Clinical and immunological response of HIV/AIDS patients receiving ART in Nyangana Mission Hospital in Namibia

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Key words

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Response/outcome

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Weight gain

CD4 cell count trend

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Abstract

Background: There is strong evidence to show that antiretroviral therapy (ART) improves the survival and quality of life of people living with HIV/AIDS (PLWHA). Namibia, one of the countries hardest hit by HIV/AIDS, has embarked on a large scale public sector roll out of ART. The Catholic Health Services is implementing an HIV/AIDS treatment program in Nyangana rural district, home to 41,000 people with an HIV seroprevalence (ANC, 2006) of 12%. **Aim**: This study aims to analyse the clinical and immunological responses and survival pattern of HIV/AIDS patients receiving ART in Nyangana District. **Objectives:** To establish the ART coverage and demographic characteristics of eligible PLWHA in Nyangana district, to describe baseline clinical profile and subsequent clinical response of HIV/AIDS patients receiving ART and to determine baseline immunological profile and the trend of CD4 count response from baseline to different follow up periods. **Study design:** This is a quantitative, cohort analysis study of routine clinical data, reviewing patients' records retrospectively. **Population and sample:** This was a census of all patients that started ART in the district between August 2004 and April 2006. **Data collection process:** **S**tandardised patient files and registers were used to abstract data as per selected variables into an Excel database. **Data analysis:** Epi Info and SPSS were used. A cohort analysis was done using descriptive and analytic statistics to determine basic characteristics, overall treatment outcome, survival analysis (KM, Cox regression), paired comparison to determine change in weight and CD4 cell count pre and post-ART. **Results:** ART is currently reaching 46% of PLWHA in need of it in Nyangana District. At baseline, the mean age was 36 years, mean weight was 48 kg and median CD4 cell count was 131 cells/µL (IDR: 75-216). Females represented 69% of patients, were more likely to have higher CD4 count at baseline ($p<0.0001$) and more likely to survive compared to males (OR: 2.3). The mean duration on ART was 20.8 and 5.1 months, respectively, for those still alive and those who died. A mortality rate of 23.5% occurred mainly in the first 3 months of initiation (60%) with TB (37.9%) and gastroenteritis (18.2%) as leading causes of death. Patients with lower body weight and poor functional status were less likely to survive (OR: 0.9 and 0.4) and those who died were twice as likely to have fair to poor self-reported adherence ($p=0.008$). Survival at 24 months was 75%.

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Declaration

I declare that *Clinical and Immunological Response of HIV/AIDS Patients Receiving ART in Nyangana Mission Hospital in Namibia* is my own work, that it has not been submitted for any degree or examination in any other University, and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Full name: Didier Mbayi Kangudie..... Date: May 15th 2008.....

Signed.....

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List of acronyms

AIDS	Acquired Immune Deficiency Syndrome
ANC	Antenatal Care
ART	Anti-Retroviral Therapy
ARV	Anti-Retrovirals
BMS	Bristol Myers Squib
CD4	Cluster of Differentiation four
CHS	Catholic Health Services
EPP	Estimation and Projection Package
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immuno-deficiency Virus
IQR	Inter Quartile Range
IUATLD	International Union Against Tuberculosis and Lung Disease
GFATM	Global Fund to fight AIDS, Tuberculosis and Malaria
KM	Kaplan-Meier
LTF	Lost to follow up
MoHSS	Ministry of Health and Social Services (Namibia)
MSF	Medecins Sans Frontieres
PLWHA	People Living with HIV and AIDS
PEPFAR	President's Emergency Plan for Aids Relief
PMTCT	Prevention of Mother to Child Transmission (HIV)
SADC	Southern African Development Community
SPSS	Statistical Package for Social Sciences
SSA	Sub-Saharan Africa
TB	Tuberculosis
UNAIDS	United Nations Joint programme on HIV/AIDS
USAID	United States Agency for International Development
WHO	World Health Organisation

Chapter 1. Introduction

It is now common knowledge that HIV/AIDS is the worst epidemic to hit the world in the history of mankind. To date, HIV/AIDS has decimated more people than all the wars known in human history. AIDS is killing close to 2.5 million each year. This is translated into more than 6,000 lives robbed per day with devastating human, economic and social impact. Yet the trend of new infections continues unabated. Every day 6,800 new infections occur fuelling the current estimate of 33.2 millions people living with HIV worldwide (*UNAIDS, 2007*).

Sub-Saharan Africa (SSA) is particularly hard hit with the highest disease burden . Of the total PLWHA, SSA is harbouring 68% of adults and 90% of children. Consequently, 78% of AIDS death in 2007 occurred in this region. However, the picture in SSA varies significantly across regions with southern Africa displaying the worst epidemic pattern. The Southern African Development Community (SADC) is home to the top 10 highest HIV prevalence rates in the world with Swaziland 39%, Botswana 32%, South Africa 29%, Lesotho 21%, Namibia 19.9% and Zimbabwe 18%. This region was estimated to have 32% of all new infections and AIDS death globally in 2007(*UNAIDS, 2007*).

In as much as this epidemic has been the worst ever recorded, the global response to it, by means of prevention, treatment, care and support services has equally been the biggest public health intervention ever undertaken in living memory (Venter, 2005; UNAIDS, 2004). In particular, the introduction of Highly Active Antiretroviral Therapy (HAART) during the Vancouver international conference in 1996 has changed the landscape of HIV/AIDS the world over. HIV/AIDS was turned from a death sentence to a chronic manageable disease for most patients in developed countries (Pomerantz, 2001). Several studies were later conducted on how to implement HAART in resource-constrained settings based on the WHO scaling up strategies. Most of these studies have demonstrated the benefit of improved quality of life, prolonged survival, regained dignity and a return to productive life for PLWHA receiving HAART.

The Namibian estimate of approximately 230,000 People Living With HIV/AIDS (PLWHA) out of a total population of 1.8 million (*MoHSS, 2006; Census, 2001*) means considerable health expenditure for the Government, misery and death for an increasing number of people if access to life saving drugs is not secured. Since 1996, HIV/AIDS is the leading cause of death in Namibia. An estimated 17,000 Namibian died of AIDS in 2005 (*MoHSS, 2006*). With help from development partners, the US President's Emergency Plan for AIDS Relief (PEPFAR) and the Global Fund (GFATM), the Namibian Ministry of Health and Social Services (MoHSS) initiated its treatment program in 2003 and by end of 2007 more than 30,000 were on HAART. Amongst other partners in the field, the Catholic Church in Namibia (second biggest public health provider after the MoHSS), fulfilling its mission of care, is running a treatment program funded by PEPFAR through USAID. This program covers 4 rural district Hospitals and provides care for just over 10% (3,500) of current ARV users in the country.

Nyangana Mission Hospital is one of the 4 districts that started the treatment program in August 2004. It was selected for this analysis based on completeness and timely reporting pattern of its ART clinic. As of end of April 2007, 590 PLWHA were enrolled on HAART in this catchment area of 41,000 population. However, longitudinal documentation and analysis of clinical recovery and immunological restoration of these patients have not yet been done. This knowledge gap is not only observed within Catholic Health Services (CHS) but also throughout the country. A sustained clinical and immunological response to ART is dependent on several factors stemming from the regimen potency to individual factors such as adherence, clinical baseline characteristics, disease stage (clinical and CD4 count). The need to conduct such cohort analysis in order to evaluate and enhance the program performance and effectiveness is critically felt amongst most ART program managers across the country. This study would be one of the first local attempts of its kind for the Catholic Mission Hospitals in Namibia and would be hopefully replicated in a multi-centre approach.

Problem statement

The introduction of ART has dramatically changed the course of HIV disease with many studies demonstrating its efficacy worldwide. The reduction in morbidity and

mortality for HIV/AIDS patients on ART is unquestionable. However, apart from amazing individual stories of treatment success across all ART sites, there is very limited longitudinal documentation and analysis of ARV treatment response in Namibia. This knowledge gap, in spite of the ongoing rapid countrywide roll out, is indicative of not only the infancy stage at which the ART program is still in Namibia but also the insufficient use of the ART Management Information System (MIS) in a systematic research agenda. Given the variability of patient characteristics, are our patients on ART responding in the same way as described elsewhere? The effectiveness of the Nyangana ART program will be evaluated using routine data that provides evidence of treatment success based mainly on clinical and immunological responses, and survival analysis.

Chapter 2. Literature review

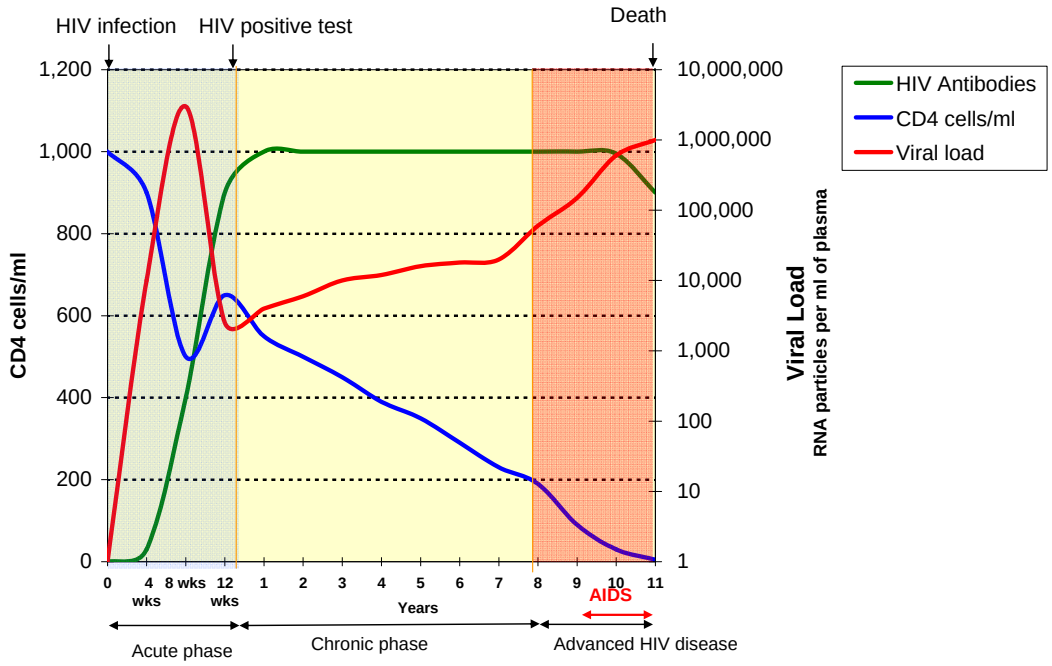
Since the discovery of the first case of HIV more than two decades ago, thousands of publications have inundated the literature. This review will look at some of the papers (published or otherwise) dealing with HAART programs in general and the analysis of cohort studies in particular.

In a context of evaluation of programme effectiveness, it helps to know what we understand by that. According to Katzenellenbogen, Joubert and Karim (1997), effectiveness, as a measure of outcome, is defined by how well a process or health intervention is working. They go on to argue that "health planners seek measures of effectiveness to establish whether health care interventions achieve their stated objectives…" Since the late nineties, several studies have been done on the effectiveness of ART in resource-poor settings. The evaluation of ART programme effectiveness will be at the centre of our discussion throughout this review.

2.1. The Highly Active Antiretroviral Therapy: HAART

Prior to HAART era, HIV infection progressed to AIDS with a subsequent average of 2 years between the onset of AIDS to death as illustrated by the figure 1 below. The disease would take its natural course without faltering with most health care facilities becoming places of death especially in developing countries where poverty and lack of food security compounded survival with HIV/AIDS.

Figure 1: Natural history of HIV/AIDS



Adapted from *Ministry of Health and Social Service (Namibia): Guidelines for the clinical management of HIV/AIDS (2002)*

It is common knowledge that in 1996, the Vancouver 11th International AIDS conference rose to the AIDS challenge when a number of presentations were made announcing the introduction of a triple combination of ARV drugs. These combinations aimed at reducing HIV replication sufficiently, restoring immune deficiency to safe levels and improving the quality and prolonging the lives of PLWHA. A death sentence was commuted into a chronic manageable disease or chronic non-curable infection (Marquez, 2004). The advent of new classes of ARV drugs and their use in combination was the breakthrough that established this combination as gold standard of evidence-based care (*WHO*, 2002).

There are 3 main classes of antiretroviral agents, one of them forming the backbone of any combination: the Nucleoside reverse Transcriptase Inhibitors (NRTI). Two drugs of this class (dual NRTI) are complemented by a third drug form either a Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI) or a Protease Inhibitor (PI) class. The combination of at least one drug from each class, and preferably 2 NRTI (backbone) and 1 NNRTI, constitutes what is commonly called Highly Active Antiretroviral Treatment (HAART). Additional classes are coming on the market and comprise Nucleotide reverse transcriptase inhibitors (NtRTI), Fusion inhibitors,

integrase inhibitors and CCR5 inhibitors. Many of these drugs are still experimental and out of reach for most developing countries.

The goals of therapy with these combinations referred to as HAART do not differ from developed to resource constrained settings. They are summarised as an improvement in quantity and quality of life by reducing HIV related morbidity and mortality through maximal and durable viral suppression and restitution and/or safeguarding of immunological function (*Guidelines for Antiretroviral Therapy in Adults*, 2005).

As acknowledged in many studies, some of the major challenges in ART provision are fundamentally an unparalleled commitment to a life long therapy, with need for the highest adherence ever achieved in any chronic medication (>95% of compliance to achieve optimal viral suppression)(Wilson *et. al.*, 2002; *WHO*, 2006), development of side effects (seldom fatal but can affect adherence) and the cost (medications, clinical and laboratory monitoring). It is therefore a recommendation in most guidelines that ARV therapy never be initiated as an emergency (except in post exposure prophylaxis and in case of Kaposi Sarcoma) (*MoHSS*, 2007). It should not be started unless patients are fully prepared and ready for a life long commitment. This readiness includes comprehensive adherence counselling and treatment of opportunistic infections prior to initiating ART.

2.2. The scaling up and accessibility of treatment programs

The demand for access to ART in developing countries was a fight for human rights. This followed the increasing frustrations on the fact that rich nations were giving access to their AIDS patients while the poor ones were told to be content with scaling up prevention efforts because of cost constraints and/or complexity of treatment regimens. In 2003, only 2% of those in need of treatment in Africa were accessing it (*WHO, 2003; UNAIDS, 2004*). Although there is no successful treatment program without serious prevention efforts, many advocacy groups could not allow this

injustice to continue as they argued rightly that "treatment and prevention are two sides of the same coin" (*WHO, 2003*).

From Professor Harries' statement in 1999, when he declared to an international gathering (Regional American IUATLD Conference in Chicago in February 1999) that "ART cannot be provided to Sub-Saharan Africa" to this day, a long, painful and joyful road has been traveled. Events happily proved him totally wrong as he later championed access to ART in Malawi and several research findings demonstrated that the provision of high quality HAART is feasible in resource-limited settings using the WHO public health approach (*WHO*, 2006). Most patient outcome such as clinical results, retention in care, adherence, mortality and loss to follow up (defaulters) are comparable to findings in the literature both for similar settings and for the developed world *(MSF, 2004).*

By now, most developing countries have introduced the ART program although hastily implemented and mainly in a vertical approach. This follows the dramatic drop in prices of ARV and other related commodities and a huge influx of international donor funds either through Global Fund with "3 by 5" initiative or through PEPFAR with "2/7/10" strategy (*WHO, 2003)*. According to the latest WHO report (2007), the coverage of HIV treatment is now reaching 28% of PLWHA in need of it worldwide from 8% in 2003 (Keith, 2007). Although this is a positive development, it is still a long way from the 2010 goal of universal access.

Access to treatment varies with gender. In Europe, intake is male dominated as the epidemic is driven and fuelled by men having sex with men and intravenous drug users (Sabin, 2003) whereas many African cohorts reveal that up to 75% or more of patients are females (Bekker, 2004; Venter, 2004). In a cohort analysis of a pilot programme to assess the efficacy of triple therapy for PLWHA in a multi-centre study (Namibia, Botswana, Lesotho, South Africa), the Bristol Myers Squib (*BMS, 2006*) team presented similar patterns of sex distribution ranging from 33.1% to 36.1% of males enrolled on ART. In the treatment program of the CHS in Namibia, the situation is not any different as revealed in their reporting with currently 35% of about

4,500 on ART being males (*CHS*, 2007). Venter (2004) argues that this "feminisation" of the epidemic with unfavourable male entry to care is largely attributed to poor health seeking behaviour and high stigma amongst males but also to activities of Prevention of Mother to Child Transmission (PMTCT) program offering an active case finding for HIV positive women. Obviously other factors are also identified such as the higher rate of infection in females and the reported male unfriendly settings of many VCT centres in the Mission facilities. The introduction of Maternal and Child Health activities (ANC and vaccination activities), meant to destigmatise the sites, has created another problem of men feeling out of place, stepping in only at time of extreme desperation and when they are already very sick. Overcoming this barrier is one of the biggest challenges of many ART programs. However, anecdotal data from the private sector in Namibia indicate more men than women accessing ART. Reasons for this seem to be mainly related to privacy. The private sector offers more privacy than public hospitals and men in need of treatment would readily go there if they are covered by their medical aid scheme.

The access to treatment in Namibia looks like a success story. According to the Namibian Minister of Health and Social Services (MoHSS) quoted in a speech by a newspaper (*The Namibian*, *2005*), as of December 2005, Namibia had close to 18,000 patients on ART of which 10% were from the CHS Mission facilities. This effectively put Namibia among only three SSA countries, the other 2 being Uganda and Botswana, to have provided ART to more than 25% of those in need of it. Models such as Spectrum have been developed to estimate the number of PLWHA who are eligible for ART based on variables such as adult HIV prevalence produced by the Estimation and Projection Package (EPP), proportion of PLWHA who are immune suppressed, consequences of the HIV/AIDS epidemic, including new infections, mortality as well as impact of treatment on survival (Stover *et al*, 2006).

For those on treatment, the fundamental question is how well they are doing since improved access to treatment is not necessarily synonymous with good quality of care.

2.3. Cohort analysis in ART programmes

The basic departing point of our investigation of the HAART programme is aligned on identifying the following: who are we serving (socio-demographic characteristics), how are we serving them (quality), for what results (response/outcome).

The use of simplified cohort analysis to monitor ART patients and evaluate their treatment outcomes is a key WHO recommendation for patient monitoring systems. This approach is not equivalent to the cohort research design but rather refers to tracking a group of patients starting ART during a specified time period. Baseline characteristics will then be compared to the status at different follow up periods (*WHO, 2006*). Ultimately, to compare to other programs, derive lessons learned and disseminate evolving best practices in HAART, we must actively evaluate effectiveness and progress.

The beneficial impact of ART on HIV related morbidity and mortality is not questionable anymore. Many European cohorts started earlier on demonstrated the successful use of ART. The only problem is that those findings were by western standards using different patient characteristics and readily available resources for viral loads and CD4 count testing and monitoring (Philipps, 2001; Egger, 2002).

On the other hand, African cohort studies, once accessibility was secured through plummeting commodity prices and fund mobilisation, started showing that ordinary African men and women can also effectively benefit from ART without excessive toxicity (*WHO*, 2006).

Goal of ART

The goal of ARV therapy is to reduce viral load below assay detection limits. Our analysis of treatment effectiveness will be based on criteria for treatment success or failure as laid down in the Southern African HIV Clinicians Society Guidelines for ARV (2005) as well as in the WHO ART guideline (WHO, 2006). Limitation in the use of viral load in many developing countries, including Namibia, makes it difficult to monitor viral activity as a direct measure of the treatment success. The latter is best

measured by the decline in viral load of at least 1 log from pre-treatment levels after 6-8 weeks of initiation of therapy or a "decline in viral load to <400 RNA copies by 24 weeks after commencement of therapy". However, in the absence of viral load, CD4 T-cell count, which measures the robustness of the immune system became, not only the most reliable proxy to determine prognosis, optimal time for therapy initiation, and monitoring but also a tool for assessment of effectiveness of ART. This is despite its measurement being approximate and with wide confidence intervals (Sheperd, Laeyendecker, Quinn, 2008). Therefore, criteria for ARV treatment failure will be based not only on virological failure but also and particularly in our resource-constrained settings, on immunological and clinical failures. Clinical acumen and immunological monitoring remain the corner stone of ART delivery system in resource-constrained settings.

WHO, 2006, defines immunological failure as a 50% drop in CD4 count from peak value or return to or fall to pre-ART baseline after 6 months of therapy or a CD4 count < 100 cells after 6 months of therapy.

Clinical failure is suggested by continued disease progression or development of new stage III or IV condition while on ART for more than 6 months. The clinical staging here refers to WHO classification of HIV-associated clinical disease. Patients are classified into stage I for those with asymptomatic disease, stage II for those with mild disease, stage III for those with advanced disease and stage IV for those with severe disease. This classification is recommended to form part of baseline assessment before entry into care and guide a number of decisions including initiation of cotrimoxazole prophylaxis and/or ART (*WHO, 2006*).

In addition to this classification, performance scale and functional status are added to determine quality of life and productivity. ART clinics have been using performance scale in the past. However, recent WHO recommendations for patient monitoring system are in favour of the use of functional status which classifies patient according to their level of activity in three classes: Working (able to perform usual work in or out of the house, go to school or for children, normal activities or playing),

Ambulatory (able to perform activities of daily living but not able to work or play) or Bed ridden (not able to perform activities of daily living) (*WHO, 2006*). In the best case scenario, given a correct clinical assessment, functional status always tallies with clinical stage resulting in patients of clinical stage III or IV falling under bedridden functional status.

The combination of clinical and immunological parameters will constitute the basis of our cohort analysis as surrogate markers for monitoring treatment success. Of note is that these are not perfect surrogate markers because CD4 counts may rise in the presence of incomplete viral suppression or drug resistance and opportunistic infections may still occur despite excellent viral suppression and immunological recovery. These are drawbacks in resource limited settings without viral load testing facilities which represent the gold standard for monitoring ART success (*WHO*, 2006).

Patients' characteristics and survival analysis

In a study conducted by Weidle *et al.*(2002) in one of the first pilot ART site in Africa (Uganda), the findings in a total of 476 revealed that at the end of the pilot period, 248 (52%) patients were still in care, 114 (24%) were lost to follow-up, 74 (16%) were known to have died, 17 (4%) were transferred out and were still receiving antiretroviral therapy, 14 (3%) discontinued antiretroviral therapy, and 9 (2%) had left the region. A different pattern of retention in care is seen in Malawi as Ferradini *et al.* (2006) results indicate that of 1,266 patients enrolled, 74% were still alive and on ART, 19% had died and 7% lost to follow up. It would appear that the mortality on HAART, which significantly affects the retention in care, varies widely between the 4% of the ART-LINC collaboration and the 19% reported above *(WHO, 2006)*.

The median age at initiation of 37 years is observed in numerous studies: a European cohort described by Phillips (2001), a Namibian interim statistical analysis (*BMS*, 2006) as well as an audit report in London (Sabin, 2003). Considering the pattern of the epidemic hitting hard the most sexually active between 20-25 years, this appears

consistent with the natural HIV disease progress whereby the need for treatment only emerges after 10 years.

In addition to women having better access to treatment, some findings suggest also a better treatment response as compared to men. Women present a profile of better baseline parameters and subsequently, at every time-point, invariably better virological and immunological response (Collazos, 2007). Though he acknowledges that it is less clear, Porter *et al* (2003), analysing some European cohort data, argued that the role of sex as a prognostic factor should be recognised as female injecting drug users seem to be at lower risk of death than do men in the same exposure category.

Age is another prognostic factor. It was suggested in several studies, cited by Porter *et al*, that older people (more than 50 years) had poor short-term and long-term response to HAART. This was naturally attributed to the slow immune function reconstitution in elderly.

With regards to clinical progression, our parameters of interest would be some selected and routinely available ones such as disease stage (as defined by WHO stage), performance scale or functional status (as defined by WHO) and weight. All these are measured at baseline and followed longitudinally to see the outcome during treatment. We know these are less reliable surrogate markers of treatment success but they are precisely what we have in most resource-poor settings. Until such a time that we are able to perform viral load, we have to rely heavily on CD4 cell count as well as selected clinical parameters such as weight gain to inform our decision on ART. The BMS, 2006, interim statistical analysis describes weight gain after 6 months on treatment and indicates that in different cohorts, the mean weight gain has been of 3.8, 4.4, 5.8 and 6.2 kg in Botswana, South Africa, Namibia and Lesotho respectively. This is from a recorded baseline median weight varying from 55.4 to 61.2 Kg. The weight gain appears to be higher in the Khayelitsha study (*MSH, 2003*) which indicates the median weight gain at 6 and 12 months duration on ART to be at 5 kg and 9 kg respectively.

Body mass index (BMI) could also be used to monitor clinical outcomes. Moore *et al* (2007) indicate a baseline median BMI of 19.7 in a Ugandan study whereas Ferradini (2006) suggests that 33% of patients in his Malawian cohort had a baseline BMI < 18.5. However, both of them did not provide the BMI progression or gain on follow up treatment to allow for comparability.

Similarly, the Charadzulu case study *(MSH, 2004*), in an attempt to describe baseline clinical information of their cohort, categorized their study population per WHO staging as follows: 11.7% stage I, 15.6% stage II, 43.3% stage III, 12.6% stage IV and 16.7% unspecified. A study in Uganda showed less severe immune suppression at baseline with 39% having WHO stage III or IV (Moore, 2007). However, in these two cases, there is no follow up data at subsequent time-points during therapy with which to document staging progression. The staging during therapy was a recent WHO recommendation and is termed T-staging. It uses, the same WHO standard staging adding "T" for patients on a minimum 6 months therapy. The patient can be staged forwards (I to IV) when deteriorating (clinical failure) or backwards (IV to I) when improving *(WHO, 2006)*.

The median CD4 count at baseline depends on several factors and has varied since earlier days when ART was being made available to the current scale up stage. At the beginning of ART programme implementation, the median CD4 count used to be lower because people delayed seeking treatment until they were very ill and severely immunosuppressed. As the programme matures and HIV-positive people are screened earlier for ART the median CD4 count of people initiating ART increased closer to the value for ART eligibility. The Khayelitsha MSF study (Kasper *et al.*, 2003) describes a median CD4 at baseline of 43 cells which has been increasing year-on-year whereas the BMS multi-centre study indicates a median baseline of 85, 92, 109 and 113 respectively in Lesotho, Namibia South Africa and Botswana cohorts.

The data from Weidle *et al.*(2002) did not indicate the clinical recovery pattern but it concluded that patients with CD4 <50 cells were more likely to die than those with

CD4>50. This is consistent with most studies that underpin the predominant prognostic role of baseline CD4 count (Egger, 2002) in addition to low body weight, Tuberculosis and anaemia as other determinant factors (Theo, 2007). Furthermore, sex distribution on ART was not given although the authors put forward that there was no gender difference in treatment response, contradicting the view of Porter *et al.* cited above.

However, the use of substandard regimens such as mono- and dual-therapies at the time of Weidle *et al.* (2002) study is likely to represent a serious caveat even if they asserted that virological and immunological responses to antiretroviral drugs were similar to those seen in North America and Europe. Despite the concern about early use of substandard regimens, many other studies including a meta-analysis by Ivers *et al.* (2005) underscore the fact that "ART treatment programs in resource-poor settings have efficacy rates similar to those reported for developed countries" though with significant differences between programs. In as much as we want to celebrate these findings, we still have to bear in mind that most programs in Africa are just over 4 years old and still need long term follow up and review.

In a Senegalese cohort analysing the trend of CD4 count recovery, Laurent *et al.* (2002) found out in a 58 treatment-naïve patients followed up that CD4 cell count rose by a median of 82, 147 and 180 cells/µL at months 6, 12 and 18, respectively. This finding is in keeping with what Bartlett and Gallant (2003) wrote:

> "*The CD4 response is generally the mirror image of the RNA decay curve, with increases that average 50-60 cells…in the first 4 months with subsequent increases at a rate of….50-100 cells…per year with good viral suppression."*

However, other studies show a more pronounced increase at 6 months such as 85 cells/µL in Charadzulu (*MSF, 2004*), 133 in Khayelitsha (*MSH, 2003*), whereas at 12 months, the same studies documented respectively 178 and 221. Moreover findings from ART-LINC cohort that include both low and high income countries did not show difference in CD4 recovery pattern between the two settings. In conclusion, it would appear that, under normal circumstances, an increase of > 100 cells/µL in the first 6 to 12 months is a characteristic response of ARV naïve patients. According to

some WHO experts, given sufficient time, even patients with critically low CD4 count (<10 cells/μL) are likely to attain a successful CD4 count response. On the other hand, they argue that some patients may possibly never exceed 200 cells/μL and hence remain at high risk of severe immuno-suppression (*WHO, 2006*).

Close monitoring and evaluation of program performance and impact assessment through longitudinal cohort analysis is needed. This will ensure a timely switch to second line therapy and prevent development and spread of a secondary HIV/AIDS epidemic with resistant strains.

Aim

This investigation, part of an ART program evaluation, is aimed at analysing the clinical and immunological response and survival of HIV/AIDS patients receiving HAART in the Nyangana Catholic Mission District in Namibia.

Objectives

1. To estimate the ART coverage in Nyangana District
2. To describe socio-demographic characteristics of eligible PLWHA enrolled in HAART in Nyangana District between August 2004 and April 2006
3. To describe baseline (pre-ART) clinical profile and subsequent clinical response (selected clinical parameters) of the target patients population
4. To determine baseline immunological profile and the trend of CD4 cell count response in the target patient population, from baseline to different follow up periods
5. To determine baseline characteristics associated with survival and/or mortality of patients receiving HAART in Nyangana district during the period under study
6. To make recommendations pertaining to case management and HAART program planning in the CHS HIV/AIDS program in order to improve patient outcome

Chapter 3. Research Methodology

3.1. Study design

This is a quantitative, analytic cohort study, retrospectively examining clinical response, immunological restoration and overall treatment outcome (survival, death) of treatment naïve HIV/AIDS patients who have been enrolled on HAART during the period of August 2004 to April 2006 in Nyangana district.

The choice of this method was justified by the fact that the investigator was using secondary routine data to conduct a longitudinal analysis of patients' progression on HAART as part of an operational research on outcome evaluation. This is also in keeping with WHO recommendations on the patient monitoring system (*WHO*, 2006). A prospective cohort study would have been the ideal design but financial and time constraints were serious limiting factors.

3.2. Population and settings

This study will analyse secondary routine data (retrospective review of patient's records) from the Nyangana ART clinic. This is a rural district of 41,000 catchment population with a 2006 ANC serosurveillance indicating 12% HIV prevalence. It is one of the four Catholic Mission facilities whose HIV treatment program was launched in August 2004. With an average monthly intake of 15 new patients, the clinic records show that as at end of 2006, 450 patients were receiving ART out of a total of 590 ever started. The observed attrition rate of 23.7% is mainly driven by the mortality on HAART which is one of the major challenges facing the programme. The investigator has access to the clinic data as the Program Manager of the CHS HIV/AIDS program.

The ART initiation was based on the national guideline eligibility criteria adapted from WHO which required: WHO stage IV regardless of CD4 cell count and WHO stage I, II or III with CD4 cell count < 200. In addition, a number of social criteria needed to be met such as fixed address for > 3 months in the area, readily accessible follow up site, absence of substance abuse and psychiatric illness and commitment to lifelong medication.

3.3. Sampling

The sampling frame includes all eligible patients that started HAART in Nyangana District between August 2004 (official launch of the program) and end of April 2006. This allowed a follow up period that ranged between 12 and 32 months in an intention to treat analysis. The sample attrition related to death, transfer out of the district and lost to follow up during this period will be considered in analysing treatment outcome and survival on HAART of this cohort.

Inclusion criteria

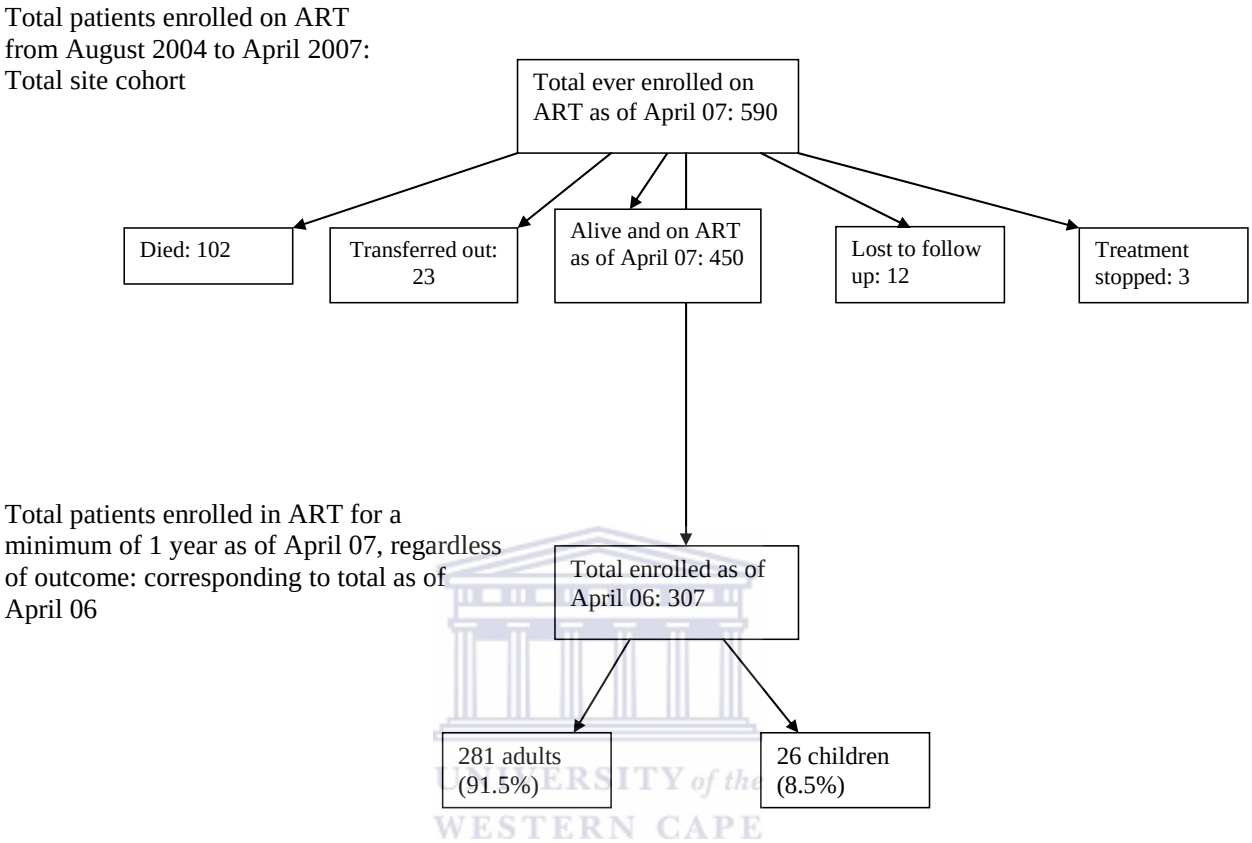
- ✓ All HIV/AIDS adult patients who were initiated on HAART in Nyangana ART clinic as treatment naïve
- ✓ HAART must have been initiated between August 2004 and April 2006 (a **minimum of one year** enrolment prior to the time of analysis regardless of outcome)
- ✓ Patient outcome must be documented (alive, died, lost to follow up or transferred out)

Exclusion criteria

- ✓ Children < 13 years

Therefore, of the total 590 patients enrolled on ART from August 2004 to April 2006, 281 adult patients met our inclusion criteria and qualified for the present analysis. In the interest of homogeneity of analysis and of the time at hand, the investigator has chosen to analyse only adult data. The following schema describes how the patient selection was done:

Figure 2: Sampling selection flow



3.4. Data collection

Data source

This is an operational study using a retrospective data enquiry from standardised patient files and registers used in the ART clinic in Nyangana. Theses data are regularly captured as part of a routine paper-based patient record system. It contains a number of variables (numerical and categorical) ranging from demographic to clinical and pharmacological information as recommended by WHO patient monitor system. The variables abstracted were sex, age, marital status, pregnancy status, date started ART, TB status at therapy initiation, baseline and subsequent reading (6, 12, 18, 24 months) of weight/BMI, CD4 cell count, WHO clinical stage (I, II, III, IV), functional status (Working, Ambulatory, Bedridden) (WHO, 2006). Adherence level was also abstracted as patient files indicated a routine collection of the last 28 days self reported adherence during clinic visits. The duration on ART by April 2007, the date, cause and place of death, the date of loss to follow up or transferring out as well as ARV regimens prescribed were additional variables, all of which were entered in an excel database by a trained data clerk. For patients who died while on ART, we relied on hospitalisation records and reports from field workers who conduct regular home visits to trace defaulters.

For the purpose of data quality assurance, after data abstraction and coding in an excel database, data cleaning was done by checking row by row searching mainly for range, transcription errors (e.g. CD4 cells in wrong field), inconsistencies (e.g. male with pregnancy status yes) and omissions. Every finding was traced back to the original patient file for validation. The use of excel advanced filter and the frequencies distribution in EPI Info proved very useful in identifying percentages and outliers.

3.5. Data analysis

Using adapted modelling approach from Stover *et al.* (2006) and personal communication from Professor Van Damme and Dr Ludwig Apers in a discussion at the Institute of Tropical Medicine in Antwerp (W. Van Damme & L. Apers, pers comm, Sept 2006), we estimated the population living with HIV/AIDS (based on district population and prevalence) and those in need of treatment at the start of the program and subsequent yearly intake. These approaches for estimate are based on

EPP and Spectrum models. Demographic characteristics (age, sex) were analysed through descriptive statistics.

Treatment outcome, baseline and follow up clinical and immunological data entered into an Excel database were analysed using EPI info 2000 or SPSS. The frequency distribution of patients on ARV by CD4 cell count categories and weight at baseline and at 6, 12, 18, 24 months was done.

The following computations were used: measures of central tendency (mean, median), measure of dispersion (range, standard deviation) for all parameters of interest (CD4 cell count, weight/BMI). Though WHO generally recommends the use of median as CD4 is usually not normally distributed, the specific distribution of CD4 cell count for each analysis (obtained through normality test) will determine the use of either mean or median. In addition, a paired comparison test of the change in CD4 cell count and weight/BMI from baseline and at 6, 12, 18 and 24 months duration on ART cross-tabulated to gender was conducted.

Patients who died during the study period were analysed with regards to possible cause of death, duration on ART before death and place of death. With death as event of interest, SPSS Kaplan-Meier probability of survival was calculated censoring for loss to follow up and transferred out.

Using a multivariate Cox regression analysis, the investigator went beyond the primary descriptive level to gain insight into the effect on survival of baseline parameters such as WHO staging, performance scale, weight, BMI, CD4 count and sex.

3.6. Reliability and Validity

Simplified ART cohort analyses are becoming standard practice and are currently recommended by WHO through longitudinal patient monitoring system. This includes careful follow up of enrolled patients at specific intervals, careful recording of minimum monitoring data and analysis of different assigned cohorts based on defined outcome. The sample size that includes all PLWHA who have enrolled and attended ARV care during the period under study in this district will provide a high level of

internal validity as no selection bias is expected. The cohort analysis approach is replicable in any ART site within the country. Generalizability of the results will be limited because clinical and immunological responses to ART may vary according to many other variables including the prevalence and maturity of the HIV/AIDS epidemic, the disease co-morbidity profile, adherence profile, the socioeconomic conditions (the Nyangana population is mainly a rural community) and models of ART delivery (e.g. entry to care requirements, follow up system). The Nyangana ART program has been built on strong reporting requirements of an international donor agency which demands high quality of data. As a result, data quality verification and system assessment have been regularly done in this site.

3.7. Limitations/Assumptions

This is mainly an observational study based on secondary analysis of routine data. Despite considerable efforts of data cleaning and validation, some incorrect entries and missing values might affect our analysis. Furthermore, the confounding effect of some unmeasured variables such as individual uptake and timing of treatment initiation, individual level of adherence, relative potency of different regimens used and more especially failure to validate clinical and immunological outcomes with viral load testing could constitute serious limitations in this study.

It is further assumed that the CD4 cell count machine provides results within appropriate reference ranges and that the coefficient of variation is not too large to affect the analysis.

3.8. Ethical statement

The study is non experimental, fundamentally based on record review and does not involve human participants or animal experiment. Therefore, no harm to human subjects is foreseeable and no consent is required in the execution of this study.

However, to protect patient identity and ensure total confidentiality, records entered into the database were done anonymously using unique patient codes that made it difficult to trace the patient whose data is being analysed. The investigator who was the Chief Medical Officer and national coordinator of the program enjoyed high

credibility in the ART clinic and made use of the existing routine data captured by the local team to abstract the necessary variables for analysis.

After approval by the UWC Higher Degrees Committee, the proposal was also approved by the Namibian MoHSS Bio-Medical Ethics Research Committee.

Chapter 4. Results

4.1. Baseline characteristics

Our study population includes all treatment naïve adult patients, enrolled in HAART during period August 2004 (programme launch) to April 2006 at Nyangana ART clinic. Of the cumulative total 590 patients ever started by April 2007, 307 patients (52%) qualified for entry of which 281 were adults (91%) and 26 were children (9%). As stated in the methodology, in the interest of homogeneity and time, only data from adult age group defined in our programme as aged 13 years and older were analysed. The results are based on observed, recorded data. There was no imputation for missing values and therefore “n” will vary depending on each variable analysed.

4.1.1. Demographic characteristics

Table 1: Demographics

Variables		Standard Deviation	Mean difference
Sex	**n=281**		
Male	87(31%)		
Female	194(69%)		
Age (years)	**n=280**		
Mean (all)	36.1	9.4	Between males and females(F=26.4, p-value<0.0001)
Male	40.3	9.9	
Female	34.3	8.6	
Minimum (all)	16		
Maximum (all)	77		
Age group (years)	**n=280**		
15-24	27(9.6 %)		
25-34	98(35%)		
35-44	109(38.9%)		
>=45	46(16.4%)		
Employment status	**n=281**		
Employed	41(14.6%)		
Unemployed	240 (85%)		
Marital status	**n=281**		
Single	80(25.5%)		
Married	130(46.3%)		
Divorced	28(10%)		
Widow(er)	45(15.3%)		

4.1.2. Estimation of ART coverage in Nyangana Hospital

Using available measure of estimates, public health practitioners continuously attempt to calculate the coverage of ART in order to put in place strategies geared towards access for all by 2010. It is currently estimated that *ART* is reaching 46% of those in need in Nyangana district).

Table 2: Estimate ART coverage in Nyangana district

Total district population	41,000
Estimated adult population (15-49) 45%	18,450
HIV prevalence in 2004 (beginning of ART)	18%
Estimated number PLWHA in 2004 (18% of 18,450)	3,321
Estimated number in need of ART at start (15% of 3,321)	498
Projected number in need second year: survival of first year (85% of 498) + 10% of estimated PLWHA	755
Projected number in need third year: survival of second year (85% of 755)+10% of estimated PLWHA	973
Total receiving treatment by end of April 07 (32 months)	450
% PLWHA receiving ART vs those in need	46%

4.1.3. Duration on HAART

We set to include data from patients with a minimum of 1 year on HAART to allow for trend analysis. This meant including patient who enrolled and initiated treatment between the launch of the ART program in August 2004 until April 2007 regardless of their outcome. By then, the overall mean duration on treatment is 16.5 months with range between 1 week (for those who died) and 32 months (for those alive). The stratified means are 5.1 and 20.8 respectively for those who died and those still alive.

4.1.4. Clinical baseline characteristics

The following baseline parameters were recorded: Weight, Height, BMI, WHO staging, functional status, and presence of TB or not.

Table 3: Clinical baseline characteristics

Variables at baseline		Standard Deviation	Difference
Weight (kg)	**n=274**		
Mean (all)	48.3	9.6	
Male	53.3	9.0	
Female	46.1	9.0	
BMI	**n=137**		
Mean (all)	19.4	3.3	
Male	20	2.4	
Female	19.2	3.6	
WHO clinical stage	**n=281**		
Stage I	13(4.7%)		No difference between male and female
Stage II	41(14.7%)		
Stage III	185(66.5%)		
Stage IV	39(14%)		
Functional status	**n=281**		No difference between male and female
Working	19(6.8%)		
Ambulatory	197(70.1%)		
Bedridden	65(23.1%)		
TB status	**n=281**		
Yes	71(25.3%)		
No	210(74.7%)		
Pregnancy status	**n=194**		
Yes	13(6.7%)		
No	181(93.3)		
Baseline regimen	**n= 281**		
D4T-3TC-NVP	233(82.9%)		
D4T-3TC-EFV	40(14.3%)		
AZT-3TC-NVP	8(2.8%)		

Data quality assurance parameters (HIVQUAL)

In order to maintain high quality standards, an approach to quality management based on performance measurement and quality improvement requires measuring a number of indicators pertaining to patient monitoring such as how well is the weight, CD4 count, WHO clinical stage monitored through the continuum of care or how well is Pulmonary TB being screened at each visit (Bruce, 2006).

Of the sample being analysed, the monitoring of CD4 count and weight was evaluated at different time intervals for patients still in care:

Table 4: Proportion of weight and CD4 cell count available at different time interval

Time interval	Expected Number at each interval	CD4 measured		Weight measured	
		Number	%	Number	%
Baseline	281	281	100	274	98
6 months	224	152	68	203	91
12 months	214	138	64	194	91
18 months	139	93	67	127	91
24 months	80	51	65	70	88

This table is indicative of challenges in data collection:

- At baseline every patient had a CD4 count and 98% had a weight charted
- An average 35% of CD4 counts were missing at each time interval
- An average 10% of weight measurements were missing at each time interval

Table 5: Regimen substitution/switch

Substitution/switch (n=281)	
Yes	55(19.6%)
No	224(79.7%)
Switch	2(0.7%)

Per WHO definition, substitution applies to change within one regimen for whatever clinical indication whereas switch refers to change from the first line to the second line regimen (*WHO*, 2006). Whereas 19.6% have experienced ART regimen substitution, the switch to second line in this cohort only occurred in less than 1% of patients after 24 months on treatment.

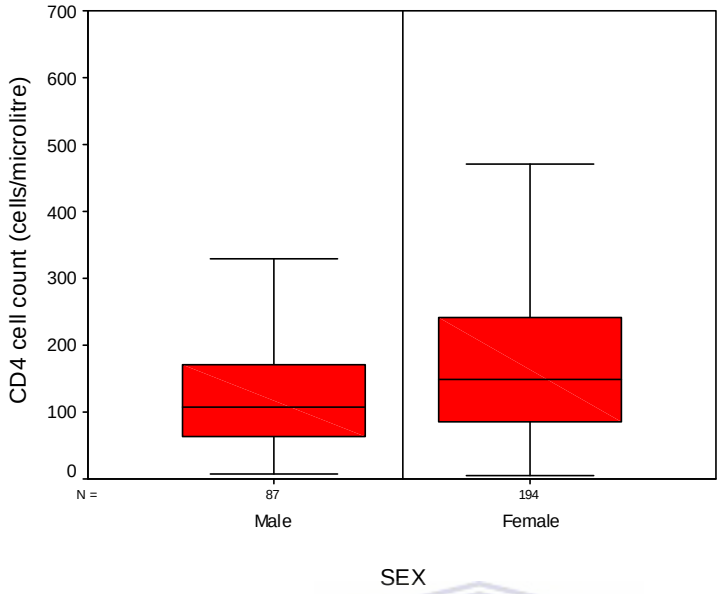
4.1.5. Baseline CD4 cell count

Immunologic status at baseline was assessed by the median and mean CD4 cell count. Mean will be used in our further discussion as the normality test showed normal distribution.

Table 6: Baseline CD4 count

Mean		166
Median		131
Std. Deviation		124
Percentiles	25	75
	50	131
	75	216
Minimum		6
Maximum		630

Figure 3: Baseline CD4 cell count stratified by sex

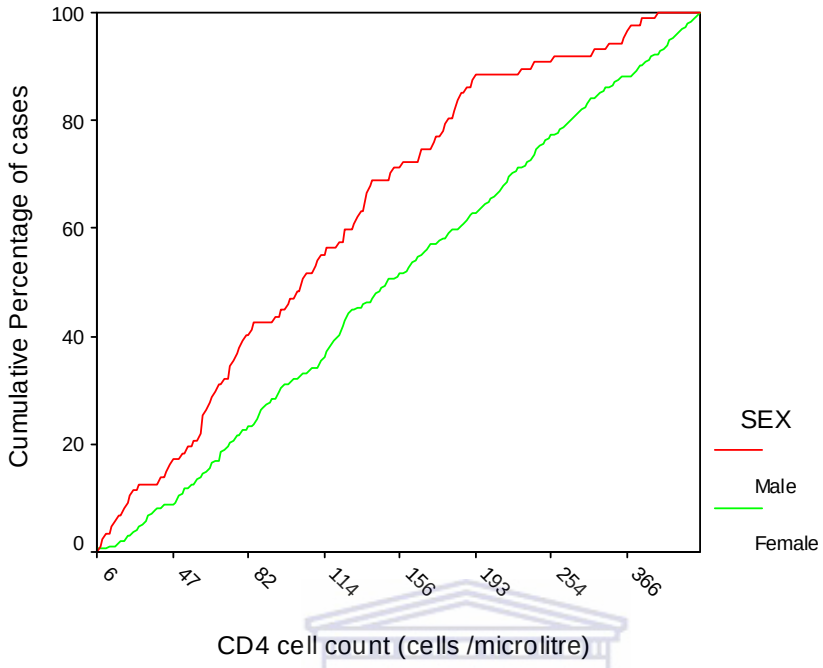


It appears that males were more likely to have lower median CD4 cell count (107) as compared to females (148), (F=14.4, p value <0.0001).

An additional illustration of CD4 cell count distribution by sex is shown below. More than 80% of males had CD4 cell count less than 200 cells/µL compared to 50% of females.

The majority of patients (72.6%) were initiated on HAART within the nationally recommended cut off of less than 200 cells, indicative of good adherence to the national guideline. It appears that females were more likely to have higher CD4 count as compared to males.

Figure 4: CD4 cell count at ART initiation by sex



CD4 cell count IQR: 75-216

4.1.6. Follow up parameters

Weight

The change in weight over the treatment period, ignoring missing values at different time intervals is as follows:

Figure 5: Mean weight at follow up intervals

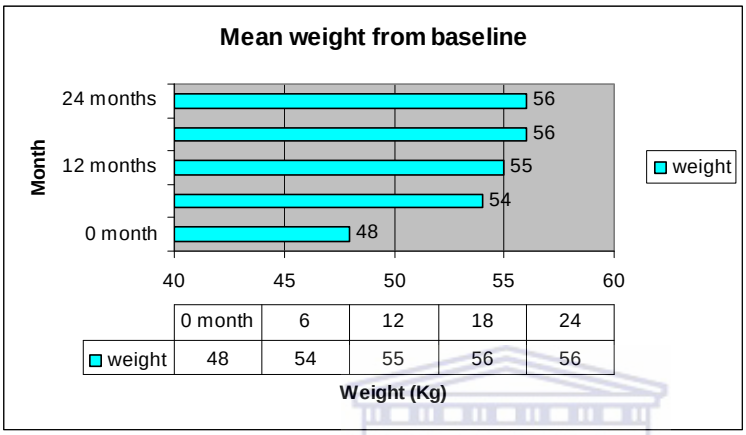


Table 7: Mean weight

Encounter	Number	Mean weight (kg)	SD	Mean difference (Kg)
Baseline	274	48.4	9.7	-
6-month	203	54.0	9.3	+5.6
12-month	194	55.5	9.8	+7.2
18-month	127	56.4	8.9	+8.1
24-month	70	56.0	8.5	+7.7

Most weight gain was observed in the first 12 months and then it appears to increase only slightly subsequently.

Functional status

Table 8: Progression of functional status at follow up

WHO functional status	Baseline (n=280)	6 months (n=215)	12 months (n=208)	24 months (n=66)
Working	19(6.8%)	16(7.4%)	43(20.7%)	45(68.2%)
Ambulatory	197(70.4%)	196(91.2%)	164(78.8%)	21(31.8%)
Bed-ridden	64(22.9%)	3(1.4%)	1(0.5%)	0

CD4 cell count response

The median CD4 count record at various follow up period defines the immunological recovery observed during ART. The median CD4 cell count recorded at different intervals using only available values showed an increase from baseline of 158 and 206 cells respectively at 6 and 12 months.

Figure 6: Median CD4 cell count at follow up intervals

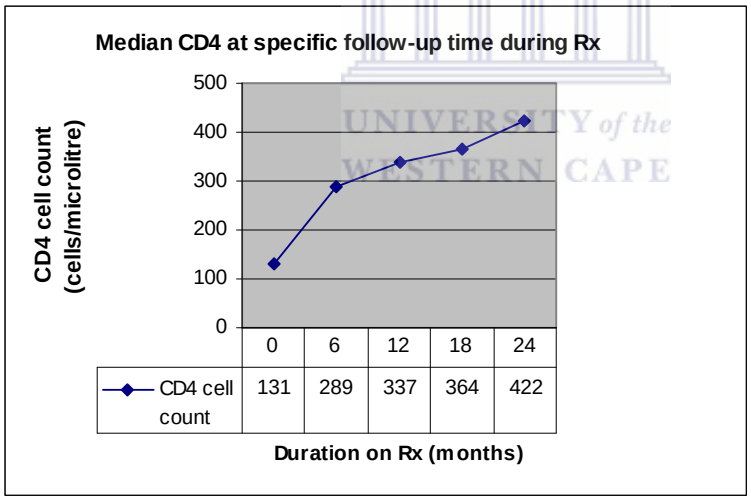


Table 9: Median CD4 cell count increase

Encounter	Number of patients	Median CD4 count	IQR	Median increase
Baseline	281	131	75-216	-
6 months	152	289	194-425	+158
12 months	138	337	232-492	+206
18 months	95	362	234-517	+231
24 months	51	422	268-542	+291

There were only 33 patients who had CD4 count values at each follow-up time. They showed CD4 cell count gain of 136 and 217 cells respectively at 6 and 12 months

Table 10: CD4 distribution per range during follow up intervals

	Baseline (n=281)	6 months (n=152)	12 months (n=138)	24 months (n=51)
0-99	36.1%	2.6%	5%	4%
100-199	36.5%	24%	13%	7.8%
>=200	27.4%	73.4%	82%	88.2%

Adherence profile

Based on self-reporting of number of pills missed during the last 28 days as documented in the patient file at the time of data collection, available data classified 242 patients into the following categories:

Good (missed 3 doses or less) 201(76.7%)

Fair (missed 4 to 8 doses) 33 (12.6%)

Poor (missed 9 doses or more) 28 (10.7%)

This dataset showed an association between level of adherence and being alive or dead.

Table 11: Association between adherence level and treatment outcome

Adherence	Died	Alive	Total
Fair or poor	17	35	52
Good	31	159	190
Total	48	194	242

OR 2.4 (95% CI: 1.17-5.28), p-value=0,008

Those who died were twice as likely to have fair or poor adherence as compared to those who survived.

4.1.7. Mortality on HAART

This cohort showed that 66 (23.5%) people died on ART. Mortality was higher amongst males as compared to females (chi square 4.42 p-value=0.035) suggesting that the odds of dying is 1.87 times greater among males as compared to females.

Table 12: Died by sex distribution

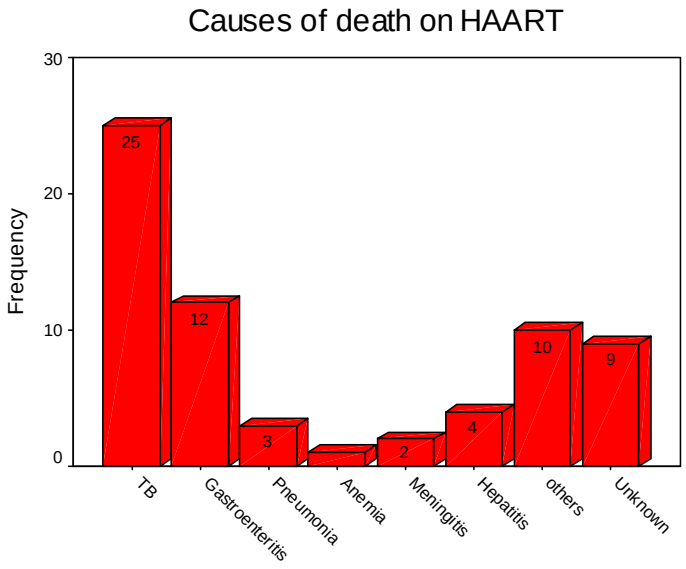
Sex	Number	Died	%
Male	87	26	29.9
Female	194	40	20.6
Total	281	66	23.5

More than 60% died within first 3 months and close to 80% within first 6 months.

Table 13: Distribution by time of death

Month	Died	%
0-3 months	40	60.6
4-6 months	12	18.2
7-12 months	7	10.6
13-24 months	7	10.6
Total	66	100

Figure 7: Distribution by cause of death



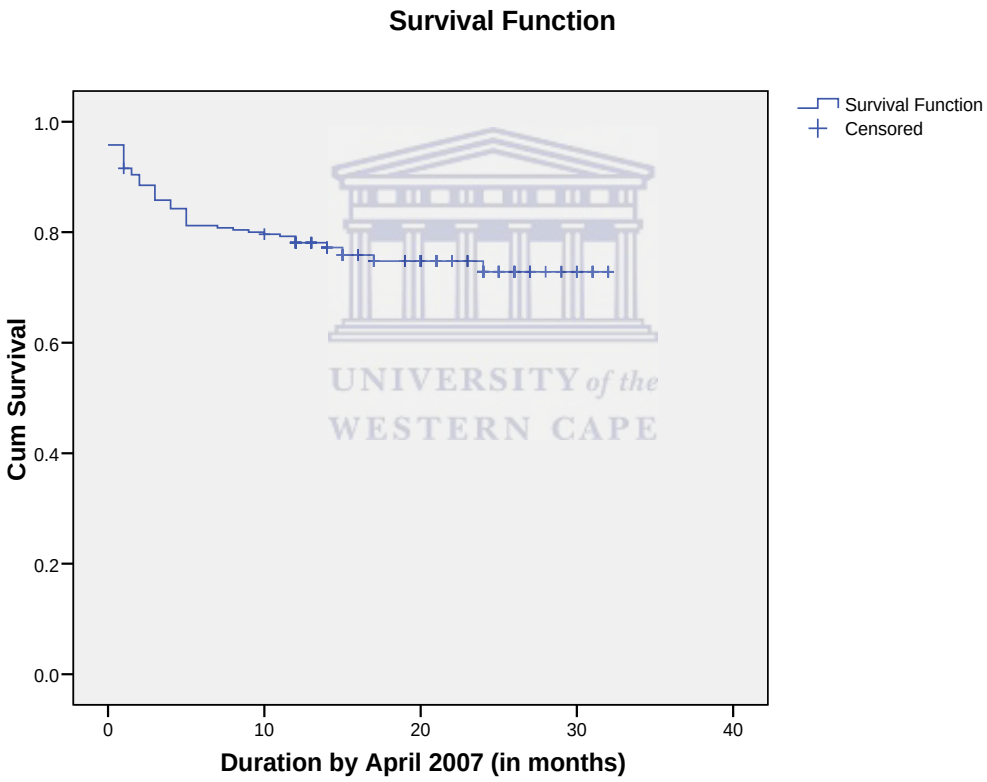
4.1.8. Survival analysis

Overall survival

Figure 8: Overall survival on ART by 32 months

Case Processing Summary

Total N	N of Events	Censored	
		N	Percent
261	66	195	74.7%

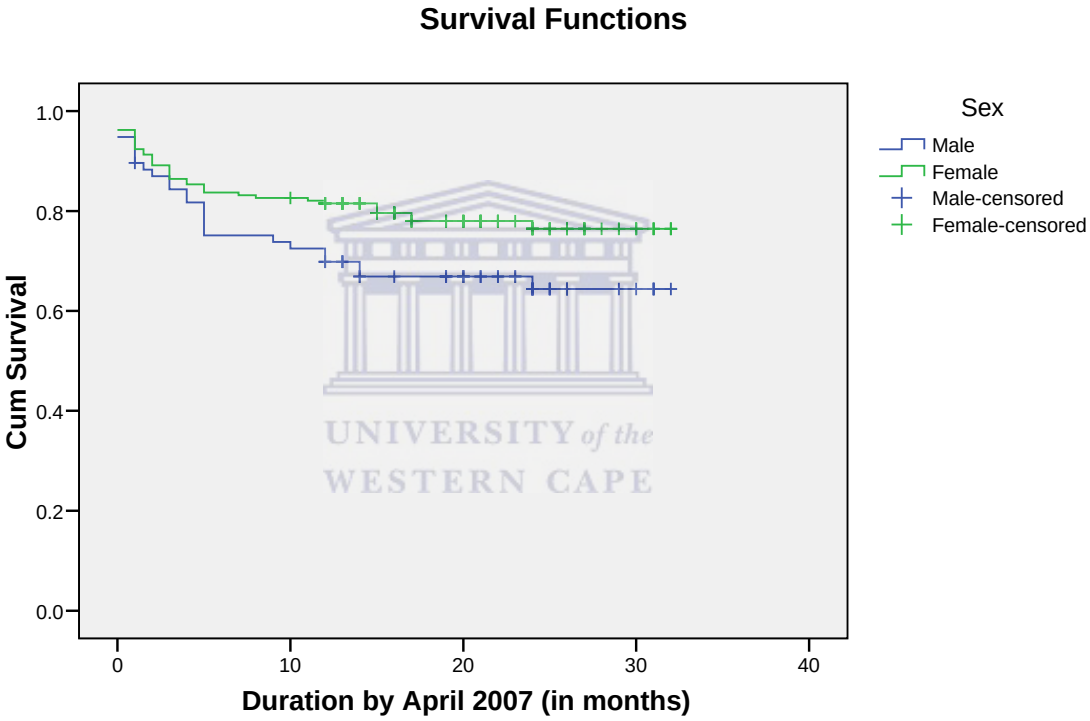


Survival by sex

Figure 9: Survival on ART by 32 months by sex

Case Processing Summary

Sex Sex	Total N	N of Events	Censored	
			N	Percent
Male	77	26	51	66.2%
Female	184	40	144	78.3%
Overall	261	66	195	74.7%



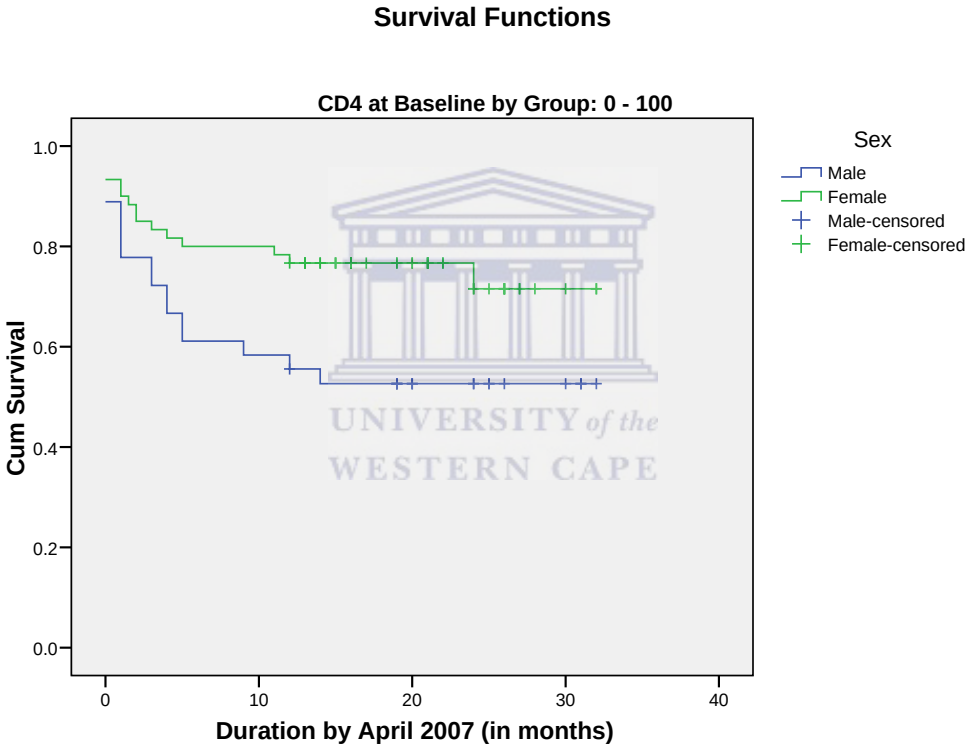
At 32 months, the probality of survival was 0.65 for males and 0.75 for females. 95% CI (21-26). This difference is stastically significant (log rank 2.7, p-value=0.05)

Figure 10: survival stratified by sex and CD4 count group

Case Processing Summary[a]

Sex Sex	Total N	N of Events	Censored	
			N	Percent
Male	36	17	19	52.8%
Female	60	15	45	75.0%
Overall	96	32	64	66.7%

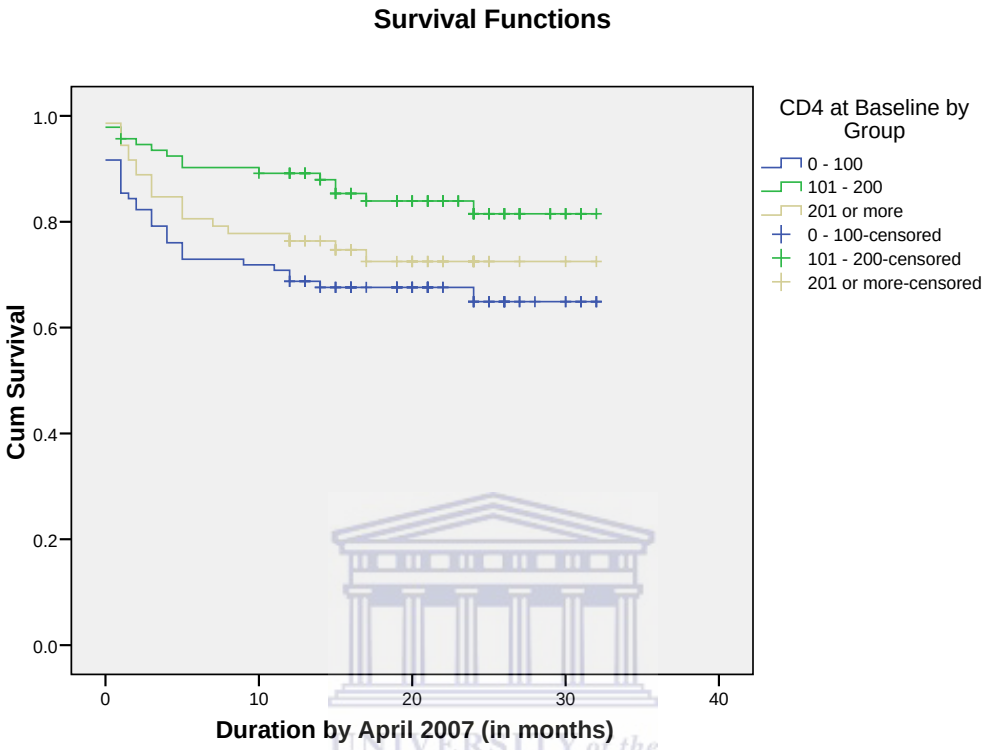
a. CD4_Baseline_group CD4 at Baseline by Group = 0 - 100



In the CD4 cell count group less than 100, females have much better survival than males. (log rank, p-value=0.029)

Survival by baseline CD4 cell count

Figure 11: Survival on ART stratified by baseline CD4 count



At 32 months, the probability of survival was 0.82 for patients with median CD4 cells count between 101 and 200 and 0.65 for those with CD4 cells count less than 100

Table 14: Cox regression analysis: association between baseline variables and survival

VARIABLES	***B***	***SE***	***WALD***	***DF***	***SIGNIFICANCE***	***EXP (B) (HR)***	***95% CI FOR EXP(B)***	
							Lower	Upper
Sex	0.834	0.334	6.234	1	0.01	2.302	1.196	4.430
Weight	-0.051	0.022	5.232	1	0.02	0.951	0.910	0.993
Functional status	-0.741	0.298	6.182	1	0.01	0.477	0.266	0.855

281 Total cases read

8 Cases with missing values

0 Valid cases with non-positive times

0 Censored cases before the earliest event in a stratum

8 Total cases dropped

273 Cases available for the analysis (all baseline variables were included with weight in Kg as continuous variable and functional status collapsed in binary variable).

The following baseline variables were associated with shorter survival: male sex (women were twice as likely to survive as compared to males), lower body weight (those with lower body weight in Kg were less likely to survive), functional status (those with fucntional status ambulatory and bed redridden were less likely to survive as compared to those with working status). In this data set, the likelihood of survival does not depend on age.

4.2. Discussion

The present study has been one of the very few research endeavours to capture longitudinal data on patients receiving ART in Namibia. Some unpublished cohort analyses have been conducted in a couple of district hospitals in Namibia. The investigator set out to assess the effectiveness of the Nyangana District ART programme by analysing clinical and immunological response as well as survival pattern of patients enrolled since the launch of the programme in August 2004 until April 2006. The following is a discussion of the findings in line with the research question and the study objectives.

Estimation of ART coverage

Based on the modelling used, ART in Nyangana District is estimated to be currently reaching 46% of those in need of it. Despite the limitations associated with this estimation approach, it provides a reasonable basis and a tool for programmatic decision making.

Compared to the Global and African region average of 28% (*WHO, UNAIDS, 2007*), it would appear that the Nyangana District HIV/AIDS programme is well on the road towards access for all. Compared to 2 years ago, the figure also represents an 84% increase from the national average announced by the Minister of Health when he

declared that Namibia was amongst the only three SSA countries to provide ART to more than 25% of those in need of it (*The Namibian, 2005*).

Demographics characteristics

The feminisation of the HIV/AIDS epidemic is apparent in this study with 69% of the 281 enrolled in ART being females. This is generally in agreement with many findings across SSA that have shown the proportion of ART clients who are women being in the range of 60 to 75%. South Africa has a worse gender inequity as findings indicate up to 76% of ART clients are female in one study (Ferradini, 2006; Venter, 2004; *MSF, 2003, BMS, 2006*). Although women bear the brunt of the disease comprising 61% of PLWHA in SSA *(UNAIDS, 2007),* a number of favourable factors related to better health seeking behaviour, lower level of stigma and availability of PMTCT services seem to play a role in their acceptance and access to ART programmes compared to men. The general poor male involvement reported in many studies and HIV/AIDS programmes has prompted a campaign in Namibia to address gender norms that might result in better utilisation of HIV-related clinical services for men.

The mean age at treatment initiation was found to be 36 years, with the minimum and maximum at 16 and 77 years respectively. The majority (90.3%) were aged 25 years and above (Table 1). This is suggestive of an HIV infection occurring in the late teen ages/earlier twenties, amongst the most sexually active, with the need for treatment emerging only 8 to 10 years later. The mean age is similar to several other studies which found mean age to be 37 years (Philips, 2001; *BMS, 2006*). A Malawian study indicated a median of 34.9 years whereas an even lower mean age of 31 years was reported in the MSF cohort in Khayelitsha *(*Ferradini,*et al*., 2006; *MSF, 2003).*

An interesting finding was the mean age disaggregated by sex. It shows a statistically significant difference with males having a mean age higher (40 years) than females (34 years) ($p<0.0001$). This is found across all studies reviewed and more especially in the BMS multicentre analysis. Explanation for this could not be found. Older age at HIV acquisition in males as well as poor health seeking behaviour amongst men as they wait long before accessing care and treatment are the leads to be explored.

Most ARV users in this study population were unemployed (85%). The current unemployment rate in Namibia stands at around 30%. However, in rural communities, including the catchment population of the ART centre in this study, higher unemployment rates have been noted resulting in poverty and lack of food security.

Clinical baseline characteristics

The table 3 displays a number of clinical measures obtained at baseline. The mean weight and BMI were respectively 48 kg and 19.4. This body weight was significantly lower than 57 kg reported by MSF (2003) in their Khayelitsha cohort. Genetic and ethnographic differences might account for these differences. Food security can not be ruled out as these are two different communities of which one is rural (Nyangana) and the other one urban (Khayelitsha). When compared to the BMS multicentre analysis, our mean weight is still lower than the range of 55.4 to 61.2 Kg. Similarly, the mean BMI of 19.4 is also lower than 19.7 reported by Moore in Uganda (2007) in Uganda. It can therefore be assumed that a general trend of lower mean body weight and BMI is observed at treatment initiation in our cohort. An implication of this could relatively higher mortality rate as observed in our cohort (Moore, 2007).

The classification of patients at baseline into WHO clinical stage revealed another important finding. More than 80% of patients were stage III and IV (advanced and severe disease) as compared to 55.9% in an MSF study (2004) and 39% in the study by Moore et al (2007). This is indicates that patients in this study were more likely to enter ART care with advanced immune suppression. This trend was observed despite availability of voluntary counselling and testing services in the district. However, as this was an earlier cohort enrolled in ART care in the first two years of the introduction of ART programme in this community, it is likely that this tendency might have been reversed. Stigma and discrimination that hampered the scale up of ART in its earlier days was wearing off as the success of therapy became apparent in most communities.

A strong relationship exists between functional status and WHO clinical stage. As most patients had advanced to severe HIV disease, it was expected that their functional status would be also unfavourable. This was confirmed by the finding that more than 90% in our patient population had a functional status either ambulatory or

bedridden. With 23% in the bedridden status, it indicates a high loss of productivity and poor quality of life associated with advanced disease stage.

With regards to TB screening, 25.3% of patients were found to have TB at ART initiation. This is more than twice the 11% reported by the study done by Libamba *et al.*(2006) in Malawi. Although efforts were being made to screen for TB at baseline there was no measure of how many patients were actually screened. A tool to capture TB screening and diagnosis at each care visit is important in these settings where HIV/TB co-infection is more than 65%. This view is supported by WHO's team of experts who recommends that high TB/HIV co-morbidity in many countries requires effective coordination, referral and integrated monitoring and evaluation of the two programmes (*WHO, 2006*).

ART regimen

At baseline, all 281 patients included in our study were initiated on the first line regimen recommended by the National guideline (Table 3). This is indicative of a high level of standardization and compliance in the public sector in Namibia. It falls in line with the WHO public-health approach to providing ART in resource limited settings. A similar compliance was reported in the Khayelitsha cohort (*MSH, 2004*) with a difference that the EFV based regimen there (because of TB) was 60% as compared to our 14.3%. With less than 1% switching to second line therapy by 24 months comparable to Libamba *et al* (2006) findings, the Nyangana ART programme presents a good prospect of a lasting first line therapy. However, without regular viral load monitoring, this finding should be taken with caution and requires further investigation that will be followed up by the investigator.

Data quality assurance

The fact that missing values were observed at each follow up period means that our longitudinal data analysis must be interpreted with caution as missing cases might differ in analytically important ways from cases where values are present. To address this issue we compared findings of mean CD4 cell count and body weight using available data to that obtained using data from patients with values at all encounters. All 281 patients had CD4 cells count reading at baseline and 98% had weight charted. However, at subsequent follow up encounters, an average 35% of CD4 cell count

could not be traced and around 10% of patients were missing body weight. This finding underscores the challenge of data collection, storage and retrieval that many ART sites are currently experiencing.

Baseline CD4 cell count

The immunological status at baseline in this study (median CD4 count of 131 cells/µl, IQR: 75-216) showed consistency with other studies as in general most patients entered ART care with advanced to severe immune suppression. Moore *et al.*(2007), Laurent *et al.* (2002) reported a median baseline CD4 count of 127 and 108 cells respectively. The Khayelitsha cohort found an even more profound immune suppression with median of 43 cells/µl. A combination of patient and provider factors may be at play. Awareness, motivation, level of stigma and discrimination are important patient factors in accessing care. On the other hand, using a cut off for treatment eligibility of 200 cells/µl may constitute a barrier to an optimal treatment initiation time. As a matter of fact, this finding should be considered as normal in terms of compliance with the national guideline. However, when disaggregated by sex, it would appear that males were more likely to have lower median CD4 cell count (107 cells/µl) as compared to females (148 cells/µl) ($F=14.4$, p-value<0.0001). This finding is similar to that of a recent publication from Collazos *et al* (2008) who found at a borderline statistical significance that the women's average CD4 cell count was higher than men's. They further argued that there was a general tendency of women having lower viral load and higher CD4 cell counts when they initiated ART as compared to their male counterparts. It can be speculated that some difference might reside in better health seeking behaviour amongst females and availability of PMTCT services that provide a canvassing ground for HIV positive women.

Follow up parameters

Weight

Serial measurements of weight at baseline and follow up periods provided the basis for comparison. Missing values at random at different follow up periods limit the analysis of trend. We compared mean weight obtained in the entire cohort using the available dataset at each encounter to mean weight obtained among patients with weight measured at all encounters. In the entire cohort the weight gains from baseline were 5.7, 7.2, 8.1 and 7.7 Kg respectively at 6, 12, 18 and 24 months. In the smaller

population with weight measurements at all visits the gains at 6 and 12 months were 4.6 and 5.6 Kg respectively. Whichever analysis we used, these findings would appear to suggest similar weight gains observed in other studies. At 6 months, the BMS analysis (2006) showed weight gains at different sites between 3.8 to 6.2 Kg. The MSF (2003) cohort indicated a gain of 5 Kg at 6 months and 9 kg at 12 months. The assumption is that a good clinical response on ART will result in weight gain that clinicians need to monitor regularly.

Functional status

The progression of functional status from bedridden through ambulatory to working status (productive life) provided additional information on clinical responses to ART. Whereas the percentage in bedridden status decreased (22.9% to 0%), the working status increased (6.8% to 68.2%) indicative of health gains achieved for PLWHA receiving ART . This is called the "Lazarus effect" by many PEPFAR programme managers. Though encouraging, this result (68.2%) is lower than the 85% fit to work reported by Libamba *et al.*(2006). The longer study period and the larger sample size in their study might account for the difference.

CD4 cell count

CD4 cell count is the best proxy of ART effectiveness in resource poor settings. We have analysed in two ways to obtain the most accurate reflection. Using the available dataset at each encounter, we had a median cell count increase of 158 and 206 cells/µL at 6 and 12 months, respectively. The gains for clients who had CD4 counts done at both 6 and 12 months were very similar - 136 and 217 cells/µL, respectively. Although these results differ from some published studies (Laurent *et al.,* 2002; Gallant, 2003) that reported a lower increase of about 85 cells at 6 months, they are consistent with those of the MSF cohort (2004) in Khayelitsha which found a similar increase of 133 and 221 at 6 and 12 months, respectively. It is argued that in general, most patients on potent regimens and with good adherence will achieve a successful CD4 count response in the course of time. By 24 months close to 90% of patients on ART had a CD4 cell count above 200 cells/µl.

These findings accord with our earlier observations which showed significant gain in weight and improvement in functional status over time.

There is a major limitation in these findings in that the impact of adherence level on all these CD4 cell count responses were not evaluated.

Adherence

Adherence is critical to the success of any ART programme. Our results are based on self-reported adherence and a once-off measurement enquiring on a 28-day medication supply. Most patients (76.7%) had an adherence rated as good by WHO standards and this dataset suggested a highly statistically significant association between adherence level and outcome. Those who died were twice more likely to have fair or poor self-reported adherence. (OR: 2.4, 95% CI: 1.17-5.28, p-value=0.008). The lack of validation with other adherence measurement method and viral load assay testing and a correlation study to CD4 cell count response are major limitations in interpreting these findings.

Treatment outcome

The cumulative treatment outcome indicated retention in care of 69% (those alive and on ART at the analysis time). The observed attrition rate of 31% is mainly driven by a relatively high mortality on ART of 23.5% (This mortality represents 75.8% of the total attrition). Although this mortality is comparable to that found by Ferradini *et al.* who reported 19%, it would seem to be relatively higher than most studies have reported. The ART-LINC cohort indicated a mortality of 4% while Libamba *et al.* (2006) had 8% in their study. It is possible that some of the studies that reported lower mortality had a higher loss to follow up as many patients would die at home without being reported as such. Active defaulter tracing and closer follow up could explain a relatively high reported death on ART.

The cumulative retention in care of 69% (mean duration 16.5 month) observed in this study was above the gloomy 60% reported recently by Rosen (2007). In his systematic review of 32 publications in 13 African countries, he found that “since the inception of large-scale ART access early in this decade, ART programs in Africa have retained about 60% of their patients at the end of 2 years”. Compared to the 80% reported in the west for the same duration, Africa has still a lot to do in improving its model of care.

Mortality on HAART is higher in males than in females. Our results showed that 29.9% of males died as compared to 20.6% of females. The odds of dying was 1.87 times greater among males as compared to females. This was supported by the KM survival analysis which indicated at 24 months better survival amongst females as compared to males with a high level of statistical significance when stratified by CD4 cell count group (cum survival of 0.71 vs. 0.55, log rank, p-value=0.029) and the Cox regression model which showed male gender associated with shorter survival (OR: 2.30, 95% CI: 1.19-4.43, p-value=0.01). According to Collazos *et al.* (2007), for the past 2 decades there are conflicting findings on the difference between men and women in their response to HIV infection and treatment.

In general, with only death events accounted for, the Kaplan-Meier probability of survival was 0.75 at 24 months. This is below the 0.81 reported by Ferradini, 2006, for the same duration. Cumulative survival appears lower in Nyangana cohort and factors such as rural population, unemployment, food security, advanced/severe disease at treatment initiation and the TB burden might account for this.

In addition, as per the Table 14, the Cox regression analysis showed that patients with lower body weight and functional status of ambulatory or bedridden were less likely to survive. This is similar to Moore *et al.* (2007) whose recent study outlined that low CD4 cell count, low body weight, TB and anaemia were major risk factors for death after ART commencement.

More than 60% died within the first 3 months and close to 80% within the first 6 months of initiating ART. This is a common feature reported in several studies in African cohorts as cited by Laurent *et al* (ref). They argued that death and loss to follow up tend to happen in the first 6 months of ART commencement. Factors such as cut off CD4 cell count for treatment initiation, patients presenting at ART clinic with advanced to severe disease, multiple co-morbidity amongst most patients and earlier immune reconstitution inflammatory syndrome are cited as possible explanation for this prevailing situation (Laurent *et al.*, 2006).

The main causes of death in our cohort were TB with 37.9% and gastroenteritis with 18.2% of cases). The proportion of unknown causes of death is relatively high

(13.6%). Most likely related to the fact that more than 25% were reported to have died at home making it difficult to accurately account for their cause of death. Nonetheless, TB is the leading cause of death of PLWHA world wide. Our findings are in agreement with this reality. On the other hand, it is not surprising that gastroenteritis comes second as in this rural setting, limited access to safe drinking water, poor sanitation and poor food hygiene contribute to water borne diseases in PLWHA.

Chapter 5. Conclusions and recommendations

5.1. Conclusion

The Namibian country driven process of scaling up ART programme in view of achieving universal access to ART for those who need it is well underway and the Nyangana District ART coverage of 46% is indicative of those efforts. However, this access to ART is characterised by poor male involvement as demonstrated by the low percentage of men enrolled in ART care. Not only is their accessibility to treatment limited but men also present with unfavourable baseline profile (advanced disease, lower CD4 cell count) resulting in poor treatment outcome (higher mortality, shorter cumulative survival). In a multivariate analysis, mortality was associated with male gender, low baseline weight and poor baseline functional status. The clinical response to ART observed through weight gain and improved functional status as well as the immunological response observed through CD4 cell count gain, comparable to findings in other similar settings, were indicators of a successful ART treatment programme. High quality ART services can be implemented in a rural setting in Namibia despite several challenges ranging from socio-economic dynamics to data management issues at the ART site.

5.2. Recommendations

Based on the findings in this study, the followings are some of our recommendations:

- Consider replicating the study in other faith-based ART sites in a multi-center analysis to allow comparability between these sites and consider national cohort analysis
- Considerable efforts need be applied to increase male participation. Formulate behavioural change communication strategies and design incentives that will go to the root of why men do not come or ultimately come late to the ART clinic
- Consider review of the optimal cut off CD4 cell count for treatment initiation to allow earlier initiation that is likely to reduce the mortality rate on HAART. Alternatively, an improved pre-ART monitoring and care might also result in

timely treatment initiation as patients followed up regularly can be started as the declining CD4 cell approaches the cut off point.

- Further analysis on this dataset can be done to explore other factors associated with mortality on HAART in order to devise strategies to improve survival of PLWHA initiating HAART in Nyangana
- Strengthen data quality to minimise missing values and allow use of simple clinical parameters such weight, functional status and WHO stage to monitor patient progress on ART
- Increase use of viral load testing opportunities to ensure monitoring of therapy, validation of adherence and timely therapy switch when required
- Improve adherence monitoring activities
- Improve TB/HIV collaborative activities in order to decrease TB-related morbidity and mortality among PLWHA attending ART care

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Annexure A

Data abstraction tool

The following were extracted from patients records (individual files and various registers)

Record No. _____

1. Date of birth_____
2. Age at HAART initiation (years) _____
3. Sex: M = 1 F=2
4. Date of HAART initiation _____
5. Quarter initiated (from August 2004): Q1=1, Q2=2, Q3=3, Q4=4, Q5=5, Q6=6, Q7=7, Q8=8
6. Pregnancy status: N/A=0 Yes=1 No=2
7. Marital status:
   - Single=1
   - Married=2
   - cohabiting=3
   - Divorced=4
   - Widow(er)=5
8. Employment: Employed=1 Unemployed=2
9. Weight (Kg)_____
10. Weight at 6, 12, 18, 24 months:_____
11. Height (m)_____
12. TB status: Yes=1 No=0
13. Baseline WHO Clinical Stage : Stage 1=1, stage 2=2, Stage 3=3, Stage 4= 4
14. WHO clinical stage at 6, 12, 18, 24 months
15. Baseline functional status:
    - Working=1
    - Ambulatory=2
    - Bedridden=3
16. Functional status at 6, 12, 18, 24 months
17. HAART regimen prescribed at start up:
    - D4T/3TC/EFV = 1

- D4T/3TC/NVP = 2
- AZT/3TC/NVP= 3

18. Therapy substitution: Yes=1 No=0
19. Therapy switch: Yes=1 No=0
20. Adherence level:
    - Good=G
    - Fair=F
    - Poor=P
21. Baseline CD4 cell count (cells/µl) _____
22. CD4 cell count at 6, 12, 18, 24 months_____
23. Duration on treatment by April 2007 (month)_____
24. Outcome by April 2007:
    - Alive=1
    - Died=2
    - Lost to follow up=3
    - Transferred out=4
25. If died, duration on treatment by the time of death event_____
26. If died, cause of death
    - TB=1
    - GE=2
    - Pneumonia=3
    - Anemia=4
    - Meningitis=5
    - Hepatitis=6
    - Others=7
    - Unknown=8
27. if died, place of death: Hospital=1, Home=2