

**Adherence to Antiretroviral Therapy by
HIV Infected Patients in Rural
UMkhanyakude District, South Africa.**

By

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Declaration

I Italia Nokulunga Mthiyane declare that:

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Dedication

This work is dedicated to my late parents especially my mother whose inspiration and unconditional love have brought me to where I am today.

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List of acronyms

ABC	: Abacavir
ADRs	: Adverse drug reactions
AIDS	: Acquired immunodeficiency syndrome
ART	: Antiretroviral therapy
ARVs	: Antiretroviral drugs
AUC	: Area under curve
AZT, ZDV	: Zidovudine
CBO	: Community based organizations
DHHS, IAS-USA	: Department of Health and Human Services, International AIDS Society of United States of America
DoH	: Department of Health
d4T	: Stavudine
ddI	: Didanosine
DOT	: Directly Observed Treatment
DOTS	: Directly Observed Treatment Short course
DSA	: Demographic Surveillance Area
EFV	: Efavirenz (Stocrin)
FBC	: Full blood count
FBO	: Faith based organizations
GI	: Gastro Intestinal
HAART	: Highly active antiretroviral therapy
HIV	: Human immunodeficiency virus
IEC	: Information, education and communication
KZN	: KwaZulu-Natal
3TC	: Lamivudine
LFT	: Liver function test
LPV	: Lopinavir
LPV/r	: Lopinavir/ritonavir
MCC	: Medicines Control Council
MTCT	: Mother-to-child transmission of HIV

NGO	: Non-governmental organization
NNRTIs	: Non-Nucleoside Reverse Transcriptase Inhibitors
NOK	: Next of kin was anyone selected by the patient as a first contact person
ALT NOK	: Alternative next of kin was anyone selected by the patient as a second contact person
NRTIs	: Nucléoside Reverse Transcriptase Inhibitors
NSP	: National Strategic Plan
NVP	: Nevirapine
OIs	: Opportunistic infections
OVC	: Orphans and Vulnerable Children
PCR	: Polymerase Chain Reaction
PEPFAR	: President's Emergency Plan for AIDS Relief
PEP	: Post exposure prophylaxis
PHC	: Primary Health Care
PIs	: Protease Inhibitors
PMTCT	: Prevention of mother-to-child-transmission
PLWHA	: People living with HIV/AIDS
RTV	: Ritonavir
Regimen 1a	: Stavudine, Lamivudine and EFV
Regimen1b	: Stavudine, Lamivudine and NVP
Regimen 2	: AZT, ddI, lopinavir/ritonavir
SMS	: Short message system
STD	: Sexually transmitted disease
STI	: Sexually transmitted infection
TAC	: Treatment Action Campaign
TB	: Tuberculosis
VCT	: Voluntary counseling and testing
VL	: Viral load
WHO	: World Health Organization

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Summary of the study

The background

HIV and AIDS is a huge problem in sub-Saharan Africa where an estimated 22.5 million people were living with HIV in 2007.¹ South Africa has the worst epidemic in the world.¹ There were about 5.5 million people living with HIV and 1000 AIDS deaths daily in South Africa by the end of 2005.¹⁷ In 2007 the number of people living with HIV in South Africa increased to 5.7 million.¹

The HIV prevalence in Umkhanyakude district, KwaZulu Natal, where Hlabisa sub-district is situated, amongst public antenatal clinic attenders was 39.8% in 2007.¹⁹ AIDS is the cause of 50.0% of deaths in the Hlabisa sub-District.¹⁵

In 2003 the South African government decided to provide antiretroviral therapy (ART) in the public health sector, giving hope to thousands of people who are in need of this intervention to improve their quality of life and reduce premature deaths.^{7,13} However adherence to antiretroviral drugs is essential for successful treatment.

Adherence to antiretroviral therapy in South Africa as in other African countries was expected to be low³¹ (<95.0%), however, in a study that was done in Cape Town during 1996 – 2001, the authors concluded that adherence was high.²⁸ The aim of that study was to identify predictors of low adherence (<95.0%) and failure of viral suppression (>400 HIV copies/mm³). Pill counts and records of treatment refills from pharmacy were used to measure adherence.²⁸ The results revealed no significant difference in adherence between patients on protease inhibitor based regimens and/or those on non-nucleoside based regimens nor with socioeconomic status, sex and HIV stage.

Independent predictors of low adherence were English language speaking, age, and three times per day dosing. The following were found to be independent predictors of failure of viral suppression: baseline viral load, <95.0% adherence, age and dual nucleoside therapy.²⁸ This study however was done in an urban area before the antiretroviral therapy (ART) roll out in South Africa when the cost of treatment limited

the accessibility of ART. These patients may have been different to patients who access free treatment in public health facilities today.

Other South African studies have also reported good adherence rates.^{39,40} In another study in Soweto, South Africa, adherence was high, 88.0% of patients achieved > 95.0% goal, 9.0% achieved 90.0-95.0% adherence and only 3.0% achieved <90.0%.³⁹ In a study done at Khayelitsha, adherence was also high, viral load level was < 400 in 88.1%, 89.2%, 84.2%, 75% and 69.7% of patients at 3, 6, 12, 18 and 24 months.⁴⁰ However, Soweto and Khayelitsha are urban and different from Hlabisa, and it is difficult to generalize these results to the sub-district. This study intended to assess how adherent patients are to antiretroviral therapy in a typical rural district in order to inform policy to enhance adherence to ART.

1.5. Aim of the study

To determine the extent of adherence and factors influencing adherence amongst HIV infected adults after one year of antiretroviral therapy in a rural area.

1.6. Specific Objectives

1. To describe the socio-demographic characteristics of HIV infected patients on antiretroviral therapy.
2. To describe persons that patients considered as confidante and disclosed their HIV positive status to.
3. To describe baseline, sixth months' and twelve months' VL and CD4 results.
4. To describe adherence of patients to antiretroviral therapy and follow up appointments.
5. To describe symptoms and side effects experienced by patients.
6. To describe rate of and reasons for changing regimen among patients on ART in the district.
7. To analyze associations between adherence, disclosure, socio-demographic characteristics, symptoms and side effects experienced and CD4 and VL results 12 months after initiating antiretroviral therapy.
8. To make recommendations to relevant stakeholders about the findings.

Methodology

The study was a retrospective cohort study involving a review of records of patients on antiretroviral therapy for the first twelve months of their treatment to obtain information about each patient's socio-demographic profile, treatment support, disclosure, laboratory blood results, dose adherence, symptoms and the side effects experienced. The population was 290 treatment naïve patients enrolled in the ART programme during the period 1 September 2004-31 August 2005. All records of these patients were sampled to reduce bias, however, 18 of them were excluded because they were children. Their adherence to any treatment including ART is dependent on an adult care giver and they are a different group with a different recording system of laboratory results particularly the CD4 count. The patients who had previously been exposed to antiretroviral treatment including post exposure prophylaxis (PEP) and single dose nevirapine, and those who had been started ART at private facilities were excluded from the study.

Adherence to ART was defined as >95.0% adherence which meant not missing more than three doses of ART per month.^{13,14} All patients who came every 30 days were considered to be appointment/attendance adherent. Follow up appointments were scheduled every 28 days and patients received treatment supply for 30 days each month. In addition each patient had received 30 days supply of ARVs at the two week follow up visit after initiation of ART. After initiation of ART patients were required to visit the clinic after two week's. Thereafter they were required to visit the clinic every 28 days. They were allowed to come anytime if they were ill or experiencing side effects.

The strength of a retrospective study is that it is easier to do, however, records are often incomplete and thus recording was a huge challenge. Patients with missing data might have been different from those whose data was available. A possible bias was whether the patients reported their adherence accurately because they may lie to avoid being scolded.

This study was conducted at all ART clinics within the Hlabisa health sub-district of Umkhanyakude District, KwaZulu-Natal Province. KwaZulu-Natal is divided into 11

Districts, one of which is Umkhanyakude which borders Mozambique. ART was started at Hlabisa Hospital in September 2004 and records of patients starting treatment between 1 September 2004 and 31 August 2005 were reviewed.

STATA version 9 was used to analyze the data. A univariate analysis was done for patients' socio-demographic data and the description of adherence reported by patients. A bivariate analysis was done to determine the associations of adherence and retention with possible determinants including disclosure, signs and symptoms experienced and treatment support. Data was stratified to compare adherence and retention of patients of different age groups. Poisson regression analysis was undertaken to develop a model of determinants predicting treatment adherence and keeping appointments and lack of adherence by patients on ART. Incidence Rate Ratios and Standard Errors are reported for univariate and multivariate analyses with statistical significance $p < 0.05$.

The primary outcome measures were treatment and appointment/attendance adherence. Treatment adherence was defined as $>95.0\%$ adherence and attendance adherence was defined as coming every 30 days for follow up visits. Patients who were ever $<95.0\%$ adherent and those who ever failed to attend follow up visits (within 30 days from last visit) were considered dose non-adherent and attendance non-adherent respectively.

Results

A total of 272 records of HIV infected patients aged >15 years were reviewed. Of these 87 (32.0%) were men and 185 (68.0%) were women. However, due to missing data the number of patients did not always add up to 272 (100%). The mean age at initiation of ART was 40 years (SD 7.8) in males and 38 years (SD 8.7) in females with a range of 15-70 years. These patients were predominantly single (60.0% males and 76.0% females), unemployed (76.0% males and 89.0% females, rural ($>95.0\%$) and with primary school (40.0%) or high school ($>20.0\%$) education.

The mean baseline CD4 count was 102 cells/mm³ and 112 cells/mm³ in males and females respectively. The majority of patients (53%) had baseline viral loads ranging

between 50000-400000 copies/ml. After six months of ART the mean CD4 count was 208.2 cells/mm³ (SD 107.7) in males and 255.1 cells/mm³ (SD 136.8) in females.

The 12 months CD4 count mean in males was 295.4 cells/mm (SD 177.3) and 335.9 cells/mm³ (SD 169.9) in females.

At six months the majority of viral loads for both male (95.2%) and female (94.7%) patients were <25 copies/ml.

At 12 months 98.3% of males and 99.9% females had viral loads <25 copies/ml.

A total of 86.0% of patients never missed a follow up visit although 6.0 % of these came before 28 days or within 30 days (2 days late) for their.

Up to 70.0% of patients were always adherent to ART and a total of 18.0% missed one to three doses during the period with 12.0% missing more than three doses during the period.

Summary, conclusion and recommendations

A total pill/dose adherence of 87.0% and 86.0% attendance adherence were achieved.

At 6 months 95.7% of males and 94.0% of females had achieved viral suppression and at 12 months 98.0% of males and 99.0% of females achieved viral suppression. The number of patients for which results were available varied considerably due to missing data especially at twelve months. The viral load results particularly affected because association of overall adherence >95.0% was based on 162, 178 and 144 viral load results at baseline, six months and twelve months respectively.

Dose or treatment adherence by patients who started ART in the first year of ART rollout was high in Hlabisa sub-District; however, qualitative studies would be helpful to explore the influence of gender, stigma and discrimination, on non-adherence.

Symptoms and side effects and adherence: Only fatigue was associated with non-adherence.

Adherence to ARVs and appointments: The higher the educational standard especially high school or matriculation, being employed, being female and single, and a CD4 count >50 cells/mm³ increased the probability of missing ART doses.

Decentralization of the ART programme to local clinics through task shifting from doctors to nurses and counsellors benefitted adherence to appointments and ARVs. Unemployment benefitted adherence to appointments.

Disclosure: No association was found between disclosure and adherence to ARVs.

Adherence was found to be a predictor of viral suppression.

No association was found between loss to follow up and the demographic characteristics of age, sex, marital status, employment status and level of education.

Recommendations

Monitoring adherence

In this study adherence was based on recall of taking medications in the past seven days which means that memory of medicine intake was likely to be good.

While a seven-day recall may be advantageous for on the spot individual patient counselling, it may not be very useful for long-term adherence monitoring. One month recall using a visual analogue scale and routine pill counts is recommended.

Counselling

Due to the probability of patients with higher educational levels missing a follow up visit, it is recommended that more emphasis be placed on adherence counselling of the more educated group of patients who seem to be neglected because they are believed to have more knowledge and to understand the importance of adherence to ART. More time needs to be spent on adherence counselling of this group to ensure that they are equipped with the knowledge that missing ART doses can lead to disease progression and that they need to take ART doses as prescribed for the rest of their lives.

Side effects

Although some patients experienced side effects, most of these side effects were not a barrier to adherence, except for fatigue. Information on how to manage this symptom needs meticulous attention.

Tracking

Although only 12.0% of patients were not adherent to ART, other recommendations include strengthening the tracking system of patients who have missed a follow up visit

and putting in place referral systems using home based care organizations and community health workers who can assist to reduce this problem.

Improving access to VL lab results

A limitation of this study was the lack of VL results. In order to monitor the effectiveness of the ART programme timeous access to VL results is extremely important and these systems need to improve. There was no association between adherence and baseline and six months viral load results, however, at 12 months non-adherence was associated with failure of viral suppression. These findings were based on available data only where viral load results and adherence data were available. At baseline calculations were based on 60% of the sample, 65% at six months and 53% at 12 months. The data that was missing could be that of patients who were not adherent to appointments and ART.

Chapter One

Introduction

1.1. Background of the study

In 2007, 33 million people worldwide were living with HIV or AIDS, with about 2.7 million new HIV infections and 2 million AIDS related deaths.¹ Of these 22 million lived in Sub-Saharan Africa, where 1.9 million of the new HIV infections and 75.0% of AIDS deaths occurred. This region in 2007 was also home to 67.0% of all people and almost 90.0% of children living with HIV, with Southern Africa sharing a large proportion of the total AIDS burden namely, 35.0% of the infections and 38% of AIDS deaths in 2007.¹ Between 2000 and 2015, life expectancy at birth in Southern Africa was expected to decrease from 43 years to 36 years.² Factors responsible for the high rate of HIV include poverty and social instability, high levels of sexually transmitted infections, sexual violence, and the low status of women, high mobility and lack of access to antiretroviral drugs (ARVs).³

South Africa has the largest number of people living with HIV in the world³ and life expectancy (without treatment) fell to 50 years for males and 53 years for females in 2004⁴ In 2008 this estimate increased to 53.3 years for males and 57.2 years for females.⁵ The HIV national prevalence rate amongst antenatal clinic attendees grew from 0.7% in 1990 to 30.2% in 2005.⁶ However, according to the antenatal survey estimates, the national HIV prevalence was 29.1% in 2006 and 28.0% in 2007⁶ suggesting the stabilizing of the epidemic. In 2005 an estimated 5.5 million people were living with HIV in South Africa. They comprised 18.8% of the adult population (15-49 years) with women accounting for about 55.0% of the HIV positive people. Women most affected were aged 25-29 years while an estimated 10.0% of males were older than 50 years.⁷

The South African government responded to the epidemic with the HIV/AIDS and STD Strategic Plan for 2000 – 2005.³ In 2003 the government adopted the Operational Plan for Comprehensive HIV and AIDS Treatment and Care. Provision of antiretroviral therapy (ART) in the public sector was included in this plan. By the beginning of 2005, about 30 000 patients

were receiving treatment in public sector, at the end of March 2006 134000 and at the end of 2006 283000-363000 South Africans were receiving ART at the public clinics in South Africa. In 2007 the South African government responded with the HIV/AIDS and STI National Strategic Plan (NSP) 2007 – 2011 for prevention; treatment, care and support; research, monitoring and evaluation; and human and legal rights.⁷

Antiretroviral treatment reduces morbidity and mortality associated with AIDS defining illnesses,^{8,9} however success of antiretroviral treatment depends on adherence to treatment. With incomplete adherence the drug levels become so low that the regimen is rendered ineffective with emergence of drug resistant strains of HIV.¹⁰ What is worse is that HIV strains that are resistant to one drug in a class are often resistant to other drugs of the same class.¹¹ With limited drug regimens available in the public health facilities, those patients that have developed resistance have limited chances of treatment and survival because of the destruction of the immune system with resultant opportunistic infections.

Measures of adherence vary from self reports, pill counts, doctor/health care worker prediction, to electro-monitoring system (EMS). The accuracy of these methods alone is not known and the levels of adherence have been used in conjunction with the virological and immunological responses to treatment.¹² In their study, Paterson and colleagues used doctor assessments, MEMS and patient self reports to measure adherence. They interpreted the results in conjunction with virological and immunological response to antiretroviral treatment and factors that affect adherence like demographic characteristics, medications, alcohol/substance abuse, health beliefs etc¹². In this study the researcher measured adherence using recorded patient self reports and the results were interpreted in conjunction with virological and immunological responses to antiretroviral treatment and considered the association of demographics, socioeconomic factors, disclosure and support, and symptoms and side effects.

1.2. Assumption

HIV infected patients who are on antiretroviral therapy have been counselled as per Department of Health (DoH) protocol about adherence to ARVs and coming to the clinic regularly.^{13,14}

1.3. Background of the study area

Hlabisa is a rural sub-District of Umkhanyakude District in northern KwaZulu Natal. It has a population of more than 220 000.¹⁵

The ART program started at Hlabisa Hospital in 2004. The first patients were initiated in September 2004. The program gradually rolled out to the rest of the fourteen of the sub-district clinics during 2005-2006. Today there are more than 7000 patients on antiretroviral therapy in the sub-district.

1.4. Research Questions

How adherent to antiretroviral therapy are HIV infected patients in the Hlabisa sub-District?

Is adherence among patients on antiretroviral therapy who experience symptoms and side effects different from those who do not?

Is adherence to antiretroviral therapy associated with demographic and socioeconomic characteristics, disclosure, social support, CD4 and viral load (VL) results?

Does adherence decrease/increase over time?

1.5. Aim of the study

To determine the extent of adherence and factors influencing adherence amongst HIV infected adults after one year of antiretroviral therapy in a rural area.

1.6. Specific Objectives

1. To describe the socio-demographic characteristics of HIV infected patients on antiretroviral therapy.
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5. To describe symptoms and side effects experienced by patients.
6. To describe rate of and reasons for changing regimen among patients on ART in the district.

7. To analyze associations between adherence, disclosure, socio-demographic characteristics, symptoms and side effects experienced and CD4 and VL results 12 months after initiating antiretroviral therapy.

8. To make recommendations to relevant stakeholders about the findings.

1.7. Summary

This chapter laid the foundation for the study in terms of background, aim and objectives, the following chapter will present the literature review relevant to the objectives of the study.

Chapter Two

Literature Review

Introduction

This section provides a description of factors that affect adherence to antiretroviral treatment. These factors are approached from psychosocial, patient, health system, regimen and cultural perspectives with scientific evidence provided from a global and local, rural and urban point of view. Before the presentation of factors that affect adherence, the prevalence of HIV and AIDS, antiretroviral therapy coverage, from a global and local point of view, the goals of ART, level of adherence and effect of adherence are presented. At the end, adherence in other chronic diseases like hypertension, diabetes mellitus, asthma and epilepsy and a relevant theoretical framework are presented.

The process of initiation of ART.

Treatment readiness training is a series of activities done from the screening visit to the antiretroviral (ARV) drug initiation visit. A multidisciplinary team is involved in the assessment of the patients to decide whether the patient should be started or delayed for a later date. Treatment readiness criteria include patient's acceptance of HIV positive status and ARVs, meeting medical criteria, absence of depression, adherence to prescribed treatment like cotrimoxazole and attendance at all scheduled visits before initiation of ART. At the first screening visit the following are done: CD4, FBC, LFT and Hepatitis B blood specimens are taken, treatment of opportunistic infections (OIs), WHO staging (1-4), TB screening, patient counselling, cotrimoxazole is given, patient information records are filled and the patient is given a return date. If the patient presents with CD4 results <200 cells/mm³, cotrimoxazole is started.^{13,14}

Patient literacy sessions start at the second visit and the first one covers stigma, disclosure and identification of a treatment supporter and positive living. At the third visit patient training covers basics of HIV, mother-to-child transmission of HIV (MTCT), treatment of opportunistic infections (OIs), HIV care and treatment and involvement of Community Based Organizations (CBOs) and Non Governmental Organizations (NGOs). The treatment counsellor or CBO

should visit the patient at home to check conditions at home, disclosure of HIV status to at least any one person who may be a family member and support structure, and facilities for drug storage.^{13,14}

At the fourth visit the patients with CD4 count less than 200 cells/mm³ are seen by the doctor to determine the stage of disease according to the WHO criteria and receive cotrimoxazole prophylaxis if the patient is not already on this. Adherence training is done at the fifth visit and the patient is started on ARVs at the sixth visit. Counselling at this visit covers ARVs and how to take them properly, side effects, drug resistance, drug interaction, monitoring and making the treatment plan, Bactrim pill count, and answering the patient's and treatment supporter's questions. The multidisciplinary team should meet before the initiation visit and make a decision to start treatment based on the patient's acceptance of a positive HIV status, absence of active depression and understanding of the meaning of taking treatment properly.^{13,14}

At the initiation visit treatment readiness is reassessed, and a cotrimoxazole count is done to monitor adherence to the treatment. ARVs are issued and it is discussed how they are taken and the expected side effects, then adherence is discussed with the patient and the treatment supporter, and written instructions are provided on the doses of the medications and how to take them.¹³

2.1. HIV and AIDS: Prevalence of disease

2.1.1. HIV and AIDS – the global situation

There was a global increase of 21.0% in the prevalence of HIV especially in East and Central Asia and Eastern Europe between 2004 and 2006. There was also a global increase in prevalence among women aged 15 years or older and this increased by one million from 2004 to 2006.¹⁶ High risk behaviour such as sex for financial gain, injecting drug use and sexual intercourse without a condom was reported in Sub-Saharan Africa, Asia, Eastern Europe and Latin America.¹⁶

Table 2.1. Comparison of Regional HIV Statistics (2006, 2007)^{1, 16}

Geographical Region	Prevalence		Incidence		AIDS Deaths		Adult Prevalence (%)	
	2006	2007	2006	2007	2006	2007	2006	2007
Sub-Saharan Africa	24.7m	22.5m	2.8m	1.7m	2.1m	1.6m	5.9	5.0
South & South								
East Asia	7.8m	4.0m	860000	340000	509000	270000	0.6	0.3
East Asia	750000	800000	100000	92000	43000	32000	0.1	0.1
Latin America	1.7m	1.6m	140000	100000	65000	58000	0.5	0.5
North America	1.4m	1.3m	42000	46000	18000	21000	0.8	0.6
Western & Central	740000	760000	22000	31000	12000	12000	0.3	0.3
Europe								
Eastern Europe &	1.7m	1.6m	270000	150000	84000	5000	0.9	0.9
Central Asia								
Middle East &	46000	380000	68000	35000	36000	25000	0.2	0.3
North Africa								
Caribbean	250000	230000	27000	17000	19000	11000	1.2	1.0
Oceania	81000	75000	7100	14000	4000	1200	0.4	0.4

Table 2.1. shows regional statistics in 2006 and 2007. The prevalence of HIV/AIDS in the Sub-Saharan Africa (5.0-5.9%) remained the highest in the world while it was lowest in East Asia (0.1%).

Table 2.2. Global summary of HIV and AIDS epidemic, 2006 and 2007^{1, 16}

		2006	2007
Number of people living with HIV	Total	39.5 million	33.2 million
	Adults	37.2 million	30.8 million
	Women	17.7 million	15.4 million
	Children <15 years	2.3 million	2.5 million
New HIV infections	Total	4.3 million	2.5 million
	Adults	3.8 million	2.1 million
	Children <15 years	530 000	420 000
AIDS deaths	Total	2.9 million	2.1 million
	Adults	2.6 million	1.7 million
	Children <15years	380 000	330 000

This table shows a 6.0% reduction in the estimated number of people living with HIV from 39.5 million in 2006¹⁶ to 33.2 million in 2007.¹ One major reason for a change in the global HIV estimates was lowering of India's HIV estimates and countries in the Sub-Saharan Africa such as Angola, Kenya, Mozambique, Nigeria and Zimbabwe some of which have lower estimates than previously reported. In Kenya and Zimbabwe there was a reported reduction of new infections due to a reduction in risky behaviour.¹

2.1.2. HIV and AIDS in Sub-Saharan Africa

In 2007 Sub-Saharan Africa had the most people living with HIV with 68.0% (22.5 million) of the total 33.2 million HIV infections in the world. Sub-Saharan Africa also accounted for 75.0% (1.6 million) of AIDS' deaths in 2007. In 2007 the majority (61.0%) of people who were living with HIV in this region were women.

Southern Africa is the hardest hit of countries in Sub-Saharan Africa accounting for 35.0% of all people living with HIV and 32.0% of all new infections in 2007.¹

2.1.3. HIV and AIDS in South Africa

South Africa has the worst AIDS epidemic in the world.¹ An estimated 4.7 million in 2001,¹ 5.5 million in 2005, and 5.7 million in 2007¹ people were living with HIV. About 1000 AIDS' deaths occurred daily in South Africa in 2005.¹⁷ About 29.0% of pregnant women were HIV positive in 2005 and 30.0% in 2006.¹⁶ There are many factors which worsen the AIDS' epidemic in South Africa and the government is sometimes blamed for not responding sufficiently.¹⁸

2.1.4. HIV in KwaZulu-Natal (KZN)

The antenatal prevalence of HIV in South Africa amongst women attending sentinel site clinics varies from province to province with some provinces more affected than others.

Table 2.3. HIV Prevalence, National antenatal survey 2002 – 2007^{6,7,19}

Province	2002	2003	2004	2005	2006	2007
KwaZulu-Natal	36.5	37.5	40.7	39.1	39.1	37.4
Gauteng	31.6	29.6	33.1	32.4	30.8	30.3
Mpumalanga	28.8	32.6	30.8	34.8	32.1	32.0
Free State	28.8	30.1	29.5	30.3	31.1	33.5
Eastern Cape	23.6	27.1	28	29.5	28.6	26.0
North West	26.2	29.9	26.7	31.8	29.0	29.0
Limpopo	15.7	17.5	19.3	21.5	20.6	18.5
Northern Cape	15.1	16.7	17.6	18.5	15.6	16.1
Western Cape	12.4	13.1	15.4	15.7	15.1	12.6
South Africa	26.5	27.9	29.5	30.2	29.1	28.0

KwaZulu-Natal had the highest antenatal prevalence throughout. This table also shows that the national antenatal HIV prevalence increased from 2002 to 2004. In 2006 prevalence showed a decline although KZN remained the province with the highest HIV prevalence, facing the challenge of ART roll out with a subsequent challenge of life long dose and appointment adherence.

In KwaZulu-Natal HIV prevalence varies from district to district (Table 2.4). In 2006 Amajuba had the highest prevalence (46.0%) while Umzinyathi had the lowest prevalence (27.9%). In 2007 eThekweni had the highest HIV prevalence (41.6%) and Umzinyathi remained the district with the lowest HIV prevalence (31.7%) although it showed a 4.0% increase from the previous years. The Provincial antenatal HIV prevalence increased between 2002 and 2006 (Table 2.4) and the antenatal prevalence for each of the eleven districts in KwaZulu-Natal is shown below.

Table 2.4. Antenatal survey results 2002, 2006 and 2007 for KwaZulu-Natal Districts^{6,19}

District	HIV Prevalence 2002 (%)	HIV Prevalence 2006 (%)	HIV Prevalence 2007 (%)
Amajuba	37.0	46.0	39.4
Sisonke	31.0	31.9	34.1
Ugu	44.0	38.9	37.3
UMkhanyakude	30.0	36.3	39.8
UMzinyathi	20.0	27.9	31.7
UThukela	42.0	35.1	36.3
UThungulu	43.0	34.6	36.0
Zululand	40.0	36.9	34.7
EThekweni	39.0	41.6	41.6
ILembe	37.0	39.1	39.1
UMgungundlovu	41.0	44.4	40.8

UMkhanyakude District had the third highest antenatal prevalence in Kwa-Zulu Natal in 2007.

2.1.5. HIV and AIDS in Hlabisa Sub-District.

Life expectancy in the Demographic Surveillance Area (DSA) was 47 years in 2000, the lowest in South Africa. AIDS is the main cause of 50.0% of all deaths for men and women.¹⁵ Deaths from AIDS are highest between 15 and 44 years.¹⁵ The HIV antenatal prevalence in UMkhanyakude district, where Hlabisa sub-district is situated, is high (39.8% in 2007).⁶ The area has an infant mortality rate of 7.4 % and a child mortality rate of 10.6 %.¹⁵

Summary

As described above HIV and AIDS are huge problems in Sub-Saharan Africa. South Africa has the worst epidemic in the world. KwaZulu Natal is the hardest hit province. AIDS is the cause of 50.0% of deaths in the Hlabisa sub-district.¹⁵ The whole region including the Hlabisa ART programme is faced with the challenge of scaling up antiretroviral treatment with its challenges that include adherence to treatment and follow up appointments.

2.2. Antiretroviral Therapy (ART)

2.2.1. Antiretroviral therapy – the global situation

Antiretroviral treatment coverage increased four times (7.0%-24.0%) in low and middle income countries between December 2003 and June 2006.¹ The ART coverage increased by 45.0% in 2007.¹ An estimated two million years of life were gained since 2002 in low and middle income countries.²⁰ About 3 million people (31.0% coverage) in low and middle income countries were on ART in 2007.¹

Table 2.5. Estimated Global ART coverage in 2006¹

Geographical region	Estimated number of people receiving ART, June 2006	Estimated number of people needing ART, June 2006	ART coverage, June 2006 (%)
Sub-Saharan Africa	1.040000	4600000	23.0
Latin America And Caribbean	345000	460000	75.0
East, South East Asia	235000	1440000	16.0
Europe and Central Asia	24000	190000	13.0
Middle East and North Africa	4000	75000	5.0
Total	1650000	6.8 million	24.0

2.2.2. Antiretroviral therapy (ART) in South Africa

In 2003 the South African government decided to provide ART in the public health sector giving hope to thousands of people who are in need of this intervention to improve their quality of life and reduce premature deaths.¹³ However, there are challenges such as lack of infrastructure and ensuring treatment literacy of patients to ensure adherence and to prevent the occurrence and spread of drug resistant strains of HIV. A total of 179 public health facilities in 2005¹, 231 in 2006²⁰ and 362 in 2007¹ were accredited for HIV and AIDS related services. About 32 060 children <15 years were receiving ART in September 2007. The table below shows the estimated number of people who were receiving ART, and number of people who needed ART in 2005-2007.

Table 2.6. Estimated ART coverage in South Africa, 2004 - 2007¹

	2004	2005	2006	2007
People receiving ART	55 000	207 000	325 000	460 000
People needing ART	1 200 000	1 400 000	1 500 000	1 700 000
Estimated ART coverage %	4.0	15.0	21.0	28.0

The ART rollout is happening at different rates in different provinces with different degrees of commitment and success from place to place. Treatment is mostly hospital based and most patients are adults. There is a challenge to decentralize management of ART to local clinics to ensure accessibility and to scale up ART among children.¹⁷

2.2.3. Antiretroviral therapy (ART) in KwaZulu-Natal

In January 2005, 8467 people were on ART in KwaZulu-Natal. The province had made considerable progress in providing ARV treatment with all 55 of its hospitals being accredited for ARV drug provision. As at the end of March 2005, 30000 ART patients were enrolled in the public health facilities, with the DoH exceeding its target by 50.0% in 2004. In this area the provincial DoH is currently fulfilling its objectives. A target of 110,000 was set for 2008/09, which will involve a considerable scaling up of treatment provision and support resources.¹⁷

2.2.4. Antiretroviral therapy (ART) in Hlabisa sub-district

This rural health district has one district hospital, Hlabisa Hospital, situated about 50 kilometers from Mtubatuba across from Mfolozi-Hluhluwe Game Park. Hlabisa Hospital has 15 residential and 4 mobile clinics.

Africa Centre (Africa Centre for Health and Population Studies) is a joint initiative of the University of KwaZulu-Natal (UKZN) and the South African Medical Research Council (MRC). It is supported by the Wellcome Trust and other funders, as a global rural research centre. It is committed to partnership with local communities to conduct policy-relevant, health and population studies in an ethical manner. It is located in the rural Hlabisa sub-district about 15 kilometers from Mtubatuba.

In partnership with Africa Centre, Hlabisa Hospital started giving antiretroviral treatment in 2004. The ART Program is embedded in the DoH antiretroviral therapy roll-out program. PEPFAR funds are used to provide extra clinical staff, training and support for DoH.

The very first patients were initiated on ART in September 2004. The program gradually rolled out to fixed clinics. Currently the DoH Program, in partnership with Africa Centre, provides ART to more than 6000 patients at all fixed clinics in the Hlabisa Sub-District. There are however many more patients who need ART in Hlabisa sub-District over and above the 7000 that are on treatment.¹⁵ Hlabisa sub-District was chosen because it is a deep rural poor area, with a hope that the results of this study would be generalizable to other rural districts in KwaZulu Natal, although the limited scope of the study and missing data may limit its generalizability. Other rural districts may be different from Hlabisa sub-District.

Summary

More people than ever before have been reached with ART in the world, but the numbers are insufficient as the ART coverage is still low and so are the challenges of beefing up adherence and prevention of loss to follow up.

2.3. Goals of antiretroviral therapy (ART)

Today South Africa has the most people on ART in the world,¹ however, a lot more people need ART to keep them healthy and to prevent HIV/AIDS deaths.¹ More adults than children access ARVs and co-infection with TB are challenges.¹ The South African National ART guidelines¹³ and international guidelines (Department of Health and Human Services, International AIDS Society of United States of America (DHHS, IAS-USA) and European guidelines) are based on the WHO ART guidelines that are cited below.²¹

There are three primary goals of ART namely:

To reduce HIV related illnesses and deaths

- To prolong life and to improve the quality of life (clinical goals). Patients should have less or no HIV related illnesses.
- To reduce viral load to undetectable levels (<400, <50, <25copies/ml) to stop, delay or prevent disease progression (virologic goals)

To raise the CD4 cell count to the normal range and keep it high above the baseline (immunologic goal).²¹

To achieve clinical, virologic and immunologic goals while maintaining treatment options, limiting drug toxicity and promote adherence (treatment goals).¹³

To reduce HIV transmission (epidemiological goals).²¹

Secondary goals of ART are to improve the uptake of VCT and safe sex; to decrease sero-conversion in discordant couples and to reduce MTCT.^{13,14}

2.4. Adherence - a key component of ART

Adherence to antiretroviral treatment is very important if patients are to reach and keep undetectable levels of viral loads, prevent opportunistic and viral mutations that confer drug resistance.^{22,23,24,25}

Thus, adherence to ART has to be exceptionally high (>95.0%) to prevent emergence of multi-drug resistant HIV.²⁴

2.4.1. Definitions of pill adherence

Adherence was defined by different authors as depicted in the table below.

Table 2.7 Definitions of adherence

Study	Year	Definition
Maskew et al.	2007	Adherence is correct and timely dosing of prescribed medications. ²⁶
Robbins et al.	2007	Differentiated between good and poor adherence. Good adherence was defined as >85.0% meaning missing less than equivalent of one day of ART per week. Poor adherence was defined as <85.0%. ²⁷
Orrel et al.	2003	Calculated adherence as a proportion of the total number of tablets dispensed minus the total number of tablets returned divided by total tablets prescribed over a period of 48 months study period. Patients who failed to bring any tablets during the 48 month period scored 0.0% adherence. ²⁸
Amico et al.	2006	Calculated adherence based on self reported number of doses taken as prescribed in the last 3 days. They defined optimal adherence as >90.0% and suboptimal adherence as <90.0%. ²⁹
Nischal et al.	2005	Defined optimal adherence as adherence that achieves a sustainable suppression of viral load below detectable levels. ³⁰
Gill et al.	2005	Defined mean adherence level as the percent of prescribed doses taken in the previous month at 12 th week visit. ³¹

These definitions are varied and some do not quantify the level of adherence. Maskew et al, Gill et al, Nischal et al, do not quantify the number of doses that must be taken correctly and timely, nor do they quantify optimal dosing. Nischal only measured adherence by viral suppression. Robbins and Amico settle for less than 95.0% adherence. These differences in the definition of adherence make it difficult to compare adherence across programmes and it is a cause for concern if optimal adherence is not quantified or <95.0%, as studies have shown a correlation between adherence and virologic response.¹² That study demonstrated that >95% adherence is essential to maintain complete viral suppression. At 3 months of antiretroviral treatment 81% of patients who were >95% adherent to their treatment had complete viral suppression. Fewer patients who were <95% achieved viral suppression in that study. Viral suppression decreased as adherence decreases.¹²

In this study, calculation of adherence was based on self reported recorded number of doses missed in the previous month for twelve months, and good adherence (>95.0%) was not missing more than 3 doses of ARVs per months as according to the national and provincial ART guidelines.^{13,14} Patients were expected to take two doses per day. They were asked if they had missed any ART doses at all, including the number of doses missed in the past seven days.

2.4.2. Rates of adherence

Adherence is a major challenge in Africa and in developed countries; however, adherence rates in Africa are often poor.³¹

In the report “No room for complacency about adherence to antiretroviral therapy in sub-Saharan Africa,”³¹ the authors discuss reports that followed an earlier report about adherence in Africa. In this report it had been reported that Africans are better adherers to ART than Americans. This report had made headlines in the New York Times in 2003 that drew attention because of the concerns about the feasibility of antiretroviral treatment in Africa. However, the results of that study may have not been generalizable because these were the results of a randomized controlled trial where adherence might have benefitted from the support the patients were getting. Some of the patients (16%) who were lost to follow up before completing 48 weeks of follow up, had been excluded from the study.

In a meta analysis to estimate adherence in North America and sub-Saharan Africa it was found that adherence was estimated at 55.0% in North America and 77.0% in Africa. This report suggested that concerns for low adherence in Africa were unfounded. It was concluded that adherence should not be a reason for delaying treatment in Africa. Reasons cited for higher adherence in Africa were fewer side effects and the less complicated regimen used in poor resource settings in Africa.³² The limitations of the study were that the study was conducted on patients who accessed treatment in new programmes before they experienced a dramatic increase in the number of patients, and before the patients had developed long term adverse events. Subjective methods of measurement of adherence were used such as self reports and pill counts.

Recent studies have revealed that most of the time adherence in Africa is often poor.^{33,34} Brown and colleagues in a study in South Africa using self reports found that although 76.0% of the patients were 100% adherent, 8.0% were <50.0% adherent. In a Senegalese study³³ adherence was >80.0%.

An adherence study that was done in Uganda in home based care programmes revealed 98.0% and 96.0% >95.0% adherence at six months and twelve months of ART respectively. In the study (Uganda) patients received weekly home delivery of ART by field workers,³⁵ but this was not the case for the Hlabisa programme at the time of this study.

These reports show that meticulous attention needs to be paid to adherence in Africa by governments and external supporters. They should not only concern themselves with scaling up roll out of ART, but they should also look at sustainability of the ART programmes by paying attention to enhancers of adherence and prevention of loss to follow up.

2.4.3. Macro factors that affect pill adherence

2.4.3.1. Africa versus the West

Although the results of a study to estimate adherence in North America and sub-Saharan Africa³² suggested that adherence in North America is poorer than in Africa, this may not be a true reflection of the level of adherence in North America for the following reasons: they were compared with new programmes in Africa which implies that adherence may change over time, the regimens in America are probably more complex than in Africa, and studies in

Africa were done in patients with limited access to treatment. Other limitations were recall bias, comparison across varied methods of measuring adherence like MEMS and self reports because self reports may overestimate adherence. Reports about poor adherence in impoverished communities in America may have interpreted that poverty is the root cause of poor adherence rather than factors that are common to poor people like drug and alcohol abuse

Results of a study in Brazil revealed that side effects were the third reason for non-adherence. This study found forgetfulness to be the main cause of non-adherence, followed by running out of medication. Other reasons found were side effects, complex dosing, fatigue and voluntary interruption.³⁶

Running out of medication and too many pills may reflect health systems' problems. Patients may run out of pill because they do not have funds to pay for them or if ART is free like in South Africa, running out of pills may reflect lack of money for transport to the facility to collect medication.

In a Canadian study young people aged 18-25 years were found to be poor adherers. The reasons they mentioned were doubting the efficacy of medications, stigma, feeling different and dosing confusion.³⁷

In an HIV Cost and Services' Utilization Study, older age, men of white origin were more adherent than younger adult African American women. They mentioned high number of pills, difficulty fitting medication into their schedule and doubting medication efficacy as reasons for poor adherence.³⁸

These studies indicate that adherence to medication is a global problem even in affluent countries and proven strategies need to be engaged to promote adherence.

2.4.3.2. Urban versus rural

Adherence in South Africa as in other African countries was expected to be low,³¹(<95.0%), however, in a study that was done in Cape Town during 1996 – 2001, the authors concluded that 'adherence is not a barrier to successful antiretroviral therapy in South Africa' because

adherence was high. The aim of the study was to identify predictors of low adherence (<95.0%) and failure of viral suppression (>400 HIV copies/ml). Pill counts and records of treatment refills from pharmacy, were used to measure adherence. The results revealed no significant difference in adherence between patients on protease inhibitor (PI) based regimens and those on non-nucleoside reverse transcriptase inhibitor (NNRTI) based regimens, nor with socioeconomic status, sex and HIV stage. Independent predictors of low adherence were English language speaking, age, and three times daily dosing. The following were found to be independent predictors of virologic failure: baseline viral load, <95.0% adherence, age and dual nucleoside therapy.²⁸ This study however was done in an urban area before the ART roll out in South Africa, when the cost of treatment limited the accessibility of ART. These patients may have been different to patients who access free treatment in public health facilities today.

In a study that was done in Soweto, Johannesburg, adherence was high: 88.0% of patients achieved > 95.0% goal, 9.0% achieved 90.0-95.0% adherence and only 3.0% achieved <90.0%.³⁹ In a study done at Khayelitsha, Cape Town, adherence was also high, viral load level was < 400 copies/ml in 88.1%, 89.2%, 84.2%, 75.0% and 69.7% of patients at 3, 6, 12, 18 and 24 months.⁴⁰ However, Soweto and Khayelitsha are different from Hlabisa, and it is difficult to generalize these results to the sub-district. This study intended to find out how adherent patients are to antiretroviral therapy in a rural district so as to find ways to enhance it.

In rural Lusikisiki, Eastern Cape, the programme report although not including adherence to antiretroviral treatment, showed that 89.5% (265/296) of patients who had viral loads determined at twelve months in the clinic based programme, achieved viral suppression which gives an indication about adherence to antiretroviral treatment.⁴¹ However, these results were based on only 49.7% and 9.5% of viral load results that were available at the clinics and the hospital respectively.

Using virologic outcomes to assess the success of the rural Mseleni ART programme in South Africa after 6 and 12 months, 85.0% and 84% of patients achieved viral suppression respectively.⁴² Unfortunately the report did not mention the percentage of the total number of patients on which these results were based on. Thus we do not know the loss to follow up rate

and how adherent these patients were because adherence was not measured.⁴² However, the study by Brown et al.,³⁴ above shows that there is a challenge of poor adherence in South Africa that should be tackled.

2.4.4. Local factors that affect adherence

2.4.4.1. Distance

Factors associated with poor adherence in Africa involve cost⁴³ and failure to disclose status to partner.⁴³ This implies that patients miss treatment doses due to lack of transport money and that pills must be taken in the absence of the partner. However, in a Zambian study distance to the health facility for ART did not predict adherence, however, more of those who had been on treatment for a longer time were adherent than those who had been on treatment for a short time.⁴⁴

2.4.4.2. Knowledge of CD4

An Edinburgh study revealed that knowledge about the increased CD4 count and VL had a positive effect of adherence.⁴⁵

In Edinburgh, Moyle found that the level of education was associated with high adherence, however, the patients missed doses due to problems with work schedules, depression, and believing in medication efficacy. Telling these patients about the improved CD4 and viral load results improved adherence.⁴⁵

2.4.4.3. Actual baseline CD4

The baseline CD4 count is associated with adherence.⁴⁶ In an HIV Epidemiologic Research (HER) study Stone and colleagues found that the probability of missing doses was reduced in patients with a higher CD4 count. One would anticipate a higher Cd4 count to be associated with a lower WHO stage of disease and less illness that could translate into not being adherent to treatment.

In an American study it was found that patients who had a higher baseline CD4 count had higher probability of missing treatment doses.⁴⁶ These contradicting results suggest that health workers should not base their prediction of adherence on baseline CD4 results.

2.4.4.4. Poverty and unemployment

Most studies on adherence tend not to focus on the role of poverty to adherence to treatment. In fact it may affect the ability to access treatment because of the cost of transport, cost of user fees and tests and supplies. Taking medications with dietary modification may also be challenging in terms of preparation of food especially if there is no electricity or safe water. In the presence of these difficulties, even the person living in poverty who fails to take medications as prescribed is categorized as not adherent without attempting to overcome the barriers associated with poverty.⁴⁷ Studies in Botswana⁴⁸ showed that user fees were associated with poor adherence. In places where ART is free, the cost of transport is associated with poor adherence.⁴⁹

2.4.4.5. Cultural role of women

Women still occupy an inferior position to men in Africa and as a result they tend to be less educated, confined at home, cannot own property and most of the time they are dependent on their male partners for subsistence and even have little influence in their sexual relationships.⁵⁰ In a study in South Africa, some women reported defaulting medication and follow up visits because of this inferior social status.⁵¹ Adherence should be discussed in a social context and encouraging couple counselling and testing might be helpful.

2.4.4.6. Beliefs

Cultural beliefs

Disease and illness may be explained in cultural terms that can be in respect of explaining the cause and its expected course, however, introduction of effective treatment may change the cultural interpretation of that disease.⁵² For example in the 1980s in Haiti, understandable cultural explanations of the cause and course of AIDS were in terms of jealousy or curse.^{53,54} Introduction of antiretroviral treatment has affected the social explanation of HIV/AIDS and suggests that it can lead to reduction of stigma and increase uptake of HIV testing and ART.⁵⁵

In a study in South Africa,⁵⁶ cultural beliefs surfaced as a barrier to adherence because patients expressed more confidence in traditional healers than Western medicine. Although patients in this study were on antiretroviral treatment they still said that they preferred

traditional medicine because it cures AIDS whereas Western medicine merely slows the process down. This may result in interruption of antiretroviral treatment.

Spiritual beliefs

Participants in a South African study,⁵¹ had turned to their religious beliefs. One participant believed that God would heal her and she interrupted treatment as a result. She had believed that AIDS was a punishment from God because of her lack of belief. The role of the health worker is to revisit the implications of treatment interruption and support spiritual beliefs that promote adherence.

2.4.4.7. Regimen complexity

Pill burden and complexity of regimens are associated with poor adherence,^{57,58,59} and belief in medication efficacy is associated with adherence.⁵⁶ It is why it is important when assessing the patient's readiness for treatment to include belief in the medication before antiretroviral treatment is started. If for example patients believe more in the traditional medicine than in the ARVs, taking ARVs may be interrupted in favour of traditional medicines.⁵⁶ Although the authors mentioned above agree that simple regimens can improve adherence,^{57,58,59} some authors³⁸ have been reported contradicting results regarding pill burden and regimen complexity. They reported that there was a positive correlation between adherence and the increased number of pills and regimen. The implications of these reviews is that guidelines for management of chronic diseases should consider pill burden and the number of doses per day to improve adherence. In fact, a lower number of pills, fewer doses per day or simpler regimens have been identified as enhancers of adherence.^{12,58,59}

2.4.4.8. Institutionalization and orphanhood

Abbadia-Barrerro and Castro's⁶⁰ study in Brazil showed that the context in which the patient lives may also influence adherence to medication antiretroviral treatment. In this study two orphaned adolescent children who lived in an orphanage were not keeping to the exact times of taking treatment. To them it was fine to take it any time as long as it was taken. Two reasons were apparent for their failure to adhere to the strict timing of medication, they wanted to be like other children who were HIV negative with whom they were living and did not take

medication and secondly they were defying the rules of the orphanage⁶⁰ as above. By delaying taking their medication they were trying to have normal lives which they had never really experienced because of orphanhood, and chronic disease while protesting against orphanage rules. This study shows the importance of investigating knowledge of the implications of poor adherence in a broader context.

2.4.4.9. Mental illness

Patients with psychiatric illness may have difficulty adhering to medications.⁶¹ Active mental illness especially depression is strongly associated with poor adherence to antiretroviral treatment^{12,62,63} Patients who are avoiding the emotional impact of a HIV positive diagnosis by depression, substance abuse and suicidal thoughts are less likely to be ready for treatment.⁶⁴ Patients with depression are less likely to be ready to start treatment and require intense education and follow up.⁶⁵

Cramer and Rosebank conducted a systematic review that revealed adherence of 76.0%, 65.0% and 58.0% by patients with physical disorders, depression and psychoses respectively.⁶¹

Depression may cause inability to concentrate due to lack of mental energy and difficulty to remember instructions like dosing time and dietary restrictions due to loss of appetite.⁶⁶ Management of depression is essential to improve adherence. Further studies are needed to establish a causality effect of the relationship between depression and adherence.

Forgetting is one of the top reasons for missing ART doses.^{58,63,67,68,}

It may be related to the lack of mental energy to remember dosing instruction that happens in depression or it may be simple forgetfulness. Perhaps management of depression may relieve forgetting.

2.4.4.10. Health care provider/patient relationship

Decentralization of services may not work if the health patient/provider relationships are not good. Health care workers should strive to establish rapport with their patients because good health provider/patient relationships have been found to improve adherence to ART by some authors.⁵⁹

2.4.4.11 Alcohol and drug abuse

Alcohol and drug abuse are repeatedly cited in the literature as associated with decreased adherence in some studies,^{12,62,38, 59} while others did not report this. HIV positive patients who use drugs, and have lower socioeconomic status are likely to have poor adherence to medication, and are not willing to adhere to long and complex treatment regimens and access medical care late.⁶⁹ A study by Wenger et al³⁸ revealed a significant difference between the adherence of heavy alcohol and drug users who were less adherent than other patients (45.0% v 56.0% p=0.003). These studies suggest that problems of poorer adherence must therefore be anticipated in alcohol and drug users and that these patients need to be helped to change this kind of behavior.

2.4.4.12. Knowledge of the relationship between viral resistance and adherence

Knowledge of the relationship between viral resistance and adherence has been found to enhance adherence.⁶² These results suggest that along with CD4 count level and its implications, health workers should take time to discuss the viral load levels and the effect of ART on VL and how to maintain viral suppression.

2.4.4.13. Self efficacy

Self efficacy is defined as believing in the ability to adhere to medication.⁷⁰

Poor self efficacy is associated with poor adherence to antiretroviral treatment and the opposite applies for high adherence.^{57,62,70}

It has also been found that individuals who rate themselves as highly self efficient to adhere to medication tend to set high goals, be more committed and involve themselves in behavior that fosters adherence.⁷¹

Some factors have been found to negatively affect self-efficacy such as poor patient health care worker relationships, regimen complexity, schedule problems, poverty⁶⁵ and regimen complexity.⁵⁹ The role of the health worker is to help patient to positive thoughts about himself and to set goals and plan behaviour that improves self efficacy.

2.4.4.14. Demographic factors

Demographic characteristics are inconsistently associated with adherence. Those that associate age with adherence, associate older age with good adherence.^{38,58} However, the contrary was found in the HER study.⁴⁶ Stone and colleagues found that younger patients had a reduced probability of missing ART doses. The implication of these reports is that age has a doubtful effect on adherence and each patient should be considered individually.

2.4.4.15. Fear, stigma and disclosure

Fear has been associated with delaying starting antiretroviral treatment by patients in Australia.⁶⁴ The patients in this study expressed fear of side effects as the reason for refusing to start ARVs. Other fears come from the possibility of rejection and discrimination if someone finds out about their positive HIV status.⁷²

Disclosure of HIV status is necessary for behavioural change to reduce new infections, access antiretroviral treatment and to reduce stigma and discrimination. It also helps the patients to access formal support through government services, community and non-governmental organizations. Further, it is also associated with condom use and negatively associated with multiple and casual partners.⁷³ In terms of adherence to ART disclosure is essential because people have reported missing treatment doses because of lack of treatment support.⁷⁴ Although disclosure is necessary to access ART in South Africa it is not a barrier.^{13,14} The consequences of disclosure may include stress due to perceptions of discrimination by family,⁷⁵ community and friends, which becomes a barrier to health care and social support.⁷⁶ Socioeconomic consequences include rejection and abandonment by family members providing financial support and support by friends and neighbours. In a study done in Paarl (Western Cape) and Umzimkhulu (KwaZulu-Natal) it was found that 33.3% of patients were abandoned by their partners after disclosing their HIV positive status. Patients from Umzimkhulu received support from family members such as mothers, and sisters, and friends and neighbours, while those of Paarl were supported by formal organizations and family.⁷⁷ The advantages of disclosure that were identified in this study were access to support groups, empowerment and community involvement and the opportunity to educate others such as family, friends and the community. Other benefits of disclosure were psychological liberation, reduction of stigma stress and depression.⁷⁸

In a study that was done at Chris Hani Baragwanath Hospital in Soweto, South Africa, it was found that 91.0% of patients had disclosed their status to at least one person, however; only 38.0% of these patients had disclosed their HIV positive status to their sexual partners. Most of these patients (71.0%) disclosed to a sibling. There was no association between age, gender, education and socio-economic status, and disclosure.³⁹

A study in the United State of America⁷⁹ revealed that the prevalence of HIV amongst women is higher than in men. Although more women than men had disclosed their HIV status, those who had not disclosed mentioned fear of rejection, isolation and abandonment.

Although disclosure is inconsistently associated with adherence, disclosure to family should be especially encouraged because patients have mentioned presence of family as an enhancer of disclosure.⁷⁰

Critical analysis of factors that affect adherence

The reviewed literature concerning factors affecting adherence, revealed that authors do not agree on all predictors of adherence as depicted in the following table of enhancers of and barriers to adherence.

Table 2.8. Critical analysis of factors that affect adherence

Author and year	Enhancers of adherence	Barriers to adherence
Maggiolo F et al. 2002	Older age, lower number of pills, fewer doses per day, shorter time on treatment	Forgetfulness, schedule problems, being away from home, young age, too many pills, food restrictions, too many doses ⁵⁸
Cheever LW et al. 1999	Self efficacy belief that medication can be fitted into daily activities, understanding, the relationship between viral	Depression, drug and alcohol abuse, poor self efficacy, certain health beliefs ⁶²

	resistance and adherence and previous adherence	
Stewart KE. 1999		Forgetting, embarrassment about ARVs ⁶⁷
Wenger N et al. 1999	Older age, male, white, positive attitude, pills fit into schedule	Drug and alcohol abuse, Schedule problem ³⁸
Paterson D et al. 1999	Simpler regimens	Depression, alcoholism, African American race, lower educational standard, higher baseline CD4 ¹²
Chesney MA, 1997	Good health care provider/patient relationships, fewer pills	Substance and alcohol abuse, inconvenient dosing, dietary restrictions, pill burden, side effects ⁵⁹
Eldred et al 1997	Believing in ability to adhere, presence of family ⁷⁰	
Amberbir et al. 2009		Depression, forgetting, Feeling sick, being busy, running out of medications ⁶³
Uzochukwu et al. 2009		Non-availability of drugs at health facility, physical discomfort, drugs remind of HIV status, no money

Ammassari et al.
2002

Self efficacy

to pay for drugs, too large tablets, fear that someone will find out, forgetting, too many tablets, out, sold drugs for other needs⁶⁸
Patient reported symptoms, stressful events, lack of family or social support, regimen complexity⁵⁷

From the abovementioned list, the top three enhancers of adherence are self efficacy,^{62, 70, 57} simple regimens^{22,59,69} older age,^{58, 38} and the top four barriers of adherence are forgetfulness,^{58,67,63,68} drug and alcohol abuse,^{62, 38, 12,59} depression^{62,12, 63} and schedule problems.^{58, 38, 63}

There were no enhancers and barriers in respect for adherence that were identified by all the authors. Some studies only identified barriers which implies enhancing factors would be the opposites of barriers and this may not be case. Side effects were not identified as barriers in these studies which were undertaken in the developed world. Perhaps a qualitative study to explore the perceptions of patients in South Africa about side effects is necessary. There seems to be more focus on barriers rather than on factors that enhance adherence. Perhaps research into the enhancers is necessary so that counselling focuses on what to do to promote adherence rather than on the negatives.

These findings imply that the health care workers should take time counselling the patient to stimulate confidence in the ability to adhere (self efficacy), encourage patients to reduce/stop alcohol intake, help the patients plan their daily activities in such a way that medications fit well into their daily routine and pay more attention to youth. These findings also show the importance of the multidisciplinary team in the preparation of patients for ART to deal with social problems that may force patients to sell their medications, manage depression and alcohol abuse. It looks like Departments of Health also need to consider regimen simplicity as one of the criteria for selection of standard ART regimens for public clinics.

2.4.5. Effects of adherence

The table below shows correlation between adherence and virologic response.

Table 2.9. Correlation between Adherence and Virologic Response to HAART¹²

Adherence to HAART	Viral load <400 copies/ml at 6 months
>95.0% adherence	81.0%
90.0-95.0% adherence	64.0%
80.0-90.0% adherence	50.0%
70.0-80.0% adherence	25.0%
<70.0% adherence	6.0%

In Uganda, virologic failure was associated with adherence < 95.0%.³⁵

The more adherent patients are, the greater the probability of maintaining viral suppression and increasing CD4 count.^{23,80}

In a study that was done in Tanzania, virologic failure in 16.0% of patients was associated with <95.0% adherence to ART.⁸¹

2.4.6. Adherence in other chronic diseases

2.4.6.1. Hypertension

Adherence to medication is enhanced if patient are involved in decision making and monitoring of their care.^{82,83} A patient should monitor her/his own blood pressure to improve adherence.⁸²

Other strategies include simplifying and minimizing the total number of doses of medication per day,⁸⁴ selection of medications that are not affected by delayed or missed dose to control the blood pressure,^{85,86} and objective monitoring of adherence with the use of microelectronic monitors.⁸⁷

Improving adherence in patients with hypertension seems to be just as challenging as in HIV infected patients and strategies employed to enhance adherence may also apply to patients that are infected with HIV. However electronic monitoring may be very expensive in rural, resource poor settings.

2.4.6.2. Asthma

In a study in Australia to determine self reported adherence to medication by patients with asthma, it was found that only 30.0% of patients used the preventer medication as prescribed, and 11.0% never used it. Reasons mentioned for poor adherence were forgetting (57%), too busy (10%), side effects (10%) and not believing it was effective (9%). Older patients were more adherent than younger patients. The study also showed that as quality of life decreased, adherence increased.⁸⁸ These findings seem to tally with findings for predictors of adherence for patients on ART who experience the same difficulties that patients with other chronic diseases experience such as forgetting,^{58,63,64} side effects,⁵⁹ being too busy⁶³ implying that ART is not different from other chronic diseases.

2.4.6.3. Epilepsy

In a cross-sectional study to assess self reported adherence and attitudes to medications by asthmatic patients, there was an association between poor control and poor adherence to medications. An association between poor control and anxiety was also found. Overall adherence was found to be a problem in epilepsy.⁸⁹

2.4.6.4. Diabetes Mellitus

A study to determine barriers in adherence to medication by diabetic patients, found that the frequently cited reasons for poor adherence were cost of medication, forgetting, more than two doses of medications per day.⁹⁰ These barriers are frequently mentioned even by patients on ART and other chronic medications like cost of medication, forgetting.^{68,88} and many doses per day.⁵⁸

Looking at the barriers of adherence to chronic medication, it seems that some reasons for missing treatment doses amongst patients on chronic medication are common to many diseases.

2.4.7. Appointment adherence

Table 2.10. Definitions of appointment non-adherence

Study	Year	Definition
Berg et al	2005	Number of missed appointments over the previous year. ⁹¹
Catz et al	1999	Non-attendance is the percentage of total medical appointments missed and had not been cancelled. ⁷⁴
Park et al	2008	A missed appointment is a time that the patient failed to keep a scheduled appointment and had not cancelled the appointment. ⁹²

All these definitions are vague. They do not quantify the time when the patient is expected to attend follow up visits. Berg's definition suggests that it takes a year before the patient is considered appointment non adherent. If medication refills are done quarterly, for example, a year is too long to record poor appointment adherence and the patient would surely have run out of medication and become a loss to follow up.

2.4.7.1. Factors affecting appointment adherence

Demographic characteristics

An American study was done in an urban community in Fenway Community Health Center, Boston, USA, to examine the correlation between missed appointments and the demographic characteristics of patients and their health status based on the CD4 count and the viral loads. Logistic regression revealed a positive correlation between total appointments missed and a decline in the CD4 count and detectable viral loads. Age was associated with missing appointments and there was no association between missing appointments and racial group, socioeconomic status and gender.⁹²

In a similar study that was done at the Earl K Long Medical Center, Louisiana, younger age was positively associated with more missed visits. No associations were found for income, gender, or sexual orientation.⁷⁴

Depression

Depression was associated with more missed visits in the Louisiana study.⁷⁴

Depression seems to play a pivotal role in missing appointments and treatment doses. Health workers should take time to identify and refer the patient for its management before commencing treatment and its management should be an ongoing process throughout.

Employment and poverty

The findings regarding the association between appointment adherence and employment are conflicting: In a study at Seoul National University Hospital, Republic of Korea to determine reasons for missing clinic appointments among HIV–infected patients, the most frequent reasons cited by patients on ART were work schedule problems (40.0%), forgetting (20.0%) and lack of motivation (10.0%).⁹²

In a study in South Africa, some of the women who had reported that they chose to remain in abusive relationships because of unemployment, said that they had interrupted their medication or failed to go for follow up appointments due to lack of money. They also reported that financial difficulties contributed to their falling ill due to lack of adequate nutrition and lack of follow up and if they find a job they often lose it due to repeated illness and absence from work.⁵¹

2.4.8. Loss to follow up

Some of the patients who start antiretroviral treatment are lost to follow up. Patients on ART require frequent follow up care, regular counselling and monitoring of CD4 count and viral loads. Loss to follow up and re-initiation procedures result in extra expenditure, besides the potential for non-adherence to ART, and the consequences of resistance to treatment and change to the second line treatment which limits the patient's future chances of ART. Inability to keep follow up visits is important because it is a predictor of adherence.³⁹

Introduction of ART in sub-Saharan Africa has significantly changed HIV and AIDS management, however, loss to follow up can undermine efforts to reduce AIDS if the causes are not established and addressed. Rosen, Fox and Gill,⁹³ used ART programme reports on line to estimate retention of patients in ART programmes in the Sub-Saharan South Africa and what causes loss to follow up. Reports between 2000 and 2007 were identified in 13 countries. Inclusion criteria were non research programmes in Sub-Saharan Africa. Exclusion criteria were reports from clinical trials, studies that reported mortality only, studies that reported on-treatment analyses, studies that could not be determined if they were intention-to treat or not and studies done on children only. They defined retention as patients that were alive and receiving antiretroviral treatment at the end of the time period. They estimated that 79.0%, 75.0% and 61.6% of patients on ART were lost to follow at 6 months, 12 months and 2 years. The best programmes retained 85.0% and the worst retained only 46.0%. The major reasons for loss of patients cited in 32 publications on 33 patient cohorts, were loss to follow up (56.0%) and death (40.0%).⁹³ The authors compared two very different outcomes to measure success of programmes, namely, death and loss to follow up and yet death is a worse outcome than loss to follow up. If for example programme 1 and programme 2 report equivalent attrition rates caused by death and loss to follow up respectively, programme 1's performance is worse than programme 2's performance although the attrition rate looks like it is the same. More-over programme managers can control these outcomes by applying very strict admission criteria that exclude very sick patients and those who are most likely to be lost to follow up, or improve the quality of care at the clinics.⁹⁴

The roll out of antiretroviral treatment in South Africa in 2004 brought hope and challenges, one of which is retention of patients in ART programmes. Highlights of two studies done in Johannesburg will be discussed. A study done at Thembaletu clinic at Helen Joseph Hospital in Johannesburg tried to explore the reasons for loss to follow up. In this study loss to follow up was defined as missing a follow up visit and failing to come to the clinic within one month of the missed visit. A total of 182 (3.0%) patients were recorded as lost to follow up. Of these 28 were found to have duplicate records and were thus not really lost to follow up, 84 had either no or incorrectly recorded contact details and only 70 were contactable. The major reason for missed visits was financial problems (34.0%) followed by death (27.14%), ART

stopped by doctor (11.43%), change of residence and receiving treatment elsewhere (8.57%), commencement of medical aid and private treatment (5.71%), incarceration (5.71%) and commencement of traditional medications (5.71%). Only 1.4% of patients lost to follow up mentioned the side effects of ART as the cause of loss to follow up.²⁶

The second study was also done at the Johannesburg Hospital adult HIV clinic.⁹⁵ A total of 267 of 1631 patients were recorded as lost to follow up. Of these 173 could be traced telephonically and asked the reasons for missing visits. Death accounted for 48.0% of loss to follow up. Other causes included transfer (25.4%), hospitalization or illness not causing death (10.4%). Very few mentioned financial difficulty (1.2%) and side effects (2.9%).⁹⁶

Although the two studies were done in urban Johannesburg, major reasons of missed visit and loss to follow up and rates differed considerably. Thembaletu clinic had less than 3.0% while Johannesburg hospital clinic had 16.37% patients lost to follow up. Thembaletu patients were lost mainly due to financial reasons (34.0%) while those of Johannesburg Hospital clinic were caused mainly by death (48.0%) of patients. In both cases it is interesting to note that deaths were associated with older age, low CD4 count and high viral loads at initiation. In both studies side effects were the least cause of loss to follow up. Both of the studies were done in urban areas and patients there may be different from those in rural areas, hence this study aimed to explore predictors of adherence to antiretroviral treatment and retention of patients in the antiretroviral program in a rural setting.

It is also clear from these studies that every programme should evaluate its own performance because although these were hospitals in urban Johannesburg, reasons for loss to follow up were totally different.

These studies reveal the following determinants of loss to follow up:

Gender, ethnicity, and age were not predictive of loss to follow up

Financial problems due to cost of transport and user fees and death were the main determinants

Factors associated with death were older age at the start of treatment, lower baseline CD4, higher baseline VL and weight loss. Side effects were the least important determinant.

2.5.1. Strategies to control/ prevent loss to follow up

Safe, simple and free ART regimens

In antiretroviral treatment patients with simpler regimens have been found to adhere better.^{12,58,59} Policy makers should consider this when selecting medications for public clinics.

Community and Home Based Care

HIV/AIDS programmes should consider home based care to overcome barriers to adherence. One such programme was started in Brazil.⁹⁷ A multidisciplinary health team consisting of a doctor, nurse, social worker, physiotherapist and a psychologist worked together to provide antiretroviral treatment for patients who were too sick to be enrolled in hospital/ambulatory ART programme. Three groups of patients were recruited into the study: Group 1 – patients who were currently enrolled in the home based care programme, Group 2 – patients who were previously enrolled in the home based care programme and Group 3 – patient who had never been enrolled into the home based care programme. Adherence was determined using three methods: 1 – interviews to determine patient self rating using a scale with 0-6 ratings, recall of last dose missed (0-4 rating), reasons for non adherence (0-3 rating) and satisfaction with the health service; method 2 – record review for demographic data, illnesses, and viral load results and successful treatment was defined as achieving a viral load <400 copies/ml in the most recent viral load test and method 3 – pill count.

Although there were no significant differences in clinical outcomes of the 3 groups, there was a trend of achieving more viral load suppression in the group that was currently enrolled in the home based care programme than the previously enrolled and the never enrolled groups.

Adherence scores were significantly different with the currently enrolled group showing more compliance, rather than the other groups.⁹⁷ These results suggest that patients always need supervision of care to remain adherent all the time as the currently enrolled group showed significant more compliance than the other two groups. This implies that DoH and funders should not only concern themselves with rollout but also retention strategies including home-based care.

In a Ugandan study where field workers delivered pre-packed antiretroviral treatment

in pill boxes, the results showed excellent retention of patients in the programme and adherence to antiretroviral treatment. Adherence was demonstrated by suppression of viral loads.³⁵

These two studies done in different settings show that home based care removes socio-economic and physical deficiency barriers to retention and adherence to antiretroviral treatment and should be considered for resource poor settings like Hlabisa sub-District, and for the patients that are too ill to visit clinics regularly.

DOT

DOT is recommended by the World Health Organization (WHO) for management of patients with tuberculosis (TB) because it improves TB cure rates, decreases deaths and prevents multi-drug-resistant TB.⁹⁸ In a study done in Spain in 2002 in patients co-infected with HIV, DOT achieved 100% TB cure rate and an increase in CD4 cells/mm³ from 133.5 (range 13-370) to 263 (range 54-410).⁹⁹ The advantages of DOT are that it ensures that the patient takes every dose of medication, helps the care giver to solve problems that might caused non-adherence and ensures monitoring of side effects.¹⁰⁰ In a study in USA and South Africa, outcomes of viral load results were used to measure success of DOT. Patients were randomly selected to receive DOT or for self administration group with administration of kaletra and FTC once or twice daily. After 24 and 48 weeks the VL of the observed and self administration groups were taken .There were no significant differences in the results to prove that DOTS was better than self administration of medication.¹⁰¹ In Cape Town in a qualitative study, health care workers mentioned that DOT was used to support patients on ART. A family member or a neighbour were used to support the patients.¹⁰² The studies, done in Spain, USA and South Africa, used different outcomes to measure success or failure of DOTS, CD4 counts and viral loads and yielded different results. The success of the study in Cape Town was not measured. So with such inconsistent results one would find it difficult to choose a method that would work in a rural district. Perhaps studies that would combine more than one method would be helpful. Looking at the results of the Spanish study, one would advocate for DOTS and the opposite would happen for the US and South African studies.

Training of health workers

Although knowledge does not always succeed in changing behaviour,¹⁰³ it is the duty of the health care workers to educate patients about antiretroviral treatment because the level of knowledge about the effect of antiretroviral treatment is associated with more adherence than educational level.¹⁰⁴ Furthermore, one of the reasons for lack of action despite awareness is inadequate knowledge.⁶⁴ Thus education should be done at a level that the patient can understand and it should be coupled with education about how HIV works and about development of resistant HIV so that the patient can understand the need to take treatment at stipulated times. In a study in South Africa, a patient who had interrupted treatment reported that he had missed the education sessions and as a result did not know/understand the instructions that were given to him. He did not know about side effects and as a result he doubled the doses.⁵¹

Training of counsellors

In South Africa, counsellors are trained in adherence to antiretroviral care and treatment according to the national antiretroviral treatment guidelines covering the basics of HIV, how HIV works in the immune system, and the psychology of behaviour change. The topics include basics of antiretroviral treatment, side effects of antiretroviral treatment and their management, the psychosocial assessment, opportunistic infections (OIs), barriers and facilitators of adherence, HIV, TB and ART, HIV and the child, pregnancy, HIV and ART, adherence counselling principles, clinical and adherence monitoring and patient literacy.¹³

The aim of adherence training is to equip HIV counsellors with the necessary skills to prepare patients for commencement of ART and to provide ongoing counselling hoping that ART programmes will be able to keep patients alive and on treatment.

In Kenya, Rwanda and Ghana, nurses were trained to provide adherence training to over 500 patients. Adherence was measured using self reporting, pharmacy refill records, appointment adherence and lack of treatment failure with excellent results, however, with increasing numbers of patients, nurses reported difficulty performing nursing duties and providing counselling to patients.¹⁰⁵ In this programme, dedicated counsellors were employed so that nurses can do their nursing functions while supporting the counsellors and as numbers of patients increase, more

counsellors will be provided to meet the demands of the counselling service to ensure adherence of patients to ART. In future it will be necessary to do an adherence survey with a larger sample to compare if adherence levels remain the same with increased number of patients as the programme grows.

The introduction of peer educators in South Africa has also had an impact in HIV programmes. In the mother-to-mothers programme pregnant HIV infected mothers are employed to provide group and one-on-one education, counselling and support to other mothers. This also help to promote disclosure and reduce stigma.¹⁰⁶

Training of nurses

Nurses undergo a HIV/AIDS management course which covers the following areas: the burden of HIV and prevention, pathogenesis and diagnosis of HIV, laboratory tests for HIV, clinical features of HIV infection, management of common OIs like TB, fungal and viral infections, STIs, neurological conditions like cryptococcal meningitis, syphilis and Bell's neuropathy, cancers associated with HIV, management of HIV infection with ARVs, palliative care, nutrition in HIV infection, HIV infection in children, adherence to ARVs, VCT, infant feeding in the context of HIV and post exposure prophylaxis (PEP).¹⁰⁷

Certificate courses for nurses in South Africa in PMTCT and ART have been introduced to provide nurses with skills to scale up ART and PMTCT and to manage side effects and opportunistic infections. Nurse mentors trained in HIV prevention care and treatment have been developed to provide on site coaching and support to other nurses. This has led to rapid scaling up of ART in the Eastern Cape. The Department of Nursing Science at the University of Fort Hare, in partnership with ICAP, has developed an Advanced Certificate for HIV science, however, revision of nursing education needs to be considered so as to include HIV in the curriculum.¹⁰⁶

In a Lesotho study, nurses received intensive theoretical and practical training in management of HIV and AIDS patients, in a nurse driven programme with a visiting doctor fortnightly or weekly, followed by quarterly in-service education and support visits. Training needs were also identified with the pre and post test scores. Lay counselors were trained to provide pre-

ART patient education, ART and TB support treatment like tracking ART eligible patients. Results showed that 80% of patients were still alive and taking treatment in the first year (12 months and 76.5% at 24 months, of adult patients).¹⁰⁸

A programme comprising three sessions for HIV positive men and women was designed to be delivered by nurses and the results showed an increase in knowledge and desire to improve adherence and self motivation.¹⁰⁹ Participants improved adherence, decreased the number of pills missed and the number of doses taken at the wrong time.

In a study in Rwanda nurses were trained and supervised to manage children <15 years on an adult fixed-dose combination of stavudine-containing antiretroviral treatment. Retention rate was 84% at 24 months and 82.8% of the children still maintained viral suppression at 18 months of treatment.¹¹⁰

These studies have shown that provision of ART by a nurse at a primary level of care is feasible and does not require a physician on site all the time.

Decentralized care

Clinic based and community led care in the delivery of HIV services in poor resource settings is endorsed by the World Health Organization for rapid scaling up of antiretroviral therapy and reducing loss to follow up.¹¹¹ Two programmes in South Africa at Lusikisiki,⁴¹ Eastern Cape and Mseleni,⁴² Kwazulu Natal, South Africa are typical decentralized programmes. Their achievements are through decentralization and task shifting, training and mentorship and capacity building.

ART is provided at primary health level of care by trained nurses under the supervision of a visiting doctor and primary health care supervising nurse, for support and quality control. Counsellors assume new roles like facilitation of support groups and scheduling of follow up appointments and community care giving.⁴¹ Community health workers provide basic support and mentorship of patients at grass roots level.

Mseleni and Lusikisiki programmes successfully integrate ART into other primary health care services. HIV infected patients are seen with all other patients like diabetes, hypertension, epilepsy, antenatal patients etc. This helps to decrease stigma and increase disclosure.^{41,42} Formation of support groups is supported by counsellors,⁴¹ and meeting regularly at the health facility.⁴¹ and meeting regularly at the clinics has also translated into greater awareness about the benefits of ART. The cost of transportation is reduced, VCT uptake improved and retention of patients is good.^{41,42}

Networking has opened opportunities of treating families because community workers know the people and their families. This facilitates enquiries about the health of other family members and encourages testing. This supports families to work together in health seeking behavior. The primary care supervision improved because frequent supervision and support visits for the ART programme strengthened support of other services as well.

Using virological outcomes to assess the success of the Mseleni ART programme⁴¹ after 6 and 12 months, 85.0% and 84% of patients achieved viral suppression respectively. Unfortunately the report did not mention on what percentage of the total number of patients these results were based. So we do not know the loss to follow up rate.

At rural Lusikisiki,⁴¹ South Africa, a comparison of outcomes at the clinic and hospital based programmes revealed the following outcomes at 12 months: death 16.8% and 14.5%; loss to follow up 2.2% and 19.3%; viral load suppression 89.5% and 78.0% respectively. The differences between loss to follow up and viral suppression at the clinics and hospital were statistically significant meaning that there was more loss to follow up and less viral suppression at the hospital than at clinics. The difference in deaths at the hospital and at the clinics was not statistically significant. These results showed that ART can be accessed at rural clinics without the availability of a doctor every day. The clinic based programme shows good adherence rates and retention of patients on ART. However, this was a retrospective study with a lot of missing data. Analysis at 12 months was based on 49.7% and 9.5% of data of CD4 count and viral load results. It would be difficult to generalize these results to other rural programmes in South Africa.

2.6. Theoretical Framework

Behavioural change is a process and adherence behaviour needs to be supported and re-inforced. Psychologists Prochaska and DiClemente have developed a five stage model that assists the understanding of adherence to ART. The trans-theoretical model or stages of change is presented.¹¹²

Precontemplation

At this stage the person is not even considering changing a particular behaviour. The reason may be because the person is not aware of the problem. In HIV the patient may not be aware that he needs ART and thus has not considered having an HIV test and CD4 count. Care must be taken when dealing with patients at this stage. The person may decide to change and go through what needs to be done just to get rid of the pressure or to benefit temporarily from the behaviour change, however, it will not be sustainable. An example is when a patient will be pressurized by the family to have an HIV test and CD4 count, or a patient who will have an HIV test and CD4 count so as to access a disability grant. In cardiac disease the problem might be discovered during routine physical examination and the patient is advised to reduce weight by starting a regular exercise programme.

Contemplation

The person is starting think about the change because he is aware of the problem. During this stage the person is beginning to consider taking ARVs for example but has not taken a step to implement the change. He may be considering the advantages and disadvantages for example good health and prolonged life versus fear of stigma and discrimination. It is at this stage that the health worker can assist the patient make a plan. In heart disease the person thinks about the benefits of weight loss in terms of good health and good looks but also wonders if he will be able to keep exercising. An exercise schedule that fits into the patients' routine is drawn with the assistance of a health care worker.

Preparation

This is the stage of active decision making to change behavior and the person decides to go to the clinic for ART, and participate in patient literacy sessions. The person starts exercising but does so inconsistently.

Action

The person has now decided that s/he wants go on ARVs. The health workers should help the patient in planning how to take ARVs. Support and encouragement are very important at this stage in ensuring that the patient adheres. Now he has been exercising consistently for less than six months. His wife decides to support him by joining the exercises and preparing healthy food for him. Together they decide to join a support group after the recommendations of the health care worker.

Maintenance

This involves patient adherence to ARVs and sustaining the behavioural change. It is difficult to maintain it over a long time. He has been exercising for more than six months and he wants to keep it that way.

One week or a month is much easier than a life time. The health worker must remember that patients may struggle to adhere to ART or exercise programme and may sometimes not be able to adhere. The health worker must remember to be non-judgmental. The following tips may be helpful to prevent non-adherence:

Explore the difficulties that the patient is facing with regards to adherence to ARVs, explore the advantages and disadvantages again, build the confidence of the patient by praising the patient for what s/he is doing right, and providing support and encouragement¹¹²

2.7. Side effects of ART

There are many side effects of ART that relate to drug regimen. Because some side effects cannot be verified by medical test and health care workers are depended on self reports by patients, patients may have been aware that side effects usually occur and report them. Some side effects have been found to be associated with adherence to ARVs but the findings are inconsistent. Some authors are vague and just say that poor adherence was associated with side

effects,⁵⁹ or feeling sick,⁶³ physical discomfort⁶⁸ without mentioning specific side effects. A few agree on some side effects that are associated with non adherence like sexual dysfunction.^{113,114}

Incidence of side effects

Some side effects seem to be associated with gender and certain ARVs like hyperlactemia or lactic acidosis that is associated with more female patients that are overweight^{115,116} than males. These studies were done in Soweto, South Africa¹¹⁶ and Botswana.¹¹⁷ Incidence in South Africa was 2.0% and 20.2 cases per 1000 with an incidence of 20.7 cases per 1000 in female patients in Botswana. These cases were also associated with NRTIs. Of the patients with lactic acidosis in South Africa 30.4% died and 57.0% (4 of 7) died in Botswana. This implies that ART programmes in Southern Africa should proactively look for signs of hyperlactemia so that patients are diagnosed early. The national Departments of Health should also consider safer regimens in poor resource settings.

In Durban, South Africa, the incidence of lactic acidosis at 18 months was 19/1000 case.¹¹⁷ All cases were overweight women although 40.0% of the sample were men. The median time on treatment was 7.5 months before having lactic acidosis, and the median peak lactate level was 9.3 mmol/l.

In another study in South Africa¹¹⁸ with a first line regimen containing Zidovudine, lamivudine and stocrin, the adverse events were as follows:

The incidence of anaemia pre ART and ON ART was the same, so there was no progressive anaemia on ART. Incidence of peripheral neuropathy was also the same pre initiation of antiretroviral treatment and on treatment. It was thus difficult to detect if it was as a result of treatment, and no patient changed treatment because of peripheral neuropathy. Stocrin was associated with central nervous system (CNS) symptoms at the 2 weeks visit with a decline afterwards. Most of patients who experienced CNS symptoms, rash and nausea were also using cotrimoxazole. The incidence of liver enzyme elevation pre-ART was 6.6/100 and on ART an incidence of 5.8/100 grade 3 and 4 hepatotoxicity occurred. Of thirty four patients, who developed hepatotoxicity, five were changed regimen and ten had to be hospitalized. It was difficult to differentiate rash due to drug sensitivity because incidences pre-ART and on ART

were similar. In this study the regimen seemed safer because it was difficult to differentiate the adverse events due to drug toxicity.

Response to side effects

All patients were on d4T. Of the 14 patients 29.0% (4) died and it took a median of 2.5 months for lactate to return to normal levels. D4T was changed to AZT. One patient refused to restart treatment due to fear and died of an opportunistic infection before recommencing treatment. In Kalafong Hospital, South Africa, patients reported side effect like abdominal pain, nausea, lethargy diarrhoea, and painful feet as reasons for poor adherence.⁵¹

Changing ART regimens

Side effects often lead to change of regimen

Studies in Kenya¹¹⁹ and South Africa¹²⁰ have shown that patients on antiretroviral treatment had regimen changes by 36 months. In Kenya, reasons for changing were adverse drug reactions (10.8%), treatment failure (1.4%), and reasons not documented (3.5%). Regimens at the start for changed patients were stavudine based (83.0%), Zidovudine based (12.7%) and other (4.3%). Most of the patients changed for adverse reactions were changed to Zidovudine (42.7%) based and tenofovir (32.8%) based regimens. Those who were changed for treatment failure were changed to ritonavir. The majority of adverse reactions were lipodystrophy (65.8%), treatment failure (11.1%), hyperlactemia, (8.4%) peripheral neuropathy (7.0%) etc. By six months and 12 months, 16 and 12 patients had been changed for lipodystrophy, 3 and 4 patients for hyperlactemia respectively, 1 for peripheral neuropathy at 12 months and 1 for treatment failure at 12 months.¹¹⁹

In South Africa, Cape Town,¹²⁰ the investigators found that 10.0% percent of patients had been switched to second line therapy by 36 months. The regimen at start of treatment was AZT based and later changed to D4T based regimen. Fewer patients were changed than had been anticipated. The percentage of patients changing from D4T to AZT for hyperlactemia was 30.0%. More women (overweight) were changed due to hyperlactemia than men, before six months of treatment. D4T accounted for more treatment substitution followed by AZT and nevirapine. The results both in Kenya and South Africa raise concerns about the use of D4T

based regimens and governments should consider phasing out D4T. These results also call for meticulous monitoring of patients on ART for serious side effects like hyperlactemia.

Another study in Johannesburg, South Africa,¹²¹ was done to determine outcomes of patients after one year of second-line treatment. It was found that 78.0% were still in the program, 77.0% with viral suppression. Those patients who were changed treatment before two VL results were greater than 1000 and those who were changed because of treatment failure not due to not adhering to treatment were more likely to achieve viral suppression. These results are encouraging for patients with treatment failure and prescription of second regimen should not be delayed for the needy patients.

2.8. Summary of literature review

HIV and AIDS prevalence is high in South Africa. In 2004 the South African government implemented the ART programme in public health facilities, but there are many challenges and adherence to therapy is one of them. The literature review on adherence to ART and retention of patients, reveals that predictors of adherence vary among programmes even in similar settings and that it is best for every programme to be evaluated. The reviews also warn against using death and loss to follow up equally to evaluate the performance of programmes. The theoretical framework presented reveals that a change of behaviour is a process and that patients may move back and forth between stages. Support and encouragement is essential to maintain adherence to ART.

Chapter Three

Research Methodology

Introduction

This chapter describes the methodology used in this adherence to ART study, namely, study design, definitions, study sites, study population, study sample, data source, data collection instrument, pilot study, validity and reliability, data management, data analysis and ethical issues.

3.1. Study design

This was a retrospective cohort study involving a review of the records of patients on antiretroviral therapy for the first twelve months of their treatment, to obtain information about adherence to antiretroviral treatment based on self reported number of doses missed per month, and the number of doses missed in the last seven days, and virologic response to treatment.

3.2. Study limitations

The scope of the study was limited by the limited time frame and focused only on one year of treatment, while adherence to chronic medication may change over a long time. The strength of a retrospective study is that it is easier to do, however, records are often incomplete and thus recording was a huge challenge. Patients with missing data might have been different from those whose data was available. A possible bias was whether the patients reported their adherence accurately because they may lie to avoid being scolded. The study also depended on the accuracy of recording by the health care worker marking the chart. A pill count was not done in the programme and a prospective study may have overcome that problem. Adherence relied heavily on self reports by patients and recall, though interviews and a prospective follow up study over a longer period of time may have been a better method to determine if adherence decreased over time. However, because the researcher funded the research operations and paid the research assistant with private funds, the time frame limited the scope of the study. Dose and appointment adherence did not always correlate because some patients who had missed a visit reported that they did not miss doses of treatment.

The study was expected to be completed before all the patients who were enrolled in the first year of the ART programme completed 18 months of treatment. However, unforeseen circumstances delayed the study, (protocol approval, obtaining ethics and DoH approval) and the limited time and lack of funds also limited the scope of the study.

3.3. Definition of terms

Adherence

Adherence means the ability to take antiretroviral therapy correctly and to come to the clinic monthly.²¹ In this study adherence referred to >95.0% adherence to ART (treatment/dose adherence) which meant not missing more than three doses of ART per month.

Appointment/attendance adherence was defined as coming to the clinic monthly irrespective of whether or not the patient came a few days earlier or 2 days later than the scheduled date (a total of 30 days). All patients who came every 30 days were considered to be appointment/attendance adherent.

ARVs/ART

ARVs are antiretroviral drugs. ART means antiretroviral therapy. The two are used interchangeably to refer to medicines that are used to suppress multiplication of HIV. Two adult regimens are recommended for use in the South African public sector:

Regimen 1a : Stavudine (d4T)/ Lamivudine (3TC) /Efavirenz (EFV)

Regimen 1b : Stavudine (d4T)/Lamivudine (3TC) /Nevirapine (NVP)

Regimen 2: Zidovudine (AZT) /Didonazine (ddI) /Lopinavir/Ritonavir (Kaletra)^{13,14}

CD4 count

CD4 count refers to the number of CD4 cells expressed as numbers in adults and as percentage in children. Normal levels range between 500 to 1400 cells/mm³.¹²² Loss to follow up

The table below shows varying definitions of loss to follow up by different authors.

Table 3.1. Definitions of loss to follow up

Study	Year	Definition
Maskew et al	2007	Loss to follow up meant a missed visit and failure to come to the clinic within one month of the missed visit date. ²⁶
Dalal et al	2008	Missing a follow up visit for at least six weeks. ⁹⁶
Coetzee et al	2004	Defined loss to follow up as a patient of unknown whereabouts for 3 months or longer. ⁴⁰
Rosen et al.	2007	Referred to patients who are alive and, taking ART at the time of the study period. Loss to follow up was defined as being 3 months late for follow up visit, however, they accepted many definitions of loss to follow up like 6, 12 or 24 months late for treatment refill. The authors also defined attrition as discontinuing ART for any reason including death, loss to follow up, and interruption of ART while still in the programme. ⁹³

The definitions of follow up listed above vary greatly and are vague with no quantification of the time referred to in terms of number of missed visits. They describe loss to follow up as missing a visit for one month, six weeks, 3 months or more up to two years. It appears that there is no consensus concerning the definition of the loss to follow up. This is a cause for concern when loss to follow up is a predictor of adherence.³⁹

In this study loss to follow referred to (a) a patient who has been traced with contact details in the medical records after missing visits and whose whereabouts have been determined but who still has not come for follow up for two consecutive months, and (b) those who could not be traced and whose whereabouts were unknown after missing two consecutive months. Those who could not be traced may have actually died. In the early years of the ART program, patients who missed an appointment were telephoned, but there was no tracking. All the patients fell in

the category of those that were called when they missed visits, however, some could be traced through cell phones or phone of next of kin or alternative next of kin and some could not be traced. After they had missed two consecutive follow up visits, whether or not they could be contacted by telephone, they were considered lost to follow up since the tracking team was only initiated in 2008.

Appointment adherence

Appointment adherence was defined as coming to the clinic monthly irrespective of whether or not the patient came a few days earlier or 2 days later than the scheduled (a total of 30 days).

Patient

For the purpose of this study, patient meant any patient who started ART between 1 September 2004 and 31 August 2005 at Hlabisa Hospital and satellite clinics namely Esiyembeni, Ezwenelisha, Gunjaneni, Inhlwathi, KwaMsane, Macabuzela, Machibini, Madwaleni, Makhowe, Mpukunyoni, Nkundusi, Ntondweni, and Somkhele (14 clinics).

Initiation Date

Initiation date means the date of starting ART. It follows a treatment readiness assessment process which takes about four weeks.

Viral load

Viral load is the concentration of free HIV in the blood plasma usually reported as copies of HIV in one millilitre of blood. The first DNA tests measured down to 10 000 copies/ml, the second generation down to 500 copies/ml and now there are very sensitive tests that can detect less than five virus copies/ml. Different tests give different results for the same sample, thus it is wise to use the same test to measure viral loads over time.

Different techniques are used to measure the viral load:

The PCR (polymerase chain reaction) uses an enzyme to multiply the HIV in the blood. The virus is marked by a chemical reaction and the markers are measured and used to calculate the amount of virus in the blood.

The bDNA (branched DNA) test combines a material that gives off light with the sample which connects with the HIV virus. The viral count is measured by measuring the amount of light.

The NASBA (nucleic acid sequence based amplification) method amplifies the viral protein.¹²² For the purpose of this study VL load refers the concentration of free HIV in blood plasma expressed in numbers.^{13,14} However the information on VL in the clinic records at six and twelve months of ART indicated that the VL was an absolute number or was within a particular range (<25, <40, <50 and <400 copies/ml).

At Hlabisa the PCR method is used.

Viral suppression

In this study viral suppression meant a viral load <400 copies/ml.

Virologic failure

It is the result of failure of viral suppression that results in the development of viral resistance. It is primary virologic failure if <10x drop in the viral load after 6-8 weeks of ART (>400 copies/ml at 4 weeks). It is secondary virologic failure if there is >10x increase of VL from the latest last recorded level (>50 copies/ml at 48 weeks or VL rebound to >400 copies after viral suppression).^{13,14}

Clinical failure

It is occurrence or recurrence of an HIV related infection after >3 months of treatment.^{13,14}

Immunologic failure

Immunologic failure means failure of the CD4 count to increase by >25 to 50 cells/mm³.¹⁴

Urban area

In this study urban area means Mtuba town and Norwood, its suburb.

Peri-urban area

In this study peri-urban referred to KwaMsane Township of Mtubatuba.

Rural area

Rural area in this study means the areas of the sub-District that were not classified as urban or peri-urban.

Next of kin

Next of kin meant the first contact person that the patient had recorded as the next of kin. It could be any person.

Alternative next of kin

Next of kin meant the second contact person that the patient had recorded as the alternative next of kin. It could also be any one.

Transactional sex

In this study transactional sex means sexual intercourse for gain.

3.4. Methods

3.4.1. Study Sites

This study was conducted at all ART clinics within the Hlabisa health sub-district of Umkhanyakude District, KwaZulu-Natal Province. KwaZulu-Natal is divided into 11 Districts, one of which is Umkhanyakude bordering Mozambique. ART was started at Hlabisa Hospital in September 2004. All patients who needed this service in the sub-district had to go Hlabisa Hospital. The roll out to some of the sub-district clinics was implemented about one year later which is the reason why these patients' records were obtained from their nearest clinics to which they were referred.

Hlabisa health district is a rural area in northern KwaZulu-Natal. It formed part of the KwaZulu homeland before the democratic elections in 1994. It has one district hospital which is the core of comprehensive health services run through a network of fixed and mobile clinics. As mentioned previously, the district has a population of 220000 rural, predominantly isiZulu speaking people with pockets of urban and peri-urban areas in the south east near the town of Mtubatuba. It has four tribal authority areas, each under an inkosi (chief).¹⁵ At present there are sixteen residential clinics that provide ART in the district. However, the study was conducted

in fourteen clinics, thirteen of these residential clinics, namely, Esiyembeni, Ezwenelisha, Gunjaneni, Inhlwathi, KwaMsane, Macabuzela, Machibini, Madwaleni, Makhowe, Mpukunyoni, Nkundusi, Ntondweni, and Somkhele clinics plus the ART clinic at Hlabisa hospital (Philanjalo clinic). Mtubatuba and Empembeni clinics were excluded because then there was no follow up care and initiation of patients on ART.

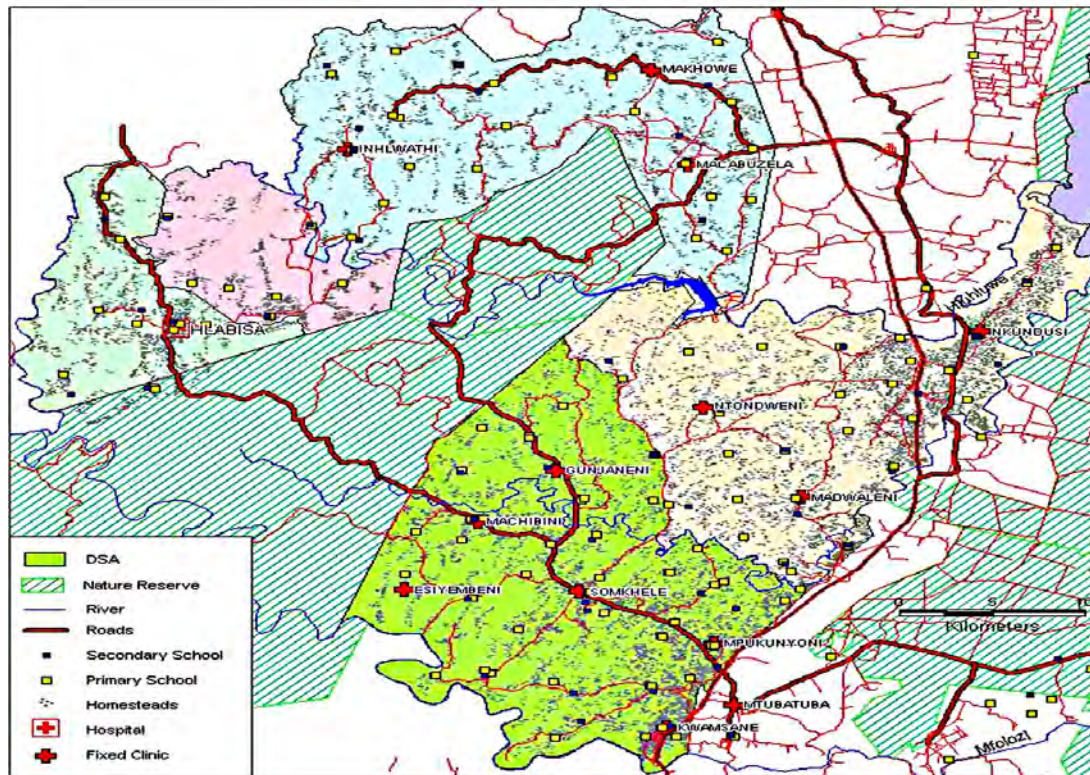


Figure 3.1. Hlabisa Hospital and Clinics in and outside the DSA¹⁵

Hlabisa Hospital is a 296 bedded hospital. Its services benefit the people of the municipalities of Hlabisa, Mtubatuba, St Lucia and part of the Big Five Kosi Bay municipality. Provision of ART started on 1 September 2004. All the clinics are supervised from the hospital and are visited by a hospital doctor every two weeks.

Table 3.2. Study Clinics

Name of clinic	Distance from Hospital (km)	Number of patients/month	ART start date
Esiyembeni	40 km	600	2006
Ezwenelisha	70 km	2500	2005
Gunjaneni	45 km	1200	2006
Inhlwathi	40 km	2000	2006
KwaMsane	60 km	3000	2005
Macabuzela	110 km	2000	2005
Machibini	33 km	1000	2005
Madwaleni	75 km	2000	2005
Makhowe	75 km	1500	2005
Mpukunyoni	43 km	2000	2006
Nkundusi	80 km	2500	2005
Ntondweni	60 km	1200	2006
Philanjalo (Hlabisa)			2004
Somkhele	40 km	2500	2005

3.4.2. Study Population

The study population was all HIV infected patients who started antiretroviral therapy between 1 September 2004 and 31 August 2005 at Hlabisa District hospital and public clinics. A total of 290 patients were enrolled in the ART programme in the first year, however, eighteen were children and were excluded from the study. A total of 272 records of adults age >15 were reviewed. There were no transfer from general practitioners and neighbouring districts during this period especially before roll out to KwaMsane clinic.

3. 4.3. Sampling

All records of 272 HIV infected patients (100%) aged >15 years who were enrolled in the ART programme between 1 September 2004 and 31 August 2005 at Hlabisa District hospital and public clinics were included in the study sample because there were a few hundred.

Inclusion criteria

HIV infected patients of both sexes age >15 years who started ART in Hlabisa District public health facilities between 1 September 2004 and 31 August 2005 and had not been on antiretroviral treatment before.

Exclusion criteria

Started ART outside Hlabisa District hospital and public clinics.

Patient who started ART after 31 August 2005.

Previous ART including PEP, single/double dose NVP.

Age <15 years. Although the original plan was to include children less than 15 years of age, this category of patients was excluded because there were very few (18) and their adherence to any treatment including ART is dependent upon adult support. They are a different group with a different recording system of laboratory results particularly the CD4 count.

3.4.4. Data collection methods

The researcher reviewed records of >15 year old patients who started ART between 1 September 2004 and 31 August 2005 to obtain information about each patient's demographic information, disclosure, laboratory blood results, adherence and symptoms experienced by the patient. Observations were recorded directly on the observation checklist by hand (see appendix 2). The questionnaire was drawn up in order to meet the objectives of the study (description of socio-demographic characteristics, disclosure, laboratory blood results, adherence, and signs and symptoms experienced. The questions on demographic data were extracted from the DoH form as needed. Pill counts and visual analogue scale were not used in the programme to record adherence.

Adherence to treatment was defined according to the South African National guidelines as >95.0% adherence which meant not missing more than three doses of ART per month.^{13,14} Due to varying definitions of loss to follow up, this study considered attendance/appointment adherence instead of loss to follow up. All patients who came every 30 days were considered to be appointment/attendance adherent. Follow up appointments were scheduled every 28 days and patients received treatment supply for 30 days each month. In addition each patient had received 30 days supply of ARVs at the two week follow up visit after initiation of ART

leaving them with enough treatment for at least 16 days after the date of the scheduled appointment. Patients who missed visits were at risk of running out of treatment resulting in treatment non adherence as well.

After initiation of ART patients were required to visit the clinic after two week's. Thereafter they were required to visit the clinic every 28 days. They were allowed to come anytime if they were ill or experiencing side effects.

Data were collected for the first twelve months of each patient's treatment.

The files were kept in locked filing cabinets in groups. These groups were formed according to dates of initiation of antiretroviral treatment up to 2 weeks. A 30 day supply of treatment was given to the patient on initiation day and repeated at the 2 weeks post initiation follow up visit, so it was possible to combine patients who had been initiated within 2 weeks to form a treatment counselling group without compromising treatment availability.

The initiation register was used to verify if all files had been obtained. Files were not removed from the ART clinic except for movement to another clinic within the sub-district. There were standard operating procedures in place for transfer and movement of patients to ensure safety of charts and maintenance of confidentiality. No transfers to and from other districts and general practitioners were recorded in the first year of the ART roll out.

Although the programme was running in 14 clinics in the sub-district with potential for filling forms differently, there were standard operating procedures in place. A standardized form was used to record signs and symptoms experienced by the patient and the counsellors and nurses were trained to ask them in a standardized way. Standard operating procedures were in place regarding the clinical care of patients during follow up visits. District trainers were responsible for on site training, support and supervision of nurses and counsellors and a monthly in-service education was done on management of side effects and signs and symptoms, counselling skills and recording of the data.

Table 3.3. Objectives, data sources, data collection instrument and research questions

Objective	Data source	Data collection Instrument	Questions
To describe the demographic characteristics of patients on ART	Patient's records	Structured observation checklist	Date of birth, age in years, sex, marital status, citizenship, next of kin, alternative next of kin, residence, highest educational standard, employment (Appendix 2, section 1).
To determine to whom patients have disclosed their HIV positive status and who their treatment supporters are.	Patient's records	Structured observation checklist	Has the patient disclosed HIV+ status to next of kin? If no, who has the patient disclosed to? Is this person a treatment supporter? If no, who is the treatment supporter? (Appendix 2, section 1.7.2 – 1.7.4.1)
To describe baseline, 6 month's and 12 month's VL and CD4 results.	Lab results in patient's records	Structured observation checklist	What were baseline, 6 month's and 12 month's CD4 and viral load results? (Appendix 2, section 2)
To describe the current state of adherence to treatment and care	Daily clinic register Patient's records	Structured observation	Date of initiation, regimen, Did the patient collect treatment on scheduled follow up visits? Yes/No/came on another day for treatment. How many treatment doses did the patient miss each month? (Appendix 2, section 3).
To describe rate and reason of changing regimen among patients on ART in the district.	Patient's records	Structured observation checklist	Did the patient change regimen? If yes, date of change. Changed to what? Reason for changing (Appendix 2, section 3).
To describe symptoms and side effects experienced by patients.	Daily register Patient's records	Observation checklist.	Did the patient experience these symptoms? Yes/No (Appendix 2, section 4).
In addition: To describe death and drop-out rates among patients on ART.	Patient's records Daily register	Structured observation checklist	Still in ART program, If no, died or loss to follow up, date of death/loss to follow up

3.5. Pilot study

One of the clinics (Hlabisa) where the study was conducted was randomly selected for the pilot study to validate the data collection instrument and to train the research assistant. The results of the pilot study were not analyzed separately. A process review is included (see Appendix 4).

3.6. Validity and reliability

To reduce bias, a field worker with a health background, who understands issues of confidentiality, was employed, trained and supervised to collect data. The research assistant was recruited from the public health students residing in Northern KwaZulu Natal. Records of all patients >15 years old who started ART between 1 September 2004 and 31 August 2005 were included in the study. The researcher monitored the data collection undertaking regular spot checks.

3.7. Data management

Completed data collection tools were obtained from the research assistant on a daily basis. Only the researcher had access to all the data, which was kept and stored and used for academic and professional development. All records were kept in a locked cupboard. No names or identification numbers were documented in the data collection instruments. Data were captured on a spread sheet by two data capturers to ensure consistency and accuracy. After data entry the data collection forms were locked in a cupboard with restricted access.

3.8. Statistical Analysis

STATA version 9 was used to analyze the data. A univariate analysis was done for patients' socio-demographic data and the description of adherence reported by patients. A bivariate analysis using Chi square compared sex, other demographic variables and VL proportions. The independent T Test was used to compare mean age, and CD4 counts by sex. Viral load proportions (percent) were categorized as follows:

Baseline viral load <10000 copies/ml, baseline viral load 10000-<50000 copies/ml, baseline viral load 50000-<400000 copies/ml and baseline viral load >400000 copies/ml.

Six months' and 12 months' viral load proportions (%) were categorized into <400 (<25, 25-50, 50-399) and >400 copies/ml.

A bivariate analysis was done to determine the associations of adherence with possible determinants including disclosure, signs and symptoms experienced and treatment support. Data were stratified to compare adherence and retention of patients of different age groups. The primary outcome measures were treatment and appointment adherence. Treatment adherence was defined as >95.0% adherence and attendance adherence was defined as not missing monthly follow up visits. Patients who were ever <95.0% adherent and those who ever failed to attend follow up visits were considered dose non-adherent and attendance non-adherent respectively.

Poisson regression analysis was undertaken to develop a model of determinants predicting treatment adherence and attendance adherence (keeping appointments) and lack of adherence by patients on ART. Incidence Rate Ratios and Standard Errors are reported for univariate and multivariate analyses. Statistical significance was $p < 0.05$ for all the analyses.

3.9. Ethical Considerations

All data were unlinked. No names or identification numbers were recorded on the forms. The study was carried out after the Biomedical Research Ethics Committee of the University of KwaZulu-Natal granted full approval of the protocol, questionnaires and other documents (see Appendix 2). Permission was also obtained from the KZN DoH, Hospital manager and managers in charge of the clinics (see Appendix 3). Confidentiality was maintained at all times. The research assistant, a professional nurse trained and understanding issues of confidentiality was responsible for collecting and capturing data. She was an MPH student and my colleague.

3.10. Summary

This study was a retrospective review of records at Hlabisa ART clinics of all treatment naïve patients >15 years of age for twelve months after initiation of antiretroviral therapy to obtain information about each patient's demographic profile, disclosure, laboratory blood results, adherence, symptoms and side effects experienced.

Chapter Four

Results

Introduction

The results are presented in respect of the objectives using tables and figures. Most of the data describing the participants are presented as percentage and number, except age in years which is presented as the mean and standard deviation. Incident rate ratios and standard errors are reported for the Poisson regressions. Due to rounding errors, percent does not always add to 100. All records of 272 patients (100%) aged >15 years were reviewed, however, due to missing data the numbers do not always add up to 272. The patients whose data are missing may have been different from the ones for which data are available and this problem may affect accurate estimation of adherence and the generalizability of results to other rural areas.

4.1. Description of patients (receiving ART at Hlabisa public clinics)

4.1.1 Socio-demographic characteristics of the study sample

Of the 272 patients, 2 (0.7%) were from Esiyembeni, 6 (2.0%) were from Ezwenelisha, 10 (4.0%) were from Gunjaneni, 93 (34.0%) were from Hlabisa Hospital (Philanjalo), 18 (7.0%) were from Inhlwathi, 90 (33.0%) were from KwaMsane, 3 (1.0%) were from Macabuzela, 3 (1.0%) were from Machibini, 3 (1.0%) were from Madwaleni, 13 (5.0%) were from Makhowe, 5 (2.0%) were from Mpukunyoni, 8 (3.0%) were from Nkundusi, 1 (0.4%) from Ntondweni, and 17 (6.0%) were from Somkhele clinics.

Table 4.1. Sex distribution of patients amongst clinics in Hlabisa sub-district, n=272

Name of Clinic	n	Male	Female
Esiyembeni	2 (0.7%)	0 (0.0%)	2 (1.1%)
Ezwenelisha	6 (2.0%)	2 (2.2%)	4 (2.2%)
Gunjaneni	10 (4.0%)	3 (3.4%)	7 (3.8%)
Hlabisa	93 (34.0%)	30 (34.4%)	63 (34.1%)
Inhlwathi	18 (7.0%)	11 (13.0%)	7 (3.8%)
KwaMsane	90 (33.0%)	28 (32.0%)	62 (33.5%)
Macabuzela	3 (1.0%)	0 (0.0%)	3 (1.6%)
Machibini	3 (1.0%)	2 (2.2%)	1 (0.5%)
Madwaleni	3 (1.0%)	1 (1.1%)	2 (1.0%)
Makhowe	13 (5.0%)	4 (5.0%)	9 (4.9%)
Mpukunyoni	5 (2.0%)	2 (2.2%)	3 (1.6%)
Nkundusi	8 (3.0%)	1 (1.1%)	7 (3.8%)
Ntondweni	1 (0.4%)	0 (0.0%)	1 (0.5%)
Somkhele	17 (6.0%)	3 (3.4%)	14 (7.7%)
Total	272 (100%)	87 (100%)	185 (100%)

The clinics that had the most patients were KwaMsane and Hlabisa (Philanjalo) which together provided two thirds of the sample. Initiation of most patients during the first year was done at Hlabisa Hospital. Later patients who volunteered to be followed up at their nearest clinics were allowed to move to their nearest clinics, hence this study was done at all clinics in the sub-district, but not all clinics had been providing ART for the same period of time. KwaMsane was one of the first the first in the sub-District to provide ART south of Hluhluwe Mfolozi game park after Hlabisa hospital, and it is the busiest in the sub-District.

All nurses and counsellors were trained in the management of patients on ART before patients were transferred from Hlabisa to other clinics. At Hlabisa and KwaMsane these patients were taken care of by staff dedicated to the ART clinic, in other clinics the same staff that provided PHC services to other patients were trained to receive these patients.

Table 4.2. Comparison of age of patients receiving ART at Hlabisa public clinics by sex, (n=272)

	Age in years at start of treatment	Total	Male		Female	p value
		n	Mean (SD)	n	Mean (SD)	
		272	40.1 (7.8)	87	37.7 (8.7)	0.027
		Total	Males		Females	p
		n	%	n	%	n
Age	11 years to 20 years	1	0.0%	0	1.0%	1
	21 years to 30 years	45	7.0%	6	21.0%	39
	31 years to 40 years	124	53.0%	46	42.0%	78
	41 years to 50 years	79	29.0%	25	29.0%	54
	51 years to 60 years	20	10.0%	9	6.0%	11
	61 years to 70 years	3	1.0%	1	1.0%	2
	Total	272	100%	87	100%	185

The majority of patients (185) who started treatment in the first year were females (68.0%) while 87 (32.0%) were males.

The males were significantly older than females ($p=0.027$). The majority of patients were 31-40 years (42.0%) followed by patients between 41-50 years of age (29.0%). Fewer young patients (21-30 years) were on ART (21.0%). These differences were statistically significant ($p=0.025$)

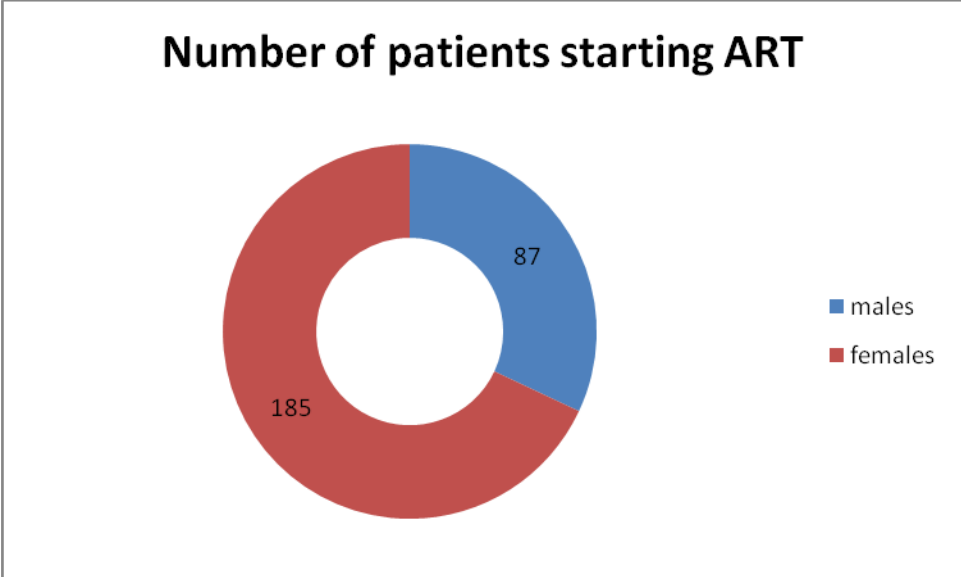


Figure 4.1 Number of patients starting ART at Hlabisa public clinics by sex n=272

Table 4.3. Educational Standard of Patients receiving ART at Hlabisa public clinics by sex, n=249

Educational Standard	Total n	Males		Females		p value
		%	n	%	n	
None	45	22.8%	18	15.9%	27	0.027
Primary	108	44.3%	35	42.9%	73	
High school	59	21.5%	17	24.7%	42	
Matriculation	35	11.4%	9	15.3%	26	
Tertiary	2	0.0%	0	1.2%	2	
Total	249	100%	79	100%	170	

Females were significantly better educated than males (p=0.027). More males (22.8%) than females (15.9%) had no education at all. The patients with no education were older with a mean age of 43 years (43.6 years and 42.6 years for males and females respectively). The majority of participants had primary school education, namely males 44.3% and females 42.9%. Participants who matriculated were even fewer for both sexes, namely males 11.4% and females 15.3%. No males had tertiary education while only 1.2% of females had tertiary education.

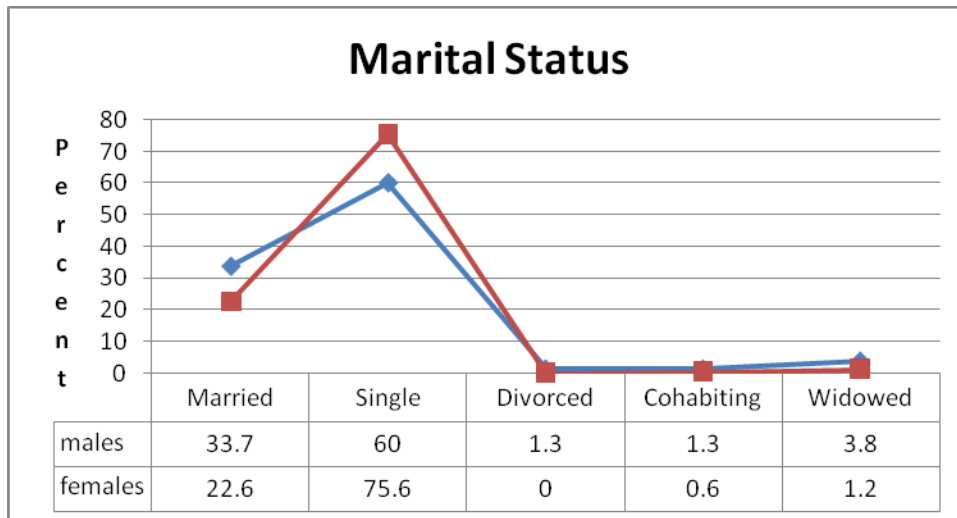


Figure 4.2. Marital status of patients of patients receiving ART at Hlabisa public clinics by sex n=248

Most of the participants were single with more single females (75.6%) than males (60.0%). There were significant gender differences with more married males and single females, and more males divorced, widowed or cohabiting (p=0.027).

Table 4.4. Employment Status of patients receiving ART at Hlabisa public clinics by sex, n=248

Employment Status	Total n	Male %	Male n	Female %	Female n	p value
Employed	36	22.8%	18	10.7%	18	0.020
Unemployed	210	76.0%	60	88.8%	150	
Employed regular part time	2	1.3%	1	0.6%	1	
Total	248	100%	79	100%	169	

The majority of the patients were unemployed and this was higher among females (88.8%) than males (76.0%) (p=0.02). Only 22.8% of males and 10.7% of females were employed full time.

Table 4.5. Residence of patients receiving ART at Hlabisa public clinics by sex, n=264

Residence	Total	Males		Females		p value
	n	%	n	%	n	
Urban	4	3.5%	3	0.6%	1	0.239
Rural	254	95.3%	81	96.7%	173	
Peri-urban	5	1.2%	1	2.2%	4	
Informal settlement	1	0.0%	0	0.6%	1	
Total	264	100%	85	100%	179	

The majority of the patients were coming from a rural area, namely, 95.7% males and 96.7% females.

Table 4.6. Next of kin of patients receiving Art at Hlabisa public clinics by sex, n=257

Next of kin	Total	Males		Females		p value
	n	%	n	%	n	
Spouse/partner	57	37.0%	30	15.3%	27	0.012
Mother	25	6.2%	5	11.4%	20	
Sister	18	6.2%	5	7.4%	13	
Other	157	50.6%	41	65.9%	116	
Total	257	100%	81	100%	176	

4.1.2. Next of kin (NOK)

This study found that most of the patients had not recorded a partner, mother, brother or sister as NOK or alternative NOK, but instead used other family members. About 51.0% of males and 66.0% of females had “other family members” recorded as their next of kin. However, among those who recorded partners, more males (37.0%) recorded their partners as NOK than did females (15.3%). There were statistically significant gender differences ($p=0.01$).

Table 4.7. Alternative NOK of patients receiving ART at Hlabisa public clinics by sex, n=187

Alternative NOK	Total		Males		Females		p value
	n	%	n	%	n	%	
Father	2	1.7%	1	0.8%	1	0.8%	0.020
Mother	13	3.5%	2	1.7%	11	8.5%	
Brother	4	6.9%	4	6.9%	0	0.0%	
Sister	15	5.2%	3	5.2%	12	9.3%	
Other	153	82.8%	48	82.8%	105	81.4%	
Total	187	100%	58	100%	129	100%	

4.1.3. Alternative next of kin

Most of those patients (82.6% males and 81.4% females) who recorded an alternative next of kin recorded other family members, who were not a father, mother, brother or sister. Further, very few fathers were recorded as alternative NOK. The alternative next of kin recorded could thus have been children, aunts, uncles, in-laws, and cousins etc. The gender differences were statistically significant ($p=0.02$). None of patients who had not recorded partners as next of kin recorded them as alternative next of kin.

Table 4.8. Disclosure of patients receiving ART at Hlabisa public clinics by sex, n=238

	Total	Male		Female		p value
		n	%	n	%	
Disclosed to NOK	Yes	215	90.4%	66	90.3%	0.464
	No	23	9.65%	7	9.7%	
	Total	238	100%	73	100%	
Disclosed to alternative						
NOK	Yes	168	93.0%	53	93.5%	0.562
	No	12	7.0%	4	6.5%	
	Total	180	100%	57	100%	

4.1.4. Disclosure

4.1.4.1 Disclosure to next of kin

Among males, 90.4% (n=66) and 90.3% among females (n=149) disclosed their HIV status to their next of kin (p=0.464), who were other family members (mostly), and mothers, sisters or spouses.

4.1.4.2. Disclosure to alternative next of kin

Most of male (93.0%) and female (94.0%) patients also disclosed their status mostly to alternative next of kin (p=0.56), although there were fewer such patients (n=168). Of the patients who had selected both a next of kin and an alternative next of kin, (n=193), there were 97.0% of females (n=132) and 96.0% (n=54) of males who disclosed to both the next of kin and the alternative next of kin. One male (50.0%) and three (75.0%) of the four females did not disclose to both the NOK and the alternative NOK.

Table 4.9. NOK is treatment supporter of patients receiving ART at Hlabisa public clinics by sex, n=180

NOK is treatment supporter		Total		Males		Females		p value
		n	%	n	%	n	%	
Yes	168	93.0%	53	93.5%	115		0.294	
No	12	7.0%	4	6.5%	8			
Total	180	100%	57	100%	123			

4.1.5. Treatment supporter

The majority of both male (93.0%) and female (93.5%) patients had recorded their next of kin as treatment supporters (p=0.29).

Table 4.10. Regimens at start of ART, n=272

Start Regimen	Total		Males		Females		p value
	n	%	n	%	n	%	
1a	206	77.0%	67	75.1%	139		0.390
1b	66	23.0%	20	24.9%	46		
Total	272	100%	37	100%	185		

4.1.6. Starting regimen

The majority of patients were put on regimen 1a (stavudine, lamivudine and stocrin) when they started ART. Males who were started on regimen 1a constituted 77.0% of all males while 75.0% of the females started on regimen 1a (p=0.39). A quarter of male and female patients were started on regimen 1b. These were likely to be females in the child bearing age; however, in the first few months after the roll out of the ART programme, NVP was more readily available in the sub-district.

Table 4.11. Patients who had regimens changed at Hlabisa public clinics by sex, n=272

Changed regimen	Total n	Males		Females		p value
		%	n	%	n	
Yes	10	6.9%	6	2.2%	4	0.067
No	262	93.1%	81	97.8%	181	
Total	272	100%	87	100%	185	

4.1.7. Change of treatment

Six (6.9%) males and four (2.2%) females had their regimens changed during the period of observation. The age of these patients ranged between 25 years and 53 years. Treatment change occurred at 1 month, 2 months and 4 months because of TB treatment, at 6 months for working shifts, at eight and nine months for hyperlactemia and at 9 for unknown reason.

Table 4.12. Reasons for changing regimens of patients receiving ART at Hlabisa public clinics by sex n=10

Reason for change	Total	Males	Females	p value
Gynaecomastia	1	16.7%	0.0%	0.330
TB treatment	5	50.0%	50.0%	
Working Shifts	1	16.7%	0.0%	
Hyperlactemia	2	0.0%	50.0%	
Unknown	1	16.7%	0.0%	
Total	10	100%	100%	

Half of the male patients who had their regimens changed, namely, those aged 43 years, 44 years and 35 years (n=3), and the female patients (n=2), aged 25 years and 33 years, had treatment changed because of starting TB treatment. The other cause for changing regimen among the other females (n=2), aged 32 years and 44 years, was hyperlactemia. Among the other three males the reasons for changing the regimen were gynecomastia (n=1), working shifts (n=1) and unknown (n=1). Their ages were 53 years, 49 years and 33 years respectively. The reason for having regimen changed in the 10th patient was recorded in the patient's chart and thus unknown.

Table 4.13. Regimens that patients were changed to by sex, n=10

Changed to which regimen	Total		Male		Female		p value
	n	%	n	%	n	%	
1a	6	66.7%	4	50.0%	2	50.0%	0.133
1b	2	33.3%	2	0.0%	0	0.0%	
D4T for AZT	2	0.0%	0	0.0%	2	50.0%	
Total	10	100%	6	100%	4	100%	

SD = Standard deviation, n = Total number of patients on whom information on the variable was available

Regimen to which patients were changed

All the TB patients whose regimens were changed, were changed from regimen 1b (stavudine, lamivudine and nevirapine) to regimen 1a (stavudine, lamivudine and efavirenz). Of males 33.0% (n=2) were also changed to regimen 1b, while half of females (n=2) were changed from D4T and put on AZT instead. The males (n=2) with gynaecomastia and unknown cause were changed from NVP to EFV.

4.2. CD4 count and Viral load results

Table 4.14. Comparison of mean CD4 count (cells/mm³) in patients on ART at Hlabisa public clinics by sex, n=272

CD4 count	Total			Male			Female			p	95% CI
	n	Mean	SD	n	Mean	SD	n	Mean	SD		
Baseline CD4	271	102.3	68.2	87	112.0	59.3	184	112.0	59.3	0.228	101-116
6 months CD4	234	208.2	107.7	75	255.1	136.8	159	255.1	136.8	0.009	223-256
12 months CD4	199	295.4	177.3	64	335.9	169.9	135	335.9	169.9	0.123	298-347

SD = standard deviation, n = Total number of patients on whom information on the variable was available varied

At initiation of ART, the mean male (102.3 cell/mm³) and female (112.0 cells/mm³) CD4 counts were similar (p=0.228), but after six months the mean CD4 female count had more than

doubled to 255.1 cells/mm³, which was significantly more than the increase in male CD4 count (p=0.009). However, by 12 months although females had a higher mean CD4 count than males (335.9 versus 295.4) this was not statistically significant (p=0.123).

Table 4.15. Comparison of viral loads in ART patients at Hlabisa public clinics by sex, n=<272.

VL copies/ml	Total		Male		Female		p value
	n	%	n	%	n	%	
Baseline VL <10000	25	7.1	5	13.1	20	13.1	0.12
Baseline VL 10000-<50000	61	24.3	17	28.8	44	28.8	
Baseline VL 50000-<400000	111	61.4	43	44.4	68	44.4	
Baseline VL >400000	26	7.1	5	13.7	21	13.7	
Total	223	100	70	100	153		
VL 6 months <25	170	84.1	58	74.2	112	74.2	0.314
VL 6 months 25 - <50	18	4.4	3	9.9	15	9.9	
VL 6 months 50 - <400	21	7.2	5	10.6	16	10.6	
VL 6 months >400	11	4.4	3	5.3	8	5.3	
Total	220	100	69	100	151		
VL 12 months <25	142	83.3	45	82.2	97	82.2	0.945
VL 12 months 25 - <50	14	9.3	5	7.6	9	7.6	
VL 12 months 50 - <400	9	5.5	3	5.1	6	5.1	
VL 12 months >400	7	1.9	1	5.1	6	5.1	
Total	172	100	54	100	118		

n = Total number of patients on whom information on the variable was available varied.

There was a lot of missing data attributed to the problem of the retrospective design especially at 12 months of treatment. Viral load turn around time was very long and the results sometimes did not come back, which may account for the discrepancy at 12 months. Missing data could have been different from the available data and this makes generalizability of results difficult.

Most of the male (61.4%) and female (44.4%) patients' baseline viral load ranged between 50000 and 400000 copies/ml followed by 10000 to 50000 copies/ml (males 24.3%; females 28.8%).

At six months there was a sharp decrease in the viral load and the majority of viral loads for both male (95.2%) and female (94.7%) patients were <400 copies/ml. At 12 months 98.3% of males and 99.9% females <400 copies/ml. However, by 6 and 12 months although a greater proportion of males than females had viral loads less than 400 copies/ml, this was not statistically significant (p=0.314 and 0.945 respectively).

The number of patients with VL >400 copies/ml dropped over the 12 months period to one male and six females. There was however a decrease in the information available for patients' VL and CD4 count at 12 months.

4.3. Adherence

4.3.1 Appointment adherence

The pattern of attendance of follow-up visits by patients is summarized in Figure 4.1. Although 86.0% came for follow up monthly, about 80.0% of all patients came monthly for follow-up exactly on the appointment day throughout the entire year, 3.0% came about seven days early or up to seven days late for one or more follow-up visits and, 3.0% came within 14 days for one or more visits during the period under observation. A total of 14.0% (n=38) of patients missed one or more visits during the period of 12 months.

Of these, 53.8% (n=21) were no longer in the programme, the majority of whom were unemployed (n=16), and other characteristics indicated that they were single (n=17) female (n=14) and with primary (n=6) or high school (n=6) education, but the differences were not statistically significant (see Appendix 5 page152). Three patients were reported to have died, 12 of those that were lost to follow up had not come back even after they/their NOK had been contacted, and it is not known if the rest were still alive or not because they/their NOK could not be contacted. Of patients on ART, 86.0% never missed a single follow up visit.

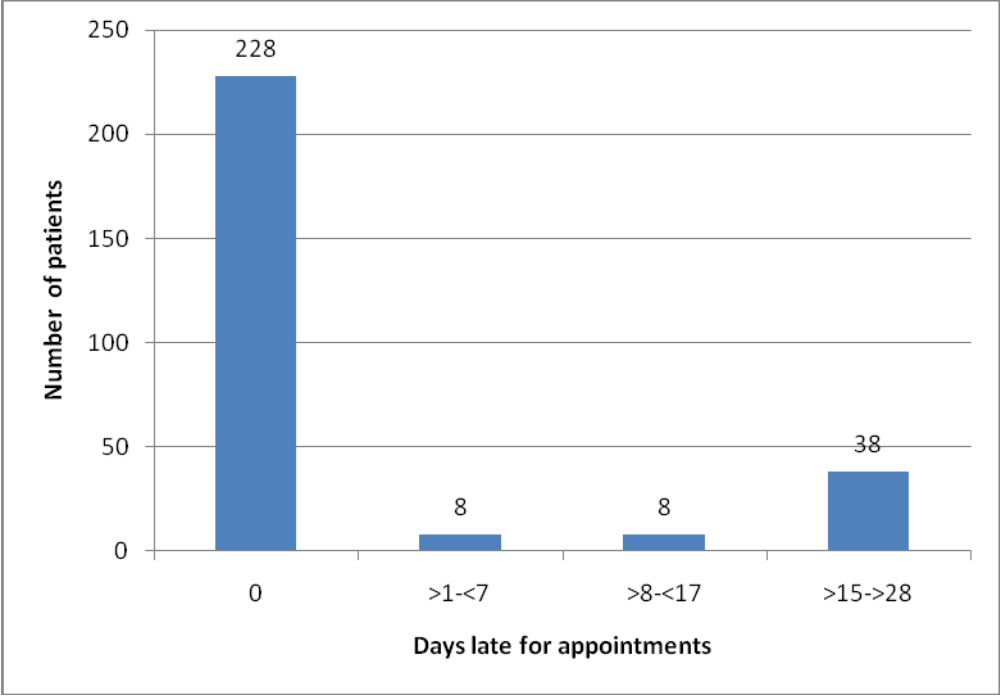


Figure 4.3. Follow up visits of patients receiving ART at Hlabisa clinics, n=272

Table 4.16. Poisson regression analyses of determinants of appointment adherence

Regression variables	Univariate analysis			Multivariate analysis		
	IRR	SE	p value	aIRR	SE	p value
High school	7.758	3.638	<0.001	5.954	2.905	<0.001
Tertiary/Matric	5.25	2.621	<0.001	5.934	2.541	0.002
Primary school	4.240	1.991	0.002	4.385	2.092	0.002
Baseline CD4 >50	1.902	0.495	0.014	1.811	0.491	0.029
Date started at centre squared (centred)	1.000	0.000	<0.001	1.000	0.000	<0.001
Date started treatment	0.991	0.002	<0.001	0.991	0.002	<0.001
Sex (female)	0.686	0.012	0.038	0.570	0.108	<0.001
Age (years) at start ART	0.988	0.011	0.169			
Employment	0.845	0.236	0.529			
Other Clinics	0.395	0.094	<0.001	0.485	0.121	0.004
KwaMsane	0.333	0.078	<0.001	0.337	0.083	<0.001

Note: IRR = Incident Rate Ratio, aIRR=Adjusted Incident Rate Ratio, SE=Standard Error

Univariate and multivariate analysis revealed that the following determinants were associated with appointment adherence, namely, sex (female), baseline CD4 count, educational level, clinic attended and date of starting treatment. There was no association between appointment adherence and age and employment status.

Sex

Female patients were less likely to miss a follow up visit than male patients on ART.

CD4 count

People with a CD4 count >50 were more likely to miss a follow up visit. The higher the CD4 count the greater the chances of their missing a follow up visit.

Educational standard

Patients who dropped out of high school had the greatest chances of missing a follow up visit followed by those who had matric or tertiary education.

Decentralized care

There was more chance of missing a follow up visit by patients from Hlabisa than all the other clinics. The time of attending follow up at the nearest clinic varied amongst patients depending on when the nearest clinic started offering ART and the willingness of the patient to take treatment at the nearest clinic. Some patients would have attended the nearest clinic for a short time if the clinic started ART in 2006, or not at all if the clinic started ART in 2006 and the patient started ART in 2004 or early 2005. The value of decentralized care was evident in this study

Date of starting treatment

The later the patient started treatment during the year under observation and the further away from the mean start date were associated with less chances of missing a follow up visit.

4.3.2. Adherence to ARVs

Patients' follow up visits were scheduled every 28 days. Patients were expected to take two doses per day which amounts to 56 doses per month ($2 \times 28 = 56$). The number of doses per year is about 672 (56×12). In this study 69.0% of patients never missed a single dose of ART (100.0% adherent).

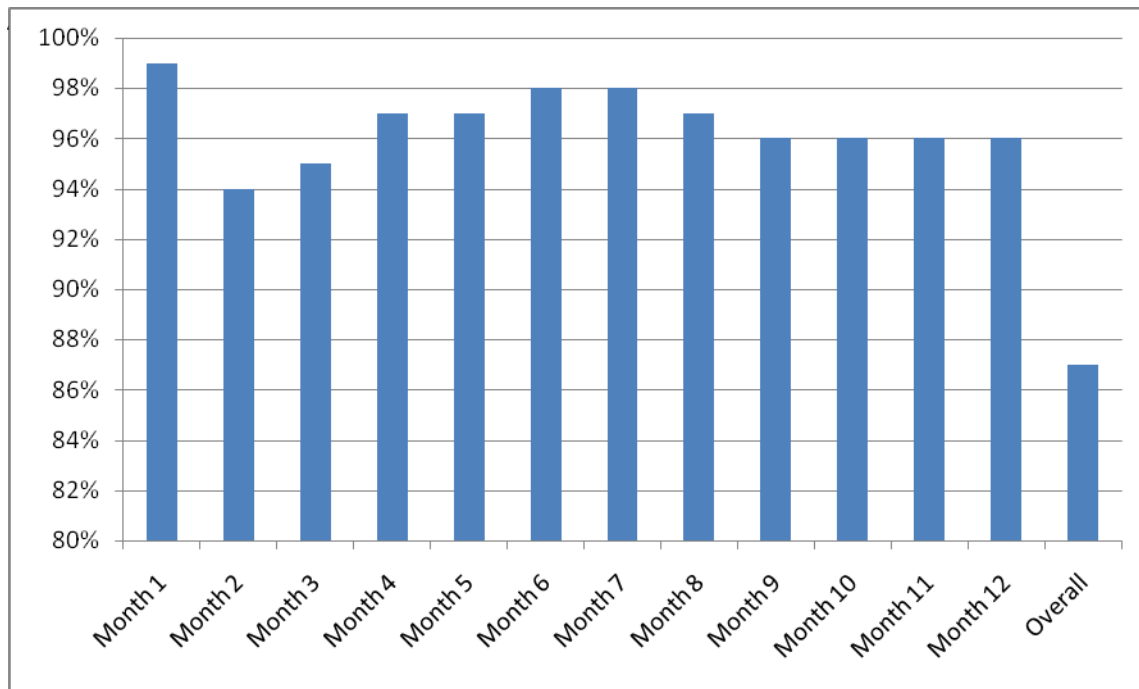


Figure 4.4. Proportion of adherent patients on ART in the first year of treatment, n=272

This graph shows the proportion of patients who were adherent to ART in the first year of treatment. This ranged from 99.0% in the first month but decreased to 94.0% in the second month. For the remainder of the period it was 95.0% or above. All patients who were ever <95.0% adherent were considered non-adherent. These could have been different patients on a monthly basis. All patients who were ever non-adherent were excluded in the overall adherence which accounts for a much lower overall adherence (87.0%).

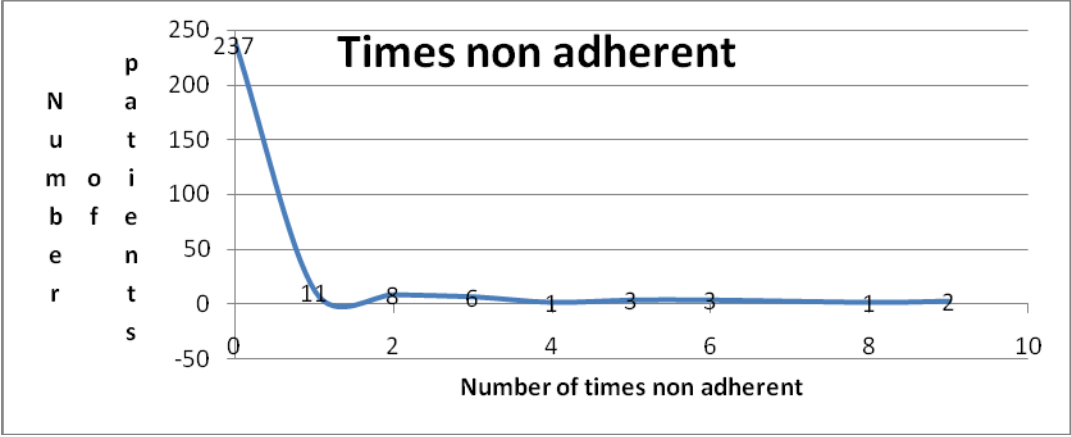


Figure 4.5. Number of times patients were not adherent to ART at Hlabisa public clinics

All patients who had taken <95.0% of ART at any one time were considered non-adherent. Of all patients on ART (n=272) a total of 237 patients (87.0%) were always adherent. The patients who were always adherent, included those who took all their ART doses (69%) and those who missed up to 3 doses (18%) at one or more months during a period of twelve months. Of non-adherent patients most were non-adherent once or twice, but two were non-adherent nine times.

Table 4.17. Demographic Characteristics of patients with >95.0% adherence,

		n=<272	Overall adherence >95.0%		
Demographic characteristic		n	Yes	No	p value
Sex	Male	87 (100%)	72 (83.0%)	15 (17.0%)	0.077
	Female	185 (100%)	167 (90.0%)	18 (10.0%)	
Age	21-30 years	38 (100%)	38 (100%)	0 (0.0%)	0.998
	31-40 years	94 (100%)	85 (90.43%)	9 (9.57%)	
	41-50 years	64 (100%)	60 (93.75%)	4 (6.25%)	
	51-60 years	14 (100%)	14 (100%)	0 (0.0%)	
Marital Status	Married	65 (100%)	63 (96.0%)	2 (4.0%)	0.013
	Single	178 (100%)	152 (85.0%)	26 (15.0%)	
Residence	Urban	4 (100%)	4 (100%)	0 (0.0%)	0.686
	Rural	254 (100%)	221 (87.0%)	33 (13.0%)	
	Peri-urban	5 (100%)	5 (100%)	0 (0.0%)	
	Informal settlement	1 (100%)	1 (100%)	0 (0.0%)	
Educational level	None	45 (100%)	43 (96.0 %)	2 (4.0%)	0.220
	Primary	108 (100%)	96 (89.0%)	12 (11.0%)	
	High School	59 (100%)	51(86.0%)	8 (14.0%)	
	Matric	35 (100%)	30 (86.0%)	5 (14.0%)	
Employment	Tertiary	2 (100%)	1 (50.0%)	1 (50.0%)	0.129
	Employed	38 (100%)	34 (89.0%)	4 (11.0%)	
	Unemployed	210 (100%)	187 (89.0%)	23 (11.0%)	

		n	Yes	No	p value
NOK	Spouse/ Partner	57 (100%)	50 (88.0%)	7 (12.0%)	0.105
	Mother	25 (100%)	22 (88.0%)	3 (12.0%)	
	Sister	18 (100%)	15 (83.0%)	3 (17.0%)	
	Other	157 (100%)	142 (90.0%)	15 (10.0%)	
Alternative	Father	2 (100%)	2 (100%)	0 (0.00%)	0.678
NOK	Mother	13 (100%)	12 (92.0%)	1 (8.0%)	
	Brother	4 (100%)	0 (0%)	4 (100%)	
	Sister	15 (100%)	14 (93.0%)	1 (7.0%)	
	Other	153 (100%)	136 (89.0%)	17 (11.0%)	

n = Number of patients on whom information on the variable was available

Marital status was associated with adherence to ARVs ($p=0.01$) but none of the other demographic variables, namely, age, residing in an urban or rural area, level of education, employment status, or selection of treatment supporter whether or not next of kin, were associated with adherence. There was a trend towards more women than men adhering to treatment but this was not statistically significant ($p=0.08$).

Table 4.18. Association of ARV Adherence with selection of treatment supporter and disclosure, n=272

Variable	>95.0% Overall adherence			p value
	n	Yes	No	
NOK is Rx supporter	202 (100%)	179 (89.0%)	23 (12.0%)	0.726
NOK is not treatment supporter	18 (100%)	16 (89.0%)	2 (11.0%)	
Alt NOK is treatment supporter	9 (100%)	8 (89.0%)	1 (11.0%)	0.650
Alt NOK is not treatment supporter	6 (100%)	0 (0.0%)	6 (100%)	
Disclosed	221 (100%)	196 (89.0%)	25 (11.0%)	0.388
Not disclosed	51 (100%)	43 (84.0%)	8 (16.0%)	

n = Total number of patients on whom information on the variables was available

There was no association found between adherence and who the treatment supporter was, nor whether or not patients had disclosed their HIV status.

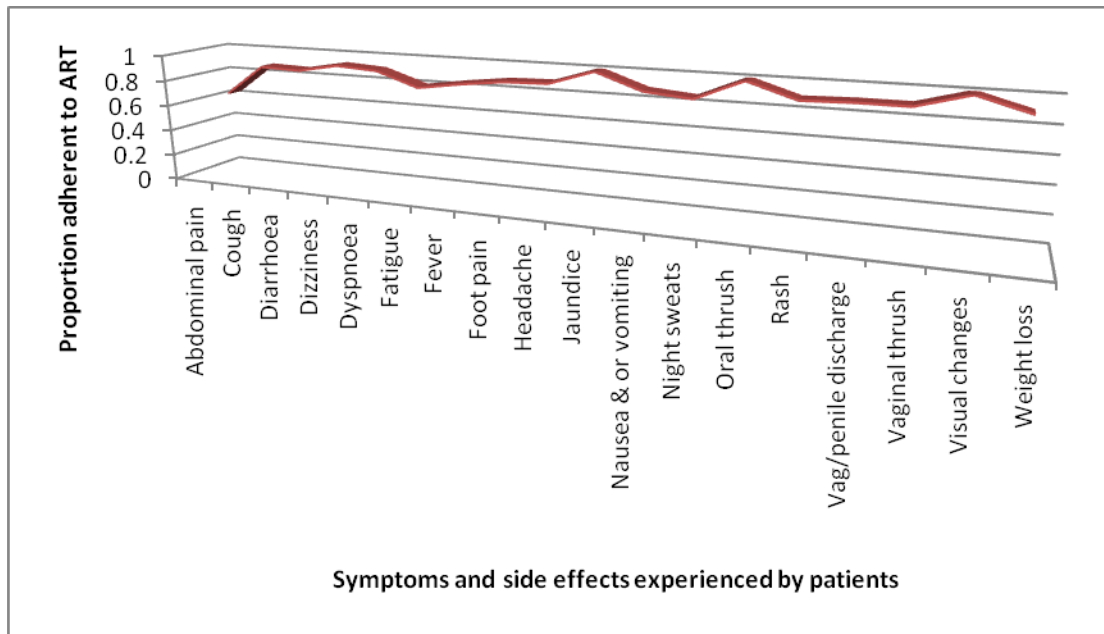


Figure 4.6. Comparison of patients’ adherence to ARV treatment by symptoms and side effects for the first year of treatment, n=272

The percentage of adherent patients with side effects varied among the side effects ranging from 63.0% to 100%. For example, among the patients with abdominal pain 63.0% were adherent as compared to those who had jaundice, oral thrush and visual changes, where 100% were adherent.

Symptoms and side effects were weight loss (51.5%), headache (43.0%), rash (43.0%), cough (38.0%), vaginal/penile discharge (32.0%), foot pain (32.0%), diarrhoea (20.0%), night sweats (10.0%), nausea and, or vomiting (10.0%), fatigue (9.0%), visual changes (9.0%), fever (7.0%), oral thrush (6.0%), vaginal thrush (3.0%), dizziness (3.0%), dyspnoea (3.0%), abdominal pain (3.0%) and jaundice (2.0%), for which adherence varied. The top five most common symptoms were weight loss, headache, rash and cough and vaginal/penile discharge.

The side effects did not differ between males and females except for rash ($p=0.004$) where more females (48.0%) than males (31.0%) had a rash.

Table 4.19. Association of patients' overall adherence >95.0% with Symptoms and Side effects, n=272

Symptom or side effect	n	Overall adherence >95%		p value
		Yes	No	
Weight loss	136 (100%)	122 (90.0%)	14 (10.0%)	0.071
Rash	113 (100%)	101 (89.0%)	12 (11.0%)	0.361
Cough	101 (100%)	88 (87.0%)	13 (13.0%)	0.362
Fatigue	24 (100%)	19 (79.0%)	5 (21.0%)	0.027
Night sweats	27 (100%)	23 (85.0%)	4 (15.0%)	0.070
Fever	19 (100%)	16 (84.0%)	3 (16.0%)	0.343
Dyspnoea	30 (100%)	27 (90.0%)	3 (10.0%)	0.081
Jaundice	4 (100%)	4 (100%)	0 (0.0%)	0.065
Oral Thrush	15 (100%)	15 (100%)	0 (0.0%)	0.153
Vaginal Thrush	9 (100%)	8 (89.0%)	1 (11.0%)	0.083
Diarrhoea	54 (100%)	46 (86.0%)	8 (14.0%)	0.057
Nausea and or vomiting	24 (100%)	21(88.0%)	3 (12.0%)	0.082
Headache	114 (100%)	102 (89.0%)	12 (11.0%)	0.354
Dizziness	25 (100%)	23 (92.0%)	2 (8.0%)	0.072
Foot pain/ Altered sensation	84 (100%)	74 (88.0%)	10 (12.0%)	0.401
Visual changes	25 (100%)	25 (100%)	0 (0.0%)	0.060
Vaginal/ penile/itching/ discharge/ burning/ sores	86 (100%)	77 (90.0%)	9 (10.0%)	0.551
Abdominal pain	8 (100%)	5 (63.0%)	3 (37.0%)	0.114
Other	152 (100%)	138 (91.0%)	14 (9.0%)	0.214

n = Total number of patients on whom information on the variable was available

Fatigue (p=0.027) was associated with adherence and there was a trend associating diarrhoea (p=0.06) with adherence, but none of the other symptoms and side effects, were associated with adherence. For these adherence varied.

Association of overall adherence >95.0% and CD4 count (cells/mm³), and viral load (copies/ml) n=<272

There was no association between CD4 count and adherence (p=0.998) although the trend was for adherent patients to have a lower mean and median CD4 at baseline assessment and higher medians and means at six month's and 12 month's assessments.

Table 4.20. Association of overall adherence >95.0% and viral load, n=178

Viral load results	Total		Yes		No		p value
	n	%	n	%	n	%	
Baseline VL <10000	20	100%	20	0.0%	20	0.362	
Baseline VL 10000-<50000	50	100%	50	0.0%	0		
Baseline VL 50000-<400000	71	96.4%	68	4.6%	3		
Baseline VL >400000	18	100%	18	0.0%	0		
Total	162	98.0%	3	2.0%	159		
VL 6 months <25	140	99.0%	142	1.0%	2	0.974	
VL 6 months 25 - <50	14	100%	14	0.0%	0		
VL 6 months 50-<400	15	100%	18	0.0%	0		
VL 6 months >400	6	100%	6	0.0%	0		
Total	178	99.0%	176	1.0%	2		
VL 12 months <25	120	99.0%	121	1.0%	1	<0.001	
VL 12 months 25 - <50	12	100%	12	0.0%	0		
VL 12 months 50 - <400	5	100%	6	5.1%	6		
VL 12 months >400	4	67.0%	4	33.0%	2		
Total	144	98.0%	141	2.0%	3		

n= Total number of patients on whom information on the variables was available

There was no association between adherence and baseline and six months viral load results, however, at 12 months non-adherence was associated with failure of viral suppression. These findings were based on available data only where viral load results and adherence data were

available. At baseline calculations were based on 60% of the sample, 65% at six months and 53% at 12 months. The data that was missing could be that of patients who were not adherent to appointments and ART.

Table 4.21. Poisson regression analyses predicting the probability of missing ART doses by patients on ART, n=272

Regression variable	Univariate analysis			Multivariate analysis		
	IRR	SE	p-value	aIRR	SE	p-value
High school education	5.326	1.057	<0.001	6.251	1.293	<0.001
Matric and tertiary	3.978	.851	<0.001	3.743	.845	<0.001
Employment (employed)	1.517	.166	<0.001	2.078	.247	<0.001
Sex (female)	2.426	.296	<0.001	2.698	.342	<0.001
Primary education	2.400	.482	<0.001	3.114	.634	<0.001
CD4>50	1.893	.248	<0.001	1.897	.259	<0.001
KwaMsane Clinic	0.411	.051	<0.001	.484	.062	<0.001
Age at start of treatment	0.992	.005	0.128			
Other clinics	0.935	.093	0.498			
Marital status (single)	1.126	.112	0.230			

IRR=Incident Rate Ratio, SE=Standard Error, aIRR= Adjusted Incident Rate Ratio

This table shows the predictors of missing ART doses by patients on ART. A higher educational standard, being employed, being female and single, and a CD4 count >50cells/mm³ increased the probability of missing ART doses. Attending KwaMsane decreased the probability of missing ART doses rather than attending follow ups at Hlabisa hospital and other clinics in the sub-district.

4.4. Summary of findings

Symptoms and side effects and adherence: Only fatigue was associated with non-adherence.

Adherence to ARVs and appointments: The higher the educational standard especially high school or matriculation, being employed, being female and single, and a CD4 count >50 cells/mm³ increased the probability of missing ART doses.

Decentralization of the ART programme to local clinics through task shifting from doctors to nurses and counsellors benefitted adherence to appointments and ARVs.

Unemployment benefitted adherence to appointments.

Disclosure: No association was found between disclosure and adherence to ARVs.

Adherence was found to be a predictor of viral suppression.

No association was found between loss to follow up and the demographic characteristics of age, sex, marital status, employment status and level of education.

4.5. Study Limitations

This study had several limitations:

- Although these findings may suggest challenges and barriers facing adherence to ART in rural areas, the research findings may not be generalizable to ARV treatment facilities in other districts that may have different characteristics.
- The short time frame restricted the scope of the study. The study focused only on just one year of treatment. With chronic medication adherence patterns over a prolonged period may change.⁴⁰
- The retrospective review of records found problems of incomplete recording and the loss of records, leading to missing data. Patients with missing data may have been different from those with available data.
- Although it was easy to collect the data on self reported adherence from the records, such data depended on recall and truthfulness. Patients may lie about adherence to prevent being scolded by health care workers. Recall can often overestimate adherence because patients tend to reflect the short term. Dose adherence often did not tie in with attendance adherence. Some patients who had missed visits reported no missed treatment doses.
- While poor adherence is an established cause of drug resistance leading to treatment failure, however, failure (represented by increasing viral load) may also be due to factors independent of poor adherence including poor drug absorption, primary drug resistance, drug interactions, inadequate potency, etc. Also, increasing viral load may not represent treatment failure or poor adherence e.g. active opportunistic infections like TB, and pneumococcal pneumonia immunizations like influenza and pneumovax can influence viral load.²¹
- The measures of actual viral load at six months and twelve months were not available and data on viral load were frequently incomplete. It was difficult to compare the viral load results with other studies.

Chapter Five

Discussion

The discussion about adherence to ART considers overall adherence and factors that affect >95.0% adherence. This is followed by consideration of factors that are associated or not associated with appointment adherence. A study limitation was the missing data associated with the retrospective design.

Introduction

This study describes the appointment and treatment adherence of the patients in Hlabisa District who started ART in the first year of the ART roll out. The study found that dose and attendance adherence of patients who started treatment in the first year of ART roll – out was high in Hlabisa District and a total dose adherence of 87.0% and attendance adherence of 86.0% was achieved and 98.0% of males and 99.0% of females achieved viral suppression at 12 months of treatment.

5.1. Adherence

5.1.1. Adherence to antiretroviral therapy

ART has many challenges and adherence is one of them.³⁰ Over 95.0% adherence does achieve viral suppression in 80.0% of patients on ART.²² The virologic treatment failure rate with <95.0% adherence may be >50.0%.²² If a patient is taking treatment twice daily 95.0% adherence means missing not more than three doses a month.^{13,14} Adherence is a predictor of success of antiretroviral therapy.¹³¹ A total of 87.0% of patients achieved >95.0% adherence to ART. These patients may have been different from those who did not start treatment in the first year of ART roll out. Apparently they were highly motivated to take treatment which was good for the ART programme because there was no waste of resources. Regular clinic attendance and adherence to Bactrim were recorded in the patient's records prior to initiation of antiretroviral treatment to predict the patient's ability to adhere to treatment although this was not used as an exclusion criterion. The twelve percent of patients who did not achieve >95.0% adherence are a cause for concern because they will eventually have virologic failure which results in opportunistic infections⁶³ which need treatment and use of second line treatment

which jeopardizes the patients' chances of successful future treatment.^{13,14} Two percent (2.0%) of the patients achieved 90.0-95.0% and 10% achieved less than 90.0% adherence. When compared to the results of a study that was done in Soweto, South Africa, where 88.0% of patients achieved > 95.0% goal, 9.0% achieved 90.0-95.0% adherence and only 3.0% achieved <90.0%,³⁹ this study reveals almost similar results with 87.0% of patients on ART achieving >95.0% adherence. However, Soweto and Khayelitsha are in urban areas, and it would have been difficult to generalize these results to a rural setting. Rural areas are associated with problems like lack of transport to the health care facility, coupled with poverty due to very low employment, and dependency on government grants.⁷⁷

Although adherent patients on a monthly basis ranged from 94.0% to 99.0%, overall adherence was 87.0% because all patients who were ever <95.0% adherent were excluded from the overall adherence. All calculations were based on available data and not on the total number of records sampled. For example if there were 144/272 patients for which data was available all calculations were based on 144 which may cause over estimation of the success or failure of this ART programme based on only 52.9% of the total number of patients. In this study adherence in terms of viral response may have been over estimated in comparison to overall dose and appointment adherence of 87.0% and 86.0% versus 98.0% according to viral load results. These limitations may also affect the generalizability of the results to other rural ART programmes in the District of UMkhanyakude, KwaZulu Natal Province and South Africa as a whole. Results of the independent tests revealed the following:

5.1.1.1. Factors that were associated with overall >95.0% adherence.

Marital status

Marital status was associated with overall >95.0% adherence to ART.

Data was available for 90.0% (248/272) of patients. The majority of patients were single and there were differences in marital status with more single females than males. These results concur with the results of a study in Pretoria.¹²³

Symptoms and side effects

Although patients suffered many symptoms and side effects (weight loss, headache, rash, cough, vaginal/penile discharge, foot pain, diarrhoea, night sweats, nausea and, or vomiting, fatigue,

visual changes, fever, oral thrush, vaginal thrush, dizziness, dyspnoea, abdominal pain and jaundice etc. for which adherence varied and did not differ among males and females except rash where more females than males had a rash), only fatigue was associated with adherence. Some studies have demonstrated varying relationships between adherence to ARVs and side effects like sexual dysfunction, fatigue,^{124, 68} vomiting,^{124,125,68} nausea⁶⁸, dizziness.⁶⁸ A study in Pretoria, South Africa showed that insomnia, headache, and abdominal pain were associated with adherence.¹²³ However, this study demonstrated no relationship between adherence and vomiting which had been shown to be a problem in three studies that were done in Italy, Brazil and Nigeria,^{124,125,68} or between some of the side effects demonstrated in the study in South Africa.¹²³ Instead this study revealed a negative association only between fatigue and adherence. Patients who experienced this symptom may have been too weak and not able to prepare food to eat and as result omitted the ARV doses.

CD4 count and viral load results

There was a lack of blood results especially viral loads at 12 months of treatment. Those patients whose results were not available could have been different from those whose results were available. They might have been non-adherent with lower CD4 cells/mm³ and higher VL copies/ml. However the findings were based on available results of 52.9% of the sample at 12 months of treatment. At a South African ART site the success reported from an ART programme was based on virologic outcomes that were based from only 9.5% of the sample.⁴¹ We do not know what percentage of results on adherence would have been available if they had measured adherence. Independent tests revealed that baseline, six months and twelve months CD4 counts were not predictive of dose adherence. However, the regression analysis revealed that patients with CD4 >50 cells/mm³ were at higher risk of missing ART doses than those who had CD4 count <50 cells/mm³. These results were similar to the results of an American study where patients with a higher CD4 were less adherent than those with a lower CD4 count.¹²⁶ This is disturbing because one would advocate for commencing ARVs earlier to prevent loss of lives of sicker patients with low CD4 count.^{26,94} However, a study at Lusikisiki,⁴¹ South Africa, showed that death of patients in the first year of treatment was associated with low baseline CD4 cells/mm³. This suggests that patients with a low CD4 count are sicker and may be motivated to take treatment.

The results of a study that was done in the Netherlands revealed that death of patients on ARVs in the first three years could be reduced by 20% if patients were initiated on ART at least when they present with 400 CD4 cells/mm³.¹²⁷ However, the results of the Hlabisa study suggested that more attention should be paid to the counselling of patients with a higher CD4 count at initiation.

There was no association between baseline and six months viral load results. However the 12 months results revealed a positive correlation between failure to obtain viral suppression and missing ART doses. These results agree with results of studies that were done in Spain,¹²⁸ Uganda,³⁵ Tanzania,⁸¹ and Cape Town, South Africa,⁴⁰ where non-adherence was identified as the risk factor for failure to achieve viral suppression (viral load <400). This study revealed higher viral suppression (99.0% and 98.0%) than the Spanish study (69.0% and 68.0%) at six and 12 months respectively.¹²⁸ It also did better than Khayelitsha (South Africa)⁴⁰ study, where 89.0% and 84.0% of patients achieved viral suppression at six and 12 months respectively. However, the results of this study were based on the results of 63.0% (172/272) and 52.9% (144/272) of the sample viral load results that were available. In rural Lusikisiki, Eastern Cape, the programme report although not including adherence to antiretroviral treatment, showed that 89.5% and 78.0% of patients who had viral loads determined at six and twelve months in the clinic based and hospital based ART programme respectively achieved viral suppression which gives an indication about adherence to antiretroviral treatment.⁴¹ However, their results were based on only 49.7% and 9.5% of the sample viral load results that were available at the clinics and the hospital respectively. In comparison to Lusikisiki, this Hlabisa ART programme achieved better results because the results at twelve months were based on more 52% of patients' compared to 9.5%. The lack of blood results seems to be a problem in both rural Hlabisa and Lusikisiki.

Using virologic outcomes to assess the success of the rural Mseleni ART programme in South Africa after 6 and 12 months, 85.0% and 84% of patients achieved viral suppression respectively.⁴² Unfortunately the report did not mention the percentage of the total number of patients on which these results were based. We do not know the loss to follow up rate and how adherent these patients were because adherence was not measured.⁴² It is thus difficult to compare the performance of rural programmes in Mseleni, Hlabisa and Lusikisiki because we

do not know how many patients Mseleni had and the number of patients for whom the results were available at six and twelve months of treatment.

There was no difference between the average baseline CD4 count and viral loads of males and females at the start of ART. The average baseline CD4 count was very much lower than 200 cells/mm³ (102.3 cells/mm³ for males and 112 cells/mm³ for females) which is one of the eligibility criteria for initiation of ART because these were the very first patients of the ART roll out in the sub-district, who had needed treatment long before it was made available. The baseline CD4 count is comparable to other sites in South Africa.²⁶ A small proportion of male (28.7%, n=25) and female (18.0%, n=34) patients respectively had CD4 count lower than 50 cells/mm³ at enrolment. Many of the patients with CD4<50 cells/mm³ may have died before starting ART. A study that was done in Free State, South Africa, revealed that the lower the CD4 count at eligibility, the higher the probability of death before starting ART. In that study about 50.0% of patients with a CD4 count <25 cells/mm³ died before starting ART.^{129,130} This implies that strategies have to be employed to ensure earlier initiation of ART to prevent death of these patients. Many people probably had lost their lives due to the unavailability of free antiretroviral treatment at public clinics. Low CD4 count resulted in many opportunistic infections causing death and the overloading of the health services. The CD4 count and viral load levels are the most important predictors of disease progression,¹³¹ and mortality tends to be high when initiating at CD4 counts <200 cells/mm³.^{126,132} In Durban, a study on the predictors of death in new initiates of antiretroviral treatment found that CD4 count <50 cells/mm³ was associated with the deaths.¹²⁵

The average CD4 count doubled in the first six months in line with undetectable levels of VL in the majority of patients (95.0-97.0%) and remained undetectable (95.0-98.0%) at 12 months. However, available data on CD4 count and viral load had decreased from baseline six months and 12 months especially at 12 months. Viral load and CD4 results of only 63.0% (172/272) patients were available at 12 months. Missing data could be different from the available data. Females tended to have a higher CD4 count at six months than males (p=0.009). The differences between baseline VL of males and females were of no statistical significance. All patients with VL <400 copies/ml were considered to have achieved undetectable levels of viral load. The lower the viral load levels, the higher the CD4 count, the lower the chances of HIV

disease progression,⁹⁷ and adherence is a determinant of CD4 count.^{132,97} There were no differences in the CD4 count of males and females at 12 months of ART. The results of this study reveal higher adherence than in a study done at Khayelitsha where viral load level was <400 copies/ml in 88.0%, 89.0%, 84.0%, 75.0% and 70.0% of patients at 3, 6, 12, 18 and 24 months⁴⁰ and in Boston, U.S.A, where 49.0% of patients had detectable viral loads after 12 months of taking ARVs.⁹¹

5.1.1.2. Factors associated with the total number of ART doses missed – Poisson regression

The level of education

The level of education, and being single, were associated with missing ART doses. It was disappointing to note that a higher educational level especially high school and tertiary education was associated with lower adherence. In a study that was done in India, it was found that a low educational level was a predictor of low adherence, however, after two sessions of adherence counseling held with patients on ARVs adherence improved and reports of missing dosing times dropped.¹⁰⁹ One would expect the more educated to be more adherent to treatment because of their supposed better understanding of the implications of not adhering to ART. The quality, content and length of counseling of the patients with a higher educational standard needs special attention, because it is possible that they are thought to be more knowledgeable and needing less counseling than the less educated, or they may not pay attention to lay counselors because they think that they know more than the lay counselors, or the lay counselors may not feel comfortable with counseling the more educated patients.

Being employed

It is not surprising to note that employment was associated with missing doses although the employment rate was very low in this community. This could be due to a change in the routine and being away from home at the time when the patient was supposed to take treatment and/or if the patient was among people who did not know his/her HIV status. If the employer is not supportive or is unaware of the employee's HIV status, the situation might be worse and the employee might do anything in his/her power to keep the job at the expense of adhering to ARVs. These findings are in line with a Korean study where the work schedule was reported as

associated with missed appointments.⁹² because missed appointment may result in missed doses if the patient runs out of treatment.

CD4 count >50 cell/mm³

Missing more doses by patients with higher CD4 count is consistent with the findings of a study that was done in USA and Canada by Wenger and Gifford.³⁸ These patients are probably not as sick as those with CD4 <50 cells/mm.³ Unlike those with lower CD4 who take treatment in order to survive, these patients are healthier and do not have serious stage 4 diseases.

Female gender

Although there were no differences in the overall >95.0% adherence to ART of males and females (Table 4.18), regression analysis revealed that those females who missed ART doses tended to miss more doses of ART than males (Table 4.22). These results are congruent with the results of the studies that were done in Canada³⁸ and America⁹⁹ where women, were found to be poorer adherers. Qualitative studies need to be done to explore the reasons why women were missing more doses than men. It could have been related to marital status because more women were single than men in this study, and may have lacked support.

The service provider/patient relationship

It is also interesting to note that KwaMsane clinic was associated with missing less treatment doses than other clinics and the hospital. The quality of provider/patient relationship may have played a role here. Although the clinics at KwaMsane and the hospital were separated from other PHC services and OPD respectively, too many patients at the hospital may have compromised the quality of care. Although there were fewer patients at other clinics than at KwaMsane clinic, the quality of care may have been compromised at other clinics since there were no staff members dedicated to providing ART as at KwaMsane clinic. The health care provider/patient relationship has been found to be a predictor of adherence.^{59,133} Cost might have played a role because it is easier and cheaper to travel to KwaMsane than other clinics and the hospital. Patients with lack of funds may have missed appointments.

5.2.1.3. Factors that were not associated with overall >95.0% adherence

Sex

Sex was not associated with overall >95.0% adherence. The majority of patients in the first year were females. This is in accordance with the results of the DoH National HIV and Syphilis survey 2006,¹⁹ which revealed that more females (2.9 million) were living with HIV than males (2.3 million). The higher proportion of females in this study also concurs with other sites in South Africa.^{26,96,123,120}

These results suggest differences in attitude towards health-seeking behavior of women and men. Other reasons could be because women in this area more willing to test for HIV than men. Hlabisa has high mobility amongst residents and there is a higher prevalence of HIV in women than men in the area.¹³⁴

Age at initiation

The average age at initiation of treatment was 40.1 and 37.7 years in males and females respectively, and males tended to be older than females. However, in this study age was not associated with adherence which implies that we do not have to worry about adherence in relation to age when rolling out ART. However, studies have often had conflicting findings regarding association of age and adherence but many that have shown an association have often shown an association between older age and good adherence,^{38,58} and amongst youth, with poor adherence.³⁷ However, in one study young persons reported missing fewer treatment doses.⁴⁶ It is worrying that the mean age at initiation was amongst the older age group because the age group with the highest prevalence is 20-29 years,⁷ although this age group may have been infected for a shorter time period. This implies that HIV awareness campaigns targeting youth may need strengthening, and clinics need to provide youth friendly services. However, these patients had come because they were sick because their CD4 count was low. The mean age is comparable with the age of patients in other sites in South Africa.^{26,95, 117,123, 135}

Marital status

Marital status was not associated with >95.0% adherence and the number of ART doses missed by regression. Data was available for 90.0% (248/272) of patients. The majority of patients

were single and there were difference in marital status with more single females than males. These results concur with the results of a study in Pretoria.¹²³

Educational standard

Available data was for 249/272 (91.5%) of patients and all calculations were based on this data. The patients with missing data could have been different from the ones with available data. The majority of patients had primary education which differs from the study in Pretoria.¹²³ This indicates the low educational standard of people in the area. A good educational level was associated with better adherence in an Edinburgh study,⁴⁵ so one would expect poor adherence in this area with most of the people with primary education, but it did not appear to be the case. There were no differences in educational level by sex.

Employment

Data availability for employment status was high (90.0% = 248/272) of patients and calculations were based on available data. There were significant differences in the employment status of males and females with more males employed than females. Most of the patients were also unemployed (88.9%), similar to a study in Pretoria (73.9%)¹²³ indicating the low level of economic status in this population. One would expect better adherence with unemployment as work schedules have been found to cause poor adherence.^{73,92} These patients may have seized the long awaited opportunity for free antiretroviral treatment which was previously available only from the private sector for persons who could afford it.

Unemployment and low educational standard are both associated with HIV infection because poverty may promote sexual favours for financial gain and the risk of multiple sexual partners. The poor are less likely to be knowledgeable about transmission of HIV because of limited educational opportunities. Factors associated with poverty like poor housing and overcrowding, poor transport, poor sanitation, poor education, inadequate food and crime are also associated with high risk of HIV infection.⁵¹

Residence

Hlabisa sub-district is predominantly rural, which is why the majority of patients were from the rural area. Being a rural area concurs with other sites in KwaZulu-Natal.^{41,42}

Next of kin and alternative next of kin

Data on next of kin was available for 257/272 patients, and 187/272 for alternative next of kin. Most of the patients had other family members as their next of kin instead of spouse or partner, probably, because the majority of patients were single. However, neither did the majority of patients' records indicate mothers, fathers and sisters as their next of kin. More male patients (37.0%) tended to have their spouses/partners as next of kin than female patients (15.0%). The differences between male and female patients in terms of selection of next of kin and alternative next of kin were statistically significant. This could be related to stigma, gender issues and the status of women in the community,⁷⁷ since patients may have been unwilling to inform their closest relatives because of their fear of disclosure.

Disclosure

Data was available for 238/ 272 patients who had data on disclosure to next of kin. Although the number of patients who had data on disclosure for alternative next of kin may appear to be low, namely only 187/272, (68.5%) had recorded an alternative next of kin, and 180 (96%) of these had disclosed to this person. There was no association between adherence and disclosure. Disclosure of their HIV status to next of kin or alternative next of kin for both male and female patients was not different. Most disclosed their HIV status to next of kin and alternative NOK the majority of whom were not sexual partners, father, mother, brother or sister but were other family members who could have been their children, aunts, cousins or uncles etc. This may have a negative influence on safe sex especially concerning the use of condoms if the partners were not aware of the positive HIV status of their partners. Disclosure to next of kin would be expected to have a positive influence on treatment adherence and regular visits to the clinic because of the support of the next of kin. The patients in this study were encouraged to bring a treatment supporter to whom they had disclosed their HIV positive status, although they were not denied treatment if they had not disclosed their status. This accounts for the high disclosure to next of kin and alternative next of kin who were usually treatment supporters. Gender

differences, stigmatization of HIV in South Africa and fear of rejection by sexual partner may be responsible for not disclosing to sexual partners as was the case in a study in Paarl, Western Cape, and Umzimkhulu, KwaZulu-Natal.⁷⁷ Not disclosing to their sexual partners is also congruent with the results of a study in Soweto where 38.0% of patients did not disclose to their sexual partners.³⁹ Adherence also decreased in Soweto due to fear of being discriminated against by sexual partners. The majority (71.0%) of those patients who disclosed their positive HIV status disclosed to siblings.³⁹ In another study that was done in Chicago, USA, respondents cited fear of rejection, fear of violence, fear of burdening the family, fear of being kicked out of the house, fear of breach of confidentiality and anger towards the partner as reasons for non disclosure.¹³⁷ Another study in Germany also revealed that stigma, discrimination, violence and rejection by a partner were major reasons for non-disclosure.¹³⁷ Qualitative studies to explore disclosure and discrimination in this community are necessary to investigate to whom patients, the reasons for not disclosing to sexual partners and to develop targeted programmes to promote HIV as a chronic disease and reduce stigma and improve adherence.⁴³

In a Tanzanian study it was found that those patients who had disclosed their HIV status were less likely to have virologic failure.⁸¹

Regimen at initiation and change of regimen

The majority of patients were put on regimen 1a (stavudine, lamivudine and stocrin) at the start of antiretroviral treatment probably because the majority of female patients had completed their families based on the average age at initiation of ART. In South Africa ARVs that are prescribed in the public clinics are limited to regimen 1a and 1b for treatment naïve patients.^{13,14} The selection of ARVs has proved successful with twice daily dosing and few were not adhering due to side effects, and therefore few changes to treatment were required. In fact patients on these regimens (NNRTIs) have been found to be the best adherers especially those on EFV,¹²⁴ and adherence has been found to be better with simpler ART regimens.⁴⁶ This could also be the result of effective counseling by the lay counsellors and nurses. All the patients who were included were treatment naïve and very few patients (10 of 272) had to change treatment. Hyperlactemia and TB seemed to be the commonest causes for changing regimen. It was interesting to note that none of women changed treatment due to pregnancy in

the first year of ART. The differences between males and females who changed treatment were not statistically significant, why they changed treatment and the regimens to which they changed. Starting TB treatment was the earliest cause of changing treatment (within 1-4 months) followed by working shifts (6 months) and lastly hyperlactemia (8-9 months) None of the patients were put on second line treatment within the first twelve months of taking ARVs. Those who changed regimens because of TB treatment were put on regimen 1a and those who were changed treatment because of hyperlactemia only substituted d4T for AZT.

The findings of this study did not correlate with the results of reviewed literature concerning side effects. Lactic acidosis seems to be a problem in Southern Africa as revealed by a study that was done in Botswana where 2% of patients developed symptomatic hyperlactemia.¹¹⁶ Two studies in South Africa revealed a high prevalence of lactic acidosis and or hyperlactemia. In a study in Soweto, South Africa, a total of 3.86% of patients had hyperlactemia or lactic acidosis.¹¹⁵ Another study in Durban, South Africa, also revealed that 1.57% of patients developed lactic acidosis.¹¹⁷ In this study a total of 1.08% of patients developed lactic acidosis. Sexual dysfunction has been cited as one of the reasons for poor adherence.¹³⁰ However, in this study, we do not know if one patient who had gynaecomastia also suffered from sexual dysfunction. Reason for changing regimen were documented in the patient's charts except for one that was recorded as unknown in this study, and one of the patients in this study whose treatment was changed due to gynaecomastia was actually recorded as gynaecomastia, not sexual dysfunction.

These findings imply that the predictors of adherence differ even in similar settings. Every programme should study predictors of adherence for a particular community. Thus these results cannot be generalized for all ART programmes even in similar settings.

This study followed patients for one year, but ART is for a lifetime. Adherence to treatment for a week or months is much easier than a lifetime. The fact that adherence was associated with date of starting treatment suggests the need for counselling and encouragement. However, through ongoing counselling, support and encouragement of patients, adherence can be maintained.¹¹²

5.2. Appointment adherence

Keeping appointment dates by 80.0% of patients was good and this is a predictor of adherence.⁹¹ The group that came early and within 14 days of the appointment date was also likely to have good adherence, however, the group that came after fourteen days were at risk of non-adherence. Patients were given one month's supply of ART at the 14 day follow up visit following initiation of treatment so that they would have at least sufficient treatment for two weeks before the next follow up visit. The worst group was the one that completely missed follow up visits. There may be other reasons for missing appointments that would lead to non-adherence to ART.⁷³ Before initiation, patients needed to demonstrate the ability to keep appointments by visiting the facility at least three times, the first time for CD4 count, and for the second and third time for baseline assessments and adherence training. Two studies in Johannesburg revealed very different factors associated with loss to follow up. One revealed financial problems as the main association followed by death, ART stopped by doctor, change of residence and receiving treatment elsewhere, commencement of medical aid and private treatment, incarceration and commencement of traditional medications and side effects of ART, as the causes of loss to follow up.²⁶ The other study revealed that 48.0% of patients who were lost to follow up were actually dead.⁹⁶ The same study also revealed that the most common causes of missing follow up visits were lack of money to travel to the clinic, not disclosing to employers and thus failing to ask for permission to go to the clinic because of fear of termination of services, and not disclosing to colleagues leading to difficulty taking treatment in their presence. Taking treatment at the correct time was found to be difficult for those who were using public transport, due to the many delays in the service.⁹⁶ In this study there was a slight difference in adherence to ART (87.0%) and appointment adherence (86.0%) suggesting minor inconsistencies in the data recorded. This could also be because patients had lied about the actual number of doses they had missed and pill counts to verify verbal reports were not done. There were no differences in the loss to follow up according to the demographic characteristics of age, sex, marital status, educational level and employment status. Death (14.0%) was not revealed as the main cause of loss to follow up as in the Johannesburg study,⁹⁶ thus a qualitative study would be helpful to reveal the causes of loss to follow up which was the main cause of missing follow up appointments in this study, however, if those patients that were in the second category of loss to follow up (unknown) (29.0%) were actually dead, a total of 9/21 (43.0%) would have died,

which is similar to the results of the Johannesburg study.⁹⁶ A tracking system was not in place to establish the cause of loss to follow up of patients who cannot be traced by telephone.

Predictors of loss to follow up vary among studies even in similar settings. In a study at Thembaletu clinic in Johannesburg financial problems were the cause of loss to follow up, followed by death,²⁶ while in a study that was done at a Johannesburg adult clinic, death was the main cause followed by transfer to another facility.⁹⁶ In other studies in Boston, USA⁹¹ and Louisiana,⁷⁴ age was associated with missing follow up appointments. However, in a Korean study a busy work schedule was cited as the main cause of missing appointments.⁹³ Due to varying definitions of loss to follow up, appointment adherence, not loss to follow up, was considered in this study.

In this study age and employment status did not predict appointment adherence but sex, educational level, CD4 count at the start of ART and the date of starting treatment were associated. Females were not likely to miss their follow up appointments. This may be because they take care of themselves and other family members better than males, and usually more females than males visit the public clinics not only for their own health but also to bring other family members. Patients with a CD4 count >50 cells/mm³ were more likely to miss follow up visits than those with CD4 count <50 cells/mm³. The patients with CD4 count >50 cells/mm³ were healthier than those with CD4 count <50 cells/mm³. The sicker patients honoured their appointment dates more than did the healthier patients. They were possibly more motivated than those who had a higher CD4 count although there could be other reasons. The higher the educational level the greater were the chances of missing a follow up appointments. This could have happened for similar reasons as adherence to ARVs.

Most of the patients on ART in the first year of the roll out of the ART program were initiated at Hlabisa Hospital. This means that all patients who needed ART had to travel to Hlabisa Hospital for initiation. The patients who attended their follow up visits at KwaMsane clinic and other clinics in the Hlabisa sub-district were less likely to miss follow up appointments than the patients who attended their follow up visits at Hlabisa hospital. The reason for that could be that it is easier and cheaper to get to KwaMsane than to Hlabisa Hospital. Patients who attended their follow up visits at other clinics in the sub-district probably attended the clinics nearest to their homes. It is also possible that some of these patients attended Hlabisa hospital in the first year of treatment because rollout to other clinics happened towards the end of the first year. Qualitative

studies to explore perceptions of discrimination and reasons for missing follow up appointments would be helpful.

Some patients who had missed a visit reported that they had not missed treatment doses. This is unlikely to be true although patients had received a month's supply of treatment at the two weeks follow up visit. This was a weakness of a retrospective study design, and a prospective design with self reports, pill counts and visual analogue scale could have been allowed further investigation. However, patients need to be helped to sustain adherence to ART. It is important to remember that patients may struggle to adhere to ART and may sometimes not be able to adhere. The counsellors and nurses must remember to be non-judgmental when dealing with patients and explore the difficulties that the patient is facing with regards to adherence to ARVs, explore the advantages and disadvantages again, build the confidence of the patient by praising the patient for what s/he is doing right, and providing support and encouragement. The stages of change model emphasizes that this is an ongoing process.¹¹²

5.2.1. Factors that were associated with the number of appointments missed - Poisson regression
The level of education and CD4 >50 cells/mm³ were the primary predictors of missing clinic visits in this study especially high school education followed by tertiary and primary school education.

Level of education

The probability of missing a clinic visit was six times higher in patients with high school education, five times in those with matric and tertiary education and four times higher in those with primary school education. This indicates that attention should be paid to adherence counselling¹¹⁰ of the educated group of patients who may be taken for granted

CD4 count >50 cell/mm³

The probability of missing a follow up visit in patients with CD4 count >50 cells/mm³ was twice as high in those patients with a CD4 count <50 cells/mm³. New ART programmes have shown that the proportion of patients with CD4 <50 is higher and decreases over time.¹³⁸ This indicates that patients entering new programmes are sicker and likely motivated to adhere to treatment which explain why those patients with CD4 count higher >50 cells/mm³ had a higher probability

of missing follow up visits. A higher CD4 count was associated with missing doses in an American study¹² which could have been related to missing follow up visits.¹³⁹ If a low baseline CD4 count is associated with higher probability of mortality¹³⁸ and a higher CD4 count is associated higher probability of poor adherence, strategies to retain patients in the ART programme need to be explored because the risk of loss of life outweighs the risk of loss to follow up.

Decentralization of services

KwaMsane and other clinics in the sub-district were protective of missing follow up visits. At the start of the ART programme all initiations were done at the hospital meaning that all patients in the sub-district had to travel to the hospital. The furthest clinic is about 65 km away. KwaMsane is easily accessible, situated along the N2, about 6km from Mtubatuba town. Many preferred to go to KwaMsane than to other clinics because of its accessibility.

In a decentralized programme in South Africa, a comparison of one year outcomes of clinics and hospital based ART programme revealed 2.2% and 19.3% loss to follow showing that satisfactory outcomes can be achieved at clinic level.⁴¹ This programme also reported an increase in clinic based ART patients and a decrease in the number of patients initiated at the hospital after one year of ART rollout, as another effect of decentralization of service.

Date of initiation

The later the patients started ART the lower their likelihood of missing follow up visits. Patients who joined the ART programme later were probably initiated at the clinic nearest to their homes or moved to the nearest clinic shortly after initiation of treatment and were thus more like to keep follow up appointments possibly due to reduced travelling cost. At Lusikisiki, South Africa,⁴¹ and Lesotho¹⁰⁸ decentralization of care resulted in increased clinic based ART patients and a decrease in the number of patients initiated at the hospital after one year of ART roll out. This might have been due to reduction in transportation cost for the patients who entered the programme later.

Employment

These results were different from the findings in Korean⁹² and Chinese¹³³ studies where work schedules were associated with greater appointment non-adherence, however, appointment non-adherence may affect dose adherence if patients wait until they run out of medications.

Personal schedule have been mentioned as being associated with adherence.^{58,62,38,63} In these studies patients mentioned barriers such as, pills needed to fit into schedule,³⁸ pills can be fitted into daily activities⁶² too busy,⁶³ and other schedule problems. This problem might be related to employment where the patient may miss follow appointments due to work. However in this study employment was not associated with appointment adherence probably because most of the patients were unemployed and also because of decentralization of care that improved accessibility of ART services.

5.3. Summary

This chapter presented a discussion of adherence to ARVs and appointments, namely, the higher the educational level, employment, being single, and a CD4 count >50 cells/mm³ increased the probability of missing ART doses. Other determinants of adherence included demographic characteristics, disclosure, support and signs and symptoms and side effects. In the following chapter the conclusion and recommendations will be presented

Chapter Six

Conclusions and Recommendations

Introduction

This chapter presents conclusions concerning the research findings and recommendations for further studies and improvement of the quality of treatment and care of patients with HIV and AIDS.

6.1. Conclusions

Although there was a limitation of missing data, from the available data the following conclusions based on the objectives were drawn from the results:

- The majority of patients enrolled in the ART programme were older single females, in a rural poor area who preferred not to disclose their positive HIV status to their sexual partners. Patients with a higher educational standard had a higher probability of missing follow up visits.
- There were no differences in disclosure by male and female patients and no associations were found between adherence, disclosure and treatment supporter.
- There were no differences between the mean baseline CD4 count of males and females. Although there was a significant increase in female CD4 counts after six months of ART, by twelve months, there were no significant differences in male and female CD4 counts. CD4 counts >50 cells/mm³ were predictive of a higher risk of missing ART doses than amongst those who had CD4 count <50 cells/mm.³ There were no differences in viral loads of males and females at baseline, nor after six and twelve months of antiretroviral treatment. Adherence was associated with viral suppression at 12 months.
- The programme was able to achieve a high overall treatment adherence of 87.0% which is comparable to that of a programme in an urban site (Soweto) in South Africa. Most of patients were also adherent to appointments (86.0%). Adherence is thus not a limitation to rolling out ART in a resource poor rural setting.
- Demographic characteristics of age, sex, residence, employment, next of kin, alternative next of kin and treatment supporter were not predictive of dose adherence and

appointment adherence. Only marital status was predictive, and being married was associated with a high probability of adherence to ART.

- The top five most common symptoms were loss of weight, headache, rash and cough, but were not associated with adherence. Although fatigue was experienced by only 9.0% of patients, those who experienced it tended to be less adherent to ART than those who did not experience this symptom. Patients need to be educated on the management of fatigue.
- Only 10 (3.7%) had to be changed regimens and hyperlactemia and TB seemed to be the main reasons for changing ART.

Other conclusions drawn from the results were the following

- The nurse/counsellor driven model used to decentralize treatment and care of patients with HIV and AIDS has proved helpful and provides support for scaling up the roll out without fear of lack of adherence.
- The feasibility of down referral to PHC clinics is confirmed by the results of this study suggesting that more people in need of treatment can receive this without compromising adherence.

6.2. Generalizability

This study was undertaken in only one rural sub-District (Hlabisa) and due to its limited scope and the problem of missing data further studies would need to be undertaken in other districts to confirm its generalizability.

6.3. Recommendations

6.3.1. Monitoring adherence

In this study adherence was based on recall of taking medications in the past seven days which means that memory of medicine intake was likely to be good.

While a seven-day recall may be advantageous for on the spot individual patient counselling, it may not be very useful for long-term adherence monitoring. One month recall using a visual analogue scale and routine pill counts is recommended.

6.3.2. Counselling

Due to the probability of patients with higher educational levels missing a follow up visit, it is recommended that more emphasis be placed on adherence counselling of the more educated group of patients who seem to be neglected because they are believed to have more knowledge and to understand the importance of adherence to ART. More time needs to be spent on adherence counselling of this group and patients with higher CD4 counts at initiation to ensure that they are equipped with the knowledge that missing ART doses can lead to disease progression and that they need to take ART doses as prescribed for the rest of their lives.

Because the majority of patients in the ART program were older women, awareness strategies and campaigns targeting engaging youth and men are necessary. The programme should also look at strategies of developing youth and men friendly environment at the clinics.

Although disclosure and treatment partner were not associated with adherence, qualitative studies are necessary to investigate disclosure and discrimination in this community because most patients preferred not to disclose to their sexual partners.

6.3.3. Side effects

Although some patients experienced side effects, most of these side effects were not a barrier to adherence, except for fatigue. Information on how to manage this symptom needs meticulous attention.

6.3.4 Tracking

Although only 12.0% of patients were non adherent, other recommendations include strengthening the tracking system of patients who have missed a follow up visit and putting in place referral systems using home based care organizations and community health workers who can assist to reduce this problem.

6.3.5 Improving access to VL lab results

A limitation of this study was the lack of VL results. In order to monitor the effectiveness of the ART programme timeous access to VL results is extremely important and these systems need to improve.

In respect of these recommendations, the researcher will present the results of the study to the sub-District and District office management teams. A copy of the report will be sent to all the clinics in the sub-District, provincial DoH HIV and AIDS office and the national HIV and AIDS Directorate.

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Appendix 1: Observation Checklist

Adherence to antiretroviral treatment by HIV infected patients in a rural District Structured Observation Check list (based on the KZNDoH form)

Date

--	--	--	--	--	--

 Site code _____ Research Assistants' Code _____

Questionnaire number

--	--	--	--

Section 1. Demographic Characteristics

1.1. Date of birth

D	D	M	M	Y	Y

1.2. Still in ART program 1 = Yes – go to 1.2. 2 = No – go to 1.1.3.1.

1.2.1. If no: 1 = died 2 = loss to follow up 3= Unknown 4= Transferred

1.2.2. Date of death/ loss to follow up/transfer

M	M	Y	Y

1.2.3. If transferred: transferred where

1.3. Age in years at initiation

1.4. Sex 1 = Male 2 = Female

1.5.1. Citizenship 1 = South African 2 = Other

1.5.2. If other Specify

1.6. Marital status 1 = Married 2 = Single 3 = Divorced 4. Cohabiting
5. Other (specify)

1.7.1. Next of kin

- 1 = Partner/spouse
 - 2 = Mother
 - 3 = Sister
 - 4 = Brother
 - 5 = Father
 - 6 = Other (Specify)
-

1.7.2. Has patient disclosed HIV+ status to next of kin? 1 = Yes 2 = No

1.7.2.1. If no, who has the patient disclosed to?

1 = Father

2 = Mother

3 = Brother

4 = Sister

5 = Grandmother

6 = Aunt

7 = Friend

8 = Other (specify)

1.7.3. Is the next of kin patient's treatment supporter? 1 = Yes 2 = No

1.7.3.1. If no, who is the treatment supporter?

1 = Father

2 = Mother

3 = Brother

4 = Sister

5 = Grandmother

6 = Aunt

7 = Friend

8 = other (specify)

1.7.4. Alternative next of kin

1 = Father

2 = Mother

3 = Brother

4 = Sister

5 = Grandmother

6 = Other (Specify)

1.7.4.1. Has patient disclosed HIV+ status to alternative next of kin?

1 = Yes 2 = No

1.8. Residential area

1 = Urban 2 = Rural 3 = Peri-urban 4 = Informal settlement

1.9. Highest Educational Standard

1 = None 2 = Primary 3 = High School 4 = Matric 5 = Tertiary

1.10. Employment

1 = Employed 2 = Unemployed 3 = Employed

regular part time 4 = Employed irregular part time

Section 2. Blood results

What were the blood results? Baseline six months 12 months

Write the results

CD4 _____ _____ _____

Viral load _____ _____ _____

Section 3. Adherence

3.1. Date of initiation.

D	D	M	M	Y	Y

3.2.1. Regimen: Mark with x

1a	1b	2	Other specify

3.2.2. Did patient change regimen

Y	N
---	---

3.2.2.1. If yes: to what

--

3.2.2.2. Reason for changing regimen

3.3. Clinic attendance and treatment

Clinic attendance and treatment	Mo nth 1	Mo nth 2	Mo nth 3	Mo nth 4	Mo nth 5	Mo nth 6	Mo nth 7	Mo nth 8	Mo nth 9	Mo nth 10	Mo nth 11	Mo nth 12
Did the patient honor ART follow up scheduled visits? 1=Yes; 2 = No; 3 = specify												
How many doses of treatment did the patient miss each month? Write the number												

Section 4. Symptoms and side effects

Did the patient experience these symptoms? 1=Yes 2=No	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12
Weight loss												
Rash												
Cough												
Fatigue												
Night sweats												
Fever												
Shortness of breath												
Jaundice												
Thrush oral												
Thrush vaginal												
Diarrhea												
Nausea/vomiting												
Headache												
Dizziness												
Foot pain/altered sensation												
Visual changes												
Vaginal/penile itching/discharge/burning/sores												
Abdominal pain												
Other (specify)												

Appendix 2: Ethics Clearance



UNIVERSITY OF
KWAZULU-NATAL

Research Office
BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Nelson R Mandela School of Medicine
Private Bag 7, Congella 4013
KwaZulu Natal, SOUTH AFRICA
Tel: 27 31 2501769
Fax: 27 31 2504609
E-mail:
Website:

18 January 2007

Mrs I Mthiyane
Dept of Community Health
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

Dear Mrs Mthiyane:

PROTOCOL: Adherence to Antiretroviral Therapy by HIV infected Patients in a Rural District. Mrs I N Mthiyane, Dept. of Community Health. Ref: H117/06

The Biomedical Research Ethics Committee considered the abovementioned application and the protocol was approved at its meeting held on 17 October 2006 pending appropriate responses to queries raised. These conditions have now been met and the study is given full ethics approval and may begin as at 18 January 2007. We acknowledge receipt of the permission from the Hlabisa Hospital Manager.

This approval is valid for one year from 18 January 2007. To ensure continuous approval, an application for recertification should be submitted a couple of months before the expiry date. In addition, when consent is a requirement, the consent process will need to be repeated annually.

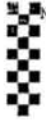
I take this opportunity to wish you everything of the best with your study. Please send the Biomedical Research Ethics Committee a copy of your report once completed.

Yours sincerely

A handwritten signature in black ink, appearing to read 'J. Moodley'.

DR J. MOODLEY
Chair: Biomedical Research Ethics Committee

Appendix 3: Permission from KZN DoH



HEALTH
KwaZulu-Natal

0333943782

HEALTH RESEARCH & Knowledge Management sub-component

10 – 103 Natalia Building,
330 Langallbalele Street
Private Bag x9051
Pietermaritzburg
3200

Tel.: 033 – 395 3070,

Fax.: 033 – 394 3782

Email.: Scelo.dlamini@kznhealth.gov.za

www.kznhealth.gov.za

Reference : HRKM052/06

Enquiries : Mr. S.S. Dlamini

Telephone : 033 – 395 3070

11 May 2007

Dear Ms. Mthiyane

Subject: Adherence research project

1. The research proposal entitled **Adherence to antiretroviral therapy by HIV infected patients in a rural District, KwaZulu-Natal, South Africa** was reviewed by the KwaZulu-Natal Department of Health. The proposal is hereby **approved** for research to be undertaken at the health facilities specified in your proposal.
2. You are requested to undertake the following:
 - a. Make the necessary arrangements with the health facilities identified in your proposal before commencing with your research project.
 - b. Provide an interim progress report and final report or dissertation (electronic and hard copies) when your research is complete.
3. Your final report or dissertation must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to scelo.dlamini@kznhealth.gov.za.

For any additional information please contact Mr. S.S. Dlamini on 033-395 3070.

Yours Sincerely

Dr. S.S.S. Buthelezi

Chairperson: Provincial Health Research Committee

KwaZulu-Natal Department of Health

uMnyango Wezempilo . Departement van Gesondheid

Fighting Disease, Fighting Poverty, Giving Hope

2604211

PERMISSION TO CONDUCT A RESEARCH STUDY/TRIAL

This must be completed and submitted to the Medical Superintendent/s / Hospital Manager/s for signature.

For King Edward VIII Hospital (KEH) and Inkosi Albert Luthuli Central Hospital (IALCH) studies please submit the document together with the following:

1. Research proposal and protocol.
2. Letter giving provisional ethical approval.
3. Details of other research presently being performed by yourself if in the employ of KEH, (individually or as a collaborator).
4. Details of any financial or human resource implications to KEH, including all laboratory tests, EEGs, X-rays, use of nurses, etc. (See Addendum 1)
5. Declaration of all funding applications / grants, please supply substantiating documentation.
6. Complete the attached KEH Form - "Research Details"

Once the document has been signed it should be returned to Mrs S Buccas, Biomedical Research Ethics Administration, Room 112 Old MRC Building.

To: Chief Medical Superintendent / Hospital Manager

Permission is requested to conduct the above research study at the hospital/s indicated below:

Site 1 address:
Albion HOSPITAL
and CLINICS

Investigator/s:
 Principal: Nokulunga Mthiyane
 Co-Investigator: _____
 Co-Investigator: _____

Signature of Chief Medical Superintendent/Hospital Manager:
[Signature]
 MEDICAL MANAGER

Date: 11th September, 2006

Site 2 address:

Investigator/s
 Principal: _____
 Co-Investigator: _____
 Co-Investigator: _____

Signature of Chief Medical Superintendent / Hospital Manager:

Date: _____

NB: Medical Superintendent/s / Hospital Manager/s to send a copy of this document to Natalia

Ewenlisha

SECTION 5 : INFORMED CONSENT

CONSENT DOCUMENT

Consent to Participate in Research

You have been asked that your clinic participate in a research study

You have been informed about the study by Mrs. Nokulunga Mthiyane.

You may contact Mrs. Mthiyane at 082 431 5608 any time if you have questions about the research.

You may contact the Medical Research Office at the Nelson R Mandela School of Medicine at 031-260 4804 if you have questions about your rights as a research subject. Permission has been obtained from KZN DoH to undertake this study.

You will be given a signed copy of this document and the information sheet which is a written summary of the research project.

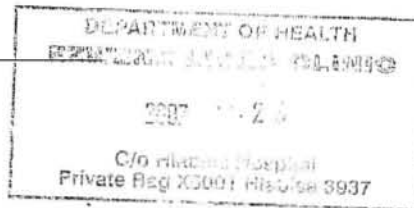
The research study, including the above information, has been described to me orally. I understand what my involvement in the study means and I voluntarily agree for my clinic to participate.

Mthiyane
Signature of Participant

23/06/07
Date

Mthiyane
Signature of Witness
(Where applicable)

23/06/07
Date



SECTION 5 : INFORMED CONSENT

CONSENT DOCUMENT

Consent to Participate in Research

You have been asked that your clinic participate in a research study

You have been informed about the study by Mrs. Nokulunga Mthiyane.

You may contact Mrs. Mthiyane at 082 431 5608 any time if you have questions about the research.

You may contact the Medical Research Office at the Nelson R Mandela School of Medicine at 031-260 4604 if you have questions about your rights as a research subject. Permission has been obtained from KZN DoH to undertake this study.

You will be given a signed copy of this document and the information sheet which is a written summary of the research project.

The research study, including the above information, has been described to me orally. I understand what my involvement in the study means and I voluntarily agree for my clinic to participate.

[Signature]
Signature of Participant

26.06.07
Date

[Signature]
Signature of Witness
(Where applicable)

26/06/07
Date

DEPARTMENT OF HEALTH
NINJANGANG C'W
8 JUN 2007
PRIV... 5001, 1408...
NINJANGANG W... 5

HLabisa

SECTION 5 : INFORMED CONSENT

CONSENT DOCUMENT

Consent to Participate in Research

You have been asked that your clinic participate in a research study

You have been informed about the study by Mrs. Nokulunga Mthiyane.

You may contact Mrs. Mthiyane at 082 431 5608 any time if you have questions about the research.

You may contact the Medical Research Office at the Nelson R Mandela School of Medicine at 031-260 4604 if you have questions about your rights as a research subject. Permission has been obtained from KZN DoH to undertake this study.

You will be given a signed copy of this document and the information sheet which is a written summary of the research project.

The research study, including the above information, has been described to me orally. I understand what my involvement in the study means and I voluntarily agree for my clinic to participate.


Signature of Participant


Signature of Witness
(Where applicable)

RECEIVED FROM THE PARTICIPANT
SOCIAL WORKER
2007-06-28
20.06.07
Date
PRIVATE BAG X50001, HLABISA 3937
UMNYANGO WEZEMPILO
20/06/07
Date

Inhlwathi

SECTION 5 : INFORMED CONSENT

CONSENT DOCUMENT

Consent to Participate in Research

You have been asked that your clinic participate in a research study

You have been informed about the study by Mrs. Nokulunga Mthiyane.

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You will be given a signed copy of this document and the information sheet which is a written summary of the research project.

The research study, including the above information, has been described to me orally. I understand what my involvement in the study means and I voluntarily agree for my clinic to participate.

Thuphelo LK 07/06/22
Signature of Participant Date

Dmaibela 07/06/22
Signature of Witness Date
(Where applicable)

DEPARTMENT OF HEALTH
INHLWATHI CLINIC
PRIVATE BAG X5001
HLABISA 3937
UMNYANGO WEZEMPILO

Inhlwathi

SECTION 5 : INFORMED CONSENT

CONSENT DOCUMENT

Consent to Participate in Research

You have been asked that your clinic participate in a research study

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You will be given a signed copy of this document and the information sheet which is a written summary of the research project.

The research study, including the above information, has been described to me orally. I understand what my involvement in the study means and I voluntarily agree for my clinic to participate.

Thompson LK 07/06/22
Signature of Participant Date

Dmaibela 07/06/22
Signature of Witness Date
(Where applicable)

DEPARTMENT OF HEALTH
INHLWATHI CLINIC
PRIVATE BAG X5001
HLABISA 3937
UMNYANGO WEZEMPILO

Mthiyane

INFORMED CONSENT

CONSENT DOCUMENT

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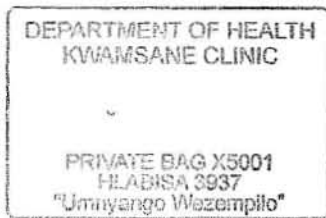
Signature of Participant

20/06/2007
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Signature of Witness
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Macabuzela

Page 13

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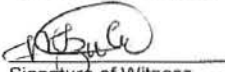
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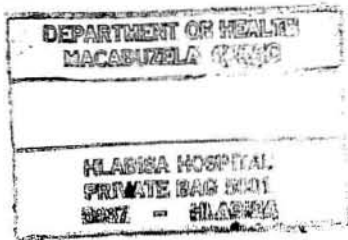
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Signature of Participant

27/06/07
Date


Signature of Witness
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[Handwritten Signature]
Signature of Participant

27/06/07
Date

[Handwritten Signature]
Signature of Witness
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I _____ been informed

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Siviso Mthiyane Rn 26.06.07
Signature of Participant Date

[Signature]
Signature of Witness
(Where applicable)

26/06/07
Date

DEPARTMENT OF HEALTH
MADWALENI CLINIC

26 JUN 2007

PRIVATE BAG X5001
HLABISA, 3937
UMNYANGO WEZEMPILO

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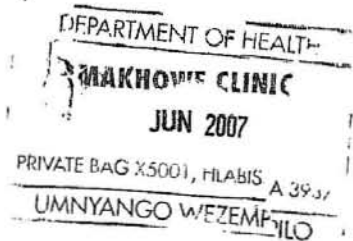
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B. Mankungu R.
Signature of Participant

26/06/07
Date

[Signature]
Signature of Witness
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M. Mthiyane
Signature of Participant

20/June 2007
Date

[Signature]
Signature of Witness
(Where applicable)

20/06/07
Date

DEPARTMENT OF
HEALTH
KZN
JUL 2007

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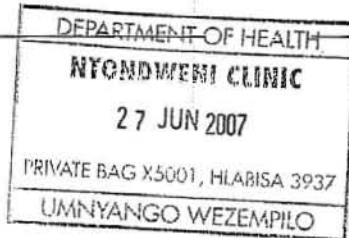
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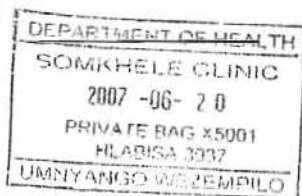
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Appendix 4

Process evaluation of the pilot study

Introduction

This review describes the experiences during a pilot study for the study: Adherence to Antiretroviral Therapy by HIV infected patients in a rural district, South Africa. It describes clinic entry, methods, data collection, lessons learnt and challenges experienced.

The purpose of the pilot study was to validate the data collection instrument and to train the research assistant.

Methods

Selection of the pilot clinic

We randomly selected Hlabisa Clinic as a pilot clinic. Each clinic name was written on a piece of paper that was folded and placed in a container. After all the papers with the names of all the relevant clinics were placed in a container, they were mixed and we asked someone who was not involved in the study to pick one of the papers. The name of the clinic in the paper that had been picked was the one where the pilot study was done. Philanjalo clinic (in Hlabisa hospital) was randomly selected.

Training the research assistant

The research assistant was trained to review patients' records, identify the required data from the data source and record it accurately in the observation schedule.

The next step was familiarizing the research assistant with the flow of patients from registration at the ART clinic on a daily basis. We used flow diagrams to show the patient flow and described activities on the first visit for CD4 count testing, obtaining the results, patient education visits, initiation visit and follow up visits, to familiarize the research assistant with the processes and patient flow including the recording at each step. We then went through all papers that are used at the ART clinics using mock charts to familiarize the research assistant, with all the recording system that were used at the ART clinics. We went through the observation tool to explain what was required and where to obtain the information in the patient's chart. We had

mock data collection exercises using the mock charts that resembled the charts at the clinics and after the research assistant was confident we moved to the clinic.

Entry at the clinic

At the clinic I introduced myself in my new role as a researcher. I was working as a trainer of the ART programme, and explained the purpose of the study, and obtained written informed consent from the sister in-charge. The research assistant was also introduced as a professional nurse and colleague who was going to collect data from the patients' records. We explained that the service would not be interrupted in any way during the study, that we need a place to sit, access to relevant records and that nothing was expected from staff members except to assist in accessing the records. We answered all the questions about the study from the staff.

Accessing the patients' chart

The files were kept in locked filing cabinets in groups. These groups consisted of fortnightly groups created according to the dates of initiation of antiretroviral treatment (for up to 2 weeks). A 30 day supply of treatment was given to the patient on initiation day and repeated at the 2 weeks post initiation follow up visit, so it was possible to combine patients for follow-up visits who had been initiated within the 2 week period, to form a group without compromising treatment availability.

The initiation register and a computer generated list of initiates for the period concerned were used to verify if all files had been obtained (This clinic at the hospital was the only ART site with a computer). Files were not removed from the ART clinic except for transfer to another clinic within the sub-district. There were standard operating procedures in place for transfer and movement of patients to ensure safety of charts and maintenance of confidentiality.

The computer generated list was only used to verify relevant charts and was left at the clinic at the end of the day and after completion of the pilot study.

The relevant data required was as follows:

Data characteristics	Data sources
Demographic data	government form
Disclosure	government form
Blood results	lab results section in chart or results file
Symptoms and side effect	flow chart, daily visit questionnaire
Number of doses missed	flow chart, daily visit questionnaire
Appointment records	Flow chart, prescription form, daily resister

Data collection

The observation schedule was used to record data about each patient's demographic information, disclosure, laboratory results adherence and symptoms and signs experienced from the relevant data sources. A total of twenty five records were reviewed in the pilot study.

Lessons learnt

The pilot study gave us information about the average time it took to locate the charts and record the data from one chart. This enabled the researcher to estimate the average number of charts per eight hour day and to estimate how long data collection would be expected to take given a certain number of patients' charts per clinic. This information enabled the setting of targets per day, per week and per month. It also assisted in providing an estimate of expenditure for the cost of hiring, and transport of, the research assistant.

It was very helpful to have a research assistant with a medical background. The training process was easy because she could understand the medical terminology and no time was wasted on that. At entry level it was helpful because there were less concerns about confidentiality from the sister in charge and other staff members at the clinic.

Explaining how the study would benefit the patients in the long term was also very helpful at entry. The staff was very helpful and cooperative.

Although spouse or partner was not in the list of choices for the alternative next of kin, there was no need to redesign the tool because this was not a popular choice for next of kin or alternative next of kin. Those patients who had not recorded a spouse or partner as next of kin also did not record their spouse/partner as an alternative next of kin.

The pilot also enabled the development of standard operating procedures for each clinic, in respect of accessing patients' charts, and use of the data collection instrument which was used in the main study. All the data was unlinked and no names or ID numbers were written anywhere in the data collection tools.

We realized during the pilot study that there were fewer men and children <15 years of age in the cohort, but decided that we would continue to collect the data and decide what to do when data collection was completed.

Challenges

The biggest challenge was missing data. The main reasons for missing data were gaps in recording or recording in a manner that was not helpful. This was particularly problematic for recording of demographic data especially next of kin. For example, where next of kin was recorded as a household member or family member, one could not tell who the person was and had to classify it as 'other'. However, this was the first time that the information collected had been used and as a trainer, the researcher was interested to further investigate adherence in the district, since this operational research could contribute to improved service delivery.

Some charts were not user friendly and it took a longer time to collect the information. Where file dividers had not been used it was difficult to locate the information. We had to learn to work systematically through the observation tool in order to leave no stone unturned.

The viral load and CD4 results also posed a challenge with a long turn around time or not being available at all. We worked through piles of results that had not been filled in the patient's chart. We filed results that were not filed; however, there were still many results that did not come back from the laboratory. CD4 count results were not a big problem at baseline level with a fairly short turn around time. Viral load results took up to 4 months to come back from the laboratory. As a result of the pilot there is now a quality improvement initiative to improve the data capturing, and a record review is undertaken every quarter.

**Appendix 5. Patients who were no longer in the ART programme,
n=21**

		n	%	p value
Sex	Male	7	33.3%	0.910
	Female	14	66.7%	
	Total	21	100%	
Marital status	Single	17	100%	0.142
	Total	17	100%	
Education	None	2	11.7%	0.615
	Primary	6	35.3%	
	High School	6	35.3%	
	Matric/tertiary	3	17.7%	
	Total	17	100%	
Employment	Unemployed	16	94.0%	0.258
	Employed	1	6.0%	
	Total	17	100%	
Why not in the programme	Died	3	14.0%	0.095
	Loss to follow up	12	57.0%	
	Unknown LTFU	6	29.0%	
	Total	21	100%	

Age	Total		Died		Loss to follow up		Unknown loss to follow up		p value
	n	%	n	%	n	%	n	%	
21-30 years	2	50%	1	50%	1	50%	0	0.0%	0.076
31-40 years	11	0.0%	0	0.0%	9	82.0%	2	18.0%	
41-50 years	7	14.3%	1	14.3%	2	28.6%	4	57.1%	
51-60 years	1	100%	1	100%	0	0.0%	0	0.0%	
Total	21	14.0%	3	14.0%	12	57.0%	6	29.0%	

n = Total number of patients on whom information on the variable was available