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Faculty of Community and Health Sciences

TITLE:

FACTORS ASSOCIATED WITH FIRST LINE HIGHLY ACTIVE ANTIRETROVIRAL THERAPY REGIMEN MODIFICATION IN NAÏVE ADULT PATIENTS AT GOBABIS DISTRICT HOSPITAL

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Supervisor: **Dr Vera Scott**

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KEY WORDS

Regimen modification

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HAART

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Factors

Cohort study

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DECLARATION

I declare that, *"Factors associated with first line highly active antiretroviral therapy regimen modification in treatment naïve adult patients at Gobabis District Hospital,"* is my own work, that this work has not been submitted for any degree or examination in any university, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Full name : Kapera Tafadzwa Justin Nyatondo

Date: 20th November 2012

Signed: 

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ABBREVIATIONS

3TC	Lamivudine
ABC	Abacavir
AIDS	Acquired Immune Deficiency Syndrome
ALT	Alanine aminotransferase
ART	Anti-retroviral Therapy
ARV	Antiretroviral
AZT	Azidothymidine/ Zidovudine
CD4	Cluster of Differentiation
EFV	Efavirenz
ePMS	Electronic Patient Monitoring System
FTC	Emtricitabine
HAART	Highly Active Antiretroviral Therapy
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
LPV-r	Lopinavir-ritonavir
MOHSS	Ministry of Health and Social Services
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine

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PEP	Post-exposure prophylaxis
PI	Protease inhibitor
PLHIV	People Living with HIV
RTV	Ritonavir
TDF	Tenofovir
WHO	World Health Organization

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ABSTRACT

Background: First line regimens give patients the best chance of long-term treatment success. It is imperative that patients stay on their original first line regimens to ensure program viability. As the ART programme matures in Namibia the proportion of patients who have had their first line regimens modified continues to increase. It is estimated that 3.1% of adults in Namibia are on second line regimens. Second line or other modified regimens are generally reserved for clinical, immunological or virological failure and toxicity related complications. These modified regimens often involve a higher pill burden, more toxicities and are often more expensive. A more detailed understanding of the factors associated with first line regimen modification could allow healthcare providers in Namibia to target these factors for intervention to reduce regimen modification and improve treatment outcomes.

Methodology: This quantitative descriptive retrospective cohort study sought to describe factors associated with first line HAART regimen modification in treatment naïve adult patients who started HAART at Gobabis State Hospital between 1st January 2007 and 31st December 2010. Utilizing data from an existing electronic patient management system, quantitative methods were used to assess the prevalence, reasons and factors associated with first line HAART regimen modification.

Results: The prevalence of HAART regimen modification was 14.1%. Treatment toxicity was the major reason (35%) for HAART regimen modification and this was largely due to D4T containing regimens. This was followed by treatment modification due to concurrent TB disease (27.3%), new drug availability (19%), pregnancy (6.6%) and virological failure (2%). A death rate of 9% was recorded by the end of the study period in each of the two groups, of those who had their first line HAART regimen modified and those who remained on original regimens respectively. There were statistically significant associations between regimen modification and type of regimen, care entry point, duration from HIV diagnosis to entry into HIV care, sex and functional status. Regimen modifications resulted in more AZT and TDF based regimes while 88.7% of patients had D4T taken off their HAART regimens.

Conclusions: HAART regimen modification at Gobabis State hospital is lower than in other settings was largely due to treatment toxicity. The death rate is high and warrants further

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exploration. Regimen modifications resulted in more AZT and TDF based regimes and more patients had D4T taken off their HAART regimens.

Recommendations: Patients still on D4T need close monitoring for side effects associated with this drug and should be promptly changed if this is the case. This study raises the important programmatic issue of the need for good data collection practices. HIV positive patients who are pregnant and those with concurrent TB disease need close monitoring to ensure that HAART regimens are modified appropriately.

CHAPTER 1-INTRODUCTION

1.1 INTRODUCTION

Namibia, with an estimated total population of 2.2 million, faces a mature generalized HIV epidemic which is primarily heterosexually transmitted (MOHSS, 2010). It is estimated that the adult HIV prevalence is 13.1%, giving a total of 178 000 people estimated to be living with HIV (UNAIDS 2010; MOHSS 2010).

As part of its multifaceted response to the epidemic, Namibia has been implementing an antiretroviral (ARV) programme in the public sector for the past eight years (Kangudie, 2008). Treatment with highly active antiretroviral therapy (HAART) started with six pilot hospitals in 2003. This was rapidly rolled out to involve all thirty four state hospitals in Namibia. In March 2011 it was estimated that about 92 000 HIV-infected adults and children were receiving ART in Namibia (MOHSS, 2011). This gave estimated coverage rates of 88% and 95% of adults and children respectively who qualified for HAART based on the CD4 <200 criteria.

Despite the high coverage of ART in Namibia a number of challenges currently affect programme implementation. According to UNICEF (2011), the high cost of the ART programme in an era of decreasing external funding coupled with inadequate human resources and technical capacity to run the program are some of the challenges. It is thus necessary to keep the HIV treatment program affordable and simple to manage through ensuring that patients remain on their first line regimens. Furthermore, it is necessary to monitor the percentage of patients starting therapy who are prescribed an appropriate first line at site level. This ensures rational drug use and therefore helps in preserving first line antiretroviral medicines

First line regimens give patients the best chance of long-term treatment success (MOHSS, 2010). As the programme matures more patients have had their first line regimens modified. It is estimated that 3.1% of adults in Namibia are on second line regimens (Niaz & Ongeri, 2011). Second line or other modified regimens are generally reserved for cases where there is documented clinical, immunological or virological failure and toxicity related complications. These modified regimens often involve a higher pill burden, more toxicity related complications are often more expensive. It is thus imperative that most patients stay on their initial first line regimens to ensure program viability. A more detailed understanding of the factors associated

with first line regimen modification could allow healthcare providers in Namibia to target those factors for intervention to reduce regime modification and improve treatment outcomes.

1.2 STUDY SETTING

This study was conducted at an anti-retroviral clinic at a rural district hospital in Namibia. This hospital is in Omaheke region located on the eastern border of Namibia and Botswana (MOHSS, 1999). The region covers a total area of 84 612 square kilometers and has a population density of 0.8 per square kilometer (GRN, 2005). Despite its huge geographical expanse of 84 612 km², Omaheke region has one health district, Gobabis. It has one district hospital located at Gobabis, one health centre and 10 primary care clinics (MOHSS, 2002). From the 2001 census, the total population for the district was estimated to be 68 039. It is estimated that 28 % of the population have livestock farming as their main source of household income (Suzman, 1995).

The anti-retroviral clinic was the first ART clinic in this region and hence has the highest case load in the region. It has been offering anti-retroviral therapy to patients in Omaheke region since 2005. It is staffed with a dedicated team of one doctor, three nurses, a pharmacist, a pharmacist's assistant, two lay counselors, a data capturer and a qualified social worker. Before starting HAART patients are counseled by the lay counselors and the nurses. The doctor initiates new patients on HAART and reviews them on subsequent visits as well. Nurses can equally review patients with no complications on their subsequent visits. The doctor or nurse appropriately codes and enters patient data onto the paper based data collection tools. This data is then entered into the electronic patient management system, (ePMS) by the data capturer.

A total of 1400 patients are currently recorded as active on treatment (Niaz & Ongeri, 2011). 90% of these patients are adults. 526 new patients were initiated on HAART in 2010 at this hospital. A patient who receives a positive HIV test result is referred to the hospital for enrolment into the general HIV wellness program and evaluated for the need to begin HAART. This assessment includes a complete medical history, physical examination to determine WHO clinical staging and other co-morbidities, a CD4 cell count, Hepatitis B Surface antigen test and a review of social eligibility criteria. At this first visit, all patients are registered into the electronic patient management system to assist with follow-up, tracking and record-keeping for overall programme management.

Patients are initiated on HAART following clinical and immunological criteria stipulated by the World Health Organization (WHO) and adopted by the Ministry of Health and Social Services (MOHSS). It is desirable for all patients to have a treatment supporter but absence of a treatment supporter is not a reason to deny treatment to a patient. Patients who develop treatment failure or treatment related toxicities have their regimens modified by the clinic staff that follows the National Guidelines for Antiretroviral Therapy-Third Edition.

1.3 PROBLEM STATEMENT

Highly active antiretroviral therapy (HAART) has dramatically improved the life expectancy of patients with human immunodeficiency virus (HIV) in Namibia. This has considerably reduced AIDS related morbidity and mortality of PLHIV (MOHSS, 2011). With 3.1% of adults in Namibia estimated to be on second line regimens and patients living longer on treatment the number of patients who have their first line HAART regimens modified is set to increase over time (Niaz & Ongeri, 2011). The characteristics of these patients and factors associated with the HAART regimen modifications in a rural setting in Namibia are largely unknown. Knowing why patients modify therapy could improve our understanding of successful HAART, guide decisions regarding initiation and management of HAART in specific patient populations such as rural settings. This will help institutions formulate strategies to reduce HAART modification and improve treatment outcomes (Cesar et al, 2010).

CHAPTER 2-LITERATURE REVIEW

2.1 Addressing the problem of HIV

The human immunodeficiency virus (HIV) epidemic remains a major global public health challenge, with an estimated 33.4 million people living with HIV worldwide. In 2008 alone, 2.7 million people were newly infected with HIV (WHO, 2010). While Sub-Saharan Africa is home to just over 10% of the world's population, it accounts for 68% of the global prevalence of HIV (UNAIDS, 2005; UNAIDS, 2010). In response to this public health problem countries in Sub-Saharan Africa started rolling out and scaling up provision of ART in the public sector. This rapid scale up of ART has been one of the success stories of sub-Saharan Africa in response to the HIV pandemic with coverage having increased from about 2% in 2003 to more than 40% five years later (Harries et al, 2010).

2.2 Successes and challenges in the scale up of HAART

Introduction of HAART has turned a formerly fatal infectious disease into a treatable condition. Benefits of HAART include suppressing the viral load leading to restoration of immune function. This helps prevent the development of opportunistic infections (Martison et al, 2003; Gentile, 2008). UNAIDS defines universal access to antiretroviral therapy as providing antiretroviral therapy to at least 80% of patients in need. As of December 2009, globally eight low- and middle-income countries had already achieved universal access and 21 additional countries had coverage rates higher than 50% (UNAIDS, 2010). Access to antiretroviral therapy in low- and middle-income countries increased from only 400 000 people receiving therapy in 2003 to 5.25 million by the end of 2009 (UNAIDS, 2010). This led to AIDS-related deaths dropping by 19% globally over the period 2004 to 2009. Another key result is a 19% decline in new HIV infections globally over the past decade.

While it is important to put qualifying patients on HAART, this action alone should not divert attention and funds away from other more fundamental political, social, and economic needs of these patients. These often determine whether patients continue, discontinue or have their HAART regimens modified. This has been a major challenge for HIV programs in Africa (McCoy et al., 2005). Data from countries with patients on HAART show that most patient

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attrition occurs within the first year of treatment initiation (UNAIDS, 2010). In 2009, the average retention rate at 12 months across low and middle-income countries was 82%, and was approximately the same among men and women (UNAIDS, 2010).

Movement of patients between private and public sectors remains a challenge. These sectors often use different criteria and regimens for starting patients on HAART. This is often compounded by the presence of poorly trained providers and medical insurance companies' control of drug choices (Stevens et al, 2004).

The recommended standard treatment guidelines have been evolving over the years as more evidence surfaced. One major recent change was the raising of the CD4 threshold below which patients should be started on HAART. Based on the new criterion for treatment initiation (CD4 cell count of below 350 cells/mm3), antiretroviral therapy coverage at the end of 2009 was 36% in 2009 compared to 52% if the previous criterion was used (UNAIDS, 2010). This does not only have financial implications on the cost of providing drugs but also stretches the service providers who are already overburdened (Van Damme, 2006). In another study, Smith (2005) projects that if countries like Zambia and Mozambique were to scale up ART for all clinically eligible patients they would require up to 4 times as many doctors. This is a challenge that besets many African nations including Namibia which may ultimately affect adequate patient monitoring to help keep patients on their HAART regimens.

2.3 Adherence to HAART and strategies to improve adherence

Adherence to antiretroviral therapy is fundamental to treatment success in patients living with HIV. Good adherence has been strongly correlated with viral suppression, reduced rates of resistance, increased survival, and improved quality of life (Chesney, 2006; WHO, 2003). On the contrary low levels of treatment adherence can be as a result of insufficient community and patient preparation, erratic and unsustainable drug supplies, and inadequate training and support of health care providers (McCoy et al., 2005). Bhat et al (2010) classify poor adherence under demographic, psychosocial and medication-related factors. These factors include treatment side effects, complex regimens, lack of social support, and feeling depressed or overwhelmed. Poor adherence ultimately leads to the development of drug resistance (Mills et al, 2006).

Development of drug resistance consequently leads to HIV treatment regimen modification if patient remains on treatment. This often has long term cost implications on HIV programmes.

National treatment programmes can use various strategies to ensure good adherence to HAART. Patient recall methods using structured self report or visual analog scales can be used to measure adherence and has been found to be valid and reliable in a systematic review of 77 studies done by Simoni et al, (2006). Additionally, pill counts and pharmacy records of medication refills can also be used to assess adherence and target adherence support (Grossberg, 2007; Bisson et al, 2008; Saberi et al, 2008). The clinic needs to have a functional appointment and patient contact system. This helps in patient follow-up when necessary (Forster et al, 2008). The patient's social networks play a pivotal role in ensuring good adherence to treatment (Nachega et al, 2010). These social networks include peer support groups and peer educators. Other innovative interventions to improve adherence include radio announcements reminding patients to take their medication, ART stations at work places, and pick-ups of prepackaged ART from local general supply stores, schools, or community-based ART refill sites rather than always from the clinic (Harries et al, 2010). However, a good supply chain logistical network needs to be established before some of these interventions can be implemented.

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2.4 Modification of first line HAART regimens: Problems of treatment failure and toxicity

First line regimens give patients the best chance of long-term treatment success (MOHSS, 2010). (see Appendix 4 & 5 for classes of antiretroviral agents and recommended HAART regimens in Namibia respectively). ART regimens need to be as non-toxic and simple to take as possible (Renaud-Thery et al, 2007). Thus, modifying therapy is to be avoided wherever possible. Modification of a HAART regimen can be defined as any alteration of one or more components of a patient's regimen, (Kumarasamy, 2006). As found in a South African study usage of simple first line regimens results in similar virologic outcomes compared to the highly individualized approach in developed countries (Keiser et al, 2008). National HIV treatment programs should thus aim to keep most of their patients on first line regimens. In a prospective study done to determine rates and causes of switching from first to second-line antiretroviral treatment

regimens in a large treatment-naive cohort in South Africa, 96% patients remained on first-line therapy while 1.7% switched to second-line regimens due to hypersensitivity reactions or lactic acidosis over 760 person-years of observation (Orrell et al, 2008). HAART may need to be modified but there must be a very good reason for doing so. Reasons for changing include treatment failure, toxicity, availability of newer and improved regimens and emergence of other concurrent illnesses such as TB (Bartlett & Gallant, 2004; WHO, 2004; MOHSS, 2010).

Unregulated use of ART may also lead to the emergence of resistant viral strains (Gallant, 2008). This leads to treatment failure necessitating regimen modification and limiting future therapeutic options. In the country Gabon, Vergne et al, (2002) showed that 58% of patients who had received unsupervised HAART without adequate health infrastructure developed major resistance mutations.

Most often HAART regimens are modified due to toxicity related events (Lugassy et al, 2010). Antiretroviral toxicities can occur in a wide range from mild and self-limiting to long-term and disabling such as D4T-associated peripheral neuropathy. Potentially fatal complications such as NRTI-associated lactic acidosis can also occur (Spencer, 2005). Some toxicities are drug class related while others are related to one particular ARV. The frequency and severity of class-related toxicities also vary among the medicines within the same class.

2.5 Considerations when modifying or stopping HAART

When an ARV regimen must be modified or stopped due to intolerance or toxicity, simple substitution of the offending agent with another ARV in the same class may be done without stopping the entire treatment. In cases of severe or life-threatening toxicity all ARVs must be stopped. These complications include peripheral neuropathy, lactic acidosis and lipoatrophy or lipodystrophy (Akileswaran et al, 2005; Fellay et al, 2001). Measures should be taken to prevent resistance from developing. This is because HIV develops resistance quickly when there are insufficient blood and tissue levels of antiretroviral medications (Bartlett & Gallant, 2004).

In conclusion, monitoring and optimally managing patients requiring HAART regimen modification requires adequate skill. This requires adequate human resources and staff training (Forster et al. 2008). This also entails strengthening the medical records systems. All the

foregoing factors combined will help minimize first line HAART regimen modification and keep future options for patients open as patients live longer on treatment.

CHAPTER 3 - METHODS

3.1. Study Aim and Objectives

3.1.1 Aim of the study

Overall, this study aims to describe the factors associated with first line highly active antiretroviral therapy (HAART) regimen modification in treatment naïve adult patients at Gobabis District Hospital.

3.1.2 Objectives of the study:

i. Describe the prevalence of regime modification in adult patients
ii. To describe the characteristics of adult patients who had their first line HAART regimens modified and those who did not.
iii. To describe the factors associated with first line HAART regimen modification in adult patients at Gobabis District Hospital.

3.2. Study Design

A quantitative descriptive retrospective cohort study was used. Using data from an existing electronic patient management system (ePMS) the cohort of adult patients who started HAART at Gobabis State Hospital between 1st January 2007 and 31st December 2010 was analyzed.

Quantitative methods were used to assess the prevalence and factors associated with first line HAART regimen modification in HIV positive adults. Those who had their regimens modified were compared with those who did not have their regimens modified. A cohort study was chosen because there was an existing electronic data set. It was thus cheaper and less time consuming for the researcher. Furthermore a cohort study is suitable when the population at risk is a well-defined group such as this one of adult patients who started HAART at Gobabis State Hospital between 1st January 2007 and 31st December 2010. A cohort study also provides a most direct measurement of the absolute risk.

Ethical approval was sought from the University of the Western Cape (UWC) Ethical Committee and from the Ministry of Health and Social Services (MOHSS) of Namibia.

3.3 Study Population

In this study, the study population was all adult patients (15 years and above) who started HAART at Gobabis State Hospital between 1st January 2007 – 31st December 2010. A total of 1407 patients were initiated on HAART during this period. HAART modification in this study referred to any alteration of one or more components of the patient's initial drug regimen

The following two groups were considered for comparison in the study:

- those who remained on original 1st line regimen during the study period
- those whose original regimens were modified during the study period

Table 1 below shows the inclusion and exclusion criteria used for the two groups.

Table 1: Inclusion and exclusion criteria

Those who remained on original 1st line regimen	**Those whose original regimens were modified**
Inclusion criteria • Treatment naïve adults 15 years and above • Started 1st line HAART between 1st January 2007 – 31st December 2010 • Had at least one follow-up visit after starting HAART • Remained on original 1st line regimen throughout the study period or up to a recorded outcome point (dead/ transferred out/ lost to follow up/ status unknown)	Inclusion criteria • Treatment naïve adults 15 years and above • Started 1st line HAART between 1st January 2007 – 31st December 2010 • Had at least one follow-up visit after starting HAART • Had original 1st line regimen modified during the study period or up to a recorded outcome point (dead/ transferred out/ lost to follow up/ status unknown)
Exclusion criteria • Patients < 15 years of age • Previous exposure to HAART	Exclusion criteria • Patients < 15 years of age • Previous exposure to HAART

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including PMTCT or PEP	including PMTCT or PEP

3.4 Sampling and Sample size

All adult patients (15 years and above) who started HAART at Gobabis State Hospital between 1st January 2007 – 31st December 2010 and meeting the study criteria mentioned above were taken.

3.5 Data Collection

Selected patient data as listed on the structured data collection tool in appendix 1 was extracted from an existing Microsoft Excel based electronic ART patient monitoring system (ePMS) database kept at Gobabis State hospital. This electronic database has been in use at the facility since 2005. It is the main electronic reporting system for HIV patient care in Namibia. The source of the data for the system is the paper based ART patient care booklet which is completed by doctors and nurses at each patient encounter. This paper based tool has been in use since 2003.

Relevant data under the following categories was abstracted from the electronic system: demographic data, baseline laboratory findings, initial HAART regimen, treatment modification history, reason for modification and follow-up laboratory findings. Data cleaning then followed which involved removing meaningless and correcting inconsistently entered data fields. At this stage it was realized that some of the desired variables were missing from the database. These variables included adherence, blood test results such as viral load, hemoglobin, ALT (a liver enzyme), creatinine, hepatitis B surface antigen, TB status at HAART initiation and history of opportunistic infections. According to the ePMS handbook used for training data capturers in Namibia these variables are supposed to be entered into the system for each patient. Thus, it would have been ideal for the researcher to refer to the original paper based clinical records but this was not possible.

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3.6 Definitions and descriptions of variables

3.6.1 Definitions

Treatment naïve: Refers to someone who has never used antiretroviral HIV drugs.

HAART regimen modification: Regimen modification was defined as any alteration of one or more components of a patient's regimen in this study. This definition broadly encompassed single, dual or whole regimen change often described as substitution or switching in other studies. HAART regimen modification was based on the principles of the Namibian national ART guidelines. Recommended HAART regimens in Namibia consist of a combination of 2 NRTIs plus an NNRTI or a boosted PI. Considerations in the selection of regimens include potency, side-effect profile, the potential for maintenance of future treatment options, convenience of the regimen (pill burden, frequency of intake, absorption), coexistent conditions (e.g. TB and hepatitis B), pregnancy, use of other medications and potential medication interactions. Individuals who cannot be maintained on the recommended regimens are supposed to have their regimens modified accordingly.

Adult patient: Adult patients were defined in this study as any patient with age equal to or greater than 15 years. This was an operational definition based on the fact that the HAART program in Namibia recognizes any patient with age equal to or greater than 15 years as an adult.

3.6.2 Definition of variables

The variables used in this study are defined in Table 1 below.

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Table 2: Definition of variables

Variable	Definition
Age	Patient's age defined as the interval in years between the date of birth to the date of starting HAART in years
Weight	Used in this study as the patient's weight in kilograms at starting HAART
Sex	Used to define whether patient was male or female
Marital status	Used in this study to identify whether patient is married or not married. 'Not married' included statuses recorded in the database as single, widowed, married or divorced
Care entry point	Describes care entry points where patient was referred from. It included the following categories:

	Medical = referred from hospital in-patient services including TB ward/clinic. PMTCT = from antenatal care clinic through the prevention of mother to child transmission program. Self referral = enrolled into care by own arrangement rather than being referred by a provider Private sector = referred from private medical providers Transfer in = Refers to a patient who has been receiving ART at one facility in the country who transfers into another in the same system with records. Other = not meeting any of the criteria above
CD4 count at HAART initiation	Patient's absolute CD4 count per mm^3 of blood. In this study the absolute CD4 count at HAART initiation was used.
Clinical stage at HAART initiation	Clinical stage of HIV disease of the patient using the WHO staging system. It classifies HIV disease into four clinical stages, 1 – 4 with stage 1 being mild HIV disease and 4 being severe HIV disease. In this study only the clinical stage at initiation of HAART was used.
Treatment Supporter	A buddy chosen by the patient before starting HAART. This could be someone at home, in the community or at the workplace, who can accompany the patient to visits and assist with daily adherence to HAART. It is desirable that all patients have a treatment supporter. Absence of a treatment supporter however is not a reason to deny treatment to a patient. The name of the treatment supporter is entered into the database. Where no name was entered it was assumed that the patient had no treatment supporter for purposes of this study.
Duration from HIV diagnosis to enrolment	This was the time interval in months between the date of HIV diagnosis and the date of enrolling into pre-ART care. This is derived from the two dates as recorded in the electronic register.

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into HIV Care	
Alive at end of study period	This variable assessed whether patient was alive as of 31st Dec 2010. Patients who had died or reported as dead had their date of death recorded in the system. Where no date of death was recorded, it was assumed that the patient was alive as of 31st December 2010
Ever put on CTX	Cotrimoxazole (CTX) reduces the risk of death and hospitalization of persons with HIV. Daily cotrimoxazole prophylaxis is recommended for persons with HIV and either WHO Clinical Stage 3 or 4 disease or any WHO clinical stage with a CD4 cell count ≤ 350. The cotrimoxazole status of patients was recorded in the electronic database.
Functional Status at HAART initiation	This variable describes the functional status of the patient HAART initiation. Patients were put in to the following categories: Working = Able to work; go to school, do housework, or farming Ambulatory = Able to perform activities of daily living but not able to work or play. Bedridden = Not able to perform activities of daily living.
HAART regimens	The highly active antiretroviral drug combination the patient was taking. These are recorded in the system using standard abbreviations.
Reason for HAART Regimen Modification	This variable indicates the reason given in the electronic record or in the patient clinical notes why the patient had his/her HAART regimen modified. The following reasons were used: **Toxicity** = Drug-related adverse events which may be acute, sub acute, or late. If a change in a regimen is needed because of toxicity and the toxicity is related to an identifiable medication in the regimen, the offending medicine can be replaced with another medicine that does not have the same side-effects.

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	New drug available = modification of HAART regimen done because of change in national guidelines recommending one drug over another. **Pregnancy** = applies to women who had regimens modified when they fell pregnant and had to be put on pregnancy friendly regimens. **TB** = regimen modified due to concurrent TB disease and patient has to take both TB treatment and HAART. Only certain HAART regimens can be used in combination with TB therapy. **TB & toxicity** = regimen modified due to both toxicity and presence of TB disease. It was impossible to separate the two categories as it was not clear from the electronic system what had started of the two complications. **Virological failure** = occurs when there is a viral load >1,000 copies/ml 24 weeks after starting HAART or viral rebound to >1,000 copies/ml on two consecutive measurements after a period of viral suppression (MoHSS, 2010). Viral load assays are recommended for patients already on treatment who are showing evidence of immunologic and or clinical failure. **Other** = any other reason not fitting in the above categories modification done to reduce pill burden, or to accommodate patient's work schedule

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3.7 Validity, Reliability and generalisability

3.7.1 Validity

Validity refers to the degree to which an instrument is able to measure what it is intended to measure (Bonita, Beaglehole &Kjellstrom, 2006). All patients who started HAART between 1st January 2007 – 31st December 2010 and meeting the rest of the study criteria participated in the study. Data was cleaned by examining for missing, erroneous and inconsistent entries.

This helped reduce sampling errors and thus increase validity. This study involved using an existing data set which had some desired variables poorly recorded or totally missing in certain

instances. These variables could have been important in establishing other predictors of regime modification. As a result this possibly reduced the study validity.

3.7.2 Reliability

Reliability means the consistency or repeatability of a measure (Bonita, Beaglehole &Kjellstrom, 2006). Different clinicians who recorded the data onto patient charts could have made coding errors hence causing measurement bias. Equally, the data capturers who are responsible for entering data from the paper based charts into the electronic system could have made errors at data capture further causing measurement bias. It was not possible to offer training to these cadres to minimize data recording and coding errors since this was a retrospective study.

3.7.3 Generalisability

This study took the entire cohort of patients who started HAART between 1st January 2007 – 31st December 2010. The results may be generalized to other patients seeking treatment at this facility. However the findings may not be generalizable to other settings in Namibia.

3.8 Analysis

Data cleaning, coding and analysis : Data was obtained from the Microsft Excel based ePMS checked for completeness, errors and cleaned. Where missing data fields were observed an attempt was made to obtain the data from the paper based patient charts. The data was then exported to the IBM SPSS 19 statistical software package for analysis. Nominal data was coded so that it could be read by the statistical package. Descriptive and analytic statistics were used in the analysis. The variables for each of the two groups were put into these categories: background characteristics; initial HAART regimen history & regimen modification patterns.

Respective variables from the two groups were then statistically compared. Descriptive statistics were applied, using frequencies and cross tabulation. Pearson and Chi-square test (χ^2) were used to compare group characteristics and differences for categorical variables. These included calculating the mean, median, and standard deviation (SD) of continuous data such as CD4 count and the frequencies (or proportions) of categorical data such as sex or marital status. Chi squared statistics were used to compare proportions between clients who had their regimens modified and those who remained on original first line regimen. To compare means between the two groups the t-test was used. The level of significance was set at $p<0.05$.

HAART regimen modification patterns were analyzed according to NRTI back bone and NNRTI choice. Further analysis was done for specific drugs to determine proportions of patients who initiated and remained on a specific drug against those who initiated on specific drug but later taken off.

3.9 Ethical and Legal Considerations

Ethical clearance was sought from the University of the Western Cape School of Public health in writing. After the protocol was ethically approved by the University of the Western Cape ethical clearance committee further approval sought and granted by the Ministry of Health and Social Services of Namibia. This is largely because this study collected information on human subjects. Background information on the aims of the study was given to ministry officials. The regional health director of Omaheke region was asked to give informed consent before the patient records from Gobabis District hospital were used.

All the information collected was treated confidentially. No names were used and only codes were used to identify individually patient records. The computer that was used for data entry and analysis was password protected.

To minimise the negative impact of the study data abstraction was carried out on less busy days and the researcher was respectful to the data capturers' and clinicians' time. Clinic staff who assisted the researcher with access to the electronic data set were reassured that their position at work would not be affected whether they assisted in the study or not and that should the results show poor practice, this would not be used in a punitive way against them. It is hoped that the findings and recommendations of this study will assist the management at Gobabis District Hospital improve the quality of care provided to patients on HAART. The study findings will be shared with MOHSS and a feedback meeting will be scheduled for Gobabis District Hospital staff.

CHAPTER 4-RESULTS

This chapter describes the results of this study which was conducted to describe factors associated with first line HAART regimen modification in treatment naïve adult patients at Gobabis State Hospital. The first section presents the characteristics of the entire cohort studied. This is then followed by a description of the characteristics of adult patients who had their first line HAART regimen modified and those who remained on original regimens. The next section then summarizes the type of HAART regimens used, the reasons and patterns of modification. The summary of major findings is given at the end of the chapter.

4.1 SAMPLE SIZE

A total of 1407 patients meeting the study criteria were started on HAART at Gobabis State Hospital between 1st January 2007 and 31st December 2010. Of these, as shown by Figure 1, one hundred and ninety nine (14.1%) had their treatment regimens modified while 1208 (85.9%) remained on their original first line regimens.

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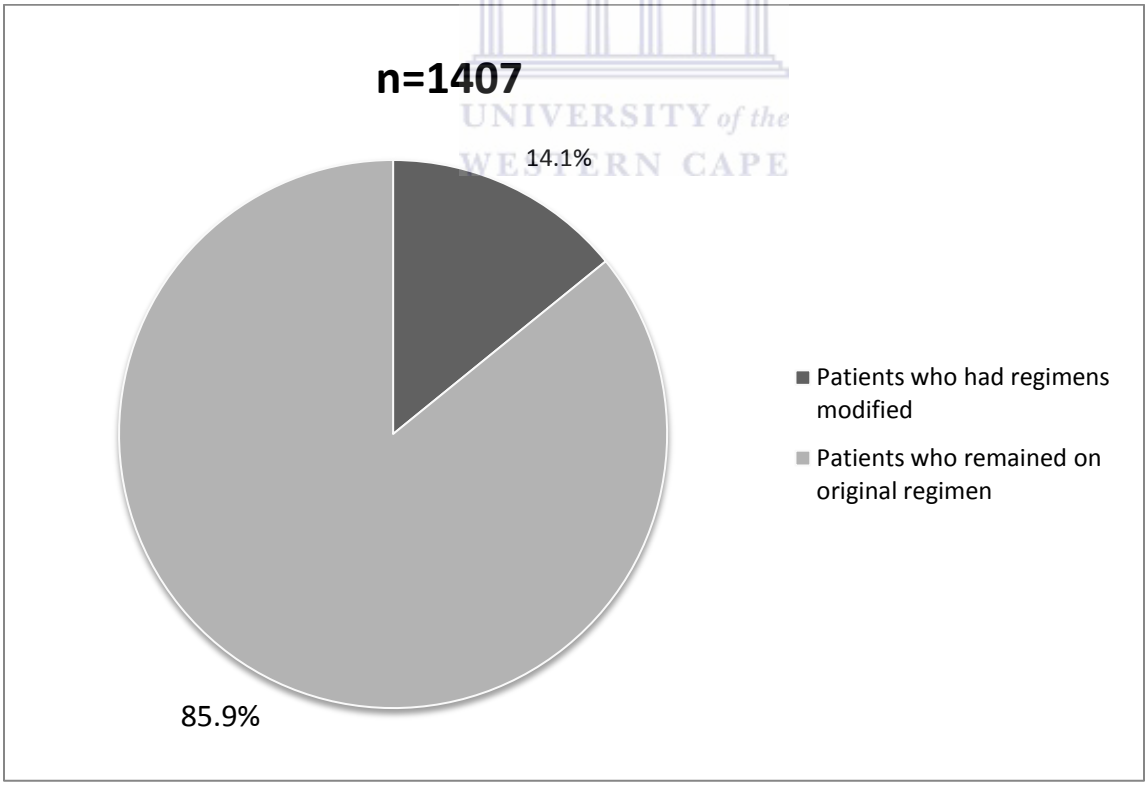

Figure 1: Pie chart showing proportions of patients who remained on original regimens and those whose regimens were modified.

4.2 REASONS FOR HAART REGIMEN MODIFICATION

Treatment toxicity, as shown in Figure 2, was the major reason for HAART regimen modification as it contributed 35.3% of the patients whose regimens were modified. This was followed by treatment modification due to concurrent TB disease which contributed 27.3% of the patients who had regimens modified. Almost 19% of the patients had their regimens modified because of new drug availability. Pregnancy contributed 6.6% of the regimen modifications and modification due to virological failure contributed only 2%.

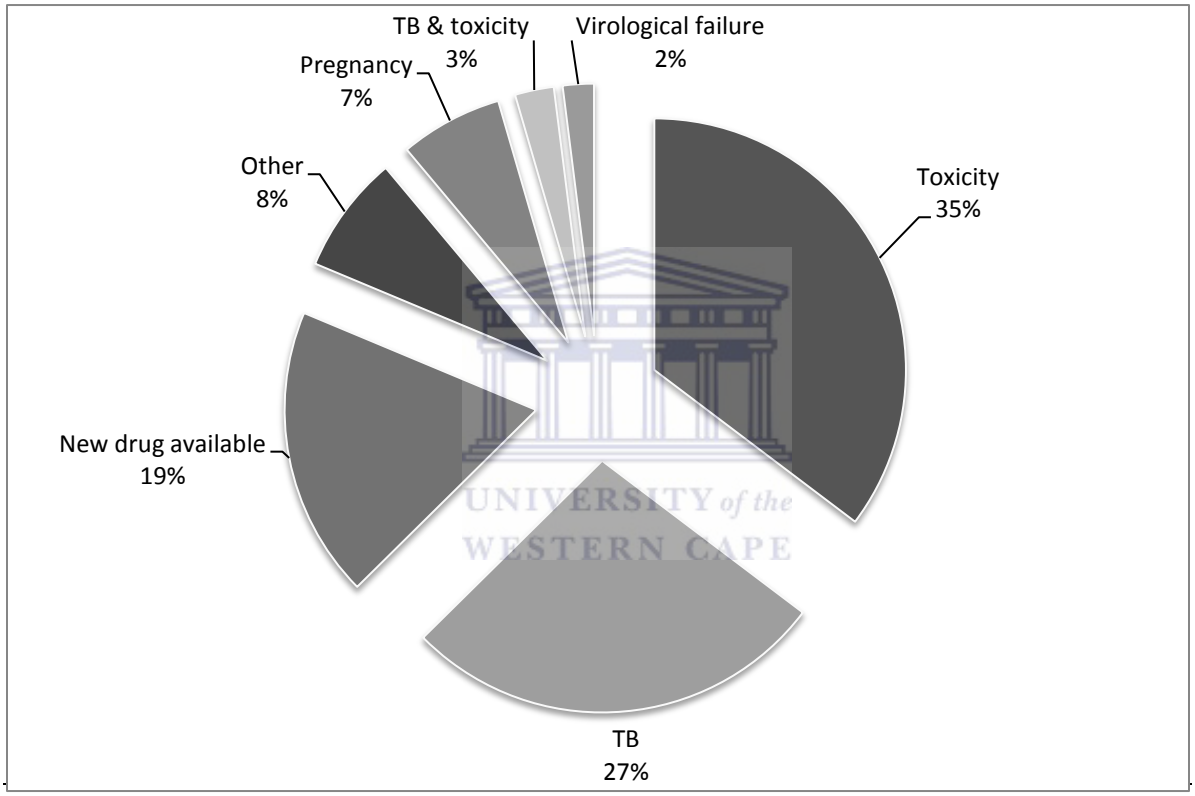

Figure 2: Pie chart showing reasons for HAART regimen modification

4.3 BACKGROUND CHARACTERISTICS FOR THE WHOLE GROUP

The median age for all patients starting HAART at Gobabis State Hospital during the study period was 38 years as shown in Table 1. Only 10% of these patients were married and females constituted 60% of the whole cohort. The commonest care entry point into the HAART program was via the 'medical' route which contributed 67%, followed by being self-referred (15%). Seventy percent of all the patients had treatment supporters.

Table 3: Background characteristics for the whole cohort

Characteristic	Frequency (Percent)
Age, years (median)	38.0
Sex n (%)	**n=1406**
Male	561 (39.9%)
Female	845 (60.1%)
Marital Status n (%)	**n=1118**
Married	119 (10.6%)
Not married	999 (88.4%)
Care Entry Point n (%)	**n=1345**
PMTCT	79 (5.9%)
Medical	903(67.1%)
Private sector	3 (0.2%)
Self Referral	207(15.4%)
Transfer in	120 (8.9%)
Other	33 (2.4%)
Presence of Treatment Supporter n (%)	**n=1406**
Yes	988 (70.3%)
No	418 (29.7%)

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Figure 3, shown below, goes on to show that patients starting HAART at Gobabis State Hospital between 1st January 2007 and 31st December 2010 were largely in the 30-39 year age group. Only 2 patients were above 80 years of age.

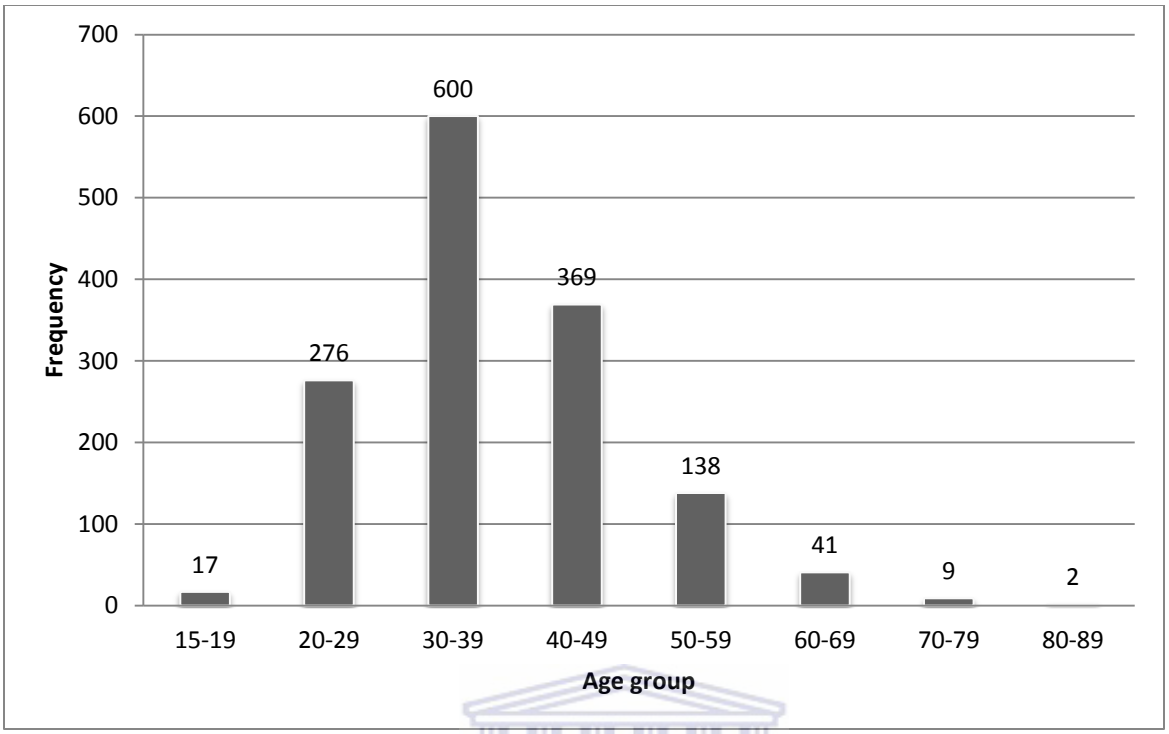

Figure 3: Age groups for the whole cohort

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4.4 BACKGROUND CHARACTERISTICS FOR EACH OF THE TWO GROUPS

There was a significant difference in the time from HIV diagnosis to entry into HIV care (p<0.0001) between patients who remained on original regimen and patients who had their regimens modified. As shown in Figure 4 below, a greater proportion (57.9%) of patients who remained on their original regimens were enrolled into HIV general wellness care during the first month of testing positive for HIV as compared to 44.2% of those who had regimens modified.

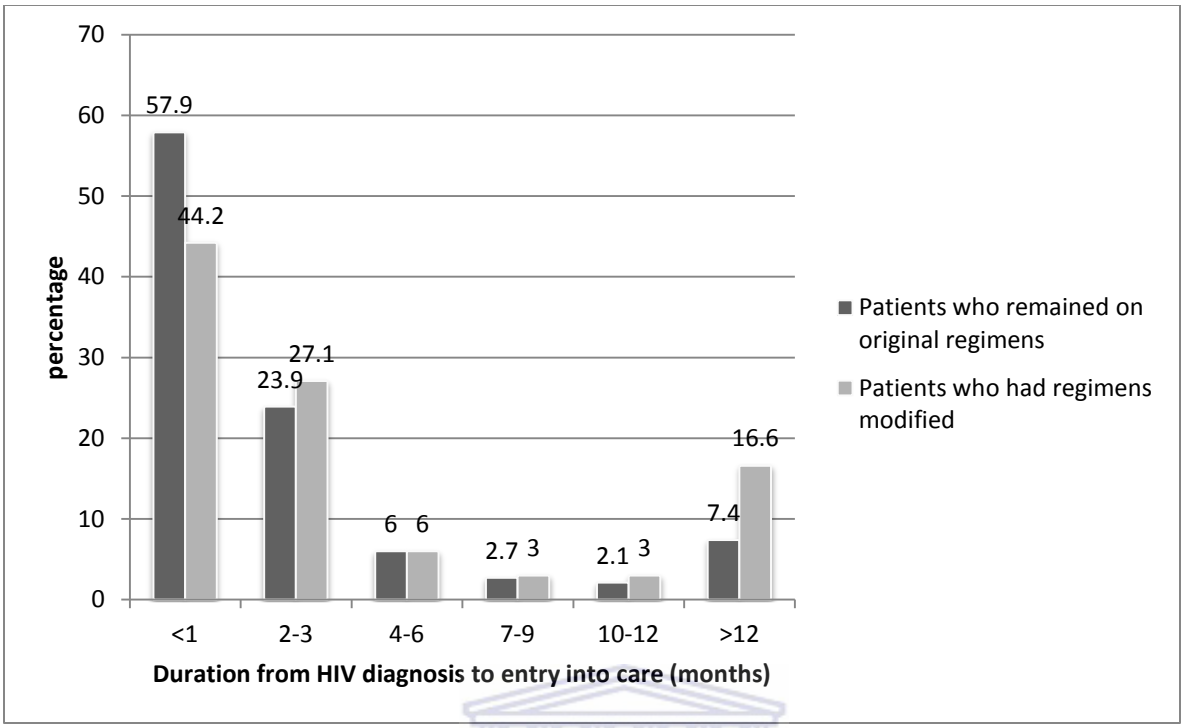

Figure 4: **Duration from HIV diagnosis to enrollment into HIV general wellness care**

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Table 2, below, shows that the median age of patients who remained on original regimen was 37.5 years with their ages ranging from 19 to 83 years. For patients who had their regimens modified, the median age was 39 years and with an age range of 19 to 64 years. Males formed 58.8% of patients who remained on original first line regimen. Proportionally there were more females (67.8%) among patients who had their regimens modified. Patients with single marital status formed the majority in both groups. Entry into HIV care via the "Medical" route was the commonest in the two groups of patients. Sixty-nine percent of patients who remained on original regimen had treatment supporters while 75% of those who modified regimens reported having treatment supporters.

There was a statistically significant association between regimen modification and sex (p=0.016), with more men than women having altered regimens. There was also a statistically significant association between regimen modification and care entry point (p<0.0001) and it seems that this was due to the higher proportion of patients who remained on the original regime entering care via the 'medical' route. The mean weight at starting HAART for patients who

remained on original regimen was 51.9kg and 54.1kg for patients who had their regimens modified with no statistically significant weight differences between the two groups (p=0.234).

As also shown in Table 2, there was an association between regimen modification and "functional status at HAART initiation" (p<0.0001). Sixty eight percent of the patients in each of the groups had been on cotrimoxazole at some point during the study period and 12.1% of patients who remained on original regimens were bed ridden at HAART initiation as compared to 2.1% amongst those who had their regimens modified. Nine percent of the patients in each of the two groups were recorded as dead by the end of the study period.

Table 4: Background and other HIV care patient characteristics of the two groups

Characteristic	**Patients who remained on original regimen**	**Patients who had regimens modified**	***p* value**
Age, years (median)	**n=1208**	**n=199**	**0.113**
	37.5	39.0	
Sex, n (%)	**n=1207**	**n=199**	**0.016**
Male	497 (41.2%)	64 (32.2%)	
Female	710 (58.8%)	135 (67.8%)	
Marital Status, n (%)	**n=952**	**n=163**	**0.170**
Married	110 (11.5%)	9 (5.5%)	
Not married	842 (88.4%)	154 (94.5)	
Care Entry Point, n (%)	**n=1171**	**n=174**	**<0.0001**
PMTCT	68 (5.8%)	11 (6.3%)	
Medical	822 (70.2%)	99 (56.9%)	
Private sector	3 (0.3%)	0(0.0%)	
Self Referral	156 (13.3%)	51 (29.3%)	
Transfer in	107 (9.1%)	13 (7.5%)	
Other	15 (1.3%)	0(0.0%)	
Presence of Treatment			

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Supporter, n (%)	**n=1208**	**n=199**	**0.089**
Yes	839 (69.4%)	150 (75.4%)	
No	369 (30.6%)	49 (24.6%)	
Mean weight, kilograms	**n=469**	**n=142**	**0.234**
	51.9	54.1	
Median CD4 count at starting HAART, cells/mm^3	**n=1208**	**n=192**	**0.625**
	154.5	173.0	
Functional Status at HAART initiation, n (%)	**n=1145**	**n=179**	**<0.0001**
Ambulatory	52 (4.5%)	21 (11.7%)	
Working	954 (83.3%)	154 (86.0%)	
Bedridden	139 (12.1%)	4 (2.2%)	
Ever put on CTX , n(%)	**n=1206**	**n=198**	**0.949**
Yes	825 (68.4%)	135 (68.2%)	
No	381 (31.5%)	63 (31.7%)	
Alive at end of study period, n (%)	**n=1207**	**n=198**	**0.954**
Yes	1097 (90.8%)	180 (90.5%)	
No	110 (9.1%)	18 (9.0%)	

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As shown below in Figure 5, 44% of patients who remained on original regimen and 58% percent of those whose regimens were modified had CD4 counts between 100-199 cells/mm^3 at HAART initiation. However, only 5.1% of patients whose regimens were modified had CD4 counts less than 50 as compared to 12.3% among those who remained on their original regimens. There were no significant CD4 count differences (p=0.625) between the two groups of patients.

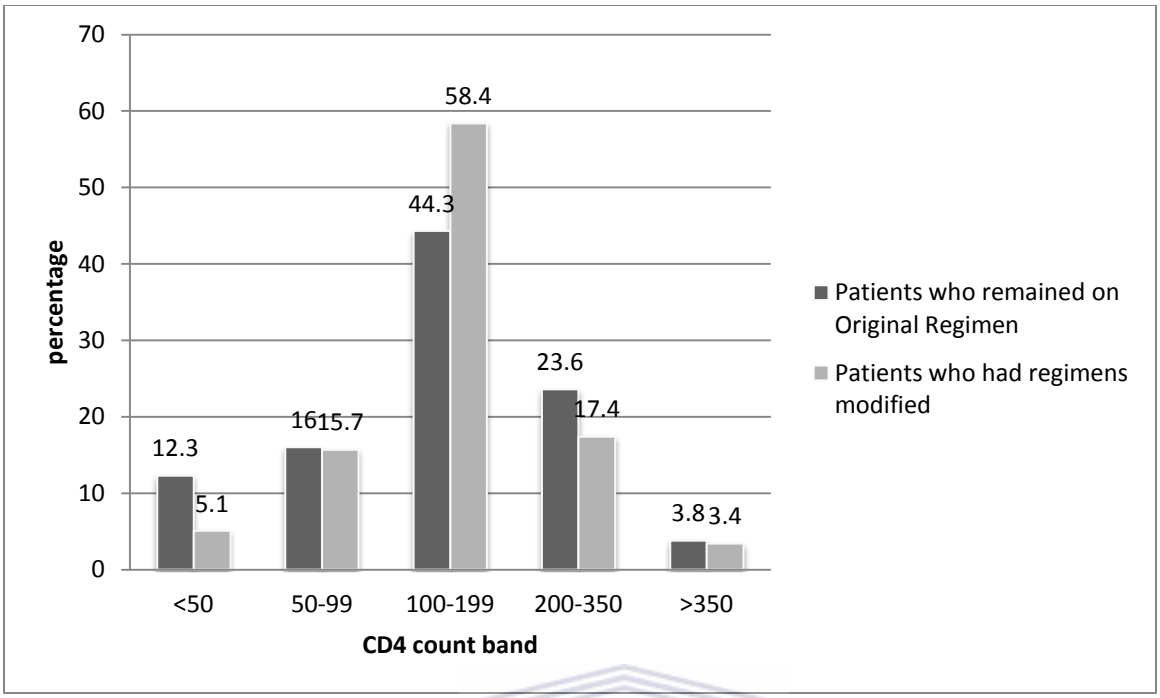

Figure 5: CD4 count band categories at starting HAART

As shown below in Figure 6, most of the patients in both groups were in WHO clinical stage 3, with almost 46% of patients who had their regimens modified and 40.7% for patients who remained on original regimen in clinical stage 3 at HAART initiation. Furthermore, 11% or less of the patients were in WHO clinical stage 1 or 4 in both groups.

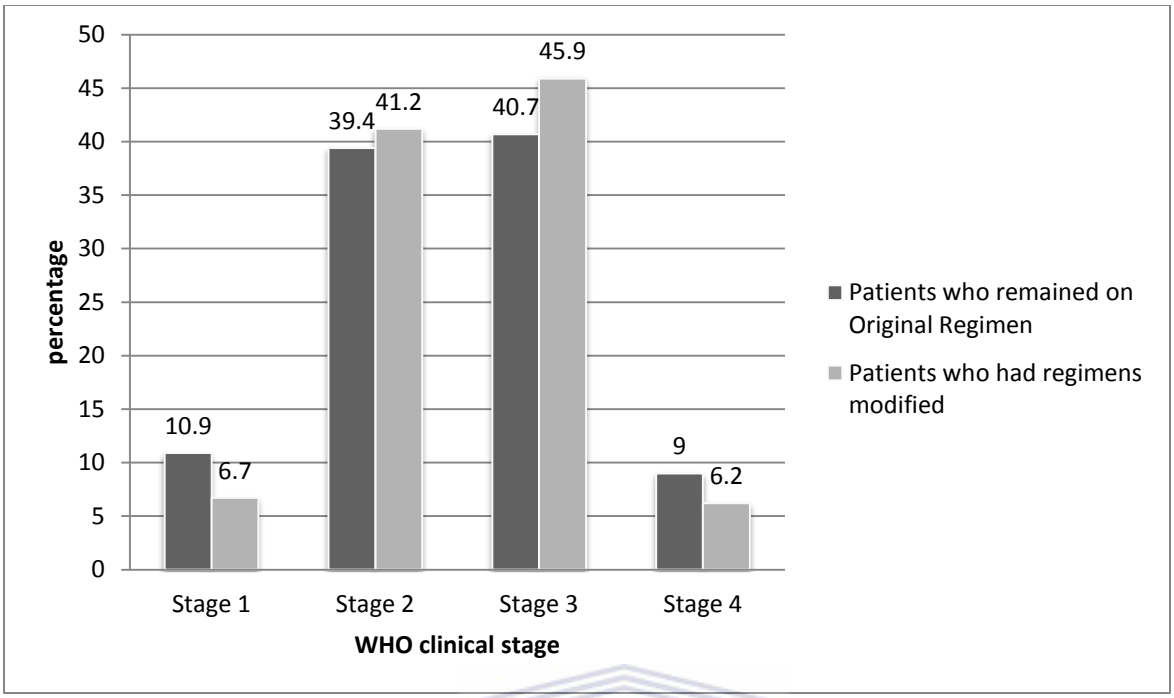

Figure 6: WHO Clinical stages of patients who remained on original regimens and those whose regimens were modified

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4.5 HAART REGIMEN HISTORY AND MODIFICATION PATTERNS

The following is an analysis of HAART regimen history and modification patterns of patients who started HAART at Gobabis State Hospital between 1st January 2007 and 31st December 2010.

4.5.1 HAART regimens at initiation for whole cohort according to NRTI back bone

Overall, AZT based regimens contributed the majority (53.4%) of regimens at initiation as shown in Figure 7.

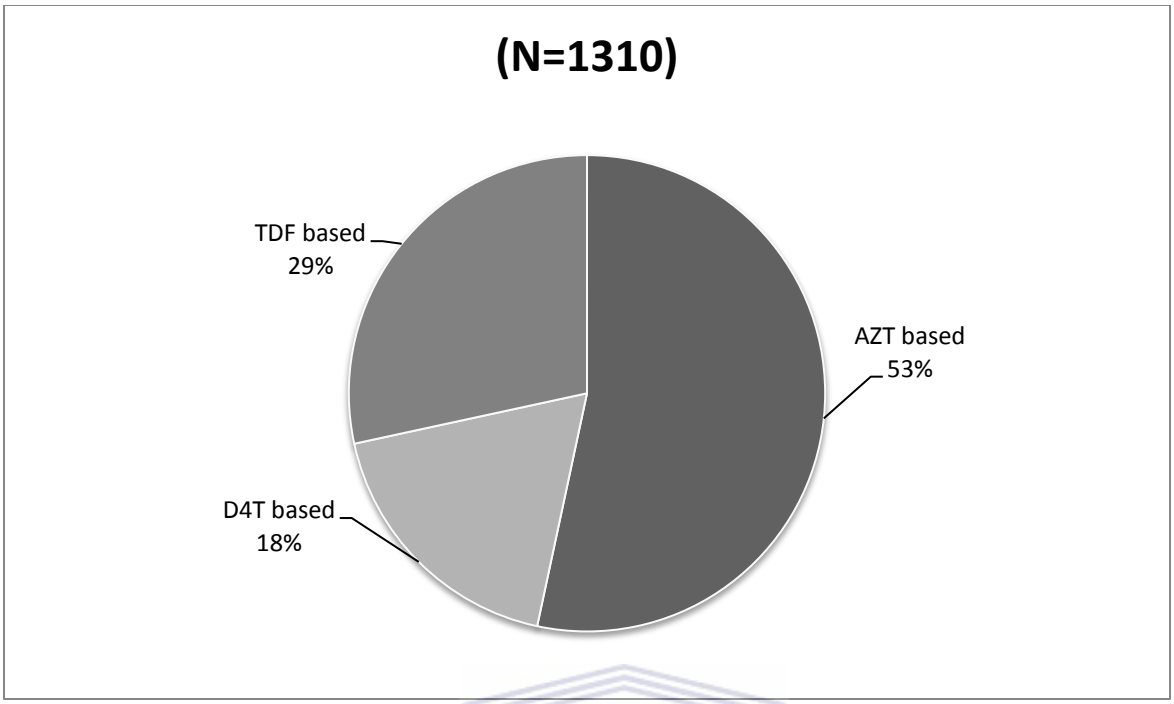

Figure 7: HAART regimens at initiation for whole cohort according to NRTI back bone

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4.5.2 HAART regimens at initiation for whole cohort patients according to NNRTI choice

In almost 75% of patients initiating HAART at Gobabis State hospital during the study period the NNRTI of choice was nevirapine. This is illustrated in the pie chart in Figure 8.

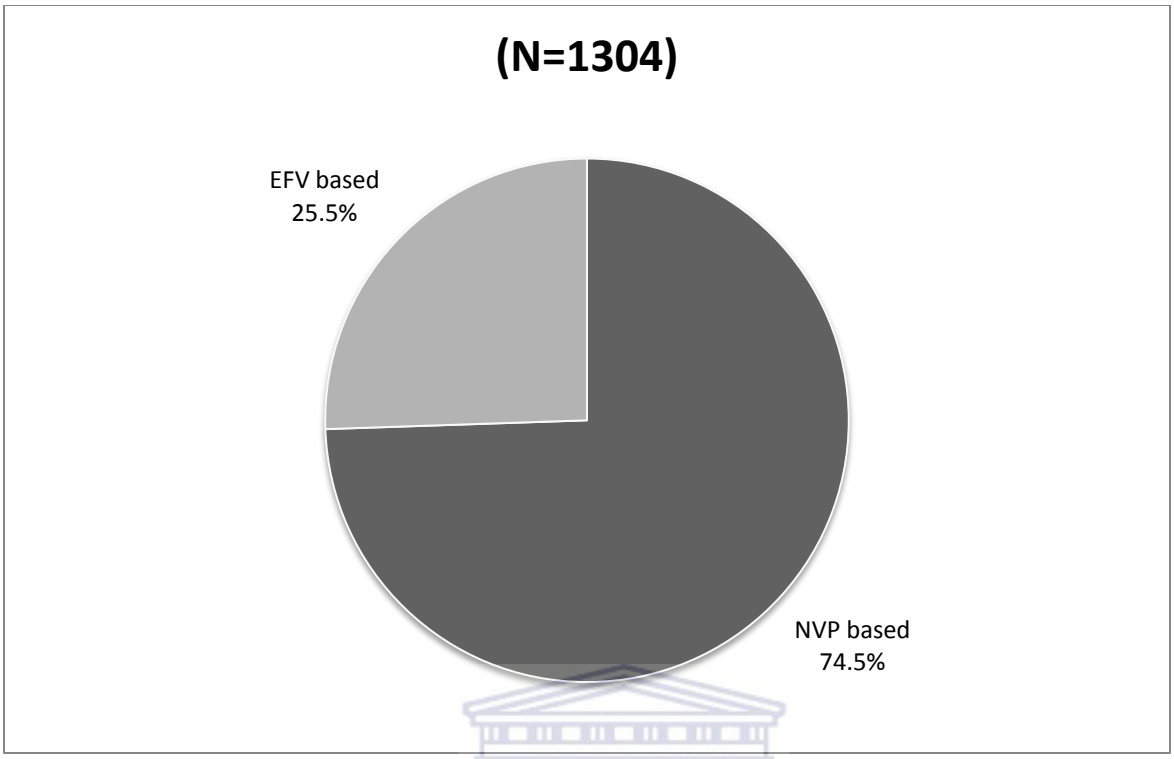

Figure 8: HAART regimens at initiation for whole cohort according to NNRTI choice

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4.5.3 HAART regimen modification patterns

The mean time before regimen modification was 16.7 months with a standard deviation of 12.8. As shown in Figure 9, regimen changes have resulted in more AZT and TDF based regimes and less D4T based. Even in those patients who have had their regimens modified, ABC-based regimens were rare. Figure 10 goes on to show that regimen modification resulted in more EFV and LPV-r containing regimens being used and less NVP containing regimen usage. Only 1% of the patients were put on the standard four drug second line regimen used in Namibia.

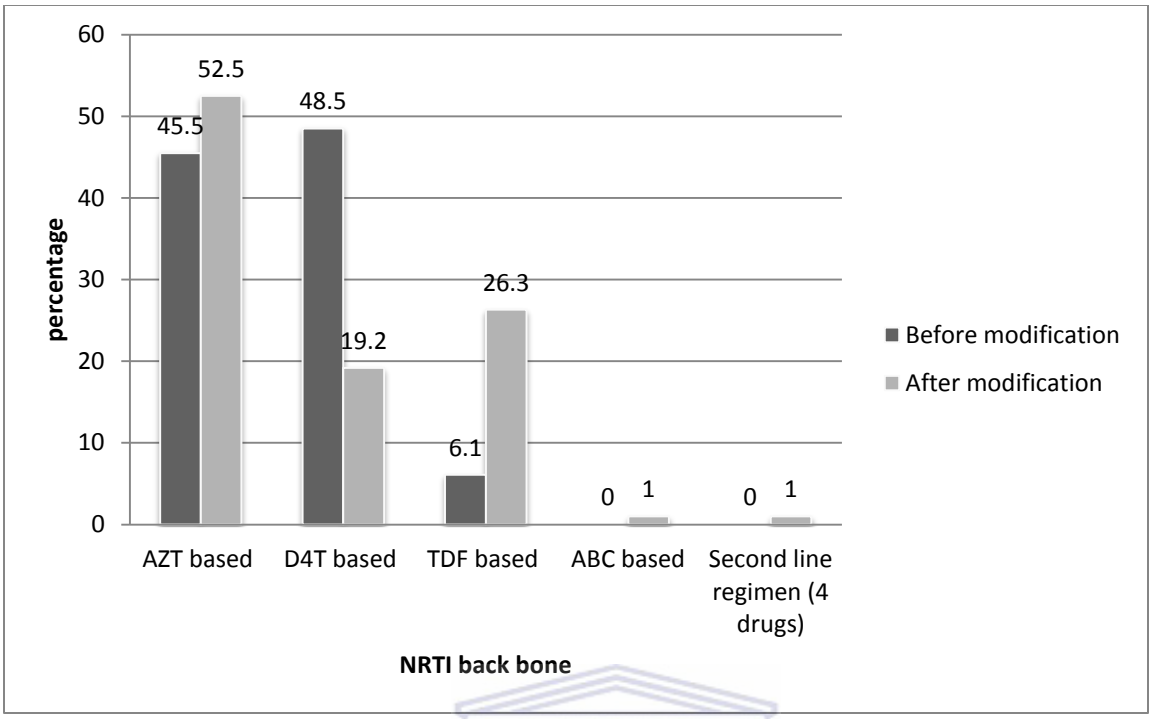

Figure 9: HAART regimens for patients who had regimens modified according to NRTI back bone

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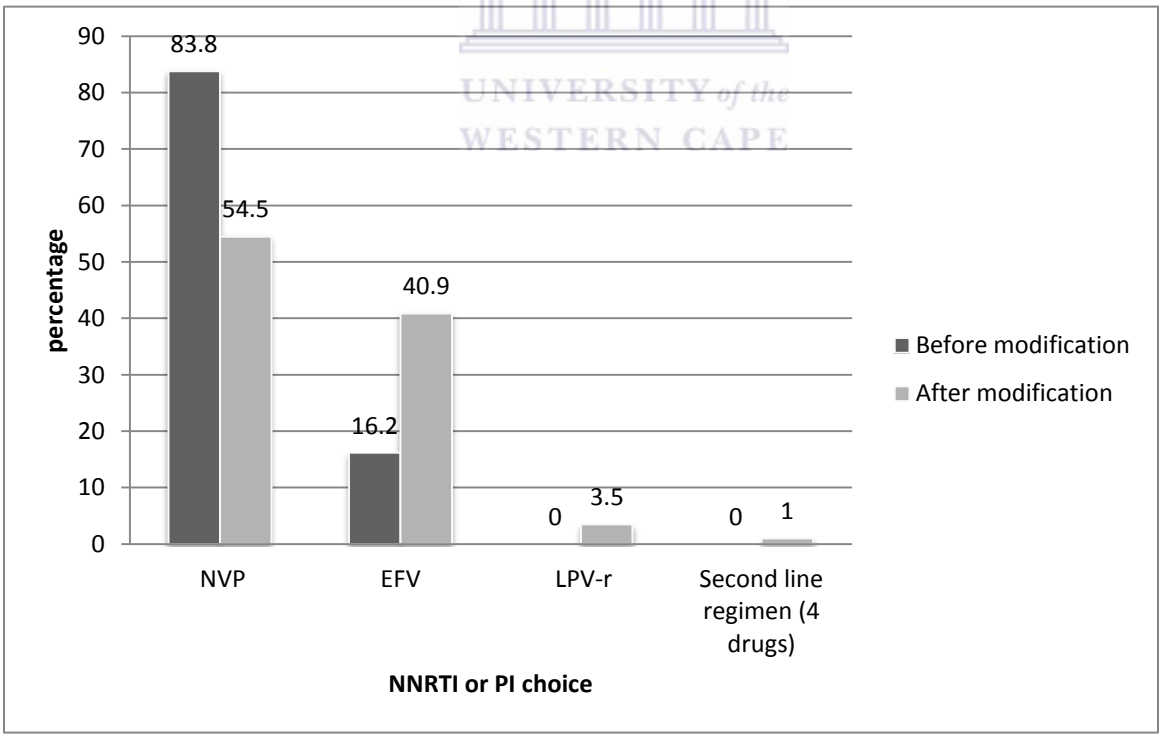

Figure 10: HAART regimens for patients who had regimens modified according to NNRTI or PI choice

As shown in Table 5 below, the biggest proportion (88.7%) of patients had D4T taken off their HAART combinations. Table 5 also highlights that there was a significant association between regimen modification and the type of original first line regimen ($p<0.0001$). According to the cross tabulation in Table 6 the most common reason to change therapy was due to D4T toxicity followed by AZT toxicity.

Table 5: Regimen modification according to specific drugs

	Patients who initiated and remained on specific drug	Patients who initiated on specific drug but later taken off	***p* value**
	n (%)	**n (%)**	
AZT-based	39 (43.3)	51 (56.7)	**<0.0001***
TDF-based	8 (66.7)	4 (33.3)	
D4T-based	11 (11.3)	86 (88.7)	
NVP	92 (55.4)	74 (44.6)	
EFV	14 (43.8)	18 (56.3)	

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Table 6: Cross tabulation of original first line regimen versus reason to change therapy

	Reason to change therapy							
Original HAART regimen	New drug available	Virological failure	Pregnancy	TB	TB & toxicity	Toxicity	Other	**Total**
AZT based	16	1	4	33	3	31	2	**90**
D4T based	21	3	8	14	0	38	12	**96**
TDF based	0	0	1	7	2	1	1	**12**
Total	**37**	**4**	**13**	**54**	**5**	**70**	**15**	**198**

SUMMARY OF RESULTS

In summary, a total of 1407 patients meeting the study criteria were started on HAART at Gobabis State Hospital between 1st January 2007 and 31st December 2010. The prevalence of HAART regimen modification was 14.1%. Treatment toxicity was the major reason for HAART regimen modification and this was largely due to D4T toxicity, concurrent TB disease (27.3%) , new drug availability (19%), pregnancy (6.6%) and virological failure (2%). Nine percent of the patients in each of the two groups were recorded as dead by the end of the study period. There were statistically significant associations between regimen modification and type of original first line regimen, care entry point, duration from HIV diagnosis to entry into HIV care, sex, and functional status at HAART initiation respectively. Regimen modifications resulted in more AZT and TDF based regimes while 88.7% of patients had D4T taken off their HAART regimens. Also, more EFV and LPV-r containing regimen usage was evident.

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CHAPTER 5 – DISCUSSION

This chapter presents the discussion of the results of the study to describe reasons and factors associated with first line regimen modification in treatment naïve adult patients on highly active antiretroviral therapy at a rural clinic in Namibia.

5.1 PREVALENCE OF HAART REGIMEN MODIFICATION

In this study, 14.1% of patients starting HAART had their treatment regimens modified. Knowing the magnitude of regimen modification is important as it provides information on the rate at which HAART regimens may be failing, evolving or not tolerated (Kirstein et al., 2002). It must be noted that different studies define HAART regimen modification differently. In this study modification of a HAART regimen was defined as any alteration of one or more components of a patient's regimen. This definition was similar to the definition used in the study done by Kumarasamy et al., (2006) in which 20% of patients modified their first-line regimen. In another study done in a resource limited setting in South India, 33% of the patients switched therapy (Chandy et al., 2011). Another study involving only women, 45.6% switched their HAART regimens (Kirstein et al., 2002). A South African study found that 72% remained on their initial regimen after 3 years of being in an HIV care treatment programme in Cape Town and concluded that adult patients can tolerate their initial HAART regimen for up to 3 years (Boulle et al., 2007). Thus, the regimen modification prevalence at Gobabis State hospital can be considered lower than in other settings.

5.2 REASONS FOR HAART REGIMEN MODIFICATION

5.2.1 Treatment toxicity

In this study, 35% of the patients whose regimens were modified were due to treatment toxicity. While studies define toxicity differently, toxicity remains one of the major reasons for treatment modification or discontinuation in various settings. An Italian study by Cicconi et al., (2010) discovered that intolerance/toxicity led to 58.5% of HAART discontinuation, (696 of 1189 patients). A retrospective study done in Rio de Janeiro, Brazil involving 670 treatment-naive

patients who received HAART between January 1996 and December 2006 observed that 40% of HAART modifications were toxicity related (Cardoso et al., 2010).

The most common reason to change therapy at Gobabis State hospital was due to D4T toxicity followed by AZT toxicity. It is now known that D4T is associated with serious potential toxicities including lactic acidosis, peripheral neuropathy and lipoatrophy (Westreich et al., 2009). Drug toxicities also have an impact on adherence (Boulle et al., 2003). The World Health Organization (WHO) now recommends that D4T should be phased out wherever possible (Bendavid et al., 2010). Modifying HAART regimens should be done appropriately to ensure good treatment outcomes such as lower death rates (Boulle et al., 2003; Subbaraman, 2003; Falco et al., 2002).

5.2.2 Concurrent TB disease

HAART regimen modification due to concurrent TB disease contributed 27.3% of the patients who had regimens modified. Namibia, with a case notification rate of 634 cases/100, 000 population in 2009, has one of the highest TB case notification rates in the world (MoHSS, 2009). While HIV is the most powerful factor known to increase the risk of TB and the benefits of treating HIV during TB treatment are well documented, it must be noted that multiple factors make it complicated to concurrently use antiretroviral and TB treatment therapy (Getahun et al, 2009). These include drug-drug interactions, presence of immune reconstitution inflammatory syndrome, overlapping HAART & TB drug side effects, adherence challenges with multi-drug therapy for the two infections and the need for coordinated care between TB and HIV care providers (de Jong et al, 2004; Middelkop, 2009). A good example of why regimen modification may be indicated is that of the TB drug called rifampicin which is a strong inducer of the cytochrome p450 cytochrome liver enzyme system that substantially lowers the levels of nevirapine but lowers the levels of efavirenz less (Lopez-Cortes et al, 2001; Patel et al, 2004). As a result, the factors listed above often lead to the modification of HAART regimens. Providers should be mindful that pulmonary tuberculosis is a WHO Clinical Stage 3 disease and extra-pulmonary TB is Clinical Stage 4. Thus patients with either diagnosis are eligible for HAART which should be initiated as soon as possible (MoHSS, 2010).

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5.2.3 Pregnancy

Pregnancy contributed 6.6% of the regimen modifications in this study. HIV positive pregnant women require HAART both for their own health and for prevention of perinatal transmission of HIV (MoHSS, 2010). Some HAART regimens have to be modified for fear of harming the unborn baby (Cooper et al, 2002). In a Botswana randomized clinical trial on antiretroviral regimens use in pregnancy, modification of HAART regimen occurred in 11% of women receiving the nevirapine, zidovudine and lamivudine combination who formed the observational group (Shapiro et al., 2010). The lower percentage (6.6%) of regimen modification in this study due to pregnancy may be due to the fact that Namibia has tended to use pregnancy friendly regimens as first line therapies. Healthcare workers have been trained to avoid using efavirenz or D4T in women of child bearing age (MoHSS, 2010).

It should also be noted that pregnancy is not uncommon in young women on HAART. This may be due to the fact that with the increasing availability of HAART and its associated improvement in health women in their reproductive years women may want to have children (Namale et al, 2007). In the DART randomized trial of ART-monitoring strategies among adults with symptomatic HIV infection and CD4 <200 cells/mm3 initiating ART in Kampala, Entebbe and Harare 9.7% women fell pregnant after a median 2.4-year follow-up (Namale et al, 2007).

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5.2.4 Availability of new drugs

Nineteen percent of the regimen modifications were due to availability of a new drug. The evolution of HAART regimens in Namibia is discussed in detail in section 5.3.5 on HAART regimen modification patterns and toxicity. Over the years, Namibia has been keeping pace with new recommendations from WHO in accordance with the latest evidence-based best practices (MoHSS, 2010). WHO now recommends HAART regimens with fewer side-effects, better toxicity profiles, less interactions and lower pill burden with the hope that simplified regimens result in savings to the health care system (WHO, 2006). These principles have resulted in newer drugs such as TDF being introduced into first line HAART regimens.

5.2.5 Virological failure

Virological failure contributed only 2% of the modifications. This is low compared to other settings. In one study to describe the reasons for, and factors associated with, modification and discontinuation of HAART regimens by Mocroft et al, (2001) 44% of the patients modified their HAART regimen due to virological failure. Patients with virological failure usually end up on second line regimens. This small contribution of virological failure to regimen modification at Gobabis District hospital means that most patients who had regimens modified remained within first line regimens.

It cannot be ruled out in this study that the low prevalence of virological failure could have been as a result of poor vigilance for virological failure at Gobabis State hospital. It is well documented that patients with higher viral loads at HAART initiation may not achieve good viral suppression (Mocroft et al., 2001; Ledergerber, 1999). Mandatory viral load testing at 6 months after initiating HAART only began in Namibia in 2008 (MoHSS, 2010). The current national guidelines recommend that if the viral load at 6 months is >1000 copies/ml, the CD4 count should be checked, intensive adherence counseling offered to the patient and repeat the viral load in 3 months (MoHSS, 2010). If this tighter protocol was in place during the time this study was done maybe more cases of virological failure could have been picked.

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5.3 FACTORS ASSOCIATED WITH HAART REGIMEN MODIFICATION

This study highlighted that there were significant associations between regimen modification and sex, marital status, care entry point, duration from HIV diagnosis to entry into HIV, functional status and type of original first line regimen. The following subsections discuss each of these factors separately.

5.3.1 Regimen type and modification patterns

There were significant differences between first line regimen drugs for patients who stayed on and those whose regimens were modified ($p<0.0001$). The largest proportion of patients had D4T taken off their HAART combinations. Consequently regimen modifications have resulted in less use of D4T based regimens while use of TDF and AZT based regimens has been increasing.

These findings may not come as a surprise seeing that the most common reason for HAART regimen modification in this study, treatment toxicity, was largely due to D4T toxicity. To

understand the HAART regimen modification patterns shown in this study it is fitting to understand how HAART drug choices have evolved in the public sector in Namibia.

D4T containing regimens were the commonest in the Namibia's public HAART program when the program was launched in 2002 (MoHSS, 2008). However, D4T lost favor due to the long term side effects associated with it which have been described above in the section on treatment toxicity (Westreich et al, 2009).

The next recommended first line NRTI agent in Namibia after D4T then became AZT in 2008. This was short lived as the country experienced a surge in patients who developed AZT induced anaemia, with some even requiring therapeutic blood transfusion (MoHSS, 2010). AZT is associated with bone-marrow toxicity, commonly manifesting as neutropenia or anemia occurring within the first 3 months of therapy (Ssali, Stöhr, Munderi et al, 2006). A study by Mengistu et al (2010) at Katutura Intermediate hospital in Namibia involving 5025 patients on HAART noted that 12.7% of the patients had substitution of their 1st line HAART regimen with 20% being AZT replacements with other NRTIs.

Following the challenges associated with D4T and AZT the NRTI of choice since 2010 in Namibia has been TDF (MoHSS, 2010). TDF also has the advantage of treating hepatitis B (HBV) co-infection (Bartlett & Gallant, 2005). Namibia has a high chronic HBV sero-prevalence, estimated by the blood transfusion service to be about 15% (MoHSS, 2010). In a South African study, a TDF based regimen (TDF/3TC/NVP) was associated with considerably better health outcomes (Bendavid et al, 2010).

In this study regimen modification resulted in more EFV containing regimens being used and less NVP containing regimen usage. High TB co-morbidity in Namibia could have contributed to this observation. As prior discussed, EFV is the NNRTI of choice in patients who have to concomitantly take rifampicin as one of the drugs on their TB regimens. HIV-infected persons with latent TB infection, have a 10% risk each year of developing active TB disease (Narain et al, 2009). In another South African study, Boulle et al (2007) found that 8% and 2% of substitutions were due to nevirapine and efavirenz toxicity respectively.

Regimen modification also resulted in more LPV-r containing regimens being used. This is not an unusual finding since LPV-r is part of standard second line regimen in Namibia (MoHSS,

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2010). It is however important to note that only 1% of the patients were put on the standard four drug second line regimen used in Namibia. This is much lower compared to the global average of an estimated 4% of adults on second-line HAART (Renaud-Thery, 2007).

5.3.2 Care entry point

Entry into HIV care via the "Medical" route was the commonest in the two groups of patients, 70% of patients who remained on original regimen and 57% of those who modified regimens respectively. In this study the 'Medical' care entry point included patients entering into HIV care from hospital in-patient services and patients co-infected with TB referred from the TB ward and clinic. Apart from TB co-infection this subset of HIV positive patients normally seeks services for treatment of other ailments such as meningitis, diarrhea, skins conditions and psychiatric diseases (Mindel & Tenant-Flowers, 2001). Floyd et al (1999), in a study to assess the HIV/AIDS epidemic's impact on demand for inpatient hospital care in a rural area of South Africa concluded that the epidemic had impacted the demand for adult tuberculosis and general medical care.

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The above mentioned medical conditions that cause HIV infected persons to utilize hospital services emphasizes the importance of providing prophylaxis for common conditions such as pneumocystis jiroveci pneumonia using cotrimoxazole and TB using isoniazid (Betz et al,2005). This finding should compel healthcare managers in Namibia to allocate more resources and strengthen HIV testing services at health facilities.

5.3.3 Duration from HIV diagnosis to entry into HIV wellness care

This study found that there was a significant difference in the duration from HIV diagnosis to entry into HIV care ($p<0.0001$) between patients who remained on original regimen and patients who had their regimens modified and 57.9% of patients who remained on their original regimens and 44.2% of those who had regimens modified respectively, were enrolled into HIV general wellness care during the first month of testing positive for HIV. It is known that rapid entry into care and initiation of HAART carries many benefits including reduction in HIV transmission (Dieffenbach et al, 2009; Granich et al, 2009; Holtgrave, 2009). The findings in this study are comparable to findings from a meta analysis to estimate the proportion of HIV-diagnosed persons who entered into care shortly after diagnosis done by Marks et al (2010), which

concluded that the majority (72%) of patients entered into care at 4 weeks from diagnosis. The mean time before regimen modification in the meta analysis was 16 months. In another Italian cohort of antiretroviral-naïve patients , 36% of patients who began a HAART regimen modified or discontinued their initial regimen over a median follow-up time of 11 months (Cicconi et al., 2010).

5.3.4 Sex

There was a statistically significant association between regimen modification and sex (p=0.016), with more men than women having altered regimes. This is an interesting finding, though difficult to explain. In a study involving HIV positive patients above 16 years at the Royal Free Hospital, London it was discovered that men start HAART late and stand a higher chance of developing co-morbidities necessitating HAART regimen modification (Sabin et al, 2004). A multicentre study done in clinics providing HAART in Africa, Latin America, and Asia comparing women and men receiving HAART concluded that women are less likely to have advanced HIV infection at HAART initiation (Braitstein et al., 2008). It is possible that men may be starting HAART late at Gobabis State hospital. This warrants further investigation.

On the contrary some studies have demonstrated sex related differences on likelihood of modifying HAART. A study done in Brazil by Cardoso et al (2010) showed that women had a higher hazard for regimen modification due to toxicity as compared to men.

5.3.5 Functional status

It was noted that patients functionally classified as 'working' were more likely to have their regimens modified compared to those in the ambulatory category who are expected to have more advanced disease. This was contrary to findings from the study by Zhou et al (2010) in which advanced disease was a predictor of treatment modification. The reasons for this finding in this Namibian cohort warrants further exploration.

5.4 OTHER GENERAL PATIENT CHARACTERISTICS

Death rate: The only treatment outcome indicator described in this study was whether the patient was alive or dead at the end of the study period. There was a significant association between regimen modification and whether patient was alive or dead at the end of the study

period. Nine percent of the patients in each of the two groups were recorded as dead by the end of the study period. This death rate is much higher as compared to a death rate of 3.7% shown by a South African study (Westreich et al, 2009). HIV treatment programs need to investigate high rates of death among patients on HAART to determine the risk factors (Bisson et al, 2008). Risk factors for death found in a Botswana study which recorded high death rates of 7.1% and 16.8% before and after patient tracing respectively were being male, low CD4 count and low hemoglobin levels (Bisson et al, 2008).

Treatment supporters: Seventy percent of all the patients had treatment supporters. This should be commended since presence of a treatment supporter is important in ensuring good treatment outcomes. A qualitative study done among HIV-infected adults in South Africa highlighted the importance and need for treatment supporters in helping maintain good adherence (Nachega et al, 2006). Similarly, a study to determine the impact of treatment supporters, though in a TB program, in Pakistan found that patients with no treatment supporters had lower treatment success rate as compared to patients who had treatment supporters (Soomro et al, 2012).

CD4 count: In this study the median CD4 counts were 155 and 173cell/mm^3 for patients who remained on original regimen and patients who had their regimens modified respectively. Contrary to the researcher's experience CD4 count was not found to be associated with regimen modification in this study. It is interesting to note that other studies discovered that regimen modification is actually associated with lower CD4 counts. A study by Zhou et al (2010) carried out among Asian patients to examine the rates and predictors of treatment modification discovered that advanced disease and lower CD4 count were associated with a higher rate of treatment modification. Similarly, Chandy et al (2011) also found low CD4 counts as a predictor of treatment switching. Though this study was conducted in a private hospital in Bangalore it was primarily based on patients from a limited resource setting similar to Namibia. It may be necessary to investigate further the above mentioned finding.

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5.5 LIMITATIONS

5.5.1 Due to the broad nature of this study it was impossible to measure and investigate all aspects related to HAART regimen modification at this hospital. As such this study may not be able to adequately explain some of the reasons why patients have their regimens

modified since it was based on records review. Consequently some of the qualitative aspects of the reasons why HAART regimens were modified or discontinued were not addressed by this study. Information obtained from this study can best be used to describe prevalence of regimen change at this facility.

5.5.2 Use and analysis of routine data is never without challenges. This study was affected by one of the challenges of retrospectively utilizing electronic databases, that of missing, inconsistent and meaningless data fields. Only factors which were properly documented in the electronic data system were included in the study. The following variables had to be excluded from the original data collection tool because they were not well documented: adherence, weight, blood test results such as viral load, hemoglobin, ALT (liver enzyme), creatinine, hepatitis B surface antigen, TB status at HAART initiation and history of opportunistic infections. Contrary to expectations, all these fields were blank. Only the CD4 counts were consistently recorded in the electronic records. While this may indicate poor patient access to laboratory testing services this could just have been poor data collection practices.

5.5.3 The challenges above could have been circumvented by referring to the paper based records. It was difficult getting access to the paper based records of the affected electronic records. Some of these records had been moved to peripheral clinics as the program had been decentralized as part of the Integrated Management of Adulthood Illnesses (IMAI). Furthermore, due to increasing number of records over the years, some records could have just been poorly filed or moved with patients who transferred out. All these issues made data collection, cleaning and analysis a mammoth task. Good data sets are essential for accurate interpretation of HIV treatment program trends.

5.5.4 This study was carried out using data from patients accessing HAART from a government health facility. This may not be truly reflective of the entire population since a significant proportion of Namibians currently access HAART from the private sector.

5.5.5 This study was carried out using data collected over a three year period. The prevalence and risk factors associated with HAART regimen modification could have varied greatly over this period depending on drug availability, changes in national policies and guidelines on HIV treatment. For example declining use of D4T from 2008 in first line regimens is expected to reduce modifications due to drug toxicity.

5.5.6 This study had a small sample size and not fully representative of all adult patients on highly active antiretroviral therapy in Namibia. Therefore the study findings cannot be generalized to all HIV positive adult patients in Namibia.

CHAPTER 6 – CONCLUSION AND RECOMMENDATIONS

6.1 CONCLUSION

The study investigated the factors associated with first line regimen modification in treatment naïve adult patients on highly active antiretroviral therapy at a rural clinic in Namibia. The results revealed that HAART regimen modification at Gobabis State hospital is lower than in other settings. Though other treatment outcomes were not studied the death rate among patients on HAART at Gobabis State is high and warrants further exploration.

The commonest reason for HAART regimen modification was toxicity largely due to D4T followed by modification due to TB/HIV co-infection. Furthermore, the fact that HAART regimens were modified due to pregnancy considerations highlights the need to continuously ensure that women of reproductive age should always be put on pregnancy friendly regimens.

Factors associated with regimen modification were type of regimen, care entry point, duration from HIV diagnosis to entry into HIV care, sex and functional status. There is need to explore how other factors such as viral load, ALT, haemoglobin and adherence impact HAART regimen modification.

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6.2 RECOMMENDATIONS

The following recommendations can be drawn from this study

- ✓ This study raises the important programmatic issue of good data collection practices. Electronic data records need to be complete in order for them to be useful in interpreting program trends. Closer supervision of data clerks is recommended and there should be more defined quality control checks directed from the national level. High patient loads, high staff turnover and less than optimal staff supervision often compound this problem. These need to be addressed if applicable.
- ✓ Any patients still on D4T need closing monitoring for side effects associated with this drug and should be promptly changed if this is the case.
- ✓ TB and HIV co- infection are the second most prevalent reason for regimen modification. It is encouraged that health care workers implement good monitoring of patients on either or both treatments of each of these diseases in order to get good treatment outcomes. The care and appropriateness of HAART regimens being used in women at Gobabis State

hospital needs close scrutiny since this study showed that some women had regimens modified because of pregnancy.

- ✓ A further study to determine the predictors of regimen modification is encouraged.

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APPENDICES

APPENDIX 1- Data collection tool

Table 7: Data collection tool

Code number: Date:

Demographic information	
1. Sex:	[1] Male [2] female
2. Date of birth (dd/mm/yy)	
3. Marital status	[1] Not married [2] Married
4. Care entry point	[1] PMTCT [2] Medical [3] Private sector [4] Self referral [5] transfer in [6] Other
5. Treatment supporter	[1] Yes [2] No
Background clinical and laboratory findings	
6. Date of HIV diagnosis	
7. Date of enrolment into general HIV wellness care	
8. Date HAART started	

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9. Clinical stage when eligible for HAART	[1] 1 [2] 2 [3] 3 [4] 4
10. Weight at start ART	kilograms, (to one decimal place)
11. Functional status at start ART	[1] Working [2] Ambulatory [3] Bed ridden
12. CD4 at start ART	Cells/mm3
13. Did patient receive cotrimoxazole prophylaxis?	[1] Yes [2] No
ARV regimen history	
14. HAART regimen at start	[1] D4T/3TC/NVP [2] D4T/3TC/EFV [3] AZT/3TC/NVP [4] AZT/3TC/EFV [5] TDF/3TC/NVP [6] TDF/3TC/EFV [7] D4T/3TC/LPV/r [8] AZT/3TC/LPV/r [9] Other (Specify)_____
15. Duration on initial 1st line regimen before modification	months
HAART regimen modification history	
16. New regimen after modification	[1] D4T/3TC/NVP [2] D4T/3TC/EFV

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	[3] AZT/3TC/NVP [4] AZT/3TC/EFV [5] TDF/3TC/NVP [6] TDF/3TC/EFV [7] D4T/3TC/LPV/r [8] AZT/3TC/LPV/r [9] AZT/3TC/TDF/LPVr [10] Other (specify) ____
17. If switch to 2nd line regimen: New regimen	[1] AZT/3TC/TDF/LPVr [2] Other (specify) ____
18. Why switch to 2nd-line?	[1] Clinical treatment failure [2] Immunologic failure [3] Other (specify)
19. Reason for HAART regimen modification	[1] Toxicity [2] TB [3] New drug available [4] Pregnancy [5] TB & toxicity [6] Virological failure [7] Other reason (specify)
Outcomes	
20. Patient status at end of study period	[1] Dead [2] Alive

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APPENDIX 2 –INFORMATION SHEET

UNIVERSITY OF THE WESTERN CAPE

School of Public Health

Private Bag X17 ● **BELLVILLE** ● 7535 ● South Africa

Tel: 021- 959 2809, Fax: 021- 959 2872

INFORMATION SHEET

Dear Participant

Thank you for your willingness to hear about this research project. Below is the outline of the project and your potential involvement. The research is being conducted for a mini thesis. This is a requirement for the Masters in Public Health which l am studying at the University of the Western Cape. If there is anything you don't understand or are unclear about, please ask me. My contact details and those of my supervisor are recorded at the end of this memo.

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Title of Research

Factors associated with first line regimen modification in treatment naïve adult patients on highly active antiretroviral therapy at a rural clinic in Namibia

What is this study about?

This is a research project being conducted by Kapera Tafadzwa Justin Nyatondo, an MPH student at the University of the Western Cape. We are gathering information related to factors associated with first line regimen modification in treatment naïve adult patients on highly active antiretroviral therapy (HAART) at a rural clinic in Namibia. A more detailed understanding of the factors associated with first line regimen modification could allow healthcare providers in Namibia to target these factors for intervention to reduce regime modification and improve treatment outcomes.

What will I be asked to do if I agree to participate?

Clinic staff will be expected to assist the researcher access the electronic data required for this study and to help retrieve clinical records where necessary.

Would my participation in this study be kept confidential?

We will do our best to keep your personal information confidential. To help protect your confidentiality, patient initials and identification codes will be used on data forms. Data form will be stored in a secure place. If we write a report or article about this research project, your identity will be protected to the maximum extent possible.

What are the risks of this research?

There are no known risks associated with participating in this research project.

What are the benefits and costs of this research?

You may not get any direct benefits from this study. However information generated from the research will allow healthcare providers in Namibia to target factors associated with treatment modification and help reduce regime modification and improve treatment outcomes.There are no costs for participating in this study other than time spent during the interview where necessary.

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Do I have to be in this research and may I stop participating at any time?

Your participation in this research is completely voluntary. You may choose not to take part at all. If you decide to participate in this research, you may stop participating at any time. If you decide not to participate in this study or if you stop participating at any time, you will not be penalized or lose any benefits to which you otherwise qualify.

Informed Consent

Your signed consent to participate in this research study is required before we proceed with the interview.

What if I have questions?

Should you have any questions regarding this study and your rights as a research participant or if you wish to report any problems you have experienced related to the study, please contact me :

Kapera Tafadzwa Justin Nyatondo

Student Number**:** 2826494

Cellphone 0812188292

Work 061-310200

E-mail nyatondojustin@hotmail.com

I am accountable to my supervisor Dr Vera Scott, MD. Her contact details are

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APPENDIX 3 -CONSENT FORM

UNIVERSITY OF THE WESTERN CAPE

School of Public Health

Private Bag X17 ● **BELLVILLE** ● 7535 ● South Africa

Tel: 021- 959 2809, Fax: 021- 959 2872

CONSENT FORM

Title of Research Project: Factors associated with first line regimen modification in treatment naïve adult patients on highly active antiretroviral therapy at a rural clinic in Namibia.

The study has been described to me in language that I understand and I freely and voluntarily agree to participate. My questions about the study have been answered. I understand that my identity will not be disclosed and that I may withdraw from the study without giving a reason at any time and this will not negatively affect me in any way.

***Participant's name*……..**

***Participant's signature*……..**

***Witness*…….**

***Date*……**

Should you have any questions regarding this study or wish to report any problems you have experienced related to the study, please contact the study coordinator:

Study Coordinator's Name: Dr Vera Scott, MD

University of the Western Cape

Private Bag X17, Belville 7535, Telephone: +27 21 959 2630 Fax: +27 21 959 2809

Email: verascott@mweb.co.za

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APPENDIX 4 - Classes of antiretroviral agents

Table 8: Classes of antiretroviral agents

CLASS	MODE OF ACTION	EXAMPLES
Nucleoside Analogue Reverse Transcriptase Inhibitors (NRTIs)	These medications inhibit the transcription of viral RNA into DNA, which is necessary for reproduction of the virus	The class includes tenofovir (TDF), zidovudine (AZT), lamivudine (3TC), didanosine (ddI), stavudine (D4T), abacavir (ABC) and emtricitabine (FTC).
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)	These medications are of a chemically different class from NRTIs, but also inhibit transcription of viral RNA into DNA	The class includes nevirapine (NVP), efavirenz (EFV), and Etravirine (ETV)
Protease inhibitors (PIs)	Act on the viral enzyme that cuts long chains of virally produced amino acids into smaller proteins.	The class includes lopinavir (LPV), indinavir (IDV), nelfinavir (NFV), saquinavir (SQV), ritonavir (RTV), atazanavir (ATV), fosamprenavir (FPV), tipranavir (TPV) and darunavir (DRV).
Fusion inhibitors	Block the virus from being able to merge with the host cell (i.e. CD4 cell) after binding.	The only currently available fusion inhibitor is enfuvirtide (ENF).

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Intergrase inhibitors	Inhibit the enzyme intergrase	Raltegravir (RAL)
CCR5 entry inhibitors	Prevent HIV infection of CD4 T-cells by blocking the CCR5 receptor	Maraviroc (MVR)

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APPENDIX 5 - Recommended HAART Regimens in Namibia

Table 9: Recommended HAART regimens in Namibia

HIV positive, ARV-naïve adults	• TDF/3TC/NVP This is the preferred first line AZT/3TC/NVP This is the alternative preferred first line. It used if CD4<350 • AZT/3TC/EFV This is also the alternative preferred first line. EFV is used if CD4>350
HIV positive, ARV-naïve pregnant women	TDF/3TC/NVP EFV included as an NNRTI option where CD4>350 after first trimester
HIV/TB co-infection	TDF/3TC/EFV ART is initiated as soon as possible in all HIV/TB co-infected patients with active TB and as soon as TB treatment is tolerated and within 8 weeks of commencement
HIV/HBV co-infection	TDF/3TC/NVP if ALT <5 TDF/3TC/EFV if ALT >5 HBSAg positive clients with CD4>350 whose ALT is >2 x upper limit of normal (ULN) or ALT<2x ULN but with HBeAg positive are eligible for treatment regardless of WHO clinical stage. NNRTI regimens that contain both TDF/3TC are used

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APPENDIX 6 - RESULTS

Table 10: Sample size

	Frequency	%
Total number of patients starting 1st line HAART between 1st January 2007 -31st December 2010	1310	100
Patients who had regimens modified	198	15.1%
Patients who remained on original regimen	1112	84.9%

Table 11: Age

	Minimum	Maximum	Mean	Standard deviation	Median	Skewness
Patients who remained on original regimen	19	83	38.8	11.14	37.5	0.875
Patients who had regimens modified	19	64	39.59	9.50	39.00	0.347

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Table 12: Pre-HAART patient characteristics

Characteristic	**Patients who remained on Original Regimen**	**Patients who had regimens modified**	**Chi**
CD4 Count n(%)	**Frequency (Percentage)**	**Frequency (Percentage)**	
>350	46 (3.8%)	6 (3.4%)	**0.625**
200-350	285 (23.6%)	31 (17.4%)	
100-199	535 (44.3%)	104 (58.4%)	
50-99	193 (16.0)	28 (15.7%)	
<50	149 (12.3%)	9 (5.1%)	
Clinical Stage	**Frequency (Percentage)**	**Frequency (Percentage)**	
1	131 (10.9%)	13 (6.7%)	**0.133**
2	476 (39.4%)	80 (41.2%)	

3 4	491 (40.7%) 109 (9.0%)	89 (45.9%) 12 (6.2%)	

Table 13: Duration from HIV diagnosis to enrollment into HIV general wellness care

Duration from HIV diagnosis to enrollment into HIV general wellness care (months)	Minimum	Maximum	Median	Standard deviation	***p* value**
Patients who remained on original regimen	0	190	0	14.12	**<0.0001***
Patients who had regimens modified	0	107	1	16.00	

Table 14: Duration from HIV diagnosis to enrollment into HIV general wellness care

Duration in months	**Patients who remained on original regimens**	**Patients who had regimens modified**
<1	657	88
2-3	271	54
4-6	68	12
7-9	31	6
10-12	24	6
>12	84	33
total	1134	199

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Table 15: HAART regimens at initiation for ALL patients according to NRTI back bone

	Remained on original regimen	Later modified	**Total**
AZT based	609	90	**699**
D4T based	143	96	**239**
TDF based	360	12	**372**
Total	**1112**	**198**	**1310**

Table 16: HAART regimens at initiation for ALL patients according to NNRTI choice

	Remained on original regimen	Later modified	**Total**
Patients on NVP	805	166	**971**
Patients on EFV	301	32	**333**
Total	**1106**	**198**	**1304**

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Table 17: HAART regimens for patients who remained on original regimen

	Frequency	Percent	Cumulative Percent
AZT/3TC/EFV	99	8.9	8.9
AZT/3TC/LPV-r	3	0.3	9.2
AZT/3TC/NVP	507	45.6	54.8
D4T/3TC/EFV	31	2.8	57.6
D4T/3TC/LPV-r	1	0.1	57.7
D4T/3TC/NVP	111	10.0	67.7
TDF/3TC/EFV	171	15.4	83.1
TDF/3TC/LPV	2	0.2	83.3

TDF/3TC/NVP	187	16.8	100.0
Total	1112	100.0	100.0

Table 18: Regimens for patients who remained on original regimen according to NRTI back bone

	Frequency	**Percent %**	**Cumulative Percent**
AZT based	609	54.8	54.8
D4T based	143	12.9	67.7
TDF based	360	32.4	100.0
Total	1112	100.0	100.0

Table 19: HAART regimens for patients who remained on original regimen according to choice of NNRTI or PI

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	Frequency	Percent	Cumulative Percent
Patients on NVP	805	72.7	72.7
Patients on EFV	301	27.2	100.0
Total	1106	100.0	100.0

Table 20: HAART regimens for patients who had regimens modified: BEFORE modification

	Frequency	Percent	Cumulative Percent
AZT/3TC/EFV	13	6.6	6.6
AZT/3TC/NVP	77	38.9	45.5
D4T/3TC/EFV	16	8.1	53.6
D4T/3TC/NVP	80	40.4	94.0
TDF/3TC/EFV	3	1.5	95.5

TDF/3TC/NVP	9	4.5	100.0
Total	198	100.0	

Table 21: HAART regimens for patients who had regimens modified: AFTER modification

	Frequency	**Percent**	**Cumulative Percent**
ABC/3TC/LPV-r	2	1.0	1.0
AZT/3TC/EFV	38	19.1	20.2
AZT/3TC/LPV-r	3	1.5	21.7
AZT/3TC/NVP	63	31.7	53.4
D4T/3TC/EFV	18	9.0	62.6
D4T/3TC/LVP-r	1	.5	63.1
D4T/3TC/NVP	19	9.5	72.7
TDF/3TC/EFV	25	12.6	85.4
TDF/3TC/LPV-r	1	.5	85.9
TDF/3TC/NVP	26	13.1	99.0
TDF/AZT/3TC/LPV-r	2	1.0	100.0
Total	198	100.0	

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Table 22: HAART regimens for patients who had regimens modified according to NRTI choice

	BEFORE			AFTER		
	Frequency n	Percent %	Cumulative Percent	Frequency n	Percent %	Cumulative Percent
AZT based	90	45.5	45.5	104	52.5	52.5
D4T based	96	48.5	94.0	38	19.2	71.7
TDF based	12	6.1	100.0	52	26.3	98.0
ABC based	0	0	100.0	2	1.0	99.0

2nd line regimen	0	0	100.0	2	1.0	100.0
Total	198	100.0	100.0	198	100.0	

Table 23: HAART regimens for patients who had regimens modified according to choice of NNRTI or PI

	BEFORE			AFTER		
	Frequency	Percent	Cumulative Percent	Frequency n	Percent %	Cumulative Percent
Patients on NVP	166	83.8	83.8	108	54.5	54.5
Patients on EFV	32	16.2	100.0	81	40.9	95.4
Patients on LPV-r	0	0	100.0	7	3.5	98.9
Second line regimen (4 drugs)	0	0	100.0	2	1.0	100
Total	198	100.0	100.0	198		

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Table 24: Pearson's X^2 test

	Pearson's X^2 test	P - value
Sex	5.791	0.016*
Marital status	6.417	0.170
Care entry point	55.956	0.000**
Presence of treatment supporter	2.894	0.089
Clinical stage	5.597	0.133
Ever put on cotrimoxazole	0.004	0.949
Functional status	28.714	0.000**

Table 25: Reason for HAART Regimen Modification

Reason for HAART Regimen Modification	**Frequency (Percentage)**
Toxicity	70 (35.3%)
TB	54 (27.3%)
New drug available	37 (18.7%)
Other	16 (7.6%)
Pregnancy	13 (6.6%)
TB & toxicity	5 (2.5%)
Virological failure	4 (2.0%)

Table 26: Cross tabulation of original first line regimen versus reason to change therapy

	Reason to change therapy							
Original HAART regimen	New drug available	Virological failure	Pregnancy	TB	TB & toxicity	Toxicity	Other	Total
AZT/3TC/EFV	1	0	4	0	1	5	2	**13**
AZT/3TC/NVP	15	1	0	33	2	26	0	**77**
D4T/3TC/EFV	6	0	5	0	0	5	0	**16**
D4T/3TC/NVP	15	3	3	14	0	33	12	**80**
TDF/3TC/EFV	0	0	1	0	0	1	1	**3**
TDF/3TC/NVP	0	0	0	7	2	0	0	**9**
Total	**37**	**4**	**13**	**54**	**5**	**70**	**15**	**198**

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Table 27: Regimen modification according to specific drugs

	Stayed on	**Taken off**
	n(%)	**n(%)**
AZT-based	39/90 (43.3)	51/90 (56.7)
TDF-based	8/12 (66.7)	4/12 (33.3)
D4T-based	11/97 (11.3)	86/97 (88.7)
NVP	92/166 (55.4)	74/166 (44.6)
EFV	14/32 (43.8)	18/32 (56.3)

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