

UNIVERSITY OF THE WESTERN CAPE

Faculty of Community and Health Sciences

**ADHERENCE TO ANTIRETROVIRAL THERAPY AMONGST
WOMEN COMMENCED ON TREATMENT DURING PREGNANCY
AT RESEARCH CLINICS IN BOTSWANA**

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DECLARATION

I, Anthony Chibuzor Ogwu declare as follows:

- That Adherence to Antiretroviral Therapy Amongst Women Commenced on Treatment During Pregnancy at Research Clinics in Botswana is my own work.
- That the research was done at the Botswana-Harvard AIDS Institute Partnership clinical research sites in Gaborone, Molepolole, Lobatse and Mochudi, Botswana.
- That this study has not been submitted for a degree or examination at another institution.
- That all the sources used have been acknowledged and adequately referenced.
- That it is my moral right to be recognized as the author of this dissertation.

Student: ANTHONY CHIBUZOR OGWU

Signed:



Date: 12 November, 2010

DEDICATION

This work is dedicated to my Lord and Savior Jesus Christ, the reason for my being and an ever present help in time of need; to my mother, Justina Adaeke Ogwu for bringing me to this world and for teaching me the principles of giving; my wife Bibi Omo for her support and patience while I completed this work; my beloved son Givanni Chukwuma, a promise from GOD fulfilled and a bundle of Joy to my family.



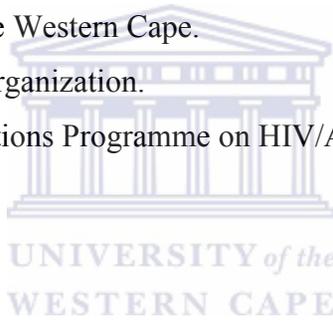
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I am also indebted to the UWC higher degrees committee for the ethical approval and also to the Botswana Ministry of Health, Health Research and Development Committee for reviewing and granting ethical approval for the conduct of the study among Mmabana study participants.

LIST OF ABBREVIATIONS

ANC:	Ante natal clinic
ARV:	Antiretroviral
AZT:	Azidothymidine
BHP:	Botswana Harvard Partnership
HAART:	Highly Active Antiretroviral Therapy
HIV:	Human Immunodeficiency Virus
AIDS:	Acquired Immunodeficiency Syndrome.
PMTCT:	Prevention of Mother to Child Transmission.
PNC:	Post natal clinic.
SD:	Standard deviation
SPSS:	Statistical Packages of the Social Sciences
UWC:	University of the Western Cape.
WHO:	World Health Organization.
UNAIDS:	Joint United Nations Programme on HIV/AIDS.
3TC:	Lamivudine.



LIST OF DEFINITIONS

1. Adherence: Taking anti retroviral drugs in prescribed doses and at agreed times.
2. Level of Adherence: How well an individual adheres to the health workers instruction on taking their medications.
3. Satisfaction: How happy the patient is with the quality of care received from the health care facility.
4. Access: How far the clinic is and how easy it is for patients to attend services there in terms of cost and opening hours.
5. Level of Knowledge: How much the patient knows about HIV/AIDS and the treatment for it.
6. Disease severity: The current stage of disease as measured by CD4 count, viral load and presence of opportunistic infections.
7. Patient- Provider relationship: How comfortable it is for patients to interact with the health care workers and discuss the problems that they may face with adhering to their medications.

ABSTRACT

Background: The widespread availability of antiretroviral therapy has led to a reduction in mortality and morbidity in HIV/AIDS patients in Botswana. However, high levels of adherence to antiretroviral drugs are necessary for good virologic and immunologic responses which are critical for improved survival. Approximately 100 women who initiated highly active antiretroviral therapy (HAART) while pregnant are currently being followed in 4 research clinics in Botswana. There is currently no data available on adherence among women initiating HAART during pregnancy at these clinics or among pregnant women on HAART elsewhere in Botswana. It is critical to study and understand the key factors that influence adherence among women receiving treatment at these clinics following initiation during pregnancy, to avert or reduce the consequences of treatment failure.

Aim: The study aimed to assess the level of adherence and to identify the barriers to adherence and the motivations for good adherence to antiretroviral therapy, amongst women who commenced treatment while pregnant at research clinics in Molepolole, Mochudi, Lobatse and Gaborone.

Study Population and Sample: All women who initiated HAART during pregnancy and were currently receiving treatment at the research clinics in Molepolole, Lobatse, Gaborone and Mochudi in Botswana.

Method: A quantitative study was conducted using a cross sectional descriptive design. Data was collected using a structured questionnaire administered to all women receiving standard care HAART at the clinics, during their monthly refill visits between 02 September and 15th October, 2009. Additional relevant information was extracted from participant's medical records using a data extraction tool. Informed consent was obtained from the women who participated in the study prior to administration of the questionnaire and subsequent data extraction from their medical records. Data was analysed with SPSS version 14 using descriptive and analytic statistics. Adherence was categorized as excellent (100%), adequate ($\geq 95\%$) and inadequate ($< 95\%$).

Results: A total of 94 women consented to the study and were interviewed across the 4 sites. The mean CD4 counts at antenatal, immediate post natal and late post natal were 266, 315 and 346 respectively. Overall adherence of the study participants was good, 99% had adequate adherence and 67% of the women had excellent adherence using pill count over a six month period. Self reported adherence was 100% for 1-day, 3-day and 7-day recall. Ninety-nine percent (99%) of the subjects received adherence counselling before initiating therapy while approximately 33% of the women received counselling at every visit. Ninety percent (90%) of the women rated the quality of services received at the clinic as very good. Reasons cited for ever missing medications were forgetfulness (18%) and not having medications at the time of the dose (13%). The participants had high knowledge of ARVs and HIV/AIDS. There was no significant difference in adherence during pregnancy, immediately post partum and the late post partum period. There was no significant association between adherence and demographic factors, socioeconomic factors, quality and adequacy of service provision as well as knowledge attitudes and perceptions towards HIV/AIDS and ARVs. Bivariate analysis showed no association in this study between the factors usually known to be associated with adherence from other studies.

Conclusions: A high level of adherence was observed among the study population, with 99% achieving adequate adherence of $\geq 95\%$ and 67% maintaining excellent adherence of 100% during the period reviewed, however these might be overestimates of actual adherence. Even if there is a degree of over-estimation the study still shows a high level of adherence among participants in a research cohort who received a higher standard of care with consistent and adequate adherence monitoring throughout their duration of care.

Recommendations: Although the study reported a high level of adherence, there is need to devise mechanisms of making the medications portable and strengthening mechanisms for reminding patients about timing of the doses. As Botswana rolls out universal access to HAART among pregnant women in the country, it will be essential to learn from this cohort experience so as to attain excellent adherence levels within the general population.

KEYWORDS

1. **ADHERENCE**
2. **ANTIRETROVIRAL THERAPY**
3. **PREGNANT WOMEN**
4. **TREATMENT FAILURE**
5. **PROMOTORS**
6. **INHIBITORS**
7. **RESISTANCE TO ART**
8. **PREVENTION OF MOTHER TO CHILD TRANSMISSION**
9. **RESEARCH CLINICS**
10. **BOTSWANA**



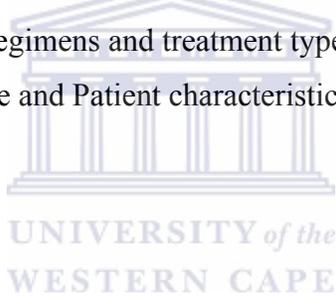
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CHAPTER 1

INTRODUCTION, PROBLEM STATEMENT AND PURPOSE

1.0 INTRODUCTION

HIV/AIDS is a major public health problem. Since the 1980's when it was first described, the spread has been astronomical. More than 33 million people worldwide were living with HIV/AIDS at the end of 2007 (UNAIDS, 2008). Worst hit by the recently discovered Human Immunodeficiency virus is Sub-Saharan Africa, which accounts for two thirds of all people infected with the virus. An estimated 22 million people are living with the virus in this region. Approximately 1.9 million new infections and 1.5 million deaths were reported in 2007 alone. This region has remained the global epicentre of the pandemic.

Botswana had a projected population of 1.74 million in 2007 (CSO, 2001). The country's national HIV prevalence is estimated at 26.9% amongst the 15-49 years age group at the end of 2007. Amongst pregnant women of the same age group attending antenatal clinics, the prevalence was 33.7% (Ministry of Health, 2007). It is estimated that 275,773 persons are living with HIV in the country of which 163,630 are females and 112,143 are males. This is second in the world only to Swaziland in terms of country prevalence. HIV/AIDS has remained the country's most important public health challenge and the biggest threat to its development (Ministry of Health, 2007).

With the widespread availability of highly active antiretroviral therapy (HAART) in Botswana, there has been a significant improvement in survival for people living with HIV/AIDS. A recent analysis of data on HIV/AIDS patients on antiretroviral therapy showed an overall 5-year survival rate of 88.8% using Kaplan-Meier estimates (Ministry of Health, 2007), but adherence to these medications has been a major concern.

Prevention of mother to child transmission (PMTCT) programmes has been achieving tremendous successes in reducing the risk of HIV transmission from infected mothers to their infants. Current standard of care in the developed world is the use of triple therapy (HAART), which has reduced vertical transmission rates to 1-2% (WHO, 2007). The

Botswana ministry of health currently uses mainly Zidovudine monotherapy and single dose Nevirapine for their PMTCT programme. HAART is available only to pregnant women with a CD4 count of less than 250 or an AIDS defining illness. This combination of basic PMTCT, and HAART when indicated, has achieved a reduction in transmission rates to <4% (Ministry of Health, 2008). HAART has the added advantages of lowering the risk of resistance developing, compared to single or dual therapy, as well as improved maternal health outcomes (Mocroft *et al.*, 2004). As the country awaits clinical trials data to inform a potential policy change towards universal HAART rollout in pregnancy, an important concern is that poor adherence to these combination therapies would be a major challenge hindering optimal benefit.

The optimal benefit of HAART includes good virologic and immunologic responses critical for decreasing intrauterine and intrapartum transmission, as well as improved maternal survival. It also has protective effects during the breastfeeding period leading to improved infant survival, if a mother chooses this feeding option (Lockman *et al.*, 2009).

One hundred and seventy HIV positive pregnant women were enrolled in the observational arm of a prevention of mother to child transmission study, at research clinics located in three peri-urban communities in Botswana, (namely Molepolole, Mochudi, Lobatse) and the capital city Gaborone between July 2006 and May 2008. The Participants were recruited from amongst women using both public and private sector antenatal facilities and were followed up till 02 September, 2010. Table 1.1 below provides a description of the study sites.

The 170 women enrolled across the four sites were part of a larger cohort of 730 HIV positive pregnant women recruited for a prevention of mother to child transmission study. They were enrolled during pregnancy and initiated on highly active antiretroviral drugs (AZT/3TC and Nevirapine) according to the Botswana standard of care criteria of CD4<200 or presence of an AIDS defining illness (Ministry of Health, 2005). The CD4 cut-off was revised upwards to 250 in November, 2008 after the study has completed accrual (Ministry of Health, 2008). The treatment they received is therefore the same as

the standard treatment provided to HIV positive pregnant women, with the same CD4 count in the public health sector in Botswana. All of them received this treatment irrespective of their CD4 counts. They were all requested to attend the research clinics for monthly follow up visits and medication refills. The remaining 560 women were randomized to receive one of two investigational HAART regimens (Kaletra and Combivir or Trizivir). Participants were required to return unused medication to the clinic at each visit. During these visits the returned pills were counted and the results were compared to the expected number of pills to be returned, based on the number of pills dispensed at the last visit. Findings were documented in the study case report forms as well as participants specific drug profile, in order to evaluate adherence. The nurses also reviewed and filed returned pill calendars which were completed by the participants.

The pill calendar is a prepared single sheet of paper, in the form of a modified monthly calendar, that enables subjects to fill in their names, study number, the time they took their medication each day and a signature, see appendix 4). Pill calendars were issued monthly and returned to the clinic by the participants at each medication refill visit. Adherence counselling was done by the nurses at each visit. It involved evaluating the challenges each woman faced in taking their medication and seeking ways of solving them together. More time was spent with patients with poor adherence whilst praises and positive reinforcement were given to those with excellent adherence.

Table 1.1: Description of the study sites

Site Name	Location	No. of rooms in the facility	No. of women in the observational arm	No. Doctors	No. nurses	Counsellors
Mochudi(Deborah Retief Hospital)	Peri urban	6	42	1	3	0
Lobatse (Athelone Hospital)	Peri urban	5	31	1	3	0
Molepolole(Scottish Livingstone Hospital)	Peri urban	8	39	1	4	2
Gaborone (Princess Marina Hospital)	Urban	5	58	1	3	2
Total		24	170	4	13	8

There are only a few studies globally on adherence to HAART during pregnancy (Sankar *et al.*, 2002; Kingston, Letham and McQuillan, 2007; Bardeguéz *et al.*, 2008; Weinberg *et al.*, 2009). Although HAART has been used in Botswana among pregnant women who are eligible since 2003, I could not find any study on adherence among women who initiated HAART during pregnancy in Botswana. A literature search on adherence, PMTCT, HAART, dual or monotherapy and Botswana as keywords was conducted using PubMed, OmniMedical Search and the Harvard University Library of Medicine. However one study has examined qualitatively the barriers to participation in PMTCT and completing HIV prophylaxis in Botswana (Kebaabetswe, 2007). The author concluded that fear of knowledge of their HIV status, infant formula distribution stigma, lack of male partners' support and negative attitudes of health workers, were significant barriers to pregnant women participating in the PMTCT programme.

In the general population in Botswana some barriers to adherence that have been identified include treatment related costs, lack of privacy, stigma, fear of disclosure and cultural beliefs; while facilitators of good adherence include perceived benefits of HAART, awareness of consequences of poor adherence and the presence of social

support mechanisms (Weiser *et al.*, 2003; Kgatlwane *et al.*, 2006; Kip, 2009).

It is important to study and understand the key factors that influence adherence at clinics initiating HAART in pregnancy, in order to avert or reduce the consequences of treatment failure, which includes the use of more complicated and expensive second, third line and salvage regimes, transmission of resistant viral mutants and high cost of hospitalization and management of opportunistic infections, as well the consequences of increased transmission of the human immunodeficiency virus to the infants (Zorilla *et al.*, 2000; Merriam *et al.*, 2003, Peltier *et al.*, 2009).

1.1 PROBLEM STATEMENT

A group of women attending research clinics in Botswana initiated combination ARV treatment (HAART) during pregnancy as per Botswana treatment guidelines and for the purpose of prevention of mother to child transmission from the antenatal until the breast feeding period, and will continue with ARV treatment indefinitely for their own health. HAART is known to be more effective for the purpose of vertical transmission prevention compared to single or dual therapy (Thomas *et al.*, 2008). HAART also decreases the morbidity and mortality of the women resulting in a further increased survival of the infants as well (Thomas *et al.*, 2008). However high levels of adherence are required to achieve maximal viral suppression required for effective prevention of transmission to infants, and for prevention of development of resistance to available antiretroviral drugs. We do not know the current level of adherence to HAART among these pregnant and breastfeeding women and we do not know which factors impact either negatively or positively upon their adherence levels.

1.2 PURPOSE

The purpose of the study was to determine the level of adherence among the women described above and the factors associated with adherence. The information obtained was intended to be used to devise strategies to improve ARV adherence amongst the women at these clinics (if improvement was required) as well as in other sites involved in the ARV rollout in Botswana, and potentially elsewhere, especially in developing countries.

CHAPTER 2

LITERATURE REVIEW

2.0 Introduction

This section reviews literature relevant to the study. The review covers the following areas; overview and significance of adherence to ART amongst HIV/AIDS patients; known levels of adherence to antiretroviral drugs; factors that affect adherence; women and adherence; adherence among pregnant women and measurement of adherence.

2.1 Overview and significance of adherence to ART amongst HIV/AIDS patients

Dramatic reductions in HIV/AIDS related morbidity and mortality has been realised in most countries where Highly Active Antiretroviral Therapy (HAART) is widely available (Anderson & Weatherburn, 1999).

HAART improves the life of HIV positive patients' through control of disease progression by viral suppression and decreased transmission of resistant viruses, decreased incidence of opportunistic infections and decreased time spent away from work due to illness or associated hospitalisations (Turner, 2002). Unfortunately the level of adherence required for keeping good control of viral replication and reducing AIDS related mortality and morbidity required to sustain these benefits, is extremely high. Adherence rates of 95% or more are required for maximal viral suppression (Paterson *et al.*, 2000). This level of adherence required for excellent adherence is supported by a study conducted within the REACH cohort in the US (Bangsberg, 2006). Bangsberg further concludes that lower levels of adherence ($\geq 70\%$) would be adequate for maintaining viral suppression especially if the patient is receiving very potent non-nucleoside reverse transcriptase inhibitor based therapy. Lack of adherence to medications is a major challenge to care, as this may lead to an increase in viral replication, development of viral mutations with consequent resistance to the few available drugs. This can result in treatment failure, increased incidence of opportunistic infections and shortened survival (Paterson *et al.*, 2000).

Among pregnant women receiving HAART, sub optimal adherence will lead to increased risk of mother to child transmission of HIV during pregnancy, delivery and breastfeeding (Vaz *et al.*, 2007). When compared to their non pregnant counterparts, Vaz and co-workers in Sao Paulo, Brazil, found a significantly higher adherence among pregnant women. Forty three percent of the pregnant women had optimal adherence as measured via pill counts. This figure although low was much higher than the 17% optimal adherence recorded by their non pregnant counterparts. Among the same group of pregnant women, adherence decreased to 21% in the postnatal period. However, the factors that motivated higher adherence among the pregnant women were not evaluated.

Vahove, Shapiro & Winters (1996), performed a careful analysis of viral load, number of doses of medications taken per day and the development of resistance among six HIV infected individuals, followed over a period of 24 weeks. They reported a decrease in viral load initially as all the participants were adherent; however, subsequent drug holidays lead to viral rebounds. This data suggests that poor adherence even within short periods may be associated with increased viral loads. However the small sample size limits the generalisability of this finding to other populations.

From a public health perspective, poor adherence to HAART may result in transmission of resistant strains of the human immunodeficiencyvirus to newly infected individuals (primary resistance). This has a negative impact on their future response to antiretroviral therapy (Poppa *et al.*, 2003). If resistance or treatment failure happens, current treatment guidelines recommends switching to a new HAART combination regimen, which may include more agents and more complex regimens, which in turn may be associated with new or unknown toxicity (Poppa *et. al*, 2003). Thus the health outcomes for individuals in this category are unpredictable and often poorer than those on first line therapy.

The socio economic consequences of poor adherence are enormous as it will result in increased use of second-line and salvage regimens, which are in general more expensive than initial regimens. More so, since low adherence is associated with an increased risk of disease progression, the cost of hospitalisation and treatment of opportunistic infections

will have a negative impact on the established cost-benefit of antiretroviral therapy (Sherr *et al*, 2007).

Poor adherence ultimately leads to severe public health consequences, namely; increased vertical and horizontal spread of the disease, increased cost of management, decreased human capital, increased social costs including care for orphans and decreased survival of children of those who are ill or dead as a result of inadequate care (Sherr *et al*, 2007).

2.2 Levels of adherence to antiretroviral drugs

Estimates of average adherence rates to HAART i.e. the use of these drugs at the right dose, frequency and at the agreed times range from 50-70% in many different social and cultural settings (Safren, 2005).

Studies in African settings have indicated adherence rates as varying from 54%-98% depending on the method used to assess adherence. Nwokike (2004) reported 83% adherence in the public sector in Botswana amongst adult males and females as measured by patients self report and pill count while Weiser *et al*, (2003) reported 54% amongst adults in the private sector using patients self report only.

Other findings by different researchers are; in Nigeria, 79% measured by patients self report amongst adults receiving care in a tertiary health care centre (Daniel, 2004); in South Africa, 77% amongst adults in the public sector measured by patients self report (Ferris, 2004) and in Uganda, 98% amongst adults in the public sector with measurement by patients self report (Munganzi, 2004). These data may not be comparable as the researchers used different methods in different settings; however it does show that the level of adherence varies amongst African countries.

Concerns about low adherence has been cited by those who question the feasibility of rapidly scaling up antiretroviral therapy programmes especially in resource poor settings (Stephens, Kaye & Corrah, 2004). Harris, (2001) argued that adherence problems would continue to be a major concern to the delivery of antiretroviral therapy in Sub-Saharan Africa. This is understandable as high levels of poverty, poor health infrastructures, poor

social security system, illiteracy and unfamiliarity with the need for long term treatment especially when feeling well, are all factors which impact upon adherence and are all factors prevalent in Sub-Saharan Africa (WHO, 2006).

However despite this truism it is worth noting that except for the study amongst private sector patients in Botswana by Weiser *et al*, (2003), all the studies listed above have reported acceptable levels of adherence. It is also interesting that Nwokike (2004) found higher adherence levels amongst the Botswana public sector patients compared to lower levels reported by Weiser *et al*, (2003) in the private sector. This is counterintuitive since the adherence inhibiting factors listed above, which are commonly cited by policy makers, are much more prevalent amongst public sector patients. It is therefore quite important to review the factors affecting adherence (both promoters and inhibitors) in more detail and to assess how they might interact with one another.

2.3 Factors affecting adherence

Multiple factors are known to affect adherence to antiretroviral therapy, these are often classified into five interwoven categories (Reiter, 2000). They include: patient variables, treatment regimens, disease characteristics, clinic setting and the patient provider relationship.

2.3.1 Patient variables

These include socio-demographic factors such as age, sex, race, income, education, literacy, housing status, HIV risk factors and psychosocial factors i.e. mental health, substance abuse, socio-cultural issues, psychosocial support and knowledge about and attitude towards HIV and its treatment (Carrieri, Caillefon & Le moing, 2002).

Patients who have a good understanding of the need to adhere to ARV's and the consequences of treatment failure tend to adhere more than those without this information (Weiser *et al*, 2003). Bangsberg and co-workers reported that 13% of patients who were prescribed ARV's were not taking them correctly, despite them believing that they were (Bangsberg, Perry & Charlesbois, 2001). Reinforcing information provided verbally with written information to take home, and by checking that information delivered has been

heard correctly, is likely to be beneficial in improving adherence as patients commonly misunderstand their health care provider's instructions (Kgatlwana *et al.*, 2006).

Socio-demographic, cultural and psychological issues have great potential to impact on adherence. Family support i.e. having to care for sick relatives and religious beliefs around illness and taking of medications may influence motivation and adherence (Klitzmann, 2004). This is starkly demonstrated by low levels of adherence amongst people who believe in divine healing (Powell-Cope, White, Henkelman & Turner, 2003). Individuals with unstable housing, i.e. not having one's own house and the need to live with different relatives/friends at different times, inevitably have compromised privacy which consequently negatively impacts on adherence (Kgatlwane *et al.*, 2006). The issue of disclosure has also been found to have serious implications for adherence; for example, the use of medication may inadvertently reveal a person's HIV status and therefore patients may be reluctant to collect their medications, to store it in common storage space such as a medicine cupboard in the home and to take it in a common area such as a kitchen (Stirratt, Remien, Smith, Copeland, Dolezal & Krieger, 2006). This need to keep the medication a secret in order to protect the privacy of their HIV status compromises adherence.

Poverty may prevent individuals from following treatment related dietary advice (Hardon *et. al.*, 2007), and lack of food at prescribed dosage intervals would result in patients being unable to take some doses of their medication such as Atazanavir which should be taken with food. Transport costs to and from health facilities for medication appointments may have a negative influence on an individual's ability to attend clinic appointments and hence to keep to their medication regimens (Kgatlwane *et al.*, 2006).

Drug and alcohol abuse may impair judgment and the ability to adopt and maintain routine medication use (Klitzmann, 2004). Also family responsibilities, such as, having to work to generate income for the family and provide care for sicker family members may require adults to place the health care needs of others before their own (Klitzmann, 2004), thus having a negative impact on their adherence to their medication. Mental health

problems such as depression have been associated with low adherence in HIV positive adults and adolescents, as have other psychological variables such as perception of one's ability to follow a medication regimen (Murphy, 2004).

2.3.2 Treatment regimens

These include the number of pills prescribed, the complexity of the regimen (dosing frequency, food instructions and the specific type of ARV). Antiretroviral medications are usually taken once or twice daily at approximately specified times and some may require food restrictions like didanosine which is usually taken on an empty stomach i.e about 30 minutes before or 2 hours after meals ((Marfatia & Makrandi, 2005). These are obviously difficult to adhere to in our busy daily lives. Most available antiretroviral drugs have unpalatable side effects such as nausea, vomiting, diarrhoea, hepatotoxicity and skin rashes, which have a negative impact on adherence levels. Thus as different regimens have different incidence, type and severity of side effects; they will have different levels of adherence (Carr, 2002). Machtinger & Bangsberg reported that increased pill burden associated with concurrent medication for other co-morbidities such as tuberculosis is clearly associated with sub-optimal adherence (Machtinger & Bangsberg, 2005).

2.3.3 Disease characteristics

Disease characteristics would include the stage and duration of HIV infection, associated opportunistic infections, and HIV related symptoms (Machtinger & Bangsberg, 2005). The severity of the illness could impact negatively or positively on adherence to ART. HIV infection has a long latent phase of about 8 to 10 years. Aside from a flu-like illness during the acute seroconversion period, infected individuals are usually asymptomatic during the latency phase. Following the latency period, there is the phase of full blown AIDS, consisting of rapidly increasing viral replication, declining cd4 counts and increasing frequency of opportunistic infections such as tuberculosis, papular pleuritic eruptions, weight loss and finally death in the absence of treatment (Weiser *et al.*, 2003). With the use of and good adherence to anti-retroviral drugs most of these opportunistic infections are usually brought under control and individuals can lead a normal, healthy life.

Experience of symptoms and their impact on patients' views about medications are usually complex (Carr, 2002). Symptoms may stimulate the use of medications by acting as a reminder or reinforcing beliefs about the necessity for treatment. However, patients' expectations of symptom relief are also likely to have an important effect. This could be problematic for adherence if expectations are unrealistic, or where treatment is given for asymptomatic disease, as occurs with HIV infection (Horne, 2001).

The desire to get well may make an individual comply with medications as prescribed. However with improved health, adherence to the medication becomes a problem as some may not understand why they have to continue taking the medications regularly, while they are healthy (Weiser *et al.*, 2003). This results in poor adherence with consequent viral rebound, increased probability of resistance developing and consequent treatment failure.

2.3.4 Clinic setting

Chesney, (2000) found that dissatisfaction with the health services is a predictor of non adherence. Factors such as the ease of accessibility of a clinic i.e. if it is on a public transport route, general clinic environment i.e friendliness of staff, short waiting time, access to continuing primary health care and child care at the same clinic, would all lead to improved adherence (Machtiger & Bangsberg, 2005). Other factors includes flexible opening hours and convenient appointment scheduling tailored to individual patients needs i.e. work, holidays and travel; ability of health care staff to address patients concerns and willingness to help when needed, as well as perceived confidentiality of the care and setting; involvement in a dedicated adherence counselling program; pleasantness of the clinic environment and satisfaction with past experience with the health care system, would all also lead to improved adherence (Hardon *et. al*, 2007). Long waiting time, poor drug supply chain with associated occasional stock-outs as well as absence of established HIV treatment guidelines were associated with sub-optimal adherence among patients on treatment in the study by Hardon cited above. Kgatlwane *et al.* (2006), in a Botswana study reported that poorly trained personnel, poor staff motivation and poor salaries lead to inadequate counseling and inadequate follow-up of

patients with consequent poor adherence.

2.3.5 Patient provider relationship

The patient provider relationship includes the patient's overall satisfaction and trust in the particular provider; the patient's opinion of the provider's competence; the provider's willingness to include the patient in the decision making process; the affective tone of the relationship (e.g. warmth, openness, cooperation); the compatibility of class, race, culture and language between patient and provider; and the adequacy of referral (Friendenberg, 2006). All these affect adherence to HAART. With an increasing number of patients to care for on a daily basis, in a busy outpatient clinic in the era of HIV/AIDS, less and less time is being spent by physicians with patients, despite long waiting times for patients (WHO, 2006). Patients may therefore not have the opportunity to discuss concerns affecting their treatment with their physicians. Consequently with time trust diminishes and patients may find it difficult to adhere to their doctors instructions.

2.4 Women and Adherence

Little is presently known about the difference, if any, in treating women compared to men with regard to medication dosing and side effects. Likewise, few studies have explored what factors motivate women to adhere to HAART. Lake *et al.* (2003), found that connectedness with healthcare providers, especially female providers, as well as being attended to by nurses and nurse practitioners experienced in HIV/AIDS care, were important for women and lead to reports of better adherence. Sankar, Lubrosky, Schumann and Roberts (2002), found among African American women taking antiretroviral drugs that sources of motivation to adhere to drugs included; a positive relationship with their physician, belief that the drugs work, religiosity and faith in God, support from family members and the belief in the power of positive thinking. This study found an adherence rate of 69% among the women.

Powell-Cope, White, Henkelman & Turner (2003), conducted a qualitative and quantitative assessment of ART adherence among 24 substance abusing HIV positive women. Their findings demonstrated that these women recognised the link between treatment benefits and adherence and most of them tracked viral loads and CD4 counts as

tangible evidence of effectiveness of treatment. Increased life span resulting in being able to spend more time with people familiarly and socially close to them such as children, a significant partner, friends and family, were expressed as advantages of adhering to ART. They also admitted that substance use was a difficult barrier to taking medication and they preferentially tended to stop ART rather than illegal drugs and alcohol. The use of reminders such as pill boxes, spirituality, adherence partners and support from family members promoted adherence among the cohort. The most common reason for missing medication was forgetfulness due to various circumstances. However, this study was conducted amongst a specific group of women in an urban setting with a small sample size which limited its generalisability to other populations.

2.5 Pregnant Women and Adherence

HAART has revolutionized Prevention of Mother to Child transmission programmes in the developed world compared to mono or dual therapy, with overall intrauterine and intrapartum transmission rates of less than 1 - 2% in non breastfeeding populations (Cooper et al. 2000; Dorenbaum *et al.*, 2002; Thorne, 2005; WHO, 2007; Townsend *et al.*, 2008; Warszawski *et al.*, 2008). Emerging data from Sub-Saharan African countries suggest higher benefits of decreased HIV transmission and improved infant survival compared to single or dual therapy in the postnatal period among breastfeeding populations (Arendt *et al.*, 2007; Shapiro *et al.*, 2009).

Successful interventions to prevent antenatal and intrapartum mother to child HIV transmission includes adherence to HAART medication and caesarean section mode of delivery (Kingston *et al.*, 2007) Low adherence has been identified as the single most important challenge to preventing vertical HIV transmission with the use of HAART (Weigberg *et al.*, 2009), current knowledge of adherence during pregnancy is limited. Poor adherence to ARVs during pregnancy can lead to suboptimal viral suppression, development of viral resistance, a higher risk of mother to child transmission (MTCT), and mother to child transmission of a resistant HIV-1 strain (Wells et al., 2000; Johnson et al., 2001).

While some studies have indicated that adherence is much higher during pregnancy than postpartum (Zorilla *et al.*, 2003; Park, Tochuku and Grigoriu, 2007, Vaz *et al.*, 2007), others have found high rates of non-adherence during pregnancy, particularly when more objective measures of adherence, such as pharmacy data or urine assays, are used (Demas *et al.*, 2005; Laine *et al.*, 2000). These findings may suggest that pregnant women are more likely to report higher adherence than they actually have.

Cotter, Gonzalez, Duthely & O'Sullivan (2004) using a hospital database of HIV positive pregnant women on antiretroviral therapy found a perinatal HIV transmission rate of 4.5%. Among the women who transmitted the virus, 41% were not adherent to their prescribed ARV medications (ie taking the medications at >95% of times), thus echoing the importance of adherence to HAART among pregnant women. However adherence among women who did not transmit the virus to their babies was not reported by the authors.

In a Brazilian study among pregnant and non pregnant women with comparable demographic characteristics, using pill counts and self reporting, 43.1% of pregnant women achieved adherence rates of $\geq 95\%$ (Vaz *et al.*, 2007). This was significantly higher than non pregnant women where only 17.1% achieved $\geq 95\%$ adherence. Although being pregnant was clearly strongly associated with higher levels of adherence the underlying motivating factors for this higher adherence were not formally assessed. It was surmised that fear of transmitting the virus to the foetus would have led to a better adherence among the pregnant women, although this was not measured in this study. It is also possible that increased expectation by the health care workers that they are taking the medication regularly, as it would prevent their child from getting infected with HIV, might result in increased reporting of higher adherence by pregnant women. This was also not assessed in the study above.

The dominant risk factor for MTCT is high maternal viral load at delivery (Thorne *et al.*, 2005; Jourdain *et al.*, 2007; Warszawski *et al.*, 2008) which is a function of sub-optimal adherence. Optimal adherence during pregnancy and delivery is necessary to ensure

adequate immunologic and virologic responses (Weinberg *et al.*, 2009; Melekhin *et al.*, 2009). In a study amongst pregnant women in the United States of America, Bardeguéz *et al.* (2008) found that pregnant women with perfect adherence (100% by self report) had lower viral loads. Out of a total of 519 eligible subjects, 75% reported perfect adherence during pregnancy. The odds of perfect adherence were significantly higher for women who initiated ARVs during pregnancy, did not have AIDS, never missed prenatal vitamins, never used illicit drugs and had generally good social relationships.

A complex set of factors likely influences adherence among HIV-infected pregnant or postpartum women. In other populations, pregnancy has been a significant motivator for reducing aberrant health behaviours (e.g. smoking and alcohol use) and women with chronic health conditions (e.g. diabetes) may improve adherence during pregnancy, but then revert to poor health behaviours postpartum (Zorilla *et al.*, 2003).

Although better ART adherence during pregnancy compared to postpartum have been shown in several studies as described above in this section, high rates of non-adherence have also been shown in both groups. Ickovics *et al.*, (2002) reported that only 50% and 34.1% of United States women studied adhered to their medications in the antenatal and postnatal periods respectively.

These analyses indicate that medication adherence is more likely during pregnancy than postpartum in HIV-infected women, perhaps provoked by the motivation to reduce vertical transmission, intensive antepartum encouragement and surveillance, or a combination of both.

2.6 Measurement of Adherence

Measurement of adherence is imperfect and lacks an established gold standard (Gill, 2005). Many studies employ various methods, either alone or in combination to measure adherence. Methods used include medication event monitoring (MEM) cap technology which involves the use of smart pill bottles that contain computer chips which electronically measure every opening of the bottle (Vitolins, 2000). This is a complex and expensive method and may only be useful in research rather than in clinical settings.

It could also be very unreliable, especially in developing countries, as patients may open the pill bottle without actually taking out pills or swallowing them. However this would constitute deliberate, premeditated and regularly carried out duping of the health worker, which is unlikely to occur unless there is a serious disagreement between the patient and the health worker on the usefulness of the medication. Other methods that have been used by researchers in developing country settings includes: pill counts, patients self reported adherence, biochemical markers, pharmacy prescription refill records and modified directly observed therapy (Gill, 2005).

Pill count adherence is usually measured by counting the pills the patient returns at each medication refill visit (Machtiger & Bangsberg, 2005). The method assumes that remaining pills in excess of what is expected represents missed doses. It can be performed in the clinic or at unannounced home visits. It is quick and easy to do, although validity of the method might be compromised as the patients may take out the pills which they should have taken, even if they haven't taken them, and hence this method may overestimate adherence. It could also underestimate adherence if at the previous dispensing the patient was inadvertently given more medication than required, or if the patient has accumulated a stock of previously unused medication and hence did not have to use all the medication received at the last dispensing in order to be fully adherent.

Patient self reported adherence is done in the clinic setting by asking the patient to recall any missed doses at specified time points in the past, for example 1-day recall, 3-day recall and 7-day recall (Machtiger & Bangsberg, 2005). It is simple, efficient and easy to perform, however it is a less sensitive measure of adherence as patients may tell the health worker what they want to hear and hence it often overestimates adherence. This method is unlikely to underestimate adherence. The method is most valid and hence most useful when there is a high degree of trust between the patient and the clinician/pharmacist.

Biochemical markers of adherence refer to measurements of the concentration of the

antiretroviral drugs in the plasma (Machtinger & Bangsberg, 2005). Plasma concentrations of some studied antiretroviral drugs have been correlated with adherence and viral load levels. The lower the drug level in the plasma, the less likely it is that the patient is optimally adhering. However this method is limited by its ability to measure only short term adherence behaviour and also drug levels may be affected by several other factors such as individual metabolic differences, poor absorption and inter-drug interaction. Hence it can overestimate and underestimate adherence levels.

Pharmacy prescription refill records can be used to assess adherence by recording the dates antiretroviral medications were dispensed to patients (Machtinger & Bangsberg, 2005). If refills are not obtained at the expected dates, it assumes that (1) the patient is completely non-adherent from the missed refill date since s/he has no medication to take; or (2) that the patient has been partially adherent since the last refill period and hence has excess pills remaining beyond the scheduled refill date, which s/he is now taking and hence has not appeared timeously for the next refill; or (3) the patient may have obtained a medication refill at a different health facility or pharmacy and adherence levels is then impossible to assess. It is therefore a poor measure of adherence and at best can be used to assess if adherence levels are very low, or complete non-adherence provided that the patient has only one or very limited places where medication refills can be issued.

Modified directly observed therapy (MDOT) adherence assessment is used when a health worker observes most but not all of the medication at the time the patient is taking them (Machtinger & Bangsberg, 2005). An example is where a health worker observes the patient taking the morning dose and pre packages the evening dose for the patient to take at home. It is useful in patients with severe difficulty adhering and also in ambulatory settings. It is an accurate and valid adherence measurement; however, it is cumbersome and labour intensive to implement. A full directly observed therapy (DOT) could similarly be used to assess adherence, but it is clearly even more cumbersome and labour intensive than MDOT.

Therefore, no single measure of adherence is appropriate for all settings or outcomes. As

adherence is a dynamic process, it is believed that the use of more than one measure might allow the strength of one method to compensate for the weakness of the other and to capture more accurately the information needed to determine adherence levels (Vitolins, 2000). In the absence of a practical gold standard, measurement of adherence is usually done by the most feasible method for the circumstances, while noting the deficiencies of the measurement method chosen. Table 2.1 below summarises the strengths and weaknesses of some of the methods used to determine adherence.

Table 2.1: Strengths and Weaknesses of different adherence measures.

Method	Strengths	Weaknesses
MEMS cap technology	Accurate	It is expensive; patients may open the bottle without taking out or swallowing the pills. This would be deliberate, premeditated and regularly carried out if doubting the health worker. However, this is unlikely to occur unless there is a serious disagreement between the patient and the health worker on the use of the medication.
Measurements of drug levels	Very accurate in determining the level of a particular drug in blood or urine.	Invasive, expensive. Measures short term adherence.
Pill count	Easy to perform, quick	Patient may return only those pills which would be left over if they had high (100%) levels of adherence rather than all the pills that are left over.
Pharmacy refill	Accurate in measuring very low adherence	Requires a lot of documentation; patients may collect medication elsewhere; coarse measurement of adherence as it measures when adherence is very low (0% or close to 0%); cannot be used to assess degree of adherence in terms of number of pills taken at appropriate times of the day.
Patient self report	Builds trust and confidence, easy to do.	Patient may want to please the health workers, thus they could give incorrect information; gives an over estimate of adherence.

CHAPTER 3

AIM AND OBJECTIVES

This chapter describes the aims and objectives of the study.

3.1 Aim

- To assess the level of adherence and to identify the barriers to adherence and motivation for good adherence to antiretroviral therapy amongst women who

commenced treatment while pregnant at research clinics in Molepolole, Mochudi, Lobatse and Gaborone.

3.2 Objectives

- To determine the proportion of women who are adequately adhering to their ART.
- To compare the socioeconomic, demographic, religious and cultural characteristics of the women who are adequately adhering and those who are not.
- To compare the knowledge and attitudes towards ARV's between the women who are adequately adhering and those who are not.
- To compare the access to and the level of satisfaction with health care services as perceived by the patients and its association with adherence.
- To compare patient's adherence with disease severity as measured by viral load, CD4 counts and presence of complications.
- To assess the association between side effects and adherence.
- To assess the association between the level of counselling and adherence.
- To assess the adherence levels in the antenatal, early postnatal (≤ 6 months) and late postnatal (≥ 6 months postpartum) periods.

CHAPTER 4 METHODOLOGY

4.0 Introduction

This section describes the study design, study population, sampling, data collection tools and methods, data analysis, validity and reliability of the study, as well as ethical considerations.

4.1 Study Design

A quantitative study was conducted using a cross-sectional descriptive design. This design enables the identification of the characteristics of the women who are adhering to their medications and those who are not, establishes the magnitude of the problem, as well as compares their characteristics. It was therefore possible to quantify the current levels of adherence to HAART at the research clinics and explore potential factors associated with the identified levels of adherence.

4.2 Study Population

The study population consisted of all women who enrolled in the observational arm of the ongoing clinical trial, who initiated antiretroviral treatment at the research clinics in Molepolole, Lobatse, Mochudi and Gaborone in Botswana and who were still being followed-up during the study period. They were being followed-up for 2 years after delivery and at the time of data collection, only 100 of the women were still being followed-up. Those who had left the study and were no longer being actively followed-up were not included in the study population as the logistical difficulties in tracing them would be considerable (they were receiving treatment at a diverse array of public and private facilities after they completed their 2 year follow-up), resulting in an inevitable low sample realisation level. The study was therefore restricted to those women who had not yet reached 2 years on treatment with the consequence that only short and medium term adherence could be assessed, as all the participants on long term treatment (> 2 years) were then excluded.

4.3 Sampling

This was not necessary because of the small sample size. All 100 women who enrolled in the observational arm of the study and were still within the 2-year active follow up period were requested to participate in the study.

4.4 Data Collection Methods

During their routine monthly HAART medication refill visits over a period of approximately six weeks, (this time was sufficient to access all prospective participants as the women attended the clinic monthly) participants were approached and the study

was introduced to them. Informed consent was then obtained from those interested in participating in the study. Following the informed consent process, the structured questionnaire was administered by a trained research assistant who understands the local language very well. Additional data were extracted from the patient's medical records using a structured data collection tool. The research assistant was trained in the study procedures and human subjects' research ethics. She also had extensive previous experience in conducting health research interviews and administering of questionnaires to research subjects.

The interviewer administered structured questionnaire had both open and closed ended questions. Participant specific identifiers were used to ensure that no participant was interviewed more than once. Participants were interviewed in a quiet private room by the research assistant who was independent of the clinic staff and the larger research study. Enough time was taken to ensure that the participants understood the questions before answering them. The questionnaire captured information on their self reported adherence levels, their socio demographic indices as well as their knowledge and perceptions towards antiretroviral therapy and other factors that may influence their adherence to treatment, as listed in the objectives section. The questionnaire was based on the literature review on adherence and it is similar to what was used in the Kgatlwane *et al.* (2006) adherence study in Botswana (see Appendix 1).

Records of their ARV regimens (and any changes since the start of their treatment), length on treatment, experience of side effects, pill counts, medication refill appointments missed in the past 6 months, current CD4 count and viral loads as well as disease stage was extracted from their clinical records (see Appendix 2). The research sites kept good records of pill counts at each medication refill visit and maintained a good diary of medication refill appointments attended or missed.

4.5 Data Analysis

Data was coded and captured electronically. Accurate coding was ensured by entering the questionnaire data into epi info and double keying at least 10% of the questionnaires

using the epi info data entry module. Data was then cleaned and exported to SPSS version 14 for analysis. Medium term adherence rates measured via pill counts for the past 6 months was defined as the number of doses taken divided by the number of doses prescribed. Due to the high levels of adherence noted among the study population, subjects were categorized as excellent adherence (taking 100% of pills), adequate adherence (taking $\geq 95\%$ of pills) and inadequate adherence (taking $< 95\%$ of pills).

Medication refill appointment records are a coarse measure of adherence, all participants were given one month's supply of medication at a time and therefore had to collect their medication refills every month. Missing one medication refill appointment within the last 6 months was categorised as inadequate adherence. Participants who attended all six medication refill appointments during the last six months were categorised as adequate adherence.

The adherence level by self report (1 day, 3 days and 7 days recall) was analysed to assess short term adherence level. Descriptive statistics was used to assess socio economic and demographic characteristics of the women, as well as other variables. Bivariate analysis comparing potential causative factors with dichotomous cut-off adherence levels was used to examine the potential factors affecting the different measures of adherence. The Chi-square test for independence was used to test the association between the various variables and the dichotomised adherence levels.

Knowledge of HIV/AIDS and ARV's was measured using a 5-point Likert scale to determine the degree of participants' responses, where 'strongly disagree' scored 1, 'disagree' scored 2, 'agree' scored 3 and 'strongly agree' scored 4. Participants who were unable to choose from 1 to 4 were scored 5 (uncertain). The composite variable, knowledge was constructed using 13 knowledge questions. Those who responded correctly to 75% of the questions were rated as having high knowledge, 50 – 74% average knowledge and $< 50\%$ as poor knowledge. Scores of 3 and 4 (agree and strongly agree) to positive questions were graded as correct, while scores of 1 and 2 (strongly disagree and disagree) to negative questions were also graded as correct responses.

Level of satisfaction with the health care system was assessed using standardised questions (Kgatlwane *et al.*, 2006). Length of time on treatment was categorised as ≥ 6 months to < 12 months, ≥ 12 months to < 18 months and ≥ 18 months to < 24 months. Participant's current viral load data (categorised as < 50 or ≥ 50) and CD4 data (categorised as < 200 or ≥ 200) were analysed descriptively. Disease severity was assessed using the WHO staging criteria for HIV/AIDS (see appendix 3). Data was analysed descriptively and then cross tabulated with adherence levels via bivariate analysis with the associated chi square test for independence reported as well.

Experience of side effects was measured via any record of any adverse event in the participants' folders during the last 6 months. Level of counselling received was defined as 'adequate' when the participants reported that they found the counselling sessions very useful or useful and 'inadequate' when the participants reported that they found the counselling sessions not useful or only slightly useful.

4.6 Piloting of the Data collection tools

The questionnaire and records review tools were piloted using 5 participants (and their folders) who were part of the final sample to check for clarity of questions, time and consistency and ease of use by the research assistant. This process helped to slightly modify the instruments and ensured that the data collection tools were adequate in design and user friendly.

4.7 Validity

There is no gold standard for measuring adherence. Self reported adherence is likely to result in an overestimation of adherence as participants may attempt to please the interviewer and recall bias may also affect the accuracy of self reporting. Pill counts are based on the fact that participants took the pills which they did not return and did not discard or retain any of them. There may also be measurement errors associated with pill counts leading to overestimation or underestimation of adherence. If a participant discards (or retains) the pills they were supposed to take and returns the exactly correct residual by deduction, it then would appear that the participant was 100% adherent leading to an overestimation of adherence. Underestimation or overestimation of

adherence may occur if the remaining returned pills were not counted correctly.

The estimates of adherence from pill count data were intended to be combined with the self reported levels of adherence in an attempt to improve the validity of the measurements, as the strengths of one measurement will compensate for the weaknesses of the other. All women in the observational arm of the main study who were still being followed up and consented to participation in the study were interviewed, this minimised the possibility of selection bias. Pharmacy refill adherence may be underestimated if the patient obtains drug from elsewhere and overestimated if patient got a refill but did not eventually swallow the pills.

The interviews were conducted by a trained research assistant who was neither part of the main project research team nor a staff member at the clinics, thus minimising the possibility of participants overrating access to services and counselling received at the clinic and overestimating adherence levels. The questionnaire was developed using an extensive literature review and a pre-existing questionnaire, and therefore it would at least have face validity. A strenuous attempt was made to use unambiguous questions and the research assistant was carefully trained to administer the questionnaire in a standardised manner. Data from the participants' medical records were highly comprehensive and accurate, as the facilities are research clinics which are geared to collecting data. The research assistant was also trained to collect the data from the medical records in a standardised manner.

4.8 Reliability

Given the standardised data collection instruments and the standardised training, reliability is likely to be high, although reliability was not formally assessed.

4.9 Ethical Considerations

HIV/AIDS is a highly stigmatizing disease, thus the highest ethical conduct was necessary for this study. Ethical clearance was obtained from UWC ethics committee. Permission to conduct the research was obtained from the research site, the Principal

investigator of the larger project and the Botswana Health Research Development Committee (HRDC). Informed consent was obtained from the patients before the questionnaire was administered to them. Participants were allowed to refuse participation and their refusal had no effect on their treatment and care. Also they could withdraw at any stage of the study without giving any reason for their withdrawal and this would not affect their treatment or care at the clinic. Careful measures were taken to maintain participants' confidentiality. Counselling was offered to those who were having problems with adhering to their medications.



CHAPTER 5

RESULTS

5.0 Introduction

This chapter gives a summary of the results of the study in both descriptive and analytical form. A total of Ninety four (94) women out of the one hundred (100) women who were still being followed-up during the study period consented, and were interviewed. Data were also extracted from their medical records. Out of the 6 women who were not interviewed, 5 did not consent, and 1 did not return for her pills during the recruitment period and could not be reached by telephone (probably moved out of the study area).

In order to understand the factors affecting adherence, the analysis examined the characteristics of the study population, the socio-economic status of participants, access to health services, adequacy of counseling, knowledge and attitudes towards HIV/AIDS and antiretroviral treatment, disease and treatment characteristics in relation to adherence to ART.

5.1 Demographic and socio economic information of study participants

Table 5.1 gives a summary of the socio-demographic characteristics of the study participants. Most of the participants (55%) were in the age group 31 – 40 years. The lowest age for participation in this study was 21years because the larger project had an age criterion; i.e. women less than 21years were excluded as 21years was the cut-off age of consent in Botswana for research purposes at the time that the project commenced.

The majority of the participants (68%) were single, and most of the participants were of Christian religious background (66%). There were no participants of Muslim and African traditional religion in this study, which is an unusual finding as both of these religions have a large minority presence in Botswana (CSO, 2001). It is possible that for some unknown reasons women in these groups did not enroll into the main study. “Other” might have been chosen in the questionnaire by those who believe in God but are not practicing any of the religions listed or chose not to disclose their religious affiliations.

A high level of education status was recorded, with 70% of the participants having received secondary education. This may reflect the fact that access to education has in the recent past been free in Botswana, with a minimal fee introduced in the past 2-3 years for some people and an ongoing government social support program for those living below the poverty line, or assessed to be exempted due to their socioeconomic status. However, there were no participants in this study with a tertiary level education despite tertiary education being government supported through a study grant and/or loan to all who qualify to be admitted to both public and private tertiary institutions (Botswana Ministry of Education and Skills Development, 2009). The lack of participants with tertiary education is probably because they are more likely to use private sector facilities which supply HAART during their pregnancy, rather than the research clinics or the public sector clinics.

Table 5.1: Socio-demographic characteristics of the participants (n=94 for all the variables)

Variable	Number	Percentage
Age		
21 – 30	36	38
31 – 40	52	55
> 40	6	6
Marital status		
Single	64	68
Married	10	11
Cohabiting	20	21
Religion		
Christian	62	66
Atheism	5	5
Other	27	29
Education		
primary or less	28	30
Secondary	66	70
Employment status		
Employed	33	35
Unemployed	45	48
self-employed	16	17

Table 5.2 gives a summary of the socio-economic characteristics of the participants. Formal employment was not high and a large majority of the participant's income was less than Botswana Pula (BWP) 1500 per month (approximately 2000 rands or 300 United States Dollars). Very few (5%) participants missed a dose of medication due to lack of food.

Table 5.2: Socio-economic characteristics of the participants

Variable	Number	Percentage
Income in Pula (n=49)		
< 500	13	27
501 – 1000	18	37
1001 – 1500	7	14
> 1500	11	22
No. in household (n=94)		
1 – 5	57	61
6 – 10	29	31
> 10	8	9
Ever missed dose due to lack of food (n=93)		
Yes	5	5
No	88	94
Electricity in compound(n=94)		
Yes	43	46
No	51	54
Toilet facility in compound (n=94)		
Yes	78	83
No	16	17
Type of toilet facility (n=94)		
Adequate (flush toilet/private pit latrine)	76	81
Inadequate (shared pit latrine with other compounds)	18	19

5.2 Levels of Adherence

5.2.1 Adherence by participant self report

No missed doses were reported by participants in the 1 day recall, 3 day recall and 7 day recall. The adherence level was hence recorded as 100% for all participants for each of the recall periods.

5.2.2 Adherence by Pill count

Pill count adherence over 6 months was very high with 99% of the participants having 95% adherence or higher. Using the “adequate” or “optimal” recommended adherence of 95%, the results indicate a very high level of adherence in this cohort. However if adherence was examined using the absolute 100% target for “excellent” adherence, the pill count adherence level was 67% (Figure 5.1).

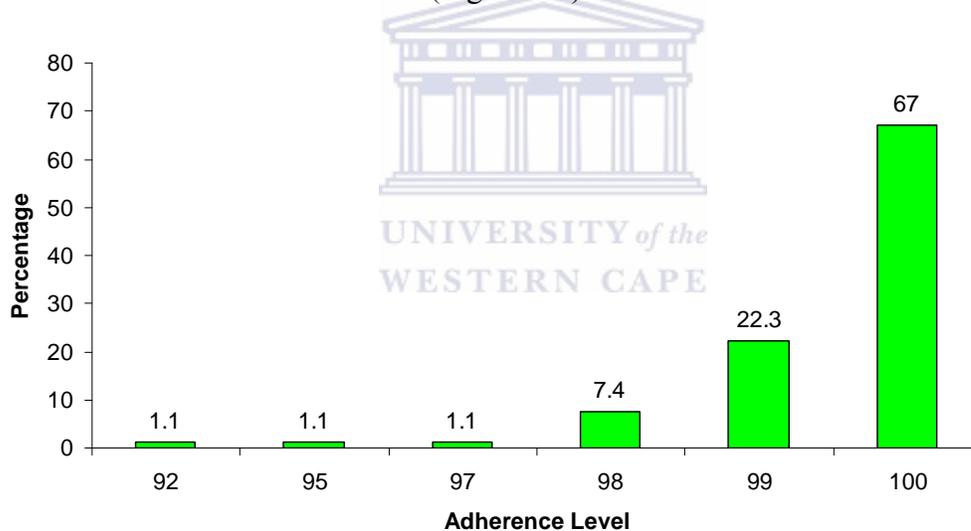


Figure 5.1: Distribution of the level of adherence of the participants as measured by pill count over a 6 months period (n=94)

As self reported adherence was 100% for everyone (section 5.2.1), I did not combine the results of self reported adherence and pill count adherence as initially planned, as doing this will not improve the validity of the results.

5.2.3 Adherence by Pill count stratified by pregnancy stage

Very high adherence levels were recorded across the three pregnancy periods. Figure 5.2

below, shows the distribution of the participant's adherence levels stratified by stages.

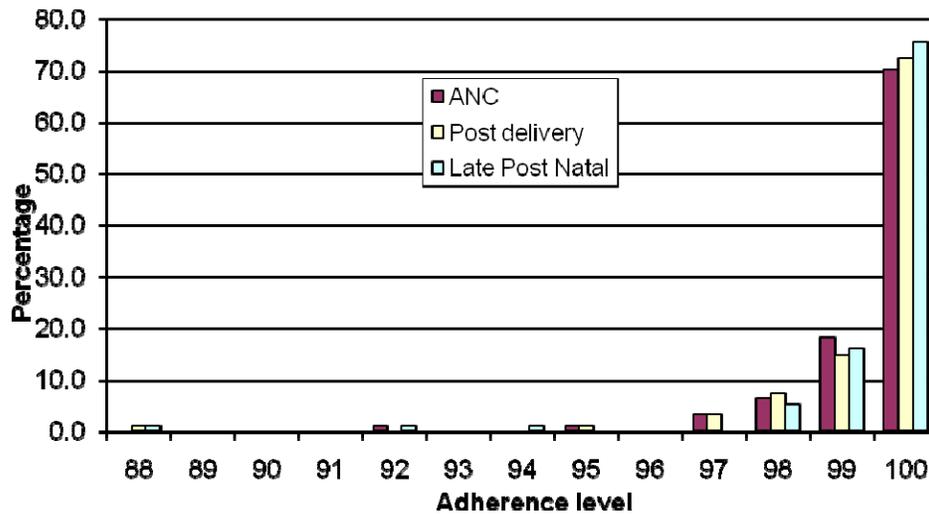


Figure 5.2: Distribution of the levels of adherence by 6 months pill count (n=94), by antenatal, post delivery (up to 6months after delivery) and late postnatal periods (greater than 6 months after delivery).

5.2.4 Adherence by missed medication refill appointment

Table 5.3 shows the frequency distribution of the missed medication refill visits in the past 6 months stratified by pregnancy stage. There was a high adherence to medication refill appointments across the scheduled pharmacy refill visits throughout the three different pregnancy stages. The mean adherence to refill appointments was 97.9% and decreased very slightly from 98.9% in the antenatal period to 96.8% in the late postnatal period (see Table 5.3).

Table 5.3: Missed medication refill appointment in the past 6months stratified by pregnancy stage.

Missed medication Refill Appointment	Antenatal period		Immediate Postnatal period		Late Postnatal Period		Mean %
	No	Percentage	No	Percentage	No	Percentage	
	Yes	1	1.1	2	2.1	3	
No	93	98.9	92	97.9	91	96.8	97.9
Total	94	100	94	100	94	100	100

5.3 Univariate Analysis of potential factors associated with Adherence.

5.3.1 Disclosure of HIV status

The level of disclosure in this cohort was very high. Eighty eight (94%) of the participants had disclosed their status to at least 1 person. Of the 6 participants who did not disclose their HIV status 5 were single and 1 was cohabiting. Figures 5.3 and 5.4 and shows disclosure stratified by marital status and who disclosed to.

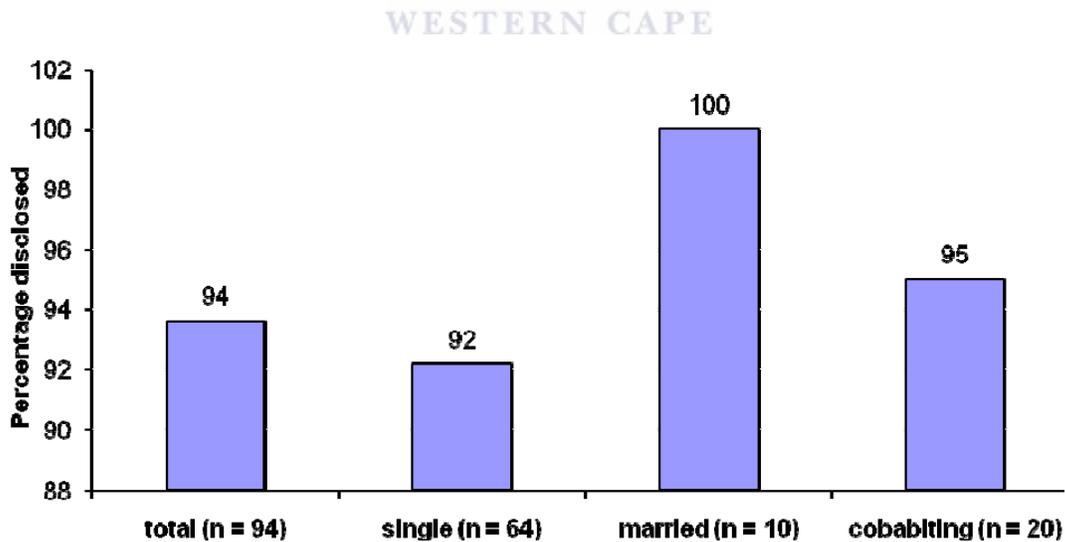


Figure 5.3: Distribution of percent disclosure stratified by marital status of the participants.

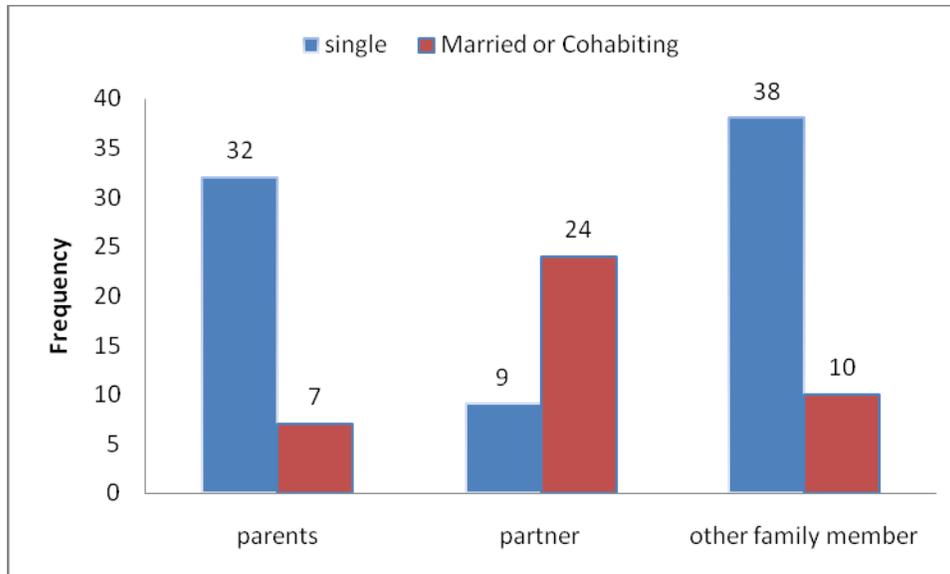


Figure 5.4: Distribution of whom in the household the participant disclosed to (multiple responses allowed) n=64 for single and n=30 for married or cohabiting

5.3.2 Access to Health services

5.3.2.1 Time to clinic and mode of transport

Figures 5.5 show the distribution of the time taken to travel to the clinic. Most of the participants took 30 minutes or less to travel to the clinic and 89% travelled for at most 1 hour (Figure 5.5). Some participants (68%) noted that there is generally a loss of income related to time taken to visit the health facility and 17 (18%) reported an increase in expenditure. Out of those who reported an increase in expenditure, 12 (71%) attributed the increase to transport costs.

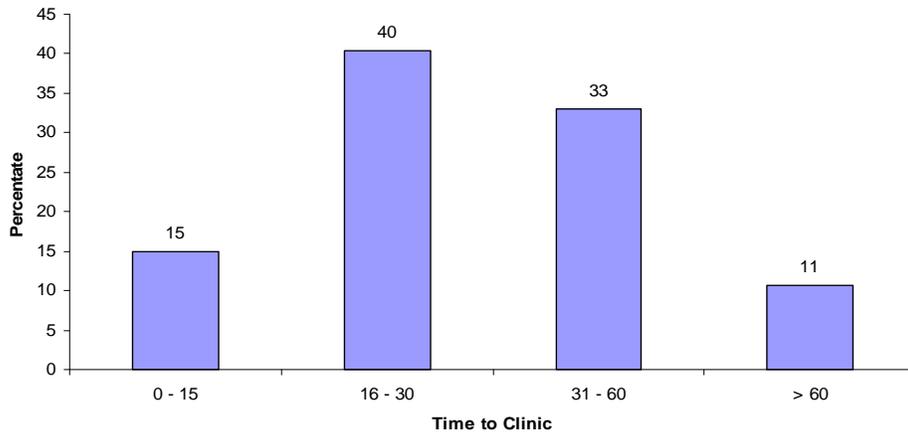


Figure 5.5: Distribution of the time taken to travel to the clinic

5.3.3 Adequacy of Service and Level of Counseling

Participants were asked to rate the frequency, adequacy and level of counseling they received at the health facility. Almost all the participants (99%) stated they were formally counseled before or when they started treatment, yet 30% stated that they have never again received formal adherence counseling after they started HAART (Figure 5.6).

Almost all participants reported being satisfied with both the adequacy of the counseling (Figure 5.7) and the overall quality of the health services (Figure 5.8).

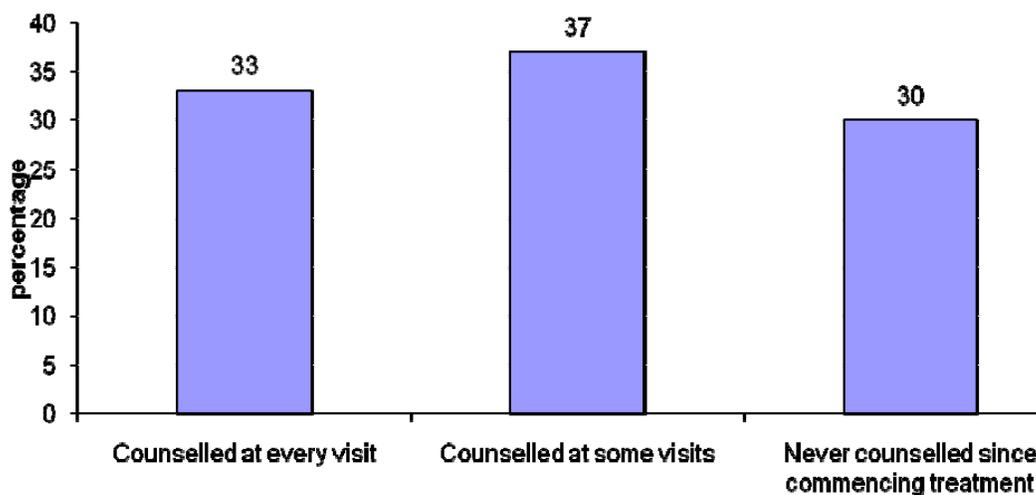


Figure 5.6: Rating of the frequency of adherence counseling by the participants (n=93)

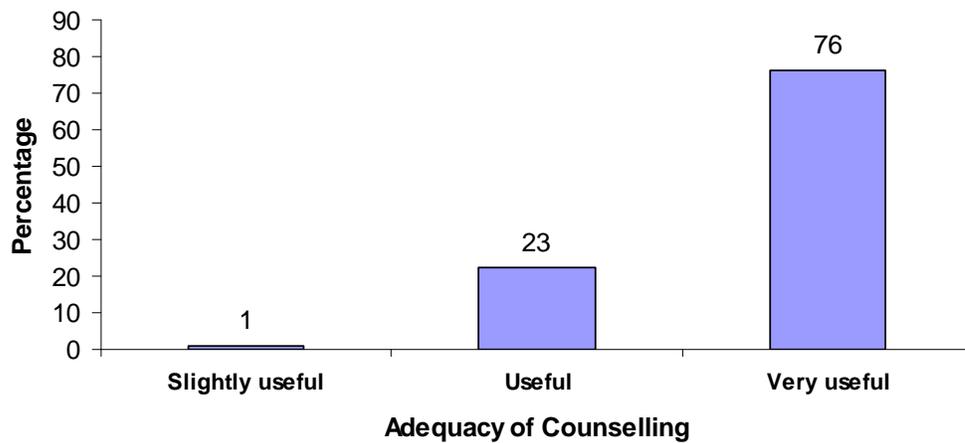


Figure 5.7: Rating of the adequacy of counseling by the participants (n=93)

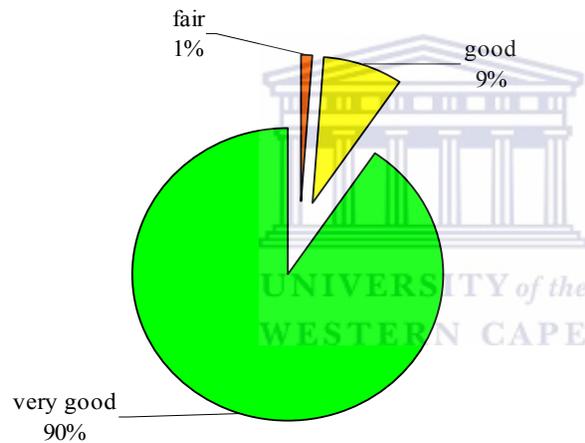


Figure 5.8: Rating of the overall quality of the services offered at the health facility (n=93).

Participants were asked if they talked to the health worker about their experience of using the medicines and if health workers enquired about and monitored their medication experiences. The results are shown in table 5.4. The overwhelmingly positive results indicate that this cohort received consistent adherence monitoring, via the pill count method.

Table 5.4: Continuing Adherence Monitoring

Adherence counseling	Number	Percent
Did you talk with the health worker about your experience of using your medicines?		
Yes	88	94
No	6	6
Total	94	100
Did the health worker ask you if you have missed a dose of your medication?		
Yes	87	99
No	1	1
Total	88	100
Did the health worker explain to you what the effects of missing a dose are?		
Yes	80	91
No	8	9
Total	88	100
Did the health worker ask if you are taking other medicines or traditional medicines?		
Yes	71	81
No	17	19
Total	88	100
Did the health worker count your pills before giving you a new supply?		
Yes	93	99
No	1	1
Total	94	100



5.3.4 Knowledge of ARV's and HIV/AIDS

In order to evaluate the impact of knowledge of ARV adherence specifically and ARVs and HIV/AIDS in general, participants were asked a series of 13 knowledge questions. There was a high level of knowledge among the participants (Table 5.5a and Table 5.5b), reinforcing the previous findings about consistent adherence monitoring and informal counseling during the health facility visits. More than 90% responded correctly to most of the knowledge questions, that is either agree or strongly agree to positive statements about ARVs and HIV/AIDS or disagree/strongly disagree about negative statements about ARVs and HIV/AIDS. Some participants were not very clear on the technical issues about what happens to the virus levels during treatment, as 87% responded correctly (Table 5.5a). Figure 5.9 ranks the high level of knowledge graphically for the percent of participants who responded correctly to the specified questions. When using the composite score (% of correct responses to knowledge questions), a total of 94.7%

achieved an excellent knowledge of greater than or equal to 75% of all questions correctly answered.

Table 5.5a: Knowledge on ARV adherence

Knowledge question: About ARVs “What happens if you stop taking your medications” N = 94	Response (%)		
	disagree	agree	uncertain
Your health will get worse?	1.1	96.8	2.1
You may develop opportunistic infections	2.1	96.8	1.1
Nothing will happen?	93.6	4.3	2.1
Your CD4 will decrease?	3.2	95.7	1.1
You may loose weight?	5.3	90.4	4.3
You may develop diarrhoea?	6.4	76.6	17.0
Your viral load will increase?	8.5	87.2	4.3

Table 5.5b: Knowledge of HIV/AIDS and ARVs

Knowledge question: About HIV/AIDS (N=94)	Response (%)		
	disagree	agree	uncertain
Disease has no cure for now and therefore I need to continue treatment forever?		100.0	
Treatment helps to prolong life?	1.1	97.9	1.1
Taking of ARV’s may result in experience of side effects like nausea, vomiting, hepatitis, low blood count and diarrhoea?	3.2	90.4	6.4
Treatment helps to reduce the chances of transmission to the unborn and breast feeding infants?	2.1	97.9	
ARV’s work by suppressing viral load and increasing CD4 counts, do you agree?	1.1	98.9	
ARV’s can interact with other drugs including indigenous or traditional medications causing serious reaction?	5.3	90.4	4.3

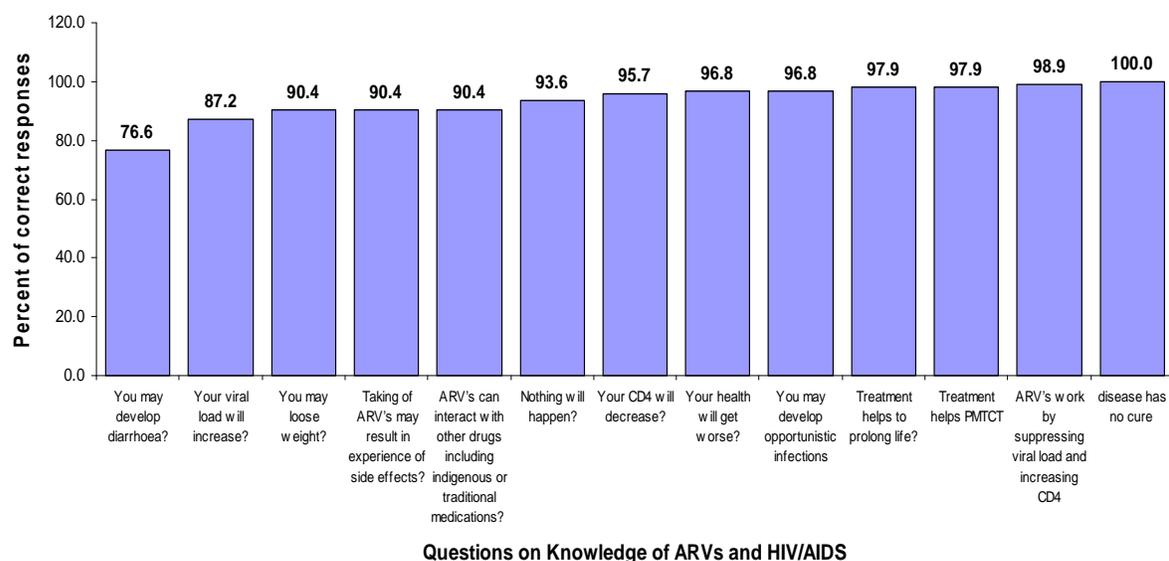


Figure 5.9: Knowledge of the participants on effects of ART and HIV/AIDS (n=94)

5.3.5 ARV regimens and duration on treatment

Most of the patients (88.3%) were on AZT/3TC/Nevaripine (AZT/3TC/NVP), the recommended initial first line drug in Botswana which was used for this cohort in the parent study (table 4.6). Most of the participants (96%) were still receiving first line treatment indicating successful response to therapy.

Table 5.6: Participants ARV regimens and treatment type

Treatment Regimen	Number	Percent
Aluvia/Combivir (ALU/CBV)	1	1.1
Aluvia/Nevirapine (ALU/NVP)	1	1.1
Aluvia/Truvada (ALU/TRU)	1	1.1
AZT/3TC/Nevirapine (AZT/3TC/NVP)	83	88.3
Nevirapine/Truvada (NVP/TRU)	8	8.5
Total	94	100.0
Regimen Type		
First Line	90	95.7
Second Line	4	4.3
Total	94	100.0

5.3.6 Reasons for Missing Medications

Participants were asked if they have ever missed any medications because of some specified reasons. A total of 18% reported to have missed some medications due to forgetfulness, while 13% did not have the pills at the time they needed to take them. Very few participants missed their medication due to the number of pills to be taken, side effects or feeling better (Figure 4.10)

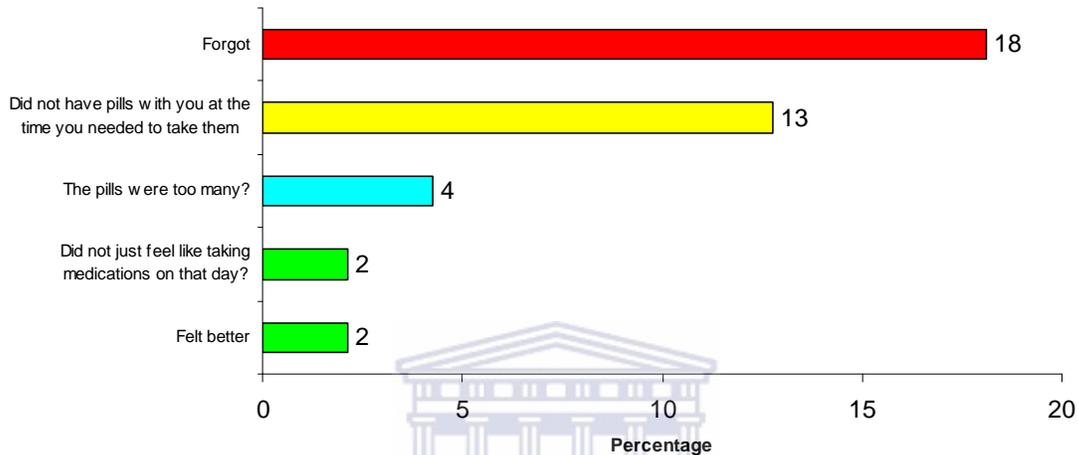


Figure 5.10: Reasons for ever missing medications (n=94)

5.3.7 Disease characteristics

Most (80%) of the participants in the study were WHO stage I/II disease. The CD4 counts levels were lower in the antenatal stage and increased with time on treatment, however these increases were not statistically significant (Figure 5.11). Figure 5.11 also shows the distribution of CD4 counts by stage. The mean CD4 counts during the antenatal, immediate postnatal and late postnatal periods were 266, 316 and 346 respectively. There was no association between the mean change in CD4 counts at the three time points: antenatal vs. immediate postnatal period ($p = 0.458$); antenatal vs. late postnatal period ($p=0.659$); and immediate postnatal vs. late postnatal period ($p=0.714$).

The proportion of subjects with undetectable viral load increased sequentially from the antenatal period (82%), through the immediate post natal period (93%) and on to late post natal period (94%). The participants had been on treatment on average for 20 months (Figure 5.12) however there was no evidence for any correlation between time on

treatment and adherence (spearman's rho = 0.064; p = 0.539).

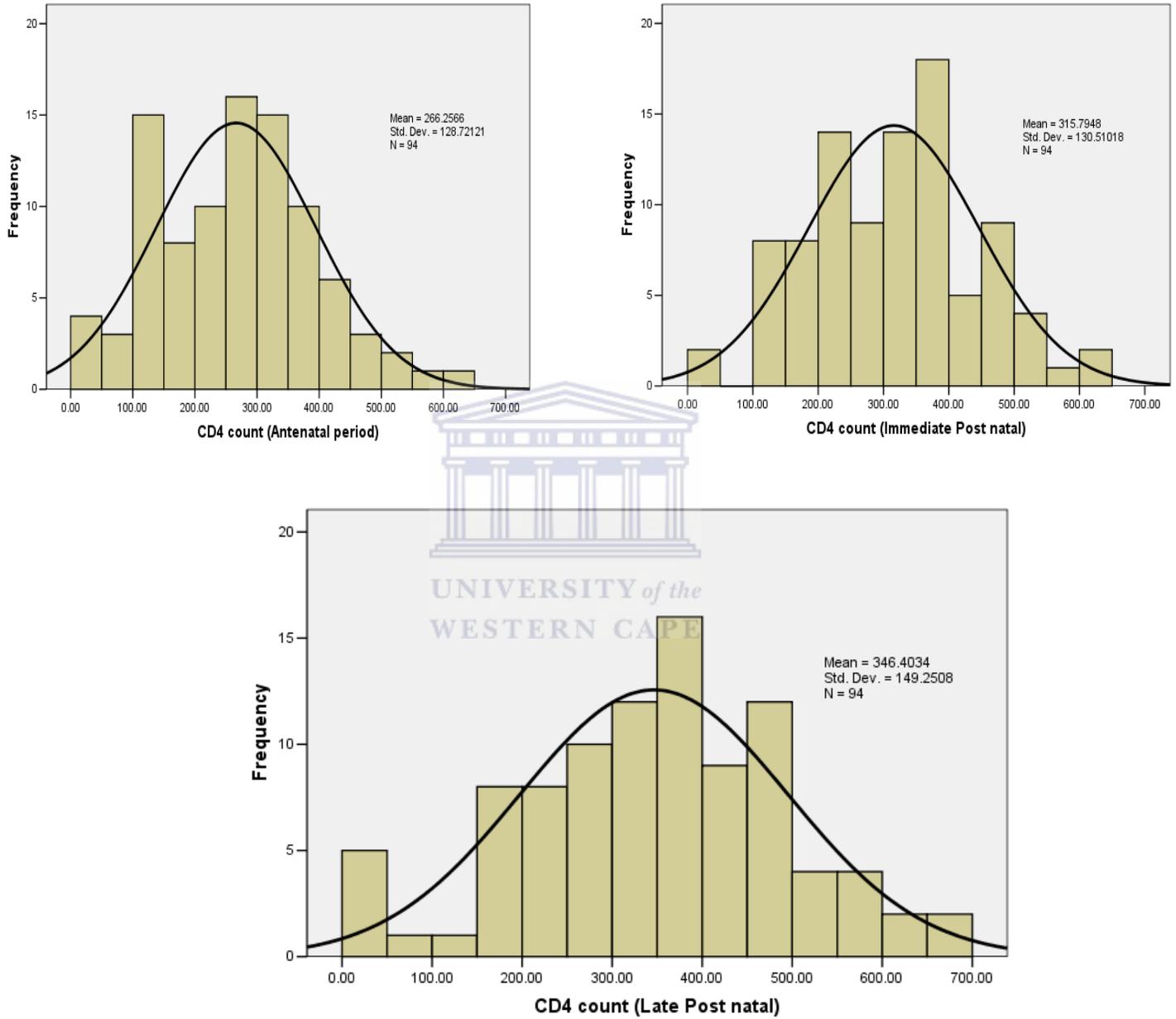


Figure 5.11: Distribution of CD4 counts at different pregnancy stages.

Figure 5.12 below shows length of participants' time on follow up in the parent study during the conduct of this study. 1(1.1%) has been on follow up for <1year while 93(98.9%) has been on follow up for more than one year

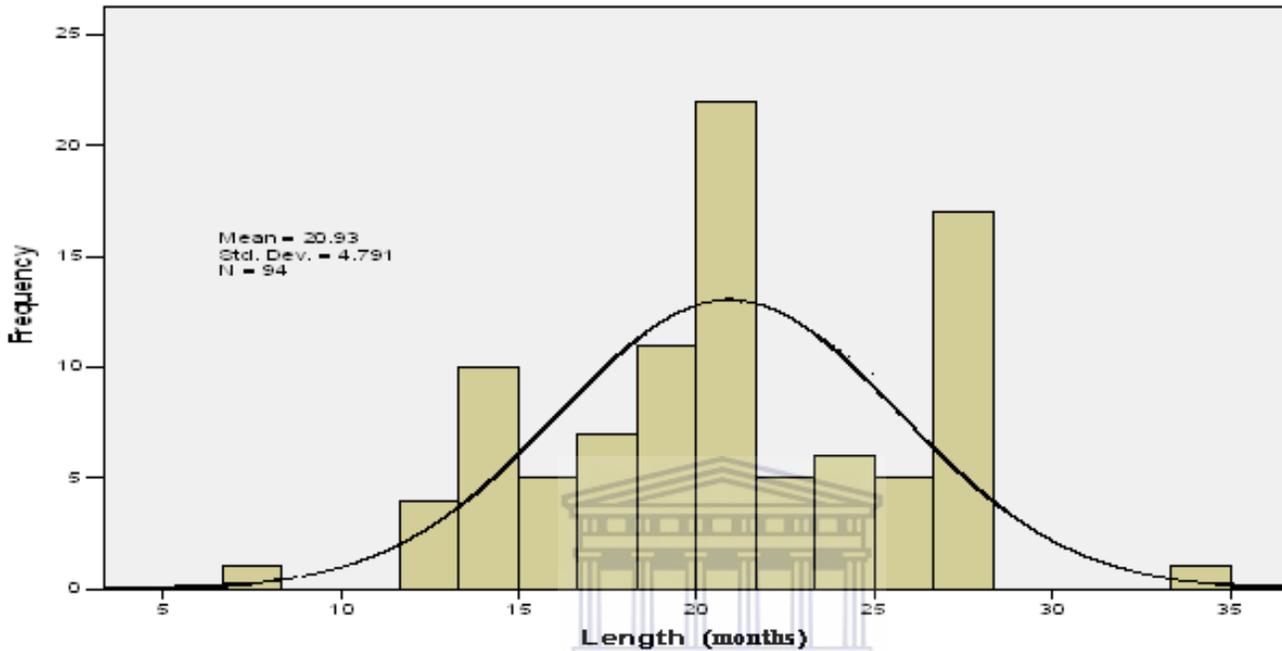


Figure 5.12: Distribution of participants' time on treatment.

5.4 Bivariate Analysis of Potential factors associated with Adherence

As self reported short term adherence was 100% for all participants and missed medication refill levels were 97.9%, it was prudent to use the 6 months pill count measure of adherence in the bivariate analysis. In order to explore the potential association of various factors with adherence, the “perfect” adherence level (100% adherence) was used, because there were only 1% of the participants in the study that did not reach the “adequate” level of greater than or equal to 95% adherence by pill count.

Table 5.8 shows a cross tabulation of various patient characteristics with “perfect” (100%) and “imperfect” <100% adherence by pill count. There was no significant finding when any of the factors were cross tabulated with “perfect” and “imperfect” adherence. , Since on bivariate analysis none of the potential predictors of adherence showed any significant association with adherence, multivariate analysis was not appropriate.

Table 5.8: Pill count Adherence and Patient characteristics

Variable	Imperfect Adherence (< 100%)	Perfect Adherence (100%)	Prevalence Ratio	95% confidence Interval	P value
Age					
<= 30	13	23			
> 30	18	40	1.16	0.63 - 2.08	0.61
Marital Status					
Single	21	43			
Married and cohabiting	10	20	0.98	0.53 - 1.82	0.55
Religion					
Christian	20	42			
Other	11	21	0.94	0.52 - 1.71	0.84
Educational Level					
primary or less	11	17			
Secondary	20	46	1.30	0.72 - 2.30	0.40
Employment					
Employed	9	24			
unemployed/self-employed	22	39	0.76	0.40 - 1.40	0.39
Income					
<= 1000	5	13			
> 1000	7	24	1.23	0.46 - 3.30	0.68
Housing					
Inadequate	5	9			
Adequate	26	54	1.10	0.42 - 1.97	0.81
Hiding medication					
Yes	2	1			
No	29	62	2.09	0.89 - 4.90	0.25*
Travel time to clinic					
<= 30 minutes	17	35			
> 30 minutes	13	28	1.03	0.57 - 1.87	0.92
Follow-up Adherence counseling					
Yes	9	22			
No	22	41	0.83	0.44 - 1.59	0.57
Knowledge of HIV/AIDS and ART					
Inadequate	25	46			
Adequate	6	17	1.34	0.85 - 1.54	0.42
First line	29	61			
Second line	2	2	1.35	0.50 - 3.60	0.60*
Stage of Pregnancy					
Antenatal	28	66			
Posnatal	24	70	1.17	0.62 - 2.47	0.51
CD4 count					
< 250	9	14			
>=250	22	49	1.26	0.68 - 2.34	0.47
Viral Load					
Detectable	8	9			
Undetectable	23	54	1.33	0.83 - 2.10	0.17
Other medical conditions					
Yes	2	4			
No	29	59	1.01	0.31 - 3.26	0.65*
Length of treatment					
= < 1 year	0	1			
> 1 year	31	62	-	-	0.67*
Side Effects					
Recorded	0	1			
Not recorded	31	62	-	-	0.67*

* Fishers exact test

CHAPTER 6

DISCUSSION, LIMITATIONS, GENERALIZABILITY, CONCLUSION AND RECOMMENDATIONS

6.1 Discussion

The use of HAART among pregnant woman has in recent years led to further reductions in mother to child transmission to less than 2% in the regions of the world where it has been implemented (WHO, 2007). Lack of adherence to HAART treatment continues to be the major cause of higher than expected vertical transmission rates of the human immunodeficiency virus as well as treatment failure. The purpose of the study was to assess the level of adherence among women who initiated HAART treatment during pregnancy at research clinics in Botswana and are expected to continue their treatment indefinitely. To my knowledge, this is the first study to report on the assessment of adherence among women who initiated treatment during pregnancy in Botswana.

Using the 6months pill count measurement we also found that 99% of participants have an “adequate” adherence level of 95% and above. The ultimate is for patients to take all their medication and achieve an “excellent” level of adherence of 100%. In this study adherence was also examined *post-hoc* using the 100% cut-off level. Using this classification, we found that 67% of the participants reached 100% adherence as measured by pill counts over the past 6 months. This finding from a research setting could have resulted from intensive close monitoring of the women and more frequent study visit schedules. Before initiating treatment most of the women consented to unscheduled home visits by members of the study team and also identified adherence partners whose role was to remind them to take their medications as prescribed.

Findings from this study are also consistent with a previous study in Botswana which reported “adequate” adherence to ART in the general population as high as 77% by pill counts and 96% by participants self report (Kgatlwane *et al.*, 2006). Despite the concerns about low adherence which have been cited by those who question the feasibility of rapidly scaling up antiretroviral therapy programmes especially in resource poor settings (Stephens, Kaye & Corrah, 2004, Raboud, 2002), this study strengthens the existing

findings from other studies that have shown that it is possible to maintain high adherence in these settings. Mills *et al.*, (2006) reported that self reported and pill count adherence rates in African settings were found to be higher than in North American settings, and noted that this may reflect a true higher adherence, or may reflect a greater desire by patients to report high adherence to health workers. Indirect evidence that high adherence levels in this study and by extension in Botswana are real is that the mother to child vertical transmission (MTCT) rates of HIV in Botswana are very low at less than 4% (Ministry of Health, 2007) and in this study they were extremely low at 0.6% for infants born to women enrolled in this cohort.

Higher levels of adherence obtained in this study may reflect the clinical trial setting in which the women were being followed. As in all research settings the quality of care in this setting is likely to be higher than what obtains in the public sector and probably is better than that experienced in the private sector as well. The frequency of contact with the health workers was also higher and is highly likely to have contributed to the higher adherence level, especially given that at each visit adherence monitoring was conducted. Alternatively the very high adherence rates could simply be an overestimate of adherence and as with all measures of adherence besides drug serum levels it is impossible to determine whether this is the case. However a synthesis of the comments above which all indicate that a high level of adherence is plausible, suggest that even if the pill count adherence is an overestimate it is still likely to be close to the actual adherence level in this population.

Given that pregnant woman are generally required to attend health facilities for regular health checks, the contacts with the health care workers during the antenatal period in the public and private sector should also serve to reinforce medication adherence, which is likely to result in pregnant women taking their medications more religiously than other people on HAART. However, the finding of no significant difference between adherence during the antenatal period, immediate postnatal and late postnatal period (when breastfeeding would have ceased) suggests that the risk of viral transmission to the child during pregnancy or breastfeeding was not a significant added motivation for adherence

in this population. Alternatively since the adherence levels were high throughout all three periods it might suggest that this added motivation was not needed to achieve high adherence. When adherence is already high it is very difficult to assess the added effect of a promoter on adherence and hence the potential additive effect of desire to reduce vertical transmission is best assessed amongst a population where adherence levels are generally low. The plausibility of this is supported in the reports by Bardequez *et al.*, (2008) & Vaz *et al.*, (2007) who reported a higher antenatal adherence and lower adherence in the postnatal period among cohorts of US and Brazilian pregnant women, where overall adherence rates were lower than in this study. The other explanation for no difference in adherence levels between the antenatal and postnatal adherence periods is that the desire to prevent vertical transmission was present in both periods, as all the participants' were required to breastfed for 6 months. This explanation would however be contradicted by the lack of difference in adherence levels between the antenatal/early postnatal and the late postnatal period as the participants did not breastfeed during the late postnatal period. In this regard it is worth noting that both the US and Brazil studies mentioned above were done amongst a non breastfeeding population.

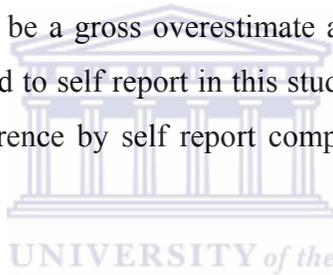
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This study showed a high level of adherence counselling with 99% having being formally counselled at least once, 70% of the participants having received more than one formal counselling session, almost all (99%) having received informal counselling during adherence monitoring and 99% of participants satisfied with the level of counselling received (Figures 5.7 and 5.8). Since this counselling was provided to everyone it is likely that it affected the overall high level of adherence.

Using the patient self report measurement we found a high degree of short term adherence to HAART among women in this population, with 100% of the patients reporting that they had 100% adherence during the last 7 days. It is possible that the participants told the research assistant what they thought she wanted to hear and hence an overestimate of adherence was obtained via this measurement. Lu *et al.*, (2008) reported that self-recall measures of antiretroviral adherence vary greatly in recall time periods

and further suggested that over reporting was higher for 3 day and 7 day recall and more reflective for the 1month recall.

During the interview participants may find it difficult or embarrassing to say that they missed their medication and therefore overestimate their adherence responses. Pill counts might therefore provide a better measure of adherence albeit with a caveat; they may overestimate adherence if the participant discards (or retains) the pills they are supposed to return to the clinic. It seems probable that only a longitudinal analysis of adherence via regular serum drug assays or biochemical markers may allow justice to be done to the subject of assessing adherence at both patient and population levels. Based on reported pill count adherence, participants self reported adherence was way too high in this study and given that pill counts itself might be an overestimate, it is reasonable to say that adherence by self report could be a gross overestimate and pill count might be a better measure of adherence compared to self report in this study. Kgatlwane *et al.*, (2006) had similar finding of higher adherence by self report compared to pill count in Botswana (96% and 75% respectively).



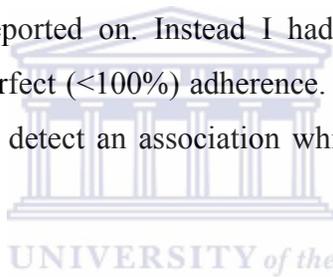
This study also reported a high adherence to medication refill appointments across the scheduled pharmacy refill visits throughout the three different pregnancy stages. The mean adherence to refill appointments was 97.9% and decreased from 98.9% in the ANC period to 96.8% in the late postnatal period. Although Pharmacy refill appointments is a very coarse measure of adherence, as it can only determine if patients are inadequately adhering but cannot determine if they are adequately adhering since collecting drugs does not necessarily mean taking them as prescribed by the health care provider (Steiner & Prochazka, 1997), the low level of missed medication refills is consistent with and supports the veracity of the high level of adherence reported in this study using pill count.

Bivariate analysis showed no association between adherence by pill count and any of the potential factors commonly found associated with adherence by other studies. The possible explanations for these findings may include the following; the sample size was not large enough to detect associations which might truly exist in this study population.

Differential measurement bias with the possibility that some of the participants categorised as perfect or excellent (100%) adherence might not be so, due to the inherent pill count measurement error described above.

The participants were very homogenous for several of the factors assessed due to the main study being a randomised clinical trial with strict inclusion and exclusion criteria. Because of this homogeneity a very large sample size would be required to find an association which might truly exist. For example there was no association of adherence with age and this might be due to all participants being 21 years or older, thus eliminating the younger women who would likely have very different adherence levels.

The participants also had very similar adherence levels (uniformly high.) Adherence levels were so high that a bivariate analysis using adequate ($\geq 95\%$) versus inadequate ($< 95\%$) adherence was not reported on. Instead I had to assess perfect or excellent (100%) adherence versus imperfect ($< 100\%$) adherence. Again, this homogeneity would require a very large sample to detect an association which might truly exist within the study population.



Because this study assessed potential factors by comparing perfect or excellent (100%) adherence versus imperfect ($< 100\%$) adherence, it differs from other adherence studies which usually compared adequate versus inadequate adherence. So the factors associated with adequate adherence might in fact not be associated with excellent adherence, or more likely they might be only weakly associated with it.

It might also be possible that the research clinic environment overrides or modifies the effect that these usually associated factors have on adherence, and thus acts as an effect modifier. This could happen in two ways. Directly by providing things which directly increases adherence such as excellent and ongoing adherence counseling. This might result in substantially increased adherence amongst all participants, and since adherence is increased in all the participants, the differences between sub-groups would be minimized. Secondly the research clinic might do this indirectly, for example by informally transmitting increased knowledge of ARVs and HIV, which the participants

could accrue due to the excellent service provided, frequent contact with the clinic, long service time per visit and increased rapport they have with the staff. This increased level of knowledge could then override the effect of several factors such as lack of general education, or low income, or lack of adequate housing for example and hence these and other related factors in this study are not associated with adherence as they were overridden. The above suggestions are mainly speculative though and would need to be confirmed or refuted by larger studies with more accurate and detailed measures of adherence.

Patients were also asked to provide reasons for potentially missing their medication. Forgetfulness was the most cited reason (18%) followed by lack of access to pills at the time doses needed to be taken (13%). There were no reported problems with pill burden, side effects or not taking medications because of feeling better. Forgetting is one of the major reasons found in many studies for poor adherence to treatment. Some studies have reported that the important barriers to adherence namely; forgetfulness, lack of access to pills, feeling better and alcohol use; were consistent across multiple settings and countries (Walsh *et al.*, 2001; Murphy *et al.*, 2004; Kgatlwane *et al.*, 2006; Mills *et al.*, 2006). In Botswana patients on ART are required to identify an adherence partner and are facilitated to choose an adherence package that will enable them not to forget their medication.

Most of the participants (97%) in this study were still on first line therapy (Table 5.6) and the majority of them have been on treatment for more than 1 year via the parent study. This indicates that there have been very few (3%) regimen failures among the women in the on-going follow-up period, although it is possible that a few of the subjects still on first line therapy are possibly failing and should have been transitioned to second line therapy. This high percentage of first line therapy, high degree of knowledge of HIV/AIDS and ARVs as well as very low MTCT rates for this cohort (0.6%) reported by the parent study (Shapiro *et al.*, 2009), indirectly supports the veracity of the key finding of high levels of adherence.

6.2 Limitations

- There is no gold standard for measuring adherence and each measure of adherence has its unique limitations. The limitations on measuring adherence which this study encountered were: the pill count measurement used in this study may have overestimated adherence as participants may have removed pills from their containers without actually swallowing them; participants might have told the health worker what they want to hear, hence self report adherence would have been overestimated; excellent pharmacy refill appointments do not necessarily translate into excellent adherence as participants might not have taken the medications as prescribed.
- Patients were being followed in a research setting and therefore their disease characteristics are fairly homogeneous and they probably receive a higher quality of care than the women attending public sector clinics. The findings may therefore not be representative of what obtains in the general population.
- Only pregnant women 21 years and older were included in the study. Anecdotal evidence suggests that younger pregnant women are less likely to adhere to their medications compared to older pregnant women.
- The patients that have left the research clinics have been excluded from the sample as they would be difficult to track. These patients started transitioning to the local clinics since august 2008 on completion of 2 years of required follow up after delivery. The exclusion of them prevented the assessment of long-term adherence, but it is unlikely that their exclusion affected the medium-term (6 months pill count) and short term (7 day recall) adherence, as they are likely to have had similar adherence levels at the equivalent time period in their treatment. This is because neither the recruitment nor management procedures changed during the study period.
- Five participants did not consent to participation in the study. Without their consent it was not possible to review their patient files for the purpose of this study. It is possible that they may have had lower adherence levels as they were informed via the study information sheet that the study intended to investigate adherence. It is however unlikely that this would have introduced a substantial

selection bias, given their small numbers.

- One person could not be reached as she did not attend the clinic during the 6 week data collection period. It is almost certain that this patient had lower adherence levels as she missed her medication refill appointment.

6.3 Generalisability

The results of this study may apply mainly to the study population. However it will also have a broader relevance especially among women who initiated antiretroviral therapy during pregnancy in urban and peri-urban communities in Botswana and countries with similar socioeconomic circumstances. However a rider to this is that generalisability would only obtain if in addition they received their treatment in a similarly supportive way to that which was provided at the research clinics.

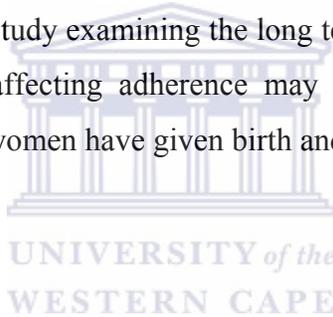
6.4 Conclusion

A high level of adherence was found among pregnant women on HAART. Ninety-nine (99%) of the participants had optimal medium term adherence of 95% or higher using 6 months pill count measurement. A 100% short term adherence was reported by participant self report based on 1-day, 3-day and 7-day recall, this is likely to be an overestimate. Sixty-seven percent of the participants had an excellent level of medium term adherence of 100% by pill count and 99% of them had an adequate adherence level of 95% or more. Although this might also be an overestimate it is likely that it is close to the actual adherence level. There were no differences observed in adherence between the antenatal, immediate postnatal and late postnatal periods. The major reasons cited by participants for missing medications were forgetfulness and not having access to medication at the time required to take the doses. There was a high knowledge of ARVs and HIV/AIDS. Access to health services and counselling was rated very high by the participants, similarly for quality of care. There were no significant associations between adherence and socio-economic variables, access to health services and knowledge of ARVs and HIV/AIDS. The lack of association in this study between the factors usually known to be associated with adherence could possibly be due to small sample size, very high and similar levels of adherence obtained, homogeneity of the population and

potential effect modification present due to the high quality of care and close monitoring provided by the research clinic environment.

6.5 Recommendations

- Counselling on adherence and routine monitoring of adherence should be done regularly and frequently (e.g. monthly), as was done in the research clinics.
- There is need to devise and provide a product for making the medication portable, such as a ‘travelling medicine holder’ and for strengthening the mechanisms for reminding patients to take their medications on a daily basis such as reminder alarms on cell phones.
- Although there is high level of medium term adherence noted among pregnant women, a longitudinal study examining the long term postnatal rates of adherence and postnatal factors affecting adherence may be critical to understand what happens long after the women have given birth and are continuing with HAART.



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APPENDIX 1: SAMPLE QUESTIONNAIRE

Date-----

Participant's number-----

A. Demographic and socio economic information

1. Age in years? -----

2. Marital status?

A= single

B= married

C= co-habiting

D= divorced

E= widowed

3. What are your religious practices?

A= Christianity

B= Islam

C= African traditional religion (worship of ancestors)

D= Atheism (believe in no God)

E= Other: _____

4. Educational level completed? _____

5. Employment status?



A= Employed

B = Unemployed

C= Self Employed

6a. How much money do you earn per month from employment if employed or self employed? _____

6b. what other income do you have?

Please list sources and amount earned from each source: _____

7. Has lack of food ever made you miss your medication?

A= Yes

B= No

8a. How many people including yourself stay in your household/compound most of the time: _____

8b. Do you have electricity in your house?

A= Yes

B= No

8c: Do you have piped water in your compound?

A= Yes

B= No

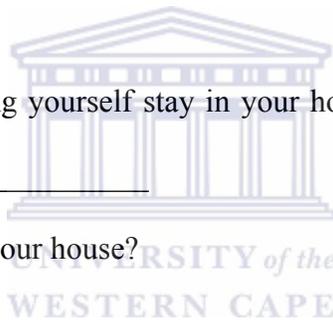
8d. Which of the following toilet facilities do you have in your home?

A= indoor flush toilet

B= Private pit latrine

C= Shared pit latrines with other compounds

D= No toilet facilities



E= Other (Please specify): _____

9a. Does anyone in your household know about your HIV status?

A= Yes

B= No

9b. If yes, who? (Please list) _____

9c. Does feeling that you have to hide your medications from those around you ever made you miss your medications?

A=Yes

B= No

9d. Do you have anyone at home to remind you to take your medications?

A= Yes

B= No

10a. Do you take alcohol? (if yes answer 9b other wise go to 10)

A= Yes

B= No

10b. Has taking alcohol ever made you miss your medication?

A=Yes

B=No

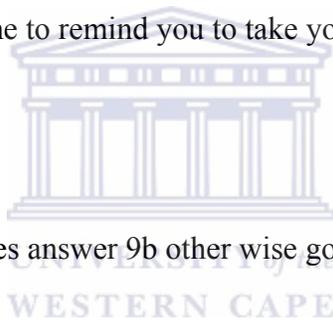
B. Access to Health services

11. Can you estimate how long it takes you to get to the clinic? _____

12. How do you come to the clinic?

A=Walking

B= Bus/taxi



C= own vehicle

D= Order (please specify): _____

13. Do you lose any income during the time you attend this clinic?

A=Yes

B=No

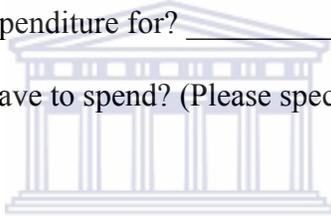
14a. Has your being on ARV resulted in increased expenditure? (if yes answer 13b, otherwise go to question 14).

A=Yes

B=No

14b. What was the increased expenditure for? _____

14c. How much extra did you have to spend? (Please specify) _____



C. Adequacy of Service and Level of Counselling

15a. Were you counselled about adherence before or since you started treatment? (if yes answer 15b otherwise go to question 15)

A= Yes

B= No

15b. How often did you receive adherence counselling after you started treatment?

A= At every visit

B= At some visits

C= Never

15c. How useful did you find the counselling sessions?

A= Not useful

B= slightly useful

C= Useful.

D= Very useful.

16a. Did you talk with the health worker about your experience of using your medicines?

(side effects, perceived effects)

A=Yes

B= No

If yes then answer 16b-d

16b. Did the health worker ask you if you have missed a dose of your medication?

A=Yes

B= No

16c. Did the health worker explain to you what the effects of missing a dose are?

A=Yes

B= No

16d. Did the health worker ask if you are taking other medicines or traditional medicines?

A=Yes

B= No

17. Did the health worker count your pill before giving you a new supply?

A=Yes

B= No

18 How would you rate the overall quality of care and services you are receiving at this clinic?

A= Poor



B= Fair

C= Good

D= Very good

D. Knowledge and attitudes towards ARV's and HIV/AIDS.

19. What do think will happen to your health if you do not take your medications regularly? (Based on the response to each of the options below, give the following scores.

1=strongly disagree, 2= disagree, 3=agree, 4= strongly agree. 5=uncertain; for use by research assistant only if patient cannot pick any of the other 4 options)

	Question	response
19a	Your health will get worse	
19b	You may develop oppportunistic infections	
19c	Nothing will happen	
19d	Your CD4 will decrease	
19e	You may lose weight:	
19f	You may develop diarrhoea	
19g	Your viral load will increase	

20. What do you know about treatment for HIV infection? (Based on the response to each of the options below, give the following scores. 1=strongly disagree, 2= disagree,, 3=agree, 4= strongly agree. 5=uncertain; for use by research assistant only if patient cannot pick any of the first 4 options)

i) The disease has no cure for now and therefore i need to continue treatment forever:

ii) Treatment helps to prolong life: _____

iii). Taking of ARV's may result in experience of side effects like nausea, vomiting, hepatitis, low blood count and diarrhoea: _____

iv) Treatment helps to reduce the chances of transmission to the unborn and breast feeding infants: _____

21. ARV's work by suppressing viral load and increasing CD4 counts, do you agree? (Based on response, give the following scores. 1=strongly disagree, 2= disagree,, 3=agree, 4= strongly agree. 5=uncertain; to be used by research assistant only if the patient cannot pick any of the first 4 options): _____

22. ARV's can interact with other drugs including indigenous or traditional medications causing serious reaction? (Based on response, give the following scores. 1=strongly disagree, 2= disagree, 3=agree, 4= strongly agree. 3=uncertain. 5=uncertain; to be used by research assistant only if the patient cannot pick any of the first 4 options): _____

23a. How do you feel about having to take medications everyday?(Please describe briefly): _____

23b. Do you feel you can skip the medications for some days and still be healthy?

A=Yes

B=No

Has any of the following made you miss your medications?

25. felt better

A= Yes

B= No

26. Did not just feel like taking medications on that day?

A=Yes

B= No

27. The pills were too many?

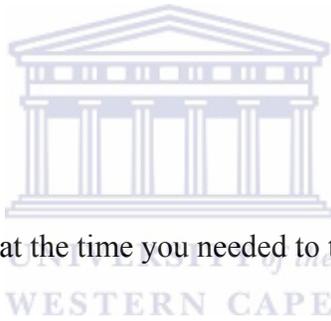
A= Yes

B= No

28. Forgot

A= Yes

B= No



29. Did not have pills with you at the time you needed to take them

A=Yes

B= No

Self reported adherence:

30a. Research assistant should ask patient and then cross out the medications the subject

took in the past seven days using the table below:

Name of Drug	Day 1		Day 2		Day 3		Day 4		Day 5		Day 6		Day 7	
	AM	PM												
	AM	PM												

	AM	PM												
	AM	PM												



**APPENDIX 2: DATA EXTRACTION FORM FROM PARTICIPANT'S
CLINICAL RECORDS.**

Date: _____

Participants Number: _____

1. Current regimen: _____

Please circle one; i) first line; ii) second line; iii) third line.

2. Length of time on treatment: _____

3a. Please review medical records and complete the table below for ARV regimen:

Name pill	Number of pills taken per dose	Number of times taken per day

3b. Is there any other medical condition that patient is receiving treatment for? (Please specify): _____

3c. Please review medical records and enter into the table below the other medications patient is taking aside from ARV's.

Name pill	Number of pills taken per dose	Number of times taken per day

Adherence in the antenatal period.

4a. Any missed medication refill appointment during pregnancy? Circle Yes or No?

If yes, number of times missed: _____

4b. Monthly Pill count records during pregnancy? (Please complete the table below)

Month	a	b	c	d	e	f	Total
Number of pills dispensed at last visit							
Expected pills at current visit							
Returned pills at current visit							
Number of doses missed							

4c. Documentation of side effects. Circle Yes or No

4d. CD4 during pregnancy (capture closest to delivery or at delivery): _____

Date drawn: _____

4e. Viral load during pregnancy (capture closest to delivery or at delivery): _____

Date drawn: _____

4f. WHO disease stage during pregnancy: _____

Adherence in the early post natal period (including breast feeding)

5a. Any missed medication refill appointment during the first six months after delivery?
Circle Yes or No?

If yes, number of times missed: _____

5b. Pill count records in the first 6months after delivery? (Please complete the table below)

Month	a	b	c	D	e	f	Total
Number of pills dispensed at last visit							
Expected pills at current visit							
Returned pills at current visit							
Number of doses missed							

5c. Documentation of side effects. Circle Yes or No

5d. CD4 at six months after delivery (or nearest time point): _____

Date drawn: _____

5e. viral load at six months after delivery (or nearest time point): _____

Date drawn: _____

5f. WHO disease stage in the first 6months after delivery: _____

Adherence in the late post natal period (review past six months).

5a. Any missed medication refill appointment in the last 6months? Circle Yes or No?

If yes, number of times missed: _____

5b. Pill count records in the last 6months? (Please complete the table below)

Month	a	b	c	D	e	f	Total
Number of pills dispensed at last visit							
Expected pills at current visit							
Returned pills at current visit							
Number of doses missed							

5c. Documentation of side effects. Circle Yes or No

5d. Most recent CD4: _____ Date drawn: _____

5e. Most recent viral load: _____ Date drawn: _____

5f. Current WHO disease stage: _____

APPENDIX 3: ADULT/ADOLESCENT WHO CLINICAL STAGING

Clinical Stage 1: Asymptomatic

Asymptomatic

Persistent generalized lymphadenopathy

Clinical Stage 2: Moderate Disease

Unexplained moderate weight loss <10% of baseline weight

Recurrent upper respiratory infections (sinusitis, otitis media, tonsillitis, pharyngitis)

Mono-dermatomal VZV

Recurrent oral ulceration

Papular pruritic eruptions

Seborrheic dermatitis

Fungal nail infections

Clinical Stage 3: Advanced Disease

Unexplained weight loss >10% of baseline

Unexplained chronic diarrhea for more than one month

Unexplained persistent fever (>37.5C, intermittent or constant) for more than one month

Persistent oral candidiasis

Oral hairy leukoplakia

Pulmonary TB

Severe bacterial infections (e.g., pneumonia, meningitis, PID,* bone/joint infection, bacteremia)

Multi-dermatomal, recurrent mono-dermatomal, or ophthalmic VZV*

Necrotizing ulcerative gingivitis, periodontitis, stomatitis

Unexplained anemia (<8gm%), neutropenia (<500/ μ L), and/or thrombocytopenia (<50,000/ μ L)

*Not part of international WHO staging, but added as frequent Botswana-specific HIV-related “advanced” conditions meriting HAART

Clinical Stage 4: Severe disease

HIV wasting syndrome

Pneumocystis pneumonia

Recurrent severe bacterial pneumonia

Chronic HSV infection (orolabial, genital, rectal for more than one month or visceral at any site)

Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs)

Extra-pulmonary TB

Kaposi’s sarcoma

CMV (retinitis or infection of other organs)

CNS toxoplasmosis

HIV encephalopathy

Extrapulmonary cryptococcosis, including meningitis

Disseminated non-TB mycobacterial infection

Progressive multifocal leukoencephalopathy

Chronic cryptosporidiosis, isosporiasis
Disseminated mycosis
Recurrent septicemia
Lymphoma (cerebral or non-Hodgkin's)
Invasive cervical carcinoma
Atypical disseminated leishmaniasis
Symptomatic HIV-associated nephropathy and cardiomyopathy

FOOT NOTE:

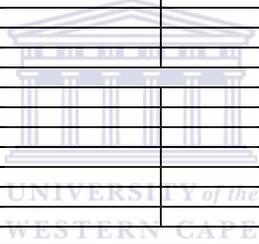
- i. A single, non-recurrent episode of mono-dermatomal VZV infection is a stage 2 condition. Recurrent mono-dermatomal VZV, a single episode of multi-dermatomal VZV, or ophthalmic VZV should be regarded as stage 3 conditions.
- ii. Recurrent severe PID is a WHO stage 3 condition.

Adapted from: *Botswana National HIV/AIDS Treatment Guidelines November 2008 Version.*

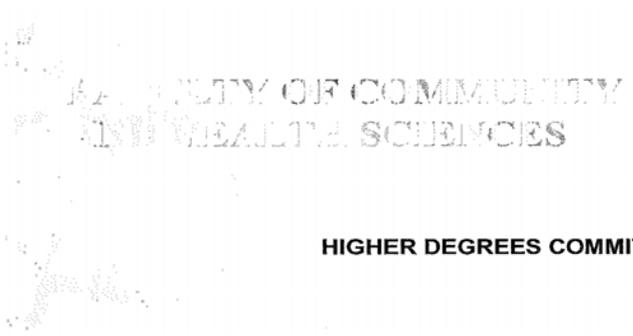


APPENDIX 4: SAMPLE PILL CALENDAR

Name	BID	Clinic phone#				
Start Date:	Weekday:	Letsatsi:	Combivir  AM	Nevirapine  AM	Combivir  PM	Nevirapine  PM
	Sunday	Tshipi				
	Monday	Mosupologo				
	Tuesday	Labobedi				
	Wednesday	Laboraro				
	Thursday	Labone				
	Friday	Labotlhano				
	Saturday	Matlhatso				
	Sunday	Tshipi				
	Monday	Mosupologo				
	Tuesday	Labobedi				
	Wednesday	Laboraro				
	Thursday	Labone				
	Friday	Labotlhano				
	Saturday	Matlhatso				
	Sunday	Tshipi				
	Monday	Mosupologo				
	Tuesday	Labobedi				
	Wednesday	Laboraro				
	Thursday	Labone				
	Friday	Labotlhano				
	Saturday	Matlhatso				
	Sunday	Tshipi				
	Monday	Mosupologo				
	Tuesday	Labobedi				
	Wednesday	Laboraro				
	Thursday	Labone				
	Friday	Labotlhano				
	Saturday	Matlhatso				



APPENDIX 5: ETHICS APPROVAL UNIVERSITY OF THE WESTERN CAPE



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HIGHER DEGREES COMMITTEE

15 June 2009

TO WHOM IT MAY CONCERN

Dear Sir/Madam

Research Project of ANTHONY CHIBUZOR OGWU (Student Number: 2616833)

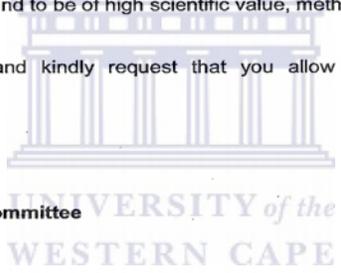
This letter confirms that ANTHONY CHIBUZOR OGWU is a registered student in the Faculty of Community and Health Sciences at the University of the Western Cape.

His research proposal entitled "Adherence to anti retroviral therapy amongst women commenced on treatment during pregnancy at research clinics in Botswana" submitted in fulfilment of the requirements for a Master of Public Health degree, has been examined by the Higher Degrees Committee and found to be of high scientific value, methodologically sound and ethical.

We fully support the research and kindly request that you allow him access to your organization.

Sincerely


DR GAVIN REAGON
Chairperson: Higher Degrees Committee



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