INVESTIGATION OF THE METHOD OF "MIXED" PILL COUNTS AS A TOOL TO DETECT DELIBERATE MASKING OF NON-ADHERENCE TO ANTIRETROVIRAL THERAPY AT NTSHEMBO CLINIC, MAMELODI HOSPITAL

by

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RESEARCH DISSERTATION

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DECLARATION

I declare that the dissertation hereby submitted to the University of Limpopo, Medunsa Campus, for the degree of Master of Science in Medicine (Pharmacy) has not previously been submitted by me for a degree at this or any other university; that it is my work in design and in execution, and that all material contained herein has been duly acknowledged.

_____ _____

Titilope Adetola Adeyinka (Ms) **Date**

[redacted]

DEDICATION

To my husband, Adeleye Awolola,

for your unending love and encouragement.

You have made a lot of sacrifices during the course of this project and you have been selflessly supportive through it all.

Your enormous faith and confidence in me kept me going.

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DISSEMINATION OF STUDY FINDINGS

A. POSTER PRESENTATION: The XVIII International AIDS Conference, Vienna, 18-23 July 2010

Medunsa Campus

Investigation of the method of "mixed pill counts" as a tool to detect deliberate masking of non-adherence to antiretroviral therapy (ART): A pilot study

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Background

Optimum levels of adherence to ART are essential for maximal suppression of viral replication, avoidance of drug resistance and long-term survival (Friedland, 2006; Mills et al, 2006). Pill counts are an indirect objective method of assessing adherence, which patients can invalidate by manipulating the number of tablets returned (Berg & Arnsten, 2006). Local health care staff reports that discarding tablets ("pill dumping") may be a means to mask non-adherence. The ability of a new concept of "mixed pill counts" to detect deliberate masking of non-adherence to ART was investigated at a public sector antiretroviral (ARV) clinic in South Africa.

Operational definitions

Normal pill count is defined as the procedure whereby the tablets remaining in each ARV tablet container are counted at a follow-up visit.

"Mixed pill count" is defined as the procedure whereby the tablets remaining in each ARV tablet container are counted at a follow-up visit after the pharmacist deliberately dispensed extra tablets during the previous visit.

%Adherence = (Number of tablets taken home – number of tablets returned) X 100 / Number of tablets that should have been taken

Truthful non-adherence: Pill count results of <100% adherence

Adherent: Pill count results of 100%

Over-compliance: Pill count results of >100%

Objectives

- To describe the incidence of adherence (exactly 100% adherence, <100% adherence, and >100% adherence) as measured by a normal pill count at the first visit, and a "mixed" pill count at the second visit for each study patient.
- To explore patients' explanations for discrepancies in pill counts.

Methods

A descriptive study was conducted during October 2009 to December 2009 at Masibambane ARV Clinic, Pretoria. Seventy-eight adult patients on Regimen 1A or 1B of ART for at least six months were recruited and each received one month's supply of ARVs on enrolment. On the first return visit, a normal pill count was done and adherence was calculated. During this visit, three-days extra supply was dispensed without the patients' knowledge. On the second return visit, a "mixed pill count" was done and adherence was calculated. At both pill counts, adherence was calculated for individual drugs, as well as for the patient's regimen. Pill count results >100% (over-compliance) were considered an indicator for suspected pill dumping. Exploratory interviews were conducted with over-compliant (>100% adherence) and truthful non-adherent (<100% adherence) patients to obtain explanations for discrepancies in pill counts. The "mixed pill count" was evaluated for its ability to unmask adherence maskers ("pill dumpers").

Results

Twenty-nine (8 males; 21 females) of the 78 patients completed the study. Forty-five percent were between ages of 31 and 40 years and 55% were employed. The main reason for drop-out was that patients' second return visit fell outside the study timeframe, mostly on account of receiving a 2-3 months' supply of ARVs on account of the festive season. Other reasons for drop-out included missed appointments, regimen changes and failure to bring remaining ARVs to the clinic.

Overall average adherence

Based on the overall average adherence calculated for each patient's regimen, four patients (14%) were over-compliant with the normal pill count, while eight patients (28%) were over-compliant with the mixed pill count. Two patients were over-compliant in both cases (Table 1).

Table 1: Number of patients within each category of adherence based on the calculated overall average adherence

		Mixed Pill Count			
	Adherence category	<100% Truthful non-adherent	100% Adherent	>100% Over-compliant	Total
Normal Pill Count	<100% Truthful non-adherent	8	3	6	17
	100% Adherent	3	5	0	8
	>100% Over-compliant	2	0	2	4
	Total	13	8	8	29

Adherence for individual ARVs

For the majority of patients, "mixed pill count" results illustrated a different adherence pattern for each of the ARVs within a regimen. Only eight patients (28%) were 100% adherent with all their ARVs. Fourteen patients (48%) were identified as being truthfully non-adherent in one or more of the ARVs in their regimen. Eleven patients (38%) were identified as over-compliant. Twelve and nine of these patients agreed to be interviewed and provided reasons for returning too many tablets (non-adherence) and for returning too few tablets (over-compliance), respectively, as shown in Table 2.

Table 2: Reasons for non-adherence (<100%) and over-compliance (>100%)

	Reasons for returning too many tablets (non-adherence)	Reasons for returning too few tablets (over-compliance)
Truthful non-adherent patients (n=12)	• Forgot • Away for a night • Family matters • Non-disclosure • No food at that time • Had tablets from previous months • Felt dizzy at work due to efavirenz	
Over-compliant patients (n=9)		• Threw them away • Taken an overdose • Non-disclosure / stigma • Could have been stolen • Might have been spilled • Spilled in water • Might be in the tablet container at work • Factory fault • Difficulty with timing • Tablets make you feel sick • Do not know what happened to the tablets

Three of the nine over-compliant patients admitted to manipulating their tablets. Reasons for manipulation are summarised and illustrated with quotations in Table 3.

Table 3: Reasons for manipulating tablets

	Reasons for tablet manipulation
Over-compliant patients(n=3)	**Changed body shape** *"Those medications have changed my body, look at me, I look like a man, my buttocks are gone, my beautiful shape is gone. I don't know what to do, should I continue to take them or just stop…"* (Female, 29 years)
	Possibility of social grant being discontinued *"…should I continue to take them or just stop, again if I stop collecting them my grant is going to be stopped also. I'm very confused"* (Female, 29 years)
	Taking extra ARVs when feeling sick; throw away when feeling fine *"But what I remember is that I used to take some extra pills when I am sick thinking that I will recover soon, so when I was ok, I threw the remaining away…"* (Male, 45 years)
	Do not need the ARVs any more *"Yes, I did throw them away, actually I think I'm fine now, I don't need any treatment at the moment."* (Female, 29 years)
	Know the tablets will be counted *"I had a lot of tablets remaining, but I flushed some of them down the toilet because you wanted to count them. If I bring back too many remaining tablets, you will say that I am not taking them."* (Female, 32 years)
	Getting a new supply and will not need remaining ARVs *"When I was ok, I threw the remaining away this morning because I was coming to collect my monthly supply"* (Male, 45 years)
	Non-disclosure *"I threw some away in the toilet, besides that, I have not told anyone about my status, so sometimes I cannot take the tablets when people are there, that is why I had many tablets."* (Female, 32 years)

Conclusion and recommendations

This pilot study indicated that the "mixed pill count" method is capable of detecting deliberate masking of non-adherence. Applying this method to a larger sample will help to estimate the frequency of manipulation of pill counts by patients. It will also help gain insight to the reasons for this behaviour, and the extent of actual non-adherence. Periodic implementation of the "mixed pill count" method is envisaged to assist clinic staff to better identify non-adherent maskers and allow for more timely intervention in order to improve their medication behaviour and potentially treatment outcomes.

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B. MANUSCRIPT SUBMITTED TO THE AFRICAN JOURNAL OF AIDS RESEARCH FOR REVIEW

The 'mixed' pill count: A tool to detect deliberate masking of non-adherence to antiretroviral therapy (ART)?

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The 'mixed' pill count: A tool to detect deliberate masking of non-adherence to antiretroviral therapy (ART)?

Abstract

High levels of adherence to ART are essential for maximal suppression of viral replication and avoidance of drug resistance. Pill counts are an indirect, objective method of assessing adherence. Patients can invalidate pill counts by manipulating the number of tablets returned. This paper describes a pilot study which investigated the ability of 'mixed' pill counts to detect deliberate masking of non-adherence to ART at a public sector ARV Clinic in Pretoria, South Africa. Seventy-eight adult patients on a first line regimen of ART were recruited. At the first return visit, a standard pill count was performed and adherence (% of tablets taken) was calculated. For the repeat prescription, three days' extra supply was dispensed without the patients' knowledge. At the second return visit, a 'mixed' pill count was performed and adherence was calculated. Patients were grouped into three categories based on calculated adherence: truthfully non-adherent (<100% adherence), adherent (100% adherence) and 'over-compliant' (>100% adherence, i.e. returning to the clinic with fewer tablets than required). Exploratory interviews were conducted with truthfully non-adherent and over-compliant patients to obtain explanations for discrepancies in pill counts. Twenty-nine (37%) patients completed the study. Reasons for drop-out or discontinuation from the study included the issue of prescriptions for 2-3 months' ARV supply, missed appointments, regimen changes and failure to return remaining tablets to the clinic. Eleven patients (38%) were identified as over-compliant in one or more of the ARVs in their regimen. Nine of these patients agreed to be interviewed, of which three admitted to manipulating their tablet numbers. Reasons for manipulation included: being 'fine now' and not in need of ARVs; changes in body shape; possibility of the social grant being terminated if non-adherent; getting a new supply and no need for remaining ARVs; knowing that the tablets would be counted for the study. This pilot study indicated that the 'mixed' pill count method is capable of detecting deliberate masking of non-adherence. Applying this method to a larger sample may better estimate the frequency of pill count manipulation by patients and help gain insight to reasons for this behaviour and the extent of actual non-adherence.

Key words: dumping, manipulation, masking, over-compliance, HAART

Introduction

Near perfect levels of adherence to antiretroviral (ARV) therapy are essential to achieve treatment success measurable in viral suppression, to maintain long-term health benefits and to avoid the development of drug resistance (Lima, Harrigan, Murray, Moore, Wood, Hogg & Montaner, 2008; Ford, Darder, Spelman, Maclean, Mills & Boulle, 2010). Despite concerted efforts of healthcare providers, pharmaceutical manufacturers and health systems to encourage adherence, irregular and incomplete ARV medication-taking behaviour is common (Liu, Golin, Miller, Hays, Beck, Sanandaji, Christian, Maldonado, Duran, Kaplan & Wenger, 2001; Liu, Miller, Hays, Wagner, Golin, Hu, Kahn, Haubrich, Kaplan & Wenger, 2006). However, since adherence to antiretroviral treatment (ART) is essential for treatment success (Lima *et al*., 2008; Ford *et al*., 2010), it is paramount that health care providers have efficient and reliable tools to measure adherence, so that poor adherence can be identified and addressed in its early stages.

Various studies document the limitations of current standard measures of ARV adherence, among them are directly administered antiretroviral therapy (DAART), therapeutic drug monitoring, self-reported adherence, electronic pill boxes, pill counts, etc. (Bartlett, 2002; Godin, Gagne & Naccache, 2003; Berg, & Arnsten, 2006; Nachega, Knowlton, Deluca & Schoeman, 2006; Maru, Kozal, Bruce, Springer & Altice, 2007; Altice & Springer, 2010). Treatment programmes use the various methods alone or in combination, in the absence of a gold standard with which to measure adherence (Berg & Arnsten, 2006; Chesney, 2006). The need for efficient and reliable measures of adherence has initiated debate about how best to measure medication-taking behaviour in public sector ART settings.

One method commonly used to measure adherence in South African public health sector ART sites is the “pill count”. The pill count is an indirect, objective method to assess medication adherence (Kalichman, Amaral, Stearns, White, Flanagan, Pope, Cherry, Cain, Eaton & Kalichman, 2007; Chalker, Andualem, Gitau, Ntaganira, Celestino, Tadeg, Waako & Ross-Degnan, 2010). The pill count method counts the total number of tablets remaining from the previous prescription and calculates the number of tablets assumed to have been taken (the difference between the number dispensed and the number remaining) divided by the number of tablets the patient was supposed to take during the period; this measure is used to estimate a percent adherence. Critics of the pill count note that this method tends to overestimate medication adherence and does not indicate true medication-taking behaviour in terms of timing and dosage (Liu *et al*., 2001; Ross-Degnan, Pierre-Jacques, Tadeg, Gitau, Ntaganira, Balikuddembe, Chalker & Wagner, 2010).

Anecdotal evidence from some ART sites, as well as literature, suggest that the pill count method can be invalidated by a patient if, in preparation for the pill count, the patient used the pill count formula to calculate the expected number of tablets to remain for a good adherence percentage and manipulates the number of remaining pills to match the calculation. Allegedly, these patients deliberately fail to return all of their tablets or discard (dump) the 'excess' tablets before coming to the clinic or pharmacy for the pill count (Kalichman *et al.*, 2007). To catch out the conjectured manipulations, some facilities evolved a new concept of a 'mixed' pill count. The 'mixed' pill count is a practice whereby the pharmacist deliberately dispenses extra tablets (a predetermined 'n' number of extra tablets more than a thirty-day supply) to a patient and records the number of extra tablets in the patient's medication file without the patient's cognizance. Upon return for a repeat prescription, the tablets remaining in the container are counted taking into calculation the 'n' number of extra tablets dispensed. If these "n" extra tablets are unaccounted for, it is considered a possible indication that the patient may have manipulated the pill count in order to mask non-adherence. Reasons for masking non-adherence would then be probed.

The hypothesised advantage of the 'mixed' pill count over the 'normal' pill count lies in the fact that the patient is not aware that extra tablets have been dispensed to him/her. As a result, it is assumed that the following three scenarios could ensue: (1) an adherent patient would return to the clinic with the extra tablets in the container because he/she is sure that all the tablets were taken as prescribed; (2) a truthfully non-adherent patient would return to the clinic with the extra tablets (and more) in the container because he/she is not attempting to mask non-adherence, so would have no need to discard any, including the extra tablets; and lastly (3) the over-compliant patient (suggestive of masking non-adherence) would *not* return to the clinic with the extra tablets in the container because his/her calculation does not account for the "n" number of extra tablets in the attempt to manipulate the pill count, in order to mask non-adherence. In all these instances, the extra tablets should act to safeguard the validity of the pill count. Inability to account for the extra tablets would allow the pharmacist to more easily identify patients who may have attempted to mask adherence by dumping tablets and also allowing the health care worker to address the issues behind adherence masking. The end result would be improved ability to identify non-adherence, which previously would have been successfully masked through dumping of tablets to match the total calculated number of expected extra tablets.

To the best of the researchers' knowledge, limited information is available on the effectiveness of the 'mixed' pill count as a measure of adherence to ARVs because it is a new concept and has not been formally evaluated. This study was designed to evaluate the 'mixed' pill count as a tool to effectively identify non-adherence to ART. It is anticipated that

more effective and earlier identification of non-adherence could contribute to an improvement in appropriate adherence counselling and ultimately adherence to ART itself. The use of a 'mixed' pill count was compared against the standard care, a normal pill count.

Operational definitions for this study

- A '**normal' pill count** is defined as the procedure whereby the tablets remaining in each ARV tablet container are counted at the follow-up visit in order to calculate the number of tablets taken by the patient divided by the number of tablets required to be taken by the patient during the previous month. Standard tablet prescriptions run on a thirty-day treatment cycle. See formula below.
- A **'mixed' pill count** is a variation of the 'normal' pill count. It is defined as the procedure whereby the tablets remaining in each ARV tablet container are counted at a follow-up visit after the pharmacist deliberately dispensed a predetermined 'n' number of extra tablets during the previous visit, without the patient being aware of the extra tablets dispensed (e.g. thirty-day standard treatment plus 'n' extra tablets). The number of extra tablets dispensed is recorded in the patient's file in an encrypted format.
- **Percent (%) adherence** is calculated as follows (Etard, Laniece, Fall, Cilote, Blazejewski, Diop, Desclaux, Ecochard, Ndoye & Elaporte, 2008; Chalker *et al.,* 2010):

$$\% \text{ Adherence} = \frac{\text{Number of tablets dispensed} - \text{Number of tablets returned at follow-up visit}}{\text{Number of tablets that should have been taken}}$$

Assumptions made for this study

The following assumptions were made prior to the commencement of the study:

- Some patients may manipulate tablet counts by discarding tablets (pill 'dumping') in order to mask poor adherence (taking too few tablets or none at all).
- Patients would dump tablets in preparation for the follow up visit without ever physically counting the total number of tablets dispensed.
- The number of tablets dumped may be based on a projected calculation of percent 'good adherence' based on an assumption that the standard thirty day treatment prescription had been dispensed.
- These 'dumping' calculations would not take into account the extra tablets resulting in patients accidentally dumping the deliberately added tablets along with the other untaken tablets. Patients would return the extra "n" number too few tablets at the next pill count.

Based on the above assumptions, the return of too few tablets (adherence >100%) would be an indicator for suspected 'pill dumping' in this study. The objectives of this pilot study were to i) describe the incidence of adherence (exactly 100% adherence, <100% adherence, and >100% adherence) as measured by a normal pill count at the first visit, and by a 'mixed' pill count at the second visit for each study patient, and ii) to explore patients' explanations for discrepancies in pill counts.

Methods

Study site

This pilot study was conducted at Masibambane ARV clinic in Tshwane District Hospital, situated in the Gauteng Province, South Africa. As at December 2009, approximately 6000 adult patients were enrolled on ARVs at the clinic. During their first six months on ART, patients attend the clinic on a monthly basis. Once they are stabilised on ART (which is usually after six months on treatment), they receive two months' supply of ARVs and attend the clinic every second month. Pill counts are only done for patients who are newly initiated on ART, when they come for their first follow-up visit after being on treatment for two weeks. Stabilised patients are not required to bring their medication when they come for a repeat prescription, as pill counts are not done for them. Non-adherent patients are identified when their CD4 counts and/or viral load suggest non-adherence. In this case, patients would be counselled by both the counsellor and the pharmacist and reasons for missed doses are investigated.

Study design

The study followed a prospective and repeated measure longitudinal design over a period of three months, from October 2009 to the end of December 2009. Enrolment of patients into the study took place during the first month. Study participants were given a normal pill count on enrolment (baseline visit), and were given a normal supply of their ARV medication. On Return Visit 1, they received a normal pill count and an additional three days' supply of each ARV medication was dispensed to them without their knowledge. At Return Visit 2, patients then received a 'mixed' pill count. Exploratory interviews were conducted with all patients returning too few dosage units at Return Visit 2 (non-adherence maskers) and with the truthfully non-adherent patients, as identified by returning too many dosage units at Return Visit 2.

Study population and sample

The target population for this study comprised treatment-naive and treatment-experienced patients, provided they were taking Regimen 1A (stavudine, lamivudine and efavirenz) or Regimen 1B (stavudine, lamivudine and nevirapine). Patients receiving one- and two-months' supply of ARVs were enrolled, to ensure that both unstabilised and stabilised patients participated in the study. Patients were first informed of the study in the morning while they were at the waiting area. Thereafter each patient was approached individually in the counselling room and screened for eligibility. Eligibility criteria included the following:

- HIV-positive adults ≥18 years of age.
- Patients on Regimen 1A or Regimen 1B.
- Patients who will be receiving their ARVs at the study site for the full duration of the study period.

The patients who agreed to take part in the study were given consent forms to sign to indicate their willingness to participate.

Data collection procedures and instruments

Data were collected by the researcher and a data collector who was trained and experienced in ART adherence counselling. Once patients consented to the study, stickers were placed on their files to indicate that they were part of the study. Patients were reminded at baseline always to come with their medication containers when they visited the clinic for a repeat prescription.

A questionnaire was used by both the researcher and the data collector to collect patients' demographic and socioeconomic status data on enrolment into the study; clinical data were extracted from the patients' files.

A count sheet was used to record the number of tablets that the patients returned to the clinic. Pill count results (adherence results) were calculated as a percentage of the tablets that should have been taken. Separate interview guides were used to interview the truthfully non-adherent (adherence <100%) and over-compliant (adherence >100%) patients soon after the pill count. Truthfully non-adherent patients were asked to inform the data collector if they found it difficult to return extra tablets, indicate how they felt about returning extra tablets, as well as explain the reasons for not taking all their tablets. Over-compliant patients (all cases) were probed for evidence of adherence masking and its underlying motivations.

Results

At enrolment, 78 eligible patients were recruited into the study. Fifty-eight (73.4%) were females and 20 (25.6%) were males. Twenty-nine (37%) of the 78 patients completed the study. The main reasons for the high losses were that patients missed appointments (39.7%) and patients' second return visit fell outside the study timeframe (12.8%), mainly due to issue of a 2-3 months' supply of ARVs to cover the festive season. Other reasons for loss to the study included regimen changes, failure to bring remaining ARVs to the clinic, hospitalisation and taking an overdose of ARVs.

Patient demographics

Table 1 shows the age and gender distribution of the patients who completed the study. Forty-five percent of the patients were between the ages of 31 and 40 years. The average age was 38 years, with the females younger (average of 36 years) than the males (average of 43 years).

Table 1: Patient population by age group and gender (n=29)

Age group (years)	Male		Female		Total	
	Number	%	Number	%	Number	%
18-30	0	0	7	24.14	7	24.14
31-40	2	6.90	11	37.93	13	44.83
41-50	5	17.24	0	0	5	17.24
>50	1	3.45	3	10.34	4	13.79
Total	**8**	**27.59**	**21**	**72.41**	**29**	**100**
Range	**31-53**		**24-59**		**24-59**	
Average (standard deviation)	**43.1 (±6.94)**		**36.1 (±9.0)**		**38 (±8.95)**	

Additional demographic characteristics of the study participants are shown in Table 2. The majority (97%) of the participants were black and spoke an African language. In terms of education, only two patients (6.9%) had completed tertiary education, while 37.9% reported to either have had no formal education or had not completed primary education. Just more than half (55.2%) of the patients were employed and 58.6% were single.

Table 2: Additional demographics of study participants (n=29)

Characteristics		Number (n=29)	%
Race	Black	28	96.6
	White	1	3.4
Language	Afrikaans	1	3.4
	Zulu	7	21.1
	Tswana	2	6.9
	Sotho	9	31.0
	Other*	10	34.5
Level of education	None/primary not completed	11	37.9
	Primary completed	5	17.2
	Secondary completed	11	37.9
	Tertiary/vocational	2	6.9
Employment status	Employed	16	55.2
	Unemployed	13	44.8
Marital status	Single	17	58.6
	Married	9	31.0
	Widowed	1	3.45

*Ndebele, Pedi, Shona or Tsonga

ARV regimens

The majority of the patients were on the first line ARV regimen with 41% of them on Regimen 1A (stavudine, lamivudine and efavirenz) and 53% on Regimen 1B (stavudine, lamivudine and nevirapine). Figure 2 below shows the different regimens the study participants were taking during the study period.

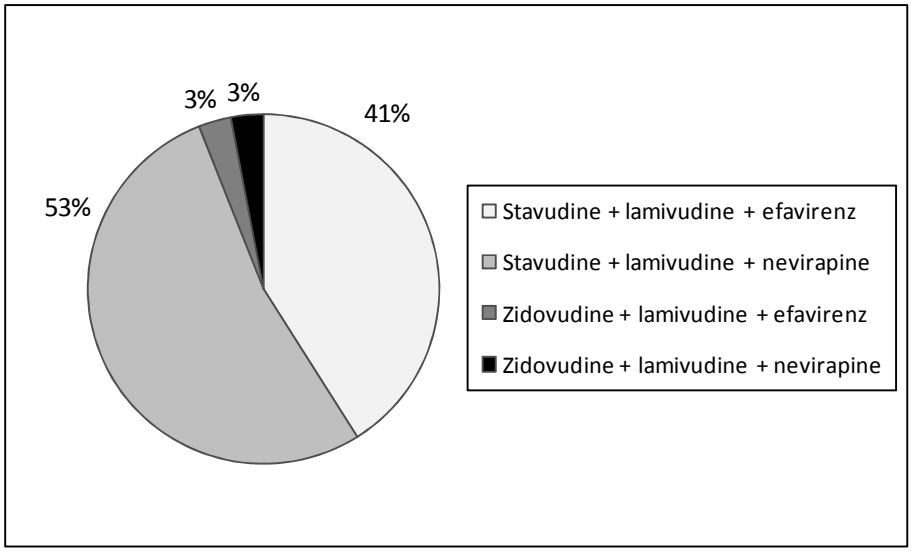

Figure 1: ARV regimens taken by study participants (n=29)

According to the inclusion criteria, patients were required to be on Regimen 1A or 1B to participate in the study. However, patients whose stavudine was substituded by zidovudine were also included in the study, because both zidovudine and stavudine belong to the same pharmacological class of ARVs (nucleoside reverse transcriptase inhibitors).

Overall average adherence for each patient's regimen

Patients were categorised as non-adherent (adherence <100%), adherent (100%) or over-compliant (adherence >100%), based on the overall average adherence calculated for each patient's regimen. Four patients (14%) were over-compliant with the normal pill count, while eight patients (28%) were over-compliant with the 'mixed' pill count. Two patients were over-compliant in both cases (Table 3).

Table 3: Number of patients within each category of adherence based on the calculated overall average adherence for each patient's regimen (n=29)

		Mixed Pill Count			
	Adherence Category	**<100% Truthful non-adherent**	**100% Adherent**	**>100% Over-compliant**	**Total (%)**
Normal Pill Count	**<100% Truthful non-adherent**	8	3	6	**17 (58.6%)**
	100% Adherent	3	5	0	**8 (27.6%)**
	>100% Over-compliant	2	0	2	**4 (13.8%)**
	Total	**13 (44.8%)**	**8 (27.6%)**	**8 (27.6%)**	**29 (100%)**

Adherence for individual ARVs

The results showed that for the majority of patients, 'mixed' pill count results illustrated a different adherence pattern for each of the ARVs within a regimen. It was noted that it was possible for a patient to appear truthfully non-adherent on average (considering the overall adherence of the three ARVs in the regimen) despite being over-compliant with one of the ARVs in the regimen. For example, adherence for the individual ARVs for one of the patients on Regimen 1B was 103% for stavudine, 103.6% for lamivudine and 80.4% for nevirapine. The overall average adherence for the regimen was 95.7%. This patient was over-compliant with two ARVs and non-adherent with one, but appeared truthfully non-adherent on average.

Only eight patients (28%) were 100% adherent with all three ARVs in their regimen. Fourteen patients (48%) were identified as being truthfully non-adherent in one or more of the ARVs in their regimen. Eleven patients (38%), of whom six (67%) were female, were over-compliant with one or more of the ARVs in their regimen, as opposed to eight (28%), of whom five (62.5%) were female, being identified as over-compliant on average.

Twelve of the truthfully non-adherent patients and nine of the over-compliant patients agreed to be interviewed. They provided reasons for returning too many tablets (non-adherence) or for returning too few tablets (over-compliance), as shown in Table 4.

Table 4: Reasons for non-adherence (<100%) and over-compliance (>100%)

Truthful non-adherent patients (n=12)	Reasons for returning too many tablets (non-adherence)	Over-compliant patients (n=9)	Reasons for returning too few tablets (over-compliance)
	• Forgot • Away for a night • Family matters • Non-disclosure • No food at that time • Had tablets from previous months • Felt dizzy at work due to efavirenz		• Threw them away • Taken an overdose • Non-disclosure / stigma • Could have been stolen • Might have been spilled • Spilled in water • Might be in the tablet container at work • Factory fault • Difficulty with timing • Tablets make you feel sick • Do not know what happened to the tablets

Three of the nine over-compliant patients admitted to manipulating their tablets. Five different reasons for manipulation were given by the three over-compliant patients. These reasons are summarised and illustrated with quotations in Table 5.

Table 5: Reasons for manipulating tablets

	Reasons for tablet manipulation
Over-compliant patients (n=3)	**Changed body shape** *"These medications have changed my body. Look at me, I look like a man, my buttocks are gone, my beautiful shape is gone. I don't know what to do, should I continue to take them or just stop…"* (Female, 29 years)
	Possibility of social grant being discontinued *"…should I continue to take them or just stop, again if I stop collecting them my grant is going to be stopped also. I'm very confused."* (Female, 29 years)
	Taking extra ARVs when feeling sick; throw away when feeling fine *"But what I remember is that I used to take some extra pills when I am sick thinking that I will recover soon. So when I was ok, I threw the remaining pills away this morning because I was coming to collect my monthly supply today."* (Male, 45 years)
	Do not need the ARVs any more *"Yes, I did throw them away. Actually I think I'm fine now, I don't need any treatment at the moment."* (Female, 29 years)
	Know the tablets will be counted *"I had a lot of tablets remaining, but I flushed some of them down the toilet because you wanted to count them. If I bring back too many remaining tablets, you will say that I am not taking them."* (Female, 32 years)

Discussion

Twenty nine (37.2%) of the 78 enrolled patients completed the study. The majority of participants at enrolment (73.4%) and completion (72.4%) were female. Gender proportions were similar to those in other adherence studies conducted in South Africa (Mapetla, 2007; Meyer, 2008; Peltzer, Friend-du Preez, Ramlagan & Anderson, 2010). Infection with HIV amongst the adult population in South Africa, is more prevalent in females than males. According to the UNAIDS (2010) global report 3.3 million (62.3%) of the 5.3 million HIV-positive adults (aged 15 years and above) in 2009 were females.

Most of the adherence maskers were female (62.5% were over-compliant on average and 67% were over-compliant in at least one ARV in the regimen). Although there were more females compared to males in the over-compliant group, this gender distribution was similar to that at enrolment. Generally, considering the small sample size, the results of this study did not show any association between gender and adherence. Similarly, the study by Rougemont, Stoll, Elia and Ngang (2009) conducted in Cameroon, reported no association between gender and adherence to ARVs.

A correlation between gender and adherence has previously been identified in the South African population. In one of the studies, female patients were found to have better levels of adherence than their male counter-parts (Bhat, Ramburuth, Singh, Titi, Antony, Chiya, Irusen, Mtyapi, Mofoka, Zibeke, Cher-Sao, Gwadiso, Sethathi, Mbondwana, & Msengana, 2010), while the opposite was reported by two other studies (Peltzer *et al.*, 2010; Williams, Storm, Montepiedra, Nichols, Kammerer, Sirois, Farley & Malee*,* 2006).

In our study 14% of participants were over-compliant (>100%) with the normal pill count at Return Visit 1, and this percentage doubled when the 'mixed' pill count was used to measure adherence at Return Visit 2. This indicates that the 'mixed' pill count method may have been able to detect the over-compliant patients who were not identified during the normal pill count.

With the 'mixed' pill count, only eight of the patients (28%) were 100% adherent with all three of the ARVs that they were taking. The majority of the patients (78%) were either non-adherent or over-compliant in one or more of the ARVs in their regimen.

This finding contrasts an adherence study conducted in South Africa by Peltzer and colleagues (2010), in which 82% of the participants (n=519) were adherent (>95%) based on the self-reported recall method. A similar study in Ethiopia (n=400) found that 96% of the patients achieved perfect adherence (Amberbir, Woldemichael, Getachew, Girma & Deribe, 2008). It must be noted though that in both these studies, perfect adherence was defined as adherence of 95% or higher, whilst in our study, perfect adherence was considered as an adherence rate of 100%. It is not surprising that the mixed pill count resulted in lower adherence in light of the criticism that self-reported adherence is known to over-estimate adherence (Liu *et al*., 2001; Berg & Arnsten, 2006; Chesney, 2006), as illustrated by studies conducted in similar settings in South Africa (Meyer, 2008; Engelbrecht, 2010).

Reasons for non-adherence given by study participants included forgetting, feeling dizzy and non-disclosure. Feeling dizzy was mentioned by patients taking efavirenz, which is a known side effect of the drug (Arendt, de Nocker, von Giesen & Nolting, 2007). The above reasons have also been reported to be barriers to adherence in previous studies conducted in Africa (Amberbir *et al.,* 2008; Olisa, Baiyewu & Sheikh, 2010) as well as in South Africa (Meyer, 2008; Mokoena, 2009).

According to Chalker and colleagues (2010), the normal pill count may overestimate patients' adherence due to the fact that patients fail to bring all of their tablets to the clinic for counting. This action was also observed in our study as some over-compliant patients said they had some tablets in a separate tablet container at work. However, throwing tablets

away to manipulate the number remaining cannot be raised with the patient if extra tablets are not dispensed to the patients, as was done in this study. Our study is, as far as we are aware, the first to prove that some patients intentionally throw tablets away in order to appear adherent or to mask their non-adherence. Since some 'over-compliant' patients admitted to throwing tablets away or flushing them down the toilet, this pilot study suggests that patient manipulation of the remaining number of tablets may be another key reason for adherence overestimation based on the normal pill count. It is possible that dispensing extra tablets could be seen as a time-consuming task for the dispenser. However, it could help improve patient care, as adherent-maskers would more likely be identified, which would allow for more appropriate and timely intervention to improve adherence behaviour for this group of patients. The occasional implementation of the mixed pill count intermingled with normal pill counts may help to safeguard against patient manipulation of the number of tablets returned.

Patients who admitted to throwing away some of their ARVs (pill dumpers), were asked why they did this (see Table 5). Experiencing side effects, which in this case was a change in body shape, was given as a reason. This finding concurs with the published literature from South Africa (Malangu, 2008; Meyer, 2008) and elsewhere (Protopopescu, Raffi, Roux, Reynes, Dellamonica, Spire, Leport & Carrieri, 2009), namely that adherence to ART is negatively affected by the side effects of the drugs. Another reason provided by two patients was that the ARVs were not necessary anymore, as the patients felt they had recovered. It was disappointing that despite health workers' efforts to prepare patients for ART, they still think that they do not need to take their ARVs if they are feeling better. This indicates that patient counselling and education need to be reinforced. Emphasis should be placed on the fact that ART is for life. Once ART has been initiated, it should not be interrupted, even if the patient feels better, as this may lead to drug resistance and deterioration to a later stage of HIV and AIDS.

Another notable reason for 'pill dumping' according a 29-year old female in our study was to prevent discontinuation of the government's HIV and AIDS social grant. This response suggested that patients receiving a social grant who are non-adherent, fear that if they stop collecting ARVs from the clinic, the monthly grant might be stopped. Subsequently, they mask their non-adherence by dumping the ARVs and coming regularly for a repeat prescription. Fear of grant discontinuation was also observed in a study conducted by Hardy and Richter (2006) in four provinces in South Africa, in which all their study participants feared that their disability grants would be withdrawn if they got better. Participants also expressed that they might not be able to find employment even if their health improved and they were declared fit to work. On the contrary, participants also stated that if they had to

choose between their ARVs and grants, they would choose their ARVs, even if it meant that their grants would be stopped if they got better. Several participants were not happy that the government only provides financial support to seriously ill people and not to those who are not yet ill.

According to the Department of Social Development (Samson, Lee, Ndlebe, Mac Quene, van Niekerk, Gandhi, Harigaya & Abrahams, 2004), one of the criteria for qualifying for a disability grant is that the grant applicants (patients) must have their disability confirmed by a medical report, and that the degree of their disability must render him/her incapable of entering the labour market and they must not have refused employment that is within his/her capabilities. The Minister of Social Development mentioned in her speech to the National Assembly in April, 2010, that over 5.2 million South Africans are unemployed (Molewa, 2010), and many of those who are employed are only earning a low income. Unemployed people rely on the government to support them financially, and this may be the sole source of income for some families. This issue could be a possible explanation why some ART patients decided to mask non-adherence and remain ill, so that their grants do not get discontinued.

Non-disclosure was identified as a reason for non-adherence as well as over-compliance (dumping tablets). Disclosure plays a very important role in adherence, as better adherence is associated with disclosure of HIV status (Meyer, 2008; Charurat, Oyegunle, Benjamin, Habib, Eze, Ele, Ibanga, Ajayi, Eng, Mondal, Gebi, Iwu, Etiebet, Abimiku, Dakum, Farley & Blattner, 2010). Therefore disclosure needs to be addressed before initiating patients on ARVs.

Limitations

Our study had some notable limitations. The sample for this study was very small since it was only a pilot, but the sample size was further decreased due to a high dropout/discontinuation rate. The findings cannot be generalised to other facilities and provinces in the country. Further investigation of the ability of the 'mixed' pill count method to detect deliberate masking of non-adherence amongst a large sample is necessary.

Conclusion

This pilot study indicated that the 'mixed' pill count method is capable of detecting deliberate masking of non-adherence. Application of this method to a larger sample will help to estimate the frequency of manipulation of pill counts by patients. It will also assist to provide insight into the reasons for this behaviour and give a better understanding of the extent of

actual non-adherence. Periodic implementation of the 'mixed' pill count method is envisaged to assist clinic staff to better identify non-adherent maskers and allow for more timely intervention in order to improve patients' medication behaviour and potentially treatment outcomes.

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ABBREVIATIONS

3TC	Lamivudine
AIDS	Acquired Immune Deficiency Syndrome
ART	Antiretroviral treatment/therapy
ARV	Antiretroviral
AZT	Zidovudine
CD4	CD4+ T-lymphocyte
CDC	Centers for Disease Control
d4T	Stavudine
DAART	Directly Administered Antiretroviral Therapy
ddI	Didanosine
DOH	Department of Health
EFV	Efavirenz
FTC	Emtricitabine
HAART	Highly active antiretroviral therapy
HIV	Human immunodeficiency virus
IDV	Indinavir
LPV	Lopinavir
LPV/r	Lopinavir/ritonavir
LZD	Lamzid®
MREC	Medunsa Research and Ethics Committee
MDR	Multi-drug resistant
MEMS	Medication events monitoring system
MSF	Médicins Sans Frontières
MMS	Microelectronic monitoring system
NIAID	National Institute of Allergy and Infectious Diseases
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
NVP	Nevirapine
PI	Protease Inhibitors
PMTCT	Prevention of mother to child transmission
TB	Tuberculosis
TDF	Tenofovir
UL	University of Limpopo
VAS	Visual analogue scale
WHO	World Health Organization

ABSTRACT

Introduction: High levels of adherence to ART are essential for maximal suppression of viral replication and avoidance of drug resistance. Pill counts are an indirect, objective method of assessing adherence. However, patients can invalidate pill counts by manipulating the number of tablets returned to the clinic in order to mask their non-adherence. The study aimed to investigate the ability of "mixed" pill counts to detect deliberate masking of non-adherence to ART at Ntshembo Clinic, Mamelodi, South Africa.

Objectives: The objectives of the study were to i) describe the incidence of adherence (exactly 100% adherence, <100% adherence, and >100% adherence) as measured by a normal pill count at the first visit, and a "mixed" pill count at the second visit for each study patient; ii) explore patients' explanations for discrepancies in pill counts; and iii) record and compare results of routine CD4 count and viral load testing, in patients with adherence rates of <95%, 95-100% and >100%, as measured by the normal pill count and the "mixed" pill count.

Method: Three hundred and seventy adult patients on a first line regimen of ART were recruited. At the first return visit (Return Visit 1), a standard (normal) pill count was performed and adherence (% of tablets taken) was calculated. For the repeat prescription, three days' extra supply was dispensed without the patients' knowledge. At the second return visit (Return Visit 2), a "mixed" pill count was performed and adherence was calculated. Patients were grouped into three categories based on calculated adherence: truthfully non-adherent (<100% adherence), adherent (100% adherence) and 'over-compliant' (>100% adherence, i.e. returning to the clinic with fewer tablets than required). Exploratory interviews were conducted with truthfully non-adherent and over-compliant patients to obtain explanations for discrepancies in pill counts.

Results: Three hundred and forty-four (92.9%) patients completed the study (40.4% males and 59.6% females). Reasons for drop-out or discontinuation from the study included regimen changes, missed appointments, and transfer or referral of patients from the study site to another ARV clinic. The overall average adherence for the study population was 97.2% at the first return visit, 100.2% at the second return visit and 98.7% over the two visits. At the second return visit, with the "mixed" pill count, 55 (16%) patients were identified as truthfully non-adherent (<100% adherence) while 43 patients (12.5%) were identified as over-compliant (>100% adherence) based on the adherence calculated for their regimen. The remaining patients (71.5%) were excellently adherent (exactly 100% adherence).

Forty-three of the non-adherent patients and 37 of the over-compliant patients agreed to be interviewed, of which five over-compliant patients admitted to manipulating their tablet numbers. Reasons for manipulation included: disliking certain ARVs, discovery of extra tablets in the tablet containers, missing doses, non-disclosure of HIV status, having tablets remaining and knowing that the tablets would be counted for the study. Reasons provided by all the interviewed patients as to why they experienced difficulties taking their ARV doses well on a daily basis included non-disclosure / stigma, pill burden, side effects, timing, forgetfulness, work-related issues, transport or distance to clinic, change of regimen, feeling sick, lack of support and stress.

The median CD4 count for the study population was 109 cells/mm^3 at commencement of ART and 377 cells/mm^3 after six months or longer on ART. The CD4 counts improved for 94.5% of the patients after six months or longer on ART, but there was no association between change in CD4 counts and adherence to ARVs (P=0.287; Fisher's exact test). With respect to viral load, 82.2% achieved undetectable viral load after at least six months on ART. Viral load was found to be highly associated with adherence to antiretroviral medication (P=0.004) in this study.

Conclusion: Overall, patients achieved fairly high adherence levels during the study period, although sub-optimal adherence was still a problem in some patients. Adherence was better at the second return visit compared to the first, emphasising the importance of attention given to individual patients in the form of adherence counselling during follow-up visits to the clinic.

This study indicated that the "mixed" pill count method may be capable of detecting deliberate masking of non-adherence. Applying this method to a larger sample may better estimate the frequency of pill count manipulation by patients and help gain insight to reasons for this behaviour and the extent of actual non-adherence.

Recommendations: Based on the findings from this study, it is imperative that adherence support should be made available to all patients, as patients have various challenges that hinder them from taking their medication properly on a daily basis. Regular counselling will also give room for the patients to express their challenges or concern (possible barriers to adherence) with regards to their treatment so that something can be done about them**.** This study was conducted over three follow-up visits for the patients. However, it is a known fact that adherence varies over time, so it is recommended that a similar study be conducted over a longer period of time.

Key words: dumping, manipulation, masking, over-compliance, adherence, HAART

CHAPTER 1
INTRODUCTION

1.1 INTRODUCTION

This introductory chapter describes the problem and rationale for the study. Operational terms used and assumptions made for the purposes of the study are explained. The research question, aim and objectives of the study and the hypotheses are provided. The chapter ends with an outline of the importance of this study.

1.2 PROBLEM STATEMENT AND RATIONALE FOR THE STUDY

Near perfect levels of adherence to antiretroviral (ARV) therapy are essential to achieve treatment success measurable in viral suppression, to maintain long-term health benefits and to avoid the development of drug resistance (Ford *et al.,* 2010; Lima *et al.,* 2008). Despite concerted efforts of healthcare providers, pharmaceutical manufacturers and health systems to encourage adherence, irregular and incomplete ARV medication-taking behaviour is common (Liu *et al.,* 2001; Liu *et al.,* 2006). However, since adherence to antiretroviral treatment (ART) is essential for treatment success (Ford *et al*., 2010; Lima *et al*., 2008), it is paramount that health care providers have efficient and reliable tools to measure adherence, so that poor adherence can be identified and addressed in its early stages.

Various studies document the limitations of current standard measures of ARV adherence, among them are directly administered antiretroviral therapy (DAART), therapeutic drug monitoring, self-reported adherence, electronic pill boxes, pill counts, etc. (Altice & Springer, 2010; Bartlett, 2002; Godin *et al.,* 2003; Maru *et al.,* 2007; Nachega *et al.,* 2006). Treatment programmes use the various methods alone or in combination, in the absence of a gold standard with which to measure adherence (Berg & Arnsten, 2006; Chesney, 2006). The need for efficient and reliable measures of adherence has initiated debate about how best to measure medication-taking behaviour in public sector ART settings.

One method commonly used to measure adherence in South African public health sector ART sites is the “pill count”. The pill count is an indirect, objective method to assess medication adherence (Chalker *et al.,* 2010; Kalichman *et al.,* 2007). The pill count method counts the total number of tablets remaining from the previous prescription and calculates the number of tablets assumed to have been taken (the difference between the number

dispensed and the number remaining) divided by the number of tablets the patient was supposed to take during the period; this measure is used to estimate a percent adherence. Critics of the pill count note that this method tends to overestimate medication adherence and does not indicate true medication-taking behaviour in terms of timing and dosage (Liu *et al.*, 2001; Ross-Degnan *et al.,* 2010).

Anecdotal evidence from some ART sites, as well as literature, suggest that the pill count method can be invalidated by a patient if, in preparation for the pill count, the patient used the pill count formula to calculate the expected number of tablets to remain for a good adherence percentage and manipulates the number of remaining pills to match the calculation. Allegedly, these patients deliberately fail to return all of their tablets or discard (dump) the 'excess' tablets before coming to the clinic or pharmacy for the pill count (Kalichman *et al.*, 2007). To catch out the conjectured manipulations, some facilities evolved a new concept of a "mixed" pill count. The "mixed" pill count is a practice whereby the pharmacist deliberately dispenses extra tablets (a predetermined 'n' number of extra tablets more than a thirty-day supply) to a patient and records the number of extra tablets in the patient's medication file without the patient's cognizance. Upon return for a repeat prescription, the tablets remaining in the container are counted taking into calculation the 'n' number of extra tablets dispensed. If these "n" extra tablets are unaccounted for, the adherence calculation would result in a greater than 100% adherence, also known as "over-compliance" or possible "masking". Adherence of greater than 100% is considered a possible indication that the patient may have manipulated the pill count in order to mask non-adherence. Reasons for masking non-adherence would then be probed.

The hypothesised advantage of the "mixed" pill count over the 'normal' pill count lies in the fact that the patient is not aware that extra tablets have been dispensed to him/her. As a result, it is assumed that the following three scenarios could ensue: (1) an adherent patient would return to the clinic with the extra tablets in the container because he/she is sure that all the tablets were taken as prescribed resulting in an adherence rating of 100%; (2) a truthfully non-adherent patient would return to the clinic with the extra tablets (and more) in the container because he/she is not attempting to mask non-adherence, so would have no need to discard any, including the extra tablets, resulting in an adherence rating of <100%; and lastly (3) the over-compliant patient (suggestive of masking non-adherence) would not return to the clinic with the extra tablets in the container because his/her calculation would not have accounted for the "n" number of extra tablets when manipulating the pill count, in order to mask non-adherence. This last scenario would result in an adherence rating of >100%. In all these instances, the extra tablets should act to safeguard the validity of the pill count. Inability to account for the extra tablets would allow the pharmacist to more easily

identify patients who may have attempted to mask adherence by dumping tablets and also allowing the health care worker to address the issues behind adherence masking. The end result would be improved ability to identify non-adherence, which previously would have been successfully masked through dumping of tablets to match the total calculated number of expected extra tablets.

To the best of the researchers' knowledge, limited information is available on the effectiveness of the "mixed" pill count as a measure of adherence to ARVs because it is a new concept and has not been formally evaluated. This study was designed to evaluate the "mixed" pill count as a tool to effectively identify non-adherence to ART. It is anticipated that more effective and earlier identification of non-adherence could contribute to an improvement in appropriate adherence counselling and ultimately adherence to ART itself. The use of a "mixed" pill count was compared against the standard care, a normal pill count.

1.3 OPERATIONAL DEFINITIONS AND ASSUMPTIONS

1.3.1 Normal pill count

A **normal pill count** is defined as the procedure whereby the tablets remaining in each ARV tablet container are counted at a follow-up visit. According to Chalker *et al.* (2009) and Etard *et al. (*2007), pill count results (% adherence) are calculated as follows:

$$\% \text{ Adherence} = \frac{\text{Number of tablets taken home} - \text{number of tablets returned}}{\text{Number of tablets that should have been taken}} \times 100$$

1.3.2 "Mixed" pill count

A **"mixed" pill count** is defined as the procedure whereby the tablets remaining in each ARV tablet container are counted at a follow-up visit after the pharmacist deliberately dispensed extra tablets during the previous visit, without the patient being aware of the extra tablets dispensed. The number of extra tablets dispensed is recorded in the patient's file in an encrypted format.

1.3.3 Assumptions

The following assumptions were made prior to the commencement of the study:

- Patients' aim is to mask poor adherence (taking too few tablets or none at all).
- In doing so, some patients may manipulate tablet counts by discarding tablets ("pill dumping").
- Patients dump tablets without physically counting the tablets dispensed.
- Patients would dump the deliberately added tablets along with the other untaken tablets. They will then return too few tablets at the next pill count.

Based on the above assumptions, pill count results >100% will be an indicator for suspected pill dumping in this study. The "mixed" pill count will unmask adherence maskers ("pill dumpers") as a result.

1.4 RESEARCH QUESTION

Is the method of "mixed" pill counts able to detect deliberate masking of non-adherence to ART?

1.5 AIM AND OBJECTIVES

1.5.1 Aim of the study

The aim of the study was to investigate the ability of "mixed" pill counts to detect deliberate masking of non-adherence to ART in a public sector practice setting.

1.5.2 Objectives of the study

The objectives of the study were as follows:

1. Describe the incidence of adherence (exactly 100% adherence, <100% adherence, and >100% adherence) as measured by a normal pill count at the first visit, and a "mixed" pill count at the second visit for each study patient.
2. Explore patients' explanations for discrepancies in pill counts.
3. Record and compare results of routine CD4 count and viral load testing, in patients with >100% adherence, ≥95 to 100% adherence, and <95% adherence, as measured by the normal pill count and the "mixed" pill count.

1.6 HYPOTHESES

Objective 1:

a) ***Null hypothesis 1:*** The proportions of patients returning too few dosage units are the same with both pill count methods.

   Alternative hypothesis 1: The proportions of patients returning too few dosage units are different with both pill count methods.

b) ***Null hypothesis 2:*** Patients returning exactly the expected number of dosage units at Visit 1 (normal pill count) are equally likely as other patients to return too few dosage units at Visit 2 ("mixed" pill count).

   Alternative hypothesis 2: Patients returning exactly the expected number of dosage units at Visit 1 (normal pill count) are more likely than other patients to return too few dosage units at Visit 2 ("mixed" pill count).

Objective 2:

This objective was achieved through qualitative methods, therefore no hypothesis testing was done.

Objective 3:

a) ***Null hypothesis 3:*** Health outcomes of patients with >100% adherence at Visit 2 (possible "adherence maskers"), of those with ≥95% to 100% adherence at Visit 2 ("truly adherent patients"), and of those with <95% adherence at Visit 2 ("non-adherent patients") are similar.

b) ***Alternative hypothesis 3:*** Health outcomes of patients with >100% adherence at Visit 2 (possible "adherence maskers"), of those with >95% to 100% adherence at Visit 2 ("truly adherent patients"), and of those with <95% adherence at Visit 2 ("non-adherent patients") are different.

1.7 IMPORTANCE OF THE STUDY

The inability to estimate a patient's adherence can have significant consequences. For example, underestimating adherence can lead to withholding treatment from someone who is ready to adhere well and benefit from treatment, whereas overestimation of adherence can contribute to poor treatment decision-making and counselling (Wagner, 2002).

This study is important because the “mixed” pill count is envisaged to serve as a tool to identify the “special” group of patients who deliberately mask their non-adherence by pill ‘dumping’ and who cannot be identified by a normal pill count.

Based on the outcomes of the study, a valid and practical method of identifying non-adherence will be recommended for implementation at ARV clinics. The periodic implementation of the “mixed” pill count method is envisaged to assist clinic staff to better identify non-adherent patients and to counsel them accordingly, in order to improve their medication behaviour and to improve practice.

1.8 SUMMARY

In this chapter the rationale for the study, which was conducted in a public sector practice setting, was outlined. The main aim of the study was to investigate the ability of “mixed” pill counts to detect deliberate masking of non-adherence to ART. The importance of conducting this type of study was highlighted and in the next chapter, the literature review on the research topic is presented.

CHAPTER 2
LITERATURE REVIEW

2.1 INTRODUCTION

In this chapter, the literature pertaining to the study is discussed. The chapter starts with an overview of HIV and AIDS, the extent of the epidemic globally, in Sub-Saharan Africa and in South Africa. This overview is followed by an overview of the classes of antiretroviral treatment. The roll-out of ARVs in South Africa, access to ART and the South African ARV guidelines are discussed. The ARV regimens and eligibility criteria for treatment initiation are then tabularised for clarity. Adherence is discussed in detail, including the definition of adherence, its importance, the existing knowledge base pertaining to rates of adherence and clinical markers of adherence. Finally, factors affecting adherence, reasons for non-adherence and methods of measuring adherence are discussed.

2.2 HIV AND AIDS

2.2.1 Explanation of HIV and AIDS

The acronym HIV stands for Human Immunodeficiency Virus (CDC, 2010; Martin, 2003). The HI virus is a retrovirus responsible for Acquired Immune Deficiency Syndrome (AIDS). There are two subtypes of HIV, namely HIV-1 and HIV-2, of which the latter is most common in Africa (CDC, 2010; Martin, 2003).

The virus destroys a subgroup of lymphocytes known as CD4 lymphocytes, which are vital in helping the body to fight diseases. This destruction of CD4 cells results in suppression of the body's immune system. Acquired Immune Deficiency Syndrome is the late stage of HIV infection by which time the immune system has been severely damaged and the body finds it difficult to defend itself against diseases and certain cancers (CDC, 2010; Martin, 2003).

Currently, there is no cure for HIV, however antiretroviral medication can slow the progression from HIV to AIDS, help to improve the health of HIV-positive people and prolong life (CDC, 2010).

2.2.2 History and origin of HIV

The proposed source of HIV infection in humans is a type of chimpanzee in West Africa. It is speculated that the chimpanzee version of the immunodeficiency virus, Simian

Immunodeficiency Virus (SIV), was transmitted to humans and mutated into HIV when humans killed the chimpanzees for meat and came into contact with their infected blood (CDC, 2010).

With time, the virus spread throughout Africa and later into other parts of the world (CDC, 2010; Van Dyk, 2008). The first cases of AIDS were recognised in Los Angeles in the United States of America in 1981 (CDC, 2010; Martin, 2003; Van Dyk, 2008).

2.2.3 Global HIV and AIDS epidemic

The HIV and AIDS epidemic is the most difficult and severe public health challenge the world faces (Nachega *et al.,* 2006). Globally, 33.3 million people live with HIV and 20.2 million of these are adults aged 15 years and above. Globally, an estimated 1.8 million people (adults and children) died due to AIDS-related illnesses in 2009. By the end of 2009, more than 16 million children were orphaned due to AIDS (UNAIDS, 2010).

2.2.4 HIV and AIDS in Sub-Saharan Africa

Sub-Saharan Africa is known as the epicentre of the AIDS epidemic because it is more heavily affected by HIV and AIDS than any other region of the world (Amberbir *et al.,* 2008; UNAIDS, 2010). More than one-tenth of the world's population lives in sub-Saharan Africa, which is home to about 68% of all HIV-positive people (Amberbir *et al.,* 2008). In 2009, this region accounted for 69.2% of new HIV infections among adults and children, as well as 72.2% of the global AIDS-related deaths (UNAIDS, 2010).

The report on the global AIDS epidemic (UNAIDS, 2009) shows that 89.8% of people living with HIV in sub-Saharan Africa are adults between the ages of 15 and 49 years. UNAIDS (2010) reported that 22.5 million people were living with HIV in sub-Saharan Africa at the end of 2009 and approximately 1.3 million additional people were infected with HIV during that year. In 2009, an estimated 1.3 million people (adults and children) died due to AIDS in this region (UNAIDS, 2010).

2.2.5 The HIV and AIDS epidemic in South Africa

There is an exceptionally severe epidemic of HIV and AIDS in South Africa (Noble, 2007; Pembrey, 2008). The country has the greatest number of people living with HIV and AIDS in the world (MSF, 2009). The majority of the population lives in informal housing and there are alarming rates of poverty, unemployment, crime and sexual violence (MSF, 2009). Statistics South Africa (2010) reported the overall HIV prevalence in South Africa to be approximately

5.24 million (10.5%), with a prevalence rate of 17% among adults aged 15 to 49 years. However, UNAIDS (2010) reported the number of people living with HIV in South Africa in 2009 to be 5.6 million, of whom 5.3 million (95%) are adults aged 15 years and above, with South Africa's epidemic still regarded as the largest in the world (UNAIDS, 2010).

Half of all the deaths that occur in South Africa are from AIDS-related causes (Robertson, 2008). According to the latest data from Statistics South Africa (2010), 281 204 (43%) of the 654 360 deaths that occurred in the country during the first half of 2010 were due to AIDS. By mid-2010, there were approximately 1.99 million AIDS orphans in South Africa. During the same time period, 370 000 new HIV infections among adults (aged 15 years and above) and 40 000 new infections among children were reported in the country (Statistics South Africa, 2010).

Cairns (2010a) stated that HIV prevalence has stabilised at 11% in South Africa, or is possibly starting to go down in younger people aged 15 to 24, as it was 9.3% in 2002 and 8.7% in 2008. The HIV prevalence in the core group of adults aged 15 to 49 rose from 15.5% in 2002 to 16.2% in 2005 and 16.8% in 2008. The proportion of people who had ever been tested for HIV in South Africa increased significantly from 25% to 56% between 2003 and 2008, while the proportion tested in the last 12 months increased from 12% in 2005 to 25% in 2008.

Khayelitsha, home to 500 000 people in South Africa, is a township located on the outskirts of Cape Town and has been said to have one of the highest HIV prevalence rates in South Africa (MSF, 2009). The KwaZulu-Natal Province recorded the highest HIV/AIDS prevalence rate among the nine provinces in the country in 2009, while Mpumalanga was the province with the second-highest and the Free State the third highest HIV prevalence rate (Avert, 2010a; El-Khatib and Richter, 2009; Health Systems Trust, 2010; Leach-Lemens, 2010a; Mpumalanga Provincial Government, 2010)

The 2003 model of the Actuarial Society of South Africa (ASSA), predicted that the number of people living with HIV will exceed 6 million by 2015, by which time around 5.4 million South Africans will have died of AIDS (Noble, 2007). Robertson (2008) reported that the average life expectancy of South Africans has dropped as a result of the epidemic. Statistics South Africa (2010) reported that life expectancy at birth declined between 2001 and 2005, but later increased, partly due to ARV roll-out. Currently, life expectancy at birth is estimated to be 53.3 years for males and 55.2 years for females. This increase in life expectancy is expected to continue. Robertson (2008) reported a similar finding of an average life expectancy of 54 years in South Africa, which according to him, would have been about 10 years longer without HIV.

2.3 ANTIRETROVIRAL TREATMENT

Antiretroviral drugs are substances that stop the activity of retroviruses such as HIV (Como, 2009). Successful ART helps to suppress HIV, maintain immunologic function and improve long-term survival in HIV-positive people (Peltzer *et al.*, 2010; Rosen *et al.*, 2007). Antiretroviral medicines are essential for HIV-positive patients to live, as one of the patients in the study by Garg *et al.* (2004) said:

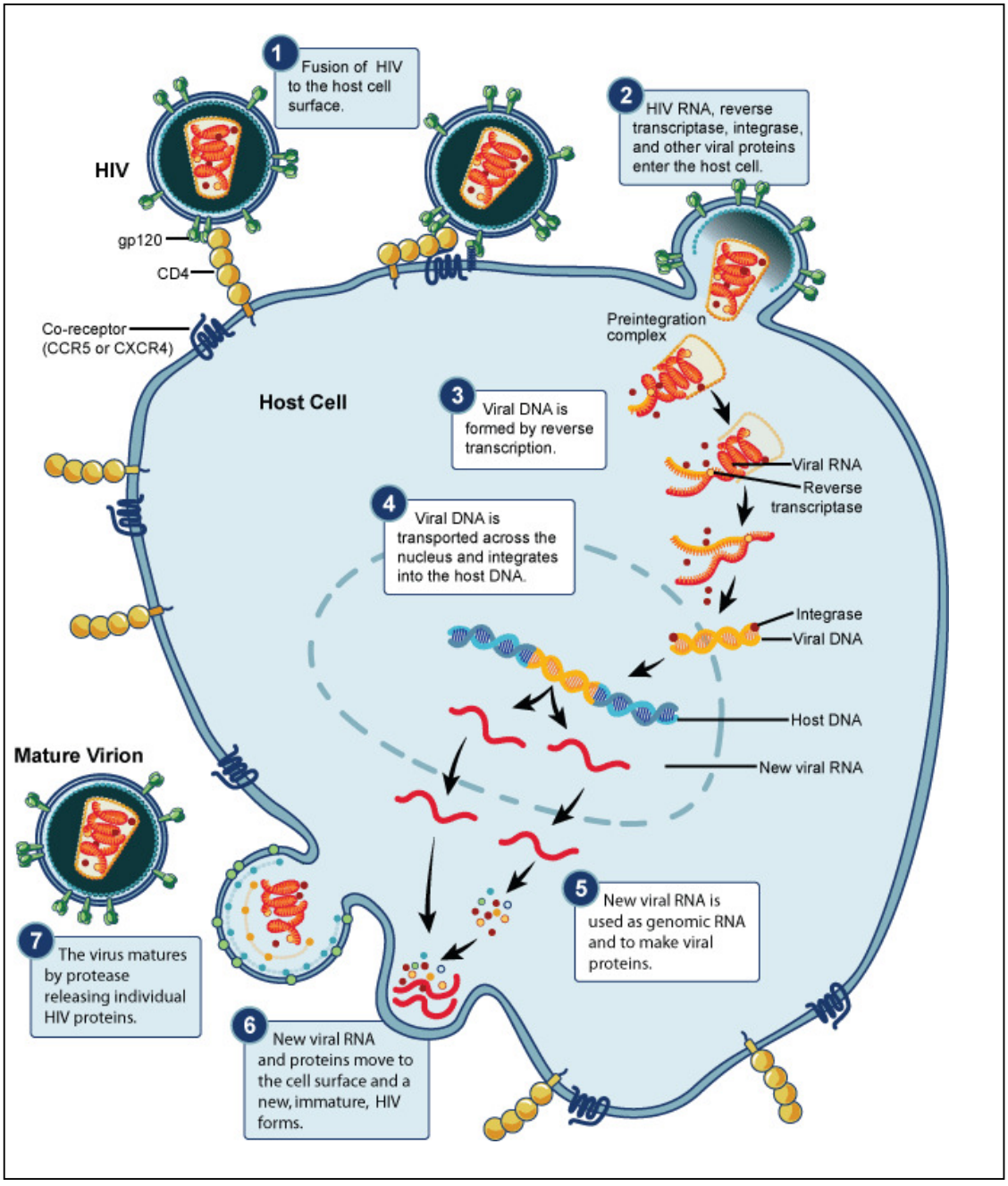
> *"People must know that a poor person like me living in a shack can take these drugs properly. They are my chance to live".* (Patient on ART in Khayelitsha, South Africa; extracted from Garg *et al.*, 2004).

2.3.1 Site of drug action

Replication of HIV consists of the following steps, as illustrated in Figure 2.1:

1. Fusion of HIV cell to the host cell surface.
2. HIV RNA, reverse transcriptase, integrase, and other viral proteins enter the host cell.
3. Viral DNA is formed by reverse transcription.
4. Viral DNA is transported across the nucleus and integrates into the host DNA.
5. New viral RNA is used as genomic RNA and to make viral proteins.
6. New viral RNA and proteins move to cell surface and a new, immature, HIV virus forms.
7. The virus matures by protease releasing individual HIV proteins.

Antiretroviral medication can potentially target any of the above steps.



Source: National Institute of Allergy and Infectious Diseases (NIAID), 2010.

Figure 2.1: The life cycle of HIV

2.3.2 Classes of antiretroviral drugs

There are seven main classes of antiretroviral drugs, namely the nucleoside reverse transcriptase inhibitors (NRTIs), non-nucleoside reverse transcriptase inhibitors (NNRTIs), nucleotide analogue reverse transcriptase inhibitors (NtRTIs) nucleotide inhibitors, protease

inhibitors (PIs), fusion inhibitors and integrase inhibitors (Coffey & Peiperl, 2010; Katzung, 2009).

The use of a combination of three antiretroviral drugs changed the prognosis of HIV/AIDS. The combination treatment is known as Highly Active Antiretroviral Therapy (HAART). A typical HAART combination would involve the following:

- Two nucleoside reverse transcriptase inhibitors with either a non-nucleoside reverse transcriptase or one or two protease inhibitors. OR
- One nucleoside reverse transcriptase inhibitor, one non-nucleoside reverse transcriptase inhibitor and one nucleotide reverse transcriptase inhibitor (DOH, 2010; Rang *et al.,* 2007; Rossiter, 2009).

2.3.2.1. Nucleoside Reverse Transcriptase Inhibitors (NRTIS)

The NRTIs act by competitive inhibition of HIV-1 reverse transcriptase and can also be incorporated into the growing viral DNA chain to cause termination. A drug in this class requires intracytoplasmic activation to the triphosphate form as a result of phosphorylation by cellular enzymes. Zidovudine (AZT), didanosine, lamivudine (3TC), zalcitabine, abacavir, stavudine (D4T) and emtricitabine (FTC) are examples of NRTIS (Katzung, 2009).

2.3.2.2. Non Nucleoside Reverse Transcriptase Inhibitors (NNRTIS)

The NNRTIs bind directly to a site on the HIV-1 reverse transcriptase, resulting in blockade of RNA- and DNA-dependent DNA polymerase activities. The binding site is near to, but distinct from, that of the NRTIs. Unlike NRTIs, the NNRTIs neither compete with nucleoside triphosphates nor require phosphorylation to be active. Examples of NNRTIs include nevirapine (NVP), delavirdine and efavirenz (EFV) (Katzung, 2009).

2.3.2.3. Nucleotide Analogue Reverse Transcriptase Inhibitors (NTRTIS)

An example of nucleotide inhibitors is tenofovir (TDF). The prodrug (tenofovir disoproxilfumate) is converted *in vivo* to tenofovir, which is an acyclic nucleoside phosphate (nucleotide) analogue of adenosine. Nucleotide inhibitors act like the NRTIs by competitively inhibiting HIV reverse transcriptase to cause chain termination after incorporation into DNA (Katzung, 2009).

2.3.2.4. Protease Inhibitors (PIs)

Protease inhibitors act during the later stages of the HIV growth cycle when the gene products are translated into polyproteins and then become immature budding particles.

Protease is responsible for cleaving these precursor molecules to produce the final structural proteins of the mature virion core. By preventing cleavage of the Gal-Pol polyprotein, protease inhibitors result in the production of immature, non-infectious viral particles. Examples of PIs include saquinavir, ritonavir, lopinavir/ritonavir (LPV/r), indinavir, nelfinavir and amprenavir (Katzung, 2009).

2.3.2.5. Entry or fusion inhibitors

Fusion inhibitors block HIV entry into target cells. Examples of drugs in this class are enfuvirtide and maraviroc. Enfuvirtide binds to the gp41 subunit of the viral envelope glycoprotein and thus prevents the conformational changes required for the fusion of the viral and cellular membranes, and it is only available in parenteral dosage form. Maraviroc binds to a protein on the CD4 cell membrane, referred to as CCR5. By doing this, HIV cannot successfully attach to CD4 cell surface and is therefore prevented from infecting healthy cells (Coffey & Peiperl, 2010; Dubois & Cohen, 2009; Hupfeld and Efferth, 2009; Katzung, 2009; Pfizer, 2007).

2.3.2.6. Integrase inhibitors

Integrase inhibitors act by binding to a viral enzyme integrase and interfere with the incorporation of reverse-transcribed DNA of the virus into the chromosomes of host cells. Examples of integrase inhibitors are raltegravir and elvitegravir (Da Silva *et al*., 2010; Dubois & Cohen, 2009; Katzung, 2009).

2.3.2.7. Maturation inhibitors

Maturation inhibitors are a new class of antiretroviral drugs. Bevirimat is the first drug in this class of ARVs to reach Phase IIb clinical trials. Maturation of HIV involves cleavage of the Gag and GagPol precursor proteins into the mature Gag proteins and the viral enzymes. Therefore, bevirimat blocks the cleavage of the capsid protein precursor into the mature capsid protein (Heider, Verheyon & Hoffmann, 2010; Hupfeld & Efferth, 2009; Salzwedel, Martin & Sakalian, 2007).

2.3.3 Adverse effects of antiretroviral drugs

Amberbir and colleagues (2008) as well as Peltzer and colleagues (2010) reported that experiencing adverse effects of antiretroviral drugs, is one of the barriers to adherence to ART. These adverse effects vary in severity and from person to person (Avert, 2010b).

Table 2.1 highlights the most common adverse effects of the frequently-used ARVs.

Table 2.1: Adverse effects of antiretroviral drugs

Drug class	Example	Common adverse effects
NRTIs	Abacavir	Rash, hypersensitivity reaction, nausea
	Didanosine	Gastrointesinal disturbances, pancreatitis and peripheral neuropathy
	Lamivudine	Infrequent, but include peripheral neuropathy and pancreatitis (rare and only reported in children)
	Stavudine	Lipoatrophy of face and limbs, peripheral neuropathy, hyperlactataemia and hepatic stenosis
	Zidovudine	Anaemia, neutropenia, leucopenia
NNRTIs	Efavirenz	Abnormal dreams, impaired concentration, insomnia, dizziness, rash, fatigue
	Nevirapine	Rash, fever, headache, nausea
Nucleotide inhibitors	Tenofovir	Nausea, vomiting, diarrhoea, flatulence
Protease Inhibitors	Ritonavir	Nausea, vomiting, diarrhoea, lipodystrophy, paresthesias, hepatitis
Fusion inhibitors	Enfuvirtide	Local injection site reactions, eiosinophilia
	Maraviroc	Diarrhoea, nausea, headache, cough, muscle spasm, insomnia
Integrase inhibitors	Raltegravir	Diarrhoea, nausea, headache, fever, rash, dizziness, pruritus, lipodystrophy, arthralgia, hyperhydrosis
Maturation inhibitors	Bevirimat	Gastrointestinal problems (constipation, diarrhoea, nausea, stomach cramps) and headaches

Source: Aidsinfo, 2010; Avert, 2010b; Dubois & Cohen, 2009; Healthline, 2010; Katzung, 2009; Helfand, 2009; Rossiter, 2009.

2.4 ACCESS TO ANTIRETROVIRAL TREATMENT

Access to ART is limited for the majority of individuals living with HIV and AIDS in sub-Saharan Africa (Nachega *et al.,* 2006). The WHO's "3 by 5" initiative launched in 2003, to have 3 million people in lower- and middle-income countries on treatment by 2005, was not achieved until 2007. By 2005, access to treatment was greatly expanded and this tripled from 400 000 in December 2003 to 1.3 million in December 2005 (Avert, 2010c).

As of December 2008, an estimated four million people in low- and middle income countries were receiving ARVs, which represents a ten-fold increase over five years (UNAIDS, 2009). Only 42% of those who needed treatment were receiving it by the end of 2008, although this

was a great improvement on the 33% of the previous year (WHO/UNAIDS/UNICEF, 2009). In Sub-Saharan Africa alone, only 44% of those in need of ART received it at the end of 2008 (Avert, 2010c).

Statistics South Africa (2010) estimated that 1.63 million people (adults and children) were in need of ART by mid 2009, but only 53.4% of those actually received it. Although access to ART in South Africa is still limited, the country now has the largest HIV treatment programme in the world. The numbers of people taking treatment expanded exponentially from nearly 33,000 in January 2005 to 744,000 in March 2009 (Cairns, 2010a). This achievement though was recently tarnished by an increasing alarm over the Free State public sector ARV programme (El-Khatib & Richter, 2009). Almost a quarter of patients eligible for HIV treatment in this province died before getting it, a further 13% disappeared from the healthcare system and 5% were still on a waiting list (Leach-Lemens, 2010a).

2.5 ANTIRETROVIRAL TREATMENT ROLLOUT IN SOUTH AFRICA

The South African Government's response to the HIV and AIDS epidemic is grounded in the HIV/AIDS and STD Strategic Plan for the period 2007-2011 (DOH, 2007). The purpose of the plan was to provide a broad national framework around the following four priority areas:

- Prevention
- Treatment, care and support
- Human and legal rights
- Monitoring, research and surveillance

In November 2003, the South African Government adopted the Operational Plan for Comprehensive HIV and AIDS Treatment and Care, which included the provision of ART free of charge to HIV-positive patients at public sector health care facilities (DOH, 2003).

According to the first National Antiretroviral Treatment Guidelines, the primary goal of ART is to decrease HIV-related morbidity and mortality (DOH, 2004). Hence the following goals should be achieved:

- The patient should experience fewer HIV-related illnesses.
- The patient's CD4 count should rise and remain above the baseline count.
- The patient's viral load should become undetectable (<400 copies/mm^3), and remain undetectable on ART.

The secondary goal is to decrease the incidence of HIV through the following actions:

- An increase in voluntary testing and counselling with more people knowing their status and practising safer sex.
- Reducing transmission in discordant couples (in discordant couples, one partner is HIV-positive and the other is HIV-negative).
- Reducing the risk of HIV transmission from mother to child.

2.5.1 Antiretroviral treatment guidelines

2.5.1.1. First South African national antiretroviral treatment guideline

South Africa's first National Antiretroviral Treatment Guidelines were published by the National Department of Health (DOH) in 2004. The criteria for the commencement of ART in HIV-positive patients, were as follows: CD4 count less than 200 cells/mm^3, irrespective of WHO stage or WHO stage IV with an AIDS-defining illness irrespective of CD4 count. In both cases, patients must express willingness and readiness to take ART adherently (DOH, 2004). These first guidelines were in use at the commencement of this study and up to the end of March, 2010.

Table 2.2 shows the two standard first-line recommended ARV regimens for adults in the South African public sector in the first (i.e previous) antiretroviral guidelines (DOH, 2004).

Table 2.2: ARV regimens for adults in the South African public sector: 2004 to March 2010

Regimen	ARV Drugs
1a	Stavudine / lamivudine / efavirenz
1b	Stavudine / lamivudine / nevirapine
2	Zidovudine / didanosine / lopinavir/ritonavir

Source: South African National Antiretroviral Treatment Guidelines (DOH, 2004)

2.5.1.2. WHO recommendations for current South African ARV guidelines (from April 2010)

In 2009, the WHO recommended that all governments adopt national policy guidelines that promote an earlier start to treatment as well as the use of less toxic first-line drugs (WHO, 2009). Table shows a comparison of the WHO 2006 guidelines with the 2009 recommendations.

Table 2.3: Comparison of WHO 2006 ART guidelines and the 2009 recommendations

	WHO 2006 guidelines	WHO 2009 recommendations
Eligibility for treatment	Start ART for all patients with advanced clinical disease and/or a CD4 count of **200cells/mm³ or less**.	Promote earlier treatment for all patients, when their CD4 count **falls to 350 cells/mm³ or less**, regardless of symptoms.
Treatment regimens	The role of Stavudine (d4T) containing regimens was recommended due to its low cost, limited need for laboratory monitoring, initial tolerability and widespread availability.	Proposed that countries progressively phase out the use of stavudine as a preferred first-line therapy option and move to less toxic alternatives such as zidovudine (AZT) and tenofovir (TDF).

Source: WHO, 2009.

2.5.1.3. Benefits of the WHO 2009 recommendations

The 2009 recommendations aim to prolong and improve the quality of life of patients by reducing the rates of death, morbidity and as well as HIV and tuberculosis (TB) transmission by starting treatment earlier (WHO, 2009). The specific benefits of the new recommendations over the 2006 guidelines are outlined below:

- Early treatment reduces viral load much sooner and thus reduces the rate of disease progression and onward HIV transmission.
- Earlier treatment boosts the immune system, making it less likely for the patient to fall sick with TB and other opportunistic diseases.
- Commencing treatment early should also act as an incentive for more people to undergo voluntary counselling and testing before waiting to develop symptoms and fall sick.

The phasing out of stavudine should enable patients to avoid disabling and disfiguring side-effects of stavudine and reduce the costs of managing these toxicities.

With HIV, it is common in resource-poor settings for patients to be diagnosed at a late stage of the disease and as a result begin ART with advanced immunodeficiency. Few of these patients attain the treatment goal of a CD4 count of 500 cells/mm³. Subsequently, the probability of lowering the risk of death and disease over time is significantly reduced for this population (Leach-Lemens, 2010b).

Accumulating evidence suggests that a very low CD4 count before starting ART, and subsequent poor immune restoration, is associated not only with an increased risk of death after starting treatment due to infectious causes, but also to a prolonged increased risk of

cardiovascular disease and cancers despite long-term viral suppression (Leach-Lemens, 2010b). The newly revised WHO guidelines will enable people living with HIV to start treatment at a higher CD4 count.

A study by Cairns (2010b) reported that in discordant couples, the chance of HIV transmission is reduced by at least 90% if the HIV-positive partner is on ART. Another important finding from this study was that untreated partners with a CD4 count of less than 200 cells/mm^3, were approximately five times more likely to transmit HIV than those with a CD4 count of more than 350 cells/mm^3, thus strengthening the case for extending ARV provision to all people with low CD4 counts.

2.5.1.4. Adaptation of the WHO 2009 recommendations in South Africa

To contribute to strengthening the public and private health sectors' capacity to deliver quality healthcare services, the South African Department of Health recently adapted some of the WHO 2009 recommendations in its ART guidelines. However, instead of initiating treatment at a CD4 count of 350 cells/mm^3 or less for everyone, the DOH recommends that this level will only apply for pregnant HIV-positive women and HIV-positive patients with TB. The objectives of the new guidelines are as follows:

- To contribute to strengthening the public and private health sectors' capacity to deliver high quality integrated health and wellness services.
- To ensure timely initiation of ARVs for treatment and prevention according to the Presidential mandates.
- To minimise unnecessary drug toxicities.

The new South African ART guidelines were implemented on 1 April 2010. Table 2.4 shows the national eligibility criteria for starting ART for adults and adolescents and table 2.5 shows the national ART regimens for adults and adolescents in South Africa.

Table 2.4: Standardised national eligibility criteria for starting ART regimens for adults and adolescents in South Africa: 2010

Not yet eligible for ART	Eligible to start ART	Require fast track (i.e. ART initiation within 2 weeks of being eligible)
• Transfer to a wellness programme for regular follow up and repeat CD4 testing 6-monthly • Advice on how to avoid HIV transmission to sexual partners and children • Initiate INH prophylaxis if asymptomatic for TB • Contraceptives and annual Pap smear	• CD4 count ≤200 cells/mm^3 irrespective of clinical stage OR • CD4 count ≤350 cells/mm^3 in patients with TB or pregnant women OR • WHO stage IV irrespective of CD4 count OR • MDR/XDR irrespective of CD4 count	• Pregnant women eligible for lifelong ART OR • Patients with very low CD4 (<100) OR • Stage 4, CD4 not yet available OR • MDR/XDR TB

Source: The South African Antiretroviral Treatment Guidelines 2010 (DOH, 2010)

Table 2.5: Standardised national ART regimens for adults and adolescents, South Africa: 2010

First Line		
All new patients needing treatment, including pregnant women	Tenofovir + lamivudine/emtricitabine + efavirenz/nevirapine	For TB co-infection efavirenz is preferred. For women of child bearing age, not on reliable contraception, nevirapine is preferred.
Currently on stavudine based regimen with no side-effects	Stavudine + lamivudine + efavirenz	Remain on stavudine if well tolerated. Early switch with any toxicity. Substitute tenofovir if at high risk of toxicity (high body mass index, low haemoglobin, older female)
Contraindication to tenofovir: renal disease	Zidovudine + lamivudine + efavirenz/nevirapine	
Second Line		
Failing an a stavudine or zidovudine-based 1st line regimen	Tenofovir + lamivudine/emtricitabine + lopinavir/ritonavir	
Failing on a tenofovir-based 1st line regimen	Zidovudine + lamivudine + lopinavir/ritonavir	
Salvage		
Failing any 2nd line regimen	Specialist referral	

Source: The South African Antiretroviral Treatment Guidelines 2010 (DOH, 2010)

2.6 ADHERENCE

2.6.1 Definition of adherence

According to the Oxford English dictionary, the word adherence is defined as *"behaving according to a particular rule or a fixed way of doing something"* (Hornby, 2000). Adherence to ART also means taking all the prescribed doses of ARVs at the right time and in the right way (Horizon/Population Council, 2004).

The above definitions have focused on adherence to medication, but adherence also encompasses numerous health-related factors that extend beyond taking prescribed medicines. The WHO (2003) explains that adherence to any regimen reflects behaviour of one type or another. Seeking medical attention, collecting prescriptions, taking medication appropriately, obtaining immunisations, attending follow-up appointments, and executing behavioural modifications that address personal hygiene, risky sexual behaviour, unhealthy diet and insufficient levels of physical activity are all examples of therapeutic behaviours. Therefore, the WHO (2003) has adopted a more comprehensive definition of adherence to long-term therapy, namely that adherence is:

> *"the extent to which a person's behaviour (taking medication, following a diet, and/or executing lifestyle changes) corresponds with agreed recommendations from a health care provider".*

2.6.2 Importance of adherence

Adherence to ART is essential for maximal suppression of viral replication and avoidance of drug resistance (Ford *et al.,* 2010; Lima *et al.,* 2008). As such, good adherence is believed to be a critical determinant of long-term survival among HIV-infected individuals (Chi *et al.,* 2009; Nischal, Khopkar & Saple, 2005*).* Successful ART requires life-long and high rates of adherence (Peltzer *et al.,* 2010; Ross-Degnan *et al.,* 2010). Adherence to ART is particularly important in HIV infection because patients can quickly become resistant to ARVs if they are not taken as prescribed. Furthermore, cross-resistance (becoming resistant to similar drugs) limits patients' future treatment options (DOH, 2004; Horizon/Population Council, 2004).

If patients understand why they need to take medication, the benefits of treatment, and how these outweigh the risks of side effects, they are more likely to be adherent (Horizon/Population Council, 2004).

The best response to ART is seen when adherence is 100%. Adherence levels below 95% have been associated with drugs not working effectively, drug resistance, poor suppression

of HIV viral load, reduced rate of increase in CD4 count, increased risk of disease progression, more time in hospital and an increased risk of death (Godin *et al*., 2003; Liu *et al.,* 2001; Mills *et al.,* 2006). The importance of adherence to ART cannot be over-emphasised, especially in the light of the limited number of antiretroviral drugs available in the South African public sector. If patients become resistant to a certain ARV, very few regimen options remain. Patients should therefore endeavour to take their medication properly on a daily basis to guard against drug resistance and save on limited resources.

2.6.3 Clinical markers of adherence

A CD4 cell is a T-lymphocyte with a large glycoprotein molecule found on the surface. It helps the body to fight against diseases and serves as the receptor for HIV. The CD4 count refers to the number of CD4 T-lymphocytes in a cubic millilitre of blood. In HIV-positive people, the CD4 count declines as the disease progresses and is used to monitor the extent of immune suppression in these individuals (Medterms, 2010).

Viral load is the measurement of the number of HIV virions in the blood, expressed as copies per millilitre. Viral load is used to guide treatment decisions and monitor response to treatment (Como, 2009).

The presence of a high viral load in the blood results in increased destruction of CD4 cells (immune system cells that fight infection), which in turn increases the risk of developing AIDS defining symptoms within a few years (Aidsmap, 2010).

Clinical algorithms and CD4 counts are still common methods to diagnose treatment failure even though they have proven to be unreliable. In most resource-poor settings, where viral load monitoring is not available, patients and medical staff are only alerted to resistance when patients suffer from opportunistic infections (MSF, 2009).

Viral load testing is costly and needs a dedicated laboratory with highly skilled staff. Apart from national reference laboratories and universities, few countries in sub-Saharan Africa can provide viral load testing for people on ARVs (Aidsmap, 2010).

In the absence of a viral load test, WHO guidelines recommend that clinical signs, such as opportunistic infections and CD4 cell count be used in order to decide if a person needs to change his/her drug regimen. However, both these tools have serious limitations. Changes in CD4 counts are difficult to interpret because of individual variations in immunological response to ART, and because clinical failure comes much later than virological failure (MSF, 2009).

In a Ugandan study, patients were followed to determine the ability of CD4 count to detect treatment failure, compared to viral load. Of the 112 patients failing treatment according to viral load, only 26 would have been detected by CD4 count (Reynolds *et al.,* 2009*).* In another study, 100 people were identified as failing treatment according to CD4 cell counts, of which only 11 were actually failing. Based on CD4 counts alone, without viral load testing, these 89 patients would therefore have been mistakenly identified as failing ART and prematurely switched from their primary ARV regimen when it was actually effectively controlling viral replication (Moore *et al.,* 2008).

Therefore, the current clinical and CD4 count-based monitoring may not accurately identify treatment failure, leading clinicians to delay switching from a failing regimen or causing them to switch too early from a regimen that is still effective (MSF, 2009).

In a study conducted by Kalichman and colleagues (2007), substantial and sustained gains in CD4 cell count were observed among adherent patients regardless of the baseline CD4 count. Moreover, it is evident that virologic failure is associated with non-adherence to ARVs as a past study has observed an undetectable viral load in 81% of the patients who were taking 95% or more of their medication (Godin *et al*., 2003). These studies showed that there is a correlation between adherence, CD4 count and viral load. This means that there needs to be an accurate method of measuring adherence in order to achieve viral load suppression, but there is no validated approach to do this yet (Ross-Degnan *et al*., 2010).

2.6.4 Adherence rates

A previous study has demonstrated that the rates of non-adherence to medications within the general population can range from 15% to 93%, with the average rate of adherence for chronic health conditions being 50% (Singh *et al*., 1996).

The efficacy of ART in suppressing HIV and improving survival rates among HIV-positive individuals has been well documented (Peltzer *et al.,* 2010), and adherence to ART strongly predicts viral suppression, development of drug resistance, disease progression and death (Bangsberg, 2010).

However, adherence levels of at least 95% are required for sustained viral suppression and to prevent drug resistance (Ford *et al.,* 2010; Lima *et al.,* 2008). While some authors defined optimal adherence as ≥95% (Lima *et al.,* 2008), others feel that that 100% adherence is required for the long-term clinical success of ART because despite HAART effectiveness, it does not completely eradicate the HI virus from the host (Cauldbeck *et al.,* 2009; Machtinger & Bangsberg, 2006).

Adherence is known to vary over time and sub-optimal adherence to ART is a common problem (Hill, Kendall & Fernandez., 2003; Horizon/Population Council, 2004). According to a review of 19 randomised control trials by Rueda and colleagues (2006), the study population that reported 95% or greater adherence at baseline ranged between 68% and 82%. Parruti *et al* (2006), n = 171, found that the prevalence of a high level of adherence (90% and above) at six months was 88.3% and slightly less than 80% at 12 months (n=50). This observation shows that the longer patients are on ART, the more likely that their adherence may decline. Meanwhile, in Mokoena (2009), prevalence of high level of adherence (95 to 100%) at approximately six months on treatment (Visit 7) was 69% (n=100), but contrary to Parruti's findings, the prevalence of high adherence increased with time to 86% after 11 months. According to Mokoena (2009), there was a high prevalence of optimal adherence in the first six months, but it was low at visit seven, then it went up again in subsequent visits. This clearly illustrates that adherence is a dynamic behaviour and individual adherence varies on a monthly basis, even for patients with high levels of adherence.

It has been suggested that people in Africa adhere better than their North American counterparts. A meta-analysis by Mills *et al.* (2006) of 27 sub-Saharan African and 31 North American studies reported that adequate adherence was observed in 77% of patients in Africa and 55% of patients in North America. Another study also showed that the proportion of people reporting ≥95% adherence in sub-Saharan Africa is higher than in North America (El-Khatib & Richter, 2009). Efforts to sustain adherence in Africa and elsewhere remain important goals to optimize outcomes for individuals and global HIV treatment (Nachega *et al.,* 2006).

Unfortunately, it is not easy for many patients to attain high rates of adherence (Cauldbeck *et al.,* 2009; Martin *et al.,* 2008). In a study of HIV treatment-naïve patients, 95% adherence was associated with maximal therapeutic effects of antiretroviral therapy, but, however 30% of patients in the study were able to attain this level (Rueda *et al.,* 2006). It has been demonstrated that a 10% higher level of adherence to ART results in a 21% reduction in disease progression (Nischal, Khopkar & Saple, 2005).

Perfect adherence is an important goal, however, some studies have reported high virologic success even with adherence rates below 95% (Bangsberg, 2006; Martin *et al.,* 2008; Paul, 2009). In a study that assessed the relationship between adherence, ARV regimen and viral load (n=1142), in patients taking NNRTIs or boosted PI-based regimens and who achieved 80% adherence, the virologic failure rate was lower than in those taking unboosted PIs (Martin, *et al.,* 2008). Similarly, when patients on boosted lopinavir were compared with

those on unboosted nelfinavir in a prospective clinical trial, virologic success was directly correlated with the level of adherence in both groups, but an adherence rate of atleast 72% was sufficient in lopinavir/ritonavir-treated patients (boosted PI), whereas >83% adherence was needed for nelfinavir-treated (unboosted PI) patients to obtain a greater than 50% probability of never having a detectable viral load (King, Brun & Kempf, 2005). According to an observational study, NNRTI-based regimens can result in virologic suppression with 53-73% adherence. However, in another study (n=2821), NNRTI-based regimens achieved virologic suppression in only 25% of patients who had 50-60% adherence, but increased to 73% in those with 90-100% adherence (Nachega *et al.,* 2007).

2.7 FACTORS WHICH AFFECT ADHERENCE

Maintaining adherence is a complex phenomenon and different life factors affect patients' ability to access and adhere to ARVs. These include patient characteristics and context, ARV regimen, clinical situation and the patient-healthcare worker relationship (El-Khatib & Richter, 2009). Although early adherence factors are essential for developing tools to assist clinicians in the identification of factors related to poor adherence prior to initiating therapy, what is required from HIV patients is prolonged (lifetime) adherence to HAART. In the developing world, it is critical to understand factors (motivators and barriers) that influence adherence to ART and apply these factors in improving existing and new programmes (Amberbir *et al.,* 2008).

These factors that influence patients' adherence to medication differ from person to person. According to the WHO (2003), such factors can be divided broadly into the five categories described below.

2.7.1 Social/economic factors

Many HIV/AIDS patients are faced with socioeconomic experiences (difficulties or realities) that they have to cope with. These experiences tend to affect their lifestyle and attitude towards their condition and therapy, some of which are described in this section.

The issue of disclosure has been found to have serious implications for adherence levels. For example, the use of medication may inadvertently reveal a person's HIV status (Meyer, 2008; Vervoort *et al.,* 2007).

Poverty also affects adherence, as it may prevent individuals from following treatment-related dietary advice. Another social factor is drug and alcohol abuse which may impair

judgement and ability to adopt and maintain routine medication use (Kgatlwane *et al.,* 2004; Vervoort *et al.,* 2007).

Peltzer and co-workers (2010) identified higher levels of adherence among rural residents than urban residents, which indicates that where one stays has an effect on one's adherence to therapy. On the contrary, a study conducted in Tanzania showed that patients living in urban areas had a higher level of ARV knowledge and more of these patients had tested for HIV, as compared to those living in the rural area (Zou *et al.,* 2009). It has been established by Vervoort and colleagues (2007) that patients' knowledge of HIV and ARVs increase the chances of good adherence, therefore, the finding of Zou *et al.* (2009) implies that urban patients may adhere more than rural ones. This could be explained by the fact that in the urban areas, transport costs may be lower and there may be fewer disruptions in access to medicines.

Maqutu, Zewotir and North (2009) studied the social, demographic, behavioural and economic factors that affect early adherence to HAART using a cross-sectional study of HIV positive adults in South Africa. The study showed that gender, treatment site and baseline CD4 cell count are significant factors to adherence. Several studies found different correlations between gender and adherence, for example, female patients were found to have better levels of adherence than their male counter-parts (Bhat *et al.,* 2010), but according to other studies, women had lower levels of adherence than men (Peltzer *et al.,* 2010; Williams *et al.,* 2006). On the other hand, Rougemont *et al. (*2009) reported that there is no association between gender and adherence to ARVs. Women who live together with children, as well as those who are married or cohabiting, have been reported to have a lower level of adherence to ARVs (Peltzer *et* al., 2010; Vervoort, 2007). This finding is contradicts that of of Bhat and colleagues (2010), in which 36.5% of the non-adherent female patients were single, while the married (63.5%) were adherent.

Some studies have confirmed that educated patients are more likely to be adherent than those with no formal education (Iliyasu *et al.,* 2005; Kleeberger, *et al.,* 2004; Peltzer *et al.,* 2010), but the opposite was the case in other studies (Bhat, *et al.,* 2010). Even the level of education of a patient's caregiver has an influence on his/her adherence. The study of Williams and colleagues (2006) found that higher caregiver level of education is associated with improved adherence.

With respect to patients' monthly income, it has been found that a middle income is associated with better adherence levels than low and high income (Rougemont *et al.,* 2009). The findings of Batavia *et al.* (2010) suggest that the provision of free HAART is associated

with higher rates of adherence. This is consistent with the study of Byakika-Tusiime *et al.* (2005), where patients experienced frequent treatment interruptions and delays in seeking medical care, because they could not afford the fees charged. Similarly, Ramadhani *et al.* (2007) reported rates of 100% adherence and higher rates of virologic failure amongst patient who had to pay for ART for a long duration. Nachega and colleagues (2010) examined the relationship between medication costs and poor adherence in South Africa, it was found that although medication costs increased with higher adherence, cost associated with HIV morbidity also decreased.

Increase in age was associated with non-adherence in the study of Williams and colleagues (2007), but in Bhat *et al.* (2010), increase in age correlated with good adherence.

2.7.2 Health system/healthcare team factors

Health system factors include the availability of transport and satisfaction with past experience with the healthcare system. The healthcare team factors include trust in the provider and clinic staff, the provider's willingness to include the patient in the decision-making process and the affective tone of the relationship, e.g warmth and openness (Kgatlwane *et al.,* 2004). Chesney (2003) found that dissatisfaction with the health services is a predictor of non-adherence. Adherence is positively affected when patients get support from pharmacists and nurses (Deschamps *et al.,* 2004). On the other hand, Ammassari *et al. (*2002) concluded that being satisfied with healthcare and the patient-provider relationship is an inconsistent factor in affecting adherence.

2.7.3 Therapy-related factors

Therapy-related factors include the number of tablets prescribed, the complexity of the regimen and medication side-effects. The complexity of the regimen and side-effects caused by it are clearly associated with sub-optimal adherence (Machtinger & Bangsberg, 2006). The immediate effect of ARVs in patients who commence ART at the asymptomatic stage might initially be perceived as deterioration in health status, and this might subsequently affect adherence negatively (Horizons/Population Council, 2004), however, this is contrary to the findings of Rougemont and colleagues (2009) in which symptomatic patients had a higher risk of non-adherence than asymptomatic patients. Peltzer and colleagues (2010) found patients on Regimen 1a of ARVs had a better adherence than those on Regimen 1b, although the difference was not statistically significant. Williams and colleagues (2006) also found no significant association between current antiretroviral therapy and adherence.

When patients are initiated on ART, it is important that they are given information on possible side effects and advice on how to handle these side effects (Vervoort *et al.,* 2007).

2.7.4 Condition-related factors

Condition-related factors include the stage and duration of HIV infection, associated opportunistic infections and HIV-related symptoms. The severity of the illness could impact negatively or positively on adherence to ART (Kgatlwane *et al.,* 2004). Having HIV-related symptoms or being admitted in hospital due to HIV complications are positively asscociated with non-adherence (Ammassari *et al.,* 2002; Peltzer *et al.,* 2010).

2.7.5 Patient-related factors

Patient-related factors include sociodemographic factors (age, gender, race, income, education) and psychosocial factors (mental health, substance abuse, socio-cultural issues and support) that influence adherence (Kgatlwane *et al.,* 2004; Machtinger & Bangsberg, 2005; Vervoort *et al.,* 2007).

Although adherence is an important factor, sub-optimal adherence to ART is a great concern relating to HIV management. Since adherence is mostly influenced by patient related factors, sub-optimal adherence needs to be addressed with patient-oriented interventions (Bhar *et al.,* 2010; Carter, 2005; WHO, 2003).

Using a buddy system, having an adult other than the biological parents as a care giver and taking antipsychotic medications are associated with good adherence (Adeyinka *et al.,* 2008; Bartlett, 2002; Williams *et al.,* 2006). Other sociodemographic factors have been discussed in Section 2.7.1.

2.8 REASONS FOR NON-ADHERENCE

People may achieve low levels of adherence for various reasons. The most frequently given reason is simply forgetting. In a study conducted by the Adult AIDS Clinical Trials Group (AACTG), 66% of 51 participants cited forgetting as their reason for non-adherence and almost the same percentage (64%) cited the same reason in another study by researchers at Johns Hopkins University (n=2554) (Bartlett, 2002; Chesney *et al.,* 2000; Eldred *et al.,* 1998). Other reasons cited by patients in both of these studies included being away from home without medication, having difficulty with the timing of medications, feeling too ill or tired to take medication, feeling depressed or overwhelmed and having too many medications or too many pills to take (Meyer, 2008; Mokoena, 2009).

Nachega and colleagues (2006) reported that cost, disclosure, alcohol abuse, and difficulty in following complex drug regimens affect adherence in sub-Saharan Africa. Other barriers to adherence include forgetting, feeling sick, being busy, lack of social support, side effects, food requirements, active mental illness and lack of patient education (Amberbir *et al.,* 2008; Nischal, Khopkar & Saple, 2005). Adherence support should be made available to all patients, as anybody is capable of both high and low levels of adherence (Carter, 2005).

2.9 MEASUREMENT OF ADHERENCE

It is accepted that with adherence levels of less than 95%, treatment can fail and the virus may become resistant. Therefore, it is crucial to be able to accurately monitor adherence rates for ART and immediately address the problems encountered (Chalker *et al.,* 2009).

There is no gold standard for evaluating adherence to medication. It may therefore be necessary to combine several methods since no method of measuring adherence is 100% accurate (Chesney, 2006; Nachega *et al.,* 2006).

Early studies in Africa reported adherence levels as high as, or higher than those observed in developed countries. However, measures used to assess adherence may vary and many have not been validated in the context of rapid ART scale-up (Chi *et al.,* 2009). Adherence to ART is one of the most important predictors of the outcome of treatment, but researchers and clinicians have been hampered by the lack of a valid, quick, simple, and inexpensive instrument to accurately measure adherence (Giordano *et al.,* 2004).

Adherence can be measured directly or indirectly. These methods are discussed below.

2.9.1 Direct methods

2.9.1.1. Directly Administered Antiretroviral Therapy (DAART) / Directly Observed Therapy (DOT)

This method involves watching as the patient takes his/her medication to ensure that it is taken correctly and at the right time (Altice and Springer, 2010; Maru *et al.,* 2007). The finding of Altice *et al.* (2007) was that DAART is most effective among patients with predictors of nonadherence. Altice and Springer (2010) concluded that DAART resources should be reserved for patients with known problematic adherence. This method is highly labour intensive and not practical outside an institutional or residential setting, as well as for regimens that require more than once- or twice-daily dosing (Bartlett, 2002).

2.9.1.2. Therapeutic drug monitoring / plasma drug testing

Measurement of the concentration of a drug or its metabolites, or of a drug plus marker in blood or urine can be used as an indication of whether the medication has been taken. The process is only useful if the pharmacokinetic profile of the drug is well defined. However, this method cannot discern whether the patient is only taking the ARVs just prior to the blood sample is taken, while missing other doses (Bartlett, 2002; Berg & Arnsten, 2006).

2.9.2 Indirect methods

Indirect measures of adherence include pill counts, questionnaires, frequency of repeat prescriptions (prescription refill), measuring physiological markers, asking patients to keep diaries, a visual analogue scale (VAS), 2-day and 7-day adherence recall and electronic medication monitoring (Berg & Arnsten, 2006).

Of all these methods, VAS is said to be the method that correlates best with clinical markers and it demonstrates good validity, compared to unannounced pill counts, HIV viral load, and a 3-day recall adherence tool (Giordano *et al.,* 2004; Mapetla, 2007). Contrary to this, Kalichman and colleagues (2009) found that adherence measured with VAS was similar to the results obtained when adherence was measured with unannounced pill counts. Adopting the VAS may save the time of both researchers and participants because it could be easily self-administered. Similar to other self-report measures, the VAS also tends to over-estimate adherence (Engelbrecht, 2010; Muller *et al.,* 2010) This was also observed in a BPharm IV research project conducted by the researcher and three other students (Adeyinka *et al.,* 2008). Another disadvantage of the VAS is that patients with low educational level may not understand the concept, and then rate their adherence incorrectly (Engelbrecht, 2010). Other common adherence measures used in research studies are as follows:

2.9.2.1. Surrogate markers

The results of viral load and CD4 monitoring tests are used as surrogates for adherence (see Section 2.6.3). It is important to note that although low adherence is frequently associated with viral rebound, it may also be observed in individuals with suppressed viral load. The CD4 count is reported to be a less sensitive marker of adherence than viral load (Poppa *et al*., 2004).

2.9.2.2. Self-report

Patient self-report is whereby a clinician or pharmacist asks patients whether they have missed any doses of their ARVs in a number of days, and if so, how many. Self-report can

either take the form of a VAS or a recall, for example, a 3-day or 7-day recall (Muller *et al.,* 2010). This method has been used extensively because of the ease with which it may be included in routine clinical practice. Though it may be a good marker of adherence, it is not perfect. There is evidence that it may over-estimate adherence and the dynamics of provider-patient relationships may clearly impact on the willingness of individuals to disclose problems, particularly in face-to-face settings (Chalker *et al.,* 2009; Godin *et al*., 2003; Kalichman *et al*., 2007; Poppa *et al*., 2004; Wagner, 2002).

In order to improve precision, and to allay concerns of recall bias, most self-assessment adherence tools ask patients to recall the specific number of missed doses in a brief time period, typically the last two to seven days (Giordano *et al.,* 2004).

2.9.2.3. Medication event monitoring system (MEMS)

The Medication Event Monitoring System (MEMS) is an electronic device fitted to tablet bottle containers which records the removal of the cap as well as the time and duration of each bottle opening. The opening of the container implies the removal of tablets, though this is not necessarily the case. This method is frequently used to measure adherence in research settings, and has been demonstrated to predict virological response to ARVs. A disadvantage of MEMS is that it may not be compatible with individual adherence strategies, such as decanting tablets on a daily or weekly basis, and it cannot be used with blister packs (Liu *et al.,* 2001; Poppa *et al*., 2004). Patients can also mask non-adherent behaviours by false openings if they are aware of the monitoring process (Meyer & Summers, 2010).

2.9.2.4. Prescription refill monitoring

Monitoring of prescription repeats (refills) can serve as a method of measuring adherence. When patients collect their ARVs on the due dates, it is assumed that this action is related to adherence to medication (Horizons/Population Council, 2004). In cases where patients do not collect their repeat prescriptions regularly or on the expected dates, the patients are assumed not to be taking their treatment between 'refills' or are missing doses and this causes the medications to last longer than they should normally last. This method is presumptive because the fact that patients are collecting their repeat prescriptions does not guarantee ARV intake. Patients may not necessarily take the medication they collect (Horizons/Population Council, 2004).

2.9.2.5. Pill counts

Because patient self-report overestimates adherence, monitoring of medication adherence requires objective and valid methods. One of the few available objective methods is pill counting (Kalichman *et al.,* 2007). This is a method where patients are asked to return to the clinic with their medication, which is then counted by a health care provider (Bell *et al.,* 2007; Liu *et al.,* 2001). This method is used to compare patients' actual and expected consumption from the last day on which they obtained their medicines (Chalker *et al.,* 2009).

Pill counts are commonly used to measure adherence but several studies have emphasised their shortcomings in the over-estimation of adherence. The method is vulnerable to fabrication and may be seen by patients as an unwelcome attempt by health care providers to police their adherence. Pill counts can also be conducted in the office or pharmacy, but this may be biased by patients failing to return all of their medication (Chalker *et al.,* 2009). Obtaining false or over-estimated adherence by this method may be prevented by conducting unannounced in-home pill counts, although this system will be too intrusive and cumbersome for common clinical practice (Bangsberg *et al*., 2003).

2.9.2.6. "Mixed" pill count

The **"mixed" pill count** is a new tablet count concept which was suggested by a pharmacist who used to work at the ARV clinic in Tshwane District Hospital (Johnson, 2008). With the "mixed" pill count, the pharmacist deliberately dispenses extra tablets (more than a month's supply) to patients and records it in the patients' medication files in an encrypted format. The patients are not aware of the extra tablets dispensed to them, neither are they aware of how many extra tablets are dispensed and for which drug. When the patient returns after a month for a repeat prescription, the tablets remaining in the container are counted. Truly adherent patients might wonder why there are extra tablets left in the container because they took their ARVs as prescribed. Non-adherent patients will return with either more tablets than the extra ones dispensed, which means that not all doses were taken as prescribed for some or other reason, or with fewer or none of the extra tablets dispensed, indicating suspected pill dumping.

This study aims to test, and possibly validate the "mixed" pill count as a method to correctly assess adherence, and to explore reasons for non-adherence and pill manipulation where necessary.

2.10 SUMMARY

In this chapter, HIV and AIDS have been explained as well as the origin of HIV. The extent of the global and local HIV and AIDS epidemic was described and the rollout of ARVs in South Africa discussed. The various sites of action and side effects of ARVs have been explained and the South African ARV treatment guidelines outlined. Factors that affect adherence were discussed. Rates and clinical markers of adherence were covered as well as the reasons for non-adherence. The importance of adherence to ART and the need to have a reliable method to measure adherence were emphasised.

In the next chapter, the methodology of this study will be discussed in detail.

CHAPTER 3

METHOD

3.1 INTRODUCTION

This chapter describes the methodology used to investigate the ability of “mixed” pill counts to detect deliberate masking of non-adherence to ART. The first section gives background information about the site where the study was conducted. This background is followed by the study design and a detailed description of the sample selection. The data collection process, which includes the data collection instruments, data collection training and the pilot phase, is discussed. The analysis of the quantitative and qualitative data, and how reliability and validity of the data were maintained, are outlined. The chapter ends with a discussion of the ethical considerations for this study.

3.2 STUDY SITE

The study was conducted at Ntshembo ARV clinic in Mamelodi Hospital in Pretoria East, Gauteng Province. In the beginning of 2010, the hospital relocated to a new building on the same premises. The ARV clinic still operates from the old hospital building. The reconstruction of the hospital has enabled the ARV clinic and ARV pharmacy to move to a more spacious section of the old hospital. Previously the clinic was operating in a small section of the hospital with limited space for the pharmacy, which did not allow for proper stock control and dispensing of medication. Figures 3.1 and 3.2 show pictures of the new hospital and ARV clinic respectively.

Figure 3.1: New Mamelodi Hospital

Figure 3.2: The researcher in front of Ntshembo ARV clinic

Antiretroviral treatment roll-out at Ntshembo clinic commenced in July 2005. At the end of June 2010, over 6000 HIV-positive patients were enrolled at this clinic, of which 4539 were on ART. The majority of the patients on ART (4312) were adults over the age of 15 years. One thousand and ninety-five adults were on Regimen 1a, 350 were on Regimen 1b, and 20 were on Regimen 2 as stipulated in the previous national ARV treatment guidelines (refer to Section 2.5.1.1). Three hundred and thirty-five adults were on other regimens. Any regimen that was not 1a, 1b or 2 according to the previous guidelines was categorised as 'others' in this clinic, including the regimens in the new guidelines (see Sections 2.5.1.1 and 2.5.1.4).

According to clinic procedures, initiation of patients on ART is done mainly on Tuesdays and Thursdays, but if these days are not convenient for the patient, initiation can be done on any other day of the week that is convenient for the patient. According to the clinic statistics for the period January 2010 to June, 2010, an average of 125 patients are initiated on ARVs per month, which translates to about 31 initiations per week.

During their first six months on ART, patients attend the clinic on a monthly basis. Once they are stabilised on ART (which is usually after six months on treatment), they attend the clinic every second month. Pill counts are done every time patients visit the clinic for a repeat prescription and the adherence percentage is calculated based on the pill count results. At the clinic, there is no specific protocol followed for adherence counselling. If a patient's adherence percentage is less than 100%, he/she is asked why some doses were missed. Non-adherent patients are counselled by both the counsellor and the pharmacist. If necessary, especially if adherence is calculated to be less than 95% or if the patient is a defaulter, he/she is referred to the social worker for further counselling and appropriate intervention.

3.3 STUDY POPULATION

The target population for this study comprised of patients that had commenced ART, regardless of their duration on treatment, provided they were taking Regimen 1a or 1b. Patients receiving one- or two-months' supply of ARVs were enrolled. This approach ensured that both stabilised and new patients participated in the study. The inclusion and exclusion criteria used in the sample selection are described in Section 3.5.2.

3.4 STUDY DESIGN

The study followed a prospective and longitudinal design over a period of six months, i.e. from February, 2010 to the end of July, 2010. Enrolment of patients into the study took place over the first two months. The study design is illustrated in Figure 3.3.

Study participants were given a normal pill count on enrolment (baseline visit), and were given a normal supply of their ARV medication. On Return Visit 1, they received a normal pill count and extra dosage units of each ARV medication were dispensed to them without their knowledge. At Return Visit 2, patients received a “mixed” pill count. Exploratory interviews were conducted with all patients returning too few dosage units at Return Visit 2 (non-adherence maskers) and with the non-adherent patients, as identified by returning too many dosage units at Return Visit 2.

Results of routine viral load and CD4 count testing at baseline and during the study period were recorded from the patients’ files.

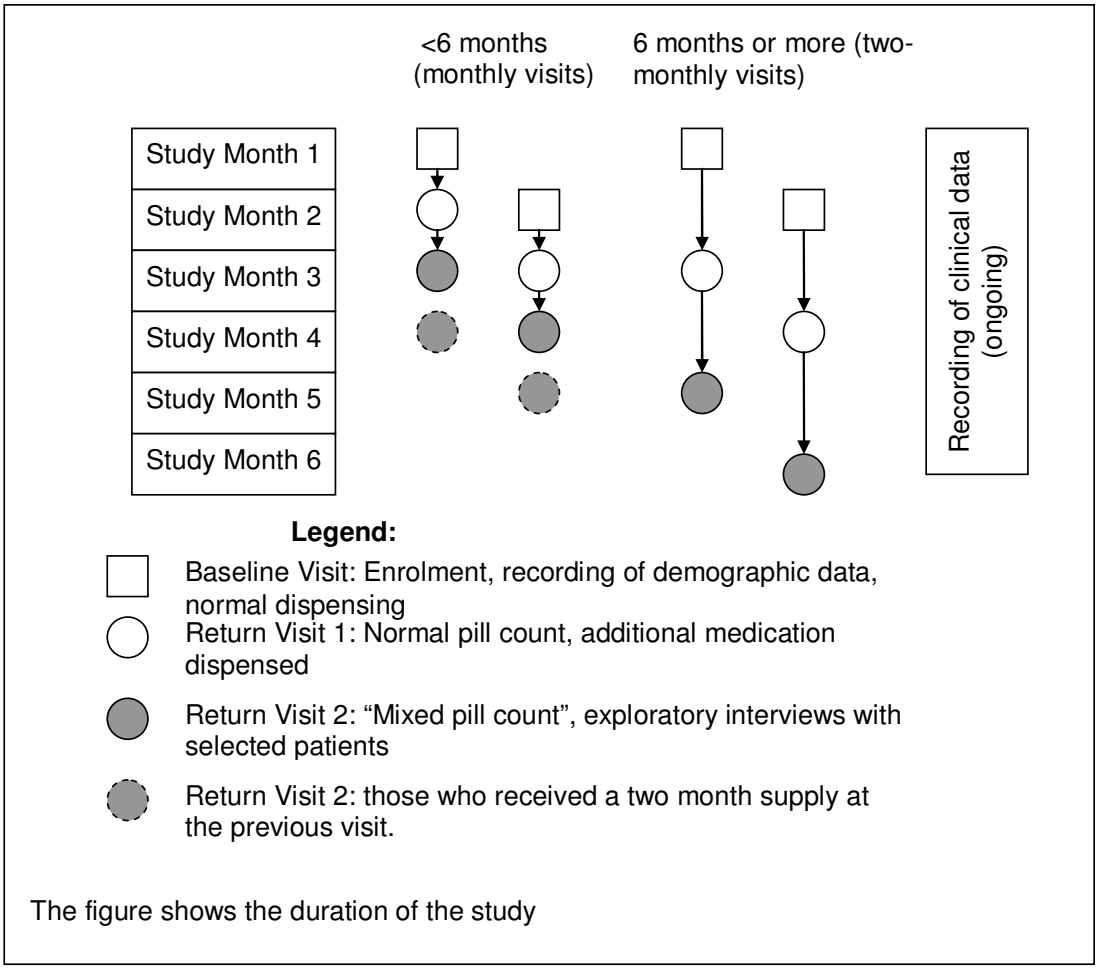


Figure 3.3: Study design

3.5 SAMPLE SELECTION AND ENROLMENT

3.5.1 Initial calculation of required sample size

Prior to the study, the required sample size was calculated with the assistance of a statistician. The sample size was determined separately for null hypotheses 1 and 3 as stated in Chapter 1, Section 1.6. Data from a 12-month longitudinal study on 100 patients[1] (Mokoena, 2009) were considered.

[1] Considering a total number of fifty-three pill counts done from months 6 onwards and close to the time of viral load testing, including only the first of repeated results for the same patient, we found that 27 of 33 "adherent" (≥95%) and 13 of 20 "non-adherent" (<95%) patients had viral loads ≤400 copies/ml plasma.

For null hypothesis 1:

Assumptions:

- Calculated adherence results >100% occur in approximately 1% of normal pill counts (Mokoena, 2009; n=974 pill counts)
- Calculated adherence results >100% occur in approximately 5% of "mixed" pill counts (odds ratio compared with normal pill counts: 5/95 : 1/99 = 5.2)
- The correlation coefficient of this outcome at the two Visits is 0.1

Required sample size (continuity-corrected chi-squared statistic or a Fisher's exact test, 5% significance level with 95% power) (Dupont & Plummer, 1998).

Total: 1027 patients at each visit

For null hypothesis 3:

Assumptions:

- In normal pill counts, 58% of results indicate 95%-100% adherence, 41% less than 95% adherence and 1% more than 100% adherence (Mokoena, 2009; n=974 pill counts)
- In "mixed" pill counts, 54% of results indicate 95%-100% adherence, 41% less than 95% adherence and 5% more than 100% adherence
- All "maskers" were rated as adherent according to normal pill counts
- 82% of "adherent" patients (normal pill count shows 95%-100% adherence) have suppressed viral loads (<400 copies/mL plasma) at the time of the pill count (Mokoena, 2009; n=33)
- 65% of "non-adherent" patients (normal pill count shows <95% adherence) have suppressed viral loads at the time of the pill count (Mokoena, 2009; n=20)
- Assuming that five in 100 "adherent" patients are in reality non-adherent, and that three of these have suppressed viral loads, the proportion for the truly adherent patients rises to 83%.

Required sample size (continuity-corrected chi-squared statistic or a Fisher's exact test, significance level of 0.05, with 95% power) (Dupont & Plummer, 1998):

85 "pill dumpers" and 910 "truly adherent patients" (and 690 non-adherent patients excluded from this analysis).

Total: 1685 patients at Visit 2

3.5.2 Inclusion and exclusion criteria

The following inclusion and exclusion criteria were used to identify whether a patient was eligible to participate in the study:

3.5.2.1. Inclusion criteria

- HIV-positive adults ≥18 years of age.
- Patients on Regimen 1a or Regimen 1b. Patients taking zidovudine in place of stavudine were also included because zidovudine and stavudine are in the same pharmacological class (refer to Chapter 2, Section 2.3.2.2).
- Patients who will be receiving their ARVs at the study site for the full duration of the study period.

3.5.2.2. Exclusion criteria

- Patients on TB treatment
- Pregnant patients
- Patients who will be down-referred to another ART site
- Patients who are not willing to provide informed consent

3.5.3 Actual sample size, selection and enrolment period

With the aim to achieve the required sample size, all treatment-experienced patients who attended the clinic were asked to participate in the study. The purpose of the study was explained to all the patients while they were sitting in the waiting area. Each patient was then approached individually to participate in the study when he/she went into the counselling room for counselling and pill-count. Patients were informed that adherence would be monitored with a pill count, but were semi-blinded, as they did not know that extra tablets would be added to their containers during the second study visit (i.e. first return visit). All

patients who fulfilled the inclusion criteria, agreed to participate and who provided consent, were enrolled in the study. Recruitment for and enrolment into the study was done by the researcher and data collector and continued for the first two months of the study period. At the end of this period, 370 patients were enrolled into the study.

The initial calculated and planned sample size of 1685 participants was not achieved for the following reasons:

- It is possible that not all patients enrolled at the clinic, were approached to participate in the study. There were three counsellors at a time on duty at the clinic, attending to patients. During the first month of enrolment, the researcher and data collector each paired with one of the counsellors in order to enrol patients into the study. After the counsellor had finished the counselling process for each patient, the patient was asked if he/she was willing to participate in the study. Consequently, patients seen by the third counsellor were not asked to participate in the study.
- In the second month of enrolment, some participants who received one month's supply of ARVs in the first month of the study already started coming back for Return Visit 1, so the researcher stopped enrolling and went to the pharmacy to ensure that extra tablets were correctly added to patients' medication containers. Therefore, in the second month of enrolment, the data collector had to do pill counts and adherence calculation for the returning participants and at the same time carry on enrolling new patients into the study. This means that in the second month of the study, only the data collector was available for enrolment of new patients into the study.
- During the two months of enrolment, quite a number of patients were on a tenofovir-containing regimen, an abacavir-containing regimen or Regimen 2. This group of patients was not eligible to participate in the study. Some participants were thus excluded at the early stages of the study because their regimens were switched to tenofovir-containing regimens. Later on in the study, some patients were switched to tenofovir since the new ARV guidelines were implemented, i.e. during the enrolment period, the rationale was that tenofovir was now part of Regimen 1, which made these patients eligible for the study. It is important to note though that when the new ARV guidelines were implemented on the 1st of April 2010, the number of patients that were enrolled into the study was still small, so it was decided that patients on tenofovir could then be included in the study since tenofovir was now regarded as a first line drug, but only two patients on tenofovir were enrolled due to the concern that if enrolment continued, the patients might not be seen during at Return Visit 2 which was the crucial part of the data collection.

- Some patients were concerned about confidentiality and did not give consent for participation, especially because they had never participated in a study at this clinic before.
- The plan was to complete data collection at the end of June, thus in the second month of enrolment (when it was three months to the end of the data collection period), only patients on a one-month supply of ARVs were enrolled so that they could visit the clinic only twice (for Return Visits 1 and 2) after enrolment into the study. Many of the stabilised patients on two-month supply of ARVs did not want to get a one-month supply for the purpose of the study. They insisted on getting a two-month supply, thus this group of patients were not enrolled into the study. If they were enrolled, they would not have been seen on the last return visit (Return Visit 2), which was the vital part of the study. However, the data collection period was later extended by a month (until July 2010) because some participants had not yet returned for their next visit and also because some laboratory results (CD4 count and viral load) were still pending.
- Due to time constraints, the data collection period could not be extended beyond July 2010 because delays had already been experienced prior to the commencement of the pilot study, which ultimately resulted in a delay in commencement of the actual study.

3.6 DATA COLLECTION

3.6.1 Data collectors

The researcher was responsible for the data collection for this study, with the assistance of one data collector. At the time of the study, the researcher was an academic pharmacist-intern at the University of Limpopo, Medunsa Campus. The data collector was recruited specifically for the purpose of the study. He was an adherence counsellor at Kalafong Hospital, and was selected as a data collector for this study because of his vast experience with HIV patients. He possessed useful skills to obtain information from patients, and this characteristic was essential for the study. In addition, he was fluent in the languages commonly spoken by the target population.

3.6.2 Data collection training

Training in conducting interviews took place prior to the pilot study, to standardise the data collection procedures. The researcher and the data collector were trained in data collection and interview techniques by one of the supervisors (Dr JC Meyer), who is experienced in questionnaire-based quantitative and qualitative research. During the training, the

researcher and the data collector conducted mock interviews with two surrogate respondents from the Department of Pharmacy, University of Limpopo, Medunsa Campus. The data collector was further trained during the pilot study at Tshwane District Hospital. The purpose was to familiarise himself with the questionnaires, refine his interviews skill and verify the ease of understanding of the questions by the respondents.

3.6.3 Pilot study

The "mixed" pill count, questionnaire, interview guides and logistics were pre-tested in a pilot study prior to the actual data collection. The objectives of the pilot study were to test the ability of the "mixed" pill count to detect non-adherence maskers, to identify logistical problems and to ensure that questions were clear to the respondents. The pilot phase of the study took place at Masibambane ARV clinic at Tshwane District Hospital over a period of three months, October 2009 to December 2009. The actual study site was not used for the pilot study because the patients who participated in the pilot study would already be aware that extra tablets were being added to their containers and might notify other patients participating in the actual study.

During this time, 78 patients who fulfilled the inclusion criteria were recruited on a daily basis for a period of one month. They received a normal pill count at their first return visit. Extra tablets were added to their tablet containers followed by a "mixed" pill count at their second return visit. Any patients returning too few or too many dosage units were interviewed to test the interview guides shown in Appendices D and E, respectively. Only 29 of the 78 participants (37.2%) completed the pilot study. The following were the reasons for patients to drop-out or to be excluded:

- Ten (12.8%) patients received a two- or three-month supply of their ARV medication because they were going away for the festive season and did not return to the clinic before the end of the study.
- Two (2.6%) patients' regimens were switched during the course of the study and these patients were excluded.
- Thirty-one (39.7%) patients did not visit the clinic on their expected date or on any other day during the study.
- Four (5.1%) patients did not return tablets to the clinic for counting.
- One (1.3%) was hospitalised and could not visit ARV clinic.

- One (1.3) patient took an overdose of his ARVs and got sick. This patient was re-initiated and also excluded from the study.

During the pilot study, difficulties that respondents had with questions in the questionnaire and interview guides were identified. Modifications were made to the data collection instruments before commencement of the actual study.

The results of the pilot study are presented and discussed in Chapter 4.

3.6.4 Data collection procedures and instruments

Once patients had consented to be included in the study, stickers were placed on their files, to indicate that they were part of the study. Patients were reminded at baseline to always come with their medication containers when they visit the clinic for a repeat prescription.

The data collection procedures and the data collection instruments used in this study are described in more detail in the following sections.

3.6.4.1. Demographic data

Demographic data were collected from patients on enrolment into the study, by both the researcher and the data collector using Appendix B1 or B2.

3.6.4.2. Clinical data

Using a questionnaire, clinical data were recorded from the patients' files. Questionnaires were available in English and Tswana (refer to Appendices B1 and B2). At enrolment into the study, the pre-ART (pre-initiation) clinical viral load and CD4 counts were recorded from the patients' files. At the end of the study, the latest (after six months or longer on ART) viral load and CD4 counts of the patients were recorded again from the file.

3.6.4.3. Pill count sheet and antiretroviral medication dispensed

At enrolment, the tablets returned by the patients were collected from them and the study patients all received a fresh supply of their ARVs. The ARVs were not topped-up as usual, in order to ensure that the number of tablets in the patients' possession was known by the researcher. The correct number of tablets consumed would then be used for adherence calculation at the two return visits.

A pill count sheet (refer to Appendix C) was used for the normal pill count as well as the "mixed" pill counts, to record the number of tablets that the patients returned to the clinic. Pill count results were calculated as a percentage of the correct consumption. For Return Visits

1 and 2, adherence data were collected by the data collector in the counselling room. The researcher was stationed at the pharmacy from Return Visit 1 so that she could add the extra tablets for the “mixed” pill count. She also identified study patients that had not been seen by the data collector for the pill count. Pill counts and calculation of adherence for these patients were then done at the pharmacy.

The researcher worked together with the pharmacist in the pharmacy, to ensure that the patients receiving a “mixed” pill count were dispensed extra tablets for each of the ARVs in the regimen, and also to ensure that the number of extra tablets dispensed was written on the patients’ pill count sheet (refer to Appendix C).

3.6.4.4. Patient interviews

The clinic has an in-house pill count sheet, which is kept in every patient’s file. The counsellors record on the pill count sheet what medications a patient is taking, how many tablets did the patient return to clinic as well as the number of tablets the patient is going home with each time the patient visits the clinic. The clinic’s pill count sheet does not allow for adherence calculations or percentages *per se*. The counsellors only do a mental calculation to estimate the patients’ adherence for the purpose of identifying those patients who are non-adherent. During the study period, the pill count sheet designed specifically for data collection in this study (Appendix C) was used and kept in patients’ files. The researcher verified the calculated adherence results on the study pill count sheets. Both the researcher and the data collector identified the patients to be interviewed, based on the calculated adherence.

After calculating adherence, the patients whose adherence was less than or greater than 100% were interviewed with the appropriate interview guide.

Interview guides for the patient interviews were available in English and the most common language spoken in the area, namely Tswana. This allowed respondents to respond in their language of preference.

Most of the interviews were conducted by the data collector in the counselling room. The researcher conducted a number of interviews for non-adherent and over-compliant patients at the pharmacy because some of the study patients went for counselling in a different counselling room than where the data collector was sitting, and therefore missed the data collector.

The initial plan was to record all interviews conducted during the study, although this was not possible. In the first place, there was only one voice recorder available, which was kept and

used by the data collector, who conducted most of the interviews in one of the counselling rooms. The interviews conducted by the researcher were done in English and were not recorded as she was in the pharmacy and only interviewed those patients who were missed by the data collector. In the second place, very few patients consented for their interview to be recorded. Overall, 80 interviews were conducted, of which most were conducted in Tswana by the data collector. Interviews were recorded for only three (3.8%) patients, who gave consent.

i) *Truthfully non-adherent patients*

An interview guide was used to interview the non-adherent but truthful patients soon after the pill count (refer to Appendices E1 and E2). Truthfully non-adherent patients were asked to honestly inform the data collector if they found it difficult to return extra tablets. They were also asked how they felt about returning extra tablets, as well as the reasons for not taking all their tablets.

ii) Non-adherence maskers

An interview guide was used to interview all patients soon after an "overcompliant" pill count (result >100%) had been identified (refer to Appendices D1 and D2). All cases were explored, for example those simply not returning any extra tablets and those masking their non-adherence by not returning some tablets, as well as those suspected of "pill dumping".

3.7 DATA CAPTURE AND ANALYSIS

3.7.1 Quantitative data

The researcher entered all data from the questionnaires into a Microsoft Excel™ spreadsheet. All entered data were cross-checked and proof-read by the data collector. The following data were recorded:

- Demographic data (refer to Appendices B1 and B2)
- Pill count results at Return Visits 1 and 2 (refer to Appendix C)
- Clinical outcomes (CD4 counts and viral loads) at ART initiation and at the end of the study (after six months or longer on ART) (see Appendices B1 and B2)

Demographic data were summarised and expressed in terms of mean values, percentages and standard deviations to give an overview of the study population.

Pill count results were used to split patients into categories as described under hypotheses 1 to 3 (refer to Section 1.6).

Viral load results were dichotomised to indicate viral suppression (viral load <400 copies/mL plasma) or otherwise.

In order to support any differences detected between the groups of patients, the clinical markers (viral load, CD4 counts and changes in CD4 counts) were summarised in terms of averages and medians for the groups as defined in null hypothesis 3 (see Section 1.6). In addition, the patients who presented with >100% adherence were compared with those with <95% and 95%-100% adherence in terms of CD4 count and viral load.

Quantitative data analysis were exported to Statistical Analysis Software (SAS) to perform statistical tests. The Fisher's exact test was used to establish if there was any significant difference in adherence between the male and female patients, and to determine if there was an association between clinical markers and adherence. A logistic regression was used to determine which demographic variable (s) correlated with adherence.

3.7.2 Qualitative data

As explained in Section 3.6.4.4, qualitative data were collected from 80 patients during the interviews at Return Visit 2. Responses were written on the English or Tswana interview guides, depending on the language in which the interview was conducted. Only three (3.8%) patients consented that their responses could be voice-recorded. All interviews conducted in Tswana were translated into English and written on the corresponding English interview guide (Appendices D1 and D2 as well as Appendices E1 and E2) where applicable. Translations were checked and verified by the data collector for accuracy and correctness. After all the interviews were available in English, they were typed-up and saved as Microsoft Word™ documents.

Transcripts and notes taken were then imported from Microsoft Word™ into NVivo9™, a software programme used for qualitative data analysis. Data were coded into categories referred to as nodes in NVivo9™, to bring meaning to the text (Richards, 2005) that is, the patients' responses to the questions were put into free nodes and similar responses were grouped together in one node. Patterns and connections within and between categories were identified. Categories with sub-categories, referred to as tree nodes in NVivo9™, were developed from the data. This was followed by a process whereby the main, recurring perceptions and ideas were developed into themes.

3.8 RELIABILITY AND VALIDITY OF DATA

The following measures were taken to ensure the reliability and the validity of the data:

- A pilot study was conducted prior to the main study to increase the reliability and validity of the data collection instruments. The pilot study was conducted at a different clinic from the study site, to prevent patients who participated in the pilot study from informing other patients that extra tablets would be added to their containers.
- The questionnaires were available in English and Tswana. They were initially constructed in English, and then translated into Tswana. Translation of the questionnaires ensured that the same information was conveyed to all participants. The data collector tried as far as possible to create a comfortable and trusting environment in which patients could honestly discuss non-adherence behaviour.
- The data collector and researcher calculated adherence with a calculator to determine which participants were to be interviewed. The adherence was re-calculated by the researcher during data capturing with Microsoft Excel™ formulas to verify that the adherence calculations were correct.
- The three interviews which were audio-recorded in Tswana were translated to English in one step, by the data collector, so that all interviews were available in one language, English.
- The researcher and data collector were trained in interview techniques in order to ensure the reliability of data collection.
- The researcher personally dispensed the additional tablets to the patients during Return Visit 1 to make sure that all the participants got extra tablets.
- Completed questionnaires were cross-checked by the researcher on a daily basis for accuracy and completeness so as to improve the validity and reliability of the data.
- Categories and themes developed from the qualitative data were discussed with and checked by the study supervisor, to increase the credibility (true value) of the qualitative findings.
- The use of NVivo9™ for the analysis of the qualitative data, provided an audit trail, which serves as evidence that trustworthy interpretation of the qualitative data were made (Richards, 2005).

3.9 BIAS

Areas where bias was likely to be introduced were addressed as follows:

- The study was conducted at a site where pill counts are being done as part of normal clinic procedures. Conducting the study at a site where pill counts are not done on a monthly basis is already an intervention, and patients might be afraid to bring back their remaining tablets for counting, which means that a variable is already introduced. Therefore, selection of a study site where normal pill counts are part of practice, reduced the possibility of patients changing their medication-taking behaviour or dumping their tablets because they knew that their tablets were being counted.
- Only interviewing English-speaking participants, would have resulted in selecting predominantly better-educated respondents. To minimise this, the data collector was fluent in English and the local language predominantly spoken in the area (i.e Tswana) so that the interview would be conducted in the language the respondents felt comfortable with. Consent forms and questionnaires were also available in English and Tswana.
- Selection bias was reduced by including all patients who met the inclusion criteria and who consented to participate in the study.
- An abbreviated title of the research was used on the consent form, so as not to influence patients' medication-taking behaviour.

3.10 ETHICAL CONSIDERATIONS

- Ethical approval to conduct the study was obtained from the University of Limpopo, Medunsa Research and Ethics Committee (MREC) before commencement of the study (see Appendices F and G).
- Approval to conduct the pilot study at Tshwane District Hospital was granted by the Chief Executive Officer (CEO) of the hospital and by the Research and Ethics Committee of the University of Pretoria (see Appendix H).
- Permission to conduct the study was obtained from the CEO of Mamelodi Hospital as well as the ARV Clinic Manager (see Appendix F).
- A consent form available in the respondent's preferred language was signed by all participants prior to enrolment in the study (see Appendices A1 and A2).

- The researcher and the data collector assured participants of the confidentiality of the data and that their responses would remain anonymous.
- Participation in the study was voluntary and participants had the right to withdraw from the study at any time without providing reasons.
- The researcher and the data collector showed integrity and were guided by ethical principles that include respecting the rights of the participants, abiding by the research design, and reporting results as they are found.

3.11 SUMMARY

In this chapter, the study site, population and design have been described. The sample selection and enrolment process, including the study period were outlined. The data collection procedures and instruments were explained in detail and the method of data capture and analysis was described. Steps taken to ensure data reliability and validity were bulleted as well as the steps taken to minimise bias. The chapter ended with an outline of the research ethics that were adhered to. The results of the pilot study and the main study are presented in Chapter 4 and Chapter 5 respectively.

CHAPTER 4

PILOT STUDY RESULTS AND DISCUSSION

4.1 INTRODUCTION

The findings of the pilot study are presented in this chapter. The chapter first outlines the demographics of the study participants, and then continues to show the ARV regimens that the patients were taking. The proportions of adherent, non-adherent and over-compliant patients are compared. This is followed by an illustration of the adherence pattern for individual ARVs. The reasons for non-adherence and over-compliance are tabulated. The reasons for tablet manipulation are presented for patients who admitted to manipulating their ARVs.

4.2 STUDY POPULATION

At enrolment, 78 eligible patients were recruited into the study. Fifty-eight (73.4%) were females and 20 (25.6%) were males. Twenty-nine (37.2%) of the 78 patients completed the study. The main reasons for the high losses were that patients missed appointments (39.7%) and patients' second return visit fell outside the study timeframe (12.8%), mainly due to the issue of 2-3 months' supply of ARVs to cover the festive season. Other reasons for loss to the study included regimen changes, failure to bring remaining ARVs to the clinic, hospitalisation and taking an overdose of ARVs.

4.2.1 Patient demographics

Table 4.1 shows the age and gender distribution of the patients who completed the study. Forty-five percent of the patients were between the ages of 31 and 40 years. The average age was 38 years, with the females younger (average of 36 years) than the males (average of 43 years).

Table 4.1: Patient population by age group and gender (N=29)

Age group (years)	Male		Female		Total	
	Number	%	Number	%	Number	%
18-30	0	0	7	24.1	7	24.1
31-40	2	6.9	11	37.9	13	44.8
41-50	5	17.2	0	0	5	17.2
>50	1	3.5	3	10.3	4	13.8
Total	**8**	**27.6**	**21**	**72.4**	**29**	**100**
Range	**31-53**		**24-59**		**24-59**	
Average (standard deviation)	**43.1 (±6.94)**		**36.1 (±9.0)**		**38 (±8.95)**	

The majority of participants at enrolment (73.4%) and completion (72.4%) were female. Gender proportions were similar to those in other adherence studies conducted in South Africa (Mapetla, 2007; Meyer, 2008; Peltzer *et al.,* 2010). Infection with HIV amongst the adult population in South Africa, is more prevalent in females than males. According to the UNAIDS (2010) global report 3.3 million (62.3%) of the 5.3 million HIV-positive adults (aged 15 years and above) in 2009 were females.

Additional demographic characteristics of the study participants are shown in Table 4.2. The majority (96.6%) of the participants were black and spoke an African language. In terms of education, only two patients (6.9%) had completed tertiary education, while 37.9% reported to either have had no formal education or had not completed primary education. Just more than half (55.2%) of the patients were employed and 58.6% were single.

Table 4.2: Additional demographic characteristics of study participants (n=29)

Characteristics		Number (n=29)	%
Race	Black	28	96.6
	White	1	3.4
Language	Afrikaans	1	3.4
	Zulu	7	21.1
	Tswana	2	6.9
	Sotho	9	31.0
	Other*	10	34.5
Level of education	None/primary not completed	11	37.9
	Primary completed	5	17.2
	Secondary completed	11	37.9
	Tertiary/vocational	2	6.9
Employment status	Employed	16	55.2
	Unemployed	13	44.8
Marital status	Single	17	58.6
	Married	9	31.0
	Widowed	1	3.5

*Ndebele, Pedi, Shona or Tsonga

4.3 ARV REGIMENS

The majority of the patients were on the first line ARV regimen with 41% of them on Regimen 1a (stavudine, lamivudine and efavirenz) and 53% on Regimen 1b (stavudine, lamivudine and nevirapine). Figure 4.1 shows the different regimens the study participants were taking during the study period.

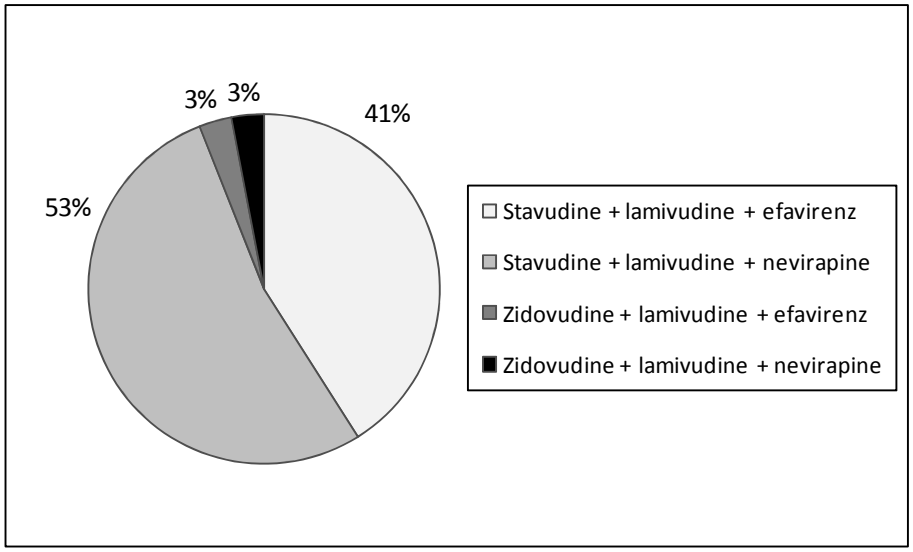


Figure 4.1: ARV regimens taken by study participants (n=29)

According to the inclusion criteria, patients were required to be on Regimen 1a or 1b to participate in the study. Patients whose stavudine was substituded by zidovudine were also included in the study, because both zidovudine and stavudine belong to the same pharmacological class of ARVs (nucleoside reverse transcriptase inhibitors).

4.4 OVERALL AVERAGE ADHERENCE FOR EACH PATIENT'S REGIMEN

Patients were categorised as non-adherent (adherence <100%), adherent (100%) or over-compliant (adherence >100%), based on the overall average adherence calculated for each patient's regimen. Four patients (13.8%) were over-compliant with the normal pill count, while eight patients (27.5%) were over-compliant with the "mixed" pill count. Two patients (6.9%) were over-compliant in both cases (Table 4.3).

Table 4.3: Number of patients within each category of adherence based on the calculated overall average adherence for each patient's regimen (n=29)

		Mixed Pill Count (Return Visit 2)			
	Adherence Category	**<100% Truthful non-adherent**	**100% Adherent**	**>100% Over-compliant**	**Total (%)**
Normal Pill Count (Return Visit 1)	**<100% Truthful non-adherent**	8	3	6	**17 (58.6%)**
	100% Adherent	3	5	0	**8 (27.6%)**
	>100% Over-compliant	2	0	2	**4 (13.8%)**
	Total (%)	**13 (44.8%)**	**8 (27.6%)**	**8 (27.6%)**	**29 (100%)**

In the pilot study 14% of participants were over-compliant (>100%) with the normal pill count at Return Visit 1, and this percentage doubled when the "mixed" pill count was used to measure adherence at Return Visit 2. This finding indicated that the "mixed" pill count method may have been able to detect the over-compliant patients who were not identified during the normal pill count.

With the "mixed" pill count, only eight of the patients (28%) were 100% adherent with all three of the ARVs that they were taking. The majority of the patients (78%) were either non-adherent or over-compliant in one or more of the ARVs in their regimen.

This finding contrasts an adherence study conducted in South Africa by Peltzer and colleagues (2010), in which 82% of the participants (n=519) were adherent (>95%) based on the self-reported recall method. A similar study in Ethiopia (n=400) found that 96% of the patients achieved perfect adherence (Amberbir *et al.,* 2008). It must be noted though that in both these studies, perfect adherence was defined as adherence of 95% or higher, whilst in our study, perfect adherence was considered as an adherence rate of 100%. It is not surprising that the "mixed" pill count resulted in lower adherence in light of the criticism that self-reported adherence is known to over-estimate adherence (Berg & Arnsten, 2006; Chesney, 2006; Liu *et al*., 2001), as illustrated by studies conducted in similar settings in South Africa (Engelbrecht, 2010; Meyer, 2008).

4.5 ADHERENCE FOR INDIVIDUAL ANTIRETROVIRALS

The results showed that for the majority of patients, "mixed" pill count results illustrated a different adherence pattern for each of the ARVs within a regimen. It was noted that it was

possible for a patient to appear truthfully non-adherent on average (considering the overall adherence of the three ARVs in the regimen) despite being over-compliant with one of the ARVs in the regimen. For example, adherence for the individual ARVs for one of the patients on Regimen 1b was 103.0% for stavudine, 103.6% for lamivudine and 80.4% for nevirapine. The overall average adherence for the regimen was 95.7%. This patient was over-compliant with two ARVs and non-adherent with one, but appeared truthfully non-adherent on average.

Only eight patients (27.6%) were 100% adherent with all three ARVs in their regimen. Fourteen patients (48.3%) were identified as being truthfully non-adherent in one or more of the ARVs in their regimen. Eleven patients (37.9%), of whom six (54.5%) were female, were over-compliant with one or more of the ARVs in their regimen, as opposed to eight (27.6%), of whom five (62.5%) were female, being identified as over-compliant on average.

Most of the adherence maskers were female (62.5% were over-compliant on average and 67.0% were over-compliant in at least one ARV in the regimen). Although there were more females compared to males in the over-compliant group, this gender distribution was similar to that at enrolment. Generally, considering the small sample size, the results of the pilot study did not show any association between gender and adherence. Similarly, the study by Rougemont *et al.* (2009) conducted in Cameroon, reported no association between gender and adherence to ARVs.

A correlation between gender and adherence has previously been identified in the South African population. In one of the studies, female patients were found to have better levels of adherence than their male counter-parts (Bhat *et al.,* 2010), while the opposite was reported by two other studies (Peltzer *et al*., 2010; Williams *et al.,*2006).

4.6 REASONS FOR NON-ADHERENCE AND OVER-COMPLIANCE

Twelve of the truthfully non-adherent patients and nine of the over-compliant patients agreed to be interviewed. They provided reasons for returning too many tablets (non-adherence) or for returning too few tablets (over-compliance), as shown in Table 4.4.

Table 4.4: Reasons for non-adherence (<100%) and over-compliance (>100%)

Truthful non-adherent patients (n=12)	Reasons for returning too many tablets (non-adherence)	Over-compliant patients (n=9)	Reasons for returning too few tablets (over-compliance)
	• Forgot • Away for a night • Family matters • Non-disclosure • No food at that time • Had tablets from previous months • Felt dizzy at work due to efavirenz		• Threw them away • Taken an overdose • Non-disclosure / stigma • Could have been stolen • Might have been spilled • Spilled in water • Might be in the tablet container at work • Factory fault • Difficulty with timing • Tablets make you feel sick • Do not know what happened to the tablets

Reasons for non-adherence given by study participants included forgetting, feeling dizzy and non-disclosure. Feeling dizzy was mentioned by patients taking efavirenz, which is a known side effect of the drug (Arendt *et al.*, 2007). The above reasons have also been reported to be barriers to adherence in previous studies conducted in Africa (Amberbir *et al.,* 2008; Olisah, Baiyewu & Sheikh, 2010) as well as in South Africa (Meyer, 2008; Mokoena, 2009).

According to Chalker and colleagues (2010), the normal pill count may overestimate patients' adherence due to the fact that patients fail to bring all of their tablets to the clinic for counting. This action was also observed in the pilot study as some over-compliant patients said they had some tablets in a separate tablet container at work. However, throwing tablets away to manipulate the number remaining cannot be raised with the patient if extra tablets are not dispensed to the patients, as was done in this study.

This pilot study is, as far as can be determined, the first to prove that some patients intentionally throw tablets away in order to appear adherent or to mask their non-adherence. Since some 'over-compliant' patients admitted to throwing tablets away or flushing them down the toilet, this pilot study suggests that patient manipulation of the remaining number of tablets may be another key reason for adherence overestimation based on the normal pill count. It is possible that dispensing extra tablets could be seen as a time-consuming task for the dispenser. However, it could help improve patient care, as adherence-maskers would more likely be identified, which would allow for more appropriate and timely intervention to improve adherence behaviour for this group of patients. The occasional implementation of the "mixed" pill count intermingled with normal pill counts may help to safeguard against patient manipulation of the number of tablets returned.

4.6.1 Reasons for 'pill dumping'

The three patients who admitted to throwing away some of their ARVs (pill dumpers), were asked why they did this (see Table 4.5). Experiencing side effects, which in this case was a change in body shape, was given as a reason. This finding concurs with the published literature from South Africa (Malangu, 2008; Meyer, 2008) and elsewhere (Protopopescu *et al.,* 2009), namely that adherence to ART is negatively affected by the side effects of the drugs. Another reason provided by two patients was that the ARVs were not necessary anymore, as the patients felt they had recovered. It was disappointing that despite health workers' efforts to prepare patients for ART, some still think that they do not need to take their ARVs if they are feeling better. This indicates that patient counselling and education need to be reinforced. Emphasis should be placed on the fact that ART is for life. Once ART has been initiated, it should not be interrupted, even if the patient feels better, as this may lead to drug resistance and deterioration to a later stage of HIV and AIDS.

Another notable reason for 'pill dumping' according to a 29-year old female in the pilot study was to prevent discontinuation of the government's HIV and AIDS social grant. This response suggested that patients receiving a social grant who are non-adherent, fear that if they stop collecting ARVs from the clinic, the monthly grant might be stopped. Subsequently, they mask their non-adherence by dumping the ARVs and coming regularly for a repeat prescription. Fear of grant discontinuation was also observed in a study conducted by Hardy and Richter (2006) in four provinces in South Africa, in which all their study participants feared that their disability grants would be withdrawn if they got better. Participants also expressed that they might not be able to find employment even if their health improved and they were declared fit to work. On the contrary, participants also stated that if they had to choose between their ARVs and grants, they would choose their ARVs, even if it meant that their grants would be stopped if they got better. Several participants were not happy that the government only provides financial support to seriously ill people and not to those who are not yet ill. Although receiving a social grant may strengthen adherence as the money could be used for transport to collect medication at the clinic (Treatment Action Campaign, 2008), Engelbrecht (2010) observed that only one fifth of the patients receiving a social grant (n=59) completed the study with e-MuM data, clinical data and attendance at some or all clinic visits, as compared to half of the patients not receiving a social grant (n=151). This observation indicates that being on a social grant does not guarantee that patients will keep clinic appointments or adhere to their medication.

According to the Department of Social Development (Samson *et al.,* 2004), one of the criteria for qualifying for a disability grant is that the grant applicants (patients) must have

their disability confirmed by a medical report, and that the degree of their disability must render him/her incapable of entering the labour market and they must not have refused employment that is within his/her capabilities. The Minister of Social Development mentioned in her speech to the National Assembly in April, 2010, that over 5.2 million South Africans are unemployed (Molewa, 2010), and many of those who are employed are only earning a low income. Unemployed people rely on the government to support them financially, and this may be the sole source of income for some families. This issue could be a possible explanation why some ART patients decided to mask non-adherence and remain ill, so that their grants do not get discontinued.

Non-disclosure was identified as a reason for non-adherence as well as over-compliance (dumping tablets). Disclosure plays a very important role in adherence, as better adherence is associated with disclosure of HIV status (Charurat *et al.,* 2010; Meyer, 2008). Therefore disclosure needs to be addressed before initiating patients on ARVs.

Three of the nine over-compliant patients admitted to manipulating their tablets. Five different reasons for manipulation were given by the three over-compliant patients. These reasons are summarised and illustrated with quotations in Table 4.5.

Table 4.5: Reasons for manipulating tablets

	Reasons for tablet manipulation
Over-compliant patients (n=3)	**Changed body shape** *"These medications have changed my body. Look at me, I look like a man, my buttocks are gone, my beautiful shape is gone. I don't know what to do, should I continue to take them or just stop…"* (Female, 29 years)
	Possibility of social grant being discontinued *"…should I continue to take them or just stop, again if I stop collecting them my grant is going to be stopped also. I'm very confused."* (Female, 29 years)
	Taking extra ARVs when feeling sick; throw away when feeling fine *"But what I remember is that I used to take some extra pills when I am sick thinking that I will recover soon. So when I was ok, I threw the remaining pills away this morning because I was coming to collect my monthly supply today."* (Male, 45 years)
	Do not need the ARVs any more *"Yes, I did throw them away. Actually I think I'm fine now, I don't need any treatment at the moment."* (Female, 29 years)
	Know the tablets will be counted *"I had a lot of tablets remaining, but I flushed some of them down the toilet because you wanted to count them. If I bring back too many remaining tablets, you will say that I am not taking them."* (Female, 32 years)

4.7 SUMMARY

The demographics, ARV regimens and adherence levels of the study participants have been presented, as well as the reasons for non-adherence and over-compliance.

The results of the main study will now be presented in the next chapter.

CHAPTER 5

MAIN STUDY RESULTS AND DISCUSSION

5.1 INTRODUCTION

The results of the main study, which was conducted at Ntshembo Clinic in Mamelodi Hospital, are presented in this chapter. A total of 370 patients were enrolled at baseline, of whom 344 (93.0%) completed the study. Adherence levels of the patients are compared with regard to their socio-demographic and socio-economic variables, as well as based on the changes in CD4 and viral load counts. Feelings of patients with regard to returning left-over ARVs to the clinic are discussed. This discussion is followed by explanations for discrepancies in pill counts, as given by the patients. The last part of this chapter covers the various difficulties patients experienced, which hindered them from taking their ARVs properly on a daily basis. The chapter ends with a section on the testing of the study hypotheses.

The results are presented in the following headings:

- Study population
- Sociodemographic characteristics
- ARV regimens
- Adherence rates
- Other sociodemographic variables and adherence
- Clinical markers
- Discrepancies in pill counts
- Barriers to ART adherence

In cases where statistical tests were performed, a significance level of $P<0.05$ was used.

5.2 STUDY POPULATION

Three hundred and seventy patients (148 males and 222 females) were enrolled into the study, of whom 344 (93.0%) completed the study. The main reasons for the 7% (26 patients) drop-out included the following:

- Eleven patients (3.0%) switched to a regimen that was not in the inclusion criteria (one patient switched to an abacavir-containing regimen, two patients switched to Regimen 2 and eight patients switched to a tenofovir-containing regimen).
- Eight patients (2.2%) defaulted during the course of the study.
- Seven patients (1.9%) were transferred from the study site to another ARV clinic.

The drop-out rate amongst female patients (7.7%) was slightly higher compared to the male patients (6.1%). Table 5.1 shows the drop-out rate per gender, as well as the reasons for drop-out.

Table 5.1: Reasons for drop-out from the study

Reason	Male (n=148)		Female (n=222)		Total (N=370)	
	Number	%	Number	%	Number	%
Regimen switched	2	1.4	9	4.1	11	3.0
Defaulted	5	3.4	3	1.4	8	2.2
Transfer-out	2	1.4	5	2.3	7	1.9
Total	9	6.1	17	7.7	26	7.0

5.3 SOCIODEMOGRAPHIC CHARACTERISTICS

5.3.1 Age and gender

Out of a total of 344 patients, 139 (40.4%) were males and 205 (59.6%) were females, as illustrated in Figure 5.1.

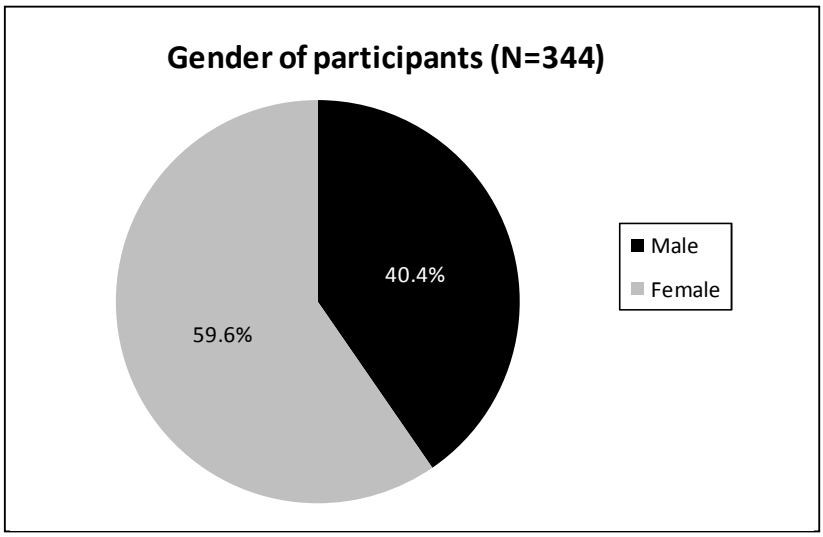


Figure 5.1: Gender distribution of study population

Most of the participants (42.2%) were between the ages of 31 and 40 years. Table 5.2 shows the age and gender characteristics of the study participants at baseline.

Table 5.2: Age and gender characteristics of study population at baseline

Age group (years)	Male (n=139)		Female (n=205)		Total (N=344)	
	Number	%	Number	%	Number	%
18-30	12	8.6	39	19.0	51	14.8
31-40	55	39.6	90	43.9	145	42.2
41-50	49	35.3	48	23.4	97	28.2
>50	23	16.5	28	13.7	51	14.8
Total	139	100	205	100	344	100
Range	24-66		20-68		20-68	
Median	41		37		38	
Mean ± SD	41.7 ± 8.75		38.7 ± 9.27		40.1 ± 9.11	

SD: Standard deviation

Figure 5.2 illustrates the gender distribution as a percentage of the total study population. On average, the male patients were slightly older than the females (mean age 41.7 versus 38.7 years), with very few male patients (3.5%; N=344) in the youngest age group (18-30 years).

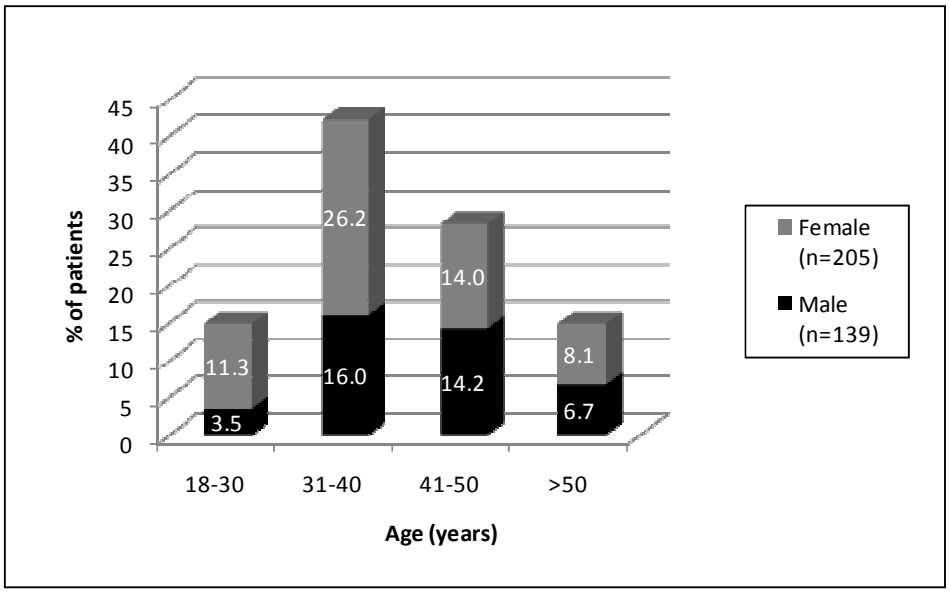


Figure 5.2: Distribution of study population according to age and gender (N=344)

The gender distribution in the actual study (40.4% males and 59.6% females) was slightly different from that in the pilot study (27.6% males and 72.4% females), but also with females predominating. A predominance of females has also been observed in other studies conducted in South Africa, over the past few years. In 2007, Mapetla conducted a study in selected ART centres in South Africa and found that there were more females (71%; n=194) than males. A similar trend was observed by Engelbrecht (2010) who conducted an adherence study at Tshepang Clinic, Dr George Mukhari Hospital in Ga-Rankuwa, in which the study population at baseline comprised of 76% females. Overall in South Africa, more females compared to males are HIV-positive. The UNAIDS (2010) global report informed that in 2009, 3.3 million (62.3%) of the 5.3 million HIV-positive adults (15 years and above) in 2009 were females. Gender data from this study also suggest that relatively more female patients than their male counterparts seek treatment for HIV.

The largest group of participants (43.9%) clustered in the age group 31-40 years (15.9% male and 26.1% female). As in the pilot study, there were more female than male patients in this age group. In the pilot study, there were no males in the 18-30 age group years, compared to the main study, where 3.5% of the males and 11.3% of the females were in this young age group. According to Statistics South Africa (2010), the prevalence of HIV is 17% among adults aged 15 to 49 years, which is higher than the overall national prevalence of 10.5%. It is evident that HIV is more prevalent in the core age group of 15 to 49 years. The age distribution of the study participants reflects the same trend.

5.3.2 Additional demographic information

Other demographic characteristics of the study population are outlined in Table 5.3.

Table 5.3: Additional demographic characteristics of study participants

Characteristics		Male (n=139)		Female (n=205)		Total (N=344)	
		Number	%[1]	Number	%[1]	Number	%[1]
Race	Black	135	97.1	202	98.5	337	98.0
	Coloured	4	2.9	3	1.5	7	2.0
Language	Afrikaans	5	3.6	5	2.4	10	2.9
	Zulu	25	18.0	32	15.6	57	16.6
	Tswana	10	7.2	17	8.3	27	7.9
	Sotho	33	23.7	57	27.8	90	26.2
	Other*	66	47.5	94	45.9	160	46.5
Level of education	None/primary not completed	13	9.4	22	10.7	35	10.2
	Primary completed	69	49.6	102	49.8	171	49.7
	Secondary completed	49	35.3	72	35.1	121	35.2
	Tertiary/ vocational	8	5.8	9	4.4	17	5.0
Employment status	Employed	77	55.4	82	40	159	46.2
	Unemployed	62	44.6	123	60	185	53.8
Marital status	Single	83	59.7	135	65.9	218	63.4
	Married	38	27.3	47	22.9	85	24.7
	Widowed	8	5.8	16	7.8	24	7.0
	Divorced	10	7.2	7	3.4	17	5.0

***** Ndebele, Pedi, Shona or Tsonga
[1] % of total in the category

5.3.2.1. Race and language

The majority of the participants (337; 98%) were black, while the remaining seven patients were coloured. This finding reflects the population around the study site. Five of the seven coloured participants mentioned that they were not staying in Mamelodi, but in Eersterus, a neighbouring suburb.

The majority of participants (97.1%) spoke an African language. The languages most commonly spoken were Sotho (26.2% of patients) and Zulu (16.6% of patients). The least spoken language was Afrikaans (2.9%).

5.3.2.2. Level of education

According to Table 5.3 and Figure 5.3, it is evident that half of the participants (49.7%) had only completed primary education. The proportion of males and females who completed primary education was the same (50%). This was also the case for the proportion of patients who attained secondary education (35.3% for males and 35.1% for females). Slightly more females (10.7%) than males (9.4%) had no education or did not complete primary education, while more males (5.8%) than females (4.4%) completed tertiary education. The results indicated that slightly more males were educated than the females.

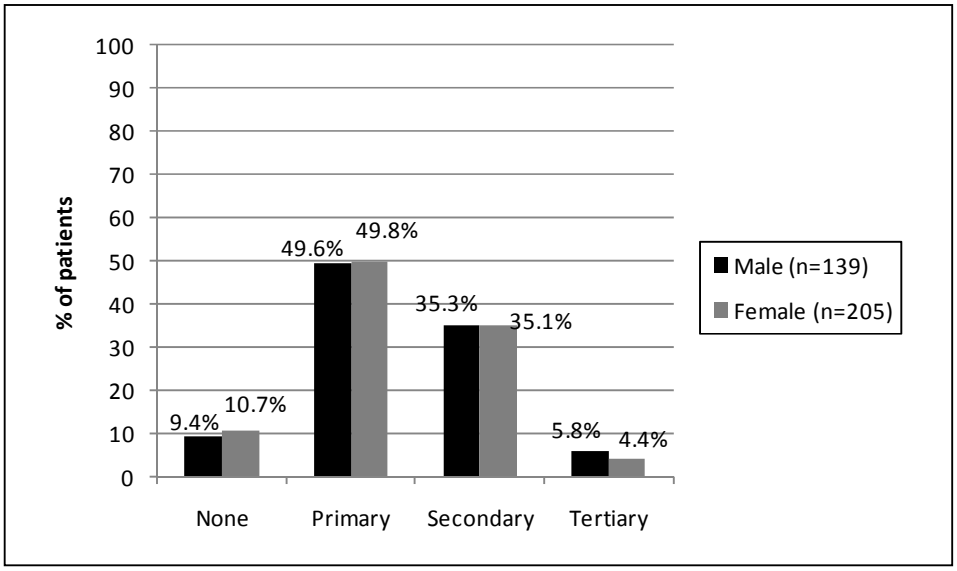


Figure 5.3: Distribution of study population by level of education and gender (N=344)

Overall, 10.2% of the study participants had no formal education or did not complete primary education (Table 5.3). This percentage is slightly higher compared to a study conducted in a similar setting in South Africa in which 7.7% (n=519) of the study participants had no formal education (Peltzer *et al.,* 2010). However, it is almost comparable to the Nigerian study of Olisah, Baiyewu and Sheikh (2010), in which 9% (n=310) of the participants had no formal education.

On the other hand, nearly half of the participants in this study (49.7%) completed primary education, which is much higher than the 20% reported by Olisah, Baiyewu and Sheikh (2010).

Forty percent of the patients in this study completed either secondary or higher formal education (35% secondary and 5% tertiary). This does not concur with any of the reviewed literature. For example, the proportion is higher than the 19.1% (n=519) reported by Peltzer and colleagues (2010) and lower than the 69% (n=688) reported by Maqutu and colleagues

(2009) in previous South African studies. This finding is further contrary to findings in other countries. In adherence studies conducted in Nigeria and Cameroon, 64.5% (n=310) and 65% (n=312) of the study participants attained secondary or higher education (Olisah, Baiyewu & Sheikh, 2010; Rougemont *et al.,* 2009).

5.3.2.3. Employment status

Figure 5.4 shows that less than half (44.6%) of the male patients were unemployed, compared to 60% of the female patients.

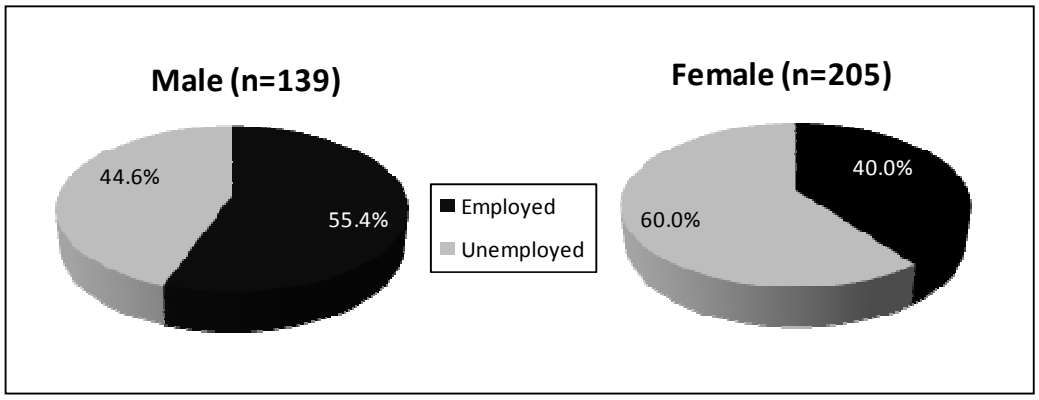


Figure 5.4: Employment status of study participants by gender (N=344)

In this study, employment varied in terms of skills, i.e. from being an unskilled worker, to being a semi-skilled worker or a petty trader. The sample population did not include any highly-skilled professionals. As illustrated in Figure 5.4, more of the males (55.4%) were employed than females (40.0%). These figures are comparable to a Kenyan study (n=159) in which more females (72%) than males (42%) had no income-generating job (Karcher *et al.,* 2007). This trend was also seen in Uganda where 36.2% of the females and 12.3% of the males were unemployed (Alibhai *et al.,* 2010).

Overall, more than half (53.8%) of the study participants were unemployed at the time of the study. A study conducted in KwaZulu-Natal, South Africa, reported a higher unemployment rate of 59.6% (n=519) amongst their study subjects (Peltzer *et al.,* 2010).

Unemployment is a major concern in South Africa, as 5.2 million South Africans were unemployed as at April, 2010 (Department of Social Development, 2010). The rate of unemployment amongst ART patients is known to be higher compared to patients not on ART (Hardy & Richter, 2010). Patients on ART are required to attend the HIV clinic consistently in order to collect their ARVs on a monthly basis and to regularly undergo medical assessments (Chalker *et al.,* 2010; DOH, 2010). If patients are unemployed, they

might not have adequate finances for transport to the ARV clinic, which will make it difficult for them to keep their clinic appointments. This will have a negative impact on their ARV adherence and subsequently on their treatment success. A correlation between missed appointments and non-adherence has been reported in previous studies (Chalker *et al.,* 2010; Oyugi *et al.,* 2004).

5.3.2.4. Marital status

The majority (63.4%) of participants in this study were single (Table 5.3). More of the females (65.9%; n=205) were single compared to their male counterparts (59.7%; n=139), and fewer females were married (22.9%) compared to 27.3% of the males (Figure 5.5).

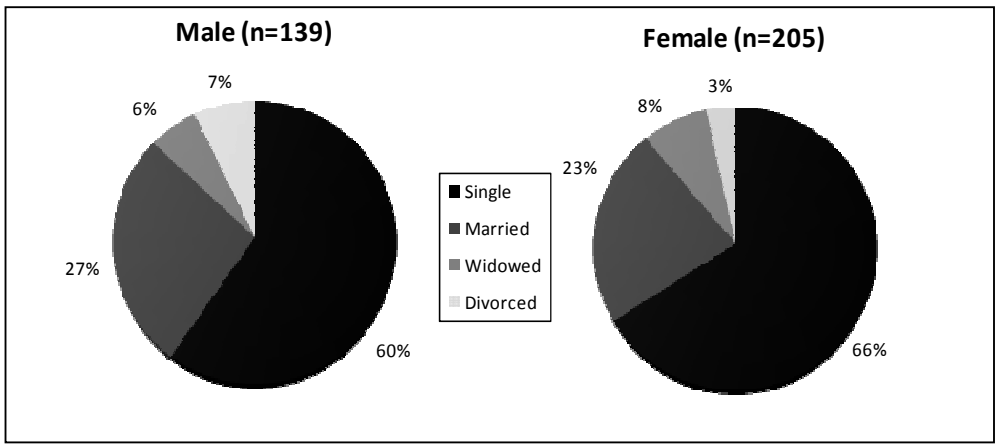


Figure 5.5: Marital status by gender (N=344)

Similar findings were reported from a study conducted in rural Uganda (n=385) where certain variables were compared among the two genders (Alibhai *et al*., 2010). A smaller proportion of the females (31.5%) was married compared to males (54%).

In our study, a small proportion of the participants was either widowed or divorced (13% and 11% of the females and males respectively). These figures were much higher in the Ugandan study in which 48% of the females and 20.9% of the males were either widowed or divorced (Alibhai *et al*., 2010).

Overall, 63.4% of the study participants were single and 24.7% were married. The remaining participants were either widowed (7%) or divorced (5%). These numbers are lower than those reported by Peltzer and co-workers (2010), in which nearly three-quarters of the participants (73.3%; n=519) were single and only 13.2% were married at the time of the study. In the Nigerian study of Olisa, Baiyewu and Sheikh (2010) (n=310), the opposite was

reported with more subjects (52.9%) being married, 21.3% single, 20.6% widowed and 0.6% separated from their spouse.

Statistics South Africa (2009) conducted a study (n=17566) to outline the factors that are associated with unemployment among South African women. An estimated 31% of the participating women were unemployed. Of these unemployed women, 85.2% were black and 71.5% were never married. These results confirmed that, at least in South Africa, race and marital status play a role in employment status of women, as was observed in this study.

The results of this study indicated, as in other sub-Saharan African countries, that there were more females and of a younger age on ART, compared to males. A possible explanation for this could be the fact that females enter the HAART programme earlier than men, probably because of their participation in the prevention of mother-to-child transmission (PMTCT) programme.

Lower educational levels amongst females could have contributed to the lower employment rate among the female participants in this study, or because they develop symptoms earlier than men.

5.3.3 Duration on ART

Table 5.4 shows that half of the patients (50.6%) were on ART for more than 24 months prior to the time of the study, while only seven patients (2%) were on ART for less than six months. Overall, the participants were on ART for a median period of 24 months, with a median of 25 months for females and 23 months for males.

At the time of data collection, the clinic initiated an average of 125 patients per month (see Section 3.2). Only seven patients less than six months on ARVs were enrolled into the study. A possible reason for this could be because there were two counselling rooms at the clinic. One of the rooms was designated to new patients, hence, the data collector or the researcher was not in contact with new patients. However, these seven new patients were enrolled into the study because the researcher saw them at the pharmacy when they came for their ARVs and asked for their consent to participate in the study.

Table 5.4: Duration on ART by gender (N=344)

Duration (months)	Male (n=139)		Female (n=205)		Total (N=344)	
	Number	%	Number	%	Number	%
<6 months	4	2.9	3	1.5	7	2.0
6 – 12 months	27	19.4	44	21.5	71	20.6
13 – 24 months	42	30.2	50	24.4	92	26.7
>24 months	66	47.5	108	52.7	174	50.6
Total	139	100	205	100	344	100
Median (months)	23		25		24	
Mean (months)	25		38		30	

A higher percentage of females (52.7%; n=205) were on ART for more than 24 months compared to the males (47.5%; n=139) (see Figure 5.6). This could be an indication that females seek and commence ART treatment earlier than men.

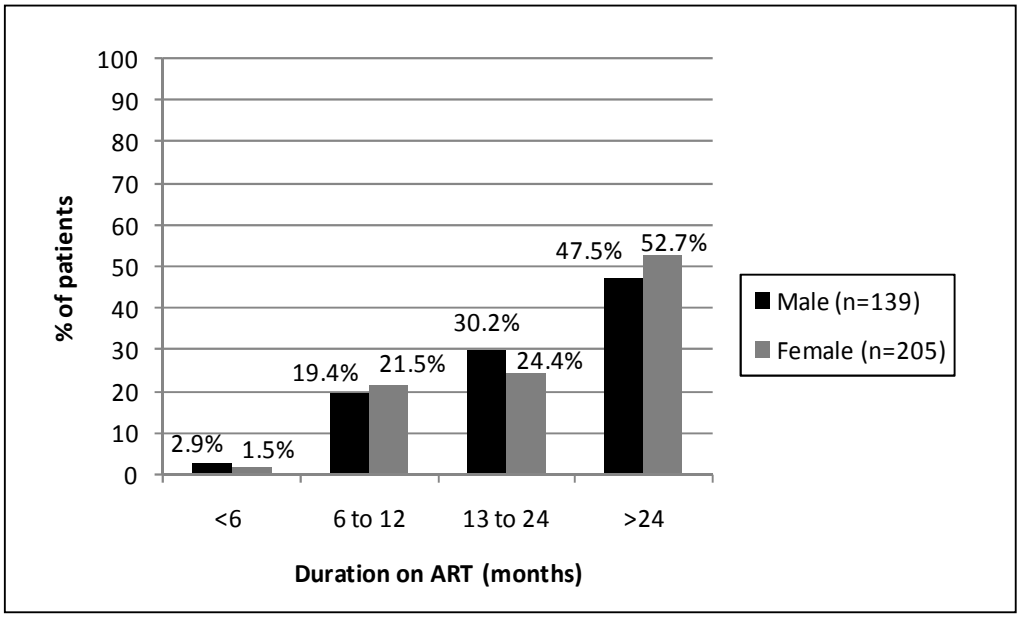
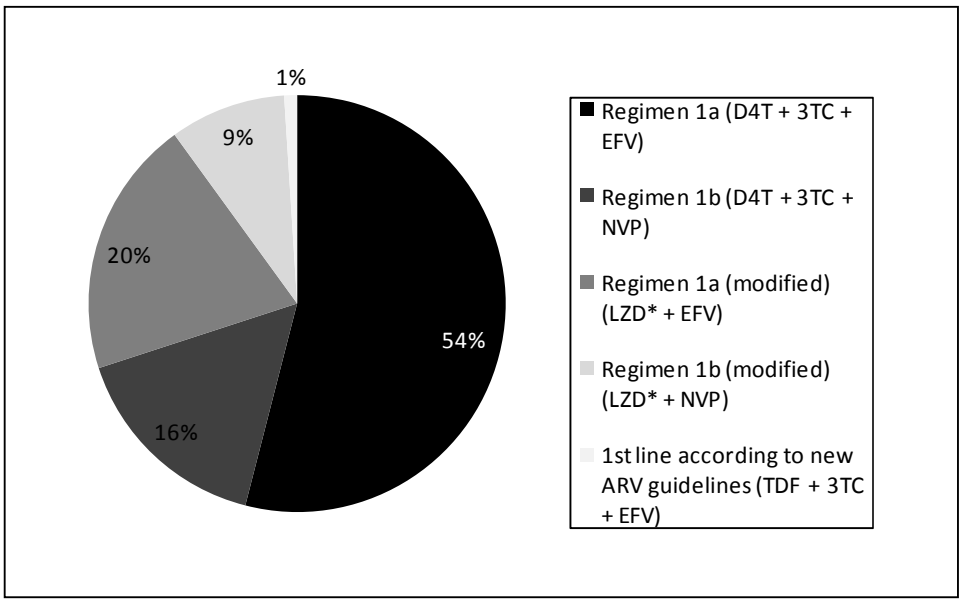


Figure 5.6: Duration on ART by gender (N=344)

5.4 ARV REGIMENS

5.4.1 Regimens at study enrolment

The previous South African National ART Guidelines (DOH, 2004) recommended that patients be initiated on Regimen 1, which includes either Regimen 1a (stavudine, lamivudine and efavirenz) or Regimen 1b (stavudine, lamivudine and nevirapine. Refer to Tables 2.2 and 2.5, in Section 2.5.1.1 for a more detailed description of the different regimens. Figure 5.7 shows the different regimens the study participants were taking at the start of the study.



*LZD: Lamzid® (**Lam**ivudine 300mg + **Zid**ovudine 300mg fixed-dose combination)

Figure 5.7: ARV regimens taken by study participants (N=344)

Most patients (54%; n=344) were on Regimen 1a at the start of the study and 16% were on Regimen 1a. Twenty percent and 9% were on Regimen 1a (modified) and Regimen 1b (modified) respectively. Only two (1%) of the patients were on the first line regimen according the new ARV guidelines (tenofovir, lamivudine and efavirenz). It must be noted though that eight (2%) patients had been excluded earlier in the study because they were switched to tenofovir-containing regimens (see Section 5.2). This took place before the tenofovir-containing regimens were implemented in April, 2010.

In previous studies conducted in similar settings in South Africa, most participants were on Regimen 1a. Mokoena (2009) and Peltzer and colleagues (2010) respectively had 76% and 79.2% of their study participants on Regimen 1a.

According to the inclusion criteria, as outlined in Section 3.5.2.1, patients were required to be on Regimen 1a or Regimen 1b to participate in the study. For both these regimens, stavudine was sometimes substituded by zidovudine. In such an instance the regimen is referred to as Regimen 1a (modified) or Regimen 1b (modified). Patients on these modified regimens were also included in the study, because both zidovudine and stavudine belong to the same pharmacological class of ARVs (nucleoside reverse transcriptase inhibitors) (Katzung, 2009; Warnke, Barreto & Temesgen, 2007).

According to the WHO (2008), compliance with guidelines such as the South African ARV guidelines, results in better quality of care, better management of medicines, and more cost-effective use of health resources.

5.4.2 Treatment switches

According to Deeks (2006), when one or more of the medications in a patient's regimen change, the process is referred to as a treatment switch. Reasons for switching treatment include the following (Bartlett, Gallant & Conradie, 2007; Deeks, 2006; DOH, 2004; DOH, 2010):

- Drug toxicity (or side effects)
- Availability of safer, more tolerable or more efficacious medications
- Virologic failure

Eighteen (5.2%) of the 344 patients enrolled in this study had their regimens switched during the course of the study. The switch pattern for these patients is outlined in Table 5.5.

Table 5.5: Treatment switches during study period (n=18)

ARV Regimen		**Patients**	
Switched from	**Switched to**	**Number**	**%**
Stavudine, Lamivudine and **Efavirenz**	Stavudine, Lamivudine and **Nevirapine**	3	16.7
Stavudine, Lamivudine and Efavirenz	Efavirenz and **Lamzid®**	4	22.2
Stavudine, Lamivudine and Efavirenz	**Tenofovir**, Lamivudine and Efavirenz	4	22.2
Stavudine, Lamivudine and **Nevirapine**	Stavudine, Lamivudine and **Efavirenz**	1	5.6
Nevirapine and **Lamzid®**	**Tenofovir, Lamivudine** and Nevirapine	3	16.7
Stavudine, Lamivudine and Nevirapine	**Tenofovir**, Lamivudine and Nevirapine	2	11.1
Efavirenz and **Lamzid®**	**Tenofovir, Lamivudine** and Efavirenz	1	5.6
Total		**18**	

Note: ARVs switched are shown in bold

Of the 18 patients whose regimens had been switched, three (16.7%) switched from Regimen 1a to Regimen 1b because they were either pregnant or planning to start a family. Efavirenz is contraindicated in pregnancy because of its teratogenicity and was replaced with nevirapine (Katzung, 2009; Rossiter, 2009). Patients on stavudine-containing regimens

switched to tenofovir- or zidovudine-containing regimens due to the adverse effects of stavudine, which is mainly lipodystrophy and/or hyperlactaemia (Montessori *et al.,* 2004; Rossiter, 2009; Sharma *et al.,* 2008). One patient switched from Regimen 1b to 1a because he was commencing anti-TB treatment, and efavirenz is preferred to nevirapine in TB co-infection (DOH, 2010; Katzung, 2009; Rossiter, 2009).

5.5 ADHERENCE RATES

The aim of the study was to investigate the ability of "mixed" pill counts to detect deliberate masking of non-adherence to ART in a public sector practice setting. Two methods (normal pill count and "mixed" pill count) were used to measure ART adherence at two consecutive clinic visits (Return Visit 1 and Return Visit 2).

The normal pill count method, as explained in Chapter 2, is an objective method in which the tablets in the patient's possession are counted by a health care worker, in order to compare the patient's actual and expected tablet consumption (percentage of tablets taken) from the last day on which he/she obtained his/her medicines until the pill count day (Bell *et al.,* 2007; Chalker *et al*., 2009; Kalichman *et al*., 2007). On the other hand, the "mixed" pill count is a new concept which was tested in this study. With the "mixed" pill count method, additional tablets are deliberately dispensed to patients (more than the regular supply) and the number of tablets dispensed is recorded in the patients' files in an encrypted format so that they are not aware of the extra tablets. When the patients visit the clinic for their next appointment, the returned tablets are counted as usual. It is expected that truly adherent patients will return to the clinic with the extra tablets that were added the previous month while the non-adherent ones will either return with more tablets than the extra ones dispensed (which means that some doses were missed for one reason or another), or with fewer or none of the extra tablets dispensed, indicating a possibility of pill dumping.

Excellent adherence to ART is required in order to achieve treatment success, maintain long-term health benefits and to avoid the development of drug resistance (Ford et al., 2010; Lima *et al.,* 2008). Irregular and incomplete ARV medication-taking behaviour is nevertheless a common occurrence (Liu *et al.,* 2006).

5.5.1 Mean adherence

At the study clinic, pill counts are performed for all patients at each return visit after ART initiation. Each study participant was followed-up for two clinic visits. The normal pill count was used to measure adherence at Return Visit 1 and the "mixed" pill count method was

used at Return Visit 2. The percentage adherence for the individual ARVs in the patient's regimen was calculated as well as the mean adherence for each patient's regimen. To calculate an overall average adherence rate, mean adherence rates for each patient's regimen were averaged across all patients for each of the two visits. Table 5.6 shows the overall average adherence for the normal pill count (Return Visit 1), for the "mixed" pill count (Return Visit 2) as well as the entire study period.

Table 5.6: Overall average adherence for the normal pill count and the "mixed" pill count

	Percentage adherence					
	Normal pill count (Return Visit 1)		Mixed Pill Count (Return Visit 2)		Overall average	
	Mean (%)	SD (%)	Mean (%)	SD (%)	Mean (%)	SD (%)
Male (n=139)	97.1%	14.62%	100.9%	8.34%	98.98%	12.04%
Female (n=205)	97.3%	8.83%	99.7%	10.94%	98.53%	10.00%
Overall average	97.2%	11.53%	100.2%	9.97%	98.7%	10.87%

The overall average adherence for the study population was 97.2% at Return Visit 1, 100.2% at Return Visit 2 and 98.7% over the two visits. Overall average adherence for males (98.98%) and females (98.53%) was similar. The average adherence in this study is higher than the average adherence of 92.4% (n=100) obtained by Mokoena (2009), in a pill count study conducted amongst a military population in South Africa. It must be noted though, that Mokoena's follow-up period was much longer (15 months) compared to this study.

5.5.2 Adherence per category

According to the literature and previous studies conducted, adherence of ≥95% is generally regarded as optimal because at this level, maximal viral suppression, CD4 count improvement as well as minimal resistance to medication are observed (Ford *et al.,* 2010; Lima *et al.,* 2008). However, the best response to ART is observed when adherence is 100% (Cauldbeck *et al.,* 2009; Mannheimer *et al.,* 2005).

Because of the design of this study, 100% adherence was regarded as optimal, to be able to distinguish between truthfully non-adherent patients and over-compliant patients (possible non-adherence maskers). Patients were stratified into three adherence categories at Return Visits 1 and 2 based on the mean adherence calculated for their regimens. These categories comprised of the following:

- Truthfully non-adherent patients (adherence <100%). These patients returned more tablets than expected which indicated that they did not take all the tablets as prescribed.
- Adherent patients (exactly 100% adherence). This category of patients had perfect adherence to ART. They returned exactly the correct number of tablets.
- Over-compliant patients (adherence >100%). These patients returned to the clinic with fewer tablets than expected, which indicated either the possibility of pill dumping or that they took more tablets than their required dose.

In certain sections of this chapter, for the purpose of comparing adherence levels obtained in this study with those from the published literature, as well as for the investigation of the association between adherence and clinical markers (see Section 5.8), a lower threshold for optimal adherence of 95-100% was also used. In these instances, patients were then also stratified according to three adherence categories namely <95% (non-adherent), 95-100% (adherent) and >100% (over-compliant). Table 5.7 shows the proportion of patients within each category of adherence at the two return visits based on the 100% and 95-100% thresholds for optimal adherence.

Table 5.7: Proportion of patients within each category of adherence at the two return visits based on the 100% and 95-100% threshold for optimal adherence (N=344)

	Adherence categories					
	<100% Truthful non-adherent	**=100% Adherent**	**>100% Over-compliant**	**<95% Non-adherent**	**95-100% Adherent**	**>100% Over-compliant**
Normal Pill Count (Return Visit 1)	174 (50.6%)	95 (27.6%)	75 (21.8%)	71 (20.6%)	198 (57.6%)	75 (21.8%)
Mixed Pill Count (Return Visit 2)	55 (16.0%)	246 (71.5%)	43 (12.5%)	22 (6.4%)	279 (81.1%)	43 (12.5%)

It is evident from Table 5.7 that the proportion of patients with optimal adherence at Return Visit 1 was much higher (57.6%) when the 95-100% threshold for optimal adherence was used compared to the 100% threshold (27.6%). The number of non-adherent patients decreased with the 95-100% threshold, from 174 (50.6%) to 71 (20.6%). The number of

optimally adherent patients also increased at Return Visit 2 with the 95-100% threshold from 246 (71.5%) patients who were 100% adherent to 279 (81.1%) who were 95-100% adherent.

It is logical that the proportion of adherent patients will increase when a lower adherence threshold is used. As observed by Mokoena (2009), the proportion of patients with at least 95% adherence was 59.3% (n=973) and the proportion was higher when a lower threshold of 90% was used (75.7%).

The percentage of patients with exactly 100% adherence at Return Visit 2 was 71.5% (Table 5.7 and Figure 5.7), and the proportion of patients with 95-100% adherence at this visit was 81.1%. These fairly good figures are much higher than those obtained by Mokoena (2009) with a normal pill count method, in which only 59.3% of the patients were atleast 95% adherent. However, the result is comparable to the results of Peltzer and co-workers (2010). They conducted a study in South Africa (n=519) with the aim of assessing the factors that contribute to ART adherence. In their study, adherence was measured using the 30-day visual analogue scale (VAS) and self-reported 4-day recall methods. They found that the percentage of adherent patients was 82.9% with the VAS and 84.5% with the self-reported recall method. Interestingly, in light of such good adherence levels observed in this study, past studies warn that adherence rates may decline the longer patients are on treatment (Amberbir *et al.,* 2008; Mokoena, 2009; Parruti *et al.,* 2006).

When optimal adherence was regarded as 100%, the proportion of patients increased from 27.6% at Return Visit 1 to 71.5% at Return Visit 2. This high proportion at Return Visit 2 is comparable with a study conducted in Bangalore, India (n=32), in which 60% of the patients were found to be 100% adherent (Cauldbeck *et al.,* 2009).

Although Table 5.6 shows that the overall average adherence for the patients at both return visits appeared to be very good (97.2% at Return Visit 1 and 100.2% at Return Visit 2), Table 5.7 illustrates that actually only 27.6% and 71.5% of the patients achieved 100% adherence at Return Visits 1 and 2 respectively. Even when the threshold for optimal adherence was reduced (95-100%), the proportion of patients who were optimally adherent, was lower (57.6% and 81.1% at Returns Visits 1 and 2 respectively).

One of the objectives of the study was to determine whether the proportions of patients who were over-compliant (returning too few dosage units) were the same with both pill count methods. Based on the average adherence calculated for each patient's regimen, Table 5.8 was constructed to show the different proportions of patients within each defined category of adherence for the normal pill count (Return Visit 1) and the "mixed" pill count (Return Visit 2).

Table 5.8: Proportion of patients within each category of adherence based on the mean adherence calculated for each patient's regimen (N=344)

		Mixed Pill Count (Return Visit 2)			
	Adherence Category*	**<100% Truthful non-adherent**	**100% Adherent**	**>100% Over-compliant**	**Total**
Normal Pill Count (Return Visit 1)	**<100% Truthful non-adherent**	32 (9.3%)	119 (34.6%)	23 (6.7%)	**174 (50.6%)**
	100% Adherent	9 (2.6%)	78 (22.7%)	8 (2.3%)	**95 (27.6%)**
	>100% Over-compliant	14 (4.1%)	49 (14.2%)	12 (3.5%)	**75[#] (21.8%)**
	Total	**55 (16.0%)**	**246 (71.5%)**	**43[#] (12.5%)**	**344 (100%)**

*Mean adherence was calculated for each patient's regimen
[#]*P*=0.001; Mc Nemar's Test

Table 5.8 shows that 75 patients (21.8%) were over-compliant with the normal pill count, while 43 patients (12.5%) were over-compliant with the "mixed" pill count. Twelve patients (3.5%) were over-compliant in both cases. The proportion of over-compliant patients at Return Visit 1 (21.8%) was compared with the over-compliant proportion at Return Visit 2 (12.5%). The difference between the groups was statistically significant (*P*=0.001; Mc Nemar's test). The proportion of patients who returned too few dosage units (over-compliant) with the "mixed" pill count was significantly smaller, than with the normal pill count.

Figure 5.8 shows the proportion of patients within each of the adherence categories for both return visits.

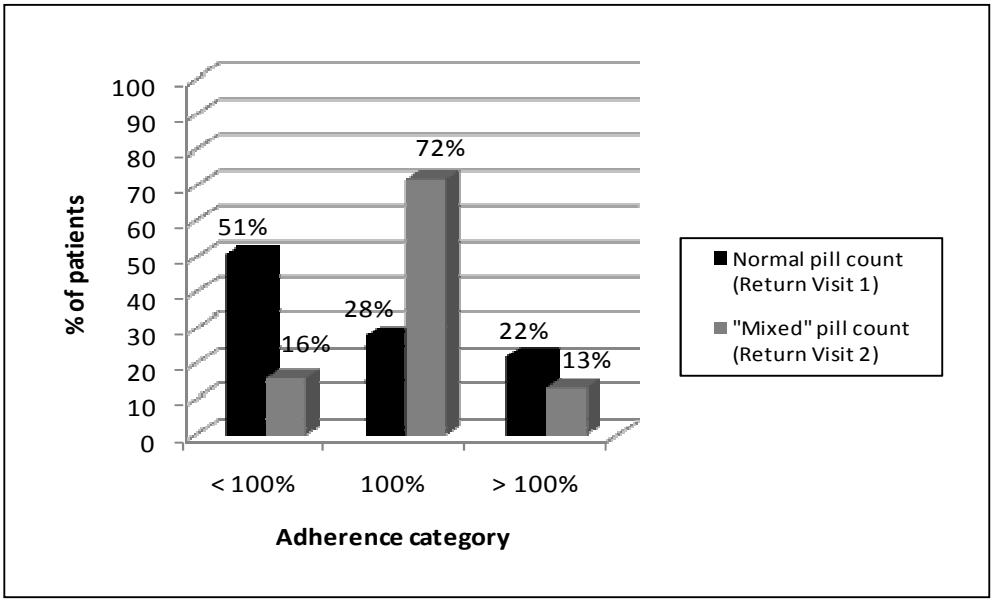


Figure 5.8: Distribution of patients according to adherence category for the normal pill count and the "mixed" pill count (N=344)

In addition, a comparison was done to determine if the group with exactly 100% adherence at Return Visit 1 (95 patients; 27.6%) were likely to be over-compliant at Return Visit 2 (Table 5.9). The proportion of patients who were exactly 100% adherent at Return Visit 1 (27.6%) was compared with the proportion who were over-compliant at Return Visit 2 (12.5%). The difference between the two proportions was statistically significant (*P*=0.0001, Mc Nemar's test). Thus, patients who were exactly 100% adherent at Return Visit 1 did not have equal chances as other patients to be over-compliant at Return Visit 2.

Table 5.9: Probability of returning too few dosage units at Return Visit 2 when 100% adherent at Return Visit 1 (N=344)

		Mixed Pill Count (Return Visit 2)		
	Adherence Category	**≤100%**	**>100%**	**Total**
Normal Pill Count (Return Visit 1)	**≠100% (not equal 100%)**	214	35	**249**
	=100%	87	8	**95 (27.6%)[#]**
	Total	**301**	**43 (12.5%)[#]**	**344**

[#]*P*=0.0001; Mc Nemar's test.

5.5.3 Adherence to individual ARVs

Eighteen patients (5.5%) switched regimens during the study period (see Section 5.4.2). The number of patients on each individual ARV medication was therefore not the same for Return Visits 1 and 2. Table 5.10 shows the percentage of patients on each individual ARV medication at the two return visits. It is evident that the majority of the patients were on stavudine, lamivudine and efavirenz (Regimen 1a).

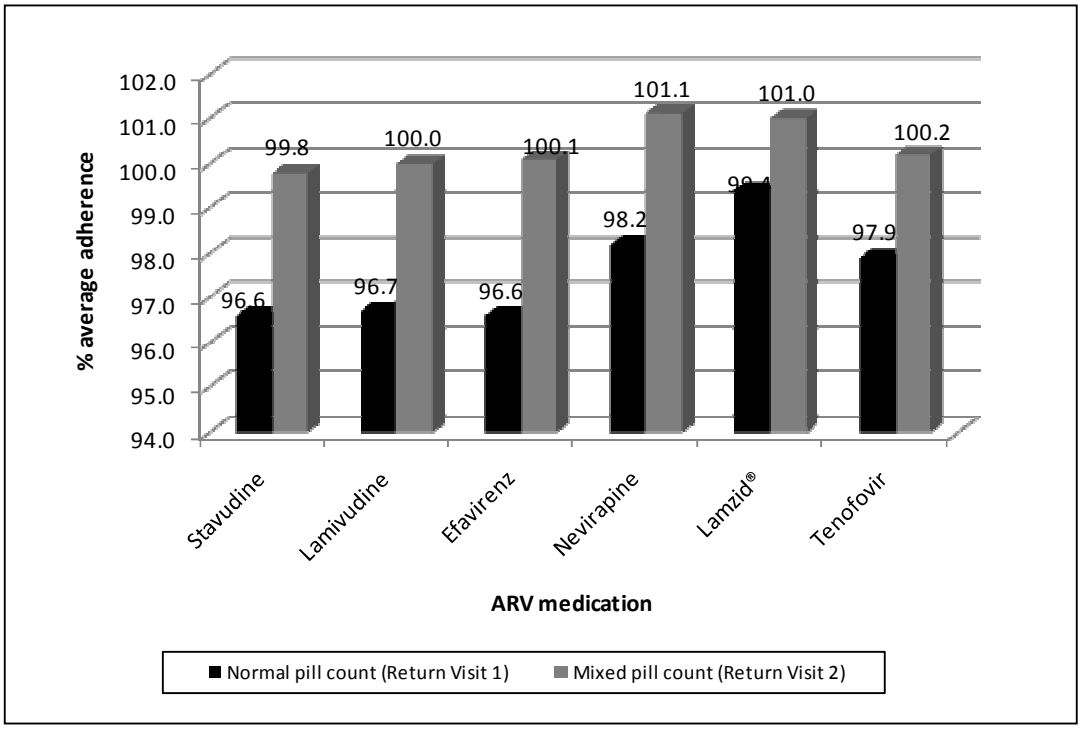
Table 5.10: Proportion of patients on each ARV medication at the two return visits (N=344)

ARV medication	Return Visit 1 (Normal Pill Count)		Return Visit 2 (Mixed Pill Count)	
	Number of patients (N=344)	%	Number of patients (N=344)	%
Tenofovir	34	9.9	13	3.8
Lamzid®*	70	20.3	105	30.5
Nevirapine	86	25	89	25.9
Efavirenz	257	74.7	256	74.4
Lamivudine	242	70.3	239	69.5
Stavudine	241	70.1	225	65.4

*Lamzid® (**Lam**ivudine 300mg + **Zid**ovudine 300mg fixed-dose combination)

5.5.3.1. Average adherence for individual ARVs

Adherence rates for each individual ARV medication were averaged across all patients for the two return visits. Figure 5.9 shows the average adherence rates for each of the ARVs at both return visits.



*Lamzid® (**Lam**ivudine 300mg + **Zid**ovudine 300mg fixed-dose combination)

Figure 5.9: Mean adherence rates for individual ARV medication at the two visits

As illustrated in Figure 5.9, average adherence at the first return visit measured with the normal pill count was below 100% for all the ARVs. At the second return visit, adherence improved with the "mixed" pill count for all the ARVs. The average adherence for lamivudine at Return Visit 2 was exactly 100%, which could be an indication that patients tolerate lamivudine better than the other drugs in their respective regimens. This better tolerability may be attributed to the fact that the side effects of lamivudine are relatively infrequent as compared to the side effects of the other ARVs (Avert, 2010b; Katzung, 2009; Rossiter, 2009). Average adherence for nevirapine was 101.1%, indicating that over-compliance (possible pill dumping) was most prevalent for nevirapine.

5.5.3.2. Over-compliance for individual ARVs

The proportion of patients returning too few tablets (over-compliant patients) were compared for the individual ARVs at the two return visits. The results of this comparison are shown in Tables 5.11 and 5.12.

Table 5.11: Proportion of the overall study population returning too few tablets (>100% adherence) per individual ARV for the two pill count methods (N=344)

ARV medication	Normal pill count at Return Visit 1			Mixed pill count at Return Visit 2			Fisher's exact test
	N	Number	%	n	Number	%	*P*
Stavudine	241	43	17.8	225	21	9.3	0.010*
Lamivudine	242	42	17.3	239	24	10.0	0.024*
Efavirenz	257	25	9.7	256	23	9.0	0.880
Nevirapine	86	23	26.7	89	8	9.0	0.003*
Lamzid®	70	17	24.3	105	16	15.2	0.168
Tenofovir	34	7	20.6	13	1	7.7	0.413

*Statistically significant
Note: The 'n' here represents the number of over-compliant patients that were taking the individual ARV medication. The difference in 'n' is because not all patients were on the same ARV medication at the two visits, and some had their regimens switched during the study.

Table 5.11 shows that the proportion of patients returning too few dosage units of the ARV medications reduced at Return Visit 2 for all the ARVs. For example, 17.8% of the patients on stavudine were over-compliant at Return Visit 1 but this proportion reduced to 9.3% at Return Visit 2. The difference between Return Visit 1 and Return Visit 2 was statistically significant ($P<0.05$; exact test) for stavudine, lamivudine and nevirapine.

Table 5.12: Proportion of over-compliant patients returning too few tablets (>100% adherence) per individual ARV for the two pill count methods (n=43)

ARV medication	Normal pill count at Return Visit 1			Mixed pill count at Return Visit 2			Fisher's exact test
	n	Number	%	n	Number	%	*P*
Stavudine	28	7	25.0	24	21	87.5	<0.001*
Lamivudine	28	7	25.0	27	24	88.9	<0.001*
Efavirenz	34	5	14.7	32	21	65.6	<0.001*
Nevirapine	10	5	50.0	12	9	75.0	0.378
Lamzid®	12	2	16.7	15	14	93.3	<0.001*
Tenofovir	4	2	50.0	5	2	40.0	1.000

*Statistically significant
Note: The 'n' here represents the number of over-compliant patients that were taking the individual ARV medication. The difference in 'n' is because not all patients were on the same ARV medication at the two visits, and some had their regimens switched during the study.

Although adherence improved in general for the overall study population at Return Visit 2, when only the 43 patients who were over-compliant at Return Visit 2 were considered, a

smaller proportion of these patients were over-compliant at Return Visit 1 compared to Return Visit 2.

From Table 5.12, it is evident that the proportion of patients returning too few dosage units at Return Visit 2 was the highest for Lamzid® (93.3% at Return Visit 2). Overall, as shown in Table 5.11, the degree of over-compliance among all the study patients was lower at Return Visit 2, which is the opposite of what was expected, and it appears as though the "mixed" pill count did not detect over-compliant patients as well as expected. Table 5.12 on the other hand, shows that among the patients who were over-compliant with the "mixed" pill count (n=43), the degree of over-compliance got worse at Return Visit 2, implying that there was a decline in the adherence levels as detected by the "mixed" pill count method in this group of patients, as more patients were over-compliant at Return Visit 2, which is in the opposite direction of what was observed in the overall population.

Of these 43 patients that were identified as over-compliant at Return Visit 2 (see Table 5.8), only 12 (27.9%) were previously over-compliant (at Return Visit 1). These patients were on ART for a median duration of 26.5 months and only one of them was on ART for less than six months. The median CD4 count after six months or longer on ART was 387 copies/mm^3. This CD4 count is below the desired level of 500 copies/mm^3 after being on ART for at least six months (Leach-Lemens, 2010b). According to the literature, CD4 count is not considered an effective predictor of adherence to ART and viral load is usually preferred when relating adherence to clinical markers (Calmy *et al*., 2007; MSF, 2009). The median viral load was non-detectable (below 400 copies/mL) for the over-compliant patients, indicating that the patients still achieved viral suppression despite the fact that they were not optimally adherent. However, this low median CD4 count may be an indication of sub-optimal adherence as some studies in the past have found an association between CD4 and adherence (Kalichman *et al.,* 2007; Lima *et al.,* 2008*).*

Over-compliance was observed for all the ARVs and was significantly higher for all the ARVs except for nevirapine and tenofovir. It is worth noting though, that the sample size for these two ARVs was small. Mapetla (2007) reported that efavirenz, stavudine and zidovudine (Lamzid® in this case) are known to cause major side effects and adherence to these ARVs in her study was lower than the required 95%. It was therefore expected that in this study, over-compliance would be more prevalent for these three drugs, but this was only the case for Lamzid®, lamivudine and stavudine. In spite of the side effects or challenges that the ARVs pose to the patients, good adherence is believed to be a critical determinant of long-term survival among HIV-infected individuals (Chi *et al.,* 2009; Nischal, Khopkar & Saple, 2005*).* Adherence to all ARVs in the regimen is important because patients can quickly

become resistant to ARVs if they are not taken as prescribed. Furthermore, cross-resistance (becoming resistant to similar drugs) limits patients' future treatment options (DOH, 2004; Horizon/Population Council, 2004). It is therefore very important for patients to understand that the benefits of treatment outweigh the risks of side effects, which could motivate them to be more adherent (Horizon/Population Council, 2004).

From the pilot study, there was some evidence that patients were having difficulties coping with the side effects of efavirenz and stavudine (dizziness and lipodystrophy respectively). Patients in the pilot study admitted to pill dumping for these ARVs. It was therefore anticipated that in the main study, the proportion of patients returning too few of these two ARVs would be much higher when compared with the proportion of patients returning too few of the other ARVs, but this was not the case.

5.6 ADHERENCE AND GENDER

Different findings have been reported in the past on correlations between gender and adherence. For example, in a study conducted in South Africa to determine the factors associated with poor adherence, female patients showed better levels of adherence than their male counter-parts (Bhat *et al.,* 2010). On the contrary, according to other studies, women were less adherent than men (Peltzer, *et al*., 2010; Williams *et al.,* 2006). Furthermore, Rougemont and colleagues (2009), reported that there is actually no association between gender and adherence to ARVs.

Table 5.13: Proportion of patients within each category of adherence according to gender (N=344)

Adherence category	Normal pill count (Return Visit 1)		Mixed pill count (Return Visit 2)	
	Male	**Female**	**Male**	**Female**
<100%	37 (26.6%)	37 (18.0)	7 (5.0%)	14 (6.8%)
100%	75 (54.0%)	120 (58.5%)	108 (77.7%)	172 (83.9%)
>100%	27 (19.4%)	48 (23.4%)	24 # (17.3%)	19 # (9.2%)
Total	**139**	**205**	**139**	**205**

P=0.0324; Fisher's exact test.

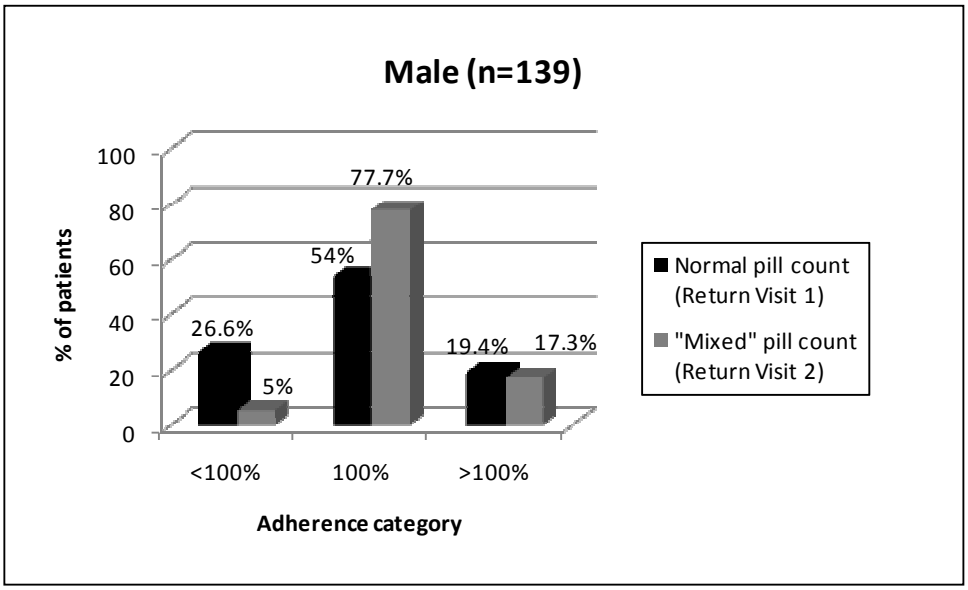


Figure 5.10: Adherence among the male participants

Table 5.13, Figure 5.10 and Figure 5.11 show that at Return Visit 1, 19.4% of the males (n=139) and 23.4% of the females (n=205) were over-compliant. At Return Visit 2, a smaller proportion of the females (9.2%) was identified as 'maskers'/dumpers, compared to 17.3% of the males. The difference in over-compliance among the genders was statistically significant (*P*=0.0324; Fisher's exact test). This means that over-compliance was significantly higher among the males than among the female patients.

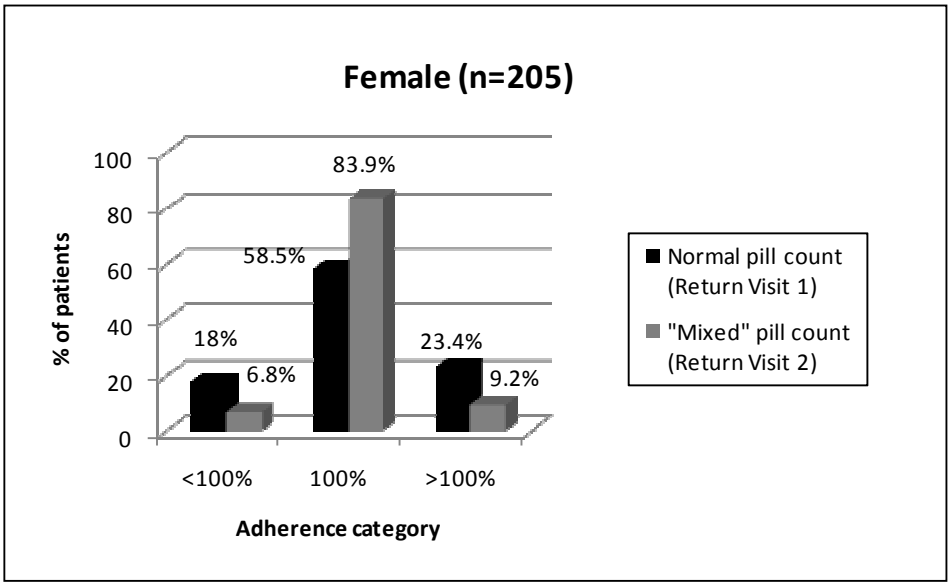


Figure 5.11: Adherence among the female participants

In terms of optimal (100%) adherence, more of the female patients were 100% adherent in the normal pill count (58.5% versus 54.0%) and in the "mixed" pill count (83.9% versus 77.7%), although this difference was not statistically significant (*P*>0.05; Fisher's exact test).

In a rural health centre in South Africa, similar results were reported by Bhat and colleagues (2010) as the female patients happened to be more adherent (100% adherence) than the males at two visits (n=168), but the difference was not statistically significant. The result is also comparable to Mokoena (2009) as adherence rates of at least 95% were observed in significantly more female visits (63.5%; n=386) than male visits (56.6%; n=588) (*P*=0.032).

5.7 OTHER SOCIODEMOGRAPHIC VARIABLES AND ADHERENCE

Previous sections (see Figures 5.9, 5.10 and 5.11) showed that adherence for the overall study population was better at Return Visit 2 than at Return Visit 1. Table 5.14 shows the proportion of patients who were over-compliant at each of the return visits, according to the different sociodemographic variables. Although adherence in general improved, which was not expected, there were still over-compliant patients at both return visits. A logistic regression was used to determine which sociodemographic variables are significant contributors to adherence and over-compliance at both return visits.

Although different studies have found various and conflicting associations between sociodemographic variables and ART adherence (Bhat *et al.,* 2010; Iliyasu *et al.,* 2005; Peltzer *et* al., 2010; Rougemont *et al.,* 2009; Vervoort, 2007; Williams *et al.,* 2007; Zou *et al.,* 2009), none of the variables investigated in this study was found to be associated with optimal adherence (100% adherence). With over-compliance, employment status appeared as a contributing factor at Return Visit 2. An odds ratio (OR) of 0.469 was obtained for the employed patients, meaning that the employed patients were about half as likely as the unemployed ones to be over-compliant. In other words, the unemployed patients were twice as likely as the employed patients to be over-compliant (OR=2.132 for unemployed patients). Since over-compliance is a form of non-adherence, our results imply that the employed patients adhered better than the unemployed ones. This finding is comparable to that obtained at the Rustenburg Provincial Hospital in South Africa, in which virologic failure was associated with non-adherence (Chabikuli *et al.,* 2010). Virologic failure was recorded in a significantly higher proportion of the unemployed patients (50.7%; n=65) than in the employed patients (40%; n=35), which means that more of the employed patients achieved good adherence levels compared to the unemployed ones (Chabikuli *et al.,* 2010). Similarly, in another part of Africa, adherence was better among the employed patients compared to the unemployed ones in Kenya (Talam *et al.,* 2008). On the contrary, in another study also in South Africa, unemployed patients were reported to adhere better (77.4%) than the employed ones (22.6%) (Peltzer *et al.,* 2010).

Based on the results (see Table 5.14), it appears that counting the tablets returned by patients improves adherence, regardless of the patient's socioeconomic status and the pill count method used. In principle, normal pill counts are performed for all patients at the study clinic during each follow-up visit. It is speculated that the study patients adhered better to their treatment because they were participating in a study that was monitoring their adherence. Another reason for this improved adherence could be that the counsellors changed their adherence counselling behaviour because of the presence of the researcher or the data collector. Patients probably also received more attention by the counsellors during the study period, hence the improved adherence. Furthermore, the original in-house pill count sheet used in the clinic did not show the patients' exact adherence percentage (see Section 3.6.4.4), but with the help of the study pill count sheet (Appendix C), the counsellors could specify to the patients what their actual adherence percentage was, and thus counselled the patients based on the percentage calculated during the study. Consequently, the fact that patients were told their adherence percentage at Return Visit 1 could have motivated them to take their medications well to improve on their adherence by Return Visit 2. In an adherence study conducted by Engelbrecht (2010), the study participants (both test and control groups) also improved on their adherence behaviour during the course of the study.

It has been established by Nischal, Khopkar and Saple (2005) that a 10% higher level of adherence to ART results in a 21% reduction in disease progression. In our study, it was observed that in each of the studied variables, the increase in adherence percentage between the first and second return visits was more than 10% (increase in adherence ranged between 12% and 37%). This is very impressive and justifies why pill counting and adherence counselling should be on-going practices at HIV clinics, which will ultimately benefit the patient's health. The study results therefore showed the importance of paying attention to or "policing" patients to ensure that they take their medication as prescribed in order to obtain maximum benefits from ART.

Table 5.14: Over-compliance among the sociodemographic variables (N=344)

Variable		Number	Patients with >100% adherence	
			Normal pill count Number (%)	Mixed pill count Number (%)
Gender	Male	139	27 (19.4%)	24 (17.2%)
	Female	205	48 (23.4%)	19 (9.3%)
Age group (years)	18-30	51	12 (23.5%)	4 (7.8%)
	31-40	145	33 (22.8%)	18 (12.4%)
	41-50	97	19 (19.6%)	16 (16.5%)
	>50	51	11 (21.6&)	5 (9.8%)
Duration of ART	<6 months	7	2 (28.6%)	0 (0%)
	6 – 12 months	71	14 (19.7%)	8 (11.3%)
	13 – 24 months	92	19 (20.6%)	8 (8.7%)
	>24 months	174	40 (23.0%)	27 (15.5%)
Race	Black	337	73 (21.7%)	42 (12.5%)
	Coloured	7	2 (28.6%)	1 (14.3%)
Language	Afrikaans	10	2 (20%)	1 (10%)
	Zulu	57	11 (19.3%)	5 (8.8%)
	Tswana	27	6 ((22.2%)	6 (22.2%)
	Sotho	90	25 (27.8%)	16 (17.8%)
	Other*	160	31 (19.4%)	15 (9.4%)
Education	None/primary not completed	35	9 (25.7%)	2 (5.7%)
	Primary completed	171	42 (24.6%)	20 (11.7%)
	Secondary completed	121	21 (17.4%)	20 (16.5%)
	Tertiary/vocational	17	3 (17.6%)	1 (5.9%)
Employment status	Employed	159	25 (15.7%)	16 (10.1%)
	Unemployed	185	50 (21.0%)	27 (14.6%)
Marital status	Single	218	46 (21.1%)	26 (11.9%)
	Married	85	21 (24.7%)	11 (12.9%)
	Widowed	24	4 (16.7%)	3 (12.5%)
	Divorced	17	4 (23.5%)	3 (17.6%)
Regimen switch	No	326	71 (21.8%)	38 (11.7%)
	Yes	18	4 (22.2%)	5 (27.8%)

***** Ndebele, Pedi, Shona or Tsonga.

As shown in Table 5.14, more of the females were over-compliant (23.4%; n=205) than the males (19.4%; n=139) at Return Visit 1. Adherence improved for both groups at Return Visit

2. The females improved more than the males (difference of 14.1% and 2.2% respectively). As mentioned in Section 5.6, significantly more of the males were over-compliant than the females at Return Visit 2. This result indicates that more of the males compared with the females were masking their adherence. According to Berg and Arnsten, (2006), one of the reasons why pill counts are considered to overestimate adherence is because patients may discard their tablets to appear adherent because they are aware that pill counts are being conducted. Therefore, it is speculated that the males engaged in "pill dumping" more than the females.

On average, taking all the ARVs in the regimen into consideration, the proportion of over-compliant patients was 43 (12.5%) at Return Visit 2 (Tables 5.7 and 5.8).

There were more males compared to females in the over-compliant group at Return Visit 2 and this gender distribution was different to that at enrolment. Therefore the results of this study showed an association between gender and adherence, which is that the females achieved better adherence levels than their male counterparts. A correlation between gender and adherence has previously been identified in the South African population, in which the female patients were found to have better levels of adherence than the males (Bhat *et al.,* 2010).

The sociodemographic characteristics of the 43 over-compliant patients as at Retrun Visit 2 are presented in Table 5.15.

Table 5.15: Demographic characteristics of the over-compliant patients at Return Visit 2 (suspected maskers) (n=43)

Variable		Original study population (N=344)		Patients with >100% adherence at Return Visit 2 (n=43)	
		Number	%	Number	%
Gender	Male	139	40.4	23	53.5
	Female	205	59.6	20	46.5
Age group (years)	18-30	51	14.8	4	9.3
	31-40	145	42.2	19	44.2
	41-50	97	28.2	16	37.2
	>50	51	14.8	4	9.3
Duration of ART	<6 months	7	2.0	1	2.3
	6 – 12 months	71	20.6	8	18.2
	13 – 24 months	92	26.7	7	18.2
	>24 months	174	50.6	27	61.4
Race	Black	337	98.0	42	97.7
	Coloured	7	2.0	1	2.3
Language	Afrikaans	10	2.9	1	2.3
	Zulu	57	16.6	5	11.4
	Tswana	27	7.9	6	13.6
	Sotho	90	26.2	16	38.6
	Other*	160	46.5	15	34.1
Education	None/primary not completed	35	10.2	2	4.5
	Primary completed	171	49.7	21	47.7
	Secondary completed	121	35.2	19	45.5
	Tertiary/vocational	17	5.0	1	2.3
Employment status	Employed	159	46.2	16	36.4
	Unemployed	185	53.8	27	63.6
Marital status	Single	218	63.4	27	61.4
	Married	85	24.7	11	25
	Widowed	24	7.0	3	6.8
	Divorced	17	5.0	2	6.8

***** Ndebele, Pedi, Shona or Tsonga.

Table 5.15 shows that the proportion of over-compliant males is slightly higher than females (53.5% versus 46.5%) but gender did not contribute to over-compliance. As explained

above, the only contributor to over-compliance is this study was employment status. The unemployed patients (63.6%) were twice as likely as the employed ones (36.4%) to be over-compliant. None of the other variables in this table played a role in over-compliance.

5.8 CLINICAL MARKERS

The CD4 count refers to the number of CD4 T-lymphocytes in a cubic millilitre of blood. In the presence of HIV, the CD4 count declines as the disease progresses and is used to monitor the extent of immune suppression in these individuals (Oguntibeju, van den Heever & Van Schalkwyk, 2009).

Viral load is the measurement of the number of HI virions in the blood. The viral load is used to guide treatment decisions and monitor response to treatment (Como, 2009).

Clinical markers for all study patients were obtained from the patients' files which contained printed blood test results from the National Health Laboratory Services (NHLS). The CD4 counts recorded at study baseline were the CD4 counts of the patients at ART initiation. Patients who were initiated on ART at a different ART clinic and who were transferred to the study clinic for ART continuation, came to the clinic with their CD4 count at ART initiation from the clinic where they previously attended. Overall, for 337 (98%) of the study patients, CD4 count results at ART initiation were available. The remaining seven (2%) patients were excluded from the analysis of CD4 counts at ART initiation.

South Africa's previous ARV guidelines (DOH, 2004; see Section 2.5.1.1) were still in use when the study participants were initiated on ART. Hence, patients were initiated on ART when their CD4 cell counts were below 200 cells/mm^3 or if they were at the WHO Stage IV of the HIV infection with an AIDS-defining illness. For the purpose of this study, the clinical markers (CD4 count and viral load) at ART initiation were recorded from patients' files for all patients at enrolment into the study. At the end of the study, the most recent readings (after six months or longer on ART) were recorded. Clinical markers for the seven patients who were not yet six months on ART, as well as for those who came late for their appointment, were recorded as soon as they were available after completion of the study.

At the end of the study, not all the participants had their most recent CD4 count and viral load results available. CD4 count values were available for 316 (92%) of the 344 participants and viral load values were available for 303 (88%) of the participants. Some of these clinical marker results were only received two months after the prescriber ordered for the test, thus a decision on whether or not to switch the patients' regimens could not be made promptly.

The fact that more CD4 count results were available than viral load results implies that the CD4 count is monitored more often than the viral load at the study clinic. The clinic is mainly guided by CD4 values and emergence of opportunistic infections in order to decide whether or not a patient is responding well to treatment. Calmy and colleagues (2007) and DOH (2006) recommended that viral load testing should supercede CD4 count as the principal marker for deciding when to switch a patient's ART regimen. Evaluating ART effectiveness based on CD4 counts alone is not adequate because CD4 cell counts depend on variation in individual immunological response to ART, and opportunistic infections manifest much later than when virological failure has occurred (MSF, 2009).

In the following sections, a lower threshold for optimal adherence of 95-100% will be used so that the clinical markers results can be compared to those obtained in past similar studies.

5.8.1 CD4 counts

5.8.1.1. CD4 counts at ART initiation and after six months or longer on ART

As illustrated in Table 5.16, the study subjects commenced ART with a median CD4 count of 109 cells/mm^3, which increased to 377 cells/mm^3 after being on treatment for six months or longer. The average CD4 count increased from 110 at ART initiation to 527 cells/mm^3 after six months of ART. This shows that on average, the desired CD4 count was reached for the study population, as achieving a CD4 count of at least 500 cells/mm^3 is the goal of effective antiretroviral treatment (Leach-Lemens, 2010b).

Table 5.16: CD4 counts at ART initiation and after six months or longer on treatment

	CD4 count (cells/mm^3)	
	ART initiation (N=344)	**After six months or longer on ART (N=316)**
Mode	37	248
Median	109	377
Mean ± SD	110 ± 63.4	527 ± 510

5.8.1.2. CD4 count according to gender

Study participants were categorised into three groups according to their CD4 counts (<100; 100-200; >200) at ART initiation and after six months or longer on treatment. Table 5.17, Figure 5.11 and Figure 5.12 show the proportion of patients in each category according to gender at ART initiation. The majority of the participants (95.0%) commenced ART with CD4 cell counts ≤200 cells / mm^3. This practice is in line with both the previous and new National ARV Guidelines (DOH, 2004; DOH, 2010), which stipulate that ART be initiated at a CD4

count of 200 cells / mm³ or less. Nearly half (46.6%) of patients started ART with a very low CD4 count of less than 100 cells / mm³. This could imply that patients either presented late for HIV testing, or they did not go to the clinic for regular follow-up and CD4 monitoring after a positive HIV test, or that the clinic might not have had the resources to monitor patients' CD4 count on a six-monthly basis as recommended (Bartlett, Gallant & Conradie, 2007; DOH, 2005; DOH, 2010).

Table 5.17: CD4 cell counts at ART initiation according to gender (N=337)

CD4 cell counts (cells / mm³)		Male (n=136)		Female (n=201)		Total (N=337)	
		Number	%	Number	%	Number	%
Category	<100	66	48.5	91	45.3	157	46.6
	100 – 200	62	45.6	101	50.2	164	48.4
	>200	8	5.9	9	4.5	23	5.0
Mean		109		111		110	
Standard deviation		66.6		61.2		63.4	
Range		2-291		4-266		2-291	

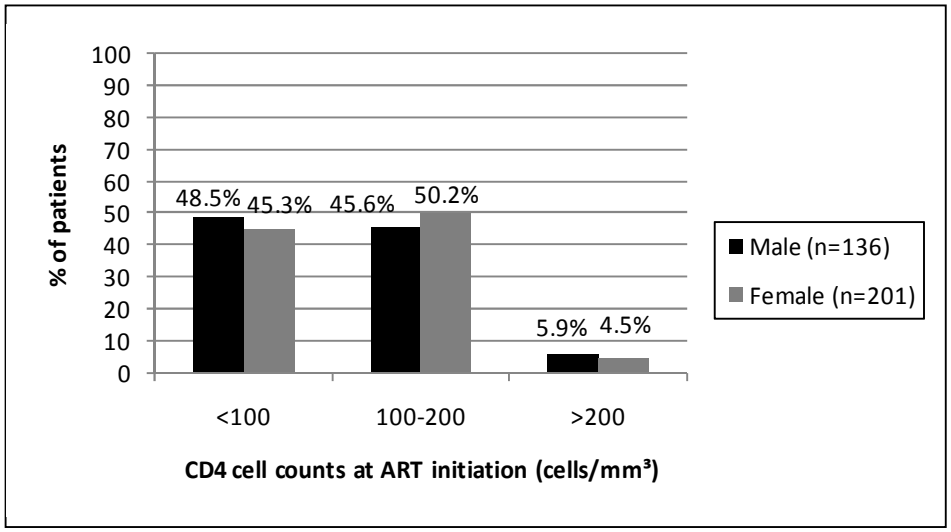


Figure 5.12: CD4 cell counts at ART initiation according to gender (N=337)

Table 5.17 illustrates that 46.6% of the patients commenced ART with CD4 cell counts of less than 100 cells / mm³. A smaller proportion of the females (45.3%, n=201) than the males (48.5%, n=136) commenced ART with a low CD4 cell count of less than 100 cells / mm³, while a larger proportion of the females (50.2%) commenced ART with higher CD4 cell counts of 100–200 cells/mm³ (Figure 5.12). This finding could indicate that females seek antiretroviral treatment a little earlier than males. A similar observation was made in a study

conducted in Uganda in which more females had higher baseline CD4 cell counts compared to males (Alibhai *et al.,* 2010). The Ugandan study further reported that men tend to delay treatment until an advanced stage of the infection is reached. These findings also concur with that of Ingle and colleagues (2010), in which men were less likely to start ART compared to women. Patients with CD4 cell counts of less than 200 cells / mm³ are at a high risk of opportunistic illnesses despite ART (Leach-Lemens, 2010b). It is therefore important that HIV-positive patients go for regular follow-up visits to the clinic in order to monitor their CD4 cell decline and commence ART as soon as they become eligible for treatment.

Table 5.18: CD4 counts after six months or longer on treatment according to gender (N=316)

CD4 cell counts (cells / mm³)		Male (n=129)		Female (n=187)		Total (N=316)	
		Number	%	Number	%	Number	%
Category	<100	7	5.4	7	3.7	10	3.2
	100 – 200	19	14.7	21	11.1	40	12.6
	>200	103	79.8	159	85.0	173	54.7
Mean		676		264		527	
Standard deviation		440		235		510	
Range		3-40029		10-1443		3-40029	

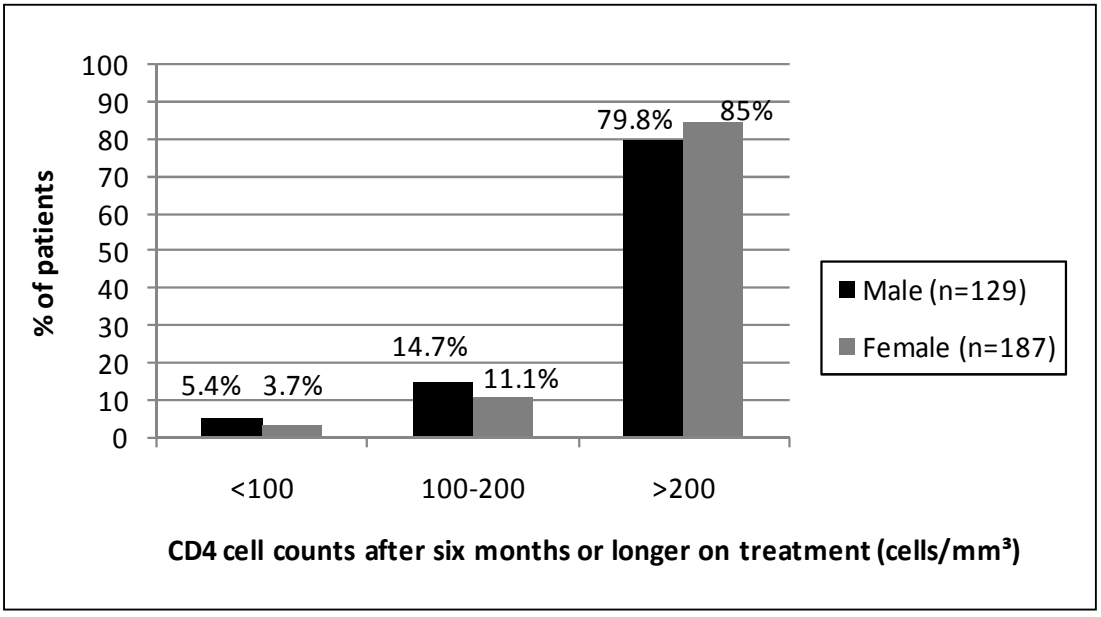


Figure 5.13: CD4 cell counts after six months or longer on ART according to gender (N=316)

As shown in Table 5.18, after six months or longer on treatment, slightly more of the females (85.0%) compared to males (79.8%) had a CD4 count greater than 200 cells / mm³. This may be an indication that the females in this study did better on ART than the males. This is not surprising because Table 5.13 showed earlier that there were more males (17.3%) with adherence of >100% than females (9.2%) at Return Visit 2 and fewer males (77.7%) than females (83.9%) achieved an adherence of exactly 100% at Return Visit 2.

5.8.1.3. Changes in CD4 count from ART initiation

Table 5.19 shows that the CD4 cell count increased for 299 (94.6%) of the 316 patients with available CD4 count readings. For 122 (40.8 %) of these 299 patients, the CD4 count increased to 500 and above. This means that only 40.8% of the patients with available CD4 values achieved the desired CD4 value of 500 cells/mm³ and above (Leach-Lemens, 2010b). The CD4 cells remained unchanged in 3.2% and declined in 2.2% of the patients from ART initiation to six months or longer on ART. A CD4 cell count decline is considered as an indicator of immune deficiency, which is a sign that the patient is either not responding well, or not adhering to ARV treatment (Leach-Lemen, 2010b; Lima *et al.,* 2008).

Table 5.19: Changes in CD4 cell counts from ART initiation to six months or longer on treatment

CD4 cell counts		Patients (n=316)	
		Number	**%**
Declined		7	2.2
Unchanged		10	3.2
Increased	***< 500****	*177*	*56.0*
	≥ 500*	*122*	*38.6*
	Sub-total	299	94.6
Total		**316**	**100**

*Breakdown of CD4 increased shown in italics

5.8.1.4. Adherence and CD4 count

As explained earlier (see Section 5.5.2), adherence of ≥95% is generally regarded as optimal because at this level, maximal viral suppression and CD4 count improvement are observed (Ford *et al.,* 2010; Lima *et al.,* 2008). However, the best response to ART is observed when adherence is 100% (Cauldbeck *et al.,* 2009; Mannheimer *et al.,* 2005). The 95-100% adherence threshold is used in this study for comparison purposes.

At Return Visit 2, the proportions of patients in the adherence categories (<95%, 95-100% and >100%) were compared in terms of changes in CD4 cell count from ART initiation to six months or longer on ART (declined, unchanged and increased) (Table 5.20). The Fisher's

exact test revealed no statistically significant association between adherence and change in CD4 counts.

Table 5.20: Association between change in CD4 count and adherence (with an optimal adherence threshold of 95%) (n=316)

		CD4 after six months or longer on treatment						
		Declined		Unchanged		Increased		Total
		Number	%	Number	%	Number	%	
Adherence category	<95%	0	0	2	10.0	18	90.0	20 (6.3%)
	95-100%	7	2.7	8	3.1	244	94.2	259 (82.0%)
	>100%	0	0	0	0	37	100.0	37 (11.7%)
	Total	7 (2.2%)		10 (3.2%)		299 (94.6%)		316

(*P*>0.287; Fisher's exact test).

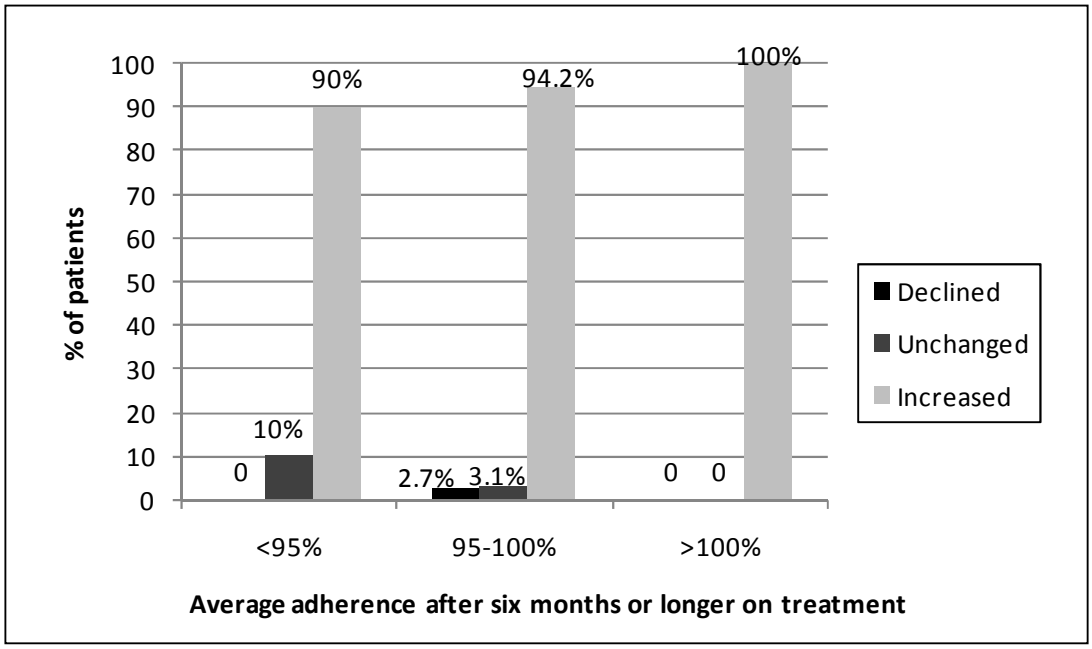


Figure 5.14: Association between change in CD4 count and adherence (with an optimal adherence threshold of 95%) (n=316)

Among the 316 patients with CD4 results available after six months or longer on treatment, 82% of them were between 95-100% adherent at Return Visit 2. As expected, a lower percentage (73.4%) was exactly 100% adherent.

An overall comparison with the Fisher's exact test showed that adherence and changes in CD4 count are independent. The overall association between CD4 counts and adherence was not statistically significant with $P>0.287$. This result contradicts that of Lima *et al.* (2008) who reported an association between adherence to ART and immunologic response. However, the result in our study highlights the limitation of the CD4 counts as a determinant of adherence, as some researchers warn that changes in CD4 counts depend on individual immunologic response to ART, so changes in viral load should rather be used as a determinant of adherence (Calmy *et al.,* 2007; MSF, 2009). Despite the fact that CD4 count did not correlate with adherence in the overall study population, it did correlate with adherence among the over-compliant patients (see Section 5.5.3.2).

5.8.2 Viral loads

The viral load readings were dichotomised to show viral suppression or otherwise. Of the 303 viral load results available at the end of the study, 249 (82%) were lower than detectable limits and 54 (18%) were detectable (Figure 5.15). A non-detectable or lower than detectable viral load is that which is below 400 copies/mL and is the ultimate goal after six months on ART (DOH, 2005; Wilson *et al.,* 2007).

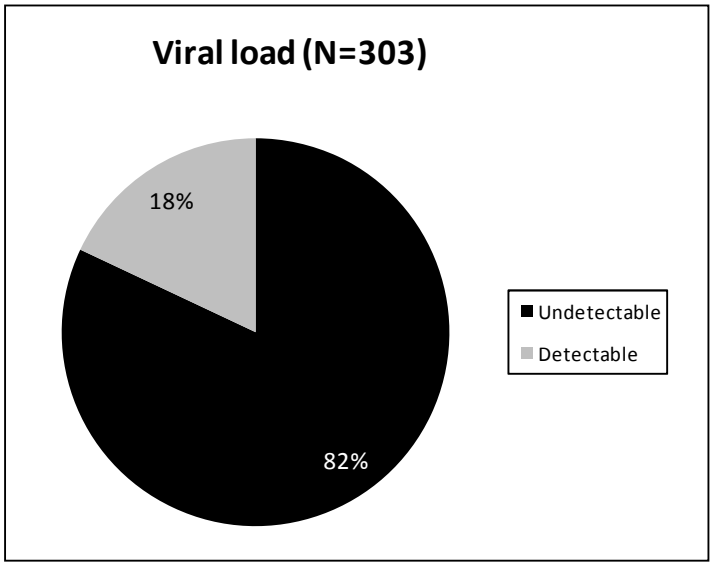


Figure 5.15: Viral load results after six months or longer on treatment (N=303)

Table 5.21 shows that the median viral load at ART initiation was 78000 copies/mL and it was zero (non-detectable) after six months on treatment.

Table 5.21: Viral load at ART baseline and study completion

Viral load (copies/mL)	ART baseline (N=344)	After 6 months or longer on ART (N=303)
Median	78000	0
Range	0-2877	0-820000

When adherence was compared among patients with detectable and non-detectable viral loads (Table 5.22), it was observed that non-detectable viral load readings were highly associated with good adherence (*P*=0.004; Fisher's exact test). A similar association was observed in a study where the long-term impact of adherence on virologic and immunologic response was investigated (Lima *et al.,* 2008). This association implies that viral load is a good marker of adherence. The median viral load was also non-detectable among the 43 over-compliant patients (see Section 5.5.3.2), most of these patients were sub-optimally adherent but their load still got suppressed, the reason for this paradoxic virologic response was not investigated in this study. Table 5.22 shows that 83.9% (n=249) of the group of patients with non-detectable viral loads and 16.1% (n=54) of those with detectable viral loads achieved optimal adherence levels of 95-100%. The proportion of patients in the adherence category of <95% was 50% for patients with detectable viral loads and also 50% for patients with non-detectable viral loads. Of the patients with adherence of >100%, 86.1% were in the non-detectable and 13.9% were in the detectable viral load group.

Table 5.22: Association between viral load and adherence (with optimal adherence threshold of 95%) (n=303)

		Viral load six months or longer on treatment				
		Non-detectable		Detectable		Total
		Number	%	Number	%	
Adherence category	**<95%**	9	50.0	9	50.0	**18**
	95-100%	209	83.9	40	16.1	**249**
	>100%	31	86.1	5	13.9	**36**
	Total	**249**		**54**		**303**

(*P*=0.004; Fisher's exact test).

After finding a significant association (*P*=0.004; Fisher's exact test) between adherence and viral load suppression, pair-wise comparisons were then carried out between each adherence category and the viral load groups. There was a statistically significant difference (*P*=0.0015) between patients with <95% adherence and those with optimal adherence (95-

100% adherence) in terms of viral load suppression (50% versus 83.9% and 50% versus 16.1% respectively). There was also a statistically significant difference (P=0.0077) between the non-adherent and over-compliant patients (50% versus 86.1% and 50% versus 13.9% respectively). However, there was no significant difference in viral load suppression among patients with optimal adherence and those with >100% adherence (83.9% versus 86.1% and 16.1% versus 13.9% respectively).

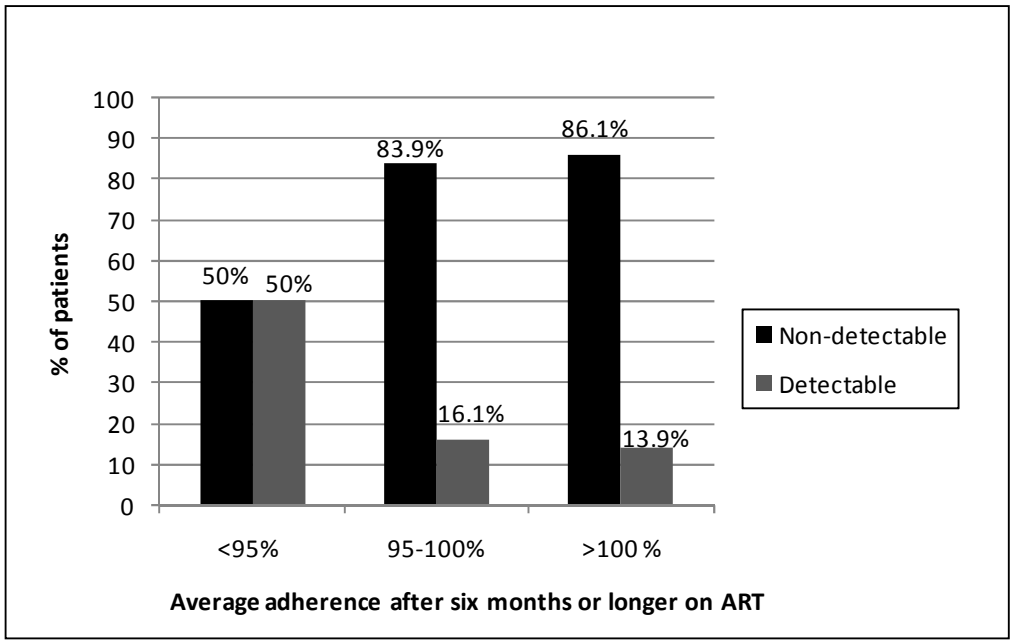


Figure 5.16: Association between viral load and adherence (with optimal adherence threshold of 95-100%) (N=303)

Table 5.22 shows that there is a difference in the degree of viral load suppression between patients with optimal adherence and those with sub-optimal adherence. The high rate of non-detectable viral load might be an indication that ART is successful in these patients and that the patients are adhering well to their treatment (Lima *et al.,* 2008; Poppa *et al.,* 2004).

5.9 DISCREPANCIES IN PILL COUNTS

When the "mixed" pill count was used to determine adherence at Return Visit 2, 55 patients were identified as truthfully non-adherent (adherence <100%) and 43 patients as over-compliant (adherence >100%) (see Section 5.5, Table 5.7). These patients were approached to be interviewed to determine the reasons for discrepancies in their pill count results. Forty three (85.5%) of the non-adherent and 37 (86%) of the over-compliant and patients agreed to be interviewed. The results of the interviews are presented in this section and are illustrated with quotations from the respondents.

5.9.1 Returning remaining tablets

Of the 55 truthfully non-adherent patients, 43 agreed to be interviewed and were asked if they always return their left-over tablets to the clinic. All, except one patient, responded 'yes' to this question. The one patient who did not always return left-over tablets explained that it was because of forgetfulness and workload at home. The patients were then asked how they felt about returning the remaining tablets to the clinic on their appointment date. This question was not applicable to the non-adherent patients who did not have any remaining tablets because they came late for their appointments. Nearly half (23; 48.9%) of the interviewed non-adherent patients reported that they were fine with returning remaining tablets to the clinic. The different feelings expressed by the patients are summarised below.

Two patients expressed the fact that they were not feeling comfortable returning their remaining tablets. One of them said the following:

> *"It's not good, but I don't have a choice because they want them"* [Patient 118, female, 32 years]

Seven patients responded that they return their remaining tablets because it is required of them by the clinic staff, as one of the female patients said:

> *"I feel nothing, I think I do it because you people from the clinic want them"* [Patient 346, female, 27 years]

In addition to the fact that they are required to return their remaining tablets for pill counting, it was evident that some of the patients also felt uncomfortable to be seen as non-adherent. One of the male patients described his feelings as follows:

> *"Yes I don't take them right, it's bad because I hate to be seen that I don't drink my medication"* [Patient 112, male, 39 years]

The above patient (patient 112, male, 39 years) admitted that he was throwing tablets into the toilet. This patient appeared to be truthfully non-adherent, so it is speculated that he only flushed the exact number of tablets that he did not take in the toilet.

One of the female patients also admitted that she had thrown away the tablets that she did not take.

> *"Okay. What happened was that because I did not take my tablets well, I decided to throw some of them in the toilet. They always complain that I don't take my tablets well"* [Patient 257, female, 41 years]

5.9.2 Tablet containers

When all the 80 interviewed patients were asked if they always kept their medication in the original container in which it was dispensed, 75 patients responded to this question. The majority (82.7%) said that they always keep their ARVs in the original containers, while 13 (17.3%) did not always use the original containers. Six of them never used original containers, while others who used original containers at home decanted their ARVs into different containers for use at work or when they were visiting friends or family. Decanting of tablets into other containers has been reported to compromise the sensitivity of pill counts for detecting non-adherence because patients may not take those decanted tablets (Kalichman *et al.,* 2005; United States Department of Veterans Affairs, 2009). Since it is not known if the patients actually took the decanted tablets, adherence may therefore be over-estimated for these patients.

5.9.3 Reasons for non-adherence

The reasons for missing doses (returning too many tablets) were explored amongst the interviewed patients. The reasons given by the respondents are summarised in Table 5.23.

Table 5.23: Reasons for non-adherence (<100%)

	Reasons for returning too many tablets (non-adherence)	Number
Truthful non-adherent patients (n=43)	Away from home	9
	Had extra/more tablets at home	4
	Discovered extra tablets were added to container	4
	Factory fault	3
	Forgetfulness	2
	Late for clinic appointment	1

Some patients provided more than one reason.

Interestingly, eight of the 43 patients who were identified as truthfully non-adherent because they were returning too many tablets, denied missing doses. Another six patients claimed not to remember missing any doses and six were not sure of what happened or why some doses were missed.

As shown in Table 5.23, four non-adherent patients discovered that extra tablets were added to their ARV containers. These patients claimed that they were returning too many tablets because they were given extra tablets. This was not a valid reason, because they returned more tablets than what was added to their containers.

Nine non-adherent patients said that that the fact that they were away from home resulted in them being non-adherent. Three of them forgot to take their ARVs with them when going out, one patient was hospitalised and did not have his ARVs with him, while two patients were away for social reasons (wedding and vigil at church).

Two patients admitted that they simply forgot to take their ARVs. Three patients thought it was a factory fault because they were sure they took their ARVs as prescribed, as one female patient said:

> *"I took everything, maybe it was factory fault, I never missed any pill."* [Patient 27, female, 48 years]

One patient missed doses because he came late for his clinic appointment and thus did not have any ARVs left to take. Similar to Meyer (2008), the results showed that family responsibilities placed demands on patients which affected their adherence. A 27-year old male patient explained how family responsibilities resulted in him reporting late for his clinic appointment:

> *"I took them as I was told and they got finished a few days ago, but my wife was in hospital and there was no one to look after the child, that is why I could not come for refill"* [Patient 345, male, 27 years]

5.9.4 Reasons for over-compliance

Over-compliant patients, who returned too few of their ARV doses, were prompted on what happened to the extra tablets dispensed to them. Nineteen (51.4%) of these patients denied ever taking any extra tablets.

The reasons for returning too few doses were explored amongst the interviewed patients and are summarised in Table 5.24.

Thirteen (35%) over-compliant patients stated that they actually discovered extra tablets in their tablet containers and tried to explain that this was the reason why the tablets did not balance after the pill count. This was not a valid explanation because they actually returned too few and not too many tablets.

Various explanations were provided by over-compliant patients as to what they did with the extra tablets. The most common reasons given, included throwing away (dumping), spilling of medication and taking an overdose. Six patients admitted that they have dumped their ARVs. One of these patients (Patient 112, male, 39 years) appeared to be a truthfully non-

adherent patient, but during the interview, he said he was dumping his tablets (see Section 5.9.1).

Table 5.24: Reasons for over-compliance (>100%)

	Reasons for returning too few tablets (over-compliance)	Number
Over-compliant patients (n=37)	Discovered extra tablets	13
	Threw them away	6
	Spilling or falling	6
	Overdose by mistake or forgot and took tablets again	6
	Children tampered or might have tampered with tablets	4
	Forgot to return all tablets	4
	Sharing	3
	Late for clinic appointment	1
	No harm in non-adherence	1
	Lifting spirit	1
	Lost	1

In certain cases, some patients provided more than one response. Some of the identified reasons are discussed in more detail in the sections below.

5.9.4.1. "Dumping" of tablets

Some patients admitted that they actually "dumped" or threw away some of their ARVs. The reasons given by patients for dumping their ARVs are summarised in Table 5.25 and are illustrated with quotations from the six respondents.

Table 5.25: Reasons for throwing tablets away (dumping)

	Reasons for tablet manipulation
Over-compliant patients (n=6)	**Dislike stavudine** *"I don't like D4T, because my friend told me that it affects erection and I threw them away and this month I ignored them again"* (Patient 112, Male, 39 years)
	Discovered there were extras *"I think you gave me extras, I'm not sure. I always take my pills correctly, so when I had a lot of pills remaining, I decided to spill them this morning before coming to clinic."* (Patient 205, Male, 50 years)
	Missing doses *"Okay. What happened was that because I did not take my tablets well, I decided to throw some of them in the toilet. They always complain that I don't take my tablets well."* (Patient 257, Female, 41 years)
	Non-disclosure *"....I don't know because I do it under the influence of alcohol and my boyfriend doesn't know that I'm positive."* (Patient 150, Female, 34 years)
	Had tablets remaining *"It is only two doses and I think it's not a big deal."* (Patient 166, Male, 37 years) *"I had some remaining tablets, then I spilled them because I did not want you to say I'm not taking my tablets."* (Patient 229, Female, 44 years)

5.9.4.2. Tablets spilling or falling

Six patients said their tablets were spilled and they could not take them again, thus they returned fewer tablets than expected. For four of the patients, the tablets spilled into water when they were trying to administer or take the tablets, while the remaining two patients said the tablets spilled when they were trying to transfer the tablets (nevirapine and lamzid®) from the blister packs into a separate container.

In the researcher's opinion, spilling of medication seems to be a convenient reason stated by the over-compliant patients who did not want to state the reason for over-compliance.

5.9.4.3. Taking extra tablets by mistake

Six of the over-compliant patients took extra ARVs. This practice was because patients sometimes forgot that they had taken their ARV dose, so they would take it again when they remembered. For instance, a 42 year old male said the following:

> *"...I have a bad memory, sometimes I forget that I had taken my treatment and I take again, only afterwards I remember that I took overdose but it's already late"* [Patient 119, male, 42 years].

Lepik (2010) gave a general approach that ARV overdose should be monitored carefully because there is very limited experience with ARV overdose and the effects of the overdose are unknown.

5.9.4.4. Children tampering with the medication

Four patients said that the reason why they returned too few tablets could be because their children knew where their ARVs are kept and they have access to them. When prompted about the missing tablets, a female patient responded as follows:

> *"Maybe my children tampered with them, because they know where I keep them and they bring them for me when it's time for me to take them"* [Patient 310, female, 39 years].

This response highlights the importance of adhering to instructions given by the pharmacist on how to correctly store the medication.

5.9.4.5. Late for clinic appointment

Only one over-compliant patient came late for her follow-up visit. This patient explained that she was late for clinic appointment due to the fact that she was bereaved:

> *"I have never taken an overdose or spilled tablets. My son's death had disturbed me. I took all of them and they are finished"* [Patient 204, female, 51 years].

Clinic appointments are missed for various reasons and are related to sub-optimal adherence (Kleeberger *et al.,* 2004). In a study conducted in Lusaka, Zambia, on cost-effective and feasible strategies urgently needed to improve timely patient follow-up and reasons for missing clinic appointments. Two hundred and seventy one (63%) of 430 patients provided reasons for missing appointments, and these reasons included feeling too sick to come to the clinic, being away from home and being too busy (Krebs, *et al.,* 2008).

Another study identified missing one or more clinic appointments as an important predictor of ART failure and viral rebound with resistance (Robins *et al.,* 2007).

5.10 BARRIERS TO ART ADHERENCE

In order to explore the barriers to ART adherence, all patients with sub-optimal adherence (truthful non-adherent and over-compliant) were asked what makes it difficult for them to take their ARV doses as prescribed on a daily basis.

Nearly half (46%) of the over-compliant patients (n=37) claimed that there was no problem for them in adhering to their ARV treatment, while three (8.1%) said they did not know what makes it difficult for them to adhere to their medication. Table 5.26 summarises the reasons mentioned for not taking ARV medications on a daily basis. Some of the difficulties are discussed in more detail in the sections below.

Table 5.26: Difficulties taking doses

Difficulty taking doses	Non-adherent patients (n=43)		Over-compliant patients (n=37)		Total (N=80)	
	Number	%	Number	%	Number	%
Non-disclosure / stigma	8	18.6	10	27.0	18	22.5
Pill burden	3	7.0	4	10.8	7	8.8
Side effects	1	2.3	3	8.1	4	5
Timing	0	0	4	10.8	4	5
Work-related	2	4.7	1	2.7	3	3.8
Forgot to take tablets	2	4.7	1	2.7	3	3.8
Feeling sick	3	7.0	0	0	3	3.8
Dislike tablets	1	2.3	1	2.7	2	2.5
Lack of support	0	0	2	5.4	2	2.5
Change of regimen	0	0	1	2.7	1	1.3
Transport/distance to clinic	0	0	1	2.7	1	1.3
Stress	1	2.3	0	0	1	1.3

Some patients gave more than one response. Some of the identified barriers to ART are discussed in more detail in the sections below.

5.10.1 Non-disclosure and stigma

Overall, the most frequent barrier to ART adherence was non-disclosure/stigma, amongst the non-adherent patients (18.6%) as well as the over-compliant patients (27.0%). While some patients had disclosed to family members, others still had disclosure problems.

One of the patients explained how non-disclosure makes it difficult for her to take her medication:

> *"I had not disclosed to my extended family, so when they are around it's not easy to drink pills, because they ask lots of questions."* [Patient 117, female, 38 years old]

The way in which patients are treated highly varies from one family to another (Duffy, 2005). In certain families, the patients are or feel isolated by their family members, which makes it difficult to cope with their disease and adhere to their treatment.

Disclosure/stigma has been identified as a barrier to adherence by studies conducted in similar settings (Mapetla, 2007; Meyer, 2008; Mokoena, 2008; Nachega *et al,* 2006). Nachega and colleagues (2004) reported that the fear of disclosure and stigmatisation are independently associated with non-adherence. Stigmatisation due to HIV/AIDS is considered a second epidemic because of its negative impact on lives (Carr *et al.,* 2004). Non-disclosure of HIV status may result in isolation, depression and anxiety and thus the patients will not seek treatment or they will not adhere properly to treatment (Carr *et al.,* 2004; Meyer, 2008).

5.10.2 Pill burden

Logically, an easy regimen would be preferable and easily tolerated at least for first-line regimens. Studies have observed that there is a reduction in adherence with increased doses per day (Nachega *et al.,* 2004; Orrell *et al.,* 2003).

In this study, pill burden was rated as the second most common barrier to adherence. Seven (8.8%) patients cited this as a barrier. Four of the over-compliant patients had a problem with pill burden compared to three of the non-adherent patients.

In the long run, patients tend to become tired of taking ARVs at specific times, as was reported by Meyer (2008). A fifty year old over-compliant female patient expressed her feelings as follows:

> *"Sometimes I get tired of these tablets, but I still take them anyway. The tablets are big"* [Patient 124, female, 50 years]

Another patient admitted that she had too many tablets to take and therefore did not take her ARVs.

> *"I was very sick for some time and I had lots of pills to take, so I decided to take those other ones. I started taking the ARVs again last week."* [Patient 38, female, 30]

Pill burden has been recognised as a barrier to ART in developed and developing countries (Mills, *et al.,* 2006) as well as in South Africa (Meyer, 2008; Mokoena, 2009; Nachega *et al.,* 2004).

5.10.3 Side effects

Side effects influence patients' decision to commence and adhere to treatment (DOH, 2006; Meyer, 2008). Several past studies have reported various reasons why patients fail to adhere to their ARVs. Parruti and colleagues (2006) informed that the lack of serious side effects is an indicator of good tolerance of therapy and a strong independent predictor of better adherence, as compared to those who experience side effects. Johnson and co-workers (2005) observed that greater numbers of side effects were reported by non-adherent patients than by the adherent ones.

Not many patients cited side effects as a barrier to adherence in this study. Overall, the side effects mentioned were those of stavudine, nevirapine and efavirenz. Although patients achieved fairly good overall average adherence for stavudine and efavirenz (96.6% in both cases), one male patient complained of stavudine side effects (affecting erection) and one female patient complained of efavirenz side effects (dizziness). Nevirapine was one of the drugs in which patients were over-compliant, however, only one patient (male) mentioned that he was experiencing skin rash due to nevirapine. A fourth patient, who was female, did not specify the side effect (s) she was experiencing.

The two male patients experiencing side effects had been on treatment for a shorter period than the females (7.5 months and 7.8 months for the males versus 23.6 months and 37.8 months for the females).

Because only four (5%) of the patients cited side effects as a barrier to ART, this low percentage may be an indication that during pre-ART counselling, patients were educated about the side effects they might experience and the importance of adhering to treatment, despite the side effects. Mokoena (2009) reported that the number of patients experiencing side effects decreased over time, from ART initiation (28%, n=100) to the 13th month (5.3%, n=38) on treatment. It is possible that the incidence of side effects had decreased among the patients at the time of this study, as the median duration on ART for the patients was 24.5 months.

5.10.4 Timing

In this study, four (5%) of the patients stated that they had difficulty with the timing of their medication and this affected their adherence. This proportion is about half of that which was reported by Adeyinka and colleagues (2008), in which 11 (10.7%) of the 103 patients cited timing as a barrier to adherence. In order to overcome this problem of timing, it was found that the patients in that study benefited from the use of mobile phones in the form of an alarm or reminder (83%) as well as the use of treatment supporters (24%).

5.10.5 Simply forgetting

In similar studies, simply forgetting to take ARVs was the most common reason for non-adherence. For example, in the study of Mokoena (2009), 17 patients (27.9%; n=61) simply forgot to take their ARVs. Similarly, with Mapetla (2007), forgetfulness (22%; n=191) was the main reason for missing doses.

However, in this study, only three out of 80 patients (3.8%) cited forgetfulness as a reason for not taking their ARVs as prescribed.

5.11 TESTING OF HYPOTHESES

Three null hypotheses and three alternative hypotheses were formulated for the objectives, at the start of this study (see Section 1.6). We hoped to reject the null hypotheses and accept the alternative hypotheses (see Table 5.27).

Table 5.27: Study hypotheses

Null hypothesis	Alternative hypothesis
Objective 1: a) ***Null hypothesis 1:*** The proportions of patients returning too few dosage units are the same with both pill count methods. b) ***Null hypothesis 2:*** Patients returning exactly the expected number of dosage units at Visit 1 (normal pill count) are equally likely as other patients to return too few dosage units at Visit 2 ("mixed" pill count).	**Objective 1:** a) ***Alternative hypothesis 1:*** The proportions of patients returning too few dosage units are different with both pill count methods. b) ***Alternative hypothesis 2:*** Patients returning exactly the expected number of dosage units at Visit 1 (normal pill count) are more likely than other patients to return too few dosage units at Visit 2 ("mixed" pill count).
Objective 2: This objective was achieved through qualitative methods, therefore no hypothesis testing was done.	
Objective 3: ***Null hypothesis 3:*** Health outcomes of patients with >100% adherence at Visit 2 (possible "adherence maskers"), of those with >95% to 100% adherence at Visit 2 ("truly adherent patients"), and of those with <95% adherence at Visit 2 ("non-adherent patients") are similar.	**Objective 3:** ***Alternative hypothesis 3:*** Health outcomes of patients with >100% adherence at Visit 2 (possible "adherence maskers"), of those with >95% to 100% adherence at Visit 2 ("truly adherent patients"), and of those with <95% adherence at Visit 2 ("non-adherent patients") are different.

5.11.1 Null hypothesis 1

Table 5.8 showed that there was a significant difference (*P*=0.001; Mc Nemar's Test) in the proportions of patients returning too few dosage units at both return visits (21.8% at Return Visit 1 and 12.5% at Return Visit 2). Although we reject the null hypothesis which stated that

the proportions would be the same and accept the alternative hypothesis, the proportion of patients who were over-compliant was lower at Return Visit 2 than at Return Visit 1, which was the opposite of what was anticipated.

Despite the fact that adherence improved for the overall study population at Return Visit 2, when the individual ARVs were considered among the over-compliant patients alone (see Table 5.12), it was observed that over-compliance among these patients increased for all the ARVs and this increase was statistically significant ($P<0.05$; Fisher's exact test), except for nevirapine and tenofovir.

5.11.2 Null hypothesis 2

As shown in Table 5.9, the proportion of patients who were exactly 100% adherent at Return Visit 1 (27.6%) was compared with the proportion that were over-compliant at Return Visit 2 (12.5%). The difference between the two proportions was statistically significant ($P=0.0001$; Mc Nemar's test), indicating that patients who were exactly 100% adherent at Return Visit 1 did not have equal chances as other patients to be over-compliant at Return Visit 2. Therefore, the second null hypothesis is also rejected while the corresponding alternative hypothesis is accepted.

5.11.3 Null hypothesis 3

As shown in Tables 5.20 and 5.22, the association between the clinical markers and adherence were investigated using the Fisher's exact test. There was no association between CD4 counts and adherence in this study ($P=0.287$), but there was an association between viral loads and adherence ($P=0.004$). Therefore, the third null hypothesis was accepted for CD4 counts (immunologic outcomes) but was rejected for the viral loads (virologic outcomes).

5.12 SUMMARY

In this chapter, the results of the data collected over three follow-up visits (study enrolment, Return Visit 1 and Return Visit 2) were presented. A total of 344 patients took part in the study.

Based on the mean adherence calculated for each patient's regimen, 75 patients (21.8%) were over-compliant with the normal pill count, while 43 patients (12.5%) were over-compliant with the "mixed" pill count. Twelve patients (3.5%) were over-compliant in both cases. The results also revealed that the females were more adherent than the males, and

fewer females were identified as over-compliant (non-adherence maskers) compared to the males. Over-compliance was more prevalent among the unemployed patients compared employed patients.

A comparison was then made between the patients' clinical markers results (CD4 and viral load) and their adherence levels. An association was found between viral load and adherence but not between CD4 count and adherence.

The reasons for achieving sub-optimal adherence levels were explored and presented in this chapter.

The results obtained in this study are summarised and concluded according to the study objectives in the next chapter.

CHAPTER 6

SUMMARY, CONCLUSION AND RECOMMENDATIONS

6.1 INTRODUCTION

Adherence to ART is essential for maximal suppression of viral replication and avoidance of drug resistance (Lima *et al.,* 2008; Chi *et al.,* 2009). The best response to ART is seen when adherence is 100% (Mills *et al.,* 2006), but patients are still considered adherent if they achieve an adherence level of ≥95% (Lima *et al.,* 2008; Peltzer *et al,* 2010; Rueda, 2006).

Maintenance of good adherence is a complex phenomenon as many different factors contribute to patients' medication taking behaviour (El-Khatib & Richter, 2009). It is therefore important to measure and monitor adherence correctly and on a regular basis. It is critical to validate methods (both old and new) of measuring adherence to ART because various studies have documented the limitations of current standard measures of ARV adherence (Altice & Springer, 2010; Bartlett, 2002; Godin *et al.,* 2003; Maru *et al.,* 2007; Nachega *et al.,* 2006). Treatment programmes use the various methods alone or in combination, in the absence of a gold standard with which to measure adherence (Berg & Arnsten, 2006; Chesney, 2006). The need for efficient and reliable measures of adherence has initiated debate about how best to measure medication-taking behaviour in public sector ART settings.

This study was based on a new adherence method and was conducted with the aim of investigating the ability of the "mixed" pill count method to detect deliberate masking of non-adherence to ART in a public sector practice setting in South Africa.

A **normal pill count** is defined as a procedure whereby the tablets remaining in each ARV tablet container are counted at a follow-up visit. With the **"mixed" pill count** the tablets remaining in each ARV tablet container are counted at a follow-up visit, after the pharmacist deliberately dispenses extra tablets during the previous visit, without the patient being aware of the extra tablets dispensed. The number of extra tablets dispensed is recorded in the patient's file in an encrypted format.

In this chapter, the results of the pilot study and the main study are summarised. Based on the results, a conclusion is made according to the three objectives and hypotheses that were formulated. Recommendations are made. The chapter ends with the limitations of the study.

6.2 SUMMARY OF RESULTS

Seventy-eight adult patients and 370 adult patients on a first line regimen of ART were recruited into the pilot study and the main study, respectively. At the first return visit (Return Visit 1), a standard (normal) pill count was performed and adherence (% of tablets taken) was calculated. For the repeat prescription, as part of the "mixed" pill count, three days' extra supply was dispensed without the patients' knowledge. At the second return visit (Return Visit 2), a "mixed" pill count was performed and adherence was calculated. Patients were grouped into three categories based on calculated adherence: truthfully non-adherent (<100% adherence), adherent (100% adherence) and 'over-compliant' (>100% adherence, i.e. returning to the clinic with fewer tablets than required). Exploratory interviews were conducted with truthfully non-adherent and over-compliant patients to obtain explanations for discrepancies in pill counts.

6.2.1 Summary of pilot study results

Twenty-nine (37.2%) of the recruited 78 patients completed the study. The majority of the patients who completed the study were female (21; 72.4%). Twenty-eight (96.6%) of the patients were black and spoke an African language. Only two patients (6.9%) had completed tertiary education, while 11 (7.9%) of the patients had no formal education or did not complete primary education. More than half (55.2%) of the patients were employed while 58.6% were single.

The majority of the patients (53%) were on Regimen 1b (stavudine, lamivudine and nevirapine). Forty-one percent were on Regimen 1a (stavudine, lamivudine and efavirenz), while others were on a modified form of these first line regimens, whereby the stavudine in the regimen had been substituted by zidovudine.

Based on the overall average adherence calculated for each patient's regimen, the patients were grouped into the three adherence categories (<100% adherence, exactly 100% adherence and >100% adherence). Two patients (6.9%) were over-compliant (>100% adherence) at both return visits. The proportion of patients that were over-compliant at Return Visit 1 was 13.8% and this doubled to 27.6% when the "mixed" pill count was used to measure adherence at Return Visit 2. With the "mixed" pill count at Return Visit 2, only eight patients (27.6%) were optimally adherent (exactly 100% adherence). When all the individual ARVs in each patient's regimen were taken into consideration, eleven patients (37.9%) were identified as over-compliant with one or more of the ARVs in their regimens at Return Visit 2, as opposed to eight (27.8%) that were identified as over-compliant at Return Visit 1.

The major reasons for non-adherence cited by the patients were forgetting, feeling dizzy and non-disclosure. The over-compliant patients gave the following reasons for over-compliance: throwing tablets away, having taken an overdose of the ARVs and non-disclosure/stigma.

Three of the over-compliant patients admitted that they threw their tablets away and gave the following reasons for doing so: change in body shape, possibility of social grant being discontinued, taking extra ARVs when feeling sick and throwing them away when feeling fine, not needing ARVs anymore, and knowing that the tablets would be counted at the clinic.

6.2.2 Summary of main study results

6.2.2.1. Study population

Out of the 370 patients who consented to participate in the study, 344 patients completed the study. The majority of those who completed the study (205; 59.6%) were female and 139 (40.4%) were male.

6.2.2.2. Age and gender

The average age of the patients was 40.1 years. Most of the participants (42.2%) were between the ages of 31 and 40 years. On average, the male patients were slightly older than the females (mean age 41.7 versus 38.7 years).

6.2.2.3. Race and language

Three hundred and thirty-seven participants (98.0%) were black, while the remaining seven patients were coloured. The majority of the participants (97.1%) spoke an African language. The languages most commonly spoken were Sotho (26.2% of patients) and Zulu (16.6% of patients). The least spoken language was Afrikaans (2.9% of patients).

6.2.2.4. Level of education and employment status

Only half of the participants (49.6%) had completed primary education. The proportion of males and females who completed primary education was the same (50%). Slightly more females (10.7%) than males (9.4%) had no education or did not complete primary education, while more males (5.8%) than females (4.4%) completed tertiary education. Overall, 10.2% of the participants had no formal education or did not complete primary education.

While less than half (46.2%) of all the participants were employed at the time of this study, more of the males (55.4%) were employed than the females (40.0%), Marital status

In this study, 63.4% of the participants were single and 24.7% were married. Others were either widowed (7.0%) or divorced (5%).

6.2.2.5. Duration on ART

Half of the participants (50.6%) had been on ART for longer than 24 months during the study and only seven (2.0%) had been on ART for less than six months. The participants were on ART for a median period of 24 months (females 25 months; males 23 months).

6.2.2.6. ARV regimens

Fifty-four percent of the patients were on Regimen 1a and 16% on Regimen 1b at the start of the study. Others were on modified forms of these regimens (where stavudine was replaced with zidovudine).

Eighteen (5.2%) of the patients had their regimens switched during the course of the study, three (16.7%) of whom switched from Regimen 1a to Regimen 1b because they were pregnant or planning to start a family.

6.2.3 Adherence rates

The normal pill count was used to measure adherence at Return Visit 1 and the “mixed” pill count was used at Return Visit 2.

Patients were stratified into three adherence categories at Return Visits 1 and 2 based on the mean adherence calculated for their regimens i.e. truthfully non-adherent patients (<100% adherence), adherent patients (exactly 100% adherence) and over-compliant patients (>100% adherence). For correlation of adherence to clinical markers, the adherence categories used were: truthfully non-adherent patients (<95% adherence), adherent patients (≥95-100% adherence) and over-compliant patients (>100% adherence).

6.2.3.1. Mean adherence

As shown in Table 5.6 (see Section 5.5.1), the overall average adherence for the patients was 97.2% at Return visit 1, 100.2% at Return Visit 2 and 98.7% over the two visits. The average adherence for the males (98.98%) was similar to that of the females (98.53%).

6.2.3.2. Adherence per category

The proportion of patients in the adherent category at Return Visit 1 was higher (57.6%) when the ≥95-100% threshold for optimal adherence was used compared to the proportion

of adherent patients when the 100% threshold was used (27.6%). The same trend was observed at Return Visit 2 where the proportion of adherent patients increased with the ≥95-100% threshold from 246 patients (71.5%) to 279 (81.1%).

At Return Visit 2, 75 patients (21.8%) were over-compliant with the normal pill count, while only 43 patients (12.5%) were over-compliant at Return Visit 2 with the "mixed" pill count (see Section 5.5.2, Tables 5.7 and 5.8). Of the 43 patients who were identified as over-compliant at Return Visit 2, only eight (18.6%) were previously optimally adherent (at Return Visit 1). More than half of the patients (23; 53.5%) were truthfully non-adherent at Return Visit 1 while 12 (27.9%) were over-compliant at both return visits.

6.2.3.3. Adherence to individual ARVs

Figure 5.9 (see Section 5.5.3.1) illustrates that the average adherence was below 100% (sub-optimal adherence) for all the ARVs in the patients' regimens at Return Visit 1, but adherence improved at Return Visit 2 for all the ARV medications.

Despite the fact that adherence improved for the total group at the second return visit, it got worse for the few patients who were over-compliant. Of all the ARVs, patients were mostly over-compliant on Lamzid®.

6.2.3.4. Adherence and gender

Fewer of the males were over-compliant at Return Visit 1 (19.4%) compared to the females (23.4%). At Return Visit 2, a smaller proportion of the females (9.2%) was identified as 'maskers' compared to 17.3% of the males. The term 'maskers' refers to non-adherent patients who resolve to hiding their non-adherence by manipulating their tablets in order to appear adherent. But because these patients are not aware that extra tablets were dispensed to them, they end up with >100% adherence (over-compliant). It was found that the difference in these gender proportions was statistically significant (P=0.0324; Fisher's exact test). Thus, over-compliance was significantly higher among the males than the females in this study. Furthermore, more of the females were 100% adherent in the normal pill count (58.5% versus 54.0% for males) and in the "mixed" pill count (83.9% versus 77.7%), although this difference was not statistically significant (P>0.05; Fisher's exact test).

6.2.3.5. Other sociodemographic variables and adherence

None of the other sociodemographic variables investigated in the main study was directly associated with adherence. However, a logistic regression revealed that employment status was associated with over-compliance. Unemployed patients were twice as likely as

employed patients to be over-compliant. Because over-compliance is a form of non-adherence, this finding implies that employed patients adhere better than the unemployed ones. In the pilot study, it was found that patients feared that their social grant might be discontinued if their CD4 count improves and they become fit to work again.

6.2.3.6. Clinical markers (CD4 count and viral load) and adherence

As explained in Chapter 5 (see Sections 5.5.2 and 5.8.1.4), adherence of ≥95% is generally regarded as optimal because at this level, maximal viral suppression and CD4 count improvement are observed (Ford *et al,* 2010; Lima *et al.,* 2008). Therefore for the clinical markers, the ≥95-100% adherence threshold was used.

The participants commenced ART with a median CD4 count of 109 cells/mm^3 and this increased to 377 cells/mm^3 at least six months on ART. At the end of the study, CD4 counts were available for 316 patients. The CD4 count declined for seven (2.3%) patients, stayed the same for 10 (3.2%) and increased for 299 (94.5%) patients. Out of the 299 with increased CD4 counts, 122 (40.8%) of them increased up to ≥500 cells/m^3. On average, the CD4 counts increased from 110 cells/mm^3 at ART initiation to 527 cells/mm^3 after six months or longer on treatment, meaning that the desired CD4 of ≥500 cells/mm^3 was achieved by the study participants on average. When the CD4 counts after six months or longer on ART were compared with the proportions of patients in the adherence categories (<95%, 95-100% and >100%), no association was found (P=0.287; Fisher's exact test). Therefore, adherence to medication did not appear to be related to the CD4 counts of the overall patients in this study. When only the over-compliant patients were considered, it seemed as though there could be an association between CD4 count and adherence, but this possible association needs to be further investigated.

Out of the 303 viral load readings that were available after six months or longer on ART, 249 (82.2%) were lower than detectable limits (<400 copies/mL) and 54 (17.8%) were detectable. When adherence was compared among patients with detectable and non-detectable viral loads, non-detectable viral load readings were highly associated with good adherence (≥95-100%) (P=0.004, Fisher's exact test). With regard to the over-compliant patients alone, viral load was surprisingly non-detectable after six months or longer on ART, yet these patients were not optimally adherent. The reason for viral load suppression in this group of patients is unknown.

6.2.4 Discrepancies in pill counts

Forty three of the 55 non-adherent patients and 37 of the 43 over-compliant patients agreed to be interviewed at Return Visit 2.

All, except one, of the interviewed patients always returned left-over tablets to the clinic during follow-up visits and nearly half of them (48.9%) were comfortable with this practice. Two felt uncomfortable about returning left-over tablets, seven brought the tablets because they felt it was a requirement by the ART clinic staff while others did so because they did not want to be seen as non-adherent patients.

Most of the patients kept their ARVs in the original container in which they were dispensed. Only 13 patients did not always use the original containers.

Nine patients were non-adherent because they were away from home at the time they were supposed to take their medication and they did not have their medication with them. Four non-adherent patients discovered that extra tablets were dispensed to them and claimed this was the reason why they were non-adherent (returning too many tablets) but this was not a valid reason as they returned more tablets than the extras that were dispensed to them. Other reasons for non-adherence as cited by the patients were factory fault, forgetfulness and being late for clinic appointment.

Thirteen of the over-compliant patients stated that they also discovered extra tablets in their tablet containers and explained that this was the reason why their tablets did not balance after pill count. Nonetheless, this was also not a valid reason as the calculation accounted for the extra tablets dispensed. The valid reasons provided for over-compliance were dumping, spilling of medication, taking extra tablets by mistake, children tampering with medication, and being some days late for the clinic appointment.

Six over-compliant patients admitted to pill dumping. One of these patients was identified as truthfully non-adherent, but he still said he was dumping his tablets. The admitted pill dumpers gave the following reasons for dumping: disliking stavudine, discovery of extra tablets, missing doses, non-disclosure and having many tablets remaining.

All the 80 interviewed patients cited the reasons why they had difficulty taking their medication properly on a daily basis. Eighteen (22.5%) mentioned non-disclosure and stigma as a barrier to adherence. Other barriers included pill burden, side effects, timing, forgetfulness, work, feeling sick, lack of support, change of regimen, transport / distance to clinic and stress.

6.3 CONCLUSION

The way in which the study objectives and hypotheses were addressed is detailed below.

6.3.1 Study objectives

6.3.1.1. Objective 1: Describe the incidence of adherence (exactly 100% adherence, <100% adherence, and >100% adherence) as measured by a normal pill count at the first visit, and a "mixed" pill count at the second visit for each study patient.

Adherence was calculated at each return visit using the normal pill count at Return Visit 1 and the "mixed" pill count at Return Visit 2.

The incidence of over-compliance was found to be doubled at Return Visit 2 in the **pilot study**, indicating that the "mixed" pill count was effective at detecting over-compliant patients who were not identified during the normal pill count at Return Visit 1. At the pilot study site, adherence is not monitored routinely, nor is adherence counselling given to patients on a monthly basis. A patient's adherence is only measured two weeks after ART initiation and then occasionally when the patient is already showing signs of immunological or virological failure. Ultimately, the patients participating in the pilot study achieved a lower level of adherence on average at Return Visit 2 than at Return Visit 1.

Based on the mean adherence calculated for each patient's regimen at the **main study** site, 75 patients (21.8%) were over-compliant with the normal pill count, while 43 patients (12.5%) were over-compliant with the "mixed" pill count. Twelve patients (3.5%) were over-compliant in both cases. The results also revealed that the females were more adherent than the males, and fewer females were identified as over-compliant (non-adherence maskers) compared to the males. The incidence of over-compliance and truthful non-adherence (<100% adherence) was unexpectedly lower at Return Visit 2 while the prevalence of optimal adherence (exactly 100% adherence) was higher.

Although overall average adherence improved at the main study site at Return Visit 2, the "mixed" pill count was still able to detect the 43 patients that were over-compliant, of whom only 12 (27.9%) were over-compliant at Return Visit 1.

A possible explanation for the improvement in adherence apparent from the "mixed" pill count could be due to several reasons. The main study site has a policy that when patients visit the ART clinic for follow-up and monthly prescription refill, they should come to the clinic with their remaining tablets for a pill count and, if necessary, adherence counselling. Another

possible explanation is that the counselling given by the counsellors might have been more thorough because of the presence of the researcher at the study site and the data collector being in the counselling room with the counsellor. In addition, patients themselves might have decided to impress the researcher because they knew that the study was on adherence and they wanted to appear excellently adherent for the sake of the study. Furthermore, the counsellors' knowledge of the exact adherence percentage of the patients at the first return visit and their ability to make the patients aware of their exact adherence score, may have motivated the patients to be more committed to taking their ARVs as prescribed and thus achieve better adherence levels at the second return visit.

It is therefore concluded that the "mixed" pill count is effective at detecting over-compliant patients (possible pill "dumpers" or non-adherence maskers) in a setting where patients are not counselled regularly and in a setting where regular counselling is a practice. The study highlights the important role played by adherence counselling provided by the health care workers at the ART clinics, because the provision of targeted counselling to patients reinforces to patients why they should take their ARVs as prescribed.

At the main study site, it was concluded in this study that employed patients are more adherent than the unemployed ones, possibly because the employed ones could afford transport to the clinic for follow-up visits and collect prescription refill promptly. Sociodemographic variables were not investigated in the pilot study, but it was observed that patients that were on social grant were more likely to be non-adherent than those who were not on social grant. This was because the patients on social grant were concerned that their grant would be withdrawn if they were adherent to their ARV medication and they were declared fit to go back to work.

6.3.1.2. Objective 2: Explore patients' explanations for discrepancies in pill counts.

This objective was achieved through semi-structured interviews administered by the researcher and the data collector to the non-adherent (<100% adherence) patients and the over-compliant (>100% adherence) patients at both the pilot and main study sites.

At the study sites, being away from home, factory fault, forgetfulness and being late for clinic appointments were cited as some of the reasons for non-adherence. The most common reasons for over-compliance were "dumping", spilling and overdose.

The patients who admitted to "dumping" of medication at the two study sites stated that they did so because they had disclosure problems, disliked the tablets or missed some doses and did not want to appear non-adherent, and fear that their social grant might be withdrawn,

Non-disclosure/stigma, pill burden, side effects and timing of medication emerged as the major barriers to adherence among all the interviewed patients.

Based on the findings from this study, it is imperative that adherence support should be made available to all patients, as patients have various challenges that hinder them from taking their medication properly on a daily basis.

6.3.1.3. Objective 3: Record and compare results of routine CD4 count and viral load testing, in patients with <95% adherence, <95 - 00% adherence, and >100% adherence, as measured by the normal pill count and the "mixed" pill count.

This objective was not covered during the pilot study as the aim of the pilot study was to test the study method and logistics.

The median CD4 count increased for the majority of the study participants after six months or longer on ART. The median viral load improved from ART initiation and was lower than detectable (<400 copies/mL) after six months or longer on ART.

Optimal adherence (95-100% threshold) did not appear to be associated with CD4 count (*P*=0.287; Fisher's exact test) but was highly associated with viral load (*P*=0.004; Fisher's exact test) after six months or longer on ART. On the contrary, among the over-compliant patients, it is possible that CD4 was associated with adherence.

6.3.2 Study hypotheses

Three null hypotheses were formulated for this study, and it was expected that these hypothesis would be rejected. The study hypotheses were not tested during the pilot study.

As shown in Table 5.27 (see Section 5.11), the first null hypothesis of the study stated that the proportions of patients returning too few dosage units (over-compliant patients) are the same with both pill count methods (normal pill count and "mixed" pill count). These proportions were not the same (21.8% with the normal pill count versus 12.5% with the "mixed" pill count) (*P*=0.001; Mc Nemar's Test). Although this null hypothesis was rejected, the proportion of over-compliant patients decreased with the "mixed" pill count rather than increasing as was the case in the pilot study.

The second null hypothesis was that the patients who achieved exactly 100% adherence at Return Visit 1 (normal pill count) are equally likely as other patients to be over-compliant at Return Visit 2 ("mixed" pill count). The patients who were exactly 100% adherent at Return

Visit 1 (95; 27.6%) were compared with those who were over-compliant at Return Visit 2 (43; 12.5%) at Return Visit 2. The difference was statistically significant (*P*=0.0001; Mc Nemar's Test). Therefore, this hypothesis was also rejected.

The last null hypothesis was that the health outcomes (CD4 count and viral load) of patients with >100% adherence, ≥95-100% adherence and <95% at Return Visit 2 are similar. Fisher's exact test revealed that adherence was not associated with CD4 count (*P*=0.287) but was associated with viral load (*P*=0.004). This result implies that the health outcomes of the patients are the same with regard to CD4 counts but are different with regard to viral load after six months or longer on ART treatment. Hence, the null hypothesis was only rejected for viral load and adherence.

6.4 RECOMMENDATIONS

The following recommendations are made based on the results of the study:

6.4.1 Recommendations to promote adherence and patient care

- **Return of left-over tablets and record keeping.** Patients should always be encouraged to bring their left-over ARVs with them whenever they visit the clinic for follow-up. This practice will help the pharmacist and counsellor to keep track of the number of tablets in the patient's possession. Clinic personnel should be encouraged to document pill count results and calculate the actual adherence percentage for all patients, at least periodically. The pill count sheet (Appendix C) developed for this study is a useful tool to achieve this and could be used in ARV clinics.
- **Regular counselling**. Patients should be counselled every time they visit the clinic for their repeat prescription and not only when there is virologic failure or a sharp drop in CD4 cell count. During counselling, the percentage adherence achieved, should be communicated to the patient.
- **Implement different methods of measuring adherence.** A number of methods should be used intermittently in order to correctly assess patients' adherence to treatment. The "mixed" pill count, in particular, should be practiced occasionally for patients who are suspected of pill manipulation.
- **Patient empowerment.** Patients who are treatment-experienced and who have a good record of consistent optimal adherence should be trained and empowered as adherence counsellors. These people can then assist with pill counts in the clinic and also possibly share their ART experience with the new patients initiated on ARVs.

- **Standard laboratory results turn-over time.** The laboratory should have a standard operating procedure or a policy to specify how long the clinic should wait before receiving the blood results (CD4 and viral load especially). This way, clinical decisions relating to the CD4 counts and viral load readings would be made promptly.
- **Further investigation or monitoring of over-compliant patients in terms of clinical markers.** As over-compliant patients are a special and manipulative group of patients, healthcare workers are encouraged to go beyond the call of duty to ensure that the clinical markers of these patients are monitored regularly. This way, the clinical markers will always be a reference point whenever pill "dumping" or manipulation is suspected.

6.4.2 Recommendations for future research

- **Study repeat.** A similar study needs to be repeated at an ART site where regular counselling is not a routine practice. This will help to evaluate if the "mixed" pill count is indeed capable of detecting patients who mask their non-adherence by manipulating or dumping their ARVs as seen in the pilot and main studies.
- **Longer study period.** This study was conducted over three follow-up visits for the patients. However, it is a known fact that adherence varies over time, so a similar study needs to be conducted over a longer period of time.
- **Data collection instruments.** The pill count sheet and interview guides used in this study are recommended for use in subsequent follow-up studies in order to obtain comparable results. The pill count sheet developed for this study will enable the counsellor and pharmacist to calculate and quantify the patients' precise adherence percentage and thus counsel them based on the quantified adherence results.

6.5 LIMITATIONS OF THE STUDY

The study had some notable limitations, and they include the following:

- The sample for this study was very small both for the pilot study and the main study, and the sample size was further decreased due to the dropout/discontinuation rate.
- The process of data collection and enrolment of patients in to the study required more personnel than was available, so this contributed to the low sample size in the main study.

- The fact that there was a data collector present in the counselling room seemed to have influenced the counselling behaviour of the counsellor, which ultimately led to an improvement in the adherence levels of the main study patients.
- Bias could have been introduced by the fact that very few patients who were on ART for less than six months were enrolled into the study.

6.6 CLOSURE

Overall, patients achieved fairly high adherence levels during the study period, although sub-optimal adherence was still a problem in some patients.

This study highlights the important role played by adherence counselling provided by the healthcare workers at the ART clinics, because the provision of targeted counselling to patients reinforces to them why they should take their ARVs as prescribed.

The study indicated that the “mixed” pill count method is capable of detecting deliberate masking of non-adherence. Application of this method to a larger sample will help to estimate the frequency of manipulation of pill counts by patients. It will also assist to provide insight to the reasons for this behaviour and give a better understanding of the extent of actual non-adherence. Periodic implementation of the “mixed” pill count method is envisaged to assist clinic staff to better identify non-adherent maskers and allow for more timely intervention in order to improve patients’ medication behaviour and treatment outcomes.

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APPENDICES

Appendix A1: University of Limpopo participant's consent form (English)

UNIVERSITY OF LIMPOPO (Medunsa Campus) PARTCIPANT'S CONSENT FORM

Statement concerning participation in a Research Project

PROJECT: MEASURING ADHERENCE TO ANTIRETROVIRAL THERAPY WITH A PILL COUNT AT NTSHEMBO CLINIC

I have heard the aims and objectives of the proposed study and was provided the opportunity to ask questions and given adequate time to rethink the issue. The aim and objectives of the study are sufficiently clear to me. I have not been pressurised to participate in any way.

I understand that participation in this Project is completely voluntary and that I may withdraw from it at any time and without supplying reasons. I understand that all information provided will be kept confidential.

I know that this Project has been approved by the Research and Ethics Committee of the University of Limpopo (Medunsa Campus) and Mamelodi Hospital. I am fully aware that the results of this Project will be used for scientific purposes and may be published. I agree to this, provided my privacy is guaranteed.

I hereby give consent to participate in this Project.

....

Name of participant Signature of participant

....

Place Date Witness

Statement by the researcher

I provided verbal information regarding this Project.

I agree to answer any future questions concerning the Project as best as I am able.

I will adhere to the approved protocol.

....…… …….

Name of researcher Signature Date Place

Appendix A2: University of Limpopo participant's consent form (Tswana)

FOROMO-TUMALANO YA MOTSAYAKAROLO YA UNIBESITHI YA LIMPOPO (KHAMPASE YA MEDUNS)

Polelo ya go tsaya karolo mo porojekeng ya dipatlisiso.

POROJEKE: TEKNYETSO YA KGOMARELO MO KALAFING YA ANTIRETROVIRAL KA PALO YA DIPILISI KWA KLINIKING YA NTSHEMBO

Ke utlwile maitlhomo le maikaelelo a thuto e e tshitshintsweng e bile ke tilwe tshomo ya go botsa dipotso le go fiwa nako e e lekaneng go akanya ka ntlha e. Maitlhomo le maikaelelo a thuto e a a tlhaloganyesega. Ga ke a gatelelwa go tsaya karolo ka gope.

Ke tlhaloganya gore go tsaya karolo mo porojekeng e ke boithaopo le gore ke ka ikgogela morago nako nngwe le nngwe kwa ntle le go neela mabaka. Ke tlhaloganya gore tshedimosetso e e tla nna khupamarama.

Ke itse go Porojeke e e amogetswe ka komiti ya Dipatlisiso le Maitshwaro ya Unibesithi ya Limpopo (Khampase ya Medunsa) le Bookelo jwa Mamelodi. Ke itse gore dipholo tsa Porojeke e di tla dirisiwa mo mabakeng a kitso le phasalatso. Ke dumalana le se, ya fela khupamarama e netefaditswe.

Ke dumalana go tsaya karolo mo Porojekeng.

....

Leina la motsayakarolo Tshaeno ya motsayakarolo

....

Lefelo Letlha Paki

Polelo ka mmatlisisi

Ke neelane ka tshekemosetso ya molomo ka ga porojeke e.

Ke dumalana go araba dipotso ka ga porojeke e mo isagong ka moo ke ka kgonang.

Ke tla kgomarela kano ee amogetsweng.

....

Leina la mmatlisisi Tshaeno Letlha Lefelo

Appendix B1: Baseline demographic questionnaire (English)

BASELINE DEMOGRAPHIC QUESTIONNAIRE

Patient Study ID:..... Date: …….. Data Collector: ……

Greet the patient and introduce yourself.

Thank you very much for your willingness to participate in the study.

Again, we guarantee that your privacy will be protected, the information gathered will only be used for this study and your name will not be mentioned anywhere. If you agree to this, we need you to sign a consent form. Would you mind signing this form to show that you agree to participate?

Thank you, because you are prepared to spend time with us in this study, it will help us to better understand antiretroviral treatment and adherence.

1) Gender

1. Male	2. Female

2) Date of birth

dd	mm	Yyyy

3) Race

1. Black	2. Coloured	3. Asian	4. White

4) Language

1. English	2. Afrikaans	3. Zulu	4. Tswana	5. Sotho	6. Other (please specify)

5) Highest level of education obtained

1.	None / primary not completed	
2.	Primary completed	
3.	Secondary (Matric)	
4.	Tertiary or vocational	

6) Employment status

1. Employed	2. Unemployed

7) Marital status

1. Single	2. Married	3. Widowed	4. Divorced

8) Contact number (optional)

9) Clinical data (last two readings, recorded at Return Visit 2)

CD4 Count

1	cells/mm³	Date:
2	cells/mm³	Date:

Viral Load

1	cells/mm³	Date:
2	cells/mm³	Date:

10) ARV commencement date

Dd	mm	yyyy

Comments / observations

_____

_____

_____

_____

Appendix B2: Baseline demographic questionnaire (Tswana)

POTSOLOTSO YA BOTSO KA GA MOTSAYAKAROLO

Itshupo ya Thuto ya molwetse:..... Letlha:……..

Motsayatshedemosetoso: ……

Dumedisa molwetsi o mo ikitsise.

Ke go lebogo thata go eletsa, go tsaya karolo mo thutong e.

Gape, re go netefaletsa gore khupamarama e tla sireletswa, tshedimosetso e e kgobokan tsweng e tla dirisetswa fela thuto e mme leina la gago ga le kitla le umakwa gope. Fa o dumalana le se, re go kopa gore o saene foromo-tumalano. A o tla tshwenyega go saena foromo e go supa fa o dumalana go tsaya karolo.

Re a leboga, ka gore o ipaakanyeditse go nna nako le rona mo thutong e, kalafi ya Antiretroviral le kgomarelo ya yona.

1) Bong

1. Tona	2. Namagadi

2) Letlha

letsatsi	kgwedi	ngwaga

3) Lotso

1. Bantsho	2. Bammala	3. Ma-Asia	4. Basweu

4) Puo

1. se-Esimane	2.se-Buru	3. se-Zulu	4.Setswana	5. Sesotho	6. E nngwe (tswee-tswee tlhalosa)

5) Maemo a thuto a a kwa godimo

1.	Ga go epe / poraemari ga e a fediwa	
2.	Poraemari e feditswe	
3.	Sekondari (Marematlou)	
4.	Thuto-kgolwane kgotsa ithutelo-tirong	

6) Maemo a tsa tiro

1. Dira	2. Motlhoka tiro

7) Maemo a lenyal

1. Nosi	2. Nyetse / nyetswe	3. Tlhokafaletswe	4. Tlhadile

8) Momoro-i kgolahanyo (itlhopelo)

9) Tshedimosetso ya se-kliniki (dipalo tsa bofelo tse pedi, di kwadilwe ka ketelo ya bobedi)

Palo ya CD4

1	disele/mm³	Letlha:
2	disele/mm³	Letlha:

Viral Load

1	disele/mm³	Letlha:
2	disele/mm³	Letlha:

10) Le tsatsi la mathomo la go nwa ditlhare

letsatsi	kgwedi	ngwaga

Dikakanyo tse dingwe gotsa ditshwaelo.

_____
_____
_____
_____
_____
_____
_____

Appendix C: Pill count sheet

Patient Study ID:..... File Number: .....

Visit (Baseline) Date:..... Pharmacist's initial: …….. Data collector's initial: ……..	Stavudine / Zidovudine	Lamivudine	Efavirenz	Nevirapine	Lamzid®
Returned					
Dispensed					
Total taken home					
Return Visit 1 Date:..... Pharmacist's initial: …….. Data collector's initial: ……..	Stavudine / Zidovudine	Lamivudine	Efavirenz	Nevirapine	Lamzid®
Returned					
Taken (dispensed – returned)					
Adherence (not returned/monthly dose)					
Dispensed					
+ Extra (mixed pill count)					
Total taken home (sum of white fields)					
Return Visit 2 Date:..... Pharmacist's initial: …….. Data collector's initial: ……..	Stavudine / Zidovudine	Lamivudine	Efavirenz	Nevirapine	Lamzid®
Returned					
Taken (dispensed – returned)					
Adherence (not returned/monthly dose)					
Dispensed					
Total taken home (sum of white fields)					

Data collector and dispensing pharmacist to complete white fields; researcher to complete or check shaded fields

Do you always take all your doses from the original container? Please explain. [Prompt whether the patient keeps his/her ARVs in another container]

Baseline: _____

_____

Return visit 1: _____

_____

Return visit 2: _____

_____

Appendix D1: English interview guide – for overcompliant patients (non-adherence maskers)

Patient Study ID:..... Date: ……. Data Collector: ……

Data collector: *The following questions serve as a guideline to determine why the patient has been overcompliant (suspected of pill dumping).*

Because it is not easy to talk and write at the same time, we would like to record this interview so that we can refer to it later for more information. Do you permit us to do so?

Note: If patient does not allow recording, go on with the interview without recording, but try as much as possible to write down everything the patient says.

We know that it is not easy to always take all your doses of ARVs at the right time and that many people on ART find it difficult and often miss doses.

1) Are these tablets the only ones that you have left? Prompt on what happened to the extra tablets.

_____

_____

_____

2) Because you are part of this study, all patients do not get the same number of tablets and we have a record of how many tablets you were given last month. Prompt again on the missing tablets.

_____

_____

_____

3) It could be very dangerous if you take an overdose of your ARVs. You can also experience unnecessary serious side effects. Did you actually take the extra tablets? Prompt again on missing tablets, e.g., ask if the tablets were spilled, if he/she gave somebody, etc.

_____

_____

_____

4) Can you tell me what makes it difficult for you to take your ARVs on a daily basis?

_____

_____

_____

5) In the last month, did you always take all your doses from the original container? Please explain. [Prompt whether the patient kept his/her ARVs in another container]

_____

_____

_____

Other observations or comments

_____

_____

Appendix D2: Tswana interview guide – for overcompliant patients (non-adherence maskers)

KAELO YA POTSOLOTSO – YA BALWETSI BA BA IKAMANYANG PHETELELA LE KALAFI (BAFITLHI BA GO SA KGOMARELE KALAFI)

Itshupo ya Thuto ya molwetse :……. Letlha :…….

Motsayatshedemosetoso :……

Motsaya tshedimosetso: *Dipotso tse di latelang ke ntlhakaelo go supa gore ke ena molwetsi a ntse a ikamanya phetelela le kalafi (palaelo ya go latlha dipilisi.*

Ka fa go se bonolo go bua o tla o kwala ka nako e le nngwe, rata go gatisa potsolotso e gore re tle re boele kwa go yona morago go bona tshedimosetso e e tletseng. A o a re letla?

Ela tlhoko: Fa molwetsi a sa letlelele kgatiso, tswelela ka potsolotso a sa gatisi, mme leka ka moo o ka kgonang go kwala sengwe le sengwe se molwetsi o se buang.

Re a itse gore ga go bonolo go tsaya dipilisi tsa gago tsa di – ARV ka nako e e siameng le gore batho ba le bantsi ba ba jang de-ARV ba bona go le boima mme gangwe le gape ba tlodisa go ja dipilisi.

1) A dipilisi tse ke tsona fela tse di setseng? Kgotlha ka ga gore go diragetseng ka dipilisi tse dingwe.

_____

_____

_____

2) Ka fa o le karolo ya thuto e, balwetsi botlhe gab a mogele palo e le nngweya dipilisi mme re na le sesupo sa palo ya dipilisi e o e neilweng kgwedi e e fetileng. Kgotlha gape ka dipilisi tse di tlhaelang.

_____

_____

_____

3) Go ka nna kotsi thata fa o ka feta selekanyo sa di-ARV. O ka itemogela ditla morago tse di sa tlhokegeng. A tota o jele dipilisi tse dingwe? Kgotlha gape ka dipilisi tse di tlhaelang, sekai, botsa fa e le gore dipilisi di tshologile, fa e le gore o file mongwe, jj.

_____

_____

_____

4) A o ka mpolelela gore ke eng se se go thatafaletsang go tsaya di-ARV tsa gago letsatsi le le letsatsi?

_____

_____

_____

5) Mo kgwedi e fetileng, a o ne o nwa dipilisi tsa gago go tswa mo thegwang ya tsona? [Botsisa gore a molwetsi o ile a ntsha dipilisi mo thegwaneng ya tsona, mme a dirisa e eseng yona].

_____

_____

_____

Ditebo tse dingwe kgotso ditshwaelo

_____

_____

_____

Appendix E1: English interview guide – for truthful non-adherent patients

Patient Study ID:..... Date:…….. Data Collector:……

Data collector: *The following questions serve as a guideline to determine how the patients feel about returning left-over tablets*

Because it is not easy to talk and write at the same time, we would like to record this interview so that we can refer to it later for more information. Do you permit us to do so?

Note: If patient does not allow recording, go on with the interview without recording, but try as much as possible to write down everything the patient says.

We know that it is not easy to always take all your doses of ARVs at the right time and that many people on ART find it difficult and often miss doses.

1) It is good that you admit not taking all your tablets. How do you feel about returning the remaining tablets?

_____

_____

_____

2) Do you always return your left-over tablets to the clinic?

YES	NO

If no, please explain why not. Prompt on what happened to the tablets not returned.

_____

_____

_____

2) Can you please tell me why you did not take all your tablets for this last month? Prompt for reasons.

_____

_____

_____

4) In the last month, did you always take all your doses from the original container? Please explain. [Prompt whether the patient kept his/her ARVs in another container]

_____

_____

_____

Other observations or comments

_____

_____

_____

Appendix E2: Tswana interview guide – for truthful non-adherent patients

KAELO YA POTSOLOTSO – YA BALWETSI BA BA BOAMMARURI BA BA SA KGOMARELENG KALAFI

Itshupo ya Thuto ya molwetse :……. Letlha :……..

Motsayatshedemosetoso :……

Motsaya tshedimosetso: *Dipotso tse di latelang ke ntlhakaelo go supa gore maikutlo a balwetsi ke eng ka ga go busa dipilisi tse di setseng.*

Ka fa go se bonolo go bua o tla o kwala ka nako e le nngwe, rata go gatisa potsolotso e gore re tle re boele kwa go yona morago go bona tshedimosetso e e tletseng. A o a re letla?

Ela tlhoko: Fa molwetsi a sa letlelele kgatiso, tswelela ka potsolotso a sa gatisi, mme leka ka moo o ka kgonang go kwala sengwe le sengwe se molwetsi o se buang.

Re a itse gore ga go bonolo go tsaya dipilisi tsa gago tsa di – ARV ka nako e e siameng le gore batho ba le bantsi ba ba jang de-ARV ba bona go le boima mme gangwe le gape ba tlodisa go ja dipilisi.

1) Go go ntle gore o amogela go sa tseye dipilisi tsa gago tsotlhe. O I kutlwa jang ka ga go busa dipilisi tse di setseng?

   _____

   _____

   _____

2) A ka gale o busetsa dipilisi tsa gago tse di setseng kwa kliniking?

EE	NYAA

Fa go se jalo, tswee-tswee tlhalosa gore ke eng go se jalo. Kgotlha ka ga gore go diragalang ka dipilisi tse di sa busiwang.

_____

_____

3) A o ka mpolelela gore ke eng o sa ja dipilisi tsa gago tsotlhe mo kgweding e e fetileng? Botsisisa gape, o battle mabaka otlhe.

_____

_____

_____

4) Mo kgweding e fetileng, a o ne o nwa dipilisi tsa gago tswa mo thegwaneng ya tsona? (Botsisisa gore a molwatsi o ile a ntsha dipilisi mo thegwaneng ya tsona, mme a dirisa e eseng yona).

_____

_____

_____

Ditebo tse dingwe kgotso ditshwael

_____

_____

_____

Appendix F: Application for MREC approval

APPLICATION FORM FOR PROPOSED RESEARCH PROJECT AT THE UNIVERSITY OF LIMPOPO
Medunsa Campus

A. **PARTICULARS OF APPLICANT/CHIEF RESEARCHER**

First name: T.A. Surname: Adeyinka Title: Ms
Department: Pharmacy Tel: 012 – 521 5058

School: Health Care Sciences Internal Box No: 218

E-mail address (Researcher): Tadeyinka@ul.ac.za

E-mail address (Supervisor, if applicable): hmeyer@ul.ac.za

B. **DETAILS OF RESEARCH PROJECT**
(Tick appropriate block(s) with a 'x'

1.a New project [X] or : Continuation of project [ ]

1.b Independent research : [ ] or : Contract research: [ ]

Post-graduate research: [X] or : Undergraduate research : [ ]

Degree (specify): MSc (Med) in Pharmacy

At which university is the degree registered? University of Limpopo (Medunsa Campus)

2.a. Title of project: Investigation of the method of "mixed pill counts" as a tool to detect deliberate masking of non-adherence to antiretroviral therapy at Ntshembo Clinic, Mamelodi Hospital

b. Co-workers (Not for post-graduate research. See Guidelines)

Name	Department/Institution	Signature
None		

c. Research Coordinator (In the case of independent or contract research)

Name	Department/Institution	Signature
None		

1

d. Supervisor (In the case of post-graduate research)

Name	Qualification	Department/ Institution	Signature
Dr JC Meyer	PhD	Pharmacy	

e. Co-supervisor (In the case of post-graduate research)

Name	Qualification	Department/Institution	Signature
Dr B Summers	PhD	Pharmacy	
Ms S Johnson	BSLA; enrolled for MPH	Foundation for Professional Development	

f. Hospital Superintendent/Health Care Manager

Name	Department/Institution	Signature
Mrs B Matlala	Ntshembo Clinic, Mamelodi Hospital	
Dr T Rossouw	Masibambane Clinic, Tshwane District Hospital	

g. Other involved departmental heads

Name	Department/Institution	Signature
N/A		

C. **SPECIAL REQUIREMENTS**

Will the research involve the following:

	Yes	No		Yes	No
Experimental animals		X	Approval from Animal ethics Committee attached (separate application form required)	NA	
Special apparatus		X	Is it available at Medunsa?	NA	
Special drugs (medicaments)		X	Explanation of who will supply the drugs attached	NA	
Radio isotopes		X	Completed radio Isotopes form attached (Appendix 4)	NA	
Special laboratory facilities		X	Is it available at Medunsa? If no, attach a statement of requirements	NA	
Electron microscopy		X	Completed Electron microscope form attached (Appendix 3)	NA	
Health care services	X		Signature of health care manager attached	X	
Statistical analysis	X		Has a statistician been consulted? If yes, attach form. (Appendix 2) If no explain.	X	

2

D. **ETHICAL ISSUES**

1. *Indemnity*

If a hospital (human, dental or veterinary) will be involved, please attach the written approval of the Superintendent. Should the use of the service laboratories be required, attached a letter of consent of the hospital management that this is in order.

2. *Consent*

Will patients/human volunteers form part of the experiment/trial/survey? If so, kindly modify the attached form, specifically for your project. (Appendix 1)

E. **BUDGET**

Who will finance this project? (Tick appropriate block with a "x")

University of Limpopo (Medunsa Campus)		Health Department		Self		Other (specify)	X
						Foundation for Professional Development	

Please indicate the institutions where application has been made for financial support or where it is intended to apply for financial support.

MRC		NRF		CSD		Other (specify)	
						NA	

NB: Approval of the research project does **NOT** imply that the requested funds will be made available to the applicant.

G. **DECLARATION BY RESEARCHER(S)**

Should this project be approved, I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research. I/we guarantee to ensure compliance with these approved conditions. Furthermore, I/we undertake **not to change the procedure as detailed in the protocol but will submit a further application to the Research Committee if changes become necessary**

SIGNATURE: _____ **DATE:** 11/05/09
CHIEF RESEARCHER: TITILOPE A. ADEYINKA

SIGNATURE: _____ **DATE:** 11/5/09
HEAD OF DEPARTMENT

SIGNATURE: _____ **DATE:** 12/05/2009
DIRECTOR OF SCHOOL

Approved 12/05/09

3

Appendix G: MREC Clearance certificate

UNIVERSITY OF LIMPOPO
Medunsa Campus

P O Medunsa
Medunsa
0204
SOUTH AFRICA

Tel: 012 - 521 4000
Fax: 012 - 560 0086

MEDUNSA RESEARCH & ETHICS COMMITTEE

CLEARANCE CERTIFICATE

MEETING: **05/2009**

PROJECT NUMBER: MREC/H/82/2009: PG

PROJECT :

Title:	Investigation of the method of "mixed pill counts" as a tool to detect deliberate masking of non-adherence to antiretroviral therapy at Ntshembo Clinic, Mamelodi Hospital.
Researcher:	Ms TA Adeyinka
Supervisor:	Dr JC Meyer
Co-supervisor:	Dr S Summers & Ms S Johnson (Foundation for Professional Development)
Hospital Superintendent:	Mrs B Matlala (Ntshembo Clinic, Mamelodi Hospital) Dr T Rossouw (Masibambane Clinic, Tshwane District Hospital
Department:	Pharmacy
School:	Health Care Sciences
Degree	MSc (Med) in Pharmacy

DECISION OF THE COMMITTEE:

MREC approved the project.

DATE: 09 June 2009

RESEARCH & PARTNERSHIP
2009 -06- 09
MEDUNSA CAMPUS

PROF GA OGUNBANJO
CHAIRPERSON MREC

Note:
i) **Should any departure be contemplated from the research procedure as approved, the researcher(s) must re-submit the protocol to the committee.**
ii) **The budget for the research will be considered separately from the protocol.**
PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES.

African Excellence - Global Leadership

Appendix H: Permission to conduct pilot study at Tshwane District Hospital

Permission to access Records / Files / Data base at

Tshwane District Hospital / Clinic

TO: Mrs OT Ubogu **FROM : Ms Titi Adeyinka**

Chief Executive Officer/Information Officer Investigator

c/o Dr Theresa Rossouw
Masibambane Clinic
Tshwane District Hospital

Re: Permission to do research at Masibambane Clinic, Tshwane District Hospital

TITLE OF STUDY: Investigation of the method of "mixed pill counts" as a tool to detect deliberate masking of non-adherence to antiretroviral therapy at Ntshembo Clinic, Mamelodi Hospital

This request is lodged with you in terms of the requirements of the Promotion of Access to Information Act. No. 2 of 2000.

I am a researcher / post-graduate student at the Department of Pharmacy at the University of Limpopo, Medunsa Campus. I am working with Dr JC Meyer, Dr B Summers, Ms S Johnson (FPD) (study supervisors).

I herewith request permission on behalf of all of us to conduct a pilot study on the above topic on the hospital / clinic grounds.

This study involves access to patient records.

The researchers request access to the following information: clinical files, record books and data bases.

We intend to publish the findings of the study in a professional journal and/ or to present them at professional meetings like symposia, congresses, or other meetings of such a nature.

We intend to protect the personal identity of the patients by assigning each individual a random code number.

We undertake not to proceed with the study until we have received approval from the Faculty of Health Sciences Research Ethics Committee, University of Pretoria.

Yours sincerely

Ms Titi Adeyinka (Principal Investigator)

Permission to do the research study at this hospital / clinic and to access the information as requested, is hereby approved.

Title and name of Chief Executive Officer: O. I. UBOGU

Name of hospital / clinic: TSHWANE DIST HOSPITAL

Signature:

Date: 15/05/09.

1 Title(s) and surname(s) of co-investigator(s) / supervisor(s)

Appendix I: Statistical analysis consultation (Medunsa)

APPENDIX 2

STATISTICAL ANALYSES

The Chairperson,
Medunsa Campus Research and Ethics Committee (MCREC),
Box _____
UNIVERSITY OF LIMPOPO
Medunsa Campus

Dear Sir/Madam

STATISTICAL ANALYSES

I have studied the research protocol of

_____T.A. Adeyinka_____

titled: Investigation of the method of "mixed pill counts" as a tool to detect deliberate masking of non-adherence to antiretroviral therapy at Ntshembo Clinic, Mamelodi Hospital

and I agree/~~do not agree~~ * to assist with the statistical analyses.

Yours sincerely,

_____
Signature: Statistician

____Monika Zweygarth_____
Name in block letters

____11 May 2009_____
Date

* Please delete which is not applicable. If you do not agree to assist with the statistical analyses, please provide reasons on a separate sheet.

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