Pre-treatment Preparation and Loss-to-Care of adults living with HIV from an antiretroviral therapy clinic in Durban, KwaZulu-Natal

Submitted to:

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BY

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EXECUTIVE SUMMARY

Introduction
The demand for comprehensive Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS) services is greater than the available supply, particularly for the provision of antiretroviral therapy. The resulting bottleneck in service delivery has considerable implications for people living with HIV and for resource management.

Aim
The purpose of this research was to investigate loss-to-care and associated variables of adult HIV-infected people who were eligible for antiretroviral therapy, from July 2004 to December 2007 at Sinikithemba HIV Clinic in Durban, KwaZulu-Natal.

Methods
An observational descriptive and analytic cohort study design was used. Secondary data sourced from Sinikithemba were collated. All HIV-infected adults, 15 years and older when registered on the TrakCare database, who were eligible for antiretroviral therapy were included in the study. Data were extracted to describe the preparation of HIV-infected adults who were eligible for antiretroviral therapy. Variables were first summarised and described before the confirmatory analytic steps were taken to measure associations at the p<0.05 significance level.

Results
Of the 10 424 HIV-infected adults registered at Sinikithemba, 5470 (52%) were eligible for antiretroviral therapy from July 2004 to December 2007 and 2979 (54%) of these were lost to care prior to initiating antiretroviral therapy. Six exposure variables were significantly associated with this loss-to-care, (gender, baseline CD4 count, pre-eligibility care, antiretroviral therapy delay, preparation step and waiting time). These variables remained significantly associated with loss-to-care even after controlling for confounding with logistic regression.
Discussion and Recommendations

With the rapid scale-up of antiretroviral therapy programmes, the outcome of those people living with HIV lost to care before commencing therapy have not been adequately documented. This large cohort enrolled over three-and-a-half years demonstrates that the loss-to-care prior to initiation of antiretroviral therapy is a significant problem that needs to be further investigated. Focusing retention strategies at the pre-antiretroviral therapy stage of HIV care will improve overall programme outcomes.
DECLARATION

I, KRYSZTAŁ-LEE NIXON declare that

I. The research reported in this dissertation, except where otherwise indicated, and is my original research.

II. This dissertation has not been submitted for any degree or examination at any other university.

III. This dissertation does not contain other persons’ data, pictures, graphs or other information, unless specifically acknowledged as being sourced from other persons.

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PUBLICATIONS OR PRESENTATIONS

1. “Why do some HIV-infected people living with HIV not get onto ARV’s at an antiretroviral clinic in Durban, KwaZulu Natal?” Poster presentation (P074) at the Public Health Association of Southern Africa Conference 2009 1 & 2 December 2009, International Conference Centre, Durban, South Africa.

ACRONYMS AND ABBREVIATIONS

<table>
<thead>
<tr>
<th>Acronym</th>
<th>Description</th>
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<tbody>
<tr>
<td>AIDS</td>
<td>Acquired Immunodeficiency Syndrome</td>
</tr>
<tr>
<td>ART</td>
<td>Antiretroviral Therapy</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
</tr>
<tr>
<td>HMIS</td>
<td>Health Management Information System</td>
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<tr>
<td>PEPFAR</td>
<td>President’s Emergency Fund for AIDS Relief, USA</td>
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<tr>
<td>PHC</td>
<td>Primary Health Care</td>
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<tr>
<td>PLHIV</td>
<td>People living with HIV and AIDS</td>
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<tr>
<td>PSA</td>
<td>Psychosocial assessment</td>
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CHAPTER I: INTRODUCTION

“Unless HIV care is available to patients at all stages of HIV infection, the long awaited chance to substantially reduce AIDS mortality with ART could fall short of its full potential” (1).

This research report outlines the problem of people living with Human Immunodeficiency Virus (PLHIV) lost to care before they are able to initiate antiretroviral therapy (ART).

In chapter 1, the background to the problem and why it was important for this study to take place is provided. Chapter 2 contains an outline of the current research on pre-ART loss-to-care, whilst in Chapter 3 the methods used to investigate the problem are described.

The final three chapters contain the results of the research, an overview and discussion of the relevance and limitations of the research findings in relation to the current literature and the conclusions and recommendations based on the research findings.

1.1 BACKGROUND

1.1.1 What is known so far?

The *Sinikithemba* HIV Clinic, at McCord Hospital has been operational since 1995. At that time access to ART was limited and only available through clinical trials or at high cost to PLHIV in the private sector.

In July 2004, *Sinikithemba* was awarded a grant\(^1\) to scale up the number of PLHIV initiated on ART to 100 per month. When the Department of Health accredited *Sinikithemba* as an ART treatment site in 2007, medication and laboratory testing were provided by the provincial Health Department.

\(^1\) United States of America, President’s Emergency Fund for AIDS Relief (PEPFAR)
The capacity of *Sinikithemba* to meet the demand for ART was stretched with the rapid expansion and large numbers of PLHIV accessing the programme. Donor funding previously used for ART medications was redirected to expand ART services through a Down Referral Programme with the local *eThekwini* Municipality.

In line with the public-private model of health-care provision at McCord Hospital, PLHIV attending *Sinikithemba* are required to contribute a minimal monthly user-fee for their care. In the study period July 2004 to December 2007 this fee was Rand 160 per month.

Despite the high numbers of PLHIV who initiate ART at *Sinikithemba*, many of those who enter into care, are lost to care ‘along the way’. Currently the resources available to follow up PLHIV lost to care are limited to those who have already initiated ART, due to the implications of the development of HIV resistance associated with interruption of ART. The policy limited follow-up means that ART-eligible\(^2\) PLHIV lost to care prior to initiating ART are not actively followed up and reasons for them no longer accessing care at *Sinikithemba* are not known.

### 1.1.2 What needs to be known?

A retrospective chart review conducted at *Sinikithemba* from July 2006 to December 2006, showed that 82 (16%) of the 501 ART-eligible PLHIV followed up at that time were lost to care before initiating ART. Telephonic follow up of these PLHIV found that 26 (32%) were deceased (2).

Understanding the reasons PLHIV do not remain in care is critical to improve patient retention and so reduce the associated case fatality. Currently a prospective research project underway at McCord Hospital is following up PLHIV from the time they were tested for HIV, and will investigate the reasons some do not remain in care and determine the proportional mortality in this cohort.

\(^2\) Eligibility for ART is determined by a CD4 count equal to or less than 200 cells/µL
However, valuable insights can be gained from retrospectively examining the existing data. Considering the length of time *Sinikithemba* has been operating, a much larger sample could be accessed than in the previous retrospective study in order to describe the problem in more detail and determine health-system and other factors associated with pre-ART\(^3\) loss-to-care.

As data are collected and analyzed for this specific stage of HIV care, it will be beneficial to compare findings and build on the current understanding of the problem. The research will assist health service managers to make informed decisions about HIV service delivery and improve the retention of PLHIV in HIV care.

### 1.1.3 What is the importance of this study?

Whilst most published literature focuses on ART programme expansion and patient retention, there are only a few sites where researchers have investigated pre-ART attrition and associated mortality (2). The high case fatality associated with pre-ART loss-to-care shown in these studies makes it imperative that we improve access to HIV care, initiation of ART, and expand the scope of care and support offered to PLHIV.

The reality is that although psychosocial and clinical status should primarily determine when and if ART is initiated, waiting lists and limited clinical services for PLHIV due to capacity and resource constraints ultimately limit the number who commenced treatment.

In 2009, the pre-ART services at *Sinikithemba* were expanded to include primary health care (PHC) services in an effort to improve the clinical status of PLHIV prior to ART initiation. Yet, without active follow up of pre-ART loss-to-care, it is difficult to understand the factors that affect the uptake of these pre-ART services and negate the potential gains of this new programme.

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\(^3\) ART eligible PLHIV who are lost to care prior to initiating ART
Understanding the variables, which influence the supply and demand for ART initiation, particularly those that can be changed and controlled through the health care system, is important to ensure current and new services are effective.

1.1.4 How will the study solve the problem?

Operational research, which describes ART preparation and analyzes the variables that affect pre-ART loss-to-care, is critical for mobilising resources to expand the uptake of HIV services and increase ART initiation.

1.2 STATEMENT OF THE PROBLEM

Providing comprehensive HIV care requires health service managers to continually expand services and improve quality of medical management as improved therapeutic and care modalities become available. In a resource-limited setting, the challenge lies not only in keeping pace with the considerable need for services, but also the manner in which service delivery is regulated according to resource availability.

Due to resource constraints, the demand for comprehensive HIV care is greater than the supply, particularly for the provision of ART. The resulting bottleneck in service delivery has considerable implications not only for the individual and the overall management of the HIV epidemic, but also for resource management.

The preparation of PLHIV for ART is a resource intensive process and needs to be understood better to optimize current service delivery and maximize the benefit of the resources invested in the health and preparation of those eligible for ART.
1.2.1 Research Hypotheses

The main hypothesis for this study is that pre-ART loss-to-care at *Sinikithemba* HIV Clinic is associated with demographic, clinical and health-system variables. These variables are specified in the following hypotheses:

- Pre-ART loss-to-care is associated with age, gender and CD4 count;
- The proportion of pre-ART loss-to-care for PLHIV varies with the different steps involved in the ART preparation process;
- PLHIV whose care is delayed for psychosocial and clinical reasons during the ART preparation process are more likely to be lost to care before initiating ART; and
- The longer the time between steps in the ART preparation process, the more likely PLHIV are lost to care before initiating ART.

1.2.2 Research Question

What proportion of adult people living with HIV eligible for ART at *Sinikithemba* HIV Clinic were lost to care before initiating ART and what variables are associated with this pre-ART loss-to-care?

1.3 PURPOSE OF THE RESEARCH

The purpose of this research was to investigate loss-to-care of adult PLHIV who were eligible for ART and the associated variables, from July 2004 to December 2007, in order to provide information that may improve pre-ART service delivery at *Sinikithemba* HIV Clinic in Durban, KwaZulu-Natal.
1.4 SPECIFIC OBJECTIVES OF THE RESEARCH

The objectives of this study were:

1. To describe the demographic and clinical characteristics of adult PLHIV in the ART preparation process;
2. To quantify loss-to-care at each stage of ART preparation;
3. To measure waiting times between each stage of the ART preparation process;
4. To analyse the association between age, gender, CD4 count and pre-ART loss-to-care;
5. To analyse the association between psychosocial and clinical delays and pre-ART loss-to-care;
6. To analyse the association of pre-ART waiting times between steps of the ART preparation process and pre-ART loss-to-care;
7. To investigate any other associations which may arise from analysis of the data; and
8. To make recommendations for improvements for ART preparation at Sinikithemba HIV Clinic based on the results of the study.

1.5 ASSUMPTION UNDERLYING THE STUDY

Every HIV-infected person should have access to HIV care and treatment. However, with South Africa having the largest HIV-infected population in the world and limited resources for health care, this is not yet the reality (3).

Understanding the demographic, clinical and health-system factors associated with pre-ART loss-to-care will assist health service managers to limit the impact of these factors on retention of PLHIV in care and ultimately reduce HIV related mortality.

PLHIV who were ART eligible within the same month, were exposed to the same waiting or booking times for ART preparation.
1.6 OPERATIONAL DEFINITIONS USED IN THE STUDY

1.6.1 Adult PLHIV

PLHIV who entered care at 15-years or older were registered as adults\(^4\) at the Sinikithemba HIV Clinic.

1.6.2 ART-Eligible

PLHIV who were eligible to initiate ART had a CD4 count equal to or lower than 200 cells/uL. In this study, those who were ART eligible were included from the time that a CD4 count was available. In the cases where PLHIV had not returned for their CD4 count result by the end of the study follow up period, they were counted as ART-eligible and lost to care at the same clinic visit.

1.6.3 ART Preparation

The clinical and psychosocial services ART-eligible PLHIV receive in preparation for ART initiation.

1.6.4 Baseline CD4 Count

The first CD4 count equal to or lower than 200 cell/uL was used as a baseline against which CD4 count improvement was measured once a PLHIV initiated ART.

1.6.5 Pre-ART

PLHIV who were eligible for ART and were undergoing ART preparation.

1.6.6 Pre-Eligibility Care

PLHIV who accessed HIV care prior to being eligible for ART and who had routine CD4 counts tests to monitor their progress to ART eligibility. This positive health-seeking

\(^4\) The Sinikithemba HIV Clinic has a different ART preparation system for children to that of adults, therefore this study only included PLHIV who were classified as adults, those 15-years or older.
behaviour meant that PLHIV would commence ART as close to the time of becoming ART eligible as possible.

1.6.7 **Pre-ART Loss-to-Care**

Pre-ART loss-to-care occurred when a PLHIV was eligible for ART and stopped accessing the pre-ART preparation services at the clinic. A PLHIV was defined as being lost to care when they had not accessed care for six months or more and the reason for not returning to the clinic was unknown.

1.6.8 **Waiting Time**

Waiting time refers to the amount of time, in days, between ART preparation steps.

1.7 **SCOPE OF THE STUDY**

Sinikithemba was the only site included in this study. Information from PLHIV on their reasons for leaving ART preparation services was not available. It was not possible to ascertain whether PLHIV had transferred care to other services or had died therefore this could not be included in the data analysis.

1.8 **CONCLUSION**

Not all eligible PLHIV receive ART and the reasons why are not fully understood. Without ART these PLHIV have a significant risk of mortality and there are public health implications related to ART-eligible PLHIV not accessing appropriate HIV care and treatment. One of the proposed strategies for reducing pre-ART loss-to-care is to expand HIV care services.

However, service-delivery uptake cannot be improved if the factors associated with patient retention are not understood. Research that assists health care managers mobilise appropriate resources in order to make targeted, effective interventions that improve quality of life in PLHIV in resource-limited settings is required.
2 CHAPTER II: LITERATURE REVIEW

INTRODUCTION

Despite the ability of antiretroviral therapy (ART) to reduce acquired immunodeficiency syndrome (AIDS) related mortality, many people living with HIV\(^5\) (PLHIV) who are eligible for ART are still not experiencing its life-saving benefits. With more than 60% of HIV-infected people live in sub-Saharan Africa, the mortality associated with failure to provide ART to all who need it is considerable and means that there is a far greater burden of case fatality than is being see in ART programmes (4,5).

It is imperative that health system research focuses not only on those PLHIV initiated on ART, but also on those who do not ‘make it’. We have to understand the differences between those PLHIV who initiate ART and those who do not so that we can better manage patient retention and the availability and accessibility of services for all PLHIV (4,6,7,8,9).

2.1 LITERATURE REVIEWED

2.1.1 Pre-ART Loss-to-Care and mortality

The Reproductive Health & HIV Research Unit (RHRU) working with the Tshepong Wellness Clinic in Klerksdorp, North West province conducted a chart review of all patient files in June 2006 to investigate concerns raised about the numbers of PLHIV no longer accessing care at the clinic (10).

A total of 5750 files were reviewed and the files were classified according to specified categories, one of which was “Pre-ART Defaulters”. This category consisted of pre-ART PLHIV who had visited the Wellness Clinic but had not returned within six weeks of their last visit date.

\(^5\) Human Immunodeficiency Virus
Of all the PLHIV not initiated on ART, 1765 (73%) were in the “Pre-ART Defaulter” category, meaning they were eligible for ART but were no longer still in care (10). Nearly half (42%) of those “Pre-ART Defaulters” were found to have died before their next scheduled visit (10). This finding is consistent with research at McCord Hospital that showed that without ART the median survival time for a PLHIV is less than a year (6).

In 2005, Lawn et al. analysed a prospective cohort of 712 treatment naïve PLHIV accessing a community based ART service to determine the “rates, risk factors and causes of death” of PLHIV prior to and following ART initiation. Similarly, they found that within 90 days of enrolment into the programme, 29 of 44 (66%) pre-ART PLHIV died (4).

More recently, Fairall et al. conducted a cohort study in the public sector ART project in the Free State in which 14 267 PLHIV were followed up for up for 20 months following enrolment in the programme. They found that 2105 (87%) of the PLHIV who had died had not initiated ART (11).

This problem is complex in that PLHIV who no longer access care may die, whilst others may be lost to care because they accessed care too late and die despite being in care (12).

The research findings show that even in those PLHIV who have accessed HIV care but are eligible for treatment, that a high proportion do not remain in care (4,6,10,11). The high mortality found in these studies is one of the main contributors to the high loss-to-care percentage, and poor or delayed health-seeking behaviour is a contributory factor in this loss-to-care.
2.1.2 Impact of ART in resource-limited settings

Due to the considerable resources required to provide comprehensive ART services, successful implementation of ART in a resource-limited setting seemed highly improbable just a few years ago. The reality of underdeveloped and under-resourced health systems, poverty, shortages in skilled health workers and the development of ART resistance seemed to overwhelm the potential benefits of introducing ART into these settings (13).

Since then, there has been remarkable expansion in the rollout of ART services in many resource-limited settings and the South African National Roll out plan implemented in 2004 has rapidly increased access to ART (14). Successful implementation of ART programmes and proven strategies and guidelines that are locally appropriate have been described, confirming that, “ART can be provided in resource-limited settings with good patient retention and clinical outcomes” (15).

In 2005, Lawn et al. showed in a prospective cohort in Cape Town that the high mortality rate of 36 deaths/100 person years found in the pre-ART stage was reduced to 3 deaths/100 person years within one year for those who received ART (4). In 2007, Rosen et al. conducted a systematic review on patient retention in ART programmes in sub-Saharan Africa and found approximately 80% retention of PLHIV after six months on ART and 60% after two years (6).

What the expansion of ART services and these figures on mortality and patient retention in ART programmes show is that the impact of ART in resource-limited settings is dependent on well functioning health systems and the effectiveness of ART programmes as much as that of drug efficacy (16).
2.1.3 Low ART coverage

In the World Health Organization "3 by 5 Report on Global Access to ART" (2006), developing countries only had 10 to 15% ART coverage. In South Africa ART coverage was estimated to be 21% (17). These figures highlight the number of PLHIV who are eligible for ART that do not have access to these services.

A simulation model of HIV infection in South Africa was used under different scenarios of scale-up and expansion of the ART programme to estimate numbers of ART-eligible PLHIV and the expected HIV-associated mortality with or without ART. For the current time line for ART scale-up in South Africa, the results showed an estimated 1.5 million deaths by 2012 (18).

One of the main reasons for low coverage and high AIDS related mortality projection is that most ART systems cannot meet the demand for ART services. Rosen et al. argue that ART services will need to be rationed in order to maximize the benefit of ART (7).

Rationing services creates a difficult ethical situation for individual ART care, but is also a public health concern with regards to HIV transmission, prevalence and the issue of ART resistance (8,14,19,17). Both HIV and AIDS prevention and treatment programmes can influence the HIV and AIDS epidemic; however, they need to be appropriately managed to provide services for every HIV-infected person. Any shortfall will continue to contribute to the pool of infection fuelling the epidemic.

2.1.4 Availability and Accessibility of HIV services

The problem is two-fold in that it is necessary to ensure that PLHIV have equitable access to services and commence care at the most appropriate time. Whilst some studies have shown very high mortality in PLHIV awaiting ART, delayed access to treatment may also account for up to two thirds of early deaths in ART PLHIV (20).
There has been a lot of focus on establishing the clinical stage at which PLHIV should initiate ART, however more attention needs to be paid to the entire process of ART preparation and delivery and its overall efficiency. To benefit fully from ART, HIV positive PLHIV should enter care before they reach advanced stages of immune suppression (9).

Health care access, health system delays and inappropriate treatment criteria are all factors that contribute to PLHIV initiating ART too late; these are also some of the factors that impact on whether or not PLHIV remain in care before or after ART initiation (1,21).

2.1.5  HIV care retention

Even if every PLHIV had access to ART exactly when it was required, we still could not expect 100% ART coverage. Patient retention has received a lot of attention in ART programmes because of the impact attrition has on the outcomes of these programme and it would be short sighted to not expect attrition to play a role in HIV care and ART preparation.

In the United States, a study in 2007 on U.S veteran’s showed that even in a system where access to HIV services was not limited and PLHIV had very few financial barriers to care, retention in HIV and ART care was still a problem (9). Factors that affect the uptake of services and patient retention are complex, especially as the health of PLHIV changes over time, retention in HIV care has been shown to be a predictor of survival with HIV infection (9, 22).

Whilst it is ultimately an individual’s choice to access care, retention is a good measure of programme effectiveness as it is affected by many interrelated factors that involve the patient as well as the structure and delivery of services by both the care provider and the public health system (22,23,24). Understanding this interplay could provide us with an objective way to predict patient retention and adherence risks and ensure PLHIV optimal response to ART
3 CHAPTER III: METHODS

3.1 INTRODUCTION

In the methods section the study design, study setting and study population is outlined. A detailed description of how the data were collected for the study and methods that were used to describe and analyse this data are provided as well. A framework for the statistical analysis of the data was used, (Table 3.3), to ensure each study objective and hypothesis was addressed and that the methods used for the statistical analysis were adequately described.

3.2 STUDY SETTING

At Sinikithemba HIV Clinic, all people living with HIV (PLHIV) who are eligible for antiretroviral therapy (ART) are clinically and psychosocially prepared before ART is initiated. ART-eligible PLHIV, 15-years or older, wishing to access ART at Sinikithemba have to meet the following ART preparation requirements:

- Registration on TrakCare, the McCord Hospital Health Management Information System (HMIS);
- Psychosocial assessment addressing patient readiness for ART;
- Proof of residence within the eThekwini Municipality;
- Ability to pay the Sinikithemba monthly user-fee;
- Booked on the ART literacy list;
- Attendance at all three ART literacy sessions; and
- Clinically screened and treated for any concurrent opportunistic infections.

The requirements for accessing ART at Sinikithemba have remained the same since the programme commenced in July 2004. Once all of these criteria are met, the PLHIV is initiated on ART at the time of the third ART literacy visit, unless clinical or psychosocial issues require ART initiation to be delayed. There are six ART preparation steps that PLHIV have to follow in order to initiate ART as shown in Figure 3.1.
Figure 3.1: Antiretroviral therapy preparation steps for people living with HIV at Sinikithemba HIV Clinic, July 2004 to December 2007.
3.2.1 The ART preparation process

People living with HIV could have their HIV and CD4 count results when they enter the ART preparation system, or they could have their HIV test and CD4 test done at Sinikithemba. If they are not yet eligible for ART, they will be advised to continue to have their CD4 count monitored every three or six months, depending on how close their CD4 count is to the policy-determined threshold for ART eligibility.

Returning regularly for follow-up HIV care is considered a demonstration of good health-seeking behaviour and for the purpose of analysis in this study is classified as ‘pre-eligibility care’.

If the CD4 count is equal to or below 200 cells/uL, PLHIV will be referred for a psychosocial assessment. Typically, the psychosocial assessment is done on the day they return to the clinic to collect their CD4 count result.

At the psychosocial assessment, ART-eligible PLHIV will be screened by a counsellor to assess whether the PLHIV has any psychosocial problems that may affect their ability to adhere to their ART medications and clinic visits. Issues dealing with stigma, difficulties disclosing to family and friends, or substance abuse problems are addressed with the PLHIV and ongoing counselling will be recommended if necessary.

In some cases, especially for PLHIV with psychological or socioeconomic problems, the PLHIV will also be referred to the social workers, psychologists, or both, for further assessment and care. Due to ART being life-saving treatment, ART initiation is only delayed for psychosocial reasons in extreme cases and in most cases, any unresolved psychosocial problems are dealt with concurrently with ART preparation and initiation if necessary.
The psychosocial counsellors will also assess the ability of PLHIV to pay the monthly clinic fee once initiated on ART and secondly whether they are currently residing in the Durban Metropolitan Area. These criteria are important indications of the ability of the PLHIV to remain in care at Sinikithemba, as they will have to have access to an income and be living in close proximity to the clinic to attend monthly clinic visits. If an HIV-infected person does not meet these criteria the counsellor, and social workers if necessary, will assist with a referral to an appropriate HIV clinic.

Once the psychosocial assessment is completed, the PLHIV will be booked for the first ART literacy session. The ART literacy sessions are group sessions facilitated by counsellors where stigma, disclosure, lifestyle and behavioural changes, the HIV life-cycle and ART medications are discussed.

The ART literacy sessions are scheduled to coincide with the clinical consultations before ART is initiated, to screen and treat PLHIV for opportunistic infections. In addition to the literacy group sessions and clinical consultation, all those preparing for commencing ART have blood samples drawn for routine laboratory testing, and with the high prevalence of tuberculosis in KwaZulu-Natal all PLHIV have a chest X-ray taken as well.

Once all these requirements are met and there are no additional clinical or psychosocial problems to deal with, the PLHIV will be initiated on ART. Typically, this will happen at the third ART literacy visit.

### 3.2.2 ART preparation waiting times

ART preparation is an intensive process and requires a substantial amount of time and resource from both the PLHIV and the health system. Due to limited clinical and psychosocial capacity, ART literacy sessions are only offered at scheduled appointment times, which may result in delays or waiting times for PLHIV who are eligible to commence ART.
In order to maximize the number of PLHIV that can be prepared for ART, the ART literacy sessions are scheduled as group sessions. However blood draws, X-rays and medical consultations have to be done individually and in order to minimize the number of return visits to the clinic for PLHIV, these are all scheduled to coincide with an ART literacy session.

The consequence of grouping these various care activities means that PLHIV can end up spending the whole day in the clinic for any one of their ART literacy visits. The literacy sessions typically last one to one-and-a-half hours, whilst a clinical consultation can take anything from 20 minutes to assess a healthy, stable patient, to an hour or more if the patient is very ill and requires stabilisation, rehydration, minor procedures or further investigations.

As PLHIV are initiated on ART, time has to be scheduled as well for staff to attend to those PLHIV on ART returning to the clinic for their monthly clinic visits for monitoring. In order to ensure that there is enough staff and clinic space to comfortably and confidentially provide services during an eight hour clinic day, the number of ART preparation PLHIV booked per ART literacy session has to be limited.

In addition to this, despite having access to donor funding and Department of Health support for medications and laboratory services, the Sinikithemba budget is limited and the number of PLHIV being prepared for ART has to be managed to ensure that the annual budget is not overspent. These resource constraints result in a limited number of ART Literacy session bookings being made available per day.

3.2.3 ART preparation Batch System

In 2004, there were only a few sites where ART could be initiated in the province. The policy to scale up ART initiation was a new concept to manage and implement rapidly. In order to process as many ART-eligible PLHIV as possible in a standardized manner staff were required adhere to the new ART guidelines and protocols. ART preparation was implemented using a ‘Batch System’.
The Batch System was an ART preparation schedule that worked on a monthly cycle taking batches of ART-eligible PLHIV through the ART preparation steps as a group. Psychosocial assessments were conducted on an individual basis as PLHIV returned for their CD4 count results. From the first ART literacy session, each step was scheduled for a specific week of each month.

In any given month, one week would be dedicated to each of the three ART literacy steps, with a one week gap in between the second and third ART literacy sessions. This allowed the entire Sinikithemba staff complement, who had never dealt with such volumes of PLHIV, to work together as a team focusing on the requirements of one specific preparation step for a defined batch of PLHIV per week. This was over and above managing the ever increasing numbers of PLHIV already on ART returning to the clinic for their ART monitoring visits.

As the numbers of PLHIV grew, clinical staff had to consult growing numbers of PLHIV on any given day and the waiting times during the day grew longer. Sinikithemba became recognised by the community as an ART initiation site and the stream of ART-eligible PLHIV entering the programme also increased, causing the booking lists for the first ART Literacy Session to get longer, with some psychosocial assessments being scheduled as far ahead as six months in advance.

Initially as more clinically trained staff were employed and additional consulting rooms were created, the waiting list could be reduced by increasing the number of booking slots available for the first ART literacy session. However, management staff often faced a dilemma in when to make these additional slots available as calling previously booked PLHIV back to fill the additional new slots, increased administration, whilst allowing newly assessed PLHIV to fill the new vacant appointments slots, effectively allowed them to jump the queue ahead of previously booked PLHIV.
It was also difficult to gauge the effect of increasing the number of slots on the clinician’s capacity as there was a delayed effect of the increased work-load. Many factors including the number of PLHIV who adhered to their scheduled clinic visits or arrived unscheduled, the number of critically ill PLHIV seen on any given day, the number of staff absent or on leave, affected whether the clinic was manageable or not. This made it difficult to ascertain the maximum number of clinical assessments that the clinic could manage per day.

With the increasing length of the waiting list as more PLHIV entered the programme, an additional management dilemma was how to fit critically ill PLHIV with low CD4 counts below 50 or even 10 cell/uL into the programme. These PLHIV required fast-tracking through the system and emergency ART, but by doing so the less sick PLHIV who entered care earlier with higher CD4 counts were disadvantaged as the appointment bookings were taken up by these sicker PLHIV.

By the end of 2006, the system and its administration had become unmanageable. Following a number of management meetings, a new system was proposed to process ART preparation PLHIV and reduce the ART preparation waiting time.

### 3.2.4 Daily ART Preparation System

The Daily ART Preparation System was implemented at the beginning of January 2007 and there was six months of overlap with the old Batch System due to the numbers of PLHIV who had been booked on the Batch System waiting list. In July 2007 the Batch System had been completely phased out and all ART preparation was managed through the Daily ART Preparation System.

The basic concept of the Daily ART Preparation System was to prepare PLHIV for ART at any stage of the process, every day, rather than at specific weeks in the month. The Sinikithemba administration system had become robust over the previous two years and the senior staff were experienced enough to manage the various ART preparation stages on the same day.
The preparation steps still had to be completed in sequence but the Daily System increased the number of ART literacy days per step from seven, one week a month, to as many working days as there were in the month. This system reduced the waiting time for PLHIV needing an ART literacy booking.

Previously if a PLHIV entered care in the middle of the month of the Batch system and had missed the first ART literacy week at the beginning of the month, they had to wait until the next month or even a couple of months later before they could slot into the next ART literacy session. In the new system if the PLHIV missed the first ART literacy session for the day, they could come back the next day for next scheduled session.

The number of bookings still had to be limited as on any given day all three literacy sessions had to be scheduled and the clinical and counselling staff could still only manage a limited total number of PLHIV per day. The staff also had to adjust to accommodate both ART preparation PLHIV at any stage in the ART preparation process as well as the ART initiated PLHIV returning for ongoing monitoring.

However with more booking days available the booking delay never exceeded one month. In fact the reverse was experienced where some PLHIV did not feel ready to book so soon and chose to delay the ART preparation themselves until they felt ready to move on with the process.

3.3 STUDY PERIOD

The study period was from 1st of July 2004, when the Sinikithemba received funding[^6] to rapidly expand the ART initiation programme, to the 31st of December 2007 so as to include the change in the ART preparation system in 2007 and allow for comparison of the two ART preparation systems. During this study period other events were identified that may have affected the process of ART preparation and these are discussed in more detail in the statistical analysis section.

[^6]: United States of America, Presidential Emergency Fund for AIDS Relief (PEPFAR)
In order to allow time for ART-eligible PLHIV to either initiate ART or be defined as lost to care - which required at least six months from the last clinic visit - enough follow up time had to be scheduled into the study timeframes. Therefore the last day of data collection was the 31st of July 2009 to allow for at least 18 months of follow-up time from the end of the study period.

3.4 TYPE OF RESEARCH

This study was classified as retrospective operational research.

3.5 STUDY DESIGN

An observational cohort study design was used.

3.6 TARGET POPULATION

The target population was adults\(^7\) living with HIV residing in the greater Durban Metropolitan Area, who are able to afford the user-fee to access care at the Sinikithemba HIV Clinic at McCord Hospital.

3.7 STUDY POPULATION

The study population included all PLHIV registered at Sinikithemba on the TrakCare\(^8\) database from July 2004 to December 2007, with a CD4 count equal to or lower than 200 cells/uL (which was the ART initiation policy at the time) within the study period.

\(^7\) PLHIV fifteen-years or older according to the Adult program definition

\(^8\) Health Management Information System
3.7.1 Selection of study population

As a retrospective review of data accessible in an electronic database, TrakCare, sampling was not necessary as all records meeting the inclusion criteria were extracted. Every PLHIV registered on TrakCare who met the following inclusion criteria was included in the study:

- All PLHIV 15-years or older, registered on TrakCare within the study period, July 2004 to December 2007; and
- A baseline CD4 count equal to or lower than 200 cells/μL within the study period.

Due to differences in the ART preparation, HIV-infected children less than 15-years old and HIV-infected pregnant women were excluded from the study.

3.8 DATA MANAGEMENT

3.8.1 Ethics

As a retrospective review, no intervention or contact with PLHIV was necessary by the Principal Investigator and the study had no direct impact on patient care. All patient records were anonymised and extracted data were stored on a single password protected computer.

Ethical approval was obtained from the Biomedical Research Ethics Committee of the Nelson R Mandela School of Medicine South Africa, reference number BE142-08 and the McCord Research Ethics Committee, reference number 250408/6.1 kn (see Appendix)
3.8.2 Data Source

When Sinikithemba received funding⁹ for rapid scale up of ART services, the HMIS TrakCare database was implemented to manage patient records. Every visit to Sinikithemba and the reason for the visit is recorded along with relevant clinical information. This system is web-based and is updated real-time at every point of service delivery, including administration, laboratory and pharmacy services.

As a comprehensive database, TrakCare was the only data source used for this study. Crystal Report Writer software was used to extract data from TrakCare and export the data into Microsoft Excel. Once validated, data were exported into statistical software packages for data analysis.

Changes to the ART preparation system over time and how they affected pre-ART loss-to-care were not explicit in the data collected and management memorandums and meeting minutes were referred to identify events or system changes that may have affected the pre-ART preparation process.

3.8.3 Variables

The key data elements required for the study were extracted from TrakCare on the 1st of August 2009 and provided the data used to generate the variables needed for data description and analysis (see appendix Table 8.1).

For example, the data element ‘Last ART Preparation Visit’ was used to create the variable ‘Lost-to-Care’. The variable was assigned a zero if PLHIV were in care within six months of the end of the study follow up period. At Sinikithemba there is no active follow up of pre-ART PLHIV who stop accessing care at the clinic, therefore if a PLHIV had not accessed care for six months or more prior to the end of the study follow up period they were defined as lost to care, and assigned a one in the database (see appendix, Table 8.2).

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⁹ United States of America, Presidential Emergency Fund for AIDS Relief (PEPFAR)
3.8.4 Reliability and Validity of Data Source

Data updated on TrakCare are validated against clinic registers and patient files by the Sinikithemba Monitoring and Evaluation Department on a daily basis. Extraction reports generated from clinical, pharmacy and laboratory modules in the TrakCare database are then cross-referenced monthly to ensure data quality.

In order to ensure the internal validity of the data extracted from TrakCare for the study, logical sorting and cross-checks were done with the extracted data to validate the extraction report. In addition to this random records were selected for back-checking against data entered into TrakCare database.

Concerning external validity, the main limiting factor is the monthly user-fee charged to PLHIV. As a state-subsidized hospital, McCord Hospital accesses donor funding and charges patient fees to cover the balance of its operational cost. The patient fees charged are higher than those at state facilities, but less than that charged in the private sector.

These factors as well as the Sinikithemba being a hospital based facility within an urban area, designed to comply with its main donor’s\textsuperscript{10} reporting requirements, limit the generalisability of the study results.

3.9 SELECTION, RECALL AND INFORMATION BIAS

As no sampling was done, selection bias was limited and with TrakCare data entry being done real-time, recall bias was also limited. However as changes to the ART preparation system and how they affected pre-ART loss-to-care were not explicit in the data collected, the effect of these events or changes on the ART preparation process could only be inferred and may have caused information bias. For example it was not possible to distinguish which PLHIV were booked for ART preparation through the Batch or Daily System during the six month period of overlap between the two systems in 2007, therefore these two systems had to be treated as mutually exclusive in the data analysis.

\textsuperscript{10} United States of America, President’s Emergency Fund for AIDS Relief (PEPFAR)
With TrakCare being an electronic system that has been customized and developed over time and with data-entry performed daily by a number of different service providers, inaccuracy due to human error, staff turn-over and training or system down-time can be expected and give rise to information bias. The Sinikithemba Monitoring and Evaluation Department crosschecks and the random data validation conducted on the extracted data for this study, limited the information bias within the study dataset.

3.10 **STATISTICAL ANALYSIS**

Variables were first summarised and described before the confirmatory analytic steps were taken to measure associations (Table 8.1, annex). The associations outlined in the study objectives, examined at the $p<0.05$ significance level, were first measured through bivariate analysis and then further analysed with multivariate methods to adjust for confounding.

SPSS$^{11}$ and Stata$^{12}$ statistical software were used to conduct the statistical analysis for this study. The University of KwaZulu Natal, Department of Public Health Medicine biostatistician, Ms Tonya Esterhuizen was consulted to ensure the correct statistical tests were used and that the interpretation of the statistical analysis and results was appropriate. All statistical tests and processes were conducted by the Principal Investigator.

The framework outlined in Table 3.1 was used to ensure each study objective and hypothesis was addressed and that the methods used for the statistical processing of data were adequately described.

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$^{11}$ SPSS version 2.0, SPSS Inc, Sommers, New York, USA.

$^{12}$ Stat release 11, StataCorp, College Station, Texas, USA.
Table 3.1: Data analysis framework for pre-antiretroviral therapy loss-to-care of people living with HIV at Sinikithemba HIV Clinic, July 2004 to December 2007.

<table>
<thead>
<tr>
<th>Exploratory analysis (descriptive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Objective 1: Describe the demographic and clinical characteristics of adult PLHIV in the ART preparation process</td>
</tr>
<tr>
<td>Objective 2: Quantify loss-to-care at each stage of ART preparation</td>
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<tr>
<td>Objective 3: Measure patient waiting times between each stage of the ART preparation process</td>
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</table>

<table>
<thead>
<tr>
<th>Confirmatory analysis (analytic)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_0$ Objective 4: Analyse the association between age, gender, CD4 count and pre-ART loss-to-care</td>
</tr>
<tr>
<td>$H_0$ Objective 2: Pre-ART Loss-to-Care is different at different ART preparation steps</td>
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<tr>
<td>$H_0$ Objective 3: Analyse the association between psychosocial and clinical delays and pre-ART loss-to-care</td>
</tr>
<tr>
<td>$H_0$ Objective 4: Analyse the association of pre-ART waiting times between steps of the ART preparation process and pre-ART loss-to-care</td>
</tr>
<tr>
<td>$H_0$ New Objective 7: Investigate any other associations which may arise from the analysis of the data</td>
</tr>
<tr>
<td>Objective 8: Recommendations for improvements for ART preparation at Sinikithemba HIV Clinic based on the results of the study.</td>
</tr>
</tbody>
</table>

3.10.1 Exploratory data analysis

As a retrospective cohort study it was necessary to firstly define the outcome and exposure variable within the data collected. As the purpose of the study was to define pre-ART loss-to-care, the outcome variable was defined as ‘Lost-to-Care’.

All PLHIV who had a CD4 count equal to or less than 200 cells/μL in the dataset were sorted according to their last clinic visit date. If they were still accessing care by the end of the study period they were assigned a zero for ‘still in care’. If they had no clinic visit for six months or more prior to the end of the study period, they were assigned a one for ‘lost to care’, as pre-ART PLHIV are not actively followed up at Sinikithemba so the reason for non-attendance was not available. The outcome group, ‘Lost-to-Care’ is an independent group from the ‘Not Lost-to-Care’ group.
Due to the length of follow-up time allowed in the study period, one-and-a-half years, every study subject had either initiated ART or had been lost to care (at least six months since last contact at the clinic with reason for non-attendance unknown) by the time data were extracted which meant there were only two outcome groups defined.

It was then necessary to define the exposure variables according to the specific objectives outlined in the study protocol:

- Age at ART-eligibility within the study period;
- Gender;
- Baseline CD4 count result equal to or lower than 200 cell/uL;
- Each ART preparation step completed;
- Waiting time between each ART preparation step completed; and
- Clinical or psychosocial consultation delays.

Finally, before any data analysis could take place two important aspects of each variable, namely the variable type and the distribution of the data, were established in order to match the underlying assumptions of the statistical tests chosen for each variable.

The one-sample Kolmogorov-Smirnov test was used to test the distribution of the continuous exposure variable types and each of these variables was found to be non-normally distributed. Therefore the median and interquartile range (IQR), rather than the mean and standard deviation, were chosen as the preferred measure of central tendency to describe continuous variables.

Proportions and 95% Confidence Intervals were calculated for the binomial or categorical exposure variables.
3.10.2 Describing demographic and clinical characteristics

In order to describe the demographic and clinical characteristics of the study subjects, the age at enrolment, gender and baseline CD4 count of PLHIV were analysed.

The proportion and 95% Confidence Interval for gender difference and the median age were calculated to describe the precision of demographic characteristics of the cohort, whilst the median baseline CD4 count was calculated to summarise the clinical characteristics.

3.10.3 Describing Loss-to-Care at each stage of ART preparation

Data on the last clinic visit and visit category were extracted from the database. PLHIV who had initiated ART and were attending the clinic for monthly follow-up visits were assigned the category ‘ART started’ and the rest of the PLHIV who were ‘Lost-to-Care’, were sorted according to the last ART preparation step they had attended.

From sorting PLHIV according to the last clinical visit, it was possible to calculate the proportion and 95% Confidence Interval of those who were lost to care at each step in the ART preparation pathway.

3.10.4 Describing ART preparation waiting times

Having the date and category of first visit, the date of the baseline CD4 count and the dates and categories of all subsequent visits, allowed for the calculation of waiting or delay time (in days) between each ART preparation step for each PLHIV.

If a PLHIV completed a specific ART preparation step more than once, the date of the last time that step was performed was used for the calculation as this indicated their progression to the next step.

At each step, the waiting time data distribution was skewed and so the median waiting time in days was calculated with the interquartile range.
3.10.5 Exploring an additional variable of interest

Exploratory data analysis assisted the researcher to get familiar with the data and new or unexpected patterns or relationships may emerge through the process, generating new hypotheses (25).

In working with the clinic visit dates, it became clear that certain PLHIV had entered care prior to being ART eligible and had returned to the clinic for CD4 monitoring prior to becoming eligible for ART. As the data were available for analysis, it was decided to include this as an additional hypothesis to test during the data analysis:

*PLHIV who accessed HIV care prior to being ART-eligible for pre-eligibility care, are less likely to be lost to care than PLHIV who entered HIV care when they were ART-eligible.*

The median time in pre-eligibility care and the median first CD4 count result prior to ART eligibility were calculated during the exploratory data analysis.

3.10.6 Confirmatory data analysis

Due to the continuous variables being non-normally distributed, non-parametric Mann-Whitney (Two Independent Sample Test) and Kruskal-Wallis (more than two independent samples) statistical tests were chosen. The categorical variables were tested with Chi-square tests, namely the Fisher’s Exact test.

Establishing a statistically significant difference in the outcome, dependent on the exposure, is important for analysing relationships between variables but it does not necessarily have clinical or public health significance. Therefore it is important to take the analysis one-step further and calculate the association between the exposure and outcome variable. In cohort studies, the preferred measure of association is the incidence risk ratio or relative risk.
In order to calculate relative risks, data needs to be categorical for the 2X2 Contingency Table calculations. With continuous numeric variables, this is possible by disaggregating the continuous data into smaller meaningful categories that can be compared for risk. For example, age can be broken down into age-bands that can be compared against each other for differing risks estimates.

Once the bivariate analysis was completed and it was clear which variables were associated with pre-ART loss-to-care, stratification and multivariate analysis was done to establish which variables had inter-relationships that were confounding the associations.

3.10.7 **Demographic and clinical factors associated with pre-ART Loss-to-Care**

Statistically significant differences in loss-to-care associated with the demographic and clinical exposure variables were tested. As a categorical variable, Chi-square Tests were used for gender and the Mann-Whitney Test for non-parametric continuous variables was used for enrolment age and baseline CD4 count.

During the analysis of the continuous variables, age at enrolment and baseline CD4 count, significant differences in the outcome based on various categories within each exposure variables were tested. These categories were then used for relative risk calculations (see appendix Table 8.2).

For convenience, three ten-year age-bands were defined for PLHIV between 30 and 50-years-old, the 15 to 29-year-olds were grouped together, and all PLHIV 50-years-old or older were grouped together.

Initially four CD4 count categories were defined, into 50 unit bands for convenience. However, relative risk calculations need to provide information that helps make clinical decisions and these arbitrary categories were not clinically significant.

Based on the CD4 median calculations, CD4 counts were divided into a 0 to 50 cell/μL category and a 51 to 200 cell/μL category. This made clinical sense given the fact that most PLHIV with CD4 counts less than 50 cells/μL were fast-tracked to initiate ART.
The association between pre-eligibility care and pre-ART loss-to-care was calculated and the relative risk of being lost to care was compared against those PLHIV who had had pre-eligibility CD4 monitoring care or not.

3.10.8 ART preparation delays associated with pre-ART Loss-to-Care

Initially when the data were processed, it was clear that there weren’t sufficient data on clinical and psychosocial delays to create a variable to analyse the association between these delays and pre-ART loss-to-care.

However, during exploratory data analysis to describe pre-ART loss-to-care at each of the pre-ART steps, a sub-group of PLHIV were identified who were lost to care at a clinical or psychosocial visit that was not a defined pre-ART preparation step. In most cases, ART was commenced at the third ART literacy visit, however some PLHIV have ART initiation delayed at this visit and are then either lost to care or initiate ART later.

It was only possible to analyse these delays at the third and final ART literacy step before ART initiation. When PLHIV who were delayed at earlier ART preparation steps, progressed onto the next ART preparation step rather than being lost to care, the delay was masked and could not be analysed.

Chi-square tests were done to test whether there was a statistically significant difference in pre-ART loss-to-care between PLHIV who had a delay in ART initiation at the third ART literacy in comparison to those PLHIV with no delays. The association was assessed using the relative risks.

3.10.9 ART preparation steps associated with pre-ART Loss-to-Care

Describing the proportion of PLHIV lost to care at each ART preparation step during the exploratory analysis was an important step in preparation for analysing the association between pre-ART loss-to-care and the other ART preparation steps.
These proportions were used in 2X2 Table to perform Chi-square tests and calculate the related relative risks of pre-ART loss-to-care at each ART preparation step.

Once it was clear at which step the greatest risk of loss-to-care occurred, it was possible to analyse waiting time between ART preparation steps, which was hypothesized to be associated with pre-ART loss-to-care.

### 3.10.10 ART preparation waiting times associated with pre-ART Loss-to-Care

Because it takes time to complete the required steps to initiate ART and that PLHIV lost to care did not complete the final ART preparation step, PLHIV lost to care in effect remained in the system for a shorter time than those who initiated ART. Therefore, despite having a time variable available it was not meaningful to calculate rate ratios and plot the exposure variables against the time to outcome on a Kaplan Meier plot as the survival curve did not reflect the true situation.

In order to test the hypotheses that pre-ART loss-to-care was associated with the waiting time or delays between ART preparation steps, it was necessary to calculate the waiting time for each PLHIV, between each ART preparation step. Without the *Sinikithemba* booking lists available to measure this across the three-and-a-half year study period, the only way to determine these waiting times was to measure the time taken per PLHIV between each preceding and successive step that was completed.

For the PLHIV lost to care, this calculation was not possible at their final ART preparation step, as they were lost to care before completing that particular step. This made it impossible to calculate the relative risks of pre-ART loss-to-care associated with the waiting time between ART preparation steps.

This problem was overcome by assuming that PLHIV who were ART eligible at the same time, whether those lost to care or ART initiated, would have had similar waiting times for ART initiation. Therefore, all PLHIV were grouped together according to the month they were confirmed to be ART-eligible, their enrolment month, and the median waiting time for each ART preparation step was calculated for each monthly enrolment group.
An area graph was plotted showing the overall time from eligibility to outcome for each monthly enrolment group in comparison to the waiting time for each of the first three ART preparation steps (CD4 to psychosocial assessment, psychosocial assessment to the first ART literacy session and the time between the first and second ART literacy session).

Given that the ART preparation system was changed in January 2007 in an attempt to reduce waiting times for ART initiation, it was important to analyse what affect this change had on ART preparation waiting time and pre-ART loss-to-care. Although there was a period of overlap between the two systems, it was not possible to delineate this in the data and they were therefore treated as mutually exclusive systems due to these data limitations.

Known changes to the ART preparation system throughout the three-and-a-half year study period were also plotted against the area graph in order to assess whether these changes had an effect on the ART preparation waiting times. As the effect of these changes was not explicit in the data collected, the effect on waiting time could only be inferred by comparing the corresponding waiting time for ART initiation when these events occurred.

The area graph provided a snapshot view of the two ART preparation systems and assisted in identifying differences in ART preparation times between the two systems. Fisher’s Exact Chi-square test was then used to test whether the January 2007 change in the ART preparation system made a statistically significant difference to ART preparation times and pre-ART loss-to-care.

Each of the variables shown to be associated with pre-ART loss-to-care in the bivariate analysis were analysed across the two different ART preparation systems. Mantel-Haenzel adjusted relative risks were calculated in order to understand the affect that the ART preparation system changes had on pre-ART loss-to-care and associated variables.
In addition to this, the median waiting time per month for each ART preparation step were categorized according to those above or below the overall median waiting time per step. This made it possible to calculate relative risks of pre-ART loss-to-care per waiting time for each ART preparation step and analyse whether enrolment months with higher median waiting times had higher proportions of PLHIV lost to care.

3.10.11 Multivariate analysis

The statistically significant variables shown to be associated with pre-ART loss-to-care through bivariate analysis were advanced to multivariate analysis in order to test confounding between variables.

Each of the associated exposure variables were analysed through logistic regression against the binary outcome of pre-ART loss-to-care. Those exposure variables, which had affected pre-ART PLHIV, were analysed together. The exposure variables, which affected only a subset of pre-ART PLHIV, were analysed separately due to the different number of observations per exposure variable.

Based on the findings from the statistical analysis, recommendations for improvement to the ART preparation system are made in the discussion chapter.
4 CHAPTER IV: RESULTS

4.1 INTRODUCTION

In this chapter, the results of the data summary and the analysis conducted for this study are described and presented. The framework used for processing the data are presented in the methods section (Table 3.3). The most important results for each study objective and hypothesis are presented in appropriate tables and figures and described in the text.

4.2 EXPLORATORY DATA ANALYSIS

4.2.1 Describing demographic and clinical characteristics

The baseline characteristics of the 5470 people living with HIV (PLHIV) registered at Sinikithemba HIV Clinic reveal that more than half, 54% (2979) of antiretroviral therapy (ART) eligible PLHIV in the period July 2004 to December 2007, were lost to care prior to initiating ART (Table 4.1). A larger proportion of females, 56% (3073) accessed ART preparation services than males, with the median CD4 count being 68 cells/uL at entry to the programme. Almost half (42%) of ART-eligible PLHIV had a baseline CD4 count below 50 cells/uL.

Two exposure variables of interest for this study were the number of PLHIV who entered pre-eligibility care and those PLHIV who were delayed in starting ART at the third ART literacy visit. Only 266 (5%) of the 5470 study subjects accessed CD4 monitoring services at Sinikithemba prior to being ART eligible, meaning that 95% (5204) of the ART eligible PLHIV included in this study, were ART eligible at the time of their first CD4 test at Sinikithemba.
In all, 633 (23%) of the 2739 ART eligible PLHIV who made it to the third ART literacy step, were delayed in progressing to the next step for either clinical or psychosocial reasons. Data will be presented in the confirmatory data analysis section showing whether these were significant factors associated with pre-ART loss-to-care.

The median time taken for an ART eligible PLHIV to reach an outcome of either ART initiation or being lost to care was 37 days. The wide interquartile range of 5 to 95 days indicates that there was considerable variation in length of care for PLHIV being prepared for ART, with some of those eligible for ART only remaining in care for 5 days or possibly less.

As the study time-period was selected to include two different ART preparation systems, the batch and Daily System, PLHIV were categorised according to the system they entered ART preparation care. The data were stratified on this variable to control for differences in these two systems. These results are described with the confirmatory data.
analysis results.

### 4.2.2 Describing Loss-to-Care at each stage of ART preparation

A total of 14 487 people were registered at *Sinikithemba* during the study period, July 2004 to December 2007. This included 4063 (28%) people who registered at the clinic for HIV testing and who were tested HIV negative. Of all the people registered at *Sinikithemba* in the study period, 72% (10 424) were HIV-infected (Figure 4.1). Almost half of these 4954 (48%) PLHIV, were lost to care before having a CD4 count done to determine their eligibility for ART.

The remaining 5470 (52%) PLHIV were classified as ART-eligible defined as having a CD4 count of 200 cell/uL or less, which could have been tested at *Sinikithemba* or elsewhere as long as there was proof of the CD4 result. Only 266 of these ART eligible PLHIV were not ART eligible when they registered with the programme. Their CD4 count was monitored until they became eligible, at which point they were then counted with the rest of the 5470 PLHIV who were ART eligible at their first visit to *Sinikithemba*.

Of the 5470 PLHIV, 625 (11%) PLHIV did not even return to the clinic to collect their CD4 count results. ART eligible PLHIV were lost to care at every step in the ART preparation process with the highest proportion of 1889 (39%), being lost to care at the psychosocial assessment step. The lowest proportion of PLHIV lost to care occurred at the next steps; 158 (5%) at the first ART literacy step and 58 (2%) at the second ART literacy step.

A further 248 (9%) of the 5470 ART-eligible PLHIV were lost to care at the third ART literacy step with only 2491 PLHIV, less than half (46%) of those ART-eligible managing to complete the preparation process and initiate ART at the clinic.
Figure 4.1: Flow of people living with HIV through the antiretroviral therapy preparation process at Sinikithemba HIV Clinic, July 2004 to December 2007.
4.2.3 Describing ART preparation waiting times

The median waiting times between each step of the ART preparation process were calculated (Figure 4.1). The median time between having a CD4 test and receiving the CD4 count results and having a psychosocial assessment, was six days. Again, the interquartile range (4 to 21) demonstrates that there was considerable variation in the length of time between these steps.

The psychosocial assessment to first ART literacy session had the longest median waiting time of 31 days, whilst the waiting time between the first, second and third ART literacy steps was 7 days (Figure 4.1). As the waiting time of zero days between the third ART literacy session and ART initiation indicates, most PLHIV initiate ART at the third ART literacy step, (Figure 4.1). The association between these waiting times and the proportion of PLHIV lost to care at these ART preparation step will be discussed in the confirmatory data analysis section.

The overall median time from ART eligibility to ART initiation was 89 days, IQR (55 to 130) and the overall median time from ART eligibility to pre-ART loss-to-care was 5 days, IQR (2 to 19).

4.3 CONFIRMATORY DATA ANALYSIS

4.3.1 Demographic and clinical factors associated with pre-ART Loss-to-Care

Baseline CD4 count was found to be significantly associated with pre-ART loss-to-care, (p<0.001, Mann-Whitney Two Independent Sample Test). Of the four baseline CD4 count categories 1375 (25%) of PLHIV with a baseline CD4 count in the CD4 category 0-50 cells/uL were lost to care (Figure 4.2). In each of the three other baseline CD4 count categories, PLHIV loss-to-care was no more than 11% per category, 562 (11%), 503 (10%) and 498 (9%) per category respectively.
Figure 4.2: Loss-to-Care percentage among antiretroviral therapy-eligible people living with HIV based on baseline CD4 result at Sinikithemba HIV Clinic, July 2004 to December 2007

In order to test this exposure variable in a way that is clinically significant, baseline CD4 counts were categorized into two categories, PLHIV with a baseline CD4 count below or equal to 50 cells/uL and those PLHIV with a baseline CD4 above 50 cells/uL.

PLHIV having a baseline CD4 count below 50 cells/uL were at a significantly greater risk of being lost to care than those PLHIV with a higher baseline CD4 count (p<0.001, Fishers Exact Chi-square Test), with a relative risk of 1.18, (95% Confidence Interval (CI): 1.12 to 1.24).

Gender was also tested and male gender was significantly associated with pre-ART loss-to-care with a relative risk of 1.08 (95% CI: 1.03 to 1.13) (p<0.02 Fishers Exact Chi-square Test). Age at enrolment was not statistically associated with pre-ART loss-to-care (p=0.195, Mann-Whitney, Two Independent Sample Test).
4.3.2 Pre-eligibility care associated with pre-ART Loss-to-Care

Study PLHIV who had accessed HIV care prior to being eligible for ART and had undergone CD4 monitoring until they were ART eligible were identified during the exploratory data analysis. Although there were only 266 (5%) PLHIV out of 5470 PLHIV who met this criteria (Figure 4.3), this positive health-seeking behaviour was found to be a statistically significant protective factor associated with pre-ART loss-to-care ($p<0.001$, Fisher Exact Chi-square Test).

Figure 4.3: The proportion, CD4 median and waiting time median of people living with HIV who accessed pre-eligibility care at Sinikithemba HIV Clinic, July 2004 to December 2007.

The PLHIV who accessed pre-eligibility care, in comparison to those who did not, had a relative risk of being lost to care of 0.66, (95% CI: 0.56 to 0.77), meaning that pre-eligibility care was protective against pre-ART loss-to-care. The median CD4 count for these PLHIV was 257 cells/uL at their first CD4 count test at Sinikithemba and the median time spent in care prior to being ART-eligible was approximately nine months (median of 257 days, IQR 116 to 474).
4.3.3 ART initiation delay associated with pre-ART Loss-to-Care

Another subset of PLHIV of interest, were those who had clinical or psychosocial delays at the third ART literacy (Figure 4.4). This subset of PLHIV were analysed to ascertain whether there was a statistically significant difference in pre-ART loss-to-care between those PLHIV delayed versus those who initiated ART.

As binomial data, these were analysed using a 2X2 Table and the Fisher’s Exact Chi-square Test and found that there was a significant difference in pre-ART loss-to-care between the two groups, those delayed versus those not (p<0.001). The relative risk was calculated as 2.18 (95% CI 1.52 to 3.13) with the median delay time being 20 days, IQR (7 to 52) (Figure 4.5).

Figure 4.4: Proportion and median time of antiretroviral therapy initiation delay among people living with HIV at Sinikithemba HIV Clinic, July 2004 to December 2007.
4.3.4 ART preparation steps associated with pre-ART Loss-to-Care

The proportion of pre-ART PLHIV lost to care at each ART preparation step was calculated with the associated relative risk (Figure 4.5). Each step was significantly associated with pre-ART loss-to-care (p<0.001, Fishers Exact Chi-square Tests). The greatest relative risk of loss-to-care is associated with the step from psychosocial assessment (RR 3.08, 95% CI 2.82 to 3.36, p<0.001, Fishers Exact Chi-square Test). The step with the next greatest risk of pre-ART loss-to-care occurs when there is a clinical or psychosocial delay between the third ART literacy session and ART initiation, (RR 2.08, 95% CI: 1.74 to 2.42, p<0.001, Fishers Exact Chi-square Test).
Figure 4.5 Loss-to-Care risk associated with antiretroviral therapy preparation steps for people living with HIV at Sinikithemba HIV Clinic, July 2004 to December 2007.
4.3.5  ART preparation waiting times associated with pre-ART Loss-to-Care.

An area graph was used to plot the median waiting time per enrolment month for the first three ART preparation steps, from July 2004 to December 2007. The overall median time from ART-eligibility to outcome was also plotted on the graph to show how this overall time trend appears to mirror the ART preparation step with the longest median waiting time per enrolment group, (Figure 4.6).

**Figure 4.6:** Median waiting times between antiretroviral therapy eligibility to outcome, and the first three preparation steps for antiretroviral therapy, per enrolment month for *Sinikithemba* HIV Clinic, July 2004 to December 2007.
The ART preparation step with the longest median waiting time per month for the period July 2004 to January 2007 is seen between the psychosocial assessment to first ART literacy step and the median time from ART eligibility to outcome appears to have a similar trend, (Figure 4.6).

In January 2007, the median waiting time for the first ART literacy session decreases sharply but the waiting time for the second ART literacy median waiting time increases. From January 2007, the median ART-eligibility to outcome time appears to mirror the waiting time for the psychosocial assessment and second ART literacy session.

The changes in median waiting time between the first three ART preparation steps correspond with the change made at Sinikithemba from the Batch ART Preparation System to the Daily ART Preparation System in January 2007.

The area graph also demonstrates the effect of increasing or decreasing the number of available ART preparation slots on the waiting time between ART preparation steps. In February 2004, due to a funding crisis, ART preparation slots were reduced and this corresponded with a spike in the first ART literacy waiting time. Ultimately, all ART-eligible PLHIV were referred to other ART initiation sites during the funding crisis and this then corresponded with a slump in the waiting time for the first ART literacy session.

Again, in September 2006 due to funding problems, the ART preparation slots were reduced and the graph shows a corresponding increase in waiting time from psychosocial assessment to the first ART literacy session.

The area graph also demonstrates the effect of the change in laboratory used by the clinic in 2007 when Sinikithemba was granted access to the National Health Laboratory System. The benefit of this change was that the cost of laboratory testing was reduced and CD4 tests were offered to PLHIV free of charge. However the turn-around time for CD4 results increased from the 6 day turn around available from the previous private laboratory to a three-week turn-around time with the National Health Laboratory System.
Table 4.2: Stratification of variables associated with the Loss-to-Care across two antiretroviral therapy preparation systems at *Sinikithemba* HIV Clinic, July 2004 to December 2007.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Batch System N (%)</th>
<th>Daily System N (%)</th>
<th>P-value</th>
<th>Crude RR 95% CI</th>
<th>Adjusted RR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ART preparation system</strong></td>
<td>3976 (73)</td>
<td>1494 (27)</td>
<td></td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Pre-ART Lost to Care</strong></td>
<td>2169 (55)</td>
<td>810 (54)</td>
<td>P =0.83</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Demographic characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1736 (44)</td>
<td>661 (44)</td>
<td>P =0.60</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Baseline CD4 cell count, median cells/uL (IQR)</strong></td>
<td>62 (22-127)</td>
<td>82 (32-138)</td>
<td>P&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD4 count ≤ 50 cells/uL, median cells/uL (IQR)</td>
<td>1765 (44)</td>
<td>538 (36)</td>
<td>P&lt;0.001</td>
<td>1.18 (1.12 – 1.24)</td>
<td>1.18 (1.12 – 1.61)</td>
</tr>
<tr>
<td><strong>Pre-Eligibility Care</strong></td>
<td>131 (3)</td>
<td>135 (9)</td>
<td>P&lt;0.001</td>
<td>0.66 (0.56 – 0.77)</td>
<td>0.66 (0.56 – 0.77)</td>
</tr>
<tr>
<td><strong>ART Initiation delay at ART literacy 3</strong></td>
<td>409 (10)</td>
<td>224 (15)</td>
<td>P&lt;0.001</td>
<td>2.18 (1.52 – 3.13)</td>
<td>2.21 (1.55 -3.16)</td>
</tr>
<tr>
<td><strong>ART Preparation Step Loss-to-Care</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline CD4 Loss-to-Care</td>
<td>2169 (55)</td>
<td>810 (54)</td>
<td>P&lt;0.001</td>
<td>1.12 (1.13 0 1.32)</td>
<td>1.12 (1.10 – 1.14)</td>
</tr>
<tr>
<td>Psychosocial Assessment Loss-to-Care</td>
<td>1811 (45)</td>
<td>543 (36)</td>
<td>P&lt;0.001</td>
<td>3.08 (2.82 – 3.26)</td>
<td>3.08 (2.91 – 3.29)</td>
</tr>
<tr>
<td>ART literacy 1 Loss-to-Care</td>
<td>277 (7)</td>
<td>188 (13)</td>
<td>P&lt;0.001</td>
<td>1.43 (1.25 – 1.63)</td>
<td>1.43 (1.24 – 1.63)</td>
</tr>
<tr>
<td>ART literacy 2 Loss-to-Care</td>
<td>218 (5)</td>
<td>89 (6)</td>
<td>P&lt;0.03</td>
<td>1.20 (1.02 – 1.40)</td>
<td>1.20 (1.02 – 1.40)</td>
</tr>
<tr>
<td>ART literacy 3 Loss-to-Care</td>
<td>178 (4)</td>
<td>70 (5)</td>
<td>P&lt;0.001</td>
<td>2.08 (1.74 – 2.48)</td>
<td>2.08 (1.74 – 2.48)</td>
</tr>
<tr>
<td><strong>ART Preparation Waiting time, median days (IQR)</strong></td>
<td>31 (4-95)</td>
<td>47 (7-95)</td>
<td>P=0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CD4 count to PSA, median days (IQR)</td>
<td>5 (3-8)</td>
<td>22 (6-37)</td>
<td>P&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PSA to ART Literacy 1, median days (IQR)</td>
<td>58 (24-81)</td>
<td>4 (1-7)</td>
<td>P&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ART Literacy 1 to 2, median days (IQR)</td>
<td>7 (7-7)</td>
<td>26 (19-55)</td>
<td>P&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ART Literacy 2 to 3, median days (IQR)</td>
<td>7 (7-7)</td>
<td>7 (7-7)</td>
<td>P&lt;0.001</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ART initiation delay, median days (IQR)</td>
<td>19 (7-49)</td>
<td>19 (10-42)</td>
<td>P =0.5</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

RR, relative risk; CI, Confidence Interval; IQR, Interquartile range.
Despite these indications of ART preparation waiting time being affected by changes to the ART preparation system, no statistically significant difference in pre-ART loss-to-care between the Batch ART Preparation System and the Daily ART Preparation System was found (p = 0.83, Fisher Exact Chi-square Test, Table 4.2).

In order to understand this better, each exposure variable that was found to be statistically associated with pre-ART loss-to-care by bivariate analysis was stratified across the two ART preparation systems and compared (Table 4.2).

No statistically significant difference in gender between the two ART preparation systems was found (p = 0.60, Fishers Exact Chi-square Test). However there was a statistically significant difference in the baseline CD4 count, with the Daily System having a higher CD4 median by twenty units (82 cells/uL) than the Batch system (62 cells/uL), (p<0.001, Mann-Whitney Two Independent Sample Test).

The proportion of PLHIV with a CD4 count less than 50 cell/uL in the Daily System, 538 (36%) was eight percent less than that of the Batch system, 1765 (44%). This was also found to be a statistically significant difference, (p<0.001, Fishers Exact Chi-square Test). However, there was no difference in the crude and adjusted relative risk of being lost to care when CD4 count was less than 50 cells/uL. Both the crude and adjusted relative risks associated with pre-ART loss-to-care were statistically significant, (p<0.001, Fishers Exact Chi-square Test).

Pre-eligibility care was significantly different between the two ART preparation systems, with six percent more PLHIV accessing CD4 monitoring services prior to being ART-eligible in the Daily System, 135 (9%), than the Batch system, 131 (3%).

There was no statistically significant difference in the CD4 counts of these PLHIV. However the time spent in pre-eligibility care was significantly different, (p <0.001, Fishers Exact Chi-square Test) with the median time in pre-eligibility care in the Daily System (397 days, IQR: 158 to 628) being more than double that of the Batch system (188 days, IQR:98 to 336).
When comparing ART initiation delays at the third ART literacy session between the Batch and Daily System, there was a slight change in the adjusted relative risk from 2.18 to 2.21, (p<0.001, Fishers Exact Chi-square Test). Unlike the Batch system, ART initiation delays at the third ART literacy visit were not associated with pre-ART loss-to-care in the Daily System.

Analysis of the association of pre-ART loss-to-care with the different ART preparation steps and the waiting times between these steps, stratified by the Batch and Daily ART Preparation Systems provided surprising results.

The changes in the median waiting time per ART preparation step and the numbers of pre-ART PLHIV lost to care at each ART preparation step were significantly different across the two ART preparation systems (p<0.001 using Mann-Whitney Two Independent Sample Test for waiting time and Fishers Exact Chi-square Test for loss-to-care).

However, despite these statistically significant differences between the two ART preparation systems, the relative risks of pre-ART PLHIV being lost to care at each step did not change.

Whilst the proportion of pre-ART PLHIV lost to care after the baseline CD4 count test and the psychosocial assessment step decreased, the proportion of pre-ART PLHIV lost to care after the three ART literacy sessions increased when comparing the Batch and Daily ART preparation steps. All of these differences were found to be statistically significant differences across the two ART preparation systems, (p<0.001 Fishers Exact Chi-square Test).

The Psychosocial Assessment waiting time was also significantly different between the two ART preparation systems, with the median waiting time decreasing from 58 days to four days in the Daily System, (p<0.001, Mann-Whitney Two Independent Sample Test).

The difference in waiting time between the second and third ART Literacy sessions was also significant, but in the opposite direction with the waiting time increasing from 7 to
26 days, (p<0.001, Mann-Whitney Two Independent Sample Test).

Due to there being no statistically significant difference in pre-A RT loss-to-care when comparing the two ART preparation systems, the only way to analyse whether the waiting time between ART preparation steps was associated with pre-A RT loss-to-care was to calculate the relative risk of pre-A RT loss-to-care per monthly enrolment group.

The only ART preparation step that was associated with pre-A RT loss-to-care, when comparing the median waiting time per monthly enrolment group was the psychosocial assessment to the first ART literacy step. The median waiting times per enrolment group were categorised according to the overall median waiting time of 31 days and tested to assess whether pre-A RT loss-to-care per enrolment group was higher when the median waiting time was higher than 31 days.

The relative risk of pre-A RT loss-to-care per enrolment group when the median waiting time between psychosocial assessment and the first ART literacy session was greater than 31 days, was 1.22 (95% CI: 1.16 to 1.25, p<0.05 Fishers Exact Chi-square test).

The relative risk calculations for waiting time between the other ART preparation steps were not found to be statistically significant.

4.3.6 Multivariate analysis

Of all the exposure variables tested against the outcome variable of pre-A RT loss-to-care, gender, baseline CD4 count, pre-eligibility care and the median waiting time between psychosocial assessment and the first ART literacy session per enrolment group, affected all pre-A RT PLHIV in the study.

Each of these exposure variables were individually tested and found to have a statistically significant association with pre-A RT loss-to-care using logistic regression, (p<0.05, Generalised Linear Model for the Binomial Family). When these exposure variables were tested together using logistic regression again to control for confounding, each exposure variable was still found to be statistically significant, (p<0.05, Generalised Linear Model
for the Binomial Family, Table 4.3).

Not all pre-ART PLHIV reached the third ART literacy step and therefore the exposure variable of ART initiation delay at the third ART literacy session could not be analysed along with the other exposure variables for all pre-ART PLHIV in the study (n=5470).

The exposure variable ART initiation delay at the third ART literacy visit was compared against the other exposure variables using logistic regression for the subset of PLHIV who did reach the third ART literacy step (n=2739). The results showed that ART initiation delay at the third ART literacy visit remained statistically significant in its association with pre-ART loss-to-care, (p<0.05, Generalised Linear Model for the Binomial Family, Table 4.3).

However the other exposure variables, gender, baseline CD4 count, pre-eligibility care and median waiting time between psychosocial assessment and the first ART literacy step per enrolment group, were no longer significantly associated with pre-ART loss-to-care.

Table 4.3: Adjusted relative risk, using logistic regression, of variables associated with Loss-to-Care, at Sinikithemba HIV Clinic, July 2004 to December 2007.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adjusted Relative Risk</th>
<th>P-value</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=5470</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.07</td>
<td>0.008</td>
<td>1.02 - 1.12</td>
</tr>
<tr>
<td>CD4 count &lt; 50 cell/uL</td>
<td>1.15</td>
<td>&lt;0.001</td>
<td>1.19 - 1.21</td>
</tr>
<tr>
<td>Pre-eligibility care</td>
<td>0.71</td>
<td>&lt;0.001</td>
<td>0.60 - 0.83</td>
</tr>
<tr>
<td>Psychosocial to first ART literacy median time &gt; 31 days</td>
<td>1.22</td>
<td>&lt;0.001</td>
<td>1.16 - 1.28</td>
</tr>
<tr>
<td>N=2739</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ART initiation delay at third ART literacy session</td>
<td>2.18</td>
<td>&lt;0.001</td>
<td>1.52 - 3.13</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>1.22</td>
<td>0.274</td>
<td>0.86 - 1.75</td>
</tr>
<tr>
<td>CD4 count &lt; 50 cell/uL</td>
<td>1.01</td>
<td>0.768</td>
<td>0.73 - 1.53</td>
</tr>
<tr>
<td>Pre-eligibility care</td>
<td>0.58</td>
<td>0.282</td>
<td>0.22 - 1.56</td>
</tr>
<tr>
<td>Psychosocial to first ART literacy median time &gt; 31 days</td>
<td>1.35</td>
<td>0.102</td>
<td>0.94 - 1.94</td>
</tr>
</tbody>
</table>
5 CHAPTER V: DISCUSSION

5.1 INTRODUCTION

The demand for comprehensive HIV services is greater than the available supply, particularly for the provision of antiretroviral therapy. The resulting bottleneck in service delivery has considerable implications not only for the individual PLHIV and the overall management of the HIV epidemic, but also for resource management. This chapter outlines and discusses the main findings of the study in relation to the context of the literature available on the topic of loss-to-care in people living with HIV (PLHIV) that are eligible for antiretroviral therapy (ART).

5.2 FINDINGS

In line with the purpose of this study, the main finding from the data analysis is that more than half (54%) of the ART-eligible adults registered for HIV care at Sinikithemba HIV Clinic from July 2004 to December 2007, were lost to care prior to initiating ART.

Statistical analysis identified six statistically significant exposure variables associated with this loss-to-care, which remained significantly associated with pre-ART loss-to-care even after controlling for confounding with logistic regression. Each of these exposure variables is discussed in the next sections of this chapter, highlighting the relevance of each and how it influenced pre-ART loss-to-care and ultimately management of the HIV epidemic.

5.2.1 Proportion of ART-eligible PLHIV who are lost to care

The recently released Department of Health National Antenatal Sentinel HIV and Syphilis Prevalence Survey in South Africa, 2009 found the HIV prevalence in adults (15 to 49 years) to be 18%. This equals 5.3 million HIV-infected South African adults with almost 1.6 million of these PLHIV requiring ART.
KwaZulu Natal is still the province with the highest prevalence of HIV infection in antenatal woman, aged 15 to 49 years, of 39.5% and had a 0.9% increase reported in the year between 2008 and 2009. Even more concerning than this, is the fact that the eThekwini district, where McCord Hospital is situated, has an even higher prevalence of HIV infection in ante-natal woman, aged 15 to 49 years, than the province, of 41.5% (3).

In relation to the similarly high pre-ART loss-to-care found at Sinikithemba of 54%, this does not paint a positive picture for the eThekwini district and the likelihood of the high HIV infection incidence being reversed in the near future. ART-eligible PLHIV are a particularly high-risk group with high viral loads and HIV transmission potential, as well as being immune-compromised and vulnerable to opportunistic infections or death (26).

As the literature on retention of PLHIV in care grows, more studies are showing similar findings on pre-ART loss-to-care and are raising the alarm for the impact this will have on the current efforts to curb the HIV epidemic. If pre-ART attrition from HIV care goes unchecked, these ART-eligible PLHIV will continue to contribute to HIV incidence as well as the overwhelming burden of HIV morbidity and mortality experienced in the province.

5.2.2 Demographic Characteristics of ART-eligible PLHIV lost to care

The larger proportion of females (3073, 56%) in comparison to males (2397, 44%) accessing ART preparation at Sinikithemba is in line with current trends showing that more female adults access HIV care than males. A number of studies on retention in HIV care have shown that male gender is a risk factor for loss-to-care (27).

As a statistically significant exposure variable associated with pre-ART loss-to-care, the importance of health systems adopting strategies targeted at getting and retaining males in HIV care is again highlighted.
Similar to other pre-ART loss-to-care studies, age at enrolment was not associated with pre-ART loss-to-care (28). The median age for ART-eligible PLHIV of 35 yrs was consistent with the 2009 HIV survey findings that the highest HIV prevalence is in the 30 to 40 year age group. According to the survey this is attributed to the increased survival of those HIV positive PLHIV on ART, however this is not applicable for this particular group of pre-ART PLHIV (3).

What is more likely is that a higher proportion of PLHIV in this age group are employed and able to pay the *Sinikithemba* clinic user-fee.

**5.2.3 Clinical Characteristics of ART-eligible PLHIV who are lost to care**

The median baseline CD4 count of 68 cell/uL for pre-ART PLHIV at *Sinikithemba* is low considering that the CD4 count threshold for ART initiation is 200 cell/uL. This is not surprising considering that 95% of the pre-ART PLHIV included in this study were ART eligible at their first clinic visit.

Two possible reasons for this are the back-log created by the pre-2004 lack of access to ART in the public sector, and that *Sinikithemba* is a hospital-based facility, which may attract sicker PLHIV than the average ART clinic. This raises the question of the clinical status of these PLHIV from delayed entry into care and presenting late for ART.

Over the years since the rapid scale up of ART initiation, *Sinikithemba* has also developed a reputation for having shorter waiting times for ART initiation than most government clinics. One of the reasons for this could be the *Sinikithemba* fee. PLHIV who initially access care at another ART clinic rather than *Sinikithemba* may eventually put the required money together to come to *Sinikithemba* to try access treatment quicker after their health has deteriorated whilst waiting for ART elsewhere.

Whatever the reason for this low baseline CD4 count, recent research findings show that the outcomes for such low baseline CD4 counts, are not good. A literature review on retention in care, conducted by Geng *et al*, described how the probability of remaining in care was lower for PLHIV with a baseline CD4 count lower than 50 cells/uL (12).
These PLHIV are most likely to die before initiating ART, and were found to have the lowest probability of initiating ART in the Free State cohort, even after accounting for the competing risk of death (28,29)

With over 40% (2303) of baseline CD4 count of PLHIV baseline CD4 count being less than 50 cells/uL, the study findings are consistent with other research findings that pre-ART loss-to-care is associated with a baseline CD4 count less than 50 cells/uL.

5.2.4 Pre-eligibility Care and ART-eligible PLHIV who are lost to care

Unfortunately whilst the reverse is also true, accessing HIV care with a CD4 count higher than the ART initiation threshold is protective against pre-ART loss-to-care, only five percent of the ART-eligible PLHIV at Sinikithemba had entered HIV care prior to being ART eligible for ongoing CD4 monitoring.

Interestingly the median first time CD4 count for these PLHIV was 257 cells/uL, not much higher than the ART initiation threshold during the study period. According to the current ART initiation guidelines, indicating ART initiation in pregnant or TB infected PLHIV, this subset of pre-eligibility or “in-eligible” PLHIV could have well been classified as ART eligible.

Despite the numbers of PLHIV who accessed HIV care prior to being ART eligible being so low and their first CD4 count being so close to the ART initiation threshold, this was still a statistically significant exposure associated with pre-ART retention in care rather than pre-ART loss-to-care.

The median time these PLHIV accessed HIV care prior to being ART-eligible was 265 days, almost nine months, which could be one of the reasons for pre-eligibility care being protective against pre-ART loss-to-care. In that time, ongoing immunological and clinical evaluation through wellness care may well have protected the patient against the risk factors associated with late presentation and actually ‘pre-disposed’ these PLHIV to initiating ART at an optimal CD4 count (28)
As a study in Ethiopia indicated, the improved survival seen over time was related to PLHIV presenting earlier with less advanced disease causing PLHIV to initiate ART earlier with better outcomes (30). Whilst it would seem that it is critical that retention mechanisms incorporate interventions to get PLHIV into care as early as possible, a review of retention in care studies showed that both low and high CD4 counts were associated with pre-ART attrition (12).

PLHIV with higher CD4 counts were more mobile and likely to be working and relatively well, which were themselves obstacles for remaining in care (12,30). Therefore, it is important that retention mechanisms are directed at the different categories of PLHIV, based on their need and motivation for accessing pre-ART care.

### 5.2.5 ART initiation delay and ART-eligible PLHIV who are lost to care

Pre-ART PLHIV who had ART initiation delayed at the third ART literacy step were more likely to be lost to care than those who had no ART initiation delay. When all the statistically significant variables associated with pre-ART loss-to-care were tested against the variable ART initiation delay with logistic regression, ART initiation delay was the only variable that remained statistically significant in its association with pre-ART loss-to-care.

However when this variable was compared across the two ART preparation systems, ART initiation delays were no longer significantly associated with pre-ART loss-to-care in the Daily ART Preparation System. This was despite the fact that the same proportion of PLHIV had ART initiation delays per ART preparation system.

One of the reasons for this change in association could be the relatively small size of this subset (n = 633), although this was not the case with the even smaller subset of PLHIV who had pre-eligibility care (n=266) and still had a significant association.
Another possible reason for ART initiation delay not being a statistically significant factor associated with pre-ART loss-to-care in the Daily ART Preparation System is that the shortened waiting time in the Daily System between the psychosocial assessment and first ART literacy step allowed PLHIV to have a clinical consultation earlier than those prepared through the Batch ART Preparation System.

This change in the exposure variable from being highly significant in one subset of PLHIV to not being significant at all in another could be for the same reason that PLHIV who access pre-eligibility care are protected against pre-ART loss-to-care. Earlier access to clinical care, which was the case in the Daily ART preparation step, provides opportunity for immunological and clinical evaluation and reduces the risk of poor outcomes (12).

Whereas PLHIV in the Batch ART Preparation System had much longer waiting times to a clinical consultation and possibly for those PLHIV, having one more delay at the third ART literacy session, which was most likely due to treatment of an opportunistic infection, may have been one delay too many.

5.2.6 ART preparation steps and ART-eligible PLHIV who are lost to care

Every time a pre-ART PLHIV has to return to the clinic there is a risk of the PLHIV being lost to care, this is demonstrated by the fact that every step in the ART preparation process at Sinikithemba, had a statistically significant associated relative risk.

In the Department of Health’s book “Tried and Tested Models For The Scale Up Of HIV Prevention, Treatment And Care From South Africa And Beyond”, a whole section, is dedicated to “closing the gaps in HIV care”. One of the key areas highlighted and addressed is that of the bottlenecks that occur around ART preparation (26).

Some of the models presented to streamline the ART preparation process propose that certain processes are “fast-tracked” such as providing access to CD4 count results without queues or delays and bundling services together to reduce the number of times a patient’s has to return to complete the process.
However, as was pointed out by the Free State study, most “immunosuppressed PLHIV cannot afford the luxury of extended pre-ART education” (28). It doesn’t matter what efforts are made to stream-line the process, the key targets of the process, ART-eligible PLHIV just are not in a position to ‘jump through all the hoops’ to complete the process. The current situation of extended waiting list for ART is that the process of ART preparation is ultimately rationing treatment to PLHIV who should all be initiated on life saving treatment.

The PLHIV who were lost to care through this process are PLHIV who are classified as having acquired immunodeficiency syndrome (AIDS) based on their CD4 counts, the associated mortality with their low CD4 counts should provide the motivation needed for the development of a better system of preparing these PLHIV for ART.

An evaluation of the efficiency of patient flow in three Ugandan clinics highlighted the fact that a PLHIV being prepared for ART could see up to five different service providers or more in one visit (31). The study recommended that the scale up of HIV services should be accompanied by evaluations aimed at maximising efficiencies, allowing more PLHIV into care without compromising the quality of care.

This is not a simple task when faced with the huge demand for ART, with such limited resources but one of the critical areas that could be addressed is the actual process of preparing PLHIV for ART. Wagner et al showed with mathematical modelling that just by reducing the number of ART preparation sessions by two could reduce by half, the numbers of ART preparation PLHIV seen in the clinic per day (32).

As was pointed out in the Free State study there has been no formal evaluation of the ART preparation process and potential alternatives to preparing ART-eligible PLHIV for lifelong HIV treatment (28).
5.2.7 ART waiting time and ART-eligible PLHIV who are lost to care

Analysis of waiting time for ART initiation is not easily done because the outcome variable – loss-to-care, masks the exposure variable, waiting time when analysed at the ART preparation step at which a PLHIV was lost to care. Retention is also a longitudinal exposure with time being a confounding factor. It is difficult to draw causal conclusions about associations as these are ever changing (12).

However the median waiting times between ART preparation steps and the overall waiting time from ART eligibility to outcome were calculated for this study and provide certain important insights for pre-ART loss-to-care.

There was a considerable difference between the median waiting times for those pre-ART PLHIV who initiated ART, almost three months, versus 5 days of those who were lost to care. Ultimately the majority of pre-ART PLHIV lost to care only remained in care long enough to get their CD4 count results before being lost to the system. What was also interesting to find was that when waiting time was analysed per ART preparation step, the PLHIV who were lost to care had shorter waiting times at previous steps than those PLHIV who ultimately initiated ART.

As the majority of pre-ART PLHIV who were lost to care had baseline CD4 counts less than 50 cells/uL, this trend was most likely due to these PLHIV being fast-tracked through the system. What is important to note is that this did not appear to improve the outcome for these PLHIV as they were still lost to care at one of the next steps. This was one of the reasons that Kaplan-Meier plots were not used to demonstrate the survival curve and time to event, as they did not reflect the true situation with regard to overall waiting time and its effect on loss-to-care.

The Free State study looked specifically at waiting time for ART as one of the factors associated with pre-ART mortality and loss-to-care, but calculated the competing risks rather than Kaplan Meier survival estimates, as the Kaplan Meier estimates potentially gave misleading impression of pre-ART mortality.
According to the authors of the Free State study, so far only three other studies in resource-limited settings have assessed the waiting time for ART, with one of them being a study done previously at Sinikithemba. (28)

This is quite surprising considering that this study also found that there was a strong relationship between waiting time for ART and the ART preparation system, amongst other health system factors. At Sinikithemba, changes made to the health system for reasons other than affecting the waiting time between steps were also shown to affect waiting time at. One such example was the increase in the time between baseline CD4 count and the psychosocial assessment visit when Sinikithemba started using provincial laboratories for CD4 testing in January 2007.

Up to January 2007, the time between CD4 count testing and the psychosocial assessment step was equivalent to the turn-around time for CD4 results from the private laboratory of 6 days. When the provincial laboratory was used the waiting time increased to a median of 22 days, which was equivalent to the CD4 turn-around time of three weeks at the provincial laboratory.

What is important to acknowledge is that although the time to ART initiation is “strongly associated with clinic-level factors”, health system changes do not necessarily have the desired impact on reducing ART preparation waiting time (28). This was clearly demonstrated by the comparison of the Batch ART Preparation System and the Daily ART Preparation System.

This change in ART preparation system was specifically implemented in an effort to reduce the waiting lists and ultimately the waiting time for ART-eligible PLHIV at the psychosocial assessment step. The psychosocial assessment step had the greatest risk of pre-ART loss-to-care and the longest waiting time to the next step, the first ART literacy session.
However, comparison of the two systems showed that despite the waiting time for the psychosocial assessment step being drastically reduced from a median of 31 days to 4 days, the overall waiting time for ART actually increased from 37 days to 47 days and there was no significant difference in the proportion of PLHIV lost to care between the two different ART preparation steps.

What was found was that although waiting time was reduced, the number of PLHIV that could be prepared for ART by the clinical staff did not change and therefore this bottleneck just ended up pushing back the waiting time to the next ART preparation step, which increased, from a median of 7 days to a median of 26 days.

This finding highlights the interplay between the demand for ART and capacity of the clinic to supply ART. Improving the flow of pre-ART preparation PLHIV through the clinic and decreasing the waiting time for ART will not have the desired effect unless the health system has the capacity to initiate and absorb the increased number of PLHIV on ART. Limited resources and capacity will always result in increased waiting times and patient attrition as patient loads increase (28).

One final result that was significant was that when waiting times between ART preparation steps was compared per enrolment month across the whole study period, only the waiting time between the psychosocial assessment and first ART literacy session was significantly associated with pre-ART loss-to-care.

Despite health management decisions having an effect on waiting times between ART preparation steps and there being an associated risk of pre-ART loss-to-care for each ART preparation step, the greatest risk of pre-ART loss-to-care remained at the psychosocial assessment step even when the waiting time was drastically reduced from more than a month to less than a week.

This again indicates that there are other factors associated with pre-ART loss-to-care, which are beyond the scope of this study and the available data.
5.3 LIMITATIONS AND CONFOUNDING

“A disregard for the social and cultural context of adherence or the imposition of adherence models which are inconsistent with local values and practises is likely to produce irrelevant and ineffective interventions” (33)

The greatest limitation of this study is that as a retrospective study only certain data elements were available for analysis. Whilst important information has been presented from this retrospective review, these findings are limited by the data available and ultimately can only reflect on pre-ART loss-to-care from the perspective of the health systems. What is critically missing is the perspective of the ART-eligible PLHIV themselves and the social, economical and cultural context they bring to the system, which could only be assessed in a prospective study with a qualitative component.

This is most clearly seen in the fact that despite changes to the associated exposure variables such as waiting time and baseline CD4 count, and logistic regression controlling for confounding between these variables, the greatest risk of pre-ART loss-to-care remained at the psychosocial assessment step. This indicates that there are other variables associated with pre-ART loss-to-care that are beyond the scope of this study.

Other studies have highlighted potential confounders such as distance and accessibility to the clinic, employment obstacles and maybe most pertinent to this study, financial barriers to care. Another possible reason for the persistent loss-to-care at the psychosocial assessment step is that this is the step at which PLHIV find out they are eligible for ART, which in some cases could be only six days after finding out their HIV status. For some PLHIV, this may just be a little too much to handle all in one week.

Without information from PLHIV themselves on their reasons for remaining in care or no longer accessing care, the conclusions drawn from this study are limited and due to the unknown affects of factors such as the clinic-fee cannot be generalised to other sites.
In addition to this, the lack of information on pre-ART loss-to-care mortality and silent transfers\(^\text{13}\), further limit the findings and conclusions that can be drawn both about the causality of pre-ART loss-to-care. Questions of whether pre-ART PLHIV are lost to care due to pre-ART mortality or whether pre-ART mortality is caused by pre-ART loss-to-care cannot be answered.

Even the high proportion of PLHIV lost to care can be questioned as it is not possible to define how many of these PLHIV are truly lost to care or are rather just lost from *Sinikithemba* due to transfer care elsewhere (12).

Although delay in ART initiation was analysed at the third ART literacy step, this analysis could not be taken further as data on clinical or psychosocial delays between the other ART preparation steps were not available. This limits the generalisability of this finding to the other ART preparation steps and raises questions of confounding despite this variable remaining highly significant after controlling for the other associated variable describe in this study.

This is especially so considering that this variable was no long significantly associated with pre-ART loss-to-care in the smaller subset of PLHIV who were prepared for ART after January 2007. Whilst this may be due to pre-ART PLHIV having better outcomes if they have reduced waiting time to their clinical consultations, this cannot be tested and confirmed without additional data.

Even the conclusions drawn from analysing the two separate ART preparation systems are limited as the total number of PLHIV between the two systems were so different, (3976 and 1484) and only one year of the Daily ART Preparation System was compared to two-and-a-half years of the Batch ART Preparation System. The differences between the two systems could also have been confounded by the six months during which the Batch system was being phased out whilst the Daily System was being implemented.

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\(^{13}\) Silent Transfers refers to PLHIV who transfer their healthcare to another facility without informing the initial health facility where they were accessing care of this transfer out.
6 CHAPTER VI: RECOMMENDATIONS AND CONCLUSIONS

6.1 INTRODUCTION

This chapter presents conclusions based on the findings and discussion of each important issue explored in the study and highlights the main implications of these findings, with recommendations for the future.

6.2 CONCLUSIONS

The main purpose of this study was to quantify and describe loss-to-care in people living with HIV (PLHIV) that are eligible for antiretroviral therapy (ART) and analyse the available demographic, clinical and health system related factors that affect pre-ART loss-to-care. With the emphasis of HIV programmes and research focused on the rapid scale-up of ART for the last few years, the pre-ART outcomes have not been adequately documented. The large sample size and three-and-a-half year follow up period provided a large dataset to demonstrate that pre-ART loss-to-care of ART-eligible PLHIV is a significant problem that needs to be further investigated.

The low median CD4 counts of pre-ART PLHIV indicates that the majority of ART-eligible PLHIV are entering ART preparation care at the end stages of acquired immunodeficiency syndrome (AIDS) disease rather than the threshold for ART initiation and this is affecting on the retention of pre-ART PLHIV in HIV care. The association of male gender with pre-ART loss-to-care, adds to the growing body of evidence that HIV health care systems are not set up to attract and retain males in care.

The high prevalence of HIV in KwaZulu Natal has resulted in the numbers of ART-eligible PLHIV exceeding the capacity of the health care system to meet the demand for ART. This has resulted in waiting lists and delays for ART-eligible PLHIV, which further impact pre-ART loss-to-care.
There is little evidence available to support the adopted process of ART preparation, yet in the absence of a better system, the ART preparation process has become a means of rationing the limited resources available for ART initiation rather than a programme focused on efficiently attracting and retaining HIV PLHIV into care at early stages of HIV infection.

The ART preparation steps associated with the longest waiting time and highest risk of pre-ART loss-to-care occurs at the point of accessing clinical care and reflects the rate-limiting effect of clinical capacity. Efforts to reduce the pre-ART waiting time at these steps did not influence overall waiting time for ART initiation and retention in care, as the clinical capacity to manage increased numbers of PLHIV did not improve.

The public health benefits of retaining PLHIV in HIV care necessitates that further research is conducted to report on the attrition points and predictors of pre-ART loss-to-care and provide evidence for the changes that need to be made to improve this situation (2).

**6.3 RECOMMENDATIONS: PROGRAMME LEVEL**

The highest mortality at ART sites with limited resources is found in those PLHIV who present late for treatment; improved access to care and treatment means improved disease stage and reduced mortality. Focusing retention strategies at the pre-ART stage and not just the ART initiation stage will have an impact on overall programme outcomes:

1. Targeted follow up of ART-eligible PLHIV at the ART preparation steps associated with the greatest risk of pre-ART loss-to-care. These strategies can focus initially on pre-ART loss-to-care ascertainment and as information and understanding of pre-ART retention improves, can inform new retention strategies.
2. Targeted recruitment and follow up of male PLHIV
3. Development of monitoring and evaluation indicators for measuring the outcomes of pre-ART retention strategies.
4. Development of pre-ART Wellness programme in order to encourage PLHIV to enter and remain in care prior to being ART eligible and ultimately improve the clinical outcomes of PLHIV prepared and initiated on ART.

5. Use emerging research findings to modify the ART preparation process in order to reduce the number of preparation visits required, decentralize the ART preparation process, address competing risks for pre-ART loss-to-care and increase the numbers of PLHIV initiated and maintained on ART.

6.4 **RECOMMENDATIONS: FURTHER STUDY**

The outcome of pre-ART programmes, including death and loss-to-care are not adequately documented as most literature is focused on the outcomes of ART programmes. It is imperative that research, specifically focused on this stage of HIV care and treatment is conducted and provides evidence for developing strategies to increase access to ART without over-saturating the clinic:

1. Systematic analysis of the flow of PLHIV through all components of the HIV programme needs to be conducted to evaluate the effectiveness of HIV care and treatment strategies and identify bottlenecks and unnecessary delays.

2. Prospective qualitative methods need to be used to follow up pre-ART PLHIV both lost to care and retained in care so that associations can be explained.

3. Longitudinal operational research evaluating the effects of changes to the ART preparation process and the association between clinical consultations and retention in care.
7 REFERENCES


### Table 8.1: List of Key Data Elements extracted from TrakCare, 01 August 2009

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<td>Result of Baseline CD4 count</td>
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<td>Category of ART Preparation Visit</td>
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<tr>
<td>ART Start Date</td>
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Table 8.2 List of Variables generated for data analysis

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