PHARMACY REFILLS AS A MEASURE OF ADHERENCE TO ANTIRETROVIRAL THERAPY FOR HIV POSITIVE PATIENTS AT MPILO CENTRAL HOSPITAL IN BULAWAYO ZIMBABWE

by

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DECLARATION

I declare that **PHARMACY REFILLS AS A MEASURE OF ADHERENCE TO ANTIRETROVIRAL THERAPY FOR HIV POSITIVE PATIENTS AT MPILO CENTRAL HOSPITAL IN BULAWAYO ZIMBABWE** is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references and that this work has not been submitted before for any other degree at any other institution.

30 June 2015

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FULL NAMES **DATE**

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ABSTRACT

This non-experimental, retrospective, descriptive and correlational study investigated adherence to antiretroviral drugs among HIV positive patients at Mpilo Central Hospital in Bulawayo Zimbabwe. Data among 118 patients was extracted from clinic registers and patient facility held medical records to determine level of adherence to ART using pharmacy refills (a non-immunological adherence parameter) and compared to CD4 cell count (an immunological adherence parameter).

Adherence levels obtained in this study using pharmacy refills was low (62.7%) and a relatively high non-adherence level of 37.3%. The pharmacy refill adherence level obtained was comparable to CD4 cell count adherence level of 64.6% (as indicated by a 50% CD4 cell count gain). These findings would seem to indicate the need for more education on the importance of adherence and further the need for better adherence monitoring systems.

KEY CONCEPTS

Pharmacy refills; Adherence to antiretroviral (ARV) drugs; Adherence levels; CD4 cell counts; antiretroviral therapy (ART); HIV/AIDS.

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Dedication

To my parents and life educators:

My father the late John Matambura Mutasa, man of integrity

My mother Nelia Mutasa, strong and loving

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LIST OF ABBREVIATIONS

3TC	Lamivudine
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
AZT	Zidovudine
cART	Combination Antiretroviral Therapy
CD4	Cluster Differentiation 4
D4T	Stavudine
DART	Development of Antiretroviral Therapy in Africa
DFID	United Kingdom Department for International Development
DNA	Deoxyribonucleic acid
EFV	Efavirenz
ESP	Expanded Support Programme
FIs	Fusion Inhibitors
GFATM	Global Fund for AIDS, Tuberculosis and Malaria
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
LPV/r	Lopinavir/ritonavir
MDGs	Millennium Development Goals
MEMS	Medication Event Monitoring Systems
MER	More Efficacious Regime
MOHCW	Ministry of Health and Child Welfare
MRCZ	Medical Research Council of Zimbabwe
MTCT	Mother to Child Transmission
MSF	Médecins Sans Frontières
OI	Opportunist Infection
NAC	National AIDS Council
NACP	National AIDS Control Programme
NDTPAC	National Drug and Therapeutics Policy Advisory Committee
NNRTIs	Non-nucleoside Reverse Transcriptase Inhibitors
NRTIs	Nucleoside reverse transcriptase inhibitors
NtRTIs	Nucleotide reverse transcriptase inhibitors
NVP	Nevirapine
PIs	Protease Inhibitors
PLWHA	People Living with HIV and AIDS
PMTCT	Prevention of Mother to Child Transmission
POC	Point-of-Care

RNA	Ribonucleic acid
RTV	Ritonavir
SdNVP	Single dose nevirapine
TDF	Tenofovir
UN	United Nations
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNICEF	United Nation Children Fund
UNISA	University of South Africa
UNGASS	United Nations General Assembly Special Session
USAID	United States Agency for International Development
WHO	World Health Organization
ZVITAMBO	Zimbabwe Vitamin A for Mothers and Babies Project

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CHAPTER 1

ORIENTATION TO THE STUDY

1.1 INTRODUCTION

The World Health Organization (WHO) defines adherence as the extent to which an individual's behaviour when taking medications changes in accordance to recommendations by the health care provider (WHO 2003:3). Because HIV is a lifelong disease, ARV drug adherence requires lifestyle and behavioural changes, accompanied by strict observation of taking the drug dosage as prescribed and at prescribed times or intervals (WHO 2003:97,100). Studies have shown that successful treatment outcomes by ARV drugs depend on achieved levels of adherence (Nachega, Hislop, Dowdy, Chaisson, Regensberg & Maartens 2007:570, 571). While 100% adherence to medication for any disease being treated is the best practice, taking treatment regimens to chronic ailments is difficult (Martin, Cacho, Codina, Tuset, Lazzari, Mallolas, Miró, Gatell & Ribas 2008:1263).

By the end of December 2009, an estimated 3.9 million people were receiving antiretroviral (ARV) drugs in sub-Saharan Africa; representing a 37% coverage rate for the region (WHO 2010b:53). In Zimbabwe, 218,589 people were on HIV treatment by the end of 2009, which was an increase from an estimated 148,144 in 2008 (WHO 2010b:55). The rapid expansion of these programmes was happening in environments of programmatic challenges such as running out of drugs, lack of access and or unavailability of services and political and economic crises; all factors that contribute to non-adherence to ARV drugs (Sanjobo, Frich & Fretheim 2008:138; Veenstra, Whiteside, Lalloo & Gibbs 2010:11-12; Zuurmond 2008:4).

Due to the high rate of HIV replication, high adherence levels are required for effective and sustained virologic suppression of the virus (Bisson, Rowh, Weinstein, Gaolathe, Frank & Gross 2008b:108; Ferguson, Donnelly, Hooper, Ghani, Fraser, Bartley, Rode, Vernazza, Lapins, Mayer & Anderson 2005:349; Nachega, Hislop, Dowdy, Lo, Omer, Regensberg, Chaisson & Maartens 2006:83-84; WHO 2003:95). For HIV, it is generally recommended that adherence levels greater than 95% be achieved (Harrigan Hogg,

Dong, Yip, Wynhoven, Woodward, Brumme, Brumme, Mo, Alexander & Montaner 2005:342-346; Nachega et al 2007:564; Wood, Hogg, Yip, Harrigan, O'Shaughnessy & Montaner 2004:267) even though there are some studies that have documented viral suppression with lower adherence levels (Nachega et al 2007:570). Unlike other chronic diseases, non-adherence to ARVs for HIV has major public health implications because of the emergence of drug-resistant viruses that can be transmitted to others and in the process diminish future treatment options at population level (Peltzer, Friend-du Preez, Ramlagan & Anderson 2010:1; Veenstra et al 2010:1; Vervoort, Borleffs, Hoepelman & Grypdonck 2007:271).

Although there are several methods found to be useful in measuring adherence to HIV medications (Chalker, Wagner, Tomson, Laing, Johnson, Wahlström & Ross-Degnan 2010:159-160; Mills, Nachega, Buchan, Orbinski, Attaran, Singh, Rachlis, Wu, Cooper, Thabane, Wilson, Guyatt & Bangsberg 2006b:683-684; Nachega et al 2007:565,571), adherence to lifelong treatment regimens is difficult to measure (Chalker et al 2010:159). While CD4 cell count and viral load assays are objective parameters used in monitoring efficacy and effectiveness including adherence and or treatment failure to HIV, these tests are not widely available in resource poor settings. Other methods to measure adherence that have been found to be useful include pill counts, pharmacy refills, patient self-report and medication event monitoring systems (MEMS) (Bisson et al 2008b:109; Nachega et al 2007:565,571; Bangsberg 2008:S274-S275). These parameters however tend to be more subjective and in most resource poor settings MEMS are not easily available (Lyimo, Van den Boogaard, Msoka, Hospers, Van der Ven, Mushi & De Bruin 2011:2). In assessing or measuring adherence, it is important to note that there are factors that contribute to a patient's ability or inability to take their medications as prescribed. These facilitating or impeding factors can be socio-demographic, behavioural or provider associated (Muyingo, Walker, Reid, Munderi, Gibb, Ssali, Levin, Katabira, Gilks, Todd & the DART Trial Team 2008:474; Peltzer et al 2010:2; Sanjobo et al 2008:139; Skovdal, Campbell, Nhongo, Nyamukapa & Gregson 2011:302, 309; WHO 2003:103; Zuurmond 2008:4). As part of on-going monitoring and evaluation of ART interventions, it is important to have simple, reliable public health tools to monitor adherence. Because data is collected and kept at the health facility offering ART, pharmacy refill data is the adherence-measuring tool proposed (Bangsberg 2008:S274; Nachega et al 2006:82-84; Nachega et al 2007:565). This

method can be used on routinely collected data to evaluate current or existing adherence levels to ART.

1.2 BACKGROUND INFORMATION ABOUT THE RESEARCH PROBLEM

The ART programme was launched by the Ministry of Health and Child Welfare (MOHCW) in 2004. Making ART accessible to all those who need it became a priority for the government of Zimbabwe. ART access was scaled up from 5 learning sites in April 2004 to 337 sites with an estimated 219 409 (55% coverage) HIV infected patients both adults and children being on ART by the end of 2009 (UNAIDS 2012:30). According to WHO, Zimbabwe recorded a 48% increase in ART coverage rate between 2008 and 2009 (WHO 2010b:55) and the coverage grew from 55% in 2010 to 79.7% by end of 2011 (UNAIDS Global AIDS response progress report 2012:31).

Critical to the success of the ART intervention, is adherence. Adherence to ART is important in order to maintain viral suppression, increase CD4 cell count, lengthen effectiveness of drug regimens and prevent development of HIV drug resistance. HIV drug resistance is a serious public health concern because of the risk of transmission of resistant viral strains. Overall good adherence to ART is important because it ultimately reduces and or prevents morbidity and mortality related to HIV. Adherence to ART is an important early warning indicator (EWI) for HIV drug resistance (HIVDR) hence the need for monitoring ART levels and to have in place the strategies for assessment and evaluation of adherence to ART. It is important for ART programme planners and implementers not to measure their success through the number of people receiving ART at a given time but also take into account their patients' successful compliance to treatment. The virologic efficacy of ART, or ‘good adherence’, is better achieved if patients stick to their treatment regimen for 95% of the time (Nachega et al 2007).

In Zimbabwe, Muyingo et al (2008:468-475) assessed adherence using drug possession ratio and pill counts among patients in a highly controlled clinical trial. Findings from this study showed that overall in the first year, 93% of the patients achieved ≥95% adherence. Further analysis however showed that only 49% of the patients achieved ≥95% adherence at every clinic visit. . Patients enrolled in the same study by (Muyingo et al 2008:474) were provided with transport and clinical care for free. Pill count was assessed at the health facility during a scheduled visit. The

accuracy of the pill count method therefore depended heavily on the trustworthiness of the patient. Some patients in efforts to not disappoint the health care worker and also to assure that more medication is dispensed have been reported to dispose of excess doses ahead of these scheduled clinic visits (Osterberg & Blaschke 2005:488-489), thereby inflating the adherence levels. The same study also reported 90% patient retention in care, which was high and may not have been a true reflection of a public health setting in Zimbabwe.

1.3 THE RESEARCH PROBLEM

Assessing virus suppression using the viral load test and immunological recovery using the CD4 cell count are two objective strategies for adherence monitoring. While CD4 testing is generally being offered for initiating and monitoring treatment, the service is not easily accessible. Viral load testing is expensive and it is not currently offered routinely. It is therefore important to use objective, less expensive and easily accessible strategies such as pharmacy refills for measuring and monitoring ARV adherence. The level of ART adherence using pharmacy refills has not been investigated among HIV positive patients in Zimbabwe.

1.4 AIM OF THE STUDY

The aim of the study was to determine the level of adherence to ART when using pharmacy refills and the extent of the relationship between ART adherence when measured by pharmacy refills and immunological parameters of CD4 count and HIV-1 RNA levels (viral load) among HIV positive patients at Mpilo Central Hospital, Zimbabwe.

1.4.1 Study objectives

The objectives of the study were to

- describe the level of adherence to ART when measured by pharmacy refills compared to CD4 cell count and viral load
- describe the relationship between adherence to ART when measured by pharmacy refills and CD4 cell count and viral load

1.5 SIGNIFICANCE OF THE STUDY

The findings of the study have potential to contribute to the existing body of knowledge on ART adherence monitoring methods. Based on the findings of the study, pharmacy refills may be used routinely to monitor adherence to ART if found reliable when compared with CD4 count and viral load. It may also be used as a screening tool for patients suspected of treatment failure to be referred for virological testing thus reduce the number of viral load tests done and inevitably the cost of providing this service.

Health facilities with no access to CD4 testing or viral load testing and health facilities that are hard to reach or health facilities that currently have to wait for a long time for such results to be returned may better manage patients with available pharmacy refills data and not risk having patients lost to follow-up. At community level, information gained is important to help strengthen messages on prevention and or risk reduction for emergence of drug resistant HIV, reduction of community related barriers to adherence and promote community related facilitators to adherence.

In addition, results from this study may provide baseline data on ART adherence levels and form a basis for prospective studies to be carried out to assess magnitude of non-adherence and give more impetus for active HIV drug resistance monitoring in Zimbabwe.

1.6 DEFINITION OF KEY WORDS AND CONCEPTS

In order to ensure that specific meanings of words or concepts used in the study are understood in the context of this study, the following words and concepts are defined:

1.6.1 Adherence

According to the Pocket Oxford English Dictionary (2005), adherence means “to stick fast to substance, person, party, and opinion”. Adherence to treatment is defined as “the extent to which the patient continues the agreed-upon mode of treatment under limited supervision when faced with conflicting demands, as distinguished from compliance and maintenance (The Free Dictionary 2013a). For the purposes of this study, adherence

refers to the extent to which HIV positive patients' behaviour of taking ART corresponds with agreed recommendations from a health care provider that ART is taken every day as prescribed and not missing any dose of ART.

1.6.2 Antiretroviral therapy (ART)

The antiretroviral drugs used as a combination of at least two different class drugs to suppress the HIV and stop the progression of HIV disease (Bean 2005:S96). ART was used in this study to refer to the drugs that the HIV positive patients are taking, prescribed in drug combinations referred to as highly active antiretroviral therapy (HAART) to suppress the HIV and stop the progression of HIV disease.

1.6.3 HIV positive

A person is said to be HIV-positive when antibodies against HIV have been detected on a blood test or gingival exudates test (commonly known as a saliva test). Synonym: seropositive (WHO 2011:79). The same definition will be used in this study.

1.6.4 Measure

According to Grove, Burns and Gray (2013:699), the "process of assigning numbers to objects, events or situations according to some rule" is known as measurement. An HIV positive patient is prescribed ART as treatment for the rest of his or her life. A patient on ART is required to visit a pharmacist at prescribed intervals to refill their prescriptions. In this study the number of ART pharmacy refill visits (at prescribed intervals) that the patient makes, is used to measure adherence as defined above.

1.6.5 Patients

A sick individual under care and treatment or any recipient of health care services from health care providers or institutions is known as a patient (MedicineNet.com). In this study, persons seeking HIV and AIDS treatment and care at Mpilo Central Hospital will be defined as patients.

1.6.6 Pharmacy refills

HIV disease is a chronic medical condition that requires treatment for the rest of the individual's life. Usually a doctor prescribes ART to the individual that requires refilling ("usually a container which becomes empty through use") (The Free Dictionary 2013b) by a pharmacists at prescribed intervals. This definition will be used in this study.

1.7 THEORETICAL FOUNDATION

The paradigm and assumptions on which this study was founded are described in the paragraphs that follow

1.7.1 Research paradigm

A paradigm is defined as "a way of looking at natural phenomena…that encompasses a set of philosophical assumptions and that guides one's approach to inquiry" (Polit & Beck 2012:736). A paradigm plays an important role of directing research efforts and organising core ideas, theoretical framework and research methods. This study will be informed and guided by the positivist paradigm. Positivism is based on a belief in universal laws and an objective reality (Parahoo 2006:49). Positivists believe in the existence of a social and physical reality 'out there' that is driven by natural laws as well as the appropriate ways of going about finding knowledge (methodology). Its methods rely heavily on quantitative measures, with relationships among variables commonly shown by means of statistics. Researchers using positivism are concerned about facts, measurable behaviour as well as cause-and-effect.

The strategies of inquiry used in quantitative research include experiments, surveys and predetermined instruments that yield statistical data (Creswell 2009:18). Parahoo (2006:50) explain that the quantitative paradigm adopts a deductive approach to research and the research process is objectively constructed and its findings are replicable and generalisable.

1.7.2 Assumptions of the study

Assumptions refer to basic principles that are accepted as being true based on logic or reason without proof (Polit & Beck 2012:720), self-evident truths, statements or axioms, the truth of which are self-evident to those who hold them regardless of their objective status, meaning or truth value (Leedy & Ormrod 2005:5). Because all research is inevitably based on assumptions, it was important for the researcher to clarify assumptions to enable the readers to understand the basis on which the research was being conducted. The study was based on the following assumptions:

- Adherence can be measured by patients' pattern of antiretroviral drug collections as recorded in the pharmacy registers.
- Adherence to ART can be predicted by virological suppression when measured by HIV-1 RNA levels.
- Adherence to ART can be predicted by increment in CD4 cell counts if patients were consistent with their ARV drug refills.
- Data was accurately recorded in the clinic registers where data for this study was extracted.
- Majority of the patients use the same pharmacy for their refills.

1.8 RESEARCH METHODOLOGY

According to Coughlan, Cronin and Ryan (2007:661), the research methodology outlines the process involved or the "nuts and bolts of how a research study is undertaken. The research process undertaken in this study is discussed more in chapter 3 of this report. Presented below is a brief outline of the research methodology followed.

1.8.1 Study design

The researcher used a non-experimental, quantitative, retrospective, descriptive and correlational design in order to achieve the objectives of this study. Chapter 3 of this dissertation details the research design used.

1.8.2 Study setting

The study was conducted at Mpilo Central Hospital a public health institution with an OI/ART clinic which was one of the Médecins Sans Frontières (MSF) Spain supported ART sites in Bulawayo city in Zimbabwe.

1.8.3 Research methods

The research methods used in the study included the population, sample and sampling procedures, data collection and data analysis.

1.8.3.1 Study population

The target population for this study was HIV positive adult patients initiated on ART between 1 October 2009 and 31 December 2009 and followed up for 12 months.

1.8.3.2 Sampling procedure

Probability sampling procedures were used to ensure that each element in the population had an equal and an independent chance of being selected and to achieve representativeness (Pilot & Beck 2012:275). Probability sampling is a technique used in quantitative research. All participant records that met the inclusion criteria were available to the researcher. The sample size of 118 was manageable and adequate for data analysis and as a result no sampling procedures were applied for this study.

1.8.3.3 Data collection

A data collection instrument was designed for this study (Annexure E) to collect data from the patients' records. Patient's data was extracted from the facility health cards, clinic opportunistic infections (OI) registers and dispensing registers kept in the pharmacy onto the data collection instrument. Each patient's OI/ART number was recorded and the required information transcribed.

1.8.3.4 Data analysis

Stata SE release 10 (STATA Corp, 2007) was used to analyse data. Details regarding the research methods used in this study are described in Chapter 3.

1.9 ETHICAL CONSIDERATIONS

The ethical protocols that were observed included permission to conduct the study from higher degrees committee of the University of South Africa and authorities of the research sites, anonymity and confidentiality as well as scientific integrity. A full description of the stated ethical issues as well as the measures taken to address each of the issues is discussed in chapter 3.

1.10 OUTLINE OF THE STUDY DISSERTATION

The study report for this research is divided into chapters outlined below:

Chapter 1: Orientation and overview of the research study.
Chapter 2: Literature review on adherence to ART.
Chapter 3: Research methodology
Chapter 4: Presentation and analysis of the study findings.
Chapter 5: Conclusions and recommendations.

1.11 CONCLUSION

This chapter provided an orientation to the study. The background information about the research problem, aim and objectives of the study, the study design, methods and ethical issues were introduced. Terms used in the study were defined, the significance of the study and ethical consideration were discussed. Lastly, an outline of the structure of the chapters of the dissertation was presented. In the next chapter, the literature review pertinent to the adherence to ART is presented

CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

In this chapter, the findings of a review of literature pertaining to ART adherence are presented. The purpose of the literature review was to familiarise and widen the researcher's knowledge base of trends and developments in the field of study of HIV and AIDS and ART adherence. By reviewing literature, the researcher was able to identify what is already known about ART adherence and knowledge gaps in literature. Literature reviews give the researcher impetus for conducting the study and help avoid unintentional duplication (Grove et al 2013:40). According to Grove et al (2013:98-99), when literature review for a study that is quantitative in design is done, the process is aimed at directing the development and implementation of the study and ultimately producing a written report thereby adding to the body of knowledge for the research area.

2.2 SCOPE OF THE LITERATURE REVIEW

A computer-assisted search was conducted using the keywords: HIV and AIDS treatment, adherence to ART and measuring adherence.The reviewed literature comprised various reports and research conducted on HIV/AIDS and ART adherence globally including the country of the study, Zimbabwe. Literature reviewed for this study was for the period between 2000 and 2013

2.3 HIV AND AIDS

The reviewed literature on HIV and AIDS is presented using the headings HIV and AIDS epidemic, HIV and AIDS disease.

2.3.1 HIV and AIDS epidemic

Three decades ago, Human Immunodeficiency Virus (HIV), was identified as the cause of Acquired Immune Deficiency Syndrome (AIDS). The predominant virus type that causes the highest HIV disease burden worldwide is HIV-1. In 2010, an estimated 34 million people were living with HIV globally, 2.7 million got newly infected and 1.8 million died (WHO 2011:11, 49). Global initiatives to tackle the epidemic have been strong, with multi prong approaches including prevention, care, support and treatment (WHO 2011:3) as well as health systems strengthening programmes (WHO 2011:4); all mutually reinforcing strategies for an effective response. The impact of these initiatives has been significant. There are indications that globally both HIV incidence and prevalence have declined (WHO 2011:13-18). Most encouraging, worldwide over 6.6 million HIV infected people were receiving antiretroviral therapy by end of 2010 (WHO 2011:97).

The vast majority of the HIV and AIDS epidemic is in sub-Saharan Africa. In 2010, an estimated 68% of all people living with HIV and AIDS were from sub-Saharan Africa (WHO 2011:24). By the end of 2009, sub-Saharan Africa was home to 22.5 million of the 33.3 million people living with HIV and AIDS worldwide (UNAIDS 2010:20) with an estimated 10.4 million in sub-Saharan Africa in need of treatment (WHO 2011:97). In the sub-Saharan region, women are disproportionately affected; accounting for 59% of the HIV infected population (WHO 2011:19). For sub-Saharan Africa, UNAIDS estimates that 1.9 million people were newly infected with HIV and 1.2 million died in 2010 (WHO 2011:10, 13, 25). Despite carrying the biggest burden of the HIV disease, slightly over 5 million people in sub-Sahara Africa were receiving ART by end of 2010, representing 49% of the total HIV infected persons on ART in low – and middle-income countries and a 30% increase in coverage from December 2009 (WHO 2011:97).

Zimbabwe is among the countries with the world's highest HIV infection rate with heterosexual contact being the main mode of transmission (WHO 2011:25, 26, 30). According to the Ministry of Health and Child Welfare (MOHCW) estimates, 14.3% of the adult population between 15-49 years were infected with HIV in 2009 (Joint United Nations Programme on HIV/AIDS (UNAIDS) Report on the Global AIDS epidemic 2010:181). Children account for 7% of people living with HIV and AIDS (PLWHA) in Zimbabwe making mother to child transmission (MTCT) an important mode of

transmission of HIV in Zimbabwe (USAID 2003:10). Over 90% of the HIV infections are due to heterosexual sexual contact (USAID 2003:10). According to WHO, Zimbabwe is among a few countries in the sub-Sahara Africa which has realised significant declines in prevalence in recent years (WHO 2011:24). In Zimbabwe, the HIV epidemic peaked in the mid-to-late 1990's with HIV prevalence among Antenatal Care (ANC) mothers exceeding 30% and 25% among adults 15-49 years (UNGASS 2010:11-12). HIV prevalence in 2009 was14.3%, marking a significant drop from the previous years (UNGASS 2010:10) and the rate has generally remained low even though there has been an observed increase to the latest prevalence rate of 15% for the year 2013 (UNAIDS 2014:4). Overall much of the decline in prevalence has been attributed to behavioural change and to ART, which is increasingly becoming more available (UNAIDS 2010:28).

2.3.2 HIV and AIDS disease

The virus that causes Acquired Immune Deficiency Syndrome (AIDS) is called the Human Immunodeficiency Virus (HIV). The virus infects the human body by integrating its viral genetic material deoxyribonucleic acid (DNA) into human cells called CD4+ T cells and redirects or takes over their purpose and normal function of fighting infections, to producing more of the virus. In clinical settings, HIV infection can be detected by measuring HIV antibodies produced against the virus. HIV antibodies can be detected in the blood approximately 3 weeks after HIV infection and can be detected throughout the individual's life (Cohen, Gay, Busch & Hecht 2010:S271-S272).

Prior to HIV antibodies being detected in the blood, HIV infection can also be detected in the blood by measuring presence of the virus itself, HIV RNA (virions) or viral load and HIV DNA using molecular techniques called polymerase chain reaction (PCR). HIV DNA PCR is generally used as a qualitative test for HIV infection and often used in public health HIV and AIDS programmes to diagnose HIV infection mostly in children less than 18 months. In more sophisticated methods, PCR can also be used to quantify how much proviral HIV DNA is integrated into the CD4+ T cells. This is increasingly becoming an important parameter to assess, since some CD4+ T cells (known as resting CD4+ T cells) may be infected (proviral DNA) and will lie dormant not replicating or producing HIV, but ready to go into viral replication if triggered (Cummins & Badley 2010:2; Sedaghat, Siliciano, Brennan, Wilke & Siliciano 2007: 1165). This form of virus

is important when considering ART treatment and the importance of adherence as the virus can emerge if ART is stopped or fails (Sedaghat et al 2007:1165-1166).

2.3.2.1 Staging of HIV disease

The CD4+ T cell counts in healthy persons range from 500-1000 cells/mm^3 and above (Alimonti, Ball, & Fowke 2003:1650; Mocroft, Phllips, Gatell, Ledergerber, Fisher, Clumeck, Losso, Lazzarin, Fatkenheuer & Lundgren 2007:411). As the virus replicates, more and more of the CD4+ T cells get destroyed and decrease in number and function and the viral load increases (Alimonti et al 2003:1650-1654). Without treatment, the individual's immune system gets compromised and more prone to other infections known as opportunistic infections (OIs) (Alimonti et al 2003:1650, Cummins & Badley 2010:1), leading to AIDS which is the end stage of the HIV disease (Cummins & Badley 2010:2). Peripheral blood CD4+ T cell count and viral load measurements are thus valuable tools for staging HIV disease and facilitate in the identification of patients eligible for ART initiation. These assays are also used as surrogate measures of adherence and in detecting treatment failure (especially with viral load). In the absence of CD4 cell count and viral load testing, The WHO has established a set of clinical guidelines based on clinical manifestations that help in the determination of eligibility for treatment and management of HIV patients. The stages are divided into four, with each stage having specified clinical conditions and or symptoms used in assessing HIV disease progression (National Drug &Therapeutics Policy Advisory Committee (NDTPAC) & AIDS and TB Unit MOHCW 2010:62). The four stages are as follows:

- Clinical Stage 1 - patient is asymptomatic. Patients may present with persistent generalised lymphadenopathy but are generally well. ART initiation is recommended if CD4 cell count is ≤350 cell/mm^3 (WHO 2010c:21, 30, 73).

- Clinical Stage 2 – patients in this stage are considered to present with mild manifestations of the opportunistic infections and HIV defining illnesses indicative of HIV progression. Manifestations involved include but are not limited to Herpes zoster, moderate unexplained weight loss, papular pruritic eruptions, recurrent bacterial and fungal infections among others. ART initiation is recommended if CD4 cell count is ≤350 cell/mm^3 (WHO 2010c:21, 29, 73).

- Clinical Stage 3 – patients in this stage are described as being in an advanced stage of the HIV illness. Patients present with severe unexplained weight loss, chronic diarrhoea, oral candidiasis, severe bacterial infections, oral hairy leukoplakia, unexplained fever, unexplained anaemia, acute necrotising ulcerative stomatitis, gingivitis or periodontitis and pulmonary TB. ART initiation is recommended irrespective of CD4 cell count (WHO 2010b:52, WHO 2010c:21, 29, 74-76).

- Clinical Stage 4 – this is considered the severe clinical stage of the HIV illness with a whole host of opportunistic infections of bacterial, fungal and parasitic origin presenting. There are considerable manifestations of tumours (e.g. Kaposi sarcoma) and involvement of organ pathologies such as those of the kidneys and heart. ART initiation is recommended irrespective of CD4 cell count (WHO 2010b:52, WHO 2010c:21, 29, 76-80).

2.3.2.2 Antiretroviral treatment

Antiretroviral drugs are treatment drugs aimed at fighting HIV infections. They do not cure or get rid of the HIV infections, but retard or prevent the virus from replicating allowing the immune system to gain control and preventing opportunistic infections from causing AIDS. HIV has a high replication and mutation rate and it has been shown that when the ARVs are not taken correctly or if doses are missed, the therapeutic levels required to retard or prevent viral replication are compromised (Harrigan, Hogg, Dong, Yip, Wynhoven, Woodward, Brumme, Brumme, Mo, Alexander & Montaner 2005:339). If the drug therapeutic levels are low, HIV is able to replicate in the presence of the antiretroviral drugs thereby creating an environment conducive for the development of drug resistance (Harrigan et al 2005:342; Peltzer et al 2010:1). The main aim of antiretroviral drugs is to control the rate at which the virus reproduces thereby reduce viral load (Deeks 2003:2002), allow restoration of CD4 cell count (Lucas 2005:413) resulting in prevention or delayed progressive immunodeficiency, reduced morbidity and mortality (Bisson, Gross, Bellamy, Chittams, Hislop, Regensberg, Frank, Maartens & Nachega 2008a:0778; Nachega 2011:209) delay progression to AIDS resulting in prolonged survival and improved quality of life (Bean 2005:S96; Bisson et al 2008a:0778; Nachega 2006:81-83). Equally important ARVs reduce selection of

resistant virus (Bean 2005:S96; Deeks 2003:2002; Fergusson 2005:349; Lucas 2005:413- 414; Harrigan et al 2005:339). When antiretroviral drugs are taken according to prescribed regimes, virus loads in blood can become undetectable, although not eliminated, making HIV disease a condition that is now manageable but not curable (Bean 2005:S96; Lucas 2005:413; Martin et al 2008:1263). For that reason, managing HIV disease requires a comprehensive multi-prong approach which includes counselling and testing as an entry point to care, prevention and treatment including opportunist infections and proper nutrition in order to control its spread (WHO 2011:24).

2.3.2.2.1 Importance of HIV-1 life cycle in treatment strategies

HIV-1 is a Ribonucleic acid (RNA) retrovirus belonging to the lentivirus family, also characterized as slow viruses. Because retroviruses have RNA and no deoxyribonucleic acid (DNA) as their genetic material, they can only replicate if they have a host cell. The retrovirus HIV infects human immune T cells that have a CD4 receptor (CD4 + T cells). These CD4+ T cells have cell surface receptors, which have high affinity for HIV to attach to and thus gain entry into the cell (Borkow & Lapidot 2005:4-6). Chemokine co-receptors CCR5 and CXCR4 mainly found on non CD4 + T cells such as macrophages and dendritic cells are central in facilitating HIV infection through these cells (Borkow & Lapidot 2005:4). A unique feature to retroviruses is that they replicate backwards. HIV, using an enzyme called reverse transcriptase replicate by going from RNA to single stranded DNA (ssDNA) to double stranded DNA (dsDNA) (Borkow & Lapidot 2005:3). The virus then uses another enzyme called integrase to insert the viral DNA into the host cell nucleus to become what is known as HIV proviral DNA. Once inside, the virus takes over the host cell's genetic code and diverts the cell's normal function of defending the body from infections to production of HIV (RNA) virions. For this function the virus uses another enzyme called protease. Virions are released from the CD4+ T cell by budding off from the cell surface or as a result of the CD4+ T cell dying (Cummins & Badley 2010:7). The released virions in turn infect more CD4+ T cells resulting in more and more infected cells producing increasingly more HIV copies. Although the human immune system responds appropriately by producing antibodies against HIV, these are not protective. HIV has a very high rate of replication, making it also very prone to replication errors that can give rise to new HIV strains due to mutations (Bean 2005:S96; Deeks 2003:2002). The implications are in part that very high, greater than 95% adherence levels are needed to suppress and sustain virus

suppression (Paterson, Swindells, Mohr, Brester, Vergis, Squier, Wagener & Singh 2000:24-28) and antiretroviral drugs have thus far been produced to target different stages of the replication cycle (Bean 2005:S96-S100; Borkow & Lapidot 2005:3-8; Emmelkamp & Rockstroh 2007:36-39).

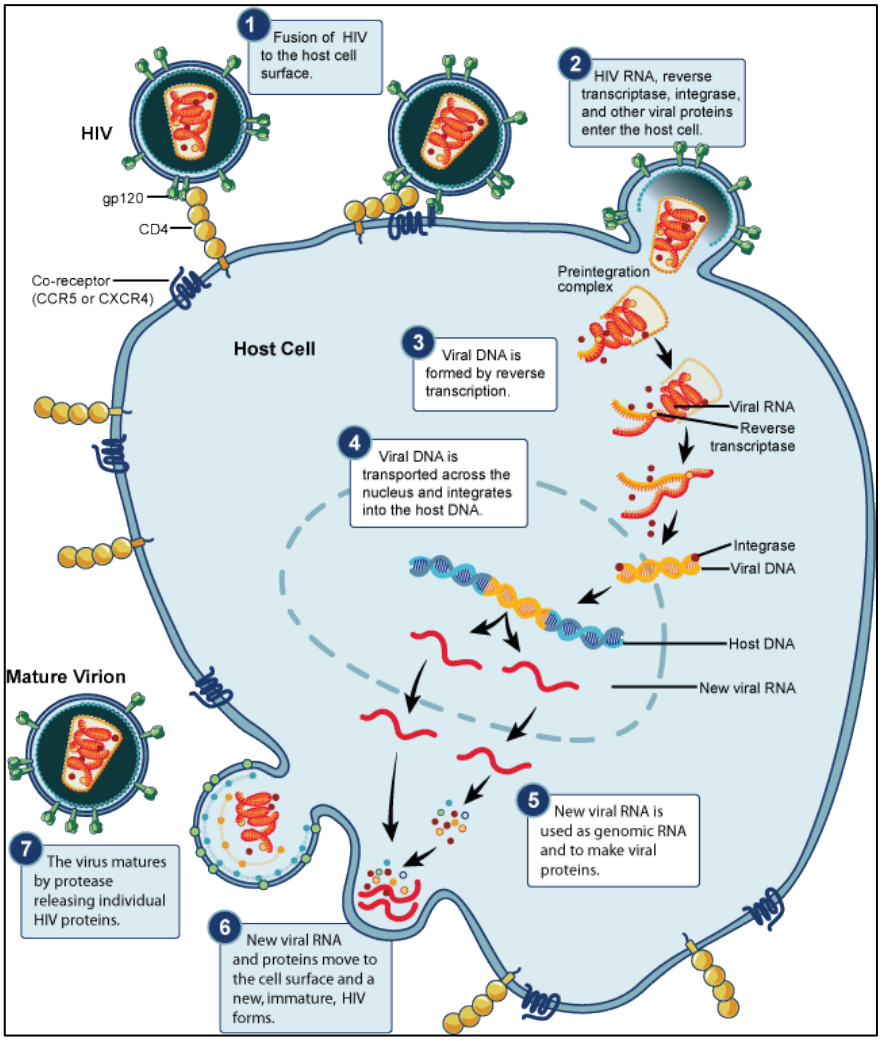

Figure 2.1 HIV-1 Replication cycle

(Google Images 2014)

2.3.2.2.2 Classes of antiretroviral drugs for HIV infection used in Zimbabwe

ARV drugs are grouped according to how they function, specifically how they interfere with the replication processor cycle focusing at critical replication stages or factors (Bean 2005:S96-S100; Emmelkamp & Rockstroh 2007:36-39; Wood R 2005: 9-51). The following are some of the classes of ARVs:

- Nucleotide and nucleoside reverse transcriptase inhibitors (NRTIs) − first approved to treat HIV in 1987(AVERT 2012; Emmelkamp & Rockstroh 2007:36).

Examples of those in use in Zimbabwe ART programme include Tenofovir, Zidovudine, Lamivudine, Stavudine, Abacavir, Emtricitabine and didanosine. These ARVs interfere with the reverse transcriptase enzyme's function of transcribing viral RNA into proviral DNA (Bean 2005:S96; NDTPAC & AIDS and TB Unit MOHCW 2010:11-12).

- Non-nucleoside reverse transcriptase inhibitors (NNRTIs) − first approved to treat HIV in 1997 (AVERT 2012). These ARVs inhibit the enzyme reverse transcriptase needed in the replication process as earlier indicated, however with some differences in the mode of action (Bean 2005:S97-S98) which essentially results in the blockage of both RNA and DNA dependent DNA polymerase functions. Examples and those in use in Zimbabwe are Nevirapine, Efavirenz,and Etravarine (NDTPAC & AIDS and TB Unit MOHCW 2010:11-12).
- Protease inhibitors (PIs) – first approved to treat HIV in 1995 (AVERT 2012). These drugs inhibit the assembly and maturation stages of the replication cycle by the enzyme protease. Infectious virons are not released into the system thereby limiting further re-infection of CD4+ T cells (Bean 2005: S98). In Zimbabwe examples of approved PIs for use include Lopinavir, Ritonavir, Atazanavir, Indinavir Darunavir and Saquinavir (NDTPAC & AIDS and TB Unit MOHCW 2010:12). Current treatment strategies for Zimbabwe have limited use of these drugs to second line regimes (NDTPAC & AIDS and TB Unit MOHCW 2010:11-12).
- Fusion inhibitors (FIs) or entry inhibitors first approved to treat HIV in 2003 (AVERT 2012) are ARVs, which interfere with the virus's ability to attach to $CD4^+$ T cells. Example is Enfuvirtide. Fusion inhibitors are not yet included in the Zimbabwe national ART regimes (NDTPAC & AIDS and TB Unit MOHCW 2010:12).
- Integrase inhibitors − first approved to treat HIV in 2007 (AVERT 2012). Example is Raltegravir. These are not yet in use in the Zimbabwe national ART programme (NDTPAC & AIDS and TB Unit MOHCW 2010:12).
- Chemokine co-receptor antagonist (CCR5 or CXCR4 receptor inhibitors). Maraviroc is one example that blocks the receptor that HIV uses to gain entry into $CD4^+$ T cells. These are also not yet in use in Zimbabwe (Emmelkamp & Rockstroh 2007:38-39; NDTPAC & AIDS and TB Unit MOHCW 2010:12).

2.3.3 Treatment protocol for HIV infection

Standard treatment protocols for HIV infection require the combination of at least three or more ARV drugs or Highly Active Antiretroviral Therapy (HAART) in order to decrease selection of resistant virus (Bean 2005:S96; Lucas 2005:413-414). Whilst monotherapy has been used in the past for the prevention of mother to child HIV transmission for pregnant women around delivery, use of one drug is no longer recommended due to the rapid development of drug resistance and treatment failure (Borkow & Lapidot 2005:3, Deeks 2003:2002; Lucas 2005:413).

In Zimbabwe triple therapy is recommended. Suppression of HIV replication and prevention of HIV drug resistance are the short to medium term goals of antiretroviral therapy adherence. Prevention or delayed progression of immune deficiency to AIDS and prolonged survival are the long-term goals of ART adherence (Deeks 2006:1489-1490, Lucas 2005:413). The national ART guidelines for Zimbabwe recommend usage of two NRTIs and one NNRTI as first-line ART drug regimens for adults and adolescents (NDTPAC & AIDS and TB Unit MOHCW 2010:22-25). Protease inhibitors (PIs) are currently used in second-line ART drug regimens together with two NRTIs (NDTPAC & AIDS and TB Unit MOHCW 2010:25). According to the national ART guidelines, adult and adolescent patients are initiated on ART under the following conditions:

- WHO stage III or IV disease (irrespective of CD4 cell count for pregnant women).
- HIV positive with CD4 cell count ≤350 cells/mm^3 regardless of WHO staging.
- HIV positive with active tuberculosis (TB) irrespective of CD4 count for pregnant women (NDTPAC & AIDS and TB Unit MOHCW 2010: 14-15, 30).

According to the national ART guidelines, adolescents are defined as persons aged between 10 and 18 years and emphasises the requirement for persons in this age group to be weighed before ART initiation so that patients weighing less than 25 kilograms can be initiated using paediatric guidelines (NDTPAC & AIDS and TB Unit MOHCW 2010:17). In pregnant women, WHO (2010) guidelines are used to assess whether a woman needs treatment prophylactically for prevention of HIV transmission to the unborn baby or treatment for her own health (WHO 2010a:2-12). According to this guidance, HIV positive pregnant women with CD4 cell count less than 350 not only

need treatment to prevent transmission to the unborn baby, but need treatment for their own health. On the other hand, women with CD4 cell counts higher than 350, are initiated on prophylactic ARVs primarily to prevent transmission of HIV to the unborn baby (WHO 2010a:2).

The National ART guidelines (NDTPAC & AIDS and TB Unit MOHCW 2007:16) also emphasize that starting ART should not be an emergency and thus acknowledges and requires adequate preparation of patients before initiating ART. The initiation protocol therefore requires the patient to undergo counselling sessions including adherence counselling prior to ARVs being dispensed. A month's supply of drugs is given to the patient and an appointment for the next pharmacy refill is given. At every subsequent pharmacy refill, the pharmacist or health care provider dispensing the ARVs is expected to review and assess adherence by using pill counts and possibly adherence cards if patient was issued one (NDTPAC & AIDS and TB Unit MOHCW 2007:24-25).

2.4 HIV AND AIDS PROGRAMMES IN ZIMBABWE

Implementation of HIV and AIDS programmes in Zimbabwe on prevention, care and treatment, support and mitigation are coordinated by the AIDS and TB Unit. The AIDS and TB Unit was set up by the government of Zimbabwe through the MOHCW in 2000 as a successor to the National AIDS Control Programme (NACP) which was set up in 1992 (AVERT 2011, USAID 2003:11). Prevention of Mother to Child Transmission of HIV (PMTCT), Care and Treatment (includes opportunist infections (OI) and antiretroviral therapy (ART) programmes), HIV testing and counselling, condom programmes and workplace prevention programmes are among the Unit's core implementation programmes. At national level ARV drugs in Zimbabwe have mainly been provided through the PMTCT and OI/ART programmes.

2.4.1 PMTCT programme in Zimbabwe

Introduced in 1999 as a pilot project in three sites, the PMTCT programme became a national programme in 2001. The goal of this programme is to provide comprehensive PMTCT services and prevent infant mortality and morbidity. Treatment strategies for this programme when first implemented focused mainly on HIV positive mothers receiving single dose nevirapine (SdNVP) at the onset of labour and nevirapine syrup to

their exposed babies immediately postpartum. This was seen as a simple, effective and easy strategy to implement especially for resource poor settings (MOHCW Trainer's Manual Module 9 2008:1; AVERT 2011). Revised August 2006, WHO PMTCT guidelines encouraged programmes to move away from single dose NVP to More Efficacious Regimen (MER), starting antenatally (28 weeks), during labour and postnatal prophylactic ARVs to the exposed infant (WHO 2006:27-32). The recommendation was based on studies that showed a reduction in the number of new infections in infants and young children and also reduced risk of HIV resistance (WHO 2006:28-32). Only a limited number of sites were able to implement this strategy owing to lack of resources resulting in Zimbabwe reporting close to 80% SdNVP use by end of 2009, about 15% combined ARVs and less than 5% ART among HIV positive pregnant women (Wilfert 2010:23).

Current PMTCT guidelines issued in 2010 by the WHO, recommends earlier initiation of prophylactic ARVs during pregnancy, initiation of ART for pregnant women in need for treatment for their own health and prolonged prophylactic ARVs for the HIV exposed infants postnatally to prevent HIV transmission during the breastfeeding period (WHO 2010a:3-9). It is estimated that with the current PMTCT ARV treatment strategy, MTCT can be reduced to less than 5% among breastfeeding populations and to less than 2% in non-breastfeeding populations (WHO 2010a:12). Central to the effectiveness and efficacy of all these ARV treatment strategies is adherence and ultimately prevention of preventable HIV drug resistance (WHO 2010a:34). Adherence studies in Zimbabwe among women and or children initiated on these different ARV treatment strategies over the years is scarce.

2.4.2 ART programme in Zimbabwe

The national ART programme in Zimbabwe started in 2003 and since then HIV positive patients have been receiving ARVs free of charge. When the programme was started, the National AIDS Council (NAC) through funds collected by a tax levy instituted by the Government of Zimbabwe channelled 50% of the funds to purchasing of ARV drugs (UNGASS 2010:14). However, when the country was undergoing economic hardships mid to late 2000, which saw world record inflation rates being recorded, value from these proceeds dwindled (AVERT 2011; UNGASS 2010:14). Leverage funds from international agencies such as the Global Fund for AIDS, Tuberculosis and Malaria

(GFATM), United Kingdom Department for International Development (DFID), United States International Development (USAID), United Nation agencies, Expanded Support Programme (ESP) and others ensured continuation of the ART programme (AVERT 2011; UNGASS 2010:14).

Initially, implementation of the ART programme was limited to Government central hospitals with decentralisation to district and some mission hospitals thereafter (MOHCW 2004:4). By December 2010, an estimated 326,241 (59%) HIV positive people were receiving ART through the National ART program, up from 218,589 the preceding year (WHO 2011:98). Between this period Zimbabwe recorded the highest percentage increase in coverage of 49%. Whilst these indicators were impressive, they still fell far below the expected 80% of the population that were in need of ART (WHO 2011:90). During the same period, the WHO HIV/AIDS clinical staging instead of CD4 count was the main criteria used for ART initiation (MOHCW 2008:12; NDTPAC & AIDS and TB Unit MOHCW 2007:10) due to lack of laboratory support ranging from shortage of qualified laboratory staff, equipment (and equipment breakdown), reagents and consumables (AVERT 2011; MOHCW 2008:12). Facilities where CD4 testing capacity can be accessed, user fees for other services rendered by the health facility and the long distances that patients have to travel to access ART services have also hampered equitable access to these HIV and AIDS services in Zimbabwe (AVERT 2011). During the peak of economic decline that Zimbabwe experienced mid to late 2000, there were reports of bribery by patients to access ARVs and patients migrating to neighbouring countries such as South Africa and Botswana to access ARVs (AVERT 2011).

The National ART programme has a monitoring and evaluation system in place. The current system is mostly paper based including patient hand held OI/ART cards and health facility registers including pharmacy ART dispensing registers. An OI/ART electronic database is still under development (MOHCW 2008:8).

Over the years, the MOHCW of Zimbabwe has implemented the OI/ART treatment programme along with other HIV preventative programmes as part of a comprehensive approach to combat the disease (WHO 2011:62). Overall treatment strategies are geared at rapidly suppressing viral replication thereby reducing viral load in the blood. Central to achieving this goal is adherence – how to maximise and sustain high adherence to ARVs once initiated.

2.5 ADHERENCE TO ART

In health the term adherence is often used to describe a patient's consistent behaviour around taking medication. The World Health Organization (WHO) defines adherence as the extent to which an individual's behaviour with regards to taking medications changes in accordance to recommendations by the health care provider (WHO 2003:3). According to WHO, the behaviour and lifestyle modifications important for successful treatment outcomes require "good communication between patient and health professional" and include negotiations, plans and discussions around how best to go about consistent taking of medication that ensures good adherence (WHO 2003:4). Central to adherence is the ability of the ART programme to make sure that the service is easily accessible and drug supplies are not interrupted once introduced. In addition adherence to ART requires the patient to take the correct dosage of prescribed drugs at the stipulated times and sticking to dietary restrictions (Peltzer et al 2010:1).

A systematic review of adherence studies that included 27 African studies (total 12,116 patients) and 31 studies in North America (total 17,573 patients) assessed adherence levels in these diverse settings and provided evidence of even higher adherence levels in resource poor settings when compared to the developed settings (Mills et al 2006b: 682). In that meta-analysis, significantly higher adherence levels ($p<.001$) were observed when comparing adherence to antiretroviral therapy between North American and African patients, with a pooled adherence estimate of 54.7% (95% CI: 48.0-61.3%) in North America compared to 77.1% (95% CI: 67.3- 85.6%) in Africa (Mills et al 2006b:682).

In another study, adherence was assessed in a cohort of 99 patients receiving antiretroviral therapy with a protease inhibitor seen in two different HIV clinics in the United States of America (USA) (Paterson et al 2000:22). In that study, adherence levels measured with MEMS in 81 patients were compared to both outcomes of virology (virologic failure defined by a viral load greater than 400 copies/mL on the last study visit) and clinical (defined by the changes in CD4 counts measured at baseline and at the last study visit – that is the difference or CD4 gain or no gain). Virologic failure at the final study visit among patients with baseline viral load of 400 copies/mL or greater was significantly associated with degree of adherence with 31% (5/16) of the patients with

95% or higher adherence levels having detectable viral load, compared to 85% (35/41) for patients with adherence levels less than 95% (Paterson et al 2000:25). For clinical outcomes assessed with CD4 count, patients with adherence level of 95% or greater had mean increase of 83 cells/mm3 compared to 6-cells/mm^3 mean increases among patients with less that 95% adherence (Paterson et al 2000:25). Opportunistic infections were only observed in patients with less than 95% adherence (3/58), further supporting and emphasising the importance of near perfect adherence required among HIV patients. This study benchmarked the degree of adherence for HIV treatment, 95% or greater which has been used in many studies on HIV ART adherence and general clinical practice have used this benchmark to define adherent and non-adherent patients.

2.5.1 Relationship between adherence and treatment outcomes

Whilst there is no consensus on what adequate adherence is, researchers are in agreement that successful ART treatment demands high adherence and National HIV treatment programmes need to focus on adherence strategies in order to preserve the effectiveness of first line therapy through sustained high levels of adherence (Bisson et al 2008a:0786). Treatment outcomes for individuals depend highly on ability to adhere and maintain high enough drug levels to retard viral replication and allow for immunological recovery.

The public health consequences of failure to adhere to ART are grave due to the potential emergence of cross-resistance (Deeks 2003:2003) where HIV becomes resistant to similar drug formulations and risk of the emergence and transmission of drug resistant HIV (Deeks 2003:2002-2003) leading to reduced treatment options available at population level (Deeks 2003:2002).

Ninety-five (95%) adherence level is considered the minimum requirement for HIV treatment success. There is evidence that not as high adherence levels can equally achieve viral suppression due to the composition of the ARVs the patient is initiated on. A study among HIV positive adults in South Africa, Nachega et al (2007:564-573) used pharmacy claims to study the relationship between adherence and virologic outcome for a cohort of 2821 patients initiated on Nonnucleoside reverse transcriptase inhibitor (NNRTI) based ART between January 1998 and March 2003. The viral load for

patients studied was greater than 400 copies/mL at initiation. Individual patient adherence levels were calculated and categorised into seven categories of 10% increments ranging from less than 50% to 100% (Nachega 2007: 565). The primary outcome of the study was the proportion of patients achieving viral suppression (less than 400 copies/mL HIV-1 RNA) from one month after ART initiation till end of follow-up (median 2.2 years), or till death or withdrawal (Nachega 2007:565-566). Pharmacy claims were used for measuring adherence. A linear dose response relationship between viral load suppression and adherence was observed and viral suppression rates of greater than 70% was significantly associated with patients with pharmacy claim rates of 80% or more (Nachega 2007:566-567). In multivariate analyses, higher pharmacy claim adherence was statistically and significantly associated with shorter time to viral suppression with a hazard ratio of 3.79 [CI; 3.13- 4.58] when comparing patients with 100% to those with 50% or less adherence levels (Nachega 2007:567). In this study with NNRTI based ART, favourable incremental virologic outcomes were observed in patients with 50% or greater adherence levels (Nachega 2007:568) with the authors concluding that with such a regimen for HIV-1 treatment, greater than 70% adherence maybe sufficient for sustained viral suppression.

In a similar study, a prospective cohort study of 1142 patients in Barcelona used announced pill counts and pharmacy claims to study the relationship between adherence level, ARV regime and viral suppression (Martin et al 2008:1263-1264). Of the 1142 patients, 662 (58%) were on NNRTI based regime, 359 (31.4%) PI boosted regime and 121 (10.6%) were on unboosted PI regime. Patients with undetectable viral load (n=1059) had a mean adherence of 95.7% compared to 76.3% (n=86) for those patients with detectable viral load. Looking at the relationship between virologic failure and adherence; patients with adherence between 80-89.9% had a 9.0 relative risk (RR) (95% CI 4.0-20.1) of virologic failure, 45.6 RR (95% CI 19.9-104.5) for patients with 70.0-79.9% adherence and finally 77.3 RR (95% CI 34.2-174.9) for patients with adherence less than 70% (Martin et al 2008:1265). The relationship between adherence and virologic failure in patients taking different ARV regimes showed that the relative risk of virologic failure was 26.6 (95% CI 3.0-230.7) for patients on unboosted PI regimes with adherence between 80-89.9%, 207.5 RR (95% CI 16.0-2696.2) for adherence between 70-79.9% when compared to patients with adherence of 90% or greater. For patients taking boosted PIs, similar trends were observed for relative risk of virologic failure being 21.5 for patients with adherence between 80-89.9%, RR of 124.7

for patients with adherence between 70-79.9% and RR of 212.0 for patients with less than 70% adherence compared to those with adherence of 90% or greater. In NNRTI based patients, RR of 4.4 (95% CI 1.4-13.3) for patients with adherence between 80-89.9%, 22,4 (95% CI 7.5-66.8) in patients with adherence between 70-79.9% and 36.9 (95% CI 12.7-107.5) for patients with adherence less than 70% when compared to those with 90% or greater. Compared to the other two ARV regimes, the 95% CI for NNRTIs were much tighter even though statistically there was no difference in relative risk of virologic failure for patients taking PI-boosted ARVs and NNRTIs. Logistic regression analysis, did however show a 2.5 higher relative risk of virologic failure in patients with <90% adherence and taking unboosted PIs, compared to patients taking boosted PIs (95% CI 1.179-5.341). Overall the ARV regime class predicted adherence, with NNRTI based patients having an overall adherence of 96.2% (CI 90-100) compared to 92.6% (CI 84.6-97.9) for those patients on PI based ARVs (Martin et al 2008:1265). These studies are in agreement with others which have shown similar "more forgiving" adherence requirements (Shuter 2008:769-773), clearly suggesting the possible different adherence levels required depending on the composition of the ARV regime, and in general also highlighting the complexity of HIV treatment which includes pharmacological, viral and host factors. Irrespective of what is considered adequate adherence; overall, different studies have pointed to the fact that adherence needs to be promoted for ART to be successful, with the ultimate goal of achieving 100% adherence promoted and recommended for every patient initiated on ART (Martin et al 2008:1267).

2.5.2 Adherence to ART and HIV drug resistance

HIV drug resistance is a major cause of concern in treatment programmes and an important reason why non-adherence, which includes among others not taking the correct dose, missing doses or not taking medications at prescribed time intervals should be discouraged. As discussed, antiviral drugs for HIV have been developed mainly to interrupt the replication cycle of the virus. Because of its very high rate of replication which is also prone to mistakes (Deeks 2003:2002), giving rise to mutations and generational viral differences (Deeks 2003:2002) maintaining high to near perfect adherence levels is a critical factor to successful and sustained interruption of the replication cycle. When drug levels fall below therapeutic levels or levels not high enough to inhibit the virus from replicating, the virus can continue to replicate in this

environment and ultimately lead to the development of viral strains that are not easily controlled by treatment and become resistant to ARVs. Drug resistant HIV can cause treatment to fail, viral load to increase and can limit the choice of drugs available for treatment (Lucas 2005:413). Even more concerning is that drug resistant viruses can be transmitted with the potential of becoming the dominant HIV strain in a population (Deeks 2003:2002-2003; Veenstra 2010:1; Vervoort et al 2007:271) requiring more resources not only to understand it but also to combat it. Another problem closely linked with drug resistance and adherence is cross-resistance. This phenomenon occurs when HIV resistant to a particular ARV drug, also becomes resistant to other ARV drugs in the same class as the primary (failing) drug causing resistance (Lucas 2005:413). The main problem presented with this situation, especially in resource constrained settings; is the limited choice of ARV drugs available to replace the failing drug and the need for more complex treatment regimens which are not readily available due to high costs.

2.5.3 Factors that influence adherence

There are several factors that can influence how well or how badly an individual adheres to ART. According to WHO, factors that can affect adherence at individual level can be categorised into five groups (which will be discussed further) namely patient factors, treatment or therapy factors, disease condition characteristics, patient-provider or health team relations and social and economic factors (WHO 2003:27-30). In order to address adherence holistically, all these factors at individual level need to be assessed and appropriate interventions implemented in order to promote good adherence (WHO 2003:31).

Skovdal et al (2011:296-318) and colleagues explored, interlinked and further distilled the five categories to 2 dimensions that of 1) contextual and 2) psychosocial dimensions that influence adherence. In that study the authors used the “health-enabling social environment model” to better understand relationships and inter-linkages between the identified prevalent factors that influence ART adherence (Skovdal et al 2011:314) The two categories are however not mutually exclusive, with some overlap between the dimensions. In that study the contextual dimensions influencing adherence were categorised into:

- **Material context** (Money, food, distance to clinic, transport costs and hospital costs).
- **Symbolic context** (Stigma, gender roles and diminishing power of traditional healers).
- **Relational context** (Social support, children and treatment partner/supporter, relationship with nurses).
- **Institutional support context** (waiting time and opening hours, counselling, periods without ARVs, churches and faith, food aid/NGOs, health service improvements) (Skovdal et al 2011:301-308).

The psychosocial dimension influencing patient behaviour to adherence was grouped into three categories:

- **Patient motivation** focuses on the factors that nurture a patient either positively (facilitators) or negatively (barriers) to taking their medication.
- **Patient participation** which requires the active participation of the patient shaping both the contextual and psychosocial environments in which they are taking ART so that they are conducive to ART adherence.
- **Psychosocial responses to ART** looks at how psychologically patients respond to their HIV disease and the treatment required (Skovdal et al 2011:309-312).

2.5.3.1 Patient factors

According to WHO, patient related factors related to the patient's ability or self-efficacy to adhere to medication is closely linked to "resources, knowledge, attitudes, beliefs, perceptions and expectations" (WHO 2003:30). These patient factors also include socio-demographic characteristics as well as psychosocial and environmental contexts in which patients may be taking their medications in, which can influence their adherence to therapy (Skovdal et al 2011:301-315). Whilst ART in many settings including Zimbabwe is now provided for free, barriers that are related to the patient of different forms still impact on how well patients adhere to medications.

Looking at both psychosocial and contextual dimensions affecting adherence, lack of resources or poverty at multidimensional levels was identified as one of the most central factors affecting adherence (Skovdal et al 2011:301-302). According to the study, because patients are counselled about the importance of good nutrition for the drugs to work effectively, a combination of lack of adequate food and money or fear of costs associated with supplementary foods, presented barriers to adherence (Skovdal et al 2011:301-303). Other barriers included distance to clinic, transport costs to seek medical care and collect monthly drug supplies and hospital administrative fees even though the ARV drugs are given for free (Skovdal et al 2011:302-303). Disempowerment within the household also undermined adherence, where economic dependence on men compromised women's self-efficacy to adhere to ART (Skovdal et al 2011:304-305).

In a qualitative study carried out in Zambia among 60 patients and 12 health care workers to assess barriers and facilitators to patients' adherence to ART identified forgetfulness, feeling better, busy work schedules, side effects from medication, excessive alcohol intake and pill burden as barriers to adherence (Sanjobo et al 2008:139). Side effects from medication impacted on patients' motivation to continue taking medication, while feeling better and healthier also gave patients cause to discontinue medication (Sanjobo et al 2008:139). Stigma related to fear of being identified as an HIV positive person; discrimination and lack of confidentiality were also reported barriers to adherence (Sanjobo et al 2008:140-141).

2.5.3.2 Treatment factors

Treatment characteristics that impact on adherence include complexity of the regime, frequency of dosage, treatment duration, frequency and severity of side effects, frequency in treatment changes and immediacy of beneficial effects (Sanjobo et al 2008:139; Skovdal et al 2011:311; WHO 2003:30). Most of these factors according to Skovdal et al (2011:309) when categorised take the psychosocial dimensions that influence adherence, mostly related to patient motivation to take drugs. These motivating factors can either be barrier or facilitator to adherence depending on the patient's experience. Seeing or experiencing health improvements and gaining weight can motivate a patient to stay on ART (adherence facilitator), whilst repeated and severe side effects (adherence barrier) can lead a patient to stop treatment (Mills et al

2006a:2051-2053; Sanjobo et al 2008:139; Skovdal et al 2011:309). In some studies health improvement is also an identified barrier to adherence since some patients discontinued their treatment because they felt better (Mills et al 2006a:2051; Sanjobo et al 2008:139). Other treatment related factors influencing adherence cited were having no time to refill prescriptions or other pharmacy-related problems such as disruption of drug access or stock-outs (Mills et al 2006a:2052), dietary restrictions or lack of food (Mills et al 2006a:2052; Sanjobo et al 2008:141; Skovdal et al 2011:302-303) to include cost for complementary food and altered meal schedules especially if patient has not disclosed their HIV status to family members (Vervoort et al 2007:275-279), complexity of regimes (Mills et al 2006a:2051) which may disrupt daily routine schedules and finally, taste, size and dosing frequency (Mills et al 2006a:2051).

2.5.3.3 Patient-provider, health system factors

The health care environment that patients receive their ART can affect medication adherence. Sanjobo et al (2008:138-140) identified some of the health services characteristics that undermine adherence as lack of information and communication between health care provider and patient, time constraints during consultation where information given under such environments can be easily misunderstood, lack of counselling skills, counselling facilities and perceived lack of confidentiality, lack of health systems to allow proper management and follow-up of patients once initiated on treatment and the long distances that patients particularly in rural setting have to travel to access care and treatment. Skovdal et al (2011:302) classifies these barriers as contextual factors that have:

- Institutional support dimension where adherence is influenced by quality of health services which includes free and available drugs, good counselling, overall time spent at the health facility and opening times that are not prohibitive;
- Symbolic dimension which focuses primarily on fear and stigma of being identified as an AIDS patient, including empowerment issues within the household for the female AIDS patients
- Relational dimension mainly that of the patient and the health providers and lastly
- Material dimension where access to transport and if available is not too exorbitant and the distance of the clinic influences attendance (Skovdal et al 2011:302).

2.5.3.4 Socio-economic and cultural factors

Many factors related to socio-economic and cultures are known to influence adherence to ART. Some of these factors have a bearing on how positively or negatively adherence can be affected. Among the factors include poverty, lack of social, emotional/psychosocial support networks, lack of food, long distance from treatment centres and associated costs, overcrowding, homelessness or unstable living conditions, unemployment, illiteracy, low level of education, culture and beliefs about illness, stigma, lack of HIV status disclosure, treatment partner/supporter, gender roles and preference of alternative treatments (Mills et al 2006a:2051; Sanjobo et al 2008:139; Skovdal et al 2011:302; WHO 2003:28).

According to Skovdal et al (2011:298), to better understand how these factors influence a patient's ART adherence behaviour, it is important to understand how these factors "are enabled or supported by the wider social environment in which behavioural decisions are made." The authors argue that theories such as information, motivation and behavioural skills model, the health belief model and the social cognitive theory that have been used to study adherence behaviour have focused at the individual's level of conscious rational choice, de-linked to the environment in which these choices are being made. Skvodal et al (2011:298) suggest that depending on the patient's context, "particular forms of behaviour are enabled or limited."

Among the socio-economic and cultural factors mentioned above, lack of HIV status disclosure impacts heavily on adherence since it influences other factors that influence adherence. Lack of HIV status disclosure can undermine a patient's ability to reach out for emotional and psychosocial support networks and treatment partner/supporter, which are facilitators of adherence. Equally stigma because of fear of being identified with the HIV disease can prevent a patient from taking initiatives that can facilitate adherence to ART, 'patient participation' (Skovdal et al 2011:315).

Non-adherence can undermine treatment success and ultimately long term health. Adherence in individual patients can fluctuate over time, influenced by a variety of factors discussed. It is therefore important for health care workers to continuously engage patients on ART in discussing issues around adherence in order to promote and optimise adherence to ART.

2.5.4 Strategies to promote ART adherence

Adherence counselling is probably the most important and critical strategy employed in preparing and equipping a patient for lifetime behaviour change with respect to taking medication to a chronic disease such as HIV. As previously mentioned, once ART has been initiated, a patient must adhere to the prescribed medications for treatment to be successful. The Zimbabwe guidelines for antiretroviral therapy emphasises the importance of good adherence counselling by pointing out that starting ARV treatment should not be seen as an emergency and can wait until adherence training/counselling has been properly given to the patient (NDTPAC & AIDS and TB Unit MOHCW 2007:11-12). This approach also embraces the fact that adherence is a dynamic process that requires the patient to become knowledgeable on the important consequences of both adherence and non-adherence to ART. Adherence counselling is therefore geared at giving the patient information so that they are prepared and they fully understand nature of HIV disease, the treatment they are embarking on and individual support systems, importance of adherence and strategies for adherence. Adherence counselling also aims to help the patient identify potential barriers to adherence and how best to address the barriers with an overall goal of ensuring patient's readiness to start treatment and to maintain high adherence in order to improve chances of successful treatment outcomes and long-term health (Deeks 2006:1489). Other strategies to promote adherence include pill boxes (Nachega, Mills & Schechter 2010:73; Vervoort et al 2007:277), treatment partner/supporter and support groups (Skovdal et al 2011:306) and electronic reminder devices such as cell phones or wristwatches or key rings (Nachega et al 2010:73).

2.5.5 Patient retention

For patients to achieve and sustain high adherence levels and minimise risk of treatment failure, ART programs must also be able to retain patients on the treatment programme. A meta-analysis assessing patient retention on ART programs in African settings involving patients not paying, partially paying and paying in full for treatment, reported average weighted mean patient retention rates of 80%, 75% and 62% at 6, 12 and 24 months respectively (Rosen, Fox & Gill 2007:1694). In that study, retention was defined as "patients known to be alive and receiving highly active ART at end of a

follow-up period", whereas attrition was defined as "discontinuation of ART for any reason, including death, loss to follow-up, and stopping ARV medications while remaining in care" (Rosen et al 2007:1692). Kaplan-Meier survival curve analyses for all studies showed attrition rate between ART initiation and 6 months at 11%, 19% between 6 months and 1 year and 10% between 1 year and 2 years (Rosen et al 2007:1694-1695).

Contrary to observed ART retention rates in other studies (Mills et al 2006a:2054-2055), and supporting the factors attributing to the observed retention rates, a randomised controlled study in Zimbabwe reported high rate patient retention in care (Muyingo et al 2008:468-475). The high retention rate does support the observation that removal of barriers to ART retention such as transport costs, clinic fees and non-disclosure can facilitate retention in care.

Other factors influencing ART retention include time off work or family duties failure to initiate those patients engaged in care whilst waiting for treatment initiation and sicker patients (Patel, Hirschhorn, Fullem, Ojikutu & Oser 2010:1-3, 7), failure to re-fill prescriptions and distance to the clinic (Patel et al 2010:7). It is therefore important for treatment programs to have a system in place to track patients lost-to-follow-up in order to retain patients in care and promote adherence to ART (Patel et al 2010:9; Rosen et al 2007:1698-1699; WHO Global HIV/AIDS response: epidemic update and health sector progress towards Universal Access: progress report 2011:84).

2.6 MEASURING AND MONITORING ADHERENCE TO ART

In order to improve HIV treatment outcomes, adherence among patients initiated on ART needs to be monitored. Strategies for measuring and monitoring adherence can be divided into immunological and non-immunological methods.

2.6.1 Immunological methods for adherence measurement and monitoring

In resource-constrained countries, immunological or biochemical based measuring methods are not always available and or easily accessible to patients on ART. Two commonly used immunological based methods for measuring and monitoring ART include CD4 cell count and viral load testing.

2.6.2 HIV RNA (viral load) quantification

HIV RNA (viral load) is used to measure or estimate the level at which HIV is being produced. It is used to measure the amount of virus in the blood and is often used to monitor HIV disease progression. Without treatment, HIV replicates or is produced unabated, leading to CD4 cell death and high viral load being detected in the blood.

In patients taking HIV treatment drugs, measurement of viral load is used to assess virologic suppression and treatment failure which are both indicative of how well the antiretroviral drugs are working. Although not routinely offered in clinical care of ART patients in Zimbabwe, viral load testing is in limited cases used to investigate patients suspected of failing on ART.

In general, a viral load that is below detection levels of the assay defines virologic suppression. High adherence level to ARVs is a predictive factor of virologic suppression together with other factors which include low baseline viral load (Deeks 2003:2003), higher baseline CD4 count at ART initiation (Deeks 2003:2003) and composition of the ARV regime (Bisson 2008b:107-109). High viral load in patients taking antiretroviral drugs is indicative of treatment failure (Deeks 2003:2002), infection with drug resistant virus (Bean 2005:S96, Deeks 2003:2003-2004, Harrigan et al 2005:339), a weakened immune system (due to CD4 T cell destruction) (Alimonti et al 2003: 1650) and transient episodes of viremia “blips” (Sedaghat et al 2007:1165).

2.6.3 CD4 cell count quantification

CD4+ T cells play an important role in the immune system of protecting the body against infections. As already mentioned, HIV is known to preferentially infect CD4 + T cells. During the HIV replication process, after proviral DNA is integrated into the CD4 cell’s genomic DNA, the HIV proviral DNA is virtually impossible to destroy (Deeks 2003:2003-2004). Infected CD4+ T cells can however be destroyed by CD8 cytotoxic cells, direct cell death and apoptosis (Alimonti et al 2003:1650-1652). Progressive CD4 cell destruction leads to fewer and fewer numbers of circulating CD4+ T cells, high levels of HIV copies (high viral load) characterised by a very weakened and

compromised immune system, vulnerable to opportunistic infections and HIV disease developing into AIDS (Alimonti et al 2003:1650).

Guidelines for ART initiation in most treatment programmes for resource-limited countries is a CD4 cell count of <350 cells/cm^3 of blood (WHO 2013:94). It is important to note that in the absence of viral load testing for OI/ART programmes in resource limited countries, WHO recommends both initiation and monitoring of ART based on clinical staging and CD4 cell count although programs are urged to reduce reliance on clinical failure definitions (WHO 2013:132-134).

Whilst the HIV clinical staging remains an important tool, the revised WHO 2010 PMTCT guidelines now puts more emphasis on CD4 testing in order to objectively identify pregnant mothers as early as 14 weeks whether they require ARV drugs for their own health or whether they require prophylactic ARV drugs to reduce risk of HIV transmission to their unborn child (WHO 2010a:2). For that reason and also due to innovation and advancement in medical tools, Zimbabwe has adopted use of POC CD4 testing thereby increasing access of CD4 testing for both the PMTCT and OI/ART programmes. For both these interventions, CD4 cell count is used mainly to guide clinicians on when to start ART. CD4 cell count is subsequently used to monitor patients initiated on art at 6-month intervals for purposes of switching to second-line therapy in the event of treatment failure (MOHCW May 2010:11).

Despite continued use of clinical staging and CD4 cell count in monitoring patient response to ARV treatment, both have limited sensitivity to detect treatment failure. Individual variations in immunological response to ART vary, making CD4 cell count changes difficult to interpret and may misguide clinicians on patient management by delaying switching of patients on failing treatment or switching patients too early on regimens still effective for viral suppression (Badri, Lawn & Wood 2008:7-8; Bisson, Gross, Strom, Rollins, Bellamy, Weinstein, Friedman, Dickinson, Frank, Strom, Gaolathe & Ndwapi 2006:1617).

Regardless of how “forgiving” some ARV regimens may be, patients on ARV therapy should be encouraged and educated on the importance of near perfect adherence once therapy is started. A study in British Columbia Canada (Wood 2004:266) showed that irrespective of baseline CD4 count, adherence was the strongest predictor of CD4 cell

count response following ART initiation. In another study, patients enrolled in a clinical trial in Uganda and Zimbabwe showed that higher CD4 cell count at ART initiation among HIV positive predicted higher adherence to treatment within the first year and more so in the first 12 weeks of treatment (Muyingo et al 2008:472), with the authors citing factors such as increased social support, health improvements facilitating adherence and clinic attendance easier owing to more strength and "increased ability to manage drug side effects" (Muyingo et al 2008:474). A meta-analysis looking at patient retention in ARV treatment programs in sub-Saharan Africa found higher rates of attrition among programs initiating patients at lower CD4 count when compared to those initiating patients at higher CD4 count (Fox & Rosen 2010:12-13).

2.6.4 Non-immunological methods for adherence measurement and monitoring

In research settings, non-immunological tools and methods for adherence measuring have been shown to be comparatively easy to use and less expensive, however there is need to better understand how reliable and scalable some of these strategies are for routine care at different levels of health care delivery.

Among non-immunological methods to consider when measuring adherence to ART that have been used include pill counts, self-reports, pharmacy refill data, electronic drug monitoring devices and directly observed treatment. In clinical settings these approaches can be utilised with a goal of identifying patterns of adherence or in identifying ART adherence problems and plan appropriate interventions (Bisson et al 2008a:0786-0789). The challenge in their usage however is that to date, none of them is considered as a gold standard and depending on the setting, some methods and or tools may be inappropriate and combining different methods may be needed to increase accuracy of measurement (Osterberg & Blaschke 2005:489).

2.6.4.1 Pill counts

An adherence monitoring strategy that involves the return of excess pills and or medication packaging to the health care provider is known as pill counting. With this method, at the patient's next clinic visit, the health care worker assesses adherence to medication by counting the number of pills the patient might still have or not have and correlate to the prescription period. Ideally an unannounced pill count in the patient's

home would give a true indication of the patient's adherence (Kalichman, Amarai, Swetsze, Eaton, Kalichman, Cherry, Detorio, Calends & Schinazi 2010:325). However, because of the stigma that may be associated with a home visit and also possible confidentiality considerations, pill count assessments are carried out at the health facility or during a scheduled outreach clinic setting.

In Zimbabwe Muyingo et al (2008:468-475) assessed adherence using drug possession ratio and pill counts among patients in a highly controlled clinical trial. Patients enrolled in this study were provided with transport and clinical care for free. Pill count was assessed at the health facility during a scheduled visit. The accuracy of the pill count method therefore depended heavily on the trustworthiness of the patient. Some patients in efforts to not disappoint the health care worker and also to assure that more medication is dispensed have been reported to dispose of excess doses ahead of these scheduled clinic visits (Osterberg & Blaschke 2005:488-489), thereby inflating the adherence levels.

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2.6.4.2 Self-reports

Self-reporting is one of the most commonly used strategies to monitor patient adherence to medication. This method utilises the patient to recall medication taking behaviour over a defined period of time which could range from a day to 30 days or even more depending on clinical settings. Whilst this method has been shown to correlate well with medication intake and viral load (Fletcher, Testa, Brundage, Chesney, Haubrich, Acosta, Martinez, Jiang & Gulick 2005:303-305), this method relies heavily on the assumption that the patient is truthful and is able to accurately recall their medication taking behaviour over the specified period. Other disadvantages encountered with use of this method are the tendency by patients to inflate their adherence behaviour and patient forgetfulness (Osterberg & Blaschke 2005:489). Self-

reported adherence monitoring can however be enhanced by using a shorter recall period by asking the patient on missed doses in most recent days, utilisation of diaries and using a non-judgmental approach (Osterberg & Blaschke 2005:490, Vervoort et al 2007:277-278) in communicating with the patient.

2.6.4.3 Pharmacy refill data

Of the non-immunological adherence measuring strategies in use, pharmacy re-fill data is one of the most objective and relatively least expensive when compared to Event Monitoring Systems (MEMS) another objective non-immunological method. In most public health facilities when patients are commenced on ART, they are required to collect their ARV drugs from the designated facility pharmacy where they are entered into a dispensing pharmacy register. Upon drug collection, the date and regime dispensed are recorded and patient is given a date for the next drug collection or refill. By assessing the patient's refill rate or on time drug collection can provide an overall indication of the patient's adherence pattern (Osterberg & Blaschke 2005:488; Nachega et al 2006:84).

In an observational cohort study of 2821 patients in South Africa to measure proportion of patients achieving viral suppression (HIV RNA less than 400 copies/mL from 1 month after HAART initiation till end of follow-up), patients were categorised into 7 categories of adherence based on calculated pharmacy refills. In that study pharmacy refill adherence was calculated and expressed as a percentage of the "number of months with HAART claims submitted, divided by the number of complete months from HAART initiation to death, withdrawal from the program" (Nachega et al 2007:565). Adherence strata with 10% increments were used with less than 50% being the lowest category up to 100%. A significant dose-response relationship was observed between patients with viral load suppression and pharmacy refill adherence for all the 7 adherence categories, with rates of sustained viral suppression ranging from 13% in the less than 50% pharmacy claim, adherence 25%, 39%, 45%, 59% 69% and 73% respectively for those in the 100% category (Nachega et al 2007:566, 569). In that study every 10% increase in pharmacy refill adherence for categories greater than 50% was associated with a 0.10 mean absolute increase in the proportion of patients with virologic suppression (Nachega et al 2007:566). When the authors looked at the time to viral suppression, patients in the high pharmacy refill adherence categories had significantly shorter time

to viral suppression when compared to those patients in the less than 50% adherence category and similarly patients in the 100% pharmacy refill adherence group had significantly shorter time to suppression when compared to adherence categories with less than 90% adherence (Nachega et al 2007:570). Over 60% of the cohort maintained pharmacy refill adherence that was more than 80% (Nachega et al 2007:568, 569, 572).

In another study adherence monitoring by pharmacy refills was superior to CD4 cell count changes in detecting virological failure at 6 and 12 months for patients initiated on NNRTI-based ART among HIV-1 infected adults from nine countries in southern Africa who subscribed to a private health care plan (Bisson et al 2008a:0778-0780). Virologic failure at 6 months was assessed by pharmacy refill data in the first 3 months of ART initiation, and at 12 months, it was the first 3 months post the 6-month follow-up date. CD4 cell count change in 6 months was measured between time of ART initiation and 6-month viral load testing and the 12-month CD4 change was measured from ART initiation to the 12-month viral load testing (Bisson et al 2008a:0780). In that study the advantage of adherence value monitoring superseded CD4 cell count because of its "overall accuracy in detecting current virologic failure" irrespective of the level of virus load used to define virologic failure and the fact that CD4 cell count monitoring identifies virologic failure retrospectively, after it has already occurred (Bisson et al 2008a:0780-0786), clearly suggesting the important and critical role of how pharmacy refill data can be used in real-time patient management.

Overall in resource limited settings, pharmacy refill adherence monitoring has been suggested as a viable and more useful strategy of early identification of virologic failure compared to CD4 cell count which could be utilised by the health care provider to screen and prioritise patients who may require viral load testing (Bisson et al 2008a:0785-0786).

2.6.4.4 Electronic drug monitoring devices

The most common method for adherence monitoring that involves electronic devices is called Event Monitoring Systems (MEMS). With this strategy the patient's medication bottle cap is inserted with a computer chip that records the events of opening and closing of the medication bottle. For each event, the date and time of the opening and

closing and duration of the opening of the medication bottle are recorded (Paterson et al 2000:22). Data on the chip can be downloaded onto a computer and analysed, allowing for adherence to be measured over a continuum.

A prospective observational study at two HIV clinics in Pittsburgh Pennsylvania and Omaha Nebraska USA studied the association between protease inhibitor adherence to ART using MEMS and patient outcomes both virologic and clinical (Paterson et al 2000:24). The level of adherence as measured by MEMS was significantly associated with risk of virologic failure and hospitalisation for patients with less than 95% adherence (Paterson et al 2000:26). Level of adherence also significantly predicated changes in CD4 cell counts with patients with greater than 95% adherence managing a mean increase of 83 cells/mm^3 compared to mean increase of 6 cells/mm^3 for patients with less than 95% adherence over the course of the study (Paterson et al 2000:24-26).

Usage of the MEMS strategy assumes that with each recorded event, the prescribed dose is taken. If a patient however decides to remove several doses with a single event for later ingestion, this may lead to underestimation of adherence or higher non-adherence rates being recorded (Osterberg & Blaschke 2005:489). Likewise if a patient opens the bottle without taking any doses, this would overestimate adherence (Osterberg & Blaschke 2005:489).

With MEMS, one kind of drug is usually used per container, making this method expensive for use with triple drug regimens such as those in use with ART and more so for resource limited settings. Another disadvantage of the MEMS strategy is that it only works if the patient consistently replaces the cap back onto the bottle after each opening. Also because of the expense and general unavailability makes this adherence measuring strategy impractical for resource-constrained countries.

2.6.4.5 Directly observed treatment (DOT)

When directly observed treatment (DOT) strategy was introduced it became standard treatment for the management of tuberculosis infections. This strategy for TB infections has been feasible and successful mainly because it is short term and not lifelong treatment as that required by HIV infected patients. The DOT version in the context of HIV infections, directly administered antiretroviral therapy (DAART) has primarily been

limited to research settings and has simply been deemed not feasible for large-scale routine clinical practice (Ford, Nachega, Engel & Mills 2009:5-6, Nachega et al 2010:72). The DOT or DAART strategy requires the patient to be physically and visually observed (usually by a health care provider) ingesting the antiretroviral drugs. It's use to improve adherence and virologic outcomes has however been suggested for HIV infected drug users (Maru, Bruce, Walton, Mezger, Springer, Shield & Altice 2008:1-2) and perhaps other identified populations at risk of poor adherence (Nachega et al 2010:73).

In resource limited settings, reliable and easy to implement methods of measuring adherence in ART intervention programmes is essential for success. This study aims to retrospectively determine the level of adherence to ART when using pharmacy refills and the extent of the relationship between ART adherence when measured by pharmacy refills and immunological parameters of CD4 count and HIV-1 RNA levels (viral load) among HIV positive patients at Mpilo Central Hospital in Bulawayo Zimbabwe. CD4 cell count is an immunological parameter recommended by the WHO to monitor treatment in resource limited settings.

2.7 CONCLUSION

A literature review was conducted to identify, summarise and synthesise research previously carried out on HIV and AIDS and treatment with a specific focus on adherence to ART. For treatment interventions to be successful, high levels of adherence are critical to prevent treatment failure and the development of drug resistant viruses. Importance of the HIV life cycle in relation to treatment development strategies was highlighted. Treatment guidelines followed by the ART intervention programmes in Zimbabwe were discussed. Barriers and enabling factors that influence adherence as well as strategies to promote adherence were discussed. Despite lack of a standard method of measuring adherence, different strategies and tools used to measure adherence were outlined. Pharmacy refill data (a non-immunological parameter) is explored for its ability to measure adherence levels to ARV drugs and assess how it compares with CD4 cell count an immunological parameter.

In the following chapter, a description of the research design and methods utilised in the study to achieve the objectives of the study is presented.

CHAPTER 3

RESEARCH DESIGN AND METHODS

3.1 INTRODUCTION

This chapter outlines the research design and methods followed in this study.

It begins with a discussion of the research design followed by the description of the research methods which included the setting, population, sample and sampling procedures, data collection and analysis procedures. Ethical principles that pertain to the study were considered.

3.2 THE RESEARCH AIMS AND OBJECTIVES

As indicated in chapter 1, the aims of the study were to determine the level of adherence to ART when using pharmacy refills and the extent of the relationship between ART adherence when measured by pharmacy refills and immunological parameters of CD4 count and HIV-1 RNA levels (viral load) among HIV positive patients at Mpilo Central Hospital, Zimbabwe. In order to achieve the aims of the study, the following objectives were formulated:

- Describe the level of adherence to ART when measured by pharmacy refills compared to CD4 cell count and viral load.
- Describe the relationship between adherence to ART when measured by pharmacy refills, CD4 cell count and viral load.

3.3 THE RESEARCH QUESTIONS

The research questions that guided the study were:

- What is the level of adherence to ART when measured by pharmacy refill compared to CD4 cell counts and viral load?

- What is the relationship between adherence to ART when measured by pharmacy refills, CD4 cell counts, and viral load?

3.4 RESEARCH DESIGN

The plan or “blueprint” of how the researcher intends to collect data for a study in order to answer research questions in given conditions is known as the research design (Grove et al 2013:214). The choice of a study design guides the researcher in planning and implementing the study in terms of how they go about the selection of a study population, sampling methods of measurement, data collection and analysis with the main objective of maximising the validity of the study (Grove et al 2013:214-215). A non-experimental, quantitative, retrospective, descriptive and correlational design was used for the purposes of this study.

3.4.1 Non-experimental research design

A non-experimental research design was used because the researcher collected data without introducing any treatment or changes to the subjects. According to Polit and Beck (2012:223), some variables although possible to manipulate cannot be manipulated for ethical reasons in human studies. In this study, withholding treatment would be unethical and hence adherence data was collected retrospectively in its natural setting to determine level of adherence to ART when measured by pharmacy refill compared to CD4 cell counts and viral load and also understand the relationship between adherence to ART when measured by pharmacy refills, CD4 cell counts and viral load.

3.4.2 Quantitative research design

A positivist paradigm following quantitative approach and research processes was used in this study. Quantitative research is a formal, objective, systematic process implemented to obtain numerical data for understanding aspects of the world. For quantitative research design, structured tools are used to generate numerical data and statistics are used to organise and interpret the data collected (Grove et al 2013:23-24). Quantitative research processes are objectively constructed and its findings are replicable and generalisable (Parahoo 2006:49).

3.4.3 Retrospective cohort design

Polit and Beck (2012:224) define retrospective cohort design studies as those investigations that try to evaluate an existing condition as a result of a phenomenon or event of the past. In that respect, the effect (existing condition) or dependent variable is evaluated to see if it can be linked to a reason (event in the past) or independent variable. A retrospective, cohort design enabled the researcher to obtain information and clarity concerning the status of the phenomena of interest; namely adherence to ART in patients initiated on ART between 1st October 2009 and 31st December 2010. The objective of this retrospective cohort research approach was to describe the relationship between the dependent variable (adherence to ART when measured by pharmacy refills) and the independent variables namely CD4 cell counts and viral load as they occurred in retrospect. According to Polit and Beck (2012:725), a dependent variable is the "outcome variable of interest" or the outcome measure influenced or caused by another variable. On the other hand, an independent variable is the variable that is "believed to cause or influence the dependent variable" (Polit & Beck 2012:730). Several other dependent variables of gender, age, marital status, living situation or type of residence, employment status and treatment supporter and or disclosure are considered and reported in Chapter 4.

Cohort studies have defined time frames of enrolment of a population sample that meets specific exposure characteristics or phenomenon and can either be prospective or retrospective (Polit & Beck 2012:224-225; Grove et al 2013:309-310). In a retrospective cohort study, exposure status or phenomenon is determined in the past for a group/cohort of patients followed over a defined period of time (Polit & Beck 2012:224; Grove et al 2013:310). In this study a retrospective cohort approach was used. Patients initiated on antiretroviral therapy between 1 October 2009 and 1 December 2009 were part of the study. The rationale for the specified period of treatment (1st October 2009 to 31st December 2010) was that patients who would have completed a year on ART were likely to have all their records complete by the time the study was conducted. The date range selected by the researcher for the cohort also took into account a period during which the Zimbabwean economic landscape had "normalised" after a serious economic down turn in the preceding three to four years. So during this

period there were adequate or normalised ART stocks and treatment was accessible to all HIV positive patients.

3.4.4 Descriptive correlational research design

A descriptive correlational research design is used to describe relationships between and or among variables in a non-manipulated environment. According to Polit and Beck (2012:226), the aim of a descriptive correlational research design is to describe the relationships among variables" without showing or inferring causality. For a descriptive correlational research design, the sample is studied as a single group (Grove et al 2013:225) and it is further defined by its ability to provide covariation or an account or description of relationships that may exist between or among variables and also identify patterns of relationships as they occur (Grove et al 2013:225-226). In addition, descriptive studies are capable of observing, describing and documenting "aspects of a situation as it naturally occurs" (Polit & Beck 2012:226). The use of the descriptive correlational design enabled the researcher to describe the statistical associations between two or more variables namely pharmacy refill data, adherence to ART and CD4 cell count and viral load among a cohort of patients initiated on ART at Mpilo Central Hospital OI/ART clinic between October 1 2009 and December 31 2009.

Correlational studies cannot be used to study causality. The cause and effect cannot be stated in correlation studies because the direction of the cause is not known and other variables may also be involved in the observed outcome (Polit & Beck 2012:224, Grove et al 2013:224-226). Further, the strength or the degree and direction of the relationship between variables can be examined (Polit & Beck 2012:224), although one is not able to determine which variable has more influence on the other. According to Polit and Beck (2012:229), one of the strengths of a correlational study design is the close to reality presentation of a phenomenon and more importantly is "seldom criticized for its artificiality). Often correlational research designs are used as a basis for further and more rigorous experimental studies (Grove et al 2013:225; Polit & Beck 2012:229) that may be able to establish causality.

3.5 RESEARCH SETTING

The study setting is defined by Polit and Beck (2012:743) as the physical location and conditions in which data collection takes place. The study was conducted at Mpilo Central Hospital which is a 938-bed government public health institution in Bulawayo, Zimbabwe. Because of its size, finding a sufficient sample was not likely to be a problem. Mpilo is the only government central hospital located in the Bulawayo Metropolitan province in the South West region of the country. It is a referral centre, not only for its province but for 4 other surrounding provinces with HIV prevalence indicated as follows: Matebeleland North, (18.3%) Matebeleland South (21.2%), Midlands (15.4%) and Masvingo (14.4%) (Zimbabwe National Statistics Agency (ZIMSTAT) and IC International 2012).

The Bulawayo health services infrastructure includes 4 hospitals (3 public hospitals which are Mpilo Central Hospital, United Bulawayo Hospitals (UBH) and 1 private hospital, Materday as well as 19 Bulawayo city polyclinics. A patient referral system is in place with the 19 clinics being the main primary health care providers. All the stated health facilities offer HIV counselling and testing, PMTCT services and maternal and child health services.

3.5.1 Mpilo Central Hospital OI/ART Clinic

Mpilo OI/ART clinic was started in 2003 as one of the first 5 ART pilot sites in Zimbabwe and was also the only public health centre offering treatment and care at no fee. There is a dedicated OI/ART pharmacy at the clinic. In addition to the regular Government of Zimbabwe funding, the OI/ART clinic at Mpilo hospital was supported by the Médecins Sans Frontières (MSF) Spain from 2004. This organisation whose name means “doctors without borders” generally focuses its operations and funding in health situations that are in a state of emergency and need special attention to combat or arrest further spread of diseases of concern. The support and funding from MSF provided for the clinic towards the HIV and AIDS pandemic and it included staff, ARV drugs and other consumables as well as access to laboratory tests including viral load testing for those suspected of failing on treatment. In December 2010, MSF Spain terminated their operations at Mpilo Hospital.

The clinic operates from Monday to Friday from 08:30am to 04:30pm except on public holidays and has a standard operating procedure which articulates the day to day operations of the clinic. Based on the clinic's statistics, on average 185 HIV positive patients are initiated on ART every month (MoHCW ART register 2009).

At the clinic, patients referred for ART are entered in a Pre-ART register where medical and psychosocial issues involved with taking ARVs are addressed. During this period patients may have a CD4 cell count done if they do not already have one. Counselling on good ARV adherence, adequate nutrition, adoption of healthy lifestyles and management of any psychosocial factors that may interfere with the patient's ability to access follow-up care is done. Pre-ART counselling sessions are also used to encourage patients to disclose their HIV status and or identify a treatment supporter. After appropriate counselling and preparedness assessment, patients at initiation of ARVs are entered into ART register and given two weeks supply of drugs. After two weeks, patients are assessed for stability mainly focusing on drug tolerance and adherence before a month's dosage is dispensed.

Patients are initially expected to come to the clinic monthly for re-fills and at every visit they are assessed for adherence. Depending on individual circumstances and drug stocks, patients can be given enough drugs for up to three to four months to lighten the burden of drug refills. Varied methods of assessing adherence to ART are used namely pill counts, self-reports and missed appointments. Whilst adherence counselling is done at every visit, more focused attention is given to patients found to be missing their appointments or patients with evident adherence levels lower than 95%.

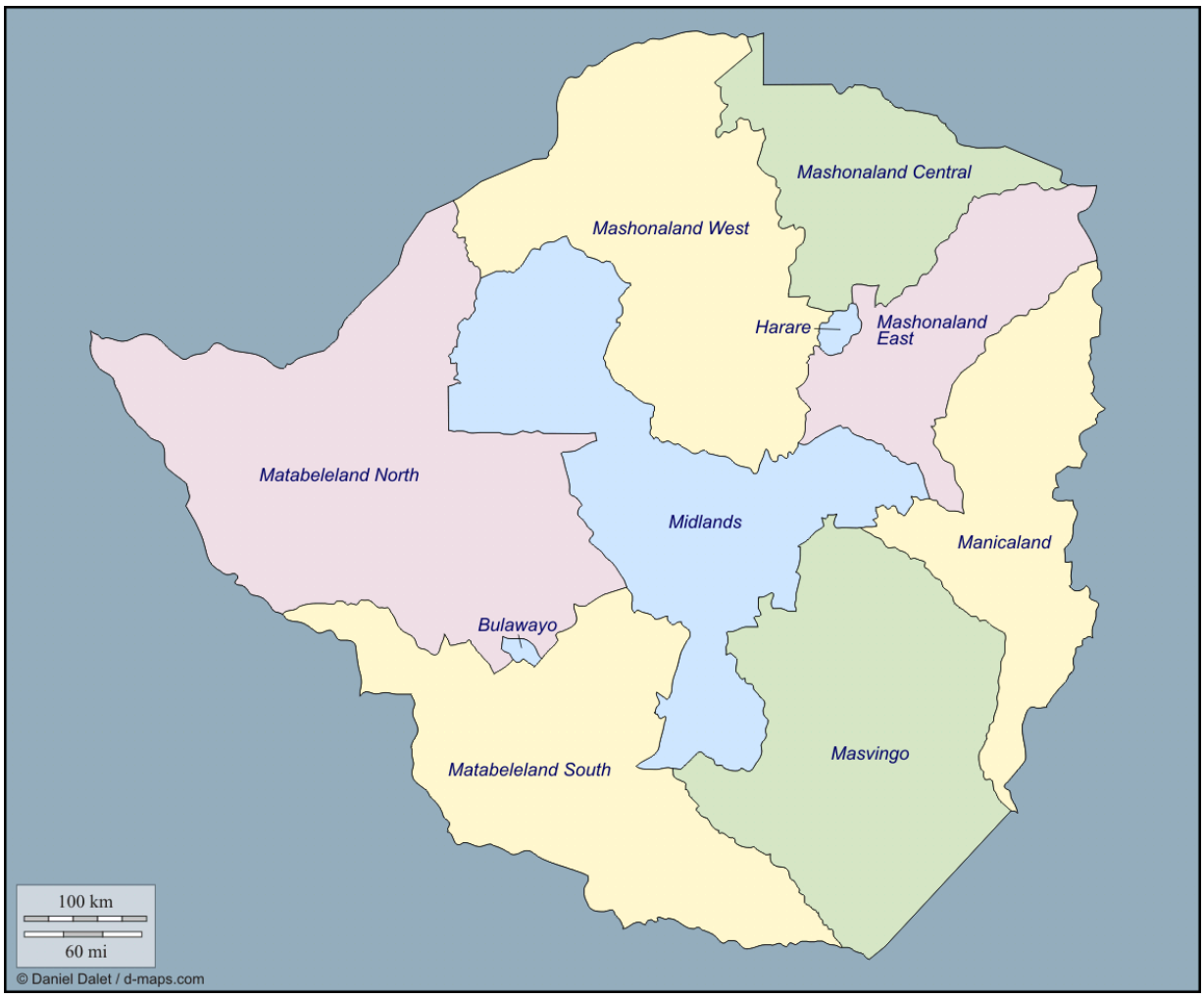


Figure 3.1: Map of Zimbabwe showing Bulawayo city in Bulawayo Province and surrounding provinces referring patients to Mpilo Central Hospital (Google Images 2012)

3.6 RESEARCH METHODS

The research methods applied in this study comprised the description of the population selected for the study, procedures and strategies for data collection and analysis. These are described in the paragraphs that follow:

3.6.1 Study population

A population is defined as entities be it individuals or objects in which specified measurement of interest or defining characteristics are represented (Polit & Beck 2012:59). It is not possible to study an entire population hence the use of a target

population derived from the population (Grove et al 2013:351). A target is defined as the "entire set of individuals or elements who meet the sampling criteria."

The target population for the study included HIV positive adult patients initiated on ART between 1 October 2009 and 31 December 2009 and followed up for 12 months. The researcher needs to further identify a population that is accessible. The accessible population represents the group from which the sample (sample frame) is taken and it provides a sample that generalises to the target population (Polit & Beck 2012:744). The accessible population were patients who met the inclusion criteria.

3.6.1.1 Inclusion criteria

Inclusion criteria defines the "characteristics that the subject or element must possess to be part of the target population" (Grove et al 2013:353). For this study HIV positive patients at an MSF-Spain supported public hospital OI/ART clinic were considered. Eligibility criteria included:

- Male and female HIV positive patients
- Patients 18 years of age and above
- Patients initiated on ART between 1 October 2009 and 31 December 2009 and were followed up for 12 months
- Patients who had CD4 cell count done on or before ART initiation

Recruitment of all persons seen at the recruitment site meeting the inclusion criteria for this study went on retrospectively from October 1 2009 to December 31 2009 and followed-up for a 12 month period. The rationale was to choose the latest recruits who were likely to present the current trends rather than old patients. The cohort date range chosen by the researcher took into consideration a period during which the Zimbabwean economic landscape had "normalised" after a serious economic downturn in the preceding three to four years. The other factor also considered finding a patient cohort that had completed a year on ART and were likely to have all their records complete by the time of the study conduct.

3.6.1.2 Exclusion criteria

Exclusion criteria are the “characteristics that can cause a person or element to be excluded from the target population” (Grove et al 2013:353). The following patients were excluded from this study:

- HIV positive patients who were younger than 18 years of age at ART initiation. Medical examinations and record forms used with adolescents and young children are different and data extracted from these records would not be compatible with the sequence of data entry in the ART registers and facility held patient records used with the adults.
- Patients who had ART treatment for less than 12 months.
- Patients who were initiated on ART prior to 1 October 2009 and after 31 December 2009.
- Patients who were initiated on ART with no baseline CD4 cell count and no subsequent or follow up CD4 count done within the specified cohort period.

3.6.2 Sample and sampling procedures

It is impractical and close to impossible in terms of time, money and feasibility to study the entire population in research. As a result, a process of choosing part or a subset of the population in order to represent the whole population is undertaken (Grove et al 2013:351-352). This is called sampling. In conducting research, a sampling plan on how to get study participants for the research study is required. According to Grove et al (2013:357), these sampling plans or strategies can either use probability or non-probability procedures with the overall aim of increasing “representativeness and decrease systematic bias”. In this study, probability sampling was used for selecting participants for the study. Probability sampling is a technique or a procedure used in quantitative research to ensure that each element in the population has an equal and independent chance of being selected and achieves representativeness (Polit & Beck 2012:280). The researcher readily had access to all records (n=118) of patients who met the inclusion criteria. The sample size of 118 was manageable and adequate for data analysis. As a result no sampling procedures were applied for this study.

The sample frame was the ART register of HIV positive patients seeking HIV care and treatment at Mpilo Central Hospital.

Figure 3.2 shows that at Mpilo Central hospital, a total of 460 patients were initiated on ART between October and December 2009 as follows 165 (36%) in October, 182 (39.5%) in November and 113 (24.5%) in December 2009. The number of patient records that met the inclusion criteria for this study was 118 and 242 were excluded because of incomplete identification, absence of baseline CD4 cell counts and absence of follow-up CD4 cell counts.

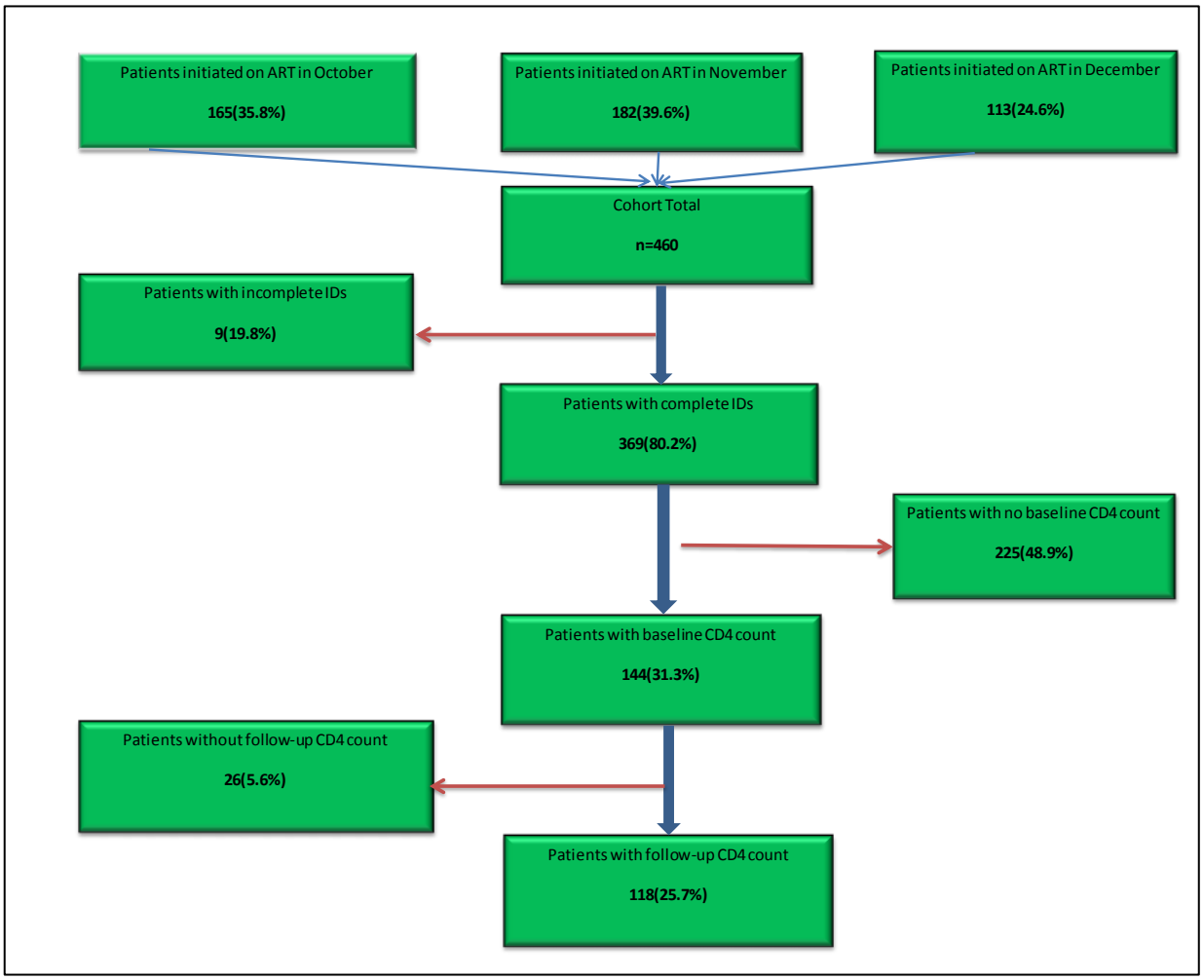


Figure 3.2: Flow chart for patients initiated on ART between October and December 2009

3.6.3 Data collection

Data is described as information that is gathered from counts, measurements responses or observations (Grove et al 2013: 507). Various methods for collecting data are used in research studies with the aim of fulfilling research objectives. A structured data collection process was adopted in this research study. The structured approach was appropriate because it facilitated the collection of data that was easy to analyse. Data was extracted from the facility health cards, facility OI registers and pharmacy dispensing registers.

3.6.3.1 Data collection instrument

With the assistance of the statistician (Annexure H), the researcher designed the data collection instrument (Annexure E). The instrument was computerised into an Excel spread sheet (Microsoft). Information was categorised into two sections namely socio-demographic and clinical data. The socio-demographic section of the data collection instrument included patient OI/ART number, marital status, employment status, gender, type of residence, number of years HIV status was known to the patient (calculated from date HIV test was done and date ART was initiated), OI/ART entry point or referral source, treatment supporter and age at ART initiation.

The clinical data section captured date of ART initiation and subsequent follow-up dates of pharmacy refill, weight, height, ARV regimen initiated, switch regime, date of switch and reason, pregnancy, date of next appointment, WHO staging and CD4 cell counts. A CD4 count at ART or before ART initiation was recorded. Follow-up CD4 cell count were recorded and if more than one follow-up CD4 count was available, the latest CD4 cell count recorded closest to the end of the follow-up period was used to calculate percent CD4 cell count gain. A 50% CD4 cell count gain was used to indicate immune recovery. Adherence level was based on the actual date of prescription re-fill thus subtracting the actual day of prescription re-fill from the date of next appointment. A seven day grace period was applied for all participants not collecting their prescription on the exact date of the next appointment. If a participant however collected their prescription earlier than the date of the next appointment, these were considered adherent and or on-time collections. Although weight and height were recorded consistently for the majority of the patients, this was not the case for the follow-up

period. For the follow-up period, both variables of height and weight were not being recorded systematically and therefore were dropped from analysis.

3.6.3.2 Data collection process

The researcher was responsible for data collection and capturing. Patients OI/ART numbers were double entered using different formats to ensure correct entry.

Patient data was transcribed from the ART register, patient facility held health cards and pharmacy dispensing registers kept in the pharmacy into the data collection excel spread sheet. Although electronic data captured using the Fuchia software by MSF Spain was availed to the researcher, the data could not be extracted for analysis because staff with access codes and knowledgeable in extracting the data left when MSF Spain support to the OI clinic ended in December 2010. Most of the viral load data which was supported by MSF Spain was captured in this database. Staff able to extract this data is now based at different MSF Spain supported facilities. However due to the logistical issues of accessing the services of the capable members of staff to extract the data and time constrains related to completing this research study the researcher decided to drop this variable from analysis. This also resulted in the researcher not able to complete one of the original secondary objectives of this research study that of comparing adherence using pharmacy-refills and viral load.

During the pre-testing exercise of the research instrument, the researcher noted that data extraction for adolescent patients was difficult. Often adolescent patients were recorded in adult registers. Facility held patient files were also found among adult files and investigations and record forms were different from those used with adults. For those reasons the researcher decided to limit the study population to adults.

Again during the pre-testing procedures of the research instrument, instead of transcribing data onto the data collection instrument for subsequent entry into the computer, data fields on the form were put into an Excel spread sheet and data captured directly from source document in an effort of reducing the chances of transcription errors. However this proved to be a challenge due to the need to use and refer to different data sources. As a result, the researcher reverted to capturing the data onto the data collection instrument with subsequent computer data entry. Some of the

data sources were photographed and the researcher cross-checked all data entered against source documents.

3.6.3.3 Use of routinely collected medical data

With relevant ethical approval, research data involving human subjects in the health sector can be obtained from data routinely collected (Grove et al 2013:517) as part of direct service provision of patient care, monitoring and or evaluation of health care delivery services. Researchers can make use of "hospital records, patient charts, physicians' order sheets, care plan statement" as a rich data source to answer certain research questions (Polit & Beck 2012:190) which may involve questions on "utilisation, appropriateness, process and outcome of care" (Worster & Haines 2004:187). The data used in this study were collected on-going as part of HIV care and treatment service provision at Mpilo OI/ART clinic.

- ***Advantages of using routinely collected medical data***

Using routinely collected data as the main source of information in research studies is advantageous in that data is already collected and readily available for careful analysis (Polit & Beck 2012:190; Worster & Haines 2004:187). Reviewing medical records enables researchers to address research question which are otherwise either impractical or unethical or both with a prospective research design (Worster & Haines 2004:187; Polit & Beck 2012:190).

- ***Disadvantages of using routinely collected medical data***

According to Polit and Beck (2012:190), when using routinely collected data, the main biases to be aware of are selective deposit and selective survival which both address "how representative" the medical records are. The other disadvantage of data gathered by reviewing medical records is that of poor quality due to missing records, incomplete records and or incorrect record entries. For this study selective deposit and selective survival were not encountered since all records for the study cohort were systematically entered in standardised OI/ART registers and other monitoring and evaluation tools developed by the Ministry of Health and Child Welfare of Zimbabwe for all patients seeking HIV care and treatment at Mpilo OI/ART clinic.

The researcher encountered poor recording of data and some variables could not be recorded because of missing data on patients' medical records. This was particularly prominent with viral load data. Very few patient medical records had viral load data captured. Viral load testing was supported by MSF and data captured into the Fuschia database. As indicated in paragraph 3.6.3.2, it was not possible to access the Fuschia database.

3.6.4 Data analysis

Statistical data analysis was conducted using Stata SE release 10 (STATA Corp, 2007). Data on patients who remained or continued, died or transferred out over the 12 months follow-up period after ART initiation were analysed. The data collected was analysed to ascertain adherence levels using pharmacy refills, which is a non-immunological adherence measurement parameter and correlated to immunological parameter of CD4 count.

Descriptive statistics of means, frequencies and percentages were used to describe and summarise the data. Association between variables and level of significance was done using the Chi-square test and a Chi-square distribution table to calculate the p-value (α =0.05 level of significance). The effect of adherence on CD4 cell count gain was investigated using logistic regression analysis. Unadjusted and adjusted odds ratios for 50% CD4 cell gain or immune recovery were calculated using univariate and multivariate logistic models. In the adjusted model gender, age, WHO clinical stages were used for adjusting the odds of adherence. The study supervisor and statistician assisted the researcher with data analysis and interpretation.

3.7 VALIDITY AND RELIABILITY

Validity and reliability can be seen as the quality assurance strategies that have to be observed and taken into consideration for a sound research study. Polit and Beck (2012:336) define validity as the extent to which the instrument measures what it is intended to measure and reliability as the degree of consistency with which the instrument measures the target attribute.

3.7.1 Validity

In quantitative research, validity is derived from the assumption that there is only one reality, which can be viewed objectively, controlled and manipulated. Face validity refers to 'whether the instrument looks as though it is measuring the appropriate construct' while content validity concerns 'the degree to which an instrument has an appropriate sample of items for the construct being measured'(Polit & Beck 2012:336). Due attention was paid by the researcher in the development of the data collection instrument to ensure that the items included were representative of what needed to be elicited (ART adherence) in accordance with the objectives of the study. The following measures were taken to ensure both face and the content validity of the instrument:

- Examination of the instrument by the researcher's supervisor and a professional statistician.
- The data collection instrument was pre-tested on data from the same data sources to be used for the study but on patients (n= 20) not included in the study. During this exercise the researcher noted that data extraction for the variables on the data collection instrument for adolescent patients was difficult. Often investigations and record forms were different from those used with adults. For those reasons the researcher decided to limit the study population to adults. For the most part data entry fields used on the research instrument tried to follow the same order as that found in the source documents mainly the ART register in order to facilitate easy and accurate data recording (Worster & Haines 2004: 189).

Construct validity, which are the relationships that exist for variables under study (Grove et al 2013:200; Polit & Beck 2012:248) considered adherence to ART, and immunological response when measured by increase or decrease in CD4 cell counts. In this study a data collection instrument was used to gather patient data on adherence, which was the patients' consistent collection of ARVs (dates of collection) from the pharmacy at the stipulated time intervals. Non-adherence was considered for patients who failed to collect ARVs within the stipulated time interval.

External validity addressed how well a study sample represented the population under study by looking at the extent to which the results can be generalised beyond the

sample used in the study (Grove et al 2013:202), the “extent to which it can be inferred that relationships observed in the study hold true over variations in people, conditions and settings” (Polit & Beck 2012:250). The relationships that exist for variables under study considered adherence to ART, and immunological response when measured by increase or decrease in CD4 cell counts. Because participants or the patient cohort for this study were recruited from an MSF supported site where HIV and AIDS dedicated physicians oversaw the OI/ART programme, and the extra funding that MSF provided for the running of the OI/ART program; patients seen in this health facility might have experienced less drug stock outs, had access to better health services and it is possible that they would have had higher adherence levels when compared to patients seeking the same services in similar government or public health facilities; which may result in low external validity.

Adherence to ART captured on the data collection instrument by dates suggests that patients’ collected ARVs (pharmacy refill) should reflect the patient’s immunological response as data captured by the CD4 cell counts. For patients who are adherent to ART, the measurement tool should detect immunological recovery by an increase in CD4 cell count and vice versa. Further adherence to ART is associated with virological suppression (as indicated in reduced or non-detectable viral load) and immunological reconstitution (as indicated by an increase in CD4 counts) (WHO 2003:95). In this study non-adherence is defined by failure to collect ARV drugs from the pharmacy at the prescribed or anticipated drug pick interval. Pharmacy refill data that was collected in this study was only compared to immunological parameters of adherence measuring. Virological data could not be collected as already discussed. It was anticipated that patients who were adherent as indicated by consistent and on time ARV pharmacy refill record would have an increase CD4 cell count**.** According to the national ART treatment guidelines, a 50% fall in CD4 cell count from on-treatment peak or persistent CD4 cell count below 100 cells/mm^3 is indicative of immunological failure. For this study, immunological recovery or CD4 cell recovery is defined by a CD4 cell count gain of 50% or greater at least 12 months after ART initiation.

3.7.2 Reliability of the data collection instrument and data quality control

In order to ensure that information is collected and recorded accurately the research instrument used must be reliable. According to Kimberlin and Winterstein (2008:2277),

reliability of an instrument takes into account the consistency, stability and repeatability of measurements. It is anticipated that if the research instrument is reliable and is administered at a different time, it would produce the same results. To ensure reliability, data for all patients recruited into the study were transcribed from source documents onto a data collection instrument by the researcher thereby optimising interrater reliability of the instrument (Kimberlin & Winterstein 2008:2277-2278). The patient OI/ART number was double entered in different formats and then compared for accuracy. In addition photographic images of the source documents for the cohort period were taken and computerised for easy access and subsequent verification and completeness. Data cleaning and verification especially for dates that did not make sense or that were miscomputed or wrongly entered in the source documents were done before data was analysed to ensure reliability in this study.

3.8 ETHICAL CONSIDERATIONS

In research there are certain ethical guidelines or principles that have to be observed in order to protect the rights of the participants and also to ensure the general ethical conduct of the study. Respect, beneficence and justice are the overarching human rights principles that need to be considered in research that involves human subjects (Polit & Beck 2012:152; Grove et al 2013:162). Embedded in these principles are the rights to (1) privacy (2) anonymity and confidentiality (3) fair treatment and protection from discomfort and harm and 4) self-determination (Polit & Beck 2012:152-15; Grove et al 2013:162-174). The ethical principles that were applied in this study include:

3.8.1 Ethical approval

In Zimbabwe health related research has to be approved by the Medical Research Council of Zimbabwe (MRCZ). Moreover, studies that involve contact with patients are required to have approval by the respective authorities where the study would have had patient contact. There was no direct patient contact in this retrospective study and patients' data was de-identified. Ethical approval to conduct the study was sought from the Medical Research Council of Zimbabwe (MRCZ) (Annexures C & D), Mpilo Hospital Ethics Committee (Annexures A & B) and the higher degrees committee of the Department of Health Studies at the University of South Africa (UNISA) (Annexure F).

Permission and support was also sought from the Ministry of Health and Child Welfare AIDS and TB Unit (Annexure G).

3.8.2 Anonymity and confidentiality

When information is collected from participants involved in a research study, it is the researcher's responsibility to maintain and uphold that individual's privacy. In research, assuring anonymity and keeping all data collected confidential can maintain the right to privacy. According to Grove et al (2013:172), anonymity in research is assured when "subject's identity cannot be linked, even by the researcher, with his or her individual responses". Further, upholding and assuring participants' right to privacy requires that the information collected is kept confidential. Parker (2005:186) maintains that respecting patient confidentiality and autonomy are the main ethical issues to be considered when using patient records without consent. With respect of patient confidentiality, the risk/benefit ratio posed by carrying out the study should be considered, especially for studies already deemed low risk. If the benefits outweigh the risks, studies on patient records with no consent are allowed (Parker 2005:184-185). Likewise respect for autonomy and privacy when using patients records without consent is justified in part for those situations where not carrying out the study poses "serious risk to others"; and also on the grounds that patients may "legitimately" and without having been explicitly consulted be expectant that their data may be put to research (Parker 2005:185). It is the researcher's responsibility to make sure that confidentiality is maintained during data collection and analysis (Grove et al 2013:172). In this study use of patient records was done on routinely collected data as part of on-going service provision. The researcher viewed this as a rich source of information on adherence which needed thorough analysis and could better inform OI/ART service delivery at Mpilo Central Hospital and possibly other similar health care delivery institutions in Zimbabwe. Only the OI/ART number was recorded for each patient in this study to ensure that the data collected could not be linked with the patient. No patient identifying information was collected. All database information was password protected and only authorised staff had access to the study information.

3.8.3 Justice

In order to uphold the principle of justice, the researcher made use of the predetermined eligibility criteria to select participants for the study to ensure proper representation in the research samples and respect for diversity in terms of age and gender (Holloway & Wheeler 2010:55).

3.9 CONCLUSION

This chapter addressed the research design and methods, taking into consideration the study population, data collection and ethical considerations. Data on a three month adult cohort of HIV positive patients initiated on ART between October and December 2009 were retrospectively collected from facility held registers and patients' medical records. Data analysis on a total of 118 patients meeting the inclusion criteria was undertaken. Chapter 4 presents the results and discussion.

CHAPTER 4

ANALYSIS, PRESENTATION AND DESCRIPTION OF RESEARCH FINDINGS

4.1 INTRODUCTION

The analysis of data and the description of the research results are presented in this chapter. The chapter begins with data management and analysis followed by the presentation of the results of the participants' socio-demographic data and the description of the level of adherence to ART when measured by pharmacy refills compared to CD4 cell count. In the last part of the chapter the relationship between the respondents' adherence to ART when measured by pharmacy refills and CD4 cell count is described.

4.2 DATA MANAGEMENT AND ANALYSIS

Data on ART adherence levels were extracted from the facility health cards, facility OI registers and pharmacy dispensing registers kept in the pharmacy by means of a data collection instrument which was computerised into a Microsoft Excel spread sheet. Data were collected from the records of patients initiated on ART between 1 October 2009 - 31 December 2009 and were followed up for 12 months. Patients OI/ART numbers were double entered using different formats to ensure correct entry. Prior to data analysis, data cleaning and verification were done and some of the data sources were photographed to enable the researcher to cross-check all data entered against source documents. The raw data were kept safe and confidential, locked up with no unauthorised access.

Data analysis was conducted using Stata SE release 10 (STATA Corp, 2007). Data on patients who remained or continued, died or were transferred out over the 12 months follow-up period after ART initiation were analysed. Descriptive statistics were used.

4.3 RESEARCH RESULTS

The results of the study are presented in the order in which data were collected, starting with the socio-demographic data followed by the clinical data.

4.3.1 Socio-demographic data

The participants' socio-demographic data that were collected included age, gender, marital status, employment status, type of residence, number of years HIV status known to patient, OI/ART entry point or referral source and treatment partner. The purpose of eliciting such information was to ensure that the participants met the inclusion criteria and to secure a descriptive profile of participants so as to ensure a basis for data analysis in relation to other sections of the data collection instrument as per the objectives of the study. In table 4.1, the age, gender, marital status, employment status and type of residence of participants are shown.

Table 4.1: Participants' age, marital status, employment status and type of residence at ART initiation by Gender (n=118)

Category	Females	%	Males	%	Total	
Age						
18-24	3	2.54	7	5.93	10	
25-29	4	3.38	17	14.40	21	
30-34	5	4.23	20	16.95	25	
35-39	3	2.54	21	17.79	24	
40-44	5	4.23	5	4.23	10	
45-49	5	4.23	5	5.23	10	
>50	13	11.01	5	5.23	18	
	38	**32.20**	**80**	**67.80**	**118 (100%)**	
Marital status						
Married	23	19.49	47	39.83	70	59.3
Single	7	5.93	12	10.17	19	16.1
Widow	4	3.38	12	10.17	16	13.6
Divorced	1	0.84	1	0.84	2	1.7
Separated	2	1.69	7	5.93	9	7.6
Not stated	1	0.84	1	0.84	2	1.7
	38	**32.20**	**80**	**67.80**	**118**	**100%**

Employment status					
Unemployed	17	14.40	65	55.08	82 69.49
Self employed	5	4.23	4	3.38	9 7.63
Formally employed	14	11.86	9	7.62	23 19.49
Student	1	0.84	0	0.00	1 0.85
Not stated	1	1.69	2	0.84	3 2.54
	38	**32.20**	**80**	**67.80**	**118 100%**
Type of residence					
Own	18	15.25	29	24.57	47 39.87
Rent/Relative	15	12.71	37	31.35	52 44.03
Not stated	5	4.23	14	11.86	19 16.10
	38	**32.20**	**80**	**67.80**	**118 100%**

4.3.1.1 Age, marital status, employment status and type of residence of participants

- **Age**

The age of patients enrolled in this study ranged from 18 to 71 years with an overall mean age of 36.9 years. The mean age for men was 34.2 years and 42.5 years for women

- **Marital status**

As shown in table 4.1, the number of participants who were married at the time of ART initiation was 70 (59.3%), 47(39.83%) of which were men and 23 (19.49% were women. Nineteen (16.1%) participants were single, 16 (13.6%) were widowed, 2 (1.7%) were divorced, 9 (7.6%) were separated and the marital status of 2 (1.7%) participants was not known.

- **Employment status**

A large number of participants 82 (69.5%) was unemployment at the time of ART initiation followed by 23 (19.8%) who were formally employed. Nine (7.61%) participants were self-employed, 1 of the participants was a student and the employment status of 3 (2.5%) participants was not recorded.

- **Type of residence**

As shown in table 4.1, a total of 52 (44%) lived in rented accommodation or lived with a relative while 47 (39.8%) patients owned their residence at the time of ART initiation. The type of residence for 19 (16.1%) patients was not recorded.

4.3.1.2 Number of years HIV status was known to the participants

Figure 4.1 shows the years (in days) that the study participants had known their HIV status when initiated on ART. The number of days was calculated as discussed in chapter 3 paragraph 3.6.3.1 by subtracting the date HIV test was recorded to have been done from the date ART was initiated. Participants in this study had known their HIV status for a mean period of 6 months with a range of 5 days to 5.7 years. The data shows that 19% (n=22) were initiated on ART after having known their HIV status in 2 months, 15% (n=18) after 1 month and 15% (n=18) after 3 months. Overall majority of the patients (68%) were initiated within the first year of knowing their HIV status. Another 10% were initiated on ART more than a year after knowing their HIV status with one (1) participant having known their HIV status for close to 6 years. A total of 26 (22%) of the participants did not have the date of HIV testing recorded.

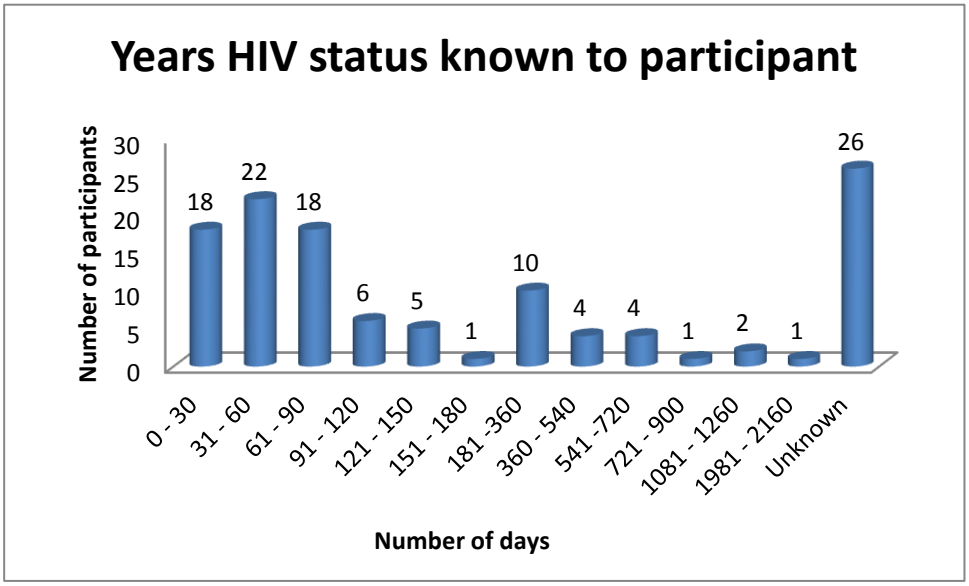


Figure 4.1: Years HIV status known to the participant

The time between knowing one's HIV status and starting ART is critical in making sure that health system referral systems are working and the continuum of care is

maintained. This is important in that patients eligible for ART initiation are not lost to follow-up and or die before interventions can be rendered (Nachega 2007:571, Nachega 2010:74-75). Furthermore, patients who start ART early or before they are too ill, are more likely to be adherent (Nachega 2006:82-83).

4.3.1.3 OI/ART entry point or referral source

Table 4.2 shows the OI/ART entry point.

Table 4.2: OI/ART Entry point or referral source (n=118)

Reason	Frequency	%
Voluntary Counseling and testing (VCT)	14	11.86
Hospital/Illness	50	42.37
Tuberculosis (TB)	6	5.08
Ante-Natal Clinic (ANC)	28	23.73
Spouse/Partner HIV positive	10	8.47
Child HIV positive	8	6.78
Not stated	2	1.69
Total	**118**	**100.00**

A large number of patients 50 (42.4%) were referred for ART initiation after having been hospitalised or experienced some illness followed by 28 (23.7%) referred by the ANC and 14(11.9%) reporting VCT as a point of entry for ART treatment. The numbers of patients reporting having an HIV test done because either a spouse or child had tested positive were 10(8.5%) and 8 (6.8%) respectively.

4.3.1.4 Treatment supporter

The significance of having a treatment supporter is that the HIV status has been disclosed. Figure 4.2 shows the participants' treatment supporters.

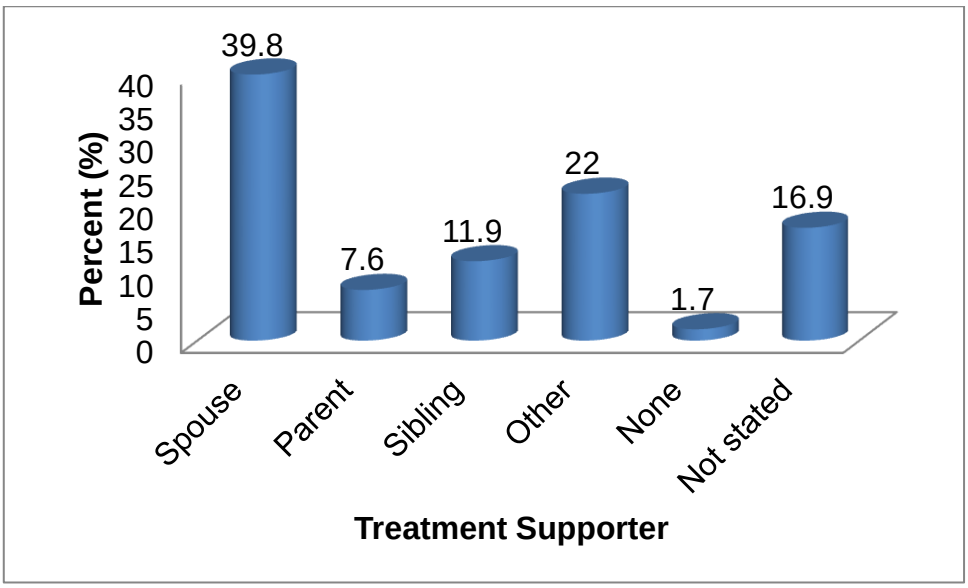


Figure 4.2: Treatment supporter

As shown in figure 4.2, 96 (81.4%) participants had treatment supporters, the majority of which were spouses, followed by other, siblings and parent. There were 2(1.7%) patients who did not have a treatment supporter while 20(16.9%) patients' records did not have records of treatment supporter data.

4.3.1.5 Age at ART initiation

Presented in (figure 4.3), are the ages of the participants at ART initiation. Majority of the participants (85%) were between 18 to 49 years old. Fifteen percent (15%) of the participants were over the age of 50 years.

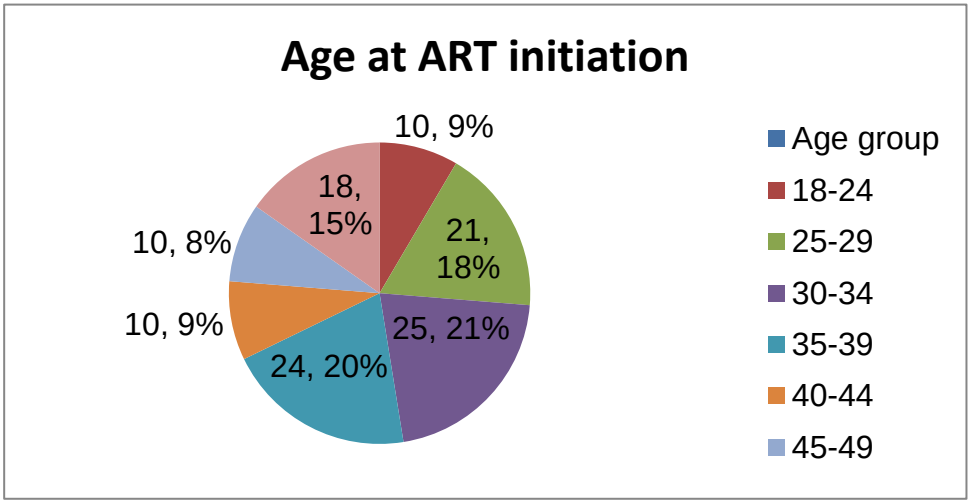


Figure 4.3: Age at ART initiation

4.3.1.6 Summary of the results of the socio-demographic data

Characteristics of the participants for this study are presented in Table 4.1. Of the 118 participants 67.8% were male and 32.2% were female. The study participants' ages ranged from 18 to 71 years, with a mean age of 36.9. Majority of the participants (59.3%) were married at ART initiation, 16.1% were single, 13.6% were widowed, 1.7% were divorced, 7.6% were separated and 1.7% did not have marital status recorded. Close to two thirds 69.5% of the study participants were unemployed, 7.63% were self-employed, 19.5% were formally employed 1 participant was a student, 1 participant was employed in the private sector and 3 participants did not have employment status recorded. Most of the participants (44%) in this study lived in rented accommodation or lived with a relative, 39.9% owned the residence they had at ART initiation and 16.1% participants did not have their type of residence recorded.

The duration that participants in this study had learnt of their HIV status ranged from 5 day to 5.7 years with a mean period of 6 months. Most participants were initiated on ART within a year of knowing their status, 10% more than a year after knowing their status and 1 participant was initiated on ART close to 6 years after being tested HIV positive. Duration of having known the HIV status could not the established for 22% of the participants because the date of HIV testing was not recorded.

The main entry point or referral source for ART initiation in this study was due to illness or having being hospitalised (42.4%). ANC referred 23.7% of the participant for ART initiation, VCT 11.9% and TB illness 5.1%. Entry for ART treatment because either spouse/partner or child had tested HIV positive accounted for 8.5% and 6.8% of the participants respectively. A very high proportion of the participants (81.4%) had a treatment supporter mostly close members of the family of spouses, siblings or parents. Only 1.7% of the participants were recorded as not having a treatment supporter and 16.9% participants did not have treatment supporter data recorded.

4.3.2 Clinical data

Clinical data collected from the participants in this study were the date that the participants were initiated on ART and the subsequent pharmacy refill dates, height and weight at ART initiation, WHO HIV/AIDS clinical stage, ART regimen initiated, ART

regimen switch and reasons for the switch and CD4 cell count at ART initiation and for the follow-up period. Variables collected in this section were used to measure and describe adherence level to ART when measured by pharmacy refills and CD4 cell count.

4.3.2.1 The dates of ART initiation

The dates of the participants' ART initiation are shown in figure 4.4.

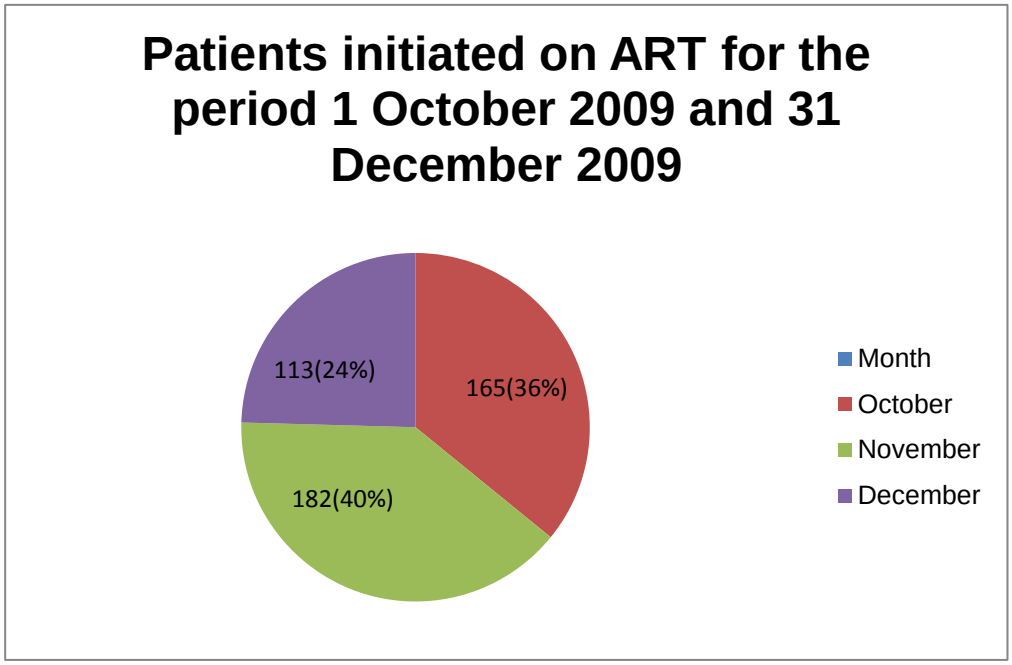


Figure 4.4: Dates of ART initiation

According to the findings, all participants met the inclusion criteria of ART initiation of 1st October – 31st December 2009.

4.3.2.2 Weight and height of participants

According to the guidelines for antiretroviral therapy in Zimbabwe, weight measurement is recommended and required for adolescents (less than 25 kg) and paediatric patients for ART initiation since dosages are determined by weight (NDTPAC & AIDS and TB Unit MOHCW 2010:17). For adult patients weight measurement is not a requirement for ART initiation. It is a good clinical practise to weigh patients seeking health care regardless of their HIV status but more so for HIV positive patients since wasting is a

common feature (NDTPAC & AIDS and TB Unit MOHCW 2010:62-63). Weight measurements are also useful in the management of patients on ART to ascertain if there is improvement in health often indicated with weight gain. Usefulness of height measurements have been indicated mainly for HIV positive infants and children where stunting has been observed (NDTPAC & AIDS and TB Unit MOHCW 2007:28).

Table 4.3 shows the anthropometric measurements of weight and height of the study participants at ART initiation. Mean weight for females was 59.7 kg and 58.2 kg for males. Mean height for females was 162 cm and 171.5 cm for males. The slightly higher mean weight in females than males could be due to the fact that 25 (65.8%) of the women in this study were pregnant and an additional 15.8% (n=6) although pregnancy was not overtly recorded, were indicated to be ANC or PPTCT patients and so were potentially pregnant or had recently been pregnant.

Follow-up weight and height measurements were not collected for this study because these were not being systematically recorded in the participants records.

Table 4.3*: Weight and height measurement at ART initiation (n=118)*

	Mean weight (kg)	**Weight Range (kg)**	**Weight not recorded**	**Total**
Male	58.2 (n=34)	35 -74	4	38
Female	59.7 (n=79)	35 - 92	1	80
Total	**113**		**5**	**118**

	Mean height (cm)	**Height Range (cm)**	**Height not recorded**	**Total**
Male	171.5 (n=33)	152 -184	5	38
Female	162 (n=72)	150 - 180	8	80
Total	**105**		**13**	**118**

4.3.2.3 WHO staging

The WHO has established a set of clinical guidelines based on clinical manifestations that help in the determination of eligibility for treatment and management of HIV patients. These clinical manifestations present themselves mainly as opportunistic

infections plus other HIV defining illnesses. As discussed in Section 2.3.2.1, the WHO has divided the stages into four, with each stage having specified clinical conditions and or symptoms used in assessing HIV disease progression (National Drug & Therapeutics Policy Advisory Committee (NDTPAC & AIDS and TB Unit MOHCW 2010:62). These guidelines have been widely utilised in many resource poor settings owing to lack of adequate trained medical personnel and laboratory infrastructure including equipment and reagents.

Table 4.4: WHO HIV clinical staging at ART initiation (n=118)

Stage	Frequency	Percent
Stage I	14	11.9
Stage II	23	19.5
Stage III	58	49.1
Stage IV	16	13.6
Not stated	7	5.9
Total	118	100.0

Table 4.4 shows the WHO clinical stages that the study participants were in at ART initiation. The majority of the patients 58 (49.2%) in this study were classified as stage III followed by 23 (19.5%) in stage II, 16 (13.6%) in stage IV, (n=16), 14 (11.9%) in stage I and the clinical stage for 7 (5.9%) participants was not recorded.

4.3.2.4 ART regimen initiated

Data from this study showed that all patients were initiated on ARVs for the period 1st October to 31st December 2009 and were followed-up for 12 months (December 2010). As indicated in chapter 2, the National ART guidelines recommend a combination of two NRTIs and one NNRTI as first-line drug regimens. Table 4.5 shows the ARV drugs grouped according to the drug class they belong to include PIs which are recommended for inclusion for patients indicated for second line treatment.

Table 4.5: ARV drug classifications

Drug Class	Acronym	Generic Name
NRTI	3TC	lamivudine
	AZT	Zidovudine
	D4T	Stavudine
	TDF	Tenofovir
NNRTI	NVP	Nevirapine
	EFV	Efavirenz
PI	LPV/r	Lopinavir/ritonavir
	RTV	Ritonavir

As shown in Figure 4.5 the data revealed that all 118 patients were initiated on ART according the National ART guidelines. On initiation 63% (n=74) of the patients were on D4T + 3TC + NVP, 19% (22) were on AZT +3TC + NVP, 12% (n=14) D4T + 3TC + EFV, 2% (n=3) were on TDF+3TC + EFV, 2% (n=3) were on AZT +3TC + EFV and 2% (n=2) were on TDF+3TC + NVP.

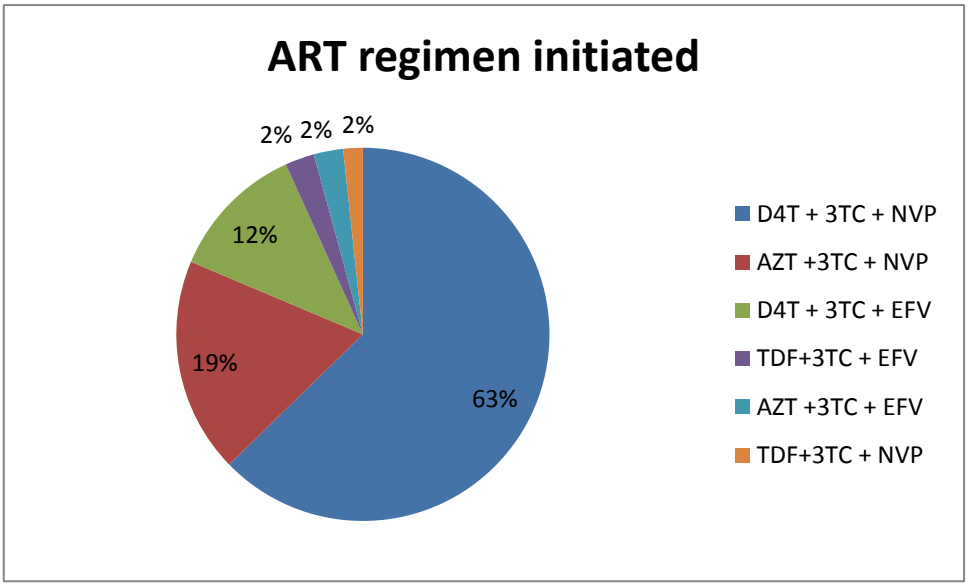


Figure 4.5: ART regimen initiated

4.3.2.5 ART regime "switch"

High adherence to ART is important in assuring good health outcomes and prevents drug failure. Patients may among other reasons fail to adhere to their treatment regimens because of factors related to the treatment itself. An ART patient may not adhere to treatment due to toxicities and or side effects of the treatment regimen. As discussed earlier, not adhering to ART can provide an environment for viral mutations

giving rise to ARV drug resistant HIV. When drug resistant mutations occur and or are transmitted, first line ARV drugs which are less costly and easier to administer are rendered ineffective. Patients are required to be switched to second line drugs that are more costly, harder to administer and often associated with more side effects (NDTPAC & AIDS and TB Unit MOHCW 2010:10, 13) Switching from first line to second line ARVs can therefore give an indication that a patient has developed resistance to ARVs and or that the patient is not adhering to treatment. ART regime switch is also indicated where drug interactions due to co-morbidities exist for example TB and pregnancy (NDTPAC & AIDS and TB Unit MOHCW 2010:27, 31-32), failure to control viral replication and side effects or toxicity. In resource poor settings, failure to maintain patients on first line regimens is a serious public health problem where issues of access and supply are also a challenge, further highlighting the importance of ART adherence. In these settings it is especially important for patients to remain on first line treatment as long as possible, to ensure sustainability of ART programs (NDTPAC & AIDS and TB Unit MOHCW 2010:5, 7, 21).

Table 4.6: Type and frequency of regimen "switch"

	Regimen Switched To n(%)								
	D4T+3TC+NVP	D4T+3TC+NVP	AZT+3TC+PLV	TDF+3TC+EFV	AZT+3TC+NVP	TDF+3TC+NVP	No switch	TOTAL	p value
Original Regimen									0.009
D4T+3TC+NVP	0	8(10.81)	1 (1.35)	1 (1.35)	3 (4.05)	0	61 (82.43)	74 (100)	
D4T+3TC+EFV	0	0	0	1 (7.14)	1 (7.14)	0	12 (85.71)	14 (100)	
TDF+3TC+EFV	0	0	0	0	0	0	3 (100)	3 (100)	
AZT+3TC+NVP	0	1 (4.55)	0	0	0	1 (4.55)	20 (90.91)	22 (100)	
AZT+3TC+EFV	1 (33.33)	0	0	0	0	0	2 (66.67)	3 (100)	
TDF+3TC+NVP	0	0	0	0	0	0	2 (100)	2 (100)	
TOTAL	**1 (0.85)**	**9 (7.63)**	**1 (0.85)**	**2 (1.69)**	**4 (3.39)**	**1 (0.85)**	**100 (84.75)**	**118 (100)**	

Data from this study is encouraging in that it shows that during the follow-up period 84.8% (n=100) remained on their original regimens and did not switch within the first-line regimens (Table 4.6). This is a statistically significant finding (p=0.009), suggesting that for the majority of the patients ARV drug resistance was being prevented and or that patients were adhering to their treatment. Most of the regimen changes that occurred 15.2% (n=18) were within first line drugs and mostly a change in the NNTRI drug (refer to Table 4.8, ARV drug classifications). This is in-line with the guidelines for antiretroviral therapy in Zimbabwe which recommends substitution of suspected drug causing toxicity and or adverse events with an alternative same class drug within first

line regimen and only resort to second line drugs where treatment failure has been indicated (NDTPAC & AIDS and TB Unit MOHCW 2010:24-25).

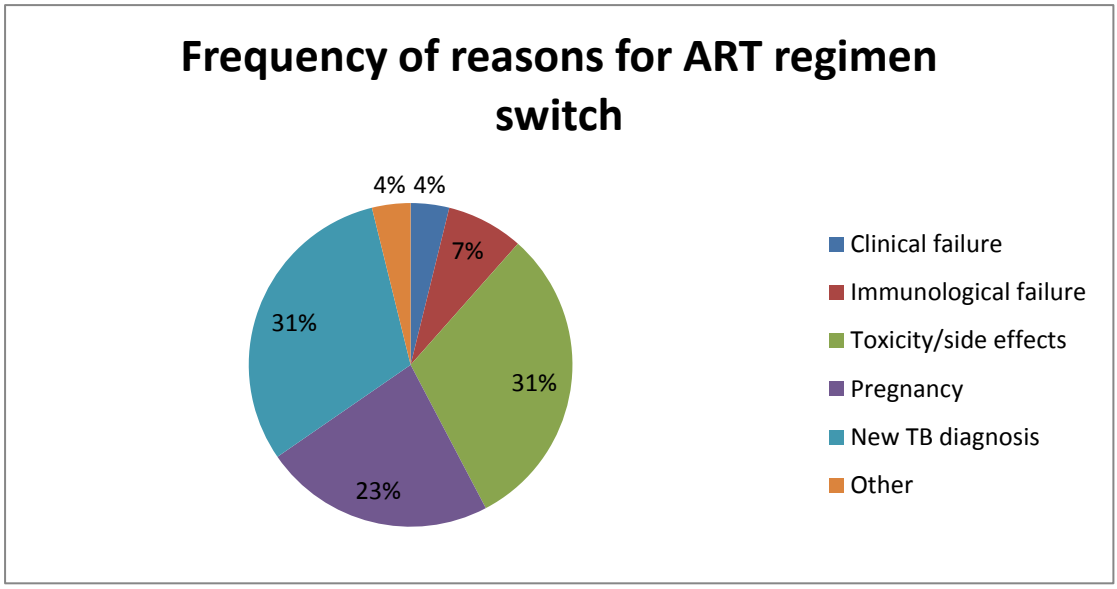


Figure 4.6: Frequency of reasons for ART regimen switch among 18 participants

As indicated in figure 4.6, the main causes for the switches that occurred were either a new TB diagnosis (31%) or toxicity/side effects (31%) followed by pregnancy (23%). Immunological failure was indicated 7%, as reason for switch, 4% for clinical failure and another 4% indicated other and or were not recorded. Only 1 patient (0.8%) switched from first-line regimen to second-line. Records of the only true switch in this study indicate that the patient also had TB and reasons indicated for the switch were that the patient was failing clinically and immunologically.

The time it took from ART initiation to “switching” ART regimen varied among the study participants, figure 4.7 and was calculated by subtracting the date the participant was initiated on ART from the date the participant had ART regimen changed. The mean time it took for participants in this study to “switch” their ART regimen was 215 days (slightly over 7 months) with a range of 13 to 433 days.

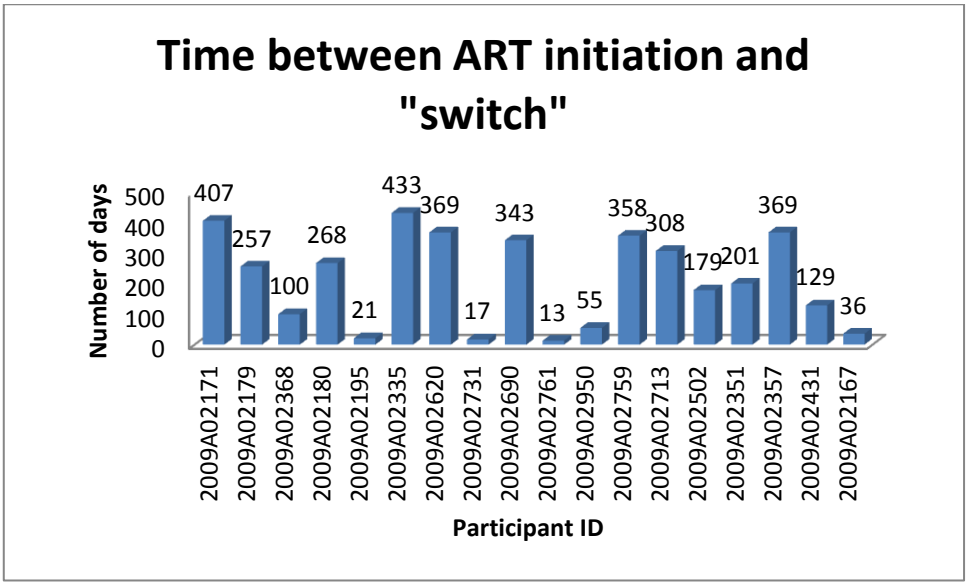


Figure 4.7: Time between ART initiation and "switch"

4.3.2.6 Subsequent follow-up dates of pharmacy refills

The national ART treatment guidelines recommend that patients initiated on ART are prescribed an ARV regimen starter pack and seen every weeks for the first month (i.e. 2 weeks + 2 weeks) to facilitate the close monitoring of ART adverse events (NDTPAC & AIDS and TB Unit MOHCW 2010:22-23, 45). Once cleared of adverse events and or side effects, the treatment guidelines recommend that patients are reviewed monthly for the first three months and three monthly thereafter.

For this study, the actual date of prescription re-fill and date of next appointment were recorded. Figure 4.8 shows a date profile of the first two pharmacy refills which shows that the majority of the participants were prescribed ART according to the treatment guidelines as described above. Of the participants, 71% collected both their first 2 weeks and second two weeks (1 month) within 14 days respectively. The data also shows that another 16% although collection was on time (within 1 month), the number of days varied from 15 days to 28 days. A total of 13% collected their prescription refills outside the acceptable range of days, with 2% of these participants having failed to collect their first month re-fills by more than 70 days.

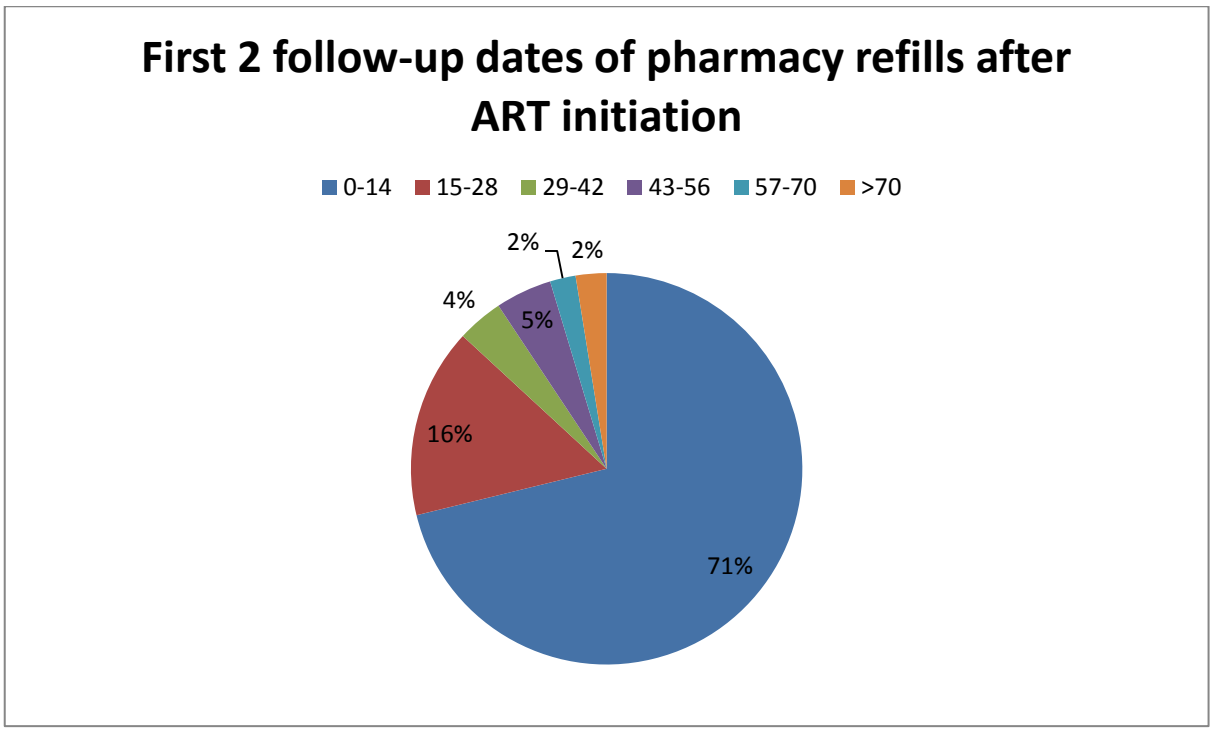


Figure 4.8: First 2 follow-up dates of pharmacy refills after ART initiation

4.3.2.7 Pharmacy refills adherence data

As discussed in chapter 2, section 4.3.2.7 pharmacy refill data has the potential of being used in real time to manage and monitor HIV positive patients' behaviour around taking ART to monitor adherence. Due to the high rate of HIV replication, high adherence levels of >95% are required for effective and sustained virologic suppression of the virus. Non-adherence to ARVs for HIV has major public health implications because of the emergence of drug-resistant viruses that can be transmitted to others and in the process diminishes future treatment options at population level. Adherence to ART treatment programs recommend that adherence should be assessed on a regular basis in order to ascertain the level of adherence interventions needed for maintenance and or improvement of adherence levels. Pharmacy refill data was used to ascertain adherence levels for patients initiated on ART between 1 October 2009 and 31 December 2009 and followed up for at least 12 months.

In this study, adherence level was based on the actual date of prescription re-fill thus subtracting the actual day of prescription re-fill from the date of next appointment. The researcher believes this approach takes into account dynamic individual patient circumstances involved in the management of the HIV disease. A seven day grace

period was applied across for all participants not collecting their prescriptions on the exact date of the next appointment. If a patient however collected their prescription earlier than the date of the next appointment, these were considered adherent and or on-time collections.

Data on pharmacy refills in this study showed that 62.7% (n=74) of the 118 patients managed to adhere (>95% adherence level) to their ARV regimens. A total of 44 patients (37.3%) had adherence levels of <95% fiigure 4.9).

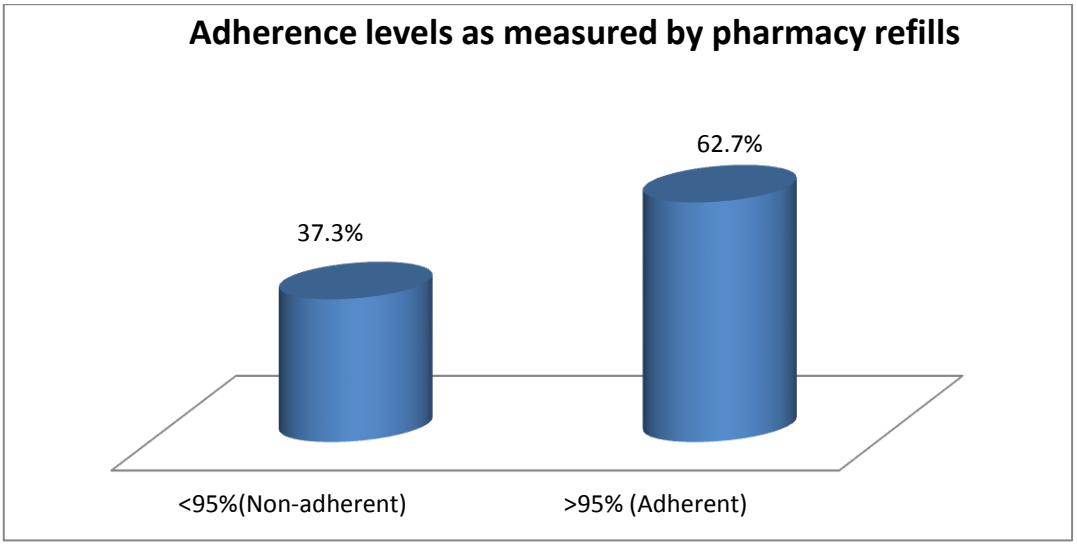


Figure 4.9: Adherence levels as measured by pharmacy refill

4.3.2.8 CD4 cell count

One of the guidelines for ART initiation is a baseline CD4 count done on or before ART initiation to establish how advanced the HIV disease is in a patient. According to the national ART treatment guidelines and as already discussed in chapter 2, ART initiation is indicated for patients in (1) WHO stage III or IV disease irrespective of CD4 cell count for pregnant women, (2) HIV positive patients with CD4 cell count ≤350 cells/mm3 regardless of WHO staging or 3) HIV positive with active tuberculosis (TB) irrespective of CD4 count for pregnant women (NDTPAC & AIDS and TB Unit MOHCW 2010:14-15, 30). The national ART treatment program, therefore utilises the CD4 cell count to inform eligibility for ART initiation and subsequently for patient management. The Immune system's response to ART is monitored by measuring CD4 cell count six monthly and is expected to rise adequately to support normal immune function (NDTPAC & AIDS and TB Unit MOHCW 2010:50, 52). Good immunological response is

expected when an HIV positive patient is adhering to treatment ≥95% of the time and this is indicated by a rise in the CD4 cell count (Paterson et al 2000:25).

Equally important and as already discussed, patients are also initiated on ART based on their WHO HIV/AIDS clinical staging. During this study period, patients at Mpilo OI/ART clinic were initiated on ART according to the national guidelines that of CD4 cell count below 200 cells/mm^3 or WHO HIV/AIDS clinical stages I, II and clinical stages III and IV irrespective of the CD4 cell count. The inclusion criteria for this study required a participant to have a baseline CD4 cell count done on or before ART initiation, hence patients initiated on ART based only on WHO clinical stage were excluded.

Data on CD4 cell counts at or before ART initiation and WHO HIV/AIDS clinical staging showed a corresponding CD4 cell count decrease from primary HIV infection/disease to advanced HIV disease. The median CD4 cell count decreased consistently with the advancing stages of HIV infection with Stage I 208, Stage II 154, Stage III 149 and Stage IV 46 (figures 4.10 and 4.11).

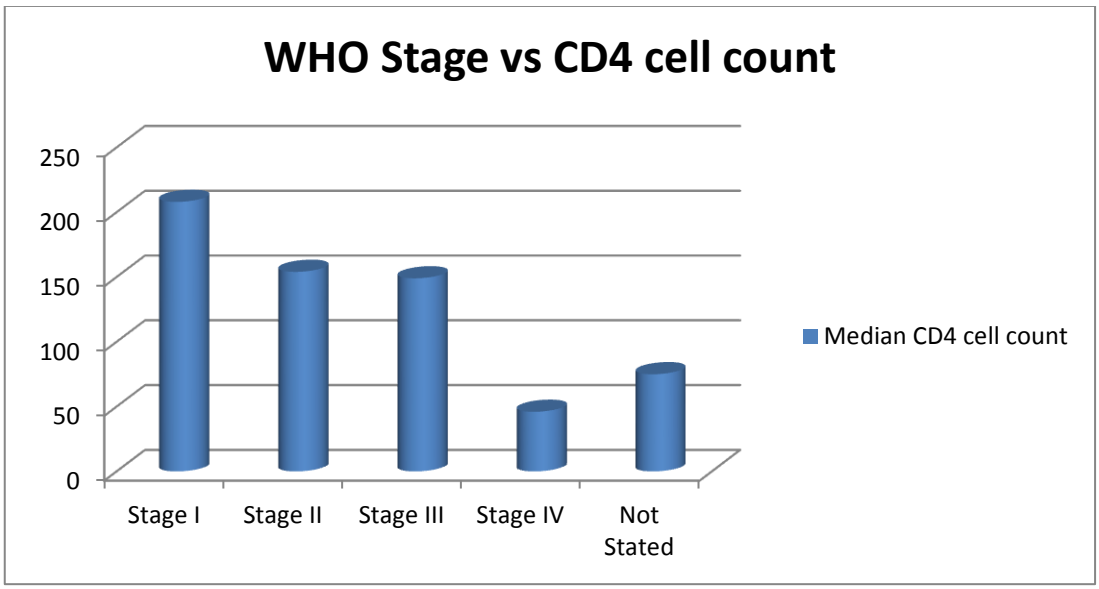
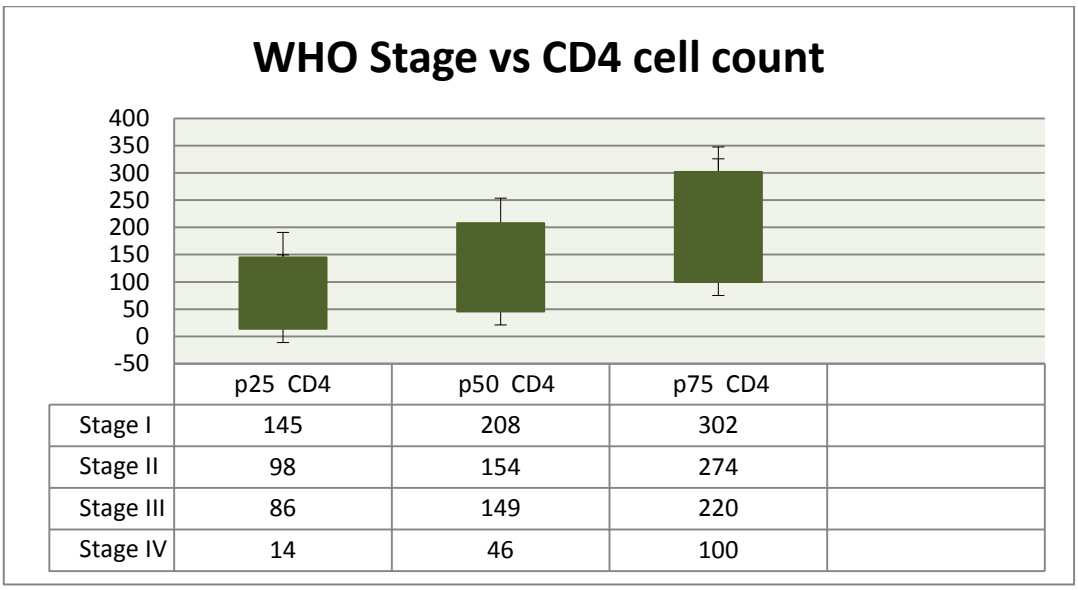


Figure 4.10: Progressively lower CD4 cell count with advancing HIV infection



	p25 CD4	p50 CD4	p75 CD4	
Stage I	145	208	302	
Stage II	98	154	274	
Stage III	86	149	220	
Stage IV	14	46	100	

Figure 4.11: CD4 cell count interquartile ranges by WHO clinical stage

CD4 cell count in healthy persons range between 500-1500 cells/mm^3 as already discussed and generally the more advanced the HIV disease is, the lesser the CD4 cell count. CD4 cell count in many resource poor settings is also used to monitor treatment response with some researchers cautioning on its sole usage for this purpose (Charles et al 2012:5) citing retrospective identification of virological failure (Bisson et al 2008:0786) and lack of specificity which could risk delaying treatment switch especially for those patients failing on first-line regimes (Charles et al 2012:5, Bisson et al 2008:0786). Despite this and as already mentioned, CD4 cell count still plays a major role in treatment monitoring in many resource poor countries.

Table 4.7: Baseline CD4 cell count at or before ART initiation

Characteristics	Category	Total	%
Baseline CD4 count (cells/mm3)	<100	42	35.6
	<200	36	30.5
	<350	35	29.7
	≥350	5	4.2
Total		**118**	**100.0**

Data for this study show that 78 (66.1%) of the participants had less than 200 cells/mm^3 when they were initiated on ART (Table 4.7). Overall 95.8% of the participants were initiated with a CD4 cell count less than 350 cells/mm^3. The mean baseline CD4 cell count for the participants in this study was 157.5 cells/mm^3. For all patients, the lowest baseline CD4 cell count was 2 cells/mm^3 and the highest 667 cells/mm^3.

4.3.2.8.1 CD4 cell count during the follow-up period

It is important to stress that National treatment and monitoring recommendations both previous and current, strongly recommend viral load testing but in the absence of virologic monitoring, persistent CD4 cell count below 100 cells/mm^3 or a decrease in CD4 cell count below pre-therapy or a 50% CD4 cell count decrease is often used to identify immunologically failing patients (Charles, Leger, Sever, Guiteau, Apollon, Gulick, Johnson, Pape & Fitzgerald 2012:1; NDTPAC & AIDS and TB Unit MOHCW 2010:54). In this study and as already described, a successful CD4 cell gain or immunological recovery was defined by a CD4 cell count gain of 50% or greater after ART initiation.

Follow-up CD4 cell count after of ART initiation for this study showed that the lowest count was 14 cells/mm^3 and highest 755 cells/mm^3, with a mean CD4 cell count of 368.1 cells/mm^3. Results of this study also showed that 97 (82.2%) of the study participants had successful 50% or greater CD4 cell count gain compared to 21 (17.8%) who failed to gain CD4 cell count by 50% or greater. Figure 4.12 shows CD4 cell count at or before ART initiation and the follow-up CD4 cell count. Analysis showed that there was a positive and statistically significant correlation between CD4 cell count at or before ART initiation and CD4 cell count during the follow-up period (r=0.46, p=<0.001).

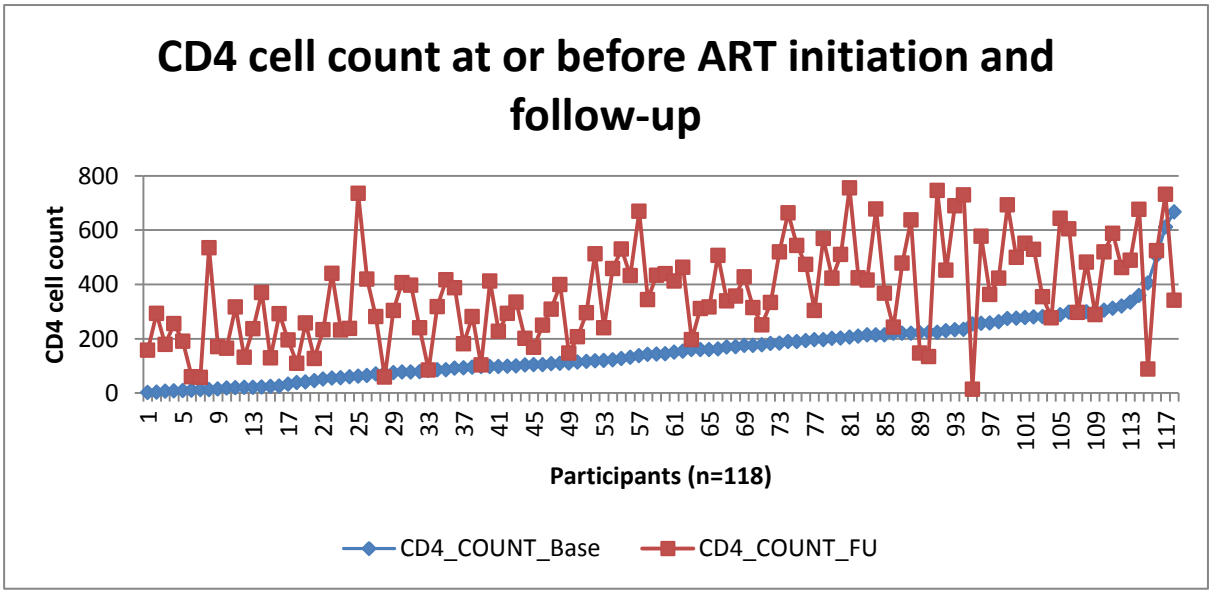


Figure 4.12: CD4 cell count at or before ART initiation and follow-up

4.3.3 Discussion of results

4.3.3.1 The level of adherence to ART when measured by pharmacy refills compared to CD4 cell count

Data on pharmacy refills in this study showed that 62.7% (n=74) of the 118 participants managed to adhere (>95% adherence level) to their ART regimens. A total of 44 participants (37.3%) were non-adherent when measured by pharmacy refills, with adherence levels of <95%. Looking at CD4 cell count, 97 (82.2%) of the study participants had successful 50% or greater CD4 cell count gain suggesting that they were adherent to their ART regimens. Of the participants, 21 (17.8%) failed to gain CD4 cell count by 50% or greater suggesting that they were not adhering to their ART regimens.

In the follow-up period after ART initiation, data for this study showed that 15.1% (n=11) participants who were adherent by pharmacy refills did not have successful 50% CD4 cell count gain after 1 year of ART (Table 4.8). A total of 10 (22.7%) participants were not adherent by pharmacy refills and did not have successful CD4 cell gain of 50%. A total of 63 (84.9%) participants who were adherent also had a successful CD4 cell recovery or gain of 50% after ART initiation. The data also showed that 34 (35.4%) were non-adherent by pharmacy refills but had successful CD4 cell count gain of 50% or higher. Overall the data showed that there was no statistical significance (p=0.296) between adherence status when measured by pharmacy refill and CD4 cell count.

Table 4.8: Pharmacy refill adherence vs 50% CD4 cell count gain

		Adherence		
		NO	**YES**	**Total (%)**
50% CD4 cell count gain	**NO**	10 (22.7%)	11 (15.1%)	21 (17.95)
	YES	34 (77.3%)	63 (84.9%)	97 (82.05)
	Total (%)	44 (37.6%)	74 (62.4%)	118 (100)

4.3.3.2 The relationship between adherence to ART when measured by pharmacy refills and CD4 cell count

Several studies have reported better outcomes for HIV/AIDS patients achieving good adherence levels to their ARVs in terms of better immunological response/recovery (increase in CD4 cell count) (Mocroft et al 2007:411; Paterson et al 2000:27), good virological response indicated by lower viral load (Paterson et al 2000:27 Nachega et al 2007:566, Bisson et al 2008;0786), marginally lower morbidity and mortality rates (Paterson et al 2000:27-28, Nachega et al 2006:82, Wood et al 2004:261) and reduced risk of developing HIV drug resistance (Nachega et al 2007:570, Wood et al 2004:261). As already discussed, the cohort for this study was initiated on ART based on a CD4 cell count below 200 cells/mm^3 and WHO HIV/AIDS clinical staging as stipulated in the national treatment strategy and guidelines.

Results for this study using logistic regression analysis in a univariate model although not statistically significant, showed that participants who were adherent by pharmacy refills were 1.66 times more likely to gain 50% CD4 cells within the first year of ART initiation (OR=1.66, p=0.299) compared to those who were not adherent.

Table 4.9: Multivariate analyses of 50% CD4 cell gain in patients on ART

50% CD4 gain	Odds Ratio	95%CI	p-value
Adherence	2.04	(0.70-5.90)	0.189
Sex	3.26	(0.77-13.7)	0.108
Age	0.94	(0.89-0.10)	0.048
WHO Stage II	3.12	(0.51-19.2)	0.218
WHO Stage III	2.11	(0.50-8.85)	0.309
WHO Stage IV	10.07	(0.80-126.2)	0.073

In multivariate analyses, covariates of adherence, sex, age and WHO clinical stage II, III and IV were included (Table 4.9). Participants who were pharmacy refill adherent were 2.04 times more likely to gain 50% CD4 cells within the first year of ART (OR=2.04, p=0.19) compared to non-adherent participants although this was not statistically significant. The odds of gaining 50% CD4 cells were 3.1 times higher for the female participants (OR=3.26, p=0.11) when compared to their male counterparts. This

however was not statistically significant. Looking at age the odds of gaining 50% CD4 cells goes down by 0.06 with increase in age (OR=0.94, p=0.048). In the model, as the WHO clinical stage increases, the odds of 50% CD4 cell gain increased with those participants in WHO clinical stage IV at ART initiation being10.1 times more likely to gain 50% CD4 cells within the first year of ART than those in stage I (OR=10.07, p=0.073).

As presented earlier, mean CD4 cell count according to WHO clinical stage I, II, III and IV were 218.3, 164.3, 159.8 and 89.7 respectively, clearly pointing to more immunocompromised patients being in stage IV. According to Mocroft et al (2007:410), patients initiating ART with relatively lower CD4 cell count, are more likely to show a greater CD4 cell count gain compared to those initiated with higher CD4 cell counts. The rate increase or gain of CD4 cell within the first year of ART initiation is also associated with previous virological failure (Bisson 2008:0780, Trotta, Cozzi-Lepri, Ammassari, Vecchiet, Cassola, Caramello, Vullo, Soscia, Chiodera, Ladisa, Abeli, Cauda, Buonuomi, Antinori Monforte 2010:462).

Data from an Italian study indicated that CD4 cell gain is compromised if the patient has a history of virologic failure compared to those who had no history of virologic failure (Trotta et al 2010:462). In earlier studies Wood et al (2004:266) showed that baseline CD4 cell count do not influence how quickly CD4 cell counts respond following ART initiation but adherence does. Further, in the same study adherence was the strongest predictor of good immune recovery and sustained CD4 cell count gain (Wood et al 2004:263-266).

A cross-sectional study in Nigeria, Tanzania, Uganda and Zambia among 2344, found a direct association between patients with CD4 cell count less than 200 cells/mm^3 and non-adherence (Memiah et al 2013:5). In that study patients were reported to having high depression levels which may have led patients to self-neglect, hopelessness and forgetfulness, cascading to non-adherence leading to low CD4 cell count and potentially early mortality (Memiah et al 2013:4-5). Studies have also shown that substantial and rapid increase in CD4 cell count happens in the first few months after ART initiation followed by a gradual but slower rate of increase after a year and subsequent years (Smith et al 2003:966-967, Smith et al 2004:1862-1863, Mocroft, Phillips, Gatell, Ledergerber, Fisher, Clumeck, Losso, Lazzarin, Fatkenheuer, Lundgren 2007:410). In

one study, 237 patients were followed prospectively and the authors showed an overall median 197 cells/mm^3 CD4 cell increase in the first year and a median 97.2 cells/mm^3 CD4 cell increase in the first month of HAART initiation. This was followed by a significant slowing down in the rate of CD4 cell increase in the following months to 1 year with similar trends observed for year 2 (median CD4 cell increase of 92 cells/mm^3) and an even slower rate of increase (CD4 cell median 50 cells/mm^3) to year 3 (Smith et al 2003:967). The key element to the observed continual and sustained immunological recovery in these studies was the ability of the patients to adhere to HAART and thus effectively supress viral replication.

4.4 CONCLUSION

ART adherence levels assessed by pharmacy refill data, a non-immunological ART adherence parameter at Mpilo Hospital OI/ART clinic together with CD4 cell count, an immunological adherence measurement parameter have been presented in this chapter. Socio-demographic data of the study participants is presented. Pharmacy refill adherence levels have been analysed against CD4 cell counts. Linkage of study findings to results of other published studies has been presented.

The next chapter presents a summary of the study, highlights some limitations of this study and makes recommendations for future research.

CHAPTER 5

SUMMARY FINDINGS, CONCLUSIONS AND RECOMMENDATIONS

5.1 INTRODUCTION

The summary of the study findings is presented in this chapter. This chapter also discusses the study limitations, makes some recommendations and suggests possible further research.

5.2 RESEARCH DESIGN AND METHOD

The aim of the study was to determine the level of adherence to ART when using pharmacy refills and the extent of the relationship between ART adherence when measured by pharmacy refills and immunological parameters of CD4 count and HIV-1 RNA levels (viral load) among HIV positive patients at Mpilo Central Hospital, Zimbabwe. The objectives of the study were to describe the level of adherence to ART when measured by pharmacy refills compared to CD4 cell count and viral load and the relationship between adherence to ART when measured by pharmacy refills and CD4 cell count and viral load.

A non-experimental, quantitative, retrospective, descriptive and correlational design was followed to achieve the study objectives using a probability sampling to select HIV positive adult patients initiated on ART between 1 October 2009 and 31 December 2009 and followed up for 12 months at Mpilo Central Hospital. The rationale was to choose the latest recruits who were likely to present the current trends rather than older patients. The cohort date range chosen by the researcher took into consideration a period during which the Zimbabwean economic landscape had “normalised” after a serious economic downturn in the preceding three to four years. The other factor also considered was finding a patient cohort that had completed a year on ART and were likely to have all their records complete by the time of conducting the study. The researcher readily had access to all records (n=118) of patients who met the inclusion criteria. The sample size of 118 was found to be manageable and adequate for

quantitative data analysis. As a result no sampling procedures were applied for this study. Stata SE release 10 (STATA Corp, 2007) was used to analyse data.

5.3 SUMMARY AND INTERPRETATION OF RESEARCH FINDINGS

A total of 118 patients were included in the study, 67.8% of which were male and 32.2% female. The study participants' ages ranged from 18 to 71 years, with a mean age of 36.9. At ART initiation, the majority of participants (59.3%) were married, 16.1% were single, 13.6% were widowed, 1.7% was divorced, 7.6% were separated and 1.7% did not have marital status recorded. Close to two thirds 69.5% of the study participants were unemployed, 7.63% were self-employed, 19.5% were formally employed 1 participant was a student, 1 participant was employed in the private sector and 3 participants did not have employment status recorded. Most of the participants (44%) in this study lived in rented accommodation or lived with a relative, 39.9% owned the residence they had at ART initiation and 16.1% participants did not have their type of residence recorded.

The duration that participants in this study had learnt of their HIV status ranged from 5 day to 5.7 years with a mean period of 6 months. Most participants were initiated on ART within a year of knowing their status, 10% more than a year after knowing their status and 1 participant was initiated on ART close to 6 years after being tested HIV positive. Duration of having known the HIV status could not the established for 22% of the participants because the date of HIV testing was not recorded.

The main entry point or referral source for ART initiation in this study was due to illness or having being hospitalised (42.4%). ANC referred 23.7% of the participant for ART initiation, VCT 11.9% and TB illness 5.1%. Entry for ART treatment because either spouse/partner or child had tested HIV positive accounted for 8.5% and 6.8% of the participants respectively. A very high proportion of the participants (81.4%) had a treatment supporter mostly close members of the family of spouses, siblings or parents. Only 1.7% of the participants were recorded as not having a treatment supporter and 16.9% participants did not have treatment supporter data recorded.

The Majority of the patients were referred for ART initiation after hospitalisation or illness (42.4%) compared to 11.9% for VCT as an ART entry point. A large proportion

(69.5%) of the study population was unemployed, and (81.4%) of the patients had a treatment supporter and or had disclosed their HIV status. Equally high was the proportion of patients having a spouse as a treatment supporter (39.8%).

With regard to the clinical data, the majority of the participants initiated on ART in this study were classified as stage III according to the WHO clinical staging guidelines for HIV/AIDS for adults and adolescents. The study results showed that there were more non-adherent participants (52.2%) in stage II, although in totality no correlation between WHO HIV/AIDS stage and adherence was seen. Participants in this study were initiated on ART according to national ART guidelines of two NRTIs and one NNRTI as first-line regimens. Majority of the participants (84.8%) remained on their original regimens with most regimen changes (15.2%) occurring within first-line drugs. One true second-line switch was recorded for this study.

- **The level of adherence to ART when measured by pharmacy refills compared to CD4 cell count and viral load**

The study results showed that the level of adherence among ART initiated patients at Mpilo Central Hospital was 62.7% (>95%) compared to 37.3% non-adherent participants (<95%) when measured by pharmacy refills. Adherence to ART based on 50% or greater CD4 cell gain showed that 82.2% of the participants were adherent compared to 17.8% who failed to gain CD4 cells by 50% or greater.

- **The relationship between adherence to ART when measured by pharmacy refills and CD4 cell count and viral load**

Data on CD4 cell count showed that there was a positive relationship between baseline/CD4 cell count at ART initiation and the follow-up CD4 cell count. There was however no significant difference in baseline CD4 cell count between adherent and non-adherent patients. A corresponding decrease in CD4 cell count from primary to advanced HIV disease was observed in this study. Multivariate analysis showed that patients who were adherent (pharmacy re-fill data) were 2.04 times more likely to gain 50% CD4 cell count within the first year of ART (p=0.19) compared to non-adherent patients. More immunocopromised patients (WHO clinical stage IV) at ART initiation were more likely to gain 50% CD4 cells within the first year of ART (p=0.073) compared

to more healthier patients. This finding would also seem to suggest that for those patients with relatively higher CD4 cell count at ART initiation, applying this criterion to assess adherence would be inappropriate because chances of gaining 50% CD4 cell count coming from a higher threshold would be highly unlikely. As a result there is high potential for these patients to be misclassified as non-adherent.

5.4 CONCLUSION

The conclusion drawn from the findings was that, using a 50% CD4 cell count gain in the 1 year follow-up period from ART initiation showed that 84.9% of the patients who had a successful CD4 cell gain of 50% were also adherent based on pharmacy refill data.

5.5 CONTRIBUTIONS OF THE STUDY

According to the findings of the study, there was a positive, albeit weak relationship between adherence measured by pharmacy refills and CD4 cell counts; suggesting that pharmacy refills can be used routinely to measure adherence in settings where CD4 cell count and viral load assays are not available. Pharmacy refills may also be used as a screening tool for patients suspected of treatment failure to be referred for virological testing thus reduce the number of viral load tests done and inevitably the cost of providing this service.

The low adherence levels data ascertained by this study highlight the need for more education on the importance of ART adherence and more accessible ART adherence monitoring tools and systems. The information gained may help strengthen messages on prevention and or risk reduction for emergence of drug resistant HIV.

5.6 RECOMMENDATIONS

The recommendations emanating from the study are based on practice (to increase ART adherence rates) and research as it pertains to ART adherence.

5.6.1 Recommendations to increase adherence rates

In order to increase and better monitor adherence at Mpilo Central Hospital OI/ART Clinic, the researcher makes the following recommendations:

- **Deploy a computerised patient data management system**

Extracting data from the different clinic registers to come up with an ART historical picture of patients at Mpilo Central Hospital OI/ART clinic was difficult and very time consuming. Although most of the data was available, comprehensively aggregating it for efficient and real time patient adherence management would almost be impossible. Hence a single computerised data management system should be installed for effective and efficient management of patients. As discussed in section 3.6.3.2, an electronic data capturing system supported by MSF Spain was successfully implemented at this OI/ART clinic before its departure in December 2010, giving evidence that deployment of a computerised patient data management system at Mpilo Central Hospital OI/ART clinic is feasible.

Records reviewed for the cohort period of this study showed that different patient identification number systems were in use and some patient data including viral load results were being captured into an information system not easily accessible to the health care provider to use in patient management. A computerised patient tracking system that has a robust patient identification system should be deployed, possibly with different modules depending on the type of care the patient is seeking at the clinic. For example, a module that seeks to monitor adherence should be able to capture pharmacy refill dates, ARV regimen dispensed, duration of dosage such that when a patient identification number is entered into the system, all relevant information related to the patient's behaviour and or history with regards to taking medication should be displayed. Flagging systems prompting the health care worker should be incorporated into the system so that if for example a patient is not adequately adhering, the health worker is prompted to refer the patient for more focussed adherence counselling before another refill can be dispensed. Equally important would be modules capturing adherence counselling that would document if there are any psychosocial issues that may have changed and can either adversely or positively affect adherence. Further, a clinical module capturing data of the variables already included in the ART registers that

include side effects, opportunistic infections and other medical manifestations would be essential. This real-time data entry capacity would be helpful in preventing multiple and at times redundant data capturing into different registers and or other electronic systems delinked to patient management. Such a system would not only aid in increasing adherence rates but would in general improve the whole ART patient management by freeing up more time for the health worker to spend with the patient, increase health care worker appreciation and use of electronic data to better improve service provision, reduce burden of patient file retrieval and re-filing, reduce health worker burnout and equally important allow the patient to spend less time at the clinic (Jamal, McKenzie & Clark 2009:26,34; Thomspson, Hudson, Wick & Ballestas 2009:109-111).

- **Establish and implement a clear method of monitoring adherence**

Adherence level established using both pharmacy refill data and CD4 cell count is low at Mpilo OI/ART clinic. Whilst CD4 count continues to be used, this parameter as suggested by others may be measuring adherence in retrospect (Bisson et al 2008:0786). If a computerised ART patient management system is in place, pharmacy refill data would be an objective, readily available, real-time and cost effective way of proactively monitoring adherence.

5.7 RECOMMENDATIONS FOR FURTHER STUDY

Adherence to ART is a dynamic phenomenon which requires on-going research. The researcher proposes further research as follows:

- A prospective research design with more than 12 months follow-up period needs to be carried out at Mpilo Central hospital or other public health institutions in Zimbabwe, to examine and monitor adherence and associated risk factors over time. Further, with this research approach, morbidity, mortality and retention in care as they relate to adherence can be better understood.
- MoHCC of Zimbabwe now has a viral load testing algorithm in place for monitoring patients on ART. Viral load testing is currently being conducted at one central laboratory in the capital of Zimbabwe Harare, with possible decentralisation to a few provincial laboratories in the near future. Samples

needing testing even with the decentralisation will require transportation and other logistical support, ultimately compromising on turn-around-time. A cost effectiveness evaluation of the viral load testing algorithm in adherence monitoring compared to pharmacy refill data should be done. Further, validation research of other non-immunological ART adherence measuring tools with viral load is needed.

- Data on adherence in older HIV positive patients on ART in resource poor settings is sparse in literature. In this study multivariate analyses seemed to suggest diminished ability to gain 50% CD4 with older aged patients although this was not statistically significant. This population would be of interest to study because in resource poor settings, this population is also caring for HIV and AIDS orphans. So understanding their behaviour with regards to ARV treatment and adherence is important not only for their own health but also because in many cases they are also treatment supporters to orphaned children and other family members. Research examining factors associated with ART adherence such as social disclosure, social support, depression and co-morbidities should be conducted.

5.8 LIMITATIONS OF THE STUDY

Limitations to this study include the following:

- A small sample was used for this study and was limited to patients initiated on ART at Mpilo Central Hospital and thus may not be representative of all patients on ART in Zimbabwe.
- This was a retrospective study and therefore not all eligible patients were included neither can causal inferences be made.
- Viral load (HIV-RNA) is strongly recommended for monitoring patients on ART mainly for virological failure which would also indicate possible failure to adhere to treatment. This parameter was part of the study aims and as already discussed this objective could not be adequately fulfilled.
- Treatment strategies including pharmacy refill periods for patients were based on individual patient circumstances. Some patients were given more than a month's supply of drugs, thus assumptions are that for the 3 or 4 months prescription the patient was adherent and thus might overestimate the overall adherence rate.

- Patient records were not included in the analysis due to incomplete data. Majority of these were due to patients with no baseline CD4 cell count. This was mainly due to the fact that patients may have been initiated on ARVs based on their WHO staging. As reported in this study, majority of the patients initiated on ART were in WHO stage IV of the HIV disease. It is very possible that many patients were well advanced in their HIV disease that baseline CD4 cell count was not a critical requirement for deciding treatment and care of the patients.
- The patient cohort for this study was recruited from an MSF supported site where HIV and AIDS dedicated physicians oversaw the OI/ART programme. Additionally, because of the extra funding that MSF provided for the running of the OI/ART program, patients seen in this health facility might have experienced less drug stock outs, had access to better health services and it is possible that they would have had higher adherence levels when compared to patients seeking the same services in similar government or public health facilities.

5.9 CONCLUDING REMARKS

This chapter presented a summary of the research findings, the conclusions reached on the basis of the findings, recommendations as well as the limitations of the study.

LIST OF REFERENCES

Alimonti, JB, Ball, TB & Fowke, KR. 2003. Mechanisms of $CD4^+$ T lymphocyte cell death in human immunodeficiency virus infection and AIDS. *Journal of General Virology* 84:1649-1661.

AVERT. 2011. *Averting HIV and AIDS. HIV and AIDS in Zimbabwe.* http://www.avert.org/aids-zimbabwe.htm#refs (accessed 2 March 2011).

AVERT. 2012. *Averting HIV and AIDS. HIV and AIDS treatment & care*. http://www.avert.org/treatment.htm (accessed 05 August 2012).

Badri, M, Lawn S, & Wood, R. 2008. Utility of CD4 cell counts for early virological failure during antiretroviral therapy in a resource-limited setting. *BioMed Central Infectious Diseases* 8:1-8.

Bangsberg, DR. 2008. Preventing HIV antiretroviral resistance through better monitoring of treatment adherence. *The Journal of Infectious Diseases* 197:S272-8.

Bean, P. 2005. New drug targets for HIV. *Clinical Infectious Diseases* 41:S96-100.

Bisson, GP, Gross, R, Bellamy, S, Chittams, J, Hislop, M, Regensberg, L, Frank, I, Maartens, G & Nachega, JB. 2008a. Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy. *PLos Medicine* 5 (5):0777-0789.

Bisson, GP, Rowh, A, Weinstein, R, Gaolathe, T, Frank, I & Gross, R. 2008b. Antiretroviral failure despite high levels of adherence: Discordant adherence-response relationship in Botswana. *Journal of Acquired Immune Deficiency Syndromes* 49:107-110.

Bisson, PB, Gross, R, Strom, JB, Rollins, C, Bellamy, S, Weinstein, R, Friedman, H, Dickinson, D, Frank, I, Strom, BL, Gaolathe, T & Ndwapi, N. 2006. Diagnostic accuracy of CD4 cell count increase for virologic response after initiating highly active antiretroviral therapy. *AIDS* 20:1613-1619.

Borkow, G & Lapidot, A. 2005. Multi-targeting the entrance door to block HIV-1. *Current Drug Targets - Infectious Disorders* 5:3-15.

Chalker, J, Wagner, A, Tomson, G, Laing, R, Johnson, K, Wahlström, R & Ross-Degnan, D. 2010. Urgent need for coordination in adopting standardized antiretroviral adherence performance indicators. *Journal of Acquired Immune Deficiency Syndromes* 53:159-161.

Charles, M, Leger, PD, Severe, P, Guiteau, C, Apollon, A, Gullick, RM, Johnson Jr., WD, Pape, JW & Fitzgerald, DW. 2012. Virologic, clinical and immunologic responses following failure of first-line antiretroviral therapy in Haiti. *Journal of the International AIDS Society* 15:1-7.

Cohen, MS, Gay, CL, Busch, MP & Hecht, FM. 2010. The detection of acute HIV infection. *The Journal of Infectious Diseases* 202(S2):S270-S277.

Coughlan, M, Cronin, P & Ryan, F. 2007. Step-by-step guide to critiquing research. Part 1: quantitative research. *British Journal of Nursing* 16:658-663.

Creswell, JW. 2009. *Research design: Qualitative, quantitative and mixed methods approaches.* Los Angeles, CA: SAGE.

Cummins, NW & Badley, AD. 2010. Mechanisms of HIV-associated lymphocyte apoptosis: 2010. *Cell Death and Disease*1:1-9.

Deeks, SG. 2003. Treatment of antiretroviral-drug-resistant HIV-1 infection. *The Lancet* 362:2002-11.

Deeks, SG.2006. Clinical review. Antiretroviral treatment of HIV infected adults. *British Medical Journal* 332:1489-1493.

Emmelkamp, JM & Rockstroh JK 2007. Evolution of HIV therapy – A review of the literature. European Infectious Diseases. (Department of Medicine I, University Clinic Bonn):36-39.

Ferguson, NM, Donnelly, CA, Hooper, J, Ghani, AC, Fraser, C, Bartley, LM, Rode, RA, Vernazza, P, Lapins, D, Mayer, SL & Anderson, RM. 2005. Adherence to antiretroviral therapy and its impact on clinical outcome in HIV-infected patients. *Journal of the Royal Society Interface* 2:349-363.

Fletcher, CV,Testa, MA, Brundage, RC, Chesney, MA, Haubrich, R, Acosta EP, Martinez, A, Jiang, H & Gulick, RM. 2005. Four measures of antiretroviral medication adherence and virologic response in AIDS Clinical Trials Group Study 359. *Journal of Acquired Immune Deficiency Syndromes 40*:301-306.

Ford, N, Nachega, JB, Engel, ME & Mills, E. 2009. *Directly observed antiretroviral therapy: a systematic review and meta-analysis of randomized clinical trials.* From: http://fieldresearch.msf.org/msf/bitstream/10144/88062/1/Ford%20Lancet%20DOTS%20for%20ARV%20Review.pdf (accessed 02 March 2011).

Fox, MP & Rosen, S. 2010. Patient retention in antiretroviral therapy programs up to three years on treatment in sub-Saharan Africa, 2007-2009: systematic review. *Tropical Medicine and International Health* 15 (Suppl 1):1-15.

Google Images. 2012. *Map of Zimbabwe.* From: http://www.google.co.zw/imgres?imgurl=http://dmaps.com/m/africa/zimbabwe/zimbabwe69 (accessed 17 August 2012).

Google Images. 2014. *HIV life cycle.*
From:
http://www.google.co.zw/url?sa=i&source=images&cd=&cad=rja&uact=8&ved=0CAgQjRw&url=http%3A%2F%2Fwww.daviddarling.info%2Fencyclopedia%2FA%2Facquired_immune_deficiency_syndrome.html&ei=6OiHVOufA-Kf7gbgvoGABg&psig=AFQjCNE6gFlZocNaUyHKa_Q71engcAv6wQ&ust=1418279528132502 (accessed 9 December 2014).

Grove, SK, Burns, N & Gray, J. 2013. *The practice of nursing research, appraisal, synthesis, and generation of evidence*. 7th edition St. Louis: Elsevier Saunders.

Harrigan, PR, Hogg, RS, Dong, WW, Yip, B, Wynhoven, B, Woodward, J, Brumme, CJ, Brumme, ZL, Mo, T, Alexander, CS & Montaner, JS. 2005. Predictors of HIV drug-resistance mutations in a large antiretroviral-naïve cohort initiating triple antiretroviral therapy. *Journal of Infectious Diseases* 191:339-347.

Holloway, I & Wheeler, S. 2010. *Qualitative research in nursing and healthcare*. 3rd edition. Wiley-Blackwell: West Sussex, UK.

Jamal, A, McKenzie, K & Clark, M. 2009. The impact of health information technology on the quality of medical and health care: A systematic review. *Health Information Management Journal 38*(3):26-37.

Joint United Nations Programme on HIV/AIDS (UNAIDS) Global Report 2010. *Report on the Global AIDS epidemic 2010*. UNAIDS Publications.

Kalichman, SC, Amarai, C, Swetsze, C, Eaton, L, Kalichman, MO, Cherry, C, Detorio, M, Caliendo, AM & Schinazi, RF. 2010. Monthly unannounced pill counts for monitoring HIV treatment adherence: tests for self-monitoring and reactivity effects. *HIV Clinical Trials* 11(6):325-331.

Kimberlin, CL & Winterstein, AG. 2008. Validity and reliability of measurement instruments used in research. *American Journal of Health-System Pharmacy* 65:2276-84.

Leedy, PD & Ormrod, JE. 2005. *Practical research: Planning and design*. 8th edition. New Jersey: Pearson Merril Prentice Hall.

Lucas, GM. 2005. Antiretroviral adherence, drug resistance, viral fitness and HIV disease progression: a tangled web is woven. *Journal of Antimicrobial Chemotherapy* 55:413-416.

Lyimo, R, van den Boogaard, J, Msoka, E, Hospers, HJ, van der Ven, A, Mushi, D & de Bruin, M. 2011. Measuring adherence to antiretroviral therapy in northern Tanzania: feasibility and acceptability of the Medication Event Monitoring System. *BioMed Central Public Health* 11(92):1-7.

Martin, M, Cacho, ED, Codina, C, Tuset, M, De Lazzari, E, Mallolas, J, Miró, JM, Gatell, JM & Ribas, J. 2008. Relationship between adherence level, type of the antiretroviral regime, and plasma HIV type 1 RNA viral load: A prospective cohort study. *AIDS Research and Human Retroviruses* 24:1263-1268.

Maru, DSR, Bruce, RD, Walton, M, Mezger, JA, Springer, SA, Shield, D & Altice, FL. 2008. Initiation, adherence and retention in a randomized controlled trial of directly administered antiretroviral therapy. *AIDS Behaviour* 12(2):1-18.

MedicineNet.com. 2013. *Definition of a patient.*
From: http://www.medicinenet.com/script/main/art.asp?articlekey=39154 (accessed 19 August 2013).

Memiah, P, Shumba, C, Etienne-Mesubi, M, Agbor, S, Hossain, MB, Komba, P, Niyang M & Biadgilign, S. 2013. The effect of depressive symptoms and CD4 count on adherence to highly active antiretroviral therapy in Sub-Saharan Africa. *Journal of the International Association of Providers of AIDS Care* 00(0):1-7.

Mills, EJ, Nachega, JB, Bangsberg, DR, Singh, S, Rachlis, B, Wu, P, Wilson, K, Buchan, I Gill, CJ & Cooper, C. 2006. Adherence to HAART: A systematic review of developed and developing nation patient reported barriers and facilitators. *PLoS Medicine* 3(11):2039-2064.

Mills, EJ, Nachega, JB, Buchan, I, Orbinski, J, Attaran, A, Singh, S, Rachlis, B, Wu, P, Cooper, C, Thabane, L, Wilson, K, Guyatt, GH & Bangsberg, DR. 2006. Adherence to antiretroviral therapy in Sub-Saharan Africa and North America, a meta-analysis. *The Journal of the American Medical Association* 296:679-690.

Ministry of Health and Child Welfare Zimbabwe. 2008. *More efficacious ARV prophylaxis for the Prevention of Mother to Child Transmission (PMTCT) Programme in Zimbabwe. A trainer's manual for the integrated approach to HIV and AIDS prevention, care, treatment and follow up for pregnant women, their babies and families. Module 9*. From: http://www.avert.org/aids-zimbabwe.htm#refs (accessed 2 March 2011).

Ministry of Health and Child Welfare. 2009. *ART register.* Harare: Government Printer.

Ministry of Health and Child Welfare. 2004. *Government of Zimbabwe HIV and AIDS Care. Plan for the nationwide provision of antiretroviral therapy 2005-2007*. Harare: Government Printer.

Mocroft, A, Phllips, AN, Gatell, J, Ledergerber, B, Fisher, M, Clumeck, N, Losso, M, Lazzarin, A, Fatkenheuer, G & Lundgren, JD. 2007. Normalisation of CD4 counts in patients with HIV-1 infection and maximum virological suppression who are taking combination antiretroviral therapy: an observational cohort study. *Lancet* 370:407-413.

MoHCW see Ministry of Health and Child Welfare (Zimbabwe).

Muyingo, SK, Walker, AS, Reid, A., Munderi, P, Gibb, DM, Ssali, F, Levin, J, Katabira, E, Gilks, C, Todd, J & the DART Trial Team 2008. Patterns of individual and population-level adherence to antiretroviral therapy and risk for poor adherence in the first year of the DART Trial in Uganda and Zimbabwe. *Journal of Acquired Immune Deficiency Syndromes* 48:468-475.

Nachega, JB, Hislop, M, Dowdy, DW, Lo, M, Omer, SB, Regensberg, L, Chaisson, RE & Maartens, G. 2006. Adherence to highly active antiretroviral therapy assessed by pharmacy claims predicts survival in HIV-infected South African adults. *Journal of Acquired Immune Deficiency Syndromes* 43:78-84.

Nachega, JB, Hislop, M., Dowdy, DW, Chaisson, RE, Regensberg, L & Maartens, G. 2007. Adherence to nonnucleoside reverse transcriptase inhibitor-based HIV therapy and virologic outcomes. *Annals of Internal Medicine* 146:564-573.

Nachega, JB, Mills, EJ & Schechter, M. 2010. Antiretroviral therapy adherence and retention in care in middle-income and low-income countries: current status of knowledge and research priorities. *Current Opinion in HIV and AIDS* 5:70-77.

National Drug and Therapeutics Policy Advisory Committee & AIDS and TB Unit MOHCW. 2007. *Guidelines for antiretroviral therapy in Zimbabwe*. Harare: Government Printer.

National Drug and Therapeutics Policy Advisory Committee & AIDS and TB Unit MOHCW. 2010. *Guidelines for antiretroviral therapy in Zimbabwe*. Harare: Government Printer.

Osterberg, L & Blaschke, T 2005. Adherence to medication. *The New England Journal of Medicin*e 353:487-497.

Parahoo, K. 2006. *Nursing research: principles, process and issues*. 2nd edition. Palgrave Macmillan: Houndsmill.

Parker, M. 2005. When is research on patient records without consent ethical? *Journal of Health Services Research & Policy* 10(3):183-186.

Patel, A, Hirschhorn,L, Fullem, A, Ojikutu, B & Oser, R. 2010. Adult adherence to treatment and retention in care. Arlington VA: USAID-AIDSTAR-ONE PROJECT Task Order.
From: http://www.aidstar-one.com/sites/default/files/AdultAdherenceTB_Final.pdf
(accessed 6 August 2012).

Paterson, DL, Swindells, S, Mohr, J, Brester, M, Vergis, EN, Squier, C, Wagener, MM & Singh, N. 2000. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Annals of Internal Medicine* 133:21-30.

Peltzer, K, Friend-du Preez, N, Ramlagan, S & Anderson, J. 2010. Antiretroviral treatment adherence among HIV patients in KwaZulu-Natal, South Africa. *BioMed Central Public Health* 10:1-10.

Pocket Oxford English Dictionary. 2005. Sv “adherence”. 10th edition. Oxford University Press.

Polit, DF & Beck, CT. 2012. *Nursing research: generating and assessing evidence for nursing practice*. 9th edition. Philadelphia: Wolters Kluwer Health and Lippincott Williams & Wilkins.

Rosen, S, Fox, MP & Gill, CJ. 2007. Patient retention in antiretroviral therapy programs in Sub-Saharan Africa: A systematic review. *PLoS Medicine* 4(10):1691-1701.

Sanjobo, N, Frich, JC & Fretheim, A. 2008. Barriers and facilitators to patients’ adherence to antiretroviral treatment in Zambia: a qualitative study. *Journal of Social Aspects of HIV/AIDS* 5:136-143.

Sedaghat, AR, Silidano, JD, Brennan, TP, Wilke, CO & Silidano, RF. 2007. Limits on replenishment of the resting $CD4^+$ T cell reservoir for HIV in patients on HAART. *PLoS Pathogens* 3(8):1165-1174.

Shuter, J. 2008. Forgiveness of non-adherence to HIV-1 antiretroviral therapy. *Journal of Antimicrobial Chemotherapy* 61:769-773.

Skovdal, M, Campbell, C, Nhongo, K, Nyamukapa, C & Gregson, S. 2011. Contextual and psychosocial influences on antiretroviral therapy adherence in rural Zimbabwe: towards a systematic framework for programme planners. *International Journal of Health Planning and Management* 26:296-318.

Smith, C, Sabin, CA, Youle, MS, Loes, SK, Lampe, FC, Madge, S, Cropley, I, Johnson, MA & Phillips, AN. 2004. Factors influencing increases in CD4 cell count of HIV-positive persons receiving long-term highly active antiretroviral therapy. *The Journal of Infectious Diseases* 190:1860-1868.

Smith, CJ, Sabin, CA, Lampe, FC, Kinloch-de-Loes, S, Gumley, H, Carroll, A, Prinz, B, Youle, M, Johnson, MA & Phillips, AN. 2003. The potential for CD4 cell increases in HIV-positive individuals who control viraemia with highly active antiretroviral therapy. *AIDS* 17:963-969.

Stata SE release 10. 2007. Stata Corporation. College Station, Texas, USA.

The Free Dictionary. 2013a. Definition of adherence.
From: http://medical-dictionary.thefreedictionary.com/adherence (accessed 19 August 2013).

The Free Dictionary. 2013b. Definition of refill.
From: http://www.thefreedictionary.com/refill (accessed 19 August 2013).

Thompson, C, Hudson, TL, Wick, R & Ballestas, HL. 2009. *Nursing know how –charting patient care.* Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins.

Trotta, MP, Cizzi-Lepr,i A, Ammassari, A, Vecchiet, J, Cassola, G, Caramello, P, Vullo, V, Soscia, F, Chiodera, A, Ladiasa, N, Abeli, C, Cauda, R, Buonuomi, AR, Antinori, A & Monforte AA. 2010. Rate of CD4+ cell count increase over periods of viral load suppression: Relationship with the number of previous virological failures. *Clinical Infectious Diseases* 51(4):456-464.

UNAIDS 2014. *Global AIDS response; country progress report Zimbabwe 2014.* UNAIDS Publications.

UNAIDS Global AIDS response progress report 2012. *Follow-up to the 2011 Political Declaration on HIV/AIDS: Intensifying our efforts to eliminate HIV/AIDS. Zimbabwe Country Report*. *Reporting period: January 2010-December 2011*. From: http://data.unaids.org/pub/Report/2010/zimbabwe_2010_country_progress_repop.=rt_en.pdf (accessed 05 September 2012).

UNGASS see United Nations General Assembly Special Session.

United Nations General Assembly Special Session 2010. *Report on HIV and AIDS. Follow-up to the Declaration of Commitment on HIV and AIDS. Zimbabwe Country report. Reporting period: January 2008 to December 2009*.
From:
http://data.unaids.org/pub/Report/2010/zimbabwe_2010_country_progress_report_en.pdf (accessed 05 September 2012).

United States Agency for International Development (USAID)/Zimbabwe HIV/AIDS Strategy FY2003 – FY2007 2003. .
From: http://pdf.usaid.gov/pdf_docs/PDACF758.pdf (accessed 16 February 2011).

Veenstra, N, Whiteside, A, Lalloo, D & Gibbs, A. 2010. *Unplanned antiretroviral treatment interruptions in Southern Africa: how should we be managing these?* 1-40. From: http://www.globalizationandhealth.com/content/pdf/1744-8603-6-4.pdf (accessed 29 January 2011).

Vervoort, SC, Borleffs, JC, Hoepelman, A & Grypdonck, M. 2007. Adherence in antiretroviral therapy: a review of qualitative studies. *AIDS* 21:271-281.

WHO – see World Health Organization.

Wilfert, CM. 2010. *Making PMTCT available.*
From: https://impaactgroup.org/files/Making%20PMTCT%20Available.pdf (accessed 02 March 2011).

Wood E, Hogg, RS, Yip, B, Harrigan, PR, O'Shaughnessy, MV & Montaner, JSG. 2004. The impact of adherence on CD4 cell count responses among HIV-infected patients. *Journal of Acquired Immune Deficiency Syndromes* 35: 261-268.

World Health Organization 2003. *Adherence to long-term therapies. Evidence for action.* WHO: Geneva.

World Health Organization 2006. *Antiretroviral drugs for treating pregnant women and preventing HIV infection in infants: Towards universal access. Recommendations for a public health approach*. WHO : Geneva.

World Health Organization 2010a. *HIV/AIDS programme*. *Strengthening health services to fight HIV/AIDS. Antiretroviral drugs for treating pregnant women and preventing HIV infection in Infants. Recommendations for a public health approach – 2010 version.* WHO: Geneva.

World Health Organization 2010b. *Towards universal access: scaling up priority HIV/AIDS interventions in the health sector: progress report 2010*. WHO: Geneva.

World Health Organization 2011. *Global HIV/AIDS response: epidemic update and health sector progress towards Universal Access. Progress Report 2011.* WHO: Geneva.

World Health Organization 2013. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection. Recommendations for a public health approach June 2013.* WHO: Geneva.

Worster, A & Haines, TH. 2004. Advanced statistics: Understanding medical record review (MRR) studies. *Academic Emergency Medicine* 11(2): 187-192.

Zimbabwe Map. From: http://www.google.co.zw/imgres?imgurl=http://d-maps.com/m/africa/zimbabwe/zimbabwe69 (accessed 8 January 2012).

Zimbabwe National Statistics Agency (ZIMSTAT) and ICF International. 2012. *Zimbabwe Demographic and Health Survey* 2010 -11. Harare: Government Printer. From: http://www.zimstat.co.zw/dmdocuments/ Census/ZDHS2011/ZDHS2011.pdf (assessed 12 August 2013).

Zuurmond, M. 2008. *Adherence to ARVS – challenges and successes*. 1-20. From: http://www.cafod.org.uk/content/download/77210/803422/version/3/file/ART+adherence+-+research+report.pdf (accessed 16 March 2011).

ANNEXURE A

LETTER REQUESTING PERMISSION TO CONDUCT THE STUDY AT THE HOSPITAL

1 September 2011

Dr. W. Ndebele
Clinical Director
Mpilo Central Hospital
Bulawayo

RE: REQUEST FOR PERMISSION TO CONDUCT RESEARCH ON PHARMACY REFILLS AS A MEASURE OF ADHERENCE TO ART AMONG HIV POSITIVE PATIENTS IN BULAWAYO ZIMBABWE

Dear Dr. Ndebele

The AIDS and TB Unit under the Ministry of Health and Child Welfare (MOHCW) coordinates programs aimed at HIV prevention, care and mitigation. This is in line with the Testing and counselling as the entry point for all HIV programs including access to Antiretroviral therapy (ART). The National ART program started in 2004 and through scaling up ART services, coverage grew from 8.3%in 2005 to 33.6% by end of 2007. Critical to the success of ART programs is continuous availability of drugs and for patients to sustain high rates of adherence.

A minimum adherence level of 95% is required for ART to work effectively. This high adherence level is needed in order to suppress and maintain suppression of HIV replication. Further, destruction of CD4 cells is reduced, development and transmission of drug resistant HIV strains is prevented, disease progression is slowed down and reconstitution of the immune system is promoted.

Measuring adherence to treatment regimes is however difficult mostly because information on how well medication has been taken by a patient is subjective. Nonetheless there are several methods, which have been found to be useful in measuring adherence to prescribed medication. These include pill counts self reports, pharmacy refill reports and medication event monitoring systems (MEMS). Because

Cover letter to Clinical Director Mpilo Central Hospital

under the national ART program patients receive ART drugs for free, I have chosen to use the pharmacy refill records to measure adherence. This will be correlated mainly to CD4 cell count since this test is offered to patients at least once within a one-year period as part of the routine monitoring system for patients on ART. Point of care CD4 testing has also been recently introduced in the country allowing more and more patients being initiated on cART to have access to this service besides usage of WHO clinical staging. I do acknowledge that the pharmacy refill records assumes that the patient is using the same pharmacy and also that the patient did swallow the drugs. Despite these limitations and assumptions, according to literature, pharmacy refill records is among one of the more accurate and less expensive way of monitoring adherence.

The proposed study will therefore be a retrospective study with data extracted from pharmacy registers, patients' clinic registers and medical records. It is hoped that if pharmacy fill records can measure adherence reliably, this could be a simple public health tool for the national ART program to use.

As part fulfilment for my MPH degree with UNISA, I would like to determine the relationship between adherence to ARVs as measured by pharmacy refills and immunological recovery as indicated by an increase in CD4 cell counts in patients aged 10 and older at the Mpilo Central Hospital in Bulawayo (please refer to protocol for inclusion/exclusion criteria).

Attached please find the study protocol for your perusal. A letter of support to carry out this study would be most appreciated. Thanking you in anticipation of a favourable response.

Yours sincerely

Kuda Mutasa
Laboratory Manager
ZVITAMBO PROJECT
1 Borrowdale Road Borrowdale, Harare

ANNEXURE B

LETTER GRANTING PERMISSION TO CONDUCT THE STUDY AT THE HOSPITAL

Reference:

Telephone:09-212011

Fax: 09-205078

ZIMBABWE

MINISTRY OF HEALTH
AND CHILD WELFARE
MPILOCENTRAL HOSPITAL
P O BOX 2096
BULAWAYO

27 September 2011

Kuda Mutasa

REQUEST FOR PERMISSION TO CONDUCT RESEARCH ON PHARMACY REFILLS AS A MEASURE OF ADHERENCE TO ART AMONG HIV POSITIVE PATIENTS IN BULAWAYO ZIMBABWE

Reference is made to your minute dated 1 September 2011 in connection with the above matter.

The institution has no objection in you undertaking the study.

May you please give us results of your study.

MPILO CENTRAL HOSPITAL
CLINICAL DIRECTOR
27 SEP 2011
P.O. BOX ... BULAWAYO

Dr J Moyo
A/CLINICAL DIRECTOR
FOR CHIEF EXECUTIVE OFFICER
MPILO CENTRAL HOSPITAL

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
10 JAN 2012
RECEIVED
P. O. BOX CY 573 CAUSEWAY, HARARE

Approval letter from Mpilo Central Hospital to conduct the research

ANNEXURE C

LETTER REQUESTING PERMISSION FROM MRCZ TO CONDUCT THE STUDY

Cover letter to MRCZ Clinical Secretary

November 11, 2011

MRCZ Secretary
Medical Research Council of Zimbabwe
Josiah Tongogara/Mazoe Street
P.O. Box CY 573
Causeway
Harare

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
10 JAN 2012
RECEIVED
P. O. BOX CY 573 CAUSEWAY, HARARE

Dear Madam

Attached please find 4 copies of a complete application package for a study to be conducted by me (Kuda Mutasa) at Mpilo Central Hospital and Ministry of Health and Child Welfare AIDS & TB unit for review by the MRC-Z. The study is entitled *"Pharmacy Refills as a Measure of Adherence to Antiretroviral Therapy for HIV Positive Patients at Mpilo Central Hospital in Bulawayo Zimbabwe"*.

Once approved, I will forward the US$50.00 student project levy.

Thank you very much.

Sincerely

Kuda Mutasa

Kuda Mutasa

MEDICAL RESEARCH COUNCIL OF ZIMBABWE

For Office Use Only

MRCZ/A/ 8292

FC ☑ EXP ☐ XMPT

Date received

10/01/12

MRCZ Application to conduct health/medical research

MRCZ FORM 101

APPLICATION TO CONDUCT HEALTH/MEDICAL RESEARCH

This form must be completed by all persons/teams intending to conduct health/medical research in Zimbabwe. Upon completion by the investigator(s) it should be submitted to the Institutional Review Board(IRB) of the institution in which/under which the research is to be conducted. Upon completion of the relevant section by the IRB, the form should be submitted to the Secretary, Medical Research Council of Zimbabwe, P O Box CY 573 , Causeway, Harare. A registration fee of ZS10000.,00 should accompany each application. Cheques should be made payable to the Medical Research Council of Zimbabwe (MRCZ)

Protocol Version Number :.....

APLICATION FORM CHECKLIST

This checklist was prepared in order to aid investigators in preparing a complete application and to help expedite review by the Ethical Review Committee. Your cooperation in completing it will be greatly appreciated.

PRINCIPAL INVESTIGATOR'S NAME: Kuda Mutasa

E-mail: kmutasa@zvitambo.co.zw

Contact cell/telephone number: 263-4-850732/3
+263 0772 270 116

- ☑ Four copies of application form duly completed.
- ☑ Four copies of protocol summary (less than 3 pages in length).
- ☑ Four copies of complete research protocol in general/funding agency format.
- ☐ Four copies of consent forms in English and local language of the study population.
- ☐ Four copies of Drug Brochure or any supplementary information (if applicable).
- ☑ Four copies of Questionnaire being administered during the study (if applicable).
- ☑ I have made a copy of this entire application package for my files.
- ☐ For clinical trials – I have also submitted an application to the MCAZ.

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
10 JAN 2012
RECEIVED
P.O. BOX CY 573 CAUSEWAY, HARARE

Kuda Mutasa

Signature: Principal Investigator

Date: November 11, 2011

Details of Research Team

Name of Principal Investigator (P.I)	**Kuda Mutasa**
Nationality of P.I	**Zimbabwean**
Existing Qualifications	**BSc MT (ASCP)**
Academic Title	**Laboratory Manager**
Institution & Dept.	**ZVITAMBO**
Postal address	**1 Borrowdale Road Borrowdale Harare**
E-mail address	**kmutasa@zvitambo.co.zw**
Telephone No.	**850732/3**
Is this research expected to lead to the award of a higher degree? (Yes/No)	**Yes**
University/Institution where registered	**UNISA**

Co-investigators Names	**Qualifications**	**Institution/Department**

Details of the Proposed Research

Title of proposed research.	Pharmacy Refills as a Measure of Adherence to Antiretroviral Therapy for HIV Positive Patients at Mpilo Central Hospital in Bulawayo Zimbabwe
Proposed starting date	**January 2012**
Proposed ending date	**April 2012**
Performance site(s) in Zimbabwe	**Mpilo Central Hospital**
Performance sites (outside Zimbabwe)	**None**
Total number of study personnel	**1**
Budget (state currency)	**US$2,325.00**
Name and address of Funding agency:	**SELF funding for a higher degree**
Status of funding :	a)Submitted for funding ☐ b)Pending ☐ c)Funded ☒

Collaborating Institutions

1st	Mpilo Central Hospital
2nd	University of South Africa
3rd	AIDS & TB Unit MOHCW

Population : Proposed inclusion criteria *(Check all that apply)*		**Type of study** *(check all that applies)*	
Males	: ☒	Survey	☐
Females	: ☒	Secondary data	: ☐
Adolescents (10 – 17 years)	: ☒	Program Project	: ☐
Children (Under 10 years of age)	: ☐	Clinical community trial	: ☐
Pregnant women	: ☒	Case control	: ☐
Foetuses	: ☐	Longitudinal study	: ☐
Elderly (over 65 years)	☒	Record review	☒
Prisoners	: ☐	Course activity	: ☐
Cognitively impaired	: ☐	Other (specify)	: ……
Hospital inpatients	: ☒		

Consent Process *(Check all that applies)*

Written : ☐ Oral : ☐ English : ☐ Local Language : ☐ None : ☒

☐ **Proposed sample size: All eligible for inclusion between October 1 2009 and December 31, 2009**

☐ **Reading level of consent document : Below Grade 3** ☐ **Below Grade 6** ☐ **Below Form 2** ☐
Below Form 4 ☐ **Above O level** ☐ **Graduate level** ☐

Determination of Risk *(Check all that applies)*

Does the research involve any of the following	**YES**	**NO**
Human exposure to ionizing radiation		X
Fetal tissue or abortus		X
Investigational new drug		X
Investigational new device		X
Existing data available via public archives/sources	X	
Existing data not available via public archives		
Observation of public behaviour		X
Is the information going to be recorded in such a way that subjects can be identified		X
Does the research deal with sensitive aspects of the subjects behaviour, sexual behavior, alcohol use or illegal conduct such as drug use		X
Could the information recorded about the individual if it became known outside of the research, place the subject at risk of criminal prosecution or civil liability		X
Could the information recorded about the individual if it became known outside of the research, damage the subjects financial standing, reputation and employability?		X

- **Do you consider the proposed research**
  - A) greater than minimal risk
  - B) minimal risk
  - C) no risk ☒

  Minimal risk is a risk where the probability and magnitude of harm or discomfort anticipated in the proposed research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical, psychological examinations or tests. For example the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examinations.

- Do any of the participating investigators and or their immediate families have an equity relationship with the sponsor of the project or the manufacturer or owner of the drug or device under investigation or serve as a consultant to any of the above?
  YES ☐ **NO** ☒
-

If yes, please submit a written statement of disclosure to the Chairman of the MRCZ

RESEARCH PROPOSAL SUMMARY

It is the MRCZ requirement that the composition of the Institutional Review Board (IRB) include individuals with varied backgrounds and education. Investigators are therefore required to four attach (4) copies of a 2-3 page (maximum 4 pages) Research Proposal Summary using the headings provided below in terminology that is understandable across disciplines.

1. **RESEARCH QUESTION TO BE ADDRESSED BY THIS PROPOSAL**
2. **RATIONALE FOR RESEARCH**
   - Describe briefly the background of the study, and state reasons for conducting it.
   - State objectives of study.
3. **METHODS**
   - Study design and rationale for that design. Explain how the study will be performed.
   - Population : Sample size, outline criteria for selection and exclusion of subjects, gender, ethnic group, performance sites (provide justification for single gender or group). For larger sample sizes on greater than minimal risk studies, provide justification of the sample size.
   - Subject's state of physical health. Indicate if healthy, ill, seriously ill or terminally ill.
   - Does the study involve any special populations: Subjects will include, minors, fetuses, abortuses, pregnant women, prisoners, mentally retarded, mentally disabled, or none of the above.
   - If subjects are from one of the above special populations explain the necessity for including them.
   - Specify source of participating subjects, e.g. hospitals, clinics, institutions, prisons, industry, unions, schools, general population, etc. *NOTE: If you plan to advertise for patients, the ad must be submitted to the MRCZ for review and approval prior to its publication and/or posting.*
   - List all research procedures and/or interventions involving human subjects (when applicable) including tests to be conducted and the analysis of samples (where applicable including where the analysis is to be done – if outside the country please justify including how the samples are to be shipped).
   - Distinguish procedures which are part of routine care from those that are part of the study
   - Questionnaire/interview instrument (when applicable)
     If the study includes either of these, a copy of the instrument is to be appended to this application. If the instrument is in development stages, provide an outline of the types of questions to be asked and the expected date of completion and submission to the MRCZ.
   - Methods of intervention Will any new drugs or biologic agents be administered to the subjects, or will previously used agents be used in a new manner? If yes, please note that you are also required to file a separate application with the Medicines Control Authority of Zimbabwe (MCAZ) and may not conduct your study without the approval of both the MCAZ and the MRCZ. You are also required to complete the relevant part in this application titled " Studies involving the testing of drugs and medical devices".
   - Methods for dealing with adverse events
   - Methods for dealing with illegal, reportable activities (e.g child abuse)

RISKS / BENEFITS TO SUBJECTS

- Describe in detail any potential risks - physical, psychological, social, legal, ethical (e.g. confidentiality), or other and assess the likelihood and seriousness of such risks (none, low, moderate, and high). Include the incidence of complications if known. You may use a narrative description if more appropriate or a table with 3 columns (Potential adverse effects, seriousness and likelihood of complications (Incidence if known.)
- Describe procedures for protecting against or minimizing potential risks.
- If the activity involves women who could become pregnant and is potentially harmful to a fetus, describe steps that will be taken to prevent pregnancy or exclude pregnant women.
- Assess potential benefits to be gained by the individual subject and explain why the benefits outweigh the risks.
- Assess benefits which may accrue to society in general as a result of the planned work.

COSTS AND COMPENSATION

- Will subjects receive any compensation, monetary or other? If monetary, how much? Will subjects be asked to assume any out-of-pocket costs for participating in the research? If yes, what? Identify expenses such as additional transportation, laboratory tests, supplies, cost of study drug if it becomes commercially available, etc.

INFORMED CONSENT

- Any kind of contact with human subjects requires a disclosure/consent process.
- Attach a copy of the consent form. Indicate how (verbal or written) informed consent will be obtained (please request for guidelines for implementing informed consent from the MRCZ Offices).
- If subjects are minors or mentally disabled, describe how and by whom permission will be granted.

- **Where** will the record of consent be stored? (Consent forms must be kept for three years after the completion of the investigation, unless otherwise stipulated by the MRCZ).

CONFIDENTIALITY ASSURANCES

Describe any means by which the subject's personal privacy is to be protected and confidentiality of data maintained. Include information on the following:

- Any sensitive information that will be gathered.
- Plans for record keeping
- Location of the data
- Data security
- Person responsible and telephone number
- Who will have access to the data
- Plans for disposal of the data upon completion of the study

CONFLICT OF INTEREST (real or apparent)

- Other than the normal scholarly gains, are there any other gains you might receive from taking part in this study?

COLLABORATIVE AGREEMENTS

- Provide letters of approval from collaborating institutions' IRBs and from other local IRBs from other sites.

INTENDED USE OF RESULTS

- Include plans for dissemination and utilization of study results

OTHER INFORMATION:

- Any other information.

Please note : Attach **4 COPIES of the full research proposal**. The full proposal should include the following: Title, objectives, background and literature review, methodology (to include research design, subjects and methods, ethical considerations, timetables etc. references, budget etc . Investigators may submit the full proposal in the funding agency format as long as it covers the above headings.

Please also attach copies of **curriculum vitae** for the Principal Investigators and all Co- investigators. The CVs should include the following : Name, Postal address, Employers name and address, Qualifications, Present Position, Past research experience (relevant) and Published Papers (relevant). Principal Investigators or co-investigators who would have already submitted their CVs during the current year are exempted from this requirement.

STUDIES INVOLVING THE TESTING OF DRUGS AND DEVICES

DRUG / DEVICE INFORMATION FORM

Please note that you are required to submit a separate application to the Medicines Control Authority of Zimbabwe for authorization to test a drug or medical device.

1. Which of the following will be used? **Not Applicable**
   - ☐ a) investigational drug(s)
   - ☐ b) new therapeutic applications for MCAZ approved drug (s)
   - ☐ c) new combination of any of the above
   - ☐ d) medical device

2. Briefly describe how this drug or device is a part of the proposed investigation.

   Not Applicable

3. For each drug or device to be used, please provide the following information:

Generic Name	**Trade or Brand Name**	**Manufacturer**

4. Please give the risks, hazards, known contraindications.

5. Please give reasons for choice of drug(s) for this study. Include pertinent animal clinical tests or appropriate citations.

6. Please provide dose schedule, route of administration, and duration of therapy.

7. Please describe assessment of patient while receiving therapy including clinical observations and laboratory tests.

SIGNATURE ASSURANCE SHEET

Principal Investigator's Assurance Statement:

I certify that the information given by me is correct to the best of my knowledge, I am familiar with and understand the Medical Research Council of Zimbabwe's policy concerning research involving human subjects (CIOMS Guidelines or Helsinki Declaration) and I agree:

(Please check all that applies)

1. [X] to accept responsibility for the scientific and ethical conduct of this research study;
2. [X] to obtain prior approval from the relevant IRB as well as the MRCZ before amending or altering the research protocol or implementing changes in the approved consent form;
3. [X] to immediately report to the relevant IRB and the MRCZ any serious adverse reactions and/or unanticipated effects on subjects which may occur as a result of this study;
4. [X] to complete and submit the Continuing annual Review Form annually (when due) as well as the Final/Study termination form at the end of the proposed study.
5. [X] to submit the final study report to the MRCZ using standard form .
6. [X] to pay one percent levy to the MRCZ upon approval of my protocol (for study monitoring and general research subjects protection requirements).

Signature  Date Nov 11, 2011

Print name KUDA MUTASA

Signature of Co-investigator _____ Date _____
Print Name _____

Signature of Co-investigator _____ Date _____
Print Name _____

Signature of Co-investigator _____ Date _____
Print Name _____

SUBMIT FOUR COPIES OF THE ENTIRE APPLICATION PROPOSAL TO THE MRCZ OFFICES
(The entire application package includes the application form, research proposal summary (2-3 pages), full research proposal (even in funding agency format), consent form and other relevant documents).

****

INSTITUTIONAL ETHICAL REVIEW BOARD REVIEW AND ENDORSEMENT REQUIRED

ANNEXURE D

LETTER GRANTING PERMISSION TO CONDUCT THE STUDY

Telephone: 791792/791193
Telefax: (263) - 4 - 790715
E-mail: mrcz@mrczimshared.co.zw
Website: http://www.mrcz.org.zw

Medical Research Council of Zimbabwe
Josiah Tongogara / Mazoe Street
P. O. Box CY 573
Causeway
Harare

MRCZ APPROVAL LETTER

Ref: **MRCZ/B/292** **11 January, 2012**

Kuda Mutasa
ZVITAMBO
1 Borrowdale Road
Borrowdale
Harare
Zimbabwe

RE: Pharmacy refills as a measure of adherence to antiretroviral therapy for HIV positive patients at Mpilo Central Hospital in Bulawayo, Zimbabwe.

Thank you for the above titled proposal that you submitted to the Medical Research Council of Zimbabwe (MRCZ) for review. Please be advised that the Medical Research Council of Zimbabwe has **reviewed** and **approved** your application to conduct the above titled study. This is based on the following documents that were submitted to the MRCZ for review:

a) Study protocol.

- **APPROVAL NUMBER : MRCZ/B/292**

This number should be used on all correspondence, consent forms and documents as appropriate.

- **APPROVAL DATE : 11 January, 2012**
- **EXPIRATION DATE : 10 January, 2013**
- **TYPE OF MEETING : Expedited Review**

After this date, this project may only continue upon renewal. For purposes of renewal, a progress report on a standard form obtainable from the MRCZ Offices should be submitted one month before the expiration date for continuing review.

- **SERIOUS ADVERSE EVENT REPORTING**: All serious problems having to do with subject safety must be reported to the Institutional Ethical Review Committee (IERC) as well as the MRCZ within 3 working days using standard forms obtainable from the MRCZ Offices.
- **MODIFICATIONS**: Prior MRCZ and IERC approval using standard forms obtainable from the MRCZ Offices is required before implementing any changes in the Protocol (including changes in the consent documents).
- **TERMINATION OF STUDY**: On termination of a study, a report has to be submitted to the MRCZ using standard forms obtainable from the MRCZ Offices.
- **QUESTIONS**: Please contact the MRCZ on Telephone No. (04) 791792, 791193 or by e-mail on mrcz@mrczimshared.co.zw.
- **Other**
- Please be reminded to send in copies of your research results for our records as well as for Health Research Database.
- You're also encouraged to submit electronic copies of your publications in peer-reviewed journals that may emanate from this study.

Yours Faithfully

.....

MRCZ SECRETARIAT
FOR CHAIRPERSON
MEDICAL RESEARCH COUNCIL OF ZIMBABWE

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
11 JAN 2012
APPROVED
P. O. BOX CY 573 CAUSEWAY, HARARE

ANNEXURE E

DATA COLLECTION INSTRUMENT

PHARMACY REFILLS AS A MEASURE OF ADHERENCE TO ANTIRETROVIRAL THERAPY FOR HIV POSITIVE PATIENTS AT MPILO CENTRAL HOSPITAL IN BULAWAYO ZIMBABWE

Name of facility: Mpilo Central Hospital

Data Collection Date: DD/MM/YYYY
Data collected by: DD/MM/YYYY

Study ID: (assign sequentially)

Patient ID: (transcribe from ART register)
HIV Test Date: DD/MM/YYYY
DOB:DD/MM/YYYY

Section A: Demographic Data

Q1. Age

- ○ 10-14
- ○ 15-19
- ○ 20-24
- ○ 25-29
- ○ 30-34
- ○ 34-39
- ○ 40-44
- ○ 45-49
- ○ 50-54
- ○ 55-59
- ○ 60+

Q2. Gender
1 = Male
2 = Female

Q3. Reason for HIV Test
1=VCT/Self
2=Hospital/Illness
3=TB
4=ANC
5= Spouse/Partner +ve
6=Child +ve

Q4. Orphan Status (for ages 10 – 18)
1 = Single orphan
2 = Double orphan

Q5. Marital status
1 = Married
2 = Single
3 = Widowed
4 = Divorced
5 = Separated

Q6. Type of residence
1 = Own
2 = Renting
3 = Living with relatives/others
4 = Not Stated

Q7. Type of Employment
1 = Unemployed
2 = Self employed
3 = Government
4 = Private
5 = Student
6 = Not stated

Q8. Treatment supporter
1 = Spouse/partner
2 = Friend
3 = Parent
4 = Sibling
5 = Other
6 = None
7 = Not sated

Q9. Referral Source
1=VCT /Self
2=Hospital/Illness
3=PPTCT
4=TB program
5=BCC clinic
6=Private sector

Section B: Clinical Data

Clinical Visits

	V0	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Date (dd/mm/yyyy)													
Weight													
Height													
ARV Regime													
Switch Regime													
Switch Date													
Reason for Sub/Switch													
WHO Staging													
Date next appointment													
Pregnancy													
Adherence (%)													

Codes for first-line ARV
1 = 1a(30) *= D4T(30)+3TC+NVP*
2 =1a(40) *= D4T(40)+3TC+NVP*
3 =1b(30) *= D4T(30)+3TC+EFV*
4 =1b(40) *=D4T(40)+3TC+EFV*

Codes for 2nd-line ARV
5 =2a *= AZT+ddI+LPV/r*

Codes for Sub/Switch
1 *= Clinical failure*
2 *= Immunological failure*
3 *= Toxicity/side effects*
4 *= Virologic failure*
5 *= Drug out of stock*
6 *= Pregnancy*
7 *= New TB diagnosis*
8 *= New drug available*
9 *= Other*

Codes for WHO Staging Codes
1 *= Stage I*
2 *= Stage II*
3 *= Stage III*
4 *= Stage IV*
5 *= Not stated*

Adherence (%) calculated

Lab results

	0	1	2	3	4	5	6	7	8	9	10	11	12	
CD4 Date														
CD4 Count														
VL Date														
VL count														
CD4 %														

Codes for CD4 cell count
1 = *Less than 100*
2 *= Less than 200*
3 *= greater than 200*
4 *= less than 350*
5 *= greater than 350*

Codes for Viral load
1 = less than 400 copies/mL
2 = greater than 400 copies/mL

OI Diseases (list):
Reason for missed dose (state):

ANNEXURE F

ETHICAL CLEARANCE

UNISA university of south africa

UNIVERSITY OF SOUTH AFRICA
Health Studies Higher Degrees Committee
College of Human Sciences
ETHICAL CLEARANCE CERTIFICATE

HSHDC/172/2013

Date: 13 March 2013 Student No: 3731-952-3

Project Title: Pharmacy refills as a measure of adherence to antiretroviral therapy for HIV positive patients at Mpilo Hospital in Bulawayo, Zimbabwe.

Researcher: K Mutasa

Degree: Masters in Public Health Code: DIS4953

Supervisor: Mrs M Chauke
Qualification: MA in Health Studies
Joint Supervisor: -

DECISION OF COMMITTEE

Approved [√] **Conditionally Approved** [ ]

Prof L Roets
CHAIRPERSON: HEALTH STUDIES HIGHER DEGREES COMMITTEE

for **Prof MM Moleki**
ACTING ACADEMIC CHAIRPERSON: DEPARTMENT OF HEALTH STUDIES

PLEASE QUOTE THE PROJECT NUMBER IN ALL ENQUIRES

ANNEXURE G

STAMPED APPROVAL FROM MOHCW AIDS AND TB UNIT TO CONDUCT THE STUDY

Relevant to MOHCW
Approved

RESEARCH PROPOSAL

PHARMACY REFILLS AS A MEASURE OF ADHERENCE TO ANTIRETROVIRAL THERAPY FOR HIV POSITIVE PATIENTS AT MPILO CENTRAL HOSPITAL IN BULAWAYO ZIMBABWE

Research to be submitted in partial fulfilment of the requirements for the

degree of

MASTER OF PUBLIC HEALTH

In the Department of Health Studies

at the

UNIVERSITY OF SOUTH AFRICA

Protocol

Approval from MOHCW AIDS & TB Unit

by

KUDA MUTASA

Student number: 37319523

kmutasa@zvitambo.co.zw

Mrs MM Van der Merwe
Supervisor

MEDICAL RESEARCH COUNCIL OF ZIMBABWE
10 JAN 2012
RECEIVED
P. O. BOX CY 573 CAUSEWAY, HARARE

MINISTRY OF HEALTH
TB & AIDS PROGRAMME
16 SEP 2011
P.O. BOX CY 1122, CAUSEWAY
ZIMBABWE
CO-ORDINATOR

September 2011

ANNEXURE H

LETTER FROM THE STATISTICIAN

ZVITAMBO
Institute for Maternal and Child Health Research

University of South Africa
Department of Health Studies
PO Box 392
UNISA 0003
South Africa

June 9, 2014

RE: STATISTICAL DATA ANALYSIS FOR UNISA MPH STUDENT KUDA MUTASA

I would like to confirm that I have assisted **Kuda Mutasa** with statistical data analysis on a dissertation research study proposal entitled "**Pharmacy refills as a Measure of Adherence to Antiretroviral Therapy for HIV Positive Patients at Mpilo Central Hospital in Bulawayo Zimbabwe**" registered with your institution. Please do not hesitate to contact me if you think I can provide any other information.

Yours faithfully

Bernard Chasekwa, BSc (Statistics)
Senior Biostatistician - Zvitambo Institute for Maternal and Child Health Research
Research Fellow MSc in Medical Statistics - The London School of Hygiene and Tropical Medicine