicians accurately document in patient records

the reasons why a particular treatment was changed. It also pointed to poor reporting on adverse effects of these medicines, which is essential in assessing the effectiveness of these new medicines and the ART programme.

6.2. Recommendations

1. D4T and NVP are the ARVs mainly associated with toxicities and patients on these drugs should be closely monitored.

2. The Ministry of Health and Social Services should regularly update the antiretroviral therapy guidelines as new and less toxic antiretrovirals become available to patients.

3. The Ministry of Health and Social Services should carry out a national study to determine the rate of substitution and switching in the antiretroviral therapy programme.

4. Further investigations should be carried out on the suitability of the patient record forms currently in use and the training provided for clinicians in adverse event recording and reporting.

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APPENDICES

APPENDIX A

DATA COLLECTION TOOL

Patient Reference Number: _____/_____ ART Site: _____

Pharmacy ref number: _____ Date of data collection: _____/_____/_____
dd mm yyyy

A. Demographic Information
1. Date of Birth: **a. __ /__ /____** **dd mm yyyy** **b. Age at ART initiation: _____** **2. Sex:** **a. Male □** **b. Female □** **3. Home Language:** **4. Treatment Supporter:** **a. Yes □** **b. No □** **c. If yes, specify relationship:**
B. Treatment Information

5. Date of ART Initiation: ___ /___ /_____
dd mm yyyy

6. Initial ART regimen (specify drugs):_____

7. Date of 1st Substitution: ____/___/___ Time to 1st Subst:_____
dd mm yyyy months

1st Substitution (specify drug(s)) _____

Reason for Substitution:_____

2nd Substitution (specify drug(s)) _____ ___/____/____ Time to 2nd Subst:_____
dd mm yyyy months

Reason for Substitution:_____

3rd Substitution (specify drug(s)) _____ ___/____/____ Time to 3rd Subst:_____
dd mm yyyy months

Reason for Substitution:_____

8. Date of 1st Switch: ____/_____/_____ Time to 1st Switch _____
dd mm yyyy months

1st Switch (specify drug(s))_____
Reason for Switch:_____

2nd Switch_(specify drug(s))_____ ____/____/___ Time to 2nd Switch_____
dd mm yyyy months

Reason for Switch_____

3rd Switch_(specify drug(s))_____ ___/____/___ Time to 3rd Switch_____
dd mm yyyy months

Reason for Switch_____

C. Clinical Outcome

9. Weight:

a. At Start of ART_____(kg)

b. Most recent_____(kg)

D. Immunological Outcome – CD4 Count

11. CD4 count at start of ART:

a. _____

12. Follow-up CD4:

a. 1st Substitution/switch _____ (Date: : ___ / ___/____)
dd mm yyyy

b. 2nd Substitution/switch: _____ (Date: : ___ / ___/____)
dd mm yyyy

c. 3rd Substitution/switch: _____ (Date: : ___ / ___/____)
dd mm yyyy

d. Most recent CD4 on ART: _____ (Date: : ___ / ___/____)
dd mm yyyy

APPENDIX B

Johannes Gaeseb
P. O. Box 8861
Bachbrecht
Windhoek

6 December 2007
The Permanent Secretary
Ministry of Health and Social Services
Private Bag 13366
Windhoek
Namibia

Dear Sir,

Re: Request for permission to do research at the Katutura Intermediate Hospital

I am a final year Master in Public Health student at the University of the Western Cape. In order to complete my degree I am required to do a mini-thesis on a research topic of my choice, but that has relevance to my current work.

It is in line with this requirement that I am requesting your good office to allow me to do my research at the Katutura Intermediate Hospital. My research title is "To Describe the extent and reasons for substituting and switching Highly Active Antiretroviral Therapy at the Katutura Intermediate Hospital in Windhoek, Namibia". This is a retrospective study and I will be required to access medical records of patients on HAART. However, it does not require any interaction with patients and very minimal interaction with clinical staff.

The confidentiality of patient information will ensured by means of patient codes. No patient names will appear on the data collection tool. The collected data will also be kept confidential. It will be kept in a locked steel cupboard in a locked office, if not in use. The computer that will be use for data entry and analysis is pass word protected. No names or any means of identification will be used in the report. The results of the study will be made available to KIH ART Clinic clinical staff, management of KIH and the management of MoHSS.

Please find attached my research protocol for your consideration.

Yours sincerely,

Johannes Gaeseb

APPENDIX C

Johannes Gaeseb
P. O. Box 8861
Bachbrecht
Windhoek

The Senior Medical Supertiendent
Katutura Intermediate Hospital
Private Bag 13366
Windhoek
Namibia

Dear Sir,

Re: Request for permission to access the patient files at the Katutura ART Clinic

I am a final year Master of Public Health student at the University of the Western Cape. In order to complete my degree I am required to do a mini-thesis on a research topic of my choice, but that has relevance to my current work.

My research study is entitled "To Describe the extent and reasons for substituting and switching Highly Active Antiretroviral Therapy at the Katutura Intermediate Hospital in Windhoek, Namibia". This is a retrospective study and does not require any interaction with patients and very minimal interaction with clinical staff.

I intend to make use of the patient files at the your hospital to collect the data for my study. Therefore, I am herewith requesting your good office to give me permission to access the patient file at the ART clinic.Say how you will protect confidentiality etc

I have already received approval for this study from the following institutions:
1) Ministry of Health and Social Services
2) University of the Western Cape Ethics Committee
3) University of the Western Cape Higher Degrees Committee.

Please find attached copies of the above-mentioned approvals and my research protocol for your easy reference.

Yours sincerely,

Johannes Gaeseb