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Adherence to highly active antiretroviral treatment and loss to follow-up of pregnent women at the Themba Lethu Clinicu

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RESEARCH REPORT

TITLE

ADHERENCE TO HIGHLY ACTIVE ANTIRETROVIRAL TREATMENT AND LOSS TO FOLLOW-UP OF PREGNANT WOMEN AT THE THEMBA LETHU CLINIC

A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of:

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CANDIDATES DECLARATION

I, Shashikala Nagar (student number 0611757A) am a post-graduate student registered for the degree Masters of Public Health (MPH) at the University of the Witwatersrand, School of Public Health.

I am submitting written work for the research report component of the aforementioned degree.

I hereby declare the following:

- I confirm that the work submitted for the above course is my own work, except where I have stated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.

Signed: _____

Date: _____

DEDICATION

I dedicate this work to all the healthcare workers, default tracers and the data management team at Themba Lethu Clinic, Right to Care and the Clinical HIV Research unit who tirelessly continue to provide selfless services to the clinic and their dedication towards 'Treating AIDS seriously'.

Shashikala Nagar

ABSTRACT

INTRODUCTION

Although much focus has been placed towards rapid scale-up of antiretroviral treatment programmes and interventions for the prevention of mother-to-child transmission of human immunodeficiency virus (HIV), very little is known about adherence to highly active antiretroviral therapy (HAART) and loss to follow-up of pregnant women in antiretroviral treatment programmes in the developing world. In this retrospective cohort analysis, we described the baseline characteristics of adult women who were pregnant at the time of HAART initiation (pregnant at start) as well as women who became pregnant during follow-up after starting HAART (pregnant after) and women who never had a pregnancy (not pregnant) during the study period. We evaluated the association of pregnancy status with adherence and loss to follow-up in these three groups of women.

MATERIALS AND METHODS

Themba Lethu Clinic is an urban public-sector antiretroviral rollout facility in Johannesburg, South Africa. A retrospective analysis was conducted of all adult women initiating HAART at this clinic between January 2005 and December 2007. Clinical data from these patients was analysed for differences in rates of loss to follow-up, and measured adherence rates based on CD4 cell count response and virologic suppression. Regression models were performed to determine independent predictors of adherence and loss to follow-up and compared between the three groups. Survival analysis, in the form of Kaplan-Meier plots and log-rank tests, was used to compare the time to becoming lost to follow up.

RESULTS

Between 1 January 2005 and 31 December 2007, 5129 women initiated HAART at Themba Lethu Clinic, Johannesburg, South Africa. Of these women, 521 (10.0%) were pregnant at the time of HAART initiation (pregnant at start) and 291 (5.6%) became pregnant during follow-up (pregnant after). Women who were pregnant at start (16.6%) of HAART had less-advanced HIV disease than the not pregnant women and pregnant women after HAART initiation 4608 (89.9%). Overall pregnant women were significantly younger than the not pregnant women and fewer pregnant women had a CD4 <100 cells/mm^3 and a WHO stage III of HIV disease. There was no significant difference in the CD4 cell count response and virological suppression between the three groups of women based on pregnancy status at 6 months and 12 months (χ^2=2.1, p=0.347 and χ^2=4.4, p=0.111 respectively). However, women pregnant at start were more likely to become lost to follow-up (χ^2=15.8, P=<.0001) during follow up. In the multivariate Cox logistic regression model, independent predictors of loss to follow-up were pregnancy, baseline CD4 cell count and age at initiation. Being pregnant was significantly associated with being loss to follow-up.

CONCLUSIONS

Pregnancy is significantly associated with defaulting treatment and becoming lost to follow-up from HAART treatment programmes. Together with being pregnant, young age and a low CD4 at baseline are high risk factors for non adherence and loss to follow-up in this sub-group of the population. Early initiation of HAART with adequate pre-treatment counselling and ongoing adherence support could help improve adherence and retention in care for patients in treatment programmes in resource-limited settings. Interventions to trace patients immediately upon missed appointments would help to reduce the number of

patients' loss to follow-up. Moreover, integration of tuberculosis (TB), antenatal care (ANC) and HIV treatment services may maximize the effectiveness of interventions aimed at reducing the loss to follow-up rate. The initiation of HAART in pregnancy requires strengthened antenatal and HIV services that target women with advanced stage disease.

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ABBREVIATIONS AND ACRONYMS

HIV	Human Immunodeficiency Virus
AIDS	Acquired Immunodeficiency Virus
HAART	Highly Active Antiretroviral Treatment
LTFU	Lost To Follow-Up
ARV	Antiretroviral
ART	Antiretroviral Therapy
CCMT	Comprehensive HIV and AIDS Care, Management and Treatment
CD4	(Cluster of Differentiation 4) is a Glycoprotein Expressed on the Surface of T-helper cells
PEPFAR	Presidents Emergency Fund for AIDS Relief
USAID	United States Agency for International Development
NGO	Non-Government Organisation
NCCED	National Committee on Confidential Enquiries into Maternal Deaths

CHAPTER 1 INTRODUCTION

1.1 BACKGROUND

HIV/AIDS is one of the most challenging and serious public health crises that the world faces today. According to the WHO 2008 statistics, AIDS has killed more than 25 million people since 1981 and it is estimated that 33.4 million people, including 2.1 million children, are now living with HIV (WHO, 2008). Approximately 420, 000 children were newly infected in 2007, of which more than 90% where from sub-Saharan Africa (UNICEF, 2007). The overwhelming majority (90%) of HIV infected children acquire the infection through mother-to-child transmission (MTCT) (UNICEF, 2008; WHO 2008).

In 2008, sub-Saharan Africa accounted for 67% of HIV infections worldwide, 68% of new HIV infections among adults and 91% of new HIV infections among children. The region also accounted for 72% of the world's AIDS-related deaths in 2008 (WHO, 2008). One of the worst affected countries in sub-Saharan Africa is South Africa. It has more people living with HIV/AIDS than any other country in the world and has a higher HIV prevalence in females than males and an increasing rate in children (WHO, 2008). Sub-Saharan Africa remains the region most heavily affected by HIV.

Early in 2004, the South African National Department of Health began implementing the Comprehensive HIV and AIDS Care, Management and Treatment (CCMT) programme. The CCMT programme affirmed the commitment of the South African government to slow down

the increasing number of HIV infections and AIDS related deaths across the country. Themba Lethu, the adult HIV Clinic at the Helen Joseph Hospital is a public hospital site of the National ARV programme. Since April 2004, the clinic has been providing antiretroviral drugs through its CCMT programme to eligible adult patients according to the National Treatment Guidelines. HIV-infected pregnant women eligible for ART treatment are referred to Themba Lethu Clinic by the Coronation Women and Children Hospital, located approximately 1 km away. From the beginning of the programme, pregnant women eligible for ART presenting at the Themba Lethu Clinic have been "fast tracked" onto triple therapy. According to the National Treatment Guidelines, patients eligible for starting antiretroviral therapy need to be prepared via a series of screening visits for treatment readiness. This process takes several weeks before the patient could initiate treatment. Pregnant women with CD4 cell count of less than 200 cell/mm^3 cannot wait 4 - 6 weeks to start treatment, but need to start immediately. When these pregnant women are referred to antiretroviral treatment sites with other adult patients already worked up and waiting for treatment, pregnant women need to "jump the queue". The reason for fast tracking these women is to ensure optimal health of the pregnant mother and her unborn child.

Maternal mortality has previously been due to direct obstetric causes such as haemorrhage, hypertension, and complications of unsafe abortion. This pattern is changing in many places as AIDS-related complications now account for a high proportion of maternal deaths (Bwirire et al., 2008; Mellins et al., 2008). AIDS defining illnesses like tuberculosis and other opportunistic infections are becoming the leading cause of maternal mortality (WHO, 2004). Most pregnant women present to the ARV clinic with low CD4 cell counts and almost in the third trimester of their pregnancy, therefore all efforts are made to ensure suppression of

HIV virus and disease progression so that chances of mother to child transmission are reduced. Triple therapy has been found to be the most effective method of preventing mother-to-child transmission as it secures the health of the women and improves survival of the child (WHO, 2004).

Since the implementation of the ART programme in 2004 almost 13 000 adult patients have been in care at the clinic, of whom approximately 9000 are currently on antiretroviral treatment. Almost 60% of this group of adult patients on treatment are women with a mean age of 29 years.

The introduction of highly active antiretroviral treatment has resulted in a significant reduction of the HIV virus and an increase in CD4 cell count. In an evaluation by Coetzee et al (2004) noted that more women (70%) with a median age of 31 years assessed treatment. Evaluation of ART programmes have found improvement in clinical outcomes and a reduction in mortality rates (Coetzee et al., 2004; Wools-Kaloustain et al., 2006; Volmink et al., 2007). However, long-term retention of patients on ART treatment programme is becoming increasingly challenging (Rosen et al., 2007; Lawn et al., 2006; Bisson et al., 2008). Poor adherence to highly active antiretroviral therapy and commitment to regular clinic attendance are growing concerns (Rosen et al., 2007; Lawn et al., 2006).

Loss to follow-up is monitored closely at Themba Lethu Clinic and an initial evaluation has indicated that many of the patients who are lost to follow-up are pregnant women. This raised the question as to whether loss to follow-up is associated with being pregnant. The loss to follow-up rate impedes the benefit of the programme and raises serious concerns

regarding the development of resistant mutations and the risk of vertical transmission (Zorilla et al., 2003; Bardeguez et al., 2008).

In April 2007, the clinic introduced proactive tracing of patients who miss their antiretroviral collection appointment, using the contact telephone number provided by the patient. In order to make contact, three calls are made at three different times on different days. However, a great majority of these people are untraceable. It is challenging to keep up with patient's changing contact details and addresses. The clinic has therefore introduced the practice of updating the patients contact details and change of address at every visit. Patients not traced through three attempted telephone calls are referred to community health workers for a home-based visit. Traced patients are counselled and encouraged to return to the clinic. Patients traced and not found by community health workers are confirmed as loss to follow-up.

Patient attrition is a major concern for ART programmes in sub-Saharan Africa (Rosen et al., 2007; Brinkhof et al., 2008; Bwirire et al., 2008; Kaplan et al., 2008). Although much efforts are made to make antiretroviral treatment accessible, commitment to long-term therapy and keeping up with regular follow-up visits has been particularly challenging for patients on antiretroviral therapy (Ive et al., 2005; Giordano et al., 2007; Carrieri et al., 2006). Rates of loss to follow-up are extremely variable, with reported cumulative rates of up to 59% (van Oosterhout et al., 2005). Many large cohorts have seen considerable losses to follow-up (LTFU) with high rates like 27-30% occurring in the first few months after initiating HAART (Nachega et al., 2006; Lawn et al., 2006; Rosen et al., 2007). Moreover, it is becoming

increasingly difficult to follow the growing population of patients and to trace those who do not return to the clinic (Dalal et al., 2008; Brinkhof et al., 2008).

Losses to follow-up of pregnant women may threaten patient care as missing clinic appointments may have a negative influence on the health of these women leading to progression of disease and increasing vulnerability to opportunistic infections which may result in death (Bisson et al., 2006). Poor adherence to ARVs during pregnancy can lead to increased risks of vertical transmission. These are serious concerns from a public health perspective.

1.2 STATEMENT OF THE PROBLEM

At Themba Lethu Clinic, monitoring and evaluation of the ART program revealed that large number of pregnant women were lost to follow-up soon after initiating HAART. This raised a concern as to whether pregnancy is associated with poor adherence and becoming lost to follow-up.

As the Health System Information Manager at the Themba Lethu Clinic, I have been involved with the input and monitoring of the clinical data. I have over the years observed that a good proportion of the LTFU patients at the clinic are pregnant women. This has inspired me to undertake the task to investigate the loss to follow-up of pregnant women at the Themba Lethu Clinic with the permission and support of the clinic's Research Advisor.

1.3 JUSTIFICATION FOR THE STUDY

Maternal health and reduction of vertical transmission are primary concerns for women with HIV infection. With the widespread access to antiretroviral therapy, mother-to-child transmission has reduced significantly (Laine et al., 2000; Rodriguez et al., 2007). However, adherence and retention on treatment particularly pregnant women have proven to be serious challenges. Pregnant women may experience additional physical, economic and emotional stress and this may influence their adherence patterns (Bardeguez et al., 2008; Laine et al., 2000). Poor adherence in pregnant women causes great concerns regarding direct transmission of HIV to their unborn child. Failure to commit to regular follow-up at the ART clinic may lead to disastrous consequences to the women's own health, including the development of viral resistance, disease progression, and death (Bardeguez et al., 2008; Lain et al., 2000). Therefore, from a public health perspective the consequence of non adherence necessitates the need to improve maternal ART adherence and better retention strategies.

Many women learn their HIV status for the first time during their antenatal visit. This leaves them with little time to digest the fact that antiretroviral therapy is a life-long process (Kaplan et al., 2008). This research aims to get a better understanding of loss to follow-up in female ART patients and the impact of pregnancy on adherence and retention.

This analysis will be important in patient management, especially in the context of large-scale implementation of the ARV treatment programmes. It is expected that the findings

generated from this study will contribute to knowledge and understanding of non adherence and loss to follow-up and whether it has any association with being pregnant. The findings will also serve as a monitoring and evaluation tool for ART programmes and better tracing mechanisms to ensure long-term retention on treatment.

1.4 STUDY OBJECTIVES

The main objective of this study was to compare baseline characteristics and outcomes between different groups of women initiated on HAART at Themba Lethu Clinic from 1st January 2005 to 31st December 2007. We differentiated three groups of women based on their pregnancy status; namely women who initiated HAART because they were pregnant ('pregnant at start'), women on HAART who later fell pregnant ('pregnant after'), and women who did not have a pregnancy during the study period ('not pregnant').

The specific research objectives were:

1. To describe the baseline characteristics of women who were not pregnant, women pregnant at start and those that became pregnant after HAART initiation.
2. To compare the adherence and loss to follow-up rates between these women based on their pregnancy status.
3. To compare the mortality experience of the three groups of women.
4. To determine if the introduction of proactive tracing of patients in April 2007 reduced the proportion of pregnant women lost to follow-up.

CHAPTER 2 LITERATURE REVIEW

This chapter reviews some salient literature on adherence to antiretroviral treatment and loss to follow-up in pregnant women. It begins by discussing adherence and its importance in an effort to understand the outcomes of poor adherence. This is followed by the discussion on the complexities of adherence with regard to its measurement and prediction. Some predictors of adherence as highlighted in this literature review which leads to loss to follow-up are presented.

2.1 INTRODUCTION

Antiretroviral therapy is widely used in pregnant women and has shown to be highly effective in improving maternal health by reducing the progressive loss of CD4 cells that leads to severe immunodeficiency. A decrease in CD4 cells below 200 cell/mm^3 is the threshold where the risk of opportunistic infections increases *(*National Treatment Guideline, 2004). Therefore, current management of HIV infections aims to prevent opportunistic infection and to reduce mortality by starting HAART before CD4 cells decline below the critical *level (*National Treatment Guideline, 2004). In the case of pregnant women it is critical to suppress the progression of the disease and reduce the risk of mother to child transmission of HIV (UNAID, 2008). However, inadequate adherence to antiretroviral therapy may result in a poor clinical and virologic outcome. High HIV viral load may in turn increase infectivity of the patient and, thus, the probability of further spread of the infection, possibly with a drug-resistant virus (Bardeguez AD, 2008; Laine C,

2000). Adherence to therapy can be one of the most important factors that contribute to the efficacy of the treatment (Nachega et.al, 2007). However, little attention has been given to the relationship between adherence to antiretroviral therapy and pregnancy in sub-Saharan Africa.

Long-term adherence to antiretroviral therapy places extraordinary demands on patients, because they need to attend a clinic on a monthly basis to get medication. The rate of missed monthly appointments and loss to follow-up is increasing rapidly. Increasing numbers of loss to follow-up may lead to an underestimation of mortality. There is an urgent need to address the individual and public health consequences of non-adherence and retention in ART programmes.

2.2 MONITORING ADHERENCE

Adherence is defined as taking doses of drugs and sticking to the treatment plan. It means taking the correct dose of drugs at the correct time and in the correct way with correct dietary requirements (Ickovics and Meade, 2002). Patients who do not adhere to their treatment plan eventually begin to miss their scheduled clinic visits. If a patient misses three antiretroviral pick-up visits within 90 days after the last scheduled visit, the patient is considered loss to follow-up.

Follow-up and adherence to ART are important measures of the performance of ART programmes. Adherence can be measured based on patient self-report (via interview, questionnaire), pill counts, electronic medication monitoring devices such as the

medication-event monitoring system, or pharmacy refill records. Clinical and laboratory measures (viral load, CD4 cell count, urine analysis) are correlated with self-reports of adherence although failure of virological suppression can occur with perfect adherence (Djomand et al., 2003). There are fears that resource limited countries are unable to ensure adherence to ART due to their weak health systems, lack of capacity and infrastructure, which impede the rapid expansion of ART programmes and services (Bekker et al., 2006; Brinkhof et al., 2008).

2.3 FACTORS ASSOCIATED WITH NON-ADHERENCE

Factors contributing to non-adherence and poor clinic attendance are multiple and complex. Many factors have been found to influence adherence to medication. Bwirire et al (2008) identified the following reasons for loss to follow-up: not being adequately prepared, fear of stigma, discrimination, household conflict and even divorce on disclosure of HIV status, lack of social support, fear of breast feeding, long waiting hours at the clinic and inability to afford transport costs. When factors of adherence are scrutinized, two broad categories appears - factors related to the ARV regimen and factors related to the HIV-infected individual.

2.3.1 Factors related to the ARV regimen

One of the challenges of adherence to antiretroviral therapy is the complexity of the regimen, the strict dietary requirements, as well as the associated side effects (Ickovics and Meade, 2002). The AIDS Clinical Trial Group 370 found that adverse side effects were the

strongest predictor of non-adherence (Ickovics and Meade, 2002). Side effects of the treatment include but are not limited to diarrhoea, fatigue, nausea, vomiting, peripheral neuropathy and metabolic changes (Brinkhof et al., 2008; Laine et al., 2000; Bwirire et al., 2008). In the trial group, these side effects were found to occur in the first to the fourth week after initiation of HAART. (Ickovics and Meade, 2002). Difficulty ingesting large pills including heavy pill burden are also found to contribute to non-adherence (Bwirire et al., 2008).

2.3.2 Factors related to pregnant women

Some studies have found an association between adherence and factors such as age, gender, race, economic status, educational level and literacy (Ickovics and Meade, 2002; Bwirire et al., 2008, Rosen 2007). Knowledge and attitude to treatment and care-giving responsibilities have been found to be related to adherence (Carrieri et al., 2006; Weiser et al., 2003). In addition, emotional, economical and physical stress as well as other demands that pregnant females experience may sway their patterns of adherence to HAART (Bardeguez et al., 2008; Laine et al., 2000). Low-level of education and having a suspicion that the antiretroviral drug may harm the baby may impact negatively on some women. Fear of disclosure and wanting to avoid taking medication in the presence of family or friends, feeling depressed, hopeless, or overwhelmed may contribute to the predictors of non-adherence, especially in the case of pregnant women who has just known her HIV status (Mills et al., 2006). Pregnant women may also encounter additional financial costs as they are required to visit the antenatal clinic as well as the ARV clinic on a monthly basis. Loss of income due to absenteeism from work, transport cost to and from the clinics, the

cost of user fees, long waiting hours and the burden of childcare during medical visits may discourage women from attending to their visits (Rosen et al., 2007; Mills et al., 2006). Other barriers include doubting the effectiveness of HAART, having a decreased quality of life; uncertainty of long-term effects and unwanted changes in body image (Mills *et al.*, 2006).

There is currently little data on ARV adherence in pregnant and post-partum women. Majority of the studies that have been conducted were in resource-rich settings. We reviewed adherence and loss to follow-up rates in general and compared the findings in the developed and the developing countries.

2.4 COMPARISON OF ADHERENCE AND OUTCOMES IN LOW AND HIGH INCOME COUNTRIES

In 2008, Brinkhof et al. used data from a network of treatment programmes in low-income countries to examine the early loss of patients starting HAART. They found that only 3% of patients were known to have died by 6 months, but an average of 21% were lost to follow-up by that time and 4% never returned after initiating treatment. Brinkhof et al (2008) found that treating a maximum number of new patients has been the priority of many public sector programmes. This implies that many sites find it increasingly difficult to cope with the growing patient population and to keep track of those not keeping up with their appointments.

Mills et al (2006) conducted a meta-analysis to evaluate estimates of adherence to antiretroviral therapy in sub-Saharan Africa and North America. The study found that favourable levels of adherence as measured through patient self-report could be achieved in the sub-Saharan Africa and suggested that concerns related to the expansion of the ART programme are unwarranted. This was evident from the findings, which showed that from a pooled estimate of ART adherence in North America, 55% of patients achieved adequate levels of adherence compared to 77% of patients in sub-Saharan Africa (Mills et al., 2006).

Similarly, correlates of adherence, namely viral load suppression and gain in median CD4 cell count has been shown to be similar in the developed and developing world. Pooled analysis of 30 treatment cohorts (18 from Africa, Asia and South America and 12 from Europe and North America) showed that 76% of patients in low-income countries compared to 77% in high income countries achieved viral load suppression after 6 months of being on ART (ART-LINC and ARTCC Group, 2006). The highest mortality occurred during the first few months after starting treatment, where 78% of deaths in low-income countries and 62% in high-income countries occurred during the first 6 months. The higher mortality in low-income countries has been attributed to co-morbidities of TB and other opportunistic infections where access to prophylaxis, diagnostic facilities and effective treatment is often more limited (ART-LINC and ART-CC Group, 2006: 822). In addition, the high mortality within the first few months on ART has been attributed to patients presenting with late stages of HIV disease (Mills et al., 2006, Rosen et al., 2007). There are a number of possible reasons why people test late, some of which are denial, stigma and confusing political statements (Ickovics and Meade, 2002; Bwirire et al., 2008, Rosen 2007). Loss to follow-up of patients

during the first few months of being initiated on HAART was found to be 15% in low income countries compared to 5% in high-income countries (ART-LINC and ART-CC Group, 2006).

2.5 ADHERENCE TO ANTIRETROVIRAL THERAPY IN PREGNANT WOMEN

Antiretroviral therapy is widely used in pregnant women and has proven to be highly effective in the prevention of mother-to-child transmission (Turner et al., 2000; Bwirire et al., 2008). The majority of studies that have been conducted on adherence in pregnant women are from resource-rich settings.

Studies in the developed world that have examined adherence to antiretroviral treatment in pregnant women using self-reporting or pill counts as an adherence measure have indicated that adherence is much higher in pregnant versus not pregnant women (Bardefuez et al., 2008; Mellins et al., 2008; Rodrigues et al., 2007).

However, when more objective measures of adherence, such as pharmacy data or blood and urine assays were used, results indicated generally poor adherence in pregnant women (Laine et al., 2000; Demas et al., 2005). In an audit report, Kingston et al (2007) evaluated that age, ethnic origin and knowledge of HIV status prior to pregnancy did not appear to be factors contributing to non-adherence but being treatment naïve and poor adherence did influence non-attendance at the clinic. This is contrary to the findings in the developing countries where better adherence was found to be independently associated with older age (>29 years) in both pregnant and non pregnant women (Rodriguez et al., 2007).

2.6 LOSS TO FOLLOW-UP

With the rapid expansion of the Antiretroviral programmes, substantial rates of loss to follow-up in resource limited settings have been identified, however the causes of loss to follow-up in these settings have received little attention (Rosen et al., 2007; Dalal et al., 2008*).* In a recent study, Dalal et al (2008) examined factors affecting retention in an urban public sector clinic in Johannesburg. Among 1631, 267 (16.4%) of the patients were classified as lost to follow-up with 65.9% being females.

In a retrospective analysis of women referred to a community based clinic in Southern Africa, Kaplan et al (2008), found that although there was no significant difference in the mortality rates of pregnant and non-pregnant women, pregnant women had a substantially higher risk of loss to follow-up both pre-treatment and once treatment had started.

Reasons for loss to follow-up were not established from Kaplan's retrospective review, however loss to initiation (13.2% in pregnant vs. 6% in non pregnant women) and loss after initiation (32% pregnant on treatment vs. 13% non pregnant on treatment) were found to be substantially higher among pregnant women. Those women that defaulted treatment were found to have done so within the first 3 months after initiation. Pregnancy and age were independently associated with loss to follow-up (Kaplan et al., 2008). In the pre-treatment analysis, they found a crude overall programmatic loss of 19.8% among pregnant women as compared with 17.1% among non-pregnant women (p <0.243). Pre-treatment mortality was significantly lower among pregnant women (0.3% vs. 4.7%; p<0.001) though the pre-treatment loss to follow-up was higher (13.3% vs. 6.0%; p<0.001).

The reason why pregnant women default treatment and become lost to follow-up is uncertain. However there is a possibility that some of patients being flagged as loss to follow-up may have transferred to another treatment facility, may have moved due to employment, or may have died (Bisson et al., 2008). The administration of antiretroviral therapy to individual patients and the ongoing monitoring and evaluation of HIV/AIDS treatment programmes critically depend on regular and complete patient follow-up (Brinkhof et al., 2008). According to the systemic review by Rosen et al (2007), ART programmes in Africa have retained about 60% of their patients at the end of two years since the beginning of large scale ART access. As per their findings, most patients in Africa initiate antiretroviral treatment only after an AIDS defining illness. In this review, loss to follow-up was found to be the main cause of attrition followed by death.

2.7 MORTALITY

Reducing maternal mortality, the fifth United Nations Millennium Development Goal, requires a thorough understanding of the causes of maternal death and of the contribution of avoidable or remediable factors. The World Health Organization (WHO) estimates that, in 2005, there were 536, 000 maternal deaths worldwide.

HIV has now become the single leading cause of death in South Africa, regardless of age, sex or race (Bradshaw and Dorrington ,2005; Pieterse et al., 2003; Dorrington et al., 2004). However, it is important to note that the burden of HIV disease is not distributed evenly across population groups in the country. When the data are disaggregated by age, race and

sex, they demonstrate that black women (South African women of African descent) of reproductive age, as well as black children under five, are bearing the brunt of morbidity and mortality in South Africa due to HIV-related opportunistic infections. Black South African women who are pregnant have the highest HIV prevalence in the country, estimated at 30.2% (Government of South Africa, 2007). South African women in the 25 to 29 age group have an estimated HIV prevalence of 33%.

According to the review by the National Committee on Confidential Enquiries into Maternal Deaths (NCCEMD) as outlined in the Saving Mothers 2005-2007 report, there has been a 20.1% increase in the number of deaths reported compared with the previous triennium (2002-2004). The "big five" causes of maternal death have remained the same, namely non-pregnancy related infections – mainly AIDS (43.7%), complications of hypertension (15.7%), obstetric haemorrhage (antepartum and postpartum haemorrhage; 12.4%), pregnancy related sepsis (9.0%) and pre-existing maternal disease (6.0%). Women less than 20 years of age were at greater risk of dying due to complications of hypertension whereas women 35 years and older were at greater risk of dying of obstetric haemorrhage, ectopic pregnancies, embolism, acute collapse and pre-existing medical disease.

Non-attendance and delayed attendance at the health institutions were the most common patient orientated problems. Poor transport facilities, lack of health care facilities and lack of appropriately trained staff were the major administrative problems. The most frequent health care provider avoidable factors were failure to follow standard protocols and poor problem recognition and initial assessment. Assessors thought 38.4% of the deaths were clearly avoidable within the health care system (patient orientated factors being excluded).

Complications of hypertension, obstetric haemorrhage, pregnancy related sepsis and non-pregnancy related infections were responsible for 4 out of 5 of avoidable deaths.

Part of the challenge is likely owing to the difficulty in initiating HAART in a midwife-driven antenatal care service and the subsequent logical demands of coordinating HIV and antenatal care.

CHAPTER 3 METHODOLOGY

3.1 INTRODUCTION

In this chapter, the study design and methodology are presented. The study population is described and selection of the study sample is explained. The data collection system at the study site is described and details of the variables to be analysed are presented. Definition of each clinical and immunological result as well as the outcomes of interest is given and the chapter ends with a review of the data analysis plan and ethical considerations of this project.

3.2 STUDY DESIGN

This study was an analytic retrospective cohort design using secondary data collected from all HIV positive women who initiated antiretroviral therapy from 1st January 2005 to 31st December 2007. Women were divided into three groups according to whether or not they were pregnant during the study period and the timing of any pregnancies in relation to the initiation of HAART. Adherence, loss to follow-up and mortality rates were the main outcomes compared between the groups.

3.3 STUDY SITE

Themba Lethu Clinic is one of the largest public antiretroviral rollout sites in South Africa. The clinic is based at Helen Joseph Hospital and its population can be considered representative of an urban population accessing antiretroviral therapy in the public sector. Moreover, this clinic uses an electronic patient management tool in real time and, as such is one of the few sites with up-to-date longitudinal data available and accessible for secondary analysis.

3.4 STUDY POPULATION

The study sample consists of 5174 females initiated on HAART at the Themba Lethu Clinic between 1st January 2005 and 31st December 2007. Since January 2005, all pregnant women eligible for HAART were referred to Themba Lethu Clinic from the Coronation Women and Children Hospital. All data from the patient's records were completely captured onto an electronic data system by December 2007. This allowed patients' longitudinal information to be evaluated. It is for this reason that the study period was chosen from 1st January 2005 to 31st December 2007. Of these 5174 women that enrolled, we had 4317 women who never had a pregnancy and 857 women that ever had a pregnancy during the study period. Although our original plan was to compare the differences between the pregnant and the non pregnant group, initial analysis revealed that the pregnant group of women could further be grouped based on the timing of the pregnancy. Women who never had a pregnancy during the study period were termed as 'not pregnant' while women that were

pregnant at initiation were referred to as 'pregnant at start' and women who fell pregnant after initiation of HAART during the study period were referred to as pregnant after. The group of women that were pregnant at initiation and had a second pregnancy during the study period was too small for comparative analysis and so was excluded for simplicity.

Exclusion criteria:

- Female patients younger than 18 years of age at the time of enrolment in the clinic were excluded from the study.
- Women who were not HAART naïve and who were transferred in from other treatment sites were excluded from the study as baseline clinical data for these women was not available and the study objective was to compare baseline characteristics with subsequent follow-up information in women based on pregnancy status.

3.5 TRACING INTERVENTION

The telephone tracing and home visit tracing was implemented in April 2007 for patients who had missed their scheduled appointments. Three telephone call attempts at three different times and days are made to trace the patient. Traced patient are counselled and a new appointment is given. Patients that cannot be contacted are referred to a team of community workers who do home visits to locate the patients by using the address provided. Those patients that cannot be found by the home visit team were confirmed lost to follow-up.

3.6 DEFINITIONS OF TERMS

Right to Care

Right to Care is a PEPFAR (President's Emergency Plan for AIDS Relief) and USAID (United States Agency for International Development) funded NGO. The NGO supports the ART implementation at the Themba Lethu Clinic in its development to build institutional capacity and establish organisational infrastructure required to support the implementation of the ART treatment programme.

Antiretroviral therapy

Anti-HIV drugs to suppress the progression of viral replication.

Adherence

ART Adherence was defined using the CD4 cell count response. An increase in CD4 cell count from the baseline CD4 cell count by a rise of 100 cells or more after initiation of HAART denotes an effective immunological response.

Adherence to ART suppresses the viral load. Hence a decrease in HIV viral RNA to less than 400 viral copies after initiating HAART denotes good virologic response due to adherence. Subsequent increases in CD4 cell count during the study also denotes good adherence with

an improvement in immunological response due to regular intake of prescribed HAART therapy.

CD4+ T-lymphocyte count

The number of "helper" CD4+ T-lymphocytes in a cubic millimeter of blood. With HIV, the absolute CD4 cell count declines as the infection progresses. The absolute CD4 cell count is frequently used to monitor the extent of immune suppression in persons with HIV.

Viral Load

Viral load means the level of virus found in the blood and is measured in the number of HIV RNA Copies/ml blood plasma. The viral load decreases with optimal treatment. The aim of the antiretroviral treatment is to have as low a viral load as possible i.e. an undetectable number of HIV RNA copies. The measuring method has become better over time and hence also the detection limit for viral load has decreased.

Virological suppression

Virological suppression was defined as a reduction of HIV viral load to less than 400copies/ml.

Defaulter

At the Themba Lethu Clinic, when a patient fails to return to the clinic one week after her/his scheduled ARV collection date, the patient is flagged as a defaulter.

Loss to follow-up

A patient is defined as lost to follow-up if she/he does not return to the clinic ≥3 months after the last scheduled medical or ARV collection visit date.

Maternal Mortality

Maternal mortality is defined as death of women while pregnant or within 42 days of termination of pregnancy from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes.

3.7 STUDY VARIABLES

The exposure measured is pregnancy and the outcomes of interest are adherence, loss to follow-up and mortality. ART adherence was measured using the CD4 cell count response and the HIV viral load suppression. If a patient was not contactable after three telephonic attempts, the tracing was referred to the home base visit team. Patients traced and not found by the home based team were confirmed as loss to follow-up.

3.8 DATA COLLECTION

This study is based on secondary data analysis of the existing data collected by the Themba Lethu Clinic. The data are captured and stored at Themba Lethu clinic in a proprietary medical management system *TherapyEdge – HIV*^{TM}. Right to Care and the Clinical HIV Research Unit of the Department of Medicine at the University of Witwatersrand agreed to provide a de-identified dataset. Any observation with values which seemed implausible were set to missing variables which were cleaned in this way included:

Height – plausible values were deemed to be between 135 and 200 centimetres

Weight - plausible values were deemed to be between 30 and 200 kilograms

CD4 cell counts – these are reported as integers by the laboratory and so values with decimal places were considered typing or capturing errors and set to missing.

TherapyEdge – HIV^{TM} serves as a clinical Electronic Medical Records (EMR) solution and an HIV/AIDS disease management tool. Longitudinal clinical data can be collected and reviewed to both evaluate treatment outcome and to identify trends in disease patterns. Patients' demographic and contact details are recorded at the initiation visit. At subsequent visits the patient's vital signs, clinical notes, new diagnoses and medication profile is recorded in real time on the electronic patient management system. Additionally, blood test results for CD4 cell count, HIV viral load, full blood count and liver function, which are done at each scheduled visit, are collected and entered onto the electronic database by trained data capturers.

3.9 DATA EXTRACTION

The data was provided to the researcher from *TherapyEdge – HIV*^{TM} after removing all personal identifying information. Baseline characteristics were obtained for the following: age, date of initiation, pregnancy status, WHO stage, CD4 cell count, viral load and employment status. Data was also obtained for the following: date of last ARV visit, date transferred out, date of death, and duration on treatment before becoming lost to follow-up. The analysis focused on female patients on HAART who met the inclusion criteria in the data set.

3.10 DATA PROCESSING METHODS AND DATA ANALYSIS

Data was analyzed using SAS v. 9.1. The baseline characteristics of the three groups of women, pregnant at start, pregnant after and not pregnant were summarised using descriptive statistics. Differences in demographic and clinical characteristics were compared between the three groups of women and associations of these characteristics with adherence and loss to follow-up were assessed using the Pearson chi-squared (χ^2) test for dichotomous variables. ANOVA was used to compare the continuous outcome variables of the three groups.

Loss to follow-up, duration on ARV treatment, CD4 cell count and viral load were used to define the key outcomes of interest. These outcomes were compared between not

pregnant women, pregnant at start and pregnant after. Potential confounders such as age and clinical stage were included in the analysis.

Logistic regression was used to estimate the associations of baseline characteristics with adherence to estimate the odds of viral load suppression at 6 month intervals after HAART initiation for the three groups of women. We first looked at the bivariate analysis of potential confounding variables before the multivariate analysis using Cox Regression models to estimate any association. Only multivariate results are presented.

Time to event analysis was performed using survival analysis techniques including Kaplan-Meier estimates, a log rank test and proportional hazard model. Survival analysis can be used to study any process where the outcome of interest is the time to the event. In case of this study the outcome of interest is the time from initiation of HAART to being loss to follow-up. Date of HAART initiation and date of final outcome were used as the start point and end point of follow-up time, respectively. Survival analysis methods correctly use both censored and uncensored observations. SAS v9.1 was used to compare survival distributions for the event-time variables of interest and to perform regression analysis based on the proportional hazards model to adjust for potential confounding variables. All statistical significance was calculated using a 5% level of significance.

3.11 ETHICAL CONSIDERATIONS

Women in this study sample were identified by a unique identifier generated randomly by the *TherapyEdge- HIV*^{TM} system. The unique identifier does not relate to the participant's

date of birth. All personal identifiers were removed prior to the data being given to the researcher for secondary analysis. The researcher was unable to identify participants in the sample or to collect informed consent from the same study population. The study was conducted according to the Standard Operating Procedure (SOP) of the Clinical HIV Research Unit governing the analysis of data from the Themba Lethu Clinic Cohort (See Appendix A). Data was provided to the researcher only after obtaining permission from the clinic and hospital authorities.

The study is a retrospective unlinked record review. The use of this retrospective data has already been passed (Blanket Approval) by the Human Research Ethics Committee (HREC), University of the Witwatersrand for use without informed consent (M060626) (APPENDIX A).

Ethical clearance for this specific study was obtained from the HREC, University of the Witwatersrand (Protocol no. M080229) (APPENDIX B). Permission to conduct the study (APPENDIX C) was also granted by the CEO of Helen Joseph Hospital where the Themba Lethu Clinic based.

CHAPTER 4 RESULTS

4.1 INTRODUCTION

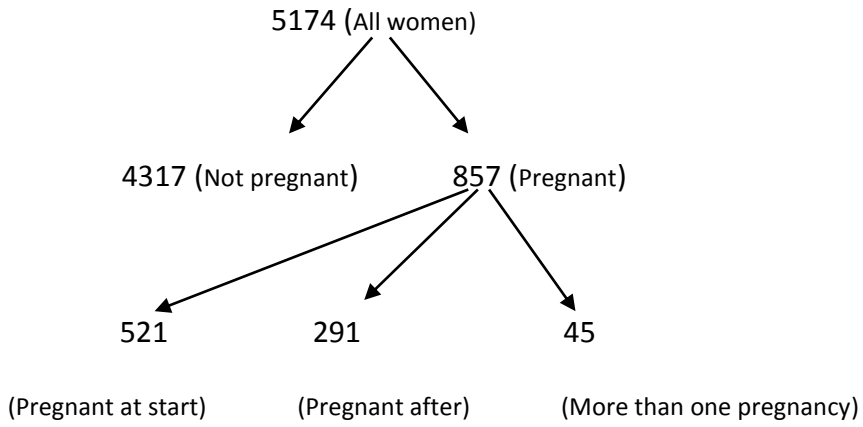
This chapter presents the key results of the study. We compare the baseline characteristics, adherence and loss to follow-up rates of three groups of women attending Themba Lethu Clinic. Women who never had a pregnancy during the study period were termed as 'not pregnant' while women that were pregnant at initiation were referred to as 'pregnant at start' and women who fell pregnant after initiation of HAART during the study period were referred to as 'pregnant after'. We then tried to determine if the introduction of the tracing intervention made any difference in the proportion of pregnant women loss to follow-up.

4.2 COHORT CHARACTERISTICS

During the period from 1st January 2005 to 31st December 2007, 5584 women were enrolled on the antiretroviral treatment programme at the Themba Lethu Clinic. Of these, 410 were excluded from the study as they were transferred into the clinic from other antiretroviral treatment programmes. All women included in the study were treatment naïve at the time of initiation of HAART and older than 18 years of age. The study sample consisted of 5174 women. 857 (16.6 %) of the women were pregnant at some stage during the study period while 4317 (83.4%) women were not. In the pregnant group, 521 (60.7%) females were pregnant at initiation of antiretroviral treatment, 291 (33.9%) became pregnant while on antiretroviral treatment and 45 (5.2 %) women were pregnant at initiation and then had a

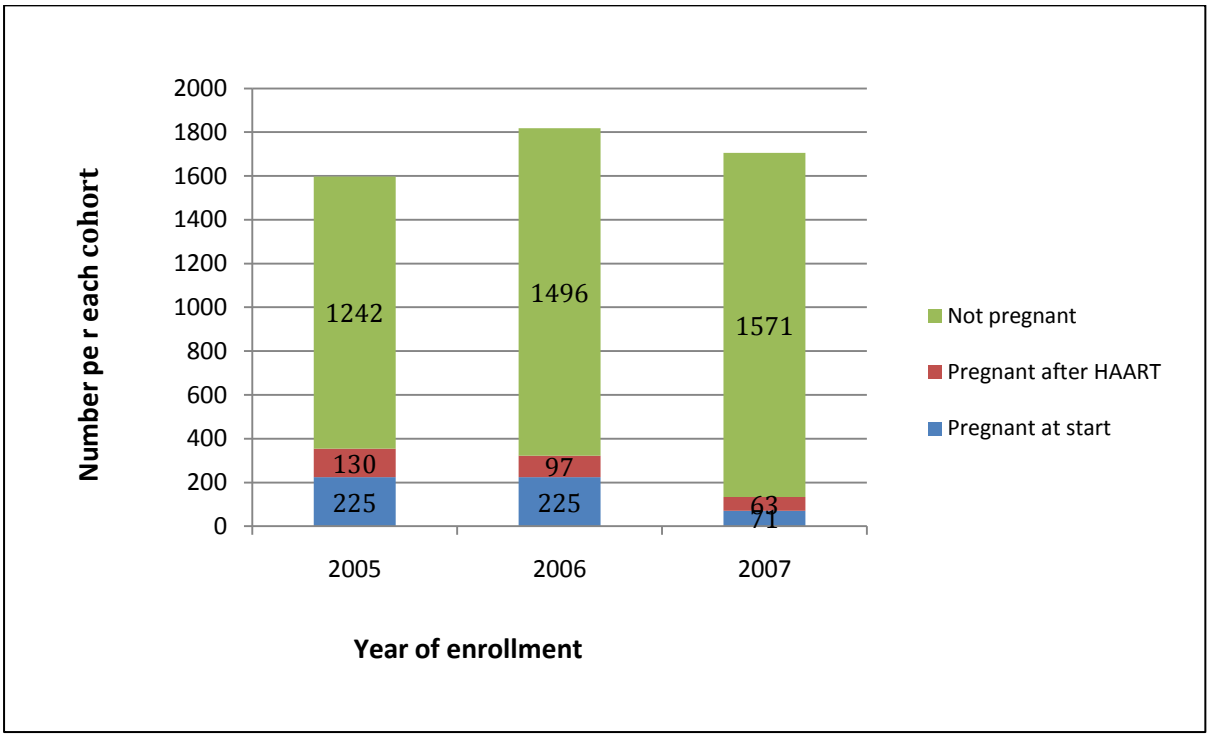
second pregnancy during the study period (Figure 1). This group of women was too small for comparative analyses and therefore we excluded it from subsequent analyses. The study sample that remained and was used in all the analysis consisted of 5129 women.

Figure 1: Women Enrolled at Themba Lethu Clinic During the Study Period



The enrolment of women at the Themba Lethu Clinic presented in Figure 2 shows that there has been a steady increase in the number of women enrolling at the clinic over the three years of the study period, 01 January 2005 to 31st December 2007. However, the proportion of women pregnant at start is seen to have dropped in the 3rd year of the study period (43% in 2005, 43% in 2006 to 14% in 2007). There was a gradual increase in the not pregnant group 29% in 2005, 35% in 2006 to 36% in 2007. However, a gradual drop was also seen in the proportion of women pregnant after starting HAART over the study period from 45% in 2005, 34% in 2006 to 22% in 2007.

Figure 2: Distribution of Women at Themba Lethu Clinic Over 3 Years



4.3 BASELINE CHARACTERISTICS OF THE THREE GROUPS OF WOMEN

The women pregnant at start were significantly younger with a mean age at initiation of (29.8 years, SD=5.06) compared to the not pregnant women with a mean age at initiation (36.2 years, SD = 8.53). There was no significant difference in the mean age (30.2 years, SD=4.93) of women pregnant at start compared to women pregnant after.

Multiple comparison of baseline CD4 cell count using Bonferroni test showed that the CD4 cell count between women pregnant at start was significantly higher than the baseline CD4 cell count of the not pregnant group ($\mathcal{F}$=38.44, ***p***=0.0001) and the women pregnant after HAART initiation, while there was no significant difference in the baseline CD4 cell count of

the not pregnant and the women pregnant after HAART ($\mathcal{F}$=7.43, ***p***=0.0856). Pregnant women had the highest average BMI of 27.1 due to the added weight of the unborn baby. However, there was no significant difference in the BMI among the women pregnant after ($\mathcal{F}$=1.10, ***p***=0.3346) and the not pregnant women.

There is a significant difference (χ^2 =181.7 ***p=***<0.001) in the baseline WHO stage among the three groups of women. Three quarters of the women pregnant at start presented with WHO stage one, while 43.2% of the women pregnant after HAART initiation and 39.7% of the not pregnant women, presented with WHO stage one. On the other hand, just over 1% women pregnant at start reported with WHO stage four compared to almost 10% not pregnant women presenting with WHO stage four.

Table 1: Baseline Characteristics at Initiation of HAART by Pregnancy Status

	Not-pregnant	Pregnant at start	Pregnant after	Statistical Test
Total (n)	4317	521	291	
Age (years) (mean, SD)	**(n=4317)** 36.2 years (8.5)	**(n=521)** 29.8years (5.0)	**(n=291)** 30.2years (4.9)	$\mathcal{F}$ = 202.81 (***p***=<0.001)†
Employment status employed % unemployed %	**(n=4317)** 38.04% 61.98%	**(n=521)** 36.2% 63.7%	**(n=291)** 32.1% 67.6%	χ^2 =4.21 (***p***=0.122)‡
Year of initiation (n, %) 2005 2006 2007	**(n=4317)** 28.8% 34.7% 36.4%	**(n=5210)** 43.1% 43.1% 13.6%	**(n=2910)** 44.6% 33.6% 21.6%	χ^2 =143,3 (***p***=<0.001)‡
Baseline CD4 cell count (cells/mm^3) (mean, SD)	**(n=3734)** 110.89cells/µL (SD=111.09)	**(n=425)** 149.33cell/µL (SD=76.50)	**(n=260)** 118.32cells/µL (SD=115.19)	$\mathcal{F}$ =24.0 (***p***=0.001) †
Baseline BMI (kg/m^2) (mean, SD)	**(n=3311)** 23.8 (SD=5.3)	**(n=399)** 27.1 (SD=5.0)	**(n=231)** 22.6 (SD=5.2)	$\mathcal{F}$=1.10 (***p***=0.3346)†
Baseline WHO I II III IV	**(n=2942)** 43.2% 14.1% 31.4% 11.2%	**(n=430)** 75.1% 13.0% 10.70% 1.16%	**(n=214)** 39.7% 16.3% 35.5% 8.8%	χ^2 =181.7 (***p***=<0.001)‡
Baseline TB (n) % No Yes	**(n=4317)** 86.0% 13.94%	**(n=521)** 96.35% 3.65%	**(n=291)** 81.44% 18.56%	χ^2 =51.0 (***p***=<0.001)‡
Baseline Hb g/dL (mean, SD)	**(n=3732)** 11.1 g/dL (4.0)	**(n=294)** 11.2 g/dL (4.0)	**(n=254)** 11.0 g/dL (2.2)	$\mathcal{F}$=0.20 (***p***=0.8177) †

† ANOVA
‡ Pearson's Chi-square
Kruskal-Wallis*

There was significant difference among the three groups of women regarding the presentation of tuberculosis at baseline (χ^2 =51.0; ***p***=<0.001). Women who were pregnant

at start had less advanced disease compared to the not pregnant women and women pregnant after.

Table 2 shows the distribution of the CD4 cell count category per pregnancy status at baseline. This confirms that these women had already a much compromised immune system prior to starting HAART. The overall CD4 cell count at initiation of HAART for this cohort was 126.1 cell/mm^3 which is significantly lower than the cut off CD4 of 200 cell/mm^3 according to the National Treatment Guideline.

Table 2 below shows that there was not much difference in the presentation of baseline CD4 cell count between the not pregnant women and the women pregnant after HAART.

Table 2: Distribution of Baseline CD4 Category Based by Pregnancy Status

Baseline CD4	Not pregnant n=3734	Pregnant at start n=425	Pregnant after n=260
<50	1258 (33.6%)	42 (9.8%)	76 (29.3%)
50-100	750 (20.0%)	71 (16.7%)	54 (20.7%)
100-200	1257 (33.6%)	213(50.1)	99 (38.0%)
>200	469 (12.5%)	99 (23.2%)	31 (11.9%)

However, there is a significant difference in the presentation of baseline CD4 cell count of women pregnant at start, the not pregnant women and the women pregnant after (χ^2 =140.1; p=0.001). Of the women pregnant at start 50% presented with CD4 cell count

between 100-200cells/ mm^3 while only 33.6% not pregnant women and 38.0% women pregnant after HAART presented with a baseline CD4 cell count between 100-200cell/ mm^3.

4.4 ADHERENCE

Two time periods were considered – CD4 cell count response 6 months after initiation of HAART and at 12 months after initiation of HAART.

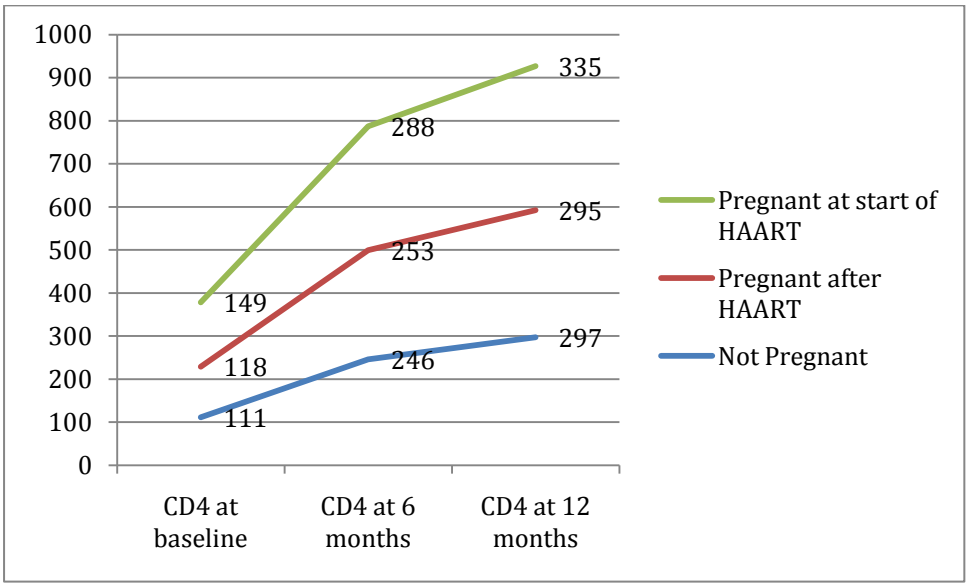
4.4.1 *CD4 cell count response*

Only 2279/5128 women (44.4% of the cohort included in this analysis) had a CD4 cell recorded at 6 months after HAART initiation. The question of interest was whether there was any difference in CD4 cell count responses between the three groups of women based on pregnancy status.

4.4.2 *CD4 cell count response at six months after HAART initiation*

The mean *overall* CD4 cell count response at 6 months was 262cell/mm^3. We looked at >50 cell/mm^3 CD4 response at 6 months and >100 cell/mm^3 CD4 cell count response at 12 months and the differences between the three groups of women based on pregnancy status are presented in Table 3.

Figure 3: Mean CD4 at 6 Month Intervals after Initiation of HAART



Women pregnant before initiation of HAART had higher baseline CD4 cell count compared to women pregnant after HAART initiation and not pregnant women and this difference between the mean CD4 cell count at 6 months and 12 months after initiation increased even further. This is shown in Figure 3 above. This progressive increase in CD4 cell count is purely attributed to the baseline immunological status of the women pregnant at start.

Table 3 below shows the percentage of women having a CD4 cell count response at 6 months and 12 months in the three different groups based on their pregnancy status. Pregnancy status had no significant advantage in terms of CD4 cell count response.

Table 3: CD4 Cell Count Response 6 and 12 Months after Initiation of HAART by Pregnancy Status

	Not-pregnant	Pregnant at start	Pregnant after	χ^2 , *P value*
Overall (n) 5128(100%)	4317	520	291	
CD4 Response at 6 months	1919 /2412 (80%)	179 / 216 (83%)	181 /220 (82%)	χ^2=2.1 (***p***=0.347)
CD4 Response at 12 months	1453 / 1958 (74%)	133 / 164 (81%)	129 / 179 (72%)	χ^2=4.4 (***p***=0.111)

4.4.3 *Bivariate and multivariate analyses of factors associated with CD4 cell count response*

We did the bivariate analysis (results not shown) and confirmed by multivariate logistic regression (Table 4) of the factors associated with evidence of adherence at 6 months. Pregnancy status did not influence a positive CD4 cell count response at six months. However, women pregnant at start were more likely to achieve a 100 cell increase in CD4 cell count both at six months and twelve months after HAART initiation. These odds were adjusted for age and baseline CD4 cell count. Both age at initiation and baseline CD4 cell count were found to have an independent association to response at six months in multivariate analysis.

Table 4: Factors Associated with CD4 Cell Count Response at 6 Months after HAART Initiation

Factors	Multivariate Models Odds Ratio	(CI)	p-value
Pregnancy			
Not Pregnant		1	
Pregnant at start	0.771	(0.476 - 1.250)	0.2917
Pregnant after	0.704	(0.428 - 1.161)	0.1692
Age at initiation	1.018	(1.003 - 1.032)	0.0185
Baseline CD4	1.004	(1.002 - 1.005)	<0.001
Baseline BMI	0.995	(0.973 - 1.018)	0.6740
Employment Status			
Employed			
Unemployed	1.173	(0.922 - 1.492)	0.1934
Baseline TB	1.027	(0.705 - 1.497)	0.8887

4.4.4 *Virological Response*

2579 participants had HIV RNA viral load records for analysis. Of these 83.9% (n=2163) not pregnant had a mean viral load of 17193.2, 8.4% (n=219), women pregnant at start had a mean viral load of 1466.9, 7.6% (n=197) women pregnant after HAART initiation had a viral load of 7969.7.

Table 5: Virological Suppression 6 and 12 Months after Initiation of HAART by Pregnancy Status

	Not-pregnant	Pregnant at start	Pregnant after	*P value*
Overall (n) 5128(100%)	4317	520	291	
Virological response at 6 months n (%)	2163(50%)	219(42%)	197(68%)	χ^2 =1.31 ***p***=0.2701
Virological response at 12 months n (%)	1457(34%)	157(30%)	152(52%)	χ^2 = 0.94 ***p***=0.3892

There were no significant differences in the proportion in the three groups of women achieving virologic suppression at six months (χ^2 =0.1.31, p=0.2701) and twelve months (χ^2 =0.94, p=0.3892) after initiating HAART.

4.4.5 *HIV viral load suppression at six months after HAART initiation*

Factors associated with suppression of HIV viral load at 6 months after initiation of HAART were investigated using a logistic regression model. Bivariate analysis was done first to check the association with possible confounders. Multivariate results are presented in Table 6.

Table 6: Factors Associated with HIV Viral Load Suppression 6 Months after HAART Initiatic

Factors	Multivariate Model Odds Ratio	(CI)	p-value
Pregnancy			
Not Pregnant		1	
Pregnant at start	1.225	(0.602 - 2.493)	0.575
Pregnant after HAART	1.150	(0.620 - 2.134)	0.656
Age at initiation	1.006	(0.986 - 1.027)	0.520
Baseline CD4	1.000	(0.998 - 1.003)	0.351
Baseline BMI	1.013	(0.979 -1.049)	0.445
Employment Status Employed			
Unemployed	1.332	(0.938 - 1.892)	0.109
Baseline TB	0.926	(0.553 - 1.550)	0.770
Baseline			
WHO1		1	
WHO2	0.764	(0.474 - 1.229)	0.268
WHO3	1.001	(90.643 - 1.559)	0.993
WHO4	1.019	(0.545 - 1.906)	0.951

After complete adjustment, women pregnant at start and women pregnant after HAART did not have significantly different odds of suppression compared to not pregnant women at 6 months (***p***=0.2701). In bivariate analysis, baseline CD4 cell count (***p***=0.030) and employment status (***p***=0.003) showed evidence of association to virolgic suppression. After adjusting for CD4 cell count and employment status in the multivariate anslysis there was a no influence of employment status or baseline CD4 cell count by pregnancy status to virological suppression. None of the coviariates significantly predicted virologic suppression at 6 months after initiation of HAART in bivariate analysis and multivariate analysis.

4.5 OUTCOMES OF WOMEN ON HAART BASED ON PREGNANCY STATUS

4.5.1 *Loss to follow-up*

Of the 5129 women in this cohort, 1318 (25.6%) women were loss to follow-up by the end of the study period (31st December 2007). Analysis based on pregnancy status revealed that 1042 (24.1%) not pregnant and 276 (33.9%) pregnant women were lost to follow-up. 215 (41.2%) women pregnant at start and 57(19.5 %) of women pregnant after were loss to follow-up at 3 months after HAART initiation. Analyses of loss to follow-up at 6 months showed that 204 (39.1%) women pregnant at start, 23 (7.9%) women pregnant after and 949 (22.0%) not pregnant women were lost to follow-up.

4.5.2 *Loss to follow-up 3 months after initiation of HAART*

The proportion of women lost to follow-up is significantly higher in women pregnant at start (χ^2 =115.3, p= <.0001) compared to not pregnant women and women pregnant after. Risk factors for loss to follow-up were estimated and. Odds ratio for variable were calculated and presented in Table7. There is evidence of a difference in odds of becoming loss to follow-up between women pregnant before and women pregnant after HAART initiation. Age at initiation, baseline CD4 cell count and employment status showed significant association with odds of becoming loss to follow-up in both bivariate and multivariate analysis. Multivariate results are presented in Table 7.

Table 7: Factors Associated with Loss to Follow-up 3 Months after Initiation

Factors	Multivariate Model		
	Odds Ratio	(CI)	p-value
Pregnancy Status			
Not pregnant	1		
Pregnant at start	1.824	(1.540 - 2.161	<.0001
Pregnant After	0.295	(0.199 - 0.437)	<.0001
Age at initiation	0.992	(0.984 - 0.999)	0.050
Baseline CD4	0.998	(0.998 - 0.999)	<.0001
Employed	1		
Unemployed	0.686	(0.603 - 0.780)	<.0001
Baseline TB	0.826	(0.640 - 1.066)	0.142
Baseline BMI	0.996	(0.981 - 1.010)	0.584

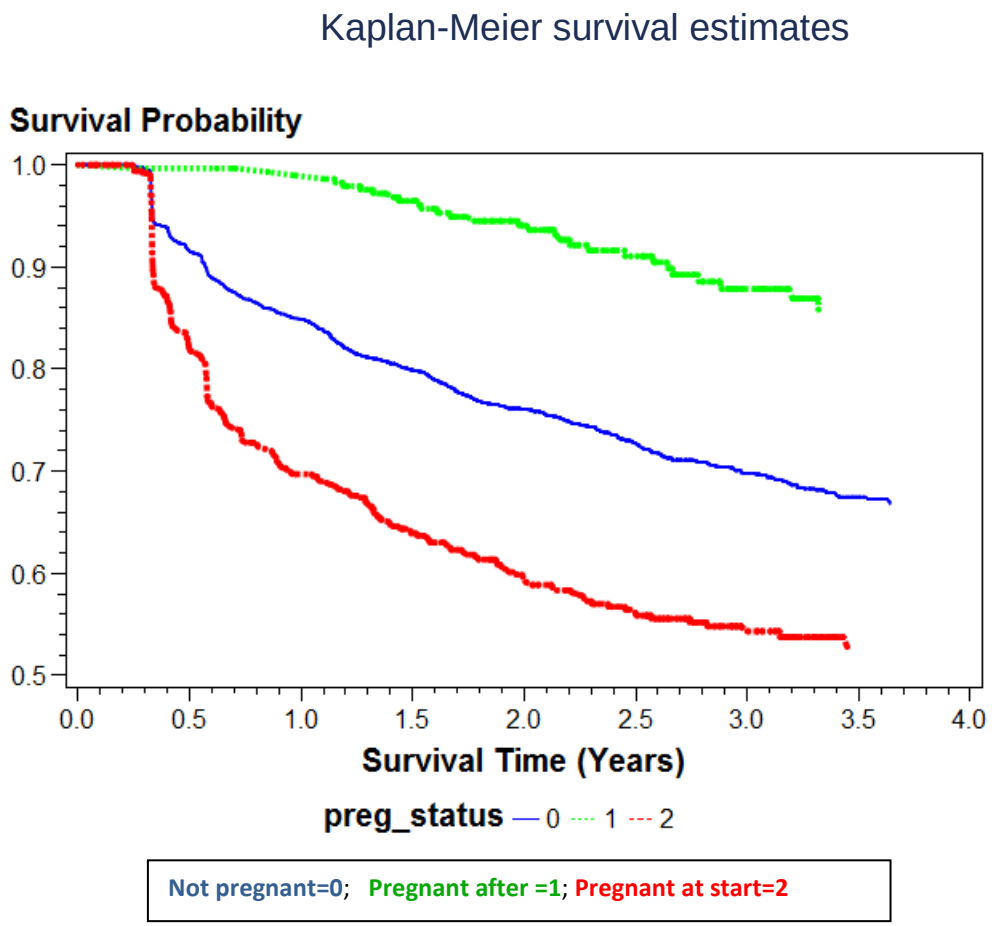
4.5.3 *Loss to follow-up 6 months after initiation of HAART*

Women, who became pregnant after initiation of HAART, seemed two times less likely of becoming loss to follow-up in bivariate analysis and three times less likely in multivariate analysis when compared to the women who were pregnant before HAART initiation. An apparent association between being pregnant and the odds of becoming loss to follow-up is observed multivariate analyses.

4.5.4 *Time to loss to follow-up*

During the study period, 3879 women that remained in the study contributed a mean of 2.1 years of observation for analysis compared to 1286 women that became loss to follow-up, contributed a mean of 1.01 years of observation in the analysis. Differences in the rate of loss to follow-up were estimated using Kaplan-Meier (KM) survival curves (figure 4) and incidence rates expressed in person-years.

Figure 4: Kaplan-Meier Plots for Loss to Follow-up for Women at Themba Lethu Clinic



Pregnancy Status	Time at risk	Incidence rate	No. of subjects	events observed
Not pregnant	2930292	<0.001	4309	1042
Pregnant at start	345218	<0.001	521	215
Pregnant after	278260	<0.001	291	29

χ^2=115.32, ***p***=<0.001

Figure 4 shows the loss to follow-up rate in all three categories of women. The highest rate of loss to follow-up is seen in the women pregnant at start (41.2%) at 3 months followed by not pregnant women (24.1%). Women pregnant after had the lowest rate of loss to follow-

up (9.94%). This trend was consistent for loss to follow-up at 3 months and loss to follow-up at 6 months after initiation.

As seen in Table 8, proportional hazard of showed that women pregnant at start were 11.9 times more likely to become loss to follow-up followed by women pregnant after who were 6.68 times more likely to become loss to follow-up when compared to not pregnant women. Being pregnant shows a significant hazard for becoming loss to follow-up.

Table 8: Hazard Ratio for Being Loss to Follow-up Based on Pregnancy Status

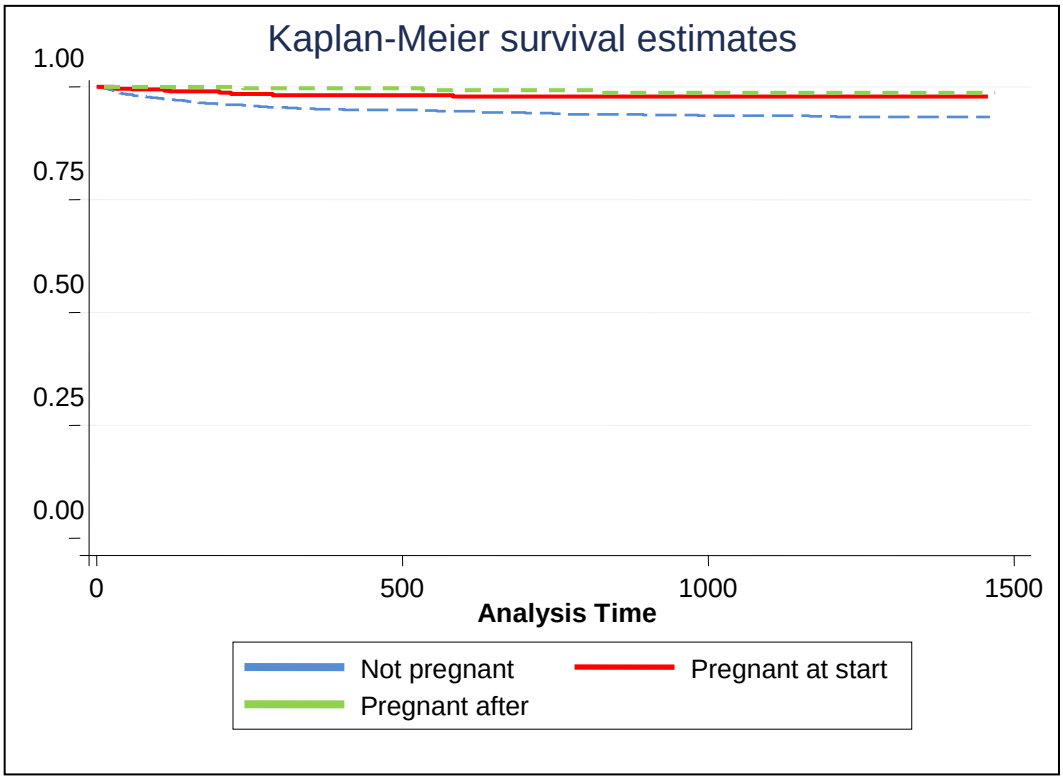
	Hazard Ratio	**95%HR confidence**	χ^2	***p value***
Not pregnant		1		
Pregnant at start	0.851	(0.777 - 0.933)	11.9	<0.0001
Post pregnant	1.170	(1.039 - 1.318)	6.68	<0.0001

4.6 MORTALITY

There were 5129/5174 women for survival analysis as we had excluded the 45 women who had a pregnancy at start and a second pregnancy later during the study. 246 deaths (4.79% of the total cohort) were recorded before the final date of 31st December 2007. Of those who died, 234/246 (95.1%) were not pregnant women, 9/246 (3.6%) women pregnant at start and 3/246 (1.2%) women pregnant after initiating HAART. The Chi-square test showed that the proportion of not pregnant women who died was significantly greater than the proportion of the women who died in both the pregnant groups (χ^2=23.92 p=<.0001).

We further analyzed the alive traced women (n=240) with those deceased and those that could not be found after tracing. Compared to those women who were traced living, those who died were found to be significantly older at initiation (37.6 vs. 35.0 years; *P*=0.0015*)*, had a much lower CD4 result at initiation (65.7cell/mm^3 vs. 118 .7cell/mm^3; *P*=<.0001). Furthermore, 52 (20.9%) of those that died (n=248, 19.1%), had tuberculosis at initiation. Both women pregnant women at start and women pregnant after were significantly younger at initiation of HAART and had less-advanced HIV disease than the not pregnant women initiating HAART.

Figure 5: Kaplan-Meier Plot s for Death for Women at Themba Lethu Clinic by Pregnancy Status



Pregnancy Status	Time at risk	Incidence rate	No. of subjects	events observed
Not pregnant	2930292	<0.001	4309	234
Pregnant at start	345218	<0.001	521	9
Pregnant after	278260	<0.001	291	3

χ^2=23.92, ***p***=<0.001

These women contributed a mean of 1.85 person years of observation for analysis during which 246 failure events (deaths) occurred. Rate of death among the three groups of women was estimated using Kaplan-Meier (KM) survival curves and incidence rates expressed per person-days. The log-rank test for equality of survivor functions showed that the time to death for not pregnant women was significantly greater than the women pregnant at start and women pregnant after (χ^2=23.92, *p*=<0.001).

Table 9: Factors Associated with Death after HAART Initiation

Factors	Multivariate Model Odds Ratio	(CI)	p-value
Pregnancy			
Not Pregnant		1	
Pregnant at start	1.534	(0.649-3.621)	0.3294
Pregnant after	5.067	(1.236-20.772)	0.0242
Age at initiation	0.972	(0.955-0.990)	0.0022
Baseline CD4	1.008	(1.00 -1.011)	<.0001
Baseline BMI	1.015	(0.983-1.047)	0.3624
Employment Status			
Employed			
Unemployed	1.190	(0.849-1.669)	0.3128
Baseline TB	0.637	(0.430-0.943)	0.0243
Baseline			
WHO I		1	
WHO II	1.528	(0.896-2.607)	0.119
WHO III	1.421	(0.894-2.258)	0.137
WHO IV	1.677	(0.953-2.949)	0.072

4.6.1 Factors associated with mortality after HAART initiation

Risk factors for mortality after initiation of HAART were estimated using Cox logistic regression model. Odds ratio for each variable was first calculated for bivariate and then the multivariate results were calculated. The multivariate results are presented in Table 9. In the bivariate analysis, women who became pregnant after HAART initiation were five times more protective to death after HAART initiation and women pregnant at start were three times more protective to death after HAART initiation when compared to not pregnant women.

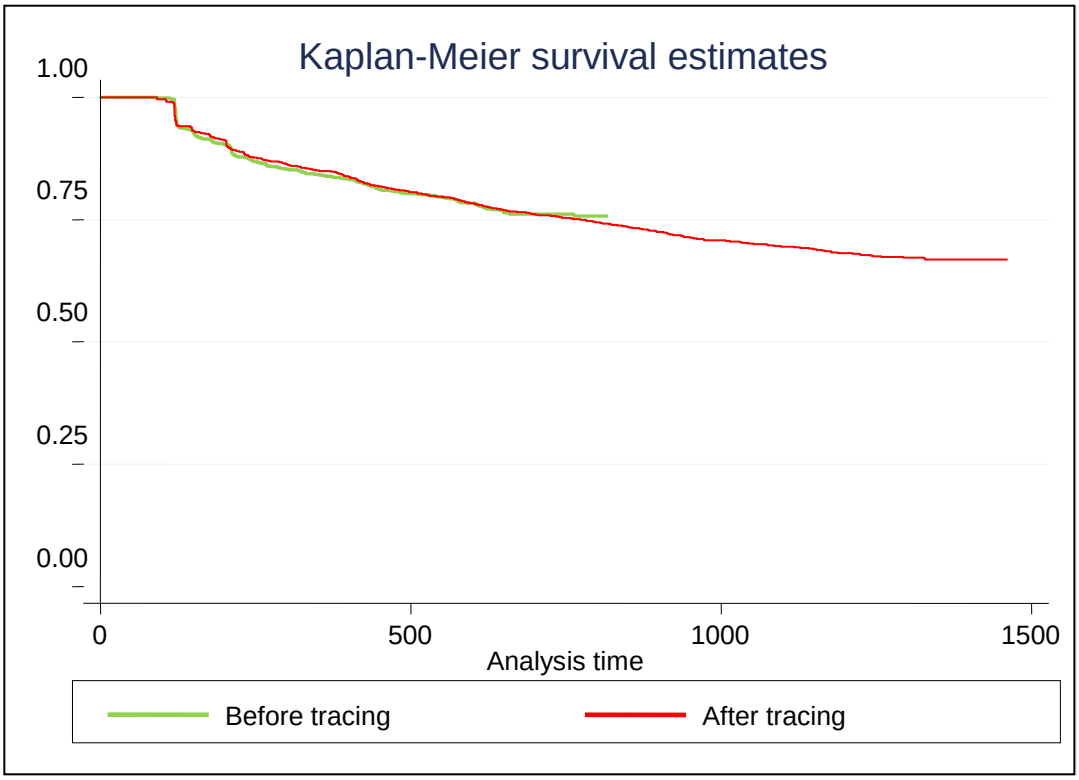
Other strong significant predictors of death in the bivariate analysis included baseline CD4 cell count and baseline WHO stage, and a weak association of age at initiation and employment status.

4.7 OUTCOMES BEFORE AND AFTER TRACING INTERVENTION

As the tracing intervention was implemented in April 2007, we looked at the experience of the three groups of women before the 31st March 2007 and their experience after. The period from 1st January 2005 until the 31st March 2007 was considered as period 1 and the time period from 1st April 2007 to 31st December 2007 was considered period 2. Not every woman in the study was at risk to become loss to follow-up in the two time periods. Those women that initiated treatment before 31st March 2007 were at risk in period 1. While women that initiated treatment after 31st March 2007 were at risk in period 2. However there may have been women who span 31st March 2007 from period 1.

In the survival analyses (Figure 6), we do not see any significant difference in the loss to follow-up rate before and after the intervention [HR=1.003 [95%CI (0.888-1.133)]; *p*=0.9509]. The reason for this is the time period between the introduction of the tracing intervention and the end of the study was only 9 months. This period is not long enough to evaluate the intervention. Moreover, it is important to understand that not all women that initiated treatment after 31st March 2007 did so at the same time. Hence there may have been women who initiated treatment very close to the end of the study period. Therefore there was not enough time to measure the outcome of the intervention.

Figure 6: Kaplan-Meier Plot for Lost to Follow-up before and After Active Tracing



HR=1.003 [95%CI (0.888-1.133)]; *p*=0.9509

Of the overall 1295 (25%) patients loss to follow-up, a total of 517 (39.9%) were unable to be traced due to incorrect contact details while 240 (18.5%) were successfully traced. Those that could be contacted provided clearer statistics and were further categorized based on the outcome of tracing. That is: - confirmed loss to follow-up, transferred out to another treatment facility, dead, and those that were traced were encouraged to return to the clinic.

4.7.1 *Analysis of outcomes before and after patient tracing*

Table 10a and Table 10b presents the outcomes before and after the implementation of the tracing intervention respectively. Prior to the tracing intervention, a total of 1318 (25.6%)

women who initiated treatment between January 2005 and December 2007 were identified to be lost to follow-up. Out of these women, those that were pregnant and loss to follow-up accounted for 276 (33.9%). Further analysis (Table 10a) revealed that women pregnant at start shows almost double the rate of loss to follow-up compared to the not pregnant women and women pregnant after initiating HAART.

Table 10a: Loss to Follow-up before Tracing Intervention

LTFU before tracing intervention				
Status	**Not pregnant (n=4317)**	**Pregnant at start (n=521)**	**Pregnant after (n=291)**	**Total (n=5129)**
Lost Before tracing	1042 (24.1%)	219(41.2%)	57 (19.5%)	1318 (25.6%)

Table 10b: Outcomes after Tracing Intervention

Outcomes of the women loss to follow-up after tracing intervention				
Total LFT-up	**Dead**	**Confirmed LTFup**	**Transferred out**	**Traced**
Not pregnant (n=1042)	236(22.6%)	377(36.1%)	267(25.6%)	162(15.5%)
Pregnant at start (n=219)	9(4.1%)	130(59.3%)	36(16.4%)	44(20.0%)
Pregnant after (n=57)	3(5.2%)	10(17.5)	12(21.0%)	32(56.1%)

The tracing intervention helped to identify the true outcomes of the 1318 (25.6%) women initially flagged as loss to follow-up (Table 10b). Women pregnant at start of HAART showed the highest rate of confirmed loss to follow-up compared to the not pregnant group and the women pregnant after initiating HAART. Of all the women confirmed to be loss to follow-up, 140 (27.0%) were pregnant women.

Among all the women that were loss to follow-up, tracing revealed that death was much higher in the not pregnant group 236 (22.6%). In this study cohort (5129), mortality was significantly lower among pregnant women compared to the not pregnant group (1.4% vs. 5.4%; *P* =<0.001). Among the pregnant group, mortality was significantly higher in the women pregnant at start (1.7 % vs. 1.0 %; *P*= <0.001) compared to the women pregnant after.

4.8 OVERALL RETENTION AFTER TRACING INTERVENTION

Combining all losses in the cohort, i.e. death, loss to follow-up and transferred out to another treatment model, the overall retention of the cohort after the tracing intervention, we found being pregnant at start and pregnant after HAART, baseline CD4 cell count and employment were significantly associated with overall retention (Table 11). Bivariate analyses (results not shown) were done first before the multivariate analyses. The hazard for lost to follow-up was significantly associated with being pregnant. Results in Table 11 confirm that there is also a strong association with being unemployed and becoming lost to follow-up.

Table 11: Factors Associated with Overall Retention after Active Tracing Intervention

Factors	Multivariate Model Hazard Ratio	(CI)	p-value
Pregnancy			
Not Pregnant		1	
Pregnant before HAART	1.909	(1.529 - 2.383)	<0.001
Pregnant after HAART	0.298	(0.183 - 0.486)	<0.001
Age at initiation	0.992	(0.983 - 1.002)	0.145
Baseline CD4	0.998	(0.997 - 0.999)	0.020
Baseline BMI	0.996	(0.981 - 1.010)	0.586
Employment Status			
Employed		1	
Unemployed	0.656	(0.556 - 0.774)	<0.001
Baseline WHO			
WHO I		1	
WHO II	0.935	(0.746 - 1.173)	0.564
WHO III	0.901	(0.733 - 1.107)	0.322
WHO IV	1.046	(0.827 - 1.180)	0.897

Table 12 summarises the factors associated with the key outcomes of this study. We find that age at initiation (p=0.0185), baseline CD4 cell count (p=<0,001), are significantly associated with adherence and CD4 cell count response. However, no variables showed any association with virologic suppression.

Table 12: Summary of Factors Related to Outcomes of Interest

Outcomes	Significant Factors Multivariate Model Hazard Ratio (CI) p-value			
Adherence (CD4 cell count response)	**Age at initiation** **Baseline CD4**	1.018 1.004	1.003-1.032 1.002-1.005	0.0185 <0,001
Viral suppression	None of the covariates significantly predicted virologic suppression			
Loss to follow-up	**Pregnant at Start** **Pregnant After** **Age at initiation** **Baseline CD4** **Unemployed**	1.824 0.295 0.992 0.998 0.686	1.540-2.161 0.199-0.437 0.984-0.999 0.998-0.999 0.603-0.780	<.0001 <.0001 0.050 <.0001 <.0001
Mortality	**Age at initiation** **Baseline CD4** **Baseline TB**	0.972 1.008 0.637	0.955-0.990 1.00 -1.011 0.430-0.943	0.0022 <0.0001 0.0243

Pregnancy is found to be strongly associated with becoming loss to follow-up. Age at initiation and being unemployed are also found to be significantly associated in becoming loss to follow-up. In the case of mortality, age at initiation, baseline CD4 and having tuberculosis at baseline are strongly associated with mortality.

CHAPTER 5 DISCUSSION

The aim of this study was to determine and describe differences in adherence and loss to follow-up in a population of HIV infected women at the Themba Lethu Clinic. Our original plan was to compare the baseline and outcome characteristics between pregnant and non pregnant women. However, our initial analyses revealed that we needed to further divide our pregnant group of women based on the timing of their pregnancy. We found that women who started treatment because they were pregnant had significant differences in their baseline and outcome characteristics compared to the women who later became pregnant after starting HAART and women who were never pregnant during the study period.

The results show that there was no difference in the immunological and virological response among the three groups of women based on pregnancy status. However, the risk of loss to follow-up was much greater in pregnant women compared to not pregnant women.

To our knowledge this is the only study that has tried to identify the association of pregnancy with adherence and loss to follow-up in HIV positive women in sub-Saharan Africa.

5.1 BASELINE CHARACTERISTICS

In our study we found age at initiation was significantly associated with immunological response. Older women have been described to show significantly better adherence in majority of other studies measuring adherence in this population (Bardeguez et al., 2008; Laine et al., 2000; Vaz et al., 2007; Nachega et al., 2007). Taking medication regularly can be overwhelming for younger individuals. Older women may have the maturity and stability in accepting the disease than the younger women. Moreover younger women may face challenges of disclosing to their partners due to fear of rejection, and may not have the social support and this may have an impact on adherence patterns and regular clinic visits. These women may have lacked the maturity to accept this chronic illness requiring life-long commitment to adherence. Moreover, these women may not have the knowledge of serostatus prior to conception; are reluctance to test in pregnancy; have fear of disclosure and denial post diagnosis, unaware of the importance of regular clinic visits and the understanding of the consequences of poor adherence (Volmink J et al., 2007). This demands a need to target teenagers for education interventions before they become sexually active. Baseline CD4 cell count is also found to be significantly associated with adherence and a positive response in CD4ce count. Accessing antiretroviral therapy with an already compromised immune system is also significantly associated with having poor CD4 cell response.

There is a steady increase in the overall enrolment of women at Themba Lethu clinic over the study period however, the distribution of women based on pregnancy status in this cohort is changing over time. The first two years of the study we found a consistent number

of women pregnant at start of HAART enrolling at the clinic, however in the third year this dropped substantially. Pregnancy after initiating HAART also seems to have dropped over the three year study period. This drop in the number of pregnant women enrolling on the ARV treatment program is of concern. Women referred from antenatal care services may never access HIV services or may prolong access until they are too ill. Most pregnant women attending the antenatal care at Coronation Women and Children Hospital learn their HIV status for the first time. These women are referred to Themba Lethu clinic for HIV management and care. One of the concerns raised from the drop seen in pregnant women enrolling in the third year may be attributed to loss to initiation. This is a growing concern of treatment denial. Pregnant women accessing HIV treatment late in their pregnancy may not have immediate benefits from the antiretroviral treatment which may increase the risk of vertical transmission. An overwhelming majority (90%) of HIV infected children acquire the infection through mother-to-child transmission (UNICEF, 2008; WHO 2008). Also according to the National Committee on Confidential Enquiries into Maternal Deaths (NCCEMD), HIV AIDS accounts for 43.7% maternal deaths. This further affirms that pregnancy is related to being loss to follow-up.

The psychosocial impact in women with HIV infection on pregnancy has been documented in women with both pre-conception and post-conception HIV diagnosis, and anxiety during pregnancy is commonly associated with disease-related stigma and fear of risk of vertical transmission (Bwirire et al., 2008; Creek et al., 2007; Bardeguez et al., 2008).

Another important reason for fewer pregnant women accessing the treatment programme may be financial constraints. Transport cost being a barrier for regular clinic visits has been

reported for the general population in a study in this setting (Maskew et al., 2006). The services and treatment at the Themba Lethu Clinic is offered free of charge but patients still need transport money to get to the clinic, which is often far from their homes or place of work. Additionally, unemployment is significantly associated with being loss to follow-up in both bivariate and multivariate analysis. Pregnant women are required to have an antenatal visit at the antenatal clinic and an ARV visit at the ARV clinic on a monthly basis. These women are probably having difficulties getting time off work for regular clinic visits or loss of income due to days of work missed may prevent them from accessing treatment. A visit to the clinic often involves a significant part of the day spent in queues.

This highlights the need to have integration of our antenatal and ARV services at primary health care level in order to provide comprehensive services at one clinic. Dispensing more than one month's supply to stable patients is another option to reduce the number of visits. Integration of antenatal services, along with TB and HIV treatment services may maximize the effectiveness of interventions aimed at patient retention and reduction in morbidity and mortality.

5.2 ADHERENCE

Women pregnant at start of HAART had a higher baseline CD4 cell count compared to the not pregnant women and the women pregnant after starting HAART, however there was no significant difference in CD4 cell count response and virological suppression in the three groups of women based on their pregnancy status at six months and twelve months after HAART initiation.

Data from previous studies have identified adherence as a strong predictor of virological outcomes and survival in people with HIV infection (Nachega et al., 2006; Nachega et al., 2007; Paterson et al., 2000). Our data is consistent with this conclusion, however pregnancy did not influence clinical outcomes in our study. We did not find any significant difference in virological suppression in the three groups of women based on their pregnancy status.

Studies from the developed world looked at adherence based on pharmacy claims. These studies showed contrasting results. Several studies of women in the United States evaluating adherence with self-reporting and pill count levels found that adherence rates to HAART were highest among pregnant women compared to non pregnant women (Vaz et al., 2007; Zorilla et al., 2003). This could be due to monthly medical appointments that are required during the antenatal period, giving an opportunity to motivate pregnant women to adhere to their ARV treatment (Vaz et al., 2007). However, results from a study using pharmacy claim adherence in a larger cohort of American women showed that observed rates in pregnant women were generally poorer than the rates reported by non pregnant women (Laine et al., 2000). Potential obstacles identified were the added emotional and physical stress that pregnant women may experience, such as nausea, worries about the complex dosing schedule of HAART (Laine et al., 2000). Since our study was a retrospective review, we were unable to determine such predictors of adherence.

We further examined the group of pregnant women based on the timing of their pregnancy and HAART initiation. We did not find any significant difference in immunological response and virological response. Contrasting results were found in a study using self-reporting to measure adherence among American women, this study found that high adherence was

significantly associated with pregnancy before starting HAART (Bardeguez et al., 2008). In contrast, a pharmacy claims-based analysis of American women found that women who became pregnant while on HAART showed better adherence compared to women who first took HAART during pregnancy (Laine et al., 2000). These studies were conducted in resource-rich settings. Possibly women who were pregnant and eligible to initiate treatment during pregnancy are given guidance on the importance of adherence to HAART for the health of the baby upon prescription of the therapy. These women may have time to invest in their baby and develop an emotional connection before they start therapy, giving them incentive and motivation to adhere. In our study, we found that pregnant women were 'fast tracked' onto ARV treatment in an effort to curb further immunodeficiency, and to prevent mother-to-child transmission. However, fast tracking these women may have deprived them from coming to terms with their HIV status and treatment readiness. Particular concerns exists around how patient preparation before HAART initiation influences long-term outcomes. There is an urgent need to educate and enrol pregnant women sooner onto triple therapy.

5.3 LOSS TO FOLLOW-UP

Women pregnant at start of HAART and women pregnant after starting HAART are both found to be significantly associated with being lost to follow-up at 3 months and 6 months after HAART initiation. In additions age at initiation, baseline CD4 cell count and employment status were strongly associated with being lost to follow-up at both 3 months and 6 months. Being lost to follow-up within 6 months after initiating HAART in our study is

consistent with the loss to follow-up identified in the general population in studies conducted in sub-Saharan Africa (Lawn et al., 2006; Dalal et al., 2008; Kaplan et al., 2008).

In this study we looked at the loss to follow-up rate of women enrolled in an urban antiretroviral treatment programme in a resource-limited setting. Over a period of 3 years the cumulative programmatic lost to follow-up was 25 %. An interesting trend was observed in the loss to follow-up rate, where we found 10% women pregnant after starting HAART, 24.1 % non pregnant women and 41.1 % women pregnant at start of HAART to be loss to follow-up. This observation indicates almost a doubling trend across the three different groups of women (10%, 24.1% and 41.2%).

The high loss to follow-up rate for pregnant women in this study is consistent with the findings presented by Kaplan et al (2008). Kaplan et al (2008) reported lost to follow up rate of 32% pregnant women compared to 13% not pregnant over 3 years on treatment in a retrospective analysis of 2131 women referred for treatment to the Hannan Crusaid Treatment Centre in Gugulethu. Kaplan defined on-treatment loss to follow-up as patients receiving ART who had not attended the clinic for 12 or more weeks. This definition is consistent with our definition.

In ART programmes, loss to follow-up rates have been shown to be influenced by programmatic characteristics, with the provision of a free service and a comprehensive treatment support system identified as contributing to higher patient retention (Rosen et al., 2007; Lawn et al., 2007).

Inadequate adherence or discontinuation of treatment raises serious public health concerns that negate much of the benefits and effectiveness of treatment programmes. From the literature review of studies on patient retention it is found that most of the deaths and attrition occurs in the first six months after initiating treatment (Rosen *et al.,* 2007). This highlights a need for better programmatic support and close monitoring in the initial months after starting HAART and maybe HAART should be initiated where ANC is provided.

Another important aspect that growing antiretroviral treatment programmes are facing is the shortage of resources like staff and infrastructure to cope with the ever increasing population requiring treatment, care and support (Rosen et al., 2007). These constraints do have a negative impact on patient care and patient retention. Treating a maximum number of new patients has been the top priority of many public sector programmes, with little documentation and tracing interventions to follow-up patients who miss visits and default treatment.

5.4 MORTALITY

Age at initiation, baseline CD4 cell count and baseline tuberculosis were found to be significantly associated with mortality. The overall mortality for the cohort was 4.8% (248 deaths) over the three year study period. In our analysis the highest rate of death was found among the not pregnant group followed by the women pregnant at start. The not pregnant group were significantly older ($\mathcal{F}$=202.82, p=<0.001) than the women pregnant at start of HAART and the women pregnant after HAART initiation. Therefore these women may be faced with other underlying conditions which further compromise the immune

system (NCCDEM, 2004-2005). Women who became pregnant after initiating HAART showed the lowest rate of death compared to the other two groups. Women who were pregnant at start of HAART were five times less likely to die compared to women who became pregnant after initiating HAART who were three times less likely to die compared to the women who were not pregnant. Low CD4 cell count and an advanced WHO stage at baseline were strong predictors of death. This confirms that women who were not pregnant were assessing treatment at an advance stage of the HIV disease, thus having an already compromised immune system. Moreover, our results show that > 30% not pregnant women had a WHO stage III and >10% had WHO stage IV at initiation. A CD4 cell count <200 cell/mm^3 is the threshold where the risks of opportunistic infections dramatically increase thus increasing the risks of mortality (National Treatment Guideline, 2004).

Delay in seeking help is the most common patient related avoidable factor seen from the low baseline immune status in our study across all groups of women. The exact meaning of this is difficult to establish as lack of transport or other factors inhibiting the woman seeking help is not recorded in the electronic system.

Pregnant women mainly learn their serostatus at the antenatal clinic. According to the review by NCCEMD (2004-2005), lack of attendance at antenatal clinics continues to be a common patient related avoidable factor and health messages must continue to stress the need to attend antenatal clinic early in pregnancy.

Our study suggests that greater attention needs to be paid to the quality of antenatal care and HIV management so that opportunities are not missed in reducing loss to follow-up and mortality in this sub-group of the population. This is comparable with the review given in the Saving Mothers report (NCCEMD 2004-2005), particularly relevant to HIV infected women, women with hypertension or other pre-existing medical conditions.

5.5 OUTCOMES AFTER THE INTRODUCTION OF TRACING INTERVENTION

Women in our study initiated ART at different times over the three year study period. Therefore not all women were at risk at the same time for becoming loss to follow-up. The tracing intervention was implemented in April 2007. Women, who initiated treatment before the 31st March 2007, were at risk from the time they enrolled on the study until 31st March and women who initiated treatment in the time period after the 31st March 2007 were at risk from there on until the end of the study. However, those women that span the 31st March timeline, where at risk for longer. Also the period before the intervention was much longer then the time period between the implementation of the tracing intervention and the end of our study. Hence the short period of 9 months was not long enough to evaluate the success of the intervention.

However, tracing did help in finding out some details of the patients (Table 11b) that were transferred out to another facility, and also details of patients whose death was never reported to the clinic. Moreover, those that could not be found after tracing were confirmed loss to follow-up. Compared to the not pregnant women and the women pregnant after HAART initiation, a higher percentage of women pregnant at start were

confirmed to be lost to follow-up. Tracing intervention also confirmed that pregnancy is strongly related to becoming loss to follow-up, with a larger majority of the women pregnant at start of HAART compared to the women pregnant after HAART and the not pregnant women. This construes that among the pregnant women those fast tracked onto treatment are at higher risk of becoming loss to follow-up.

Patients who could not be found after tracing were due to the poor demographic data recorded in the electronic case files. It is unclear whether patients provided incorrect contact details due to fear of disclosure or whether the details obtained by the clinic staff were inadequate. This is a serious concern as contact information that is incorrect, out dated or not available could relate to the risk of disease progression leading to death. The patients that are too ill and weak may not be able to come to the clinic. Another aspect is the time lapse between being lost to follow up and actual tracing. Moreover in an urban environment, it is generally difficult to trace mobile patients. Moreover, home visit tracing could prove to be rather costly, therefore the emphasis should be on prevention of lost to follow up. Our study suggests that telephone tracing soon after a missed appointment may reduce the treatment default gap. By reducing LTFU, adherence would indirectly be improved which is a key in HAART care.

Death that was recorded for patients after the tracing intervention was implemented, used the date the information was identified by the community tracers as the death date. Therefore there may have been deaths that occurred prior to the implementation of the tracing intervention but because the death was not reported to the clinic there was no record in the patients' electronic file. Thus a sudden rise in the number of deaths after the

tracing intervention is noticed. Majority of the deaths may have occurred shortly after the initiation of HAART. This is due to the severely compromised immune system that could not show much response to antiretroviral treatment. Low baseline CD4 cell count and poor immunological response after starting HAART is attributed to this assumption.

Our study showed that becoming loss to follow-up was strongly associated with being pregnant. Being pregnant, baseline CD4 cell count, age and unemployment were found to be significantly associated in both bivariate and multivariate analysis.

This is a huge public health concern as the outcome of these untraced pregnant women could not be determined. This again underestimates the mortality rate in the pregnant women. The high lost to follow up rate in this sub group of the population is of particular concern as it not only has an impact on the morbidity and mortality of the mother but also more likely to increase the risk of mother to child transmission and the development of resistant HIV strains. Orphaning due to the lost of a primary caretaker is another public health concern.

5.7 LIMITATIONS

This study had the following limitations:

Although much effort is focused on the collection and capturing of data at Themba Lethu Clinic, the accuracy of the collected data could not be verified against any source due to the

de-identified nature of the data. Moreover, missing data in particular, the precision of the data of deceased patients was largely dependent on verbal feedbacks from family members or friends. This could not be cross referenced with the national death register for ascertainment of death dates.

Another limitation is we did detailed analysis of 3 and 6 months for immunological and 6 months for virological response but the international indicator seems to be 1 year. We could not do the analyses for twelve months due to a large amount of missing data.
Furthermore, our loss to follow-up definition did not seem to apply exactly the same throughout as some of the women where more actively traced.

One limitation of the study is the study period. There was not much time to evaluate the introduction of the proactive tracing. The tracing intervention was introduced in April 2007 and the study ended in December 2007. Therefore the time period for the risk to become loss to follow-up faced by the patients who started treatment prior April 2007 was not the same compared to the time period for the risk to become loss to follow-up faced by those patients that initiated treatment after April 2007 until the end of the study. Therefore the time to evaluate the true outcome the tracing intervention was far too short.
Identifying the factors that put the different groups of women at risk for poor adherence is essential in targeting appropriate interventions. In our study adjusted analysis showed only a few factors associated with adherence and lost to follow up. Demographic data like income, marital status, socio-economic status, and education level and disclosure status have been identified from literature review as significant variables associated with adherence and lost to follow up rates. However these data were unavailable to us as they

are not routinely collected. Another limitation was additional information on baseline opportunistic infections was not available and therefore could not be controlled for in any of the analyses.

As this study was a retrospective analysis, the actual reasons for patients defaulting treatment and not returning to the clinic could not be established. The reason for reviewing the data of all women enrolled at Themba Lethu Clinic between January 2005 and December 2007 is that the clinic began to enrol female patients referred from the Coronation Women and Children's Hospital since January 2005. Moreover this clinic uses an electronic data system in real time in one of the largest public antiretroviral rollout site that is representative of urban population with a database with up-to-date longitudinal data.

To improve the quality of data, the lay counsellors and reception clerks need to be trained and educated to have a better understanding of the importance of correct contact information. Also from a data management perspective it is vital to understand that input of poor quality data, means poor outputs and evaluations. "Garbage in is garbage out"

CHAPTER 6 CONCLUSION AND RECOMMENDATIONS

To our knowledge this is one of the first studies of HAART adherence and loss to follow-up of pregnant women in sub-Saharan Africa. Moreover the clinical database at Themba Lethu Clinic is one of the biggest databases using a real time patient health management system. Therefore the findings are quite persuasive as they are from a rich cohort that is representative of an urban population accessing antiretroviral therapy in the public sector.

The strong association of pregnancy to adherence and loss to follow-up is of particular concern as it will not only impact on the morbidity and the mortality of the mother, but also is likely to result in an increased risk of HIV transmission to the child and a high possibility of transmission of resistant viral strain. This analysis points to the urgent need for a more focused intervention to identify why this sub-group of the population is at high risk of defaulting treatment. It also identifies that pregnant women requires additional longitudinal interventions for programmatic retention. There is an urgent priority to strengthen our health system with the integration of antenatal care and HIV services.

We therefore need strategies in large cohorts to improve education levels which could help improve treatment denial and in turn improve patient retention. Tracing via telephone may have its own challenges due to the ever changing mobile phone numbers, and home visit may be far too costly and difficult in both urban areas and informal settlements. This study suggests that improvement in pre-treatment counselling with special focus to pregnant women coupled with education and continuous adherence support during treatment would improve the management of patients in large cohorts and also the outcome of treatment

programmes. One of the major challenges of telephone tracing and home visits are the errors in collecting accurate data, the low rate of literacy of our lay counsellors and the intensive supervision of accurate data entry. Therefore training and educating the frontline administrators in understanding the importance of correct contact information may significantly improve the rates of tracing and decrease the loss to follow-up rates.

Mortality within the first few months after HAART initiation may be due to the late stage at which many patients present for treatment, this indicates the need for early initiation and better tracing interventions to follow-up lost to initiation. Antiretroviral services should be integrated with primary health care services thus allowing an opportunity for a larger number of women to know their serostatus earlier and access treatment with higher CD4 cell count and less advanced HIV disease.

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APPENDIX A: Blanket approval for research at Themba Lethu Clinic (M060626)

APPENDIX B: Approval for current study (M080226)

APPENDIX C: Permission to conduct research at Themba Lethu Clinic by Helen Joseph Hospital CEO