

**THE IMPACT OF AN ELECTRONIC MEDICATION
MONITORING SYSTEM ON THE ADHERENCE OF
PATIENTS TO ANTIRETROVIRAL MEDICATION AT
THE TSHEPANG CLINIC,
DR GEORGE MUKHARI HOSPITAL**

by

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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), in the Faculty of Health Sciences, School of Health Care Sciences, has not previously been submitted by me for a degree at this or any other university; that it is my work in design and execution, and that all material contained herein has been duly acknowledged.

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SUMMARY

Introduction: The Human Immunodeficiency Virus (HIV) pandemic has become a global “monster” and much effort and funds have been channelled by various stake holders to change the deadly course of this threatening disease. Adherence has been identified as a critical element in optimal treatment of the disease with antiretroviral (ARV) medicines.

A literature review was conducted on relevant facets of the HI virus, Acquired Immune Deficiency Syndrome (AIDS), disease prevention and treatment with ARVs, treatment obstacles, the importance of a sustained adherence level of at least 95% and the treatment interventions to promote medication adherence.

Objectives: The objectives of this study were to evaluate the e-MuM electronic monitoring system (electronic microprocessor, reminder unit [a specialised wristwatch] and software program) for practicality, impact and effectiveness on ARV adherence, to test the ease of use for the patient and pharmacist, to get feedback from patients and clinic staff and finally to make recommendations concerning possible adaptations and the ideal use of the e-MuM system.

Method: The design was a four phase, prospective, randomised experimental, longitudinal study, conducted at the Tshepang Clinic of the Dr George Mukhari Hospital in Garankuwa using 210 volunteer patients. . After signing a consent form, patients were randomized into test and control groups, balanced according to gender and time on treatment. At the end of the baseline phase (only written adherence data collection), both groups were given their stavudine tablets in an electronic monitoring (e-MuM) container (from the end of the second month). The test group received interventions in the form of a alarm watch reminder unit (end of Phase 1), followed by visual (based on e-MuM generated graphs) and verbal feedback (end of Phases 2, 3 and 4). Other adherence tools used to evaluate and compare adherence in this study included a self-assessment questionnaire for gathering quantitative and qualitative data, visual analogue scale (VAS), 2-day and 7-day recall, tablet counts and the biological markers of the patients at the start and end of the study

Results: There was no statistically significant difference between demographic data of the two groups at any point during the study. The mean time on treatment of the test group patients increased relative to baseline by the end of the study, which follows a reported trend that patients who have been on treatment for longer, tend to remain in studies.

The e-MuM system revealed a large scattering of adherence results in both groups. Medication taken within an hour of the correct time was regarded as “strict” adherence and that taken at any time on the correct day as “lenient” adherence. The most significant increase in mean strict adherence was from Phase 2 to Phase 4 (after two verbal and visual feedback sessions). The adherence increase for the test group was 18.8% and 14.3% for the control group. The mean strict adherence level was 36.1% for the test group and 29.8% for the control group for the full period. The mean lenient adherence for the full period was 45.5% for the test group and for the control group it was 36.6%. The difference between the two groups in adherence increase over time, did not reach the statistically significant level of $P < 0.05$.

One of the difficulties in the study data interpretation of the self-reported adherence was due to patients’ decanting habits. Patients were asked to state whether and how often they removed their tablets from the original container into another container (decanting). Decanting habit options included daily, weekly, no decanting and unspecified decanting habits. Patients’ decanting habits varied greatly. From decanting data available for a total of 209 patients, a majority (145) reported at least two different types of decanting habits for the study period, while five patients reported every decanting habit. Patients statements on their decanting habits were compared with the data recorded by the e-MuM system, but did not correlate at an individual level and were found not reliable enough to permit adjustment of the adherence levels that were calculated by the e-MuM system.

Although self-assessment adherence measures exhibited a high degree of correlation, this was in stark contrast with the data obtained from the e-MuM. The mean adherence according to the Visual Analogue Scale (VAS) for the test group and control group was 87.7% and 88.4% respectively. Some of the study participants (11%) marked their adherence out of bounds on the 10cm solid line used for VAS. Despite frequent explanations from staff, some patients were not able to understand the abstract nature of the VAS. This observation may be related to patient educational level, as the majority of study participants (82%) had an incomplete secondary education or lower. In addition, clinic staff and data collectors commented that patients did not want to admit to being non-adherent.

The mean stated adherence with the 7-day recall was 93.6% for the test group and 92.8% for the control group patients. The 2-day recall was omitted at the end of Phase 2. Adherence measured with tablet counts could not be used as it was only available in 60% of visits by test group patients and 64% of control group patients, as a result of patients not returning their remaining tablets at follow-up visits.

Although positive tendencies in biological markers (CD4 and viral load [VL]) were evident towards the end of the study, differences between the groups did not reach statistical significance. The mean increase in CD4 count in the test group over the full period was 76.2 cells/mm³ and the number of patients in the test group with VL < 400 copies/ml increased from 72% to 89%. The mean increase in CD4 count in the control group was 72.2 cells/mm³ and the number of patients with VL < 400 copies/ml increased from 65% to 75%.

Conclusion: The results of the study illustrated that the e-MuM system could be integrated in a normal clinic routine but additional staff and facilities (hardware) would be needed. The e-MuM system could be particularly helpful with new or suspected non-adherent patients. The disadvantage of the electronic monitoring system is its ability to monitor only one drug per container. It could be used with a fixed combination single tablet regimen.

Patients were positive about the reminder unit as a tool to improve adherence. Doctors had mixed opinions of the usefulness of feedback graphs in monitoring adherence. Some patients disagreed with feedback results and this may reflect the anomalies caused by the range of decanting habits.

The test group reached higher average rates of adherence than the control group, as judged by e-MuM recorded events, but differences were not statistically significant. The e-MuM data do not reflect adherence as such, merely container opening patterns, which makes it difficult to interpret results.

In focus groups, patients and staff expressed their views about the use of the e-MuM system. No difficulty in the ease of use was reported by patients or staff. Notwithstanding this, a large portion of patients did decant tablets for various reasons, which made calculation of true adherence rates very difficult. A group of patients suggested routine use of the e-MuM system, to keep them conscious of their medication regimen while staff suggested limited use for new patients and non-adherent patients.

The size of the container was the biggest obstacle according to patients and clinic staff and a small, more portable container was suggested. The sturdiness of the e-MuM lid with the microprocessor used for the study was questionable.

Recommendations: Based on the results of this study, suggestions to increase adherence and utilise the e-MuM system are offered. The ideal medication dosage interval for patients, whose adherence patterns are being monitored electronically, would be once

daily. For the e-MuM system to be practical, the device (container with embedded micro chip) has to be small, portable and sturdy. Patients will have to be educated to take every dose directly from the e-MuM container. For optimal e-MuM data interpretation, patient medication taking behaviour, including decanting of tablets must be accurately identified. A trained, dedicated, sensitive person has to interpret data and give feedback to patients.

ABBREVIATIONS AND ACRONYMS

3TC	Lamivudine
AACTG	Adult AIDS Clinical Trial Group
ABC	Abacavir
AETC	AIDS Educational & Training Centres
AFSA	AIDS Foundation South Africa
AIDS	Acquired Immune Deficiency Syndrome
AMPATH	Academic Model for The Prevention and Treatment of HIV/AIDS
ART	Antiretroviral Therapy
ART-LINC	The Antiretroviral Therapy in Lower-Income Countries
ARV	Antiretroviral
ARVs	Antiretrovirals
AZT	Zidovudine
BMI	Body Mass Index
BUS	Business Unity South Africa
CBOs	Community-Based Organizations
CDC	Centers for Disease Control and Prevention
COSATU	Congress of South African Trade Unions
CSIR	Council for Scientific and Industrial Research
D4T	Stavudine
DAART	Directly Observed ART
DCIs	Data Collection Instruments
DDL	Didanosine
DNA	Deoxiribonucleicacid
DOH	National Department of Health
DOT	Directly Observed Therapy
EFV	Efavirenz
EFG	Elvitegravir
ELISA	Enzyme-Linked Immuno-Sorbent Assay
EM	Electronic Monitoring
ENF	Enfuvirtide
FCT	Emtricitabine
FGD	Focus Group Discussion
FOTO	Five-Days-On, Two-Days-Off
FPD	Foundation for Professional Development
GDP	Gross Domestic Product
GIT	Gastro-Intestinal Tract

GP	Glycoprotein
HAART	Highly Active Antiretroviral Therapy
HIV	Human Immunodeficiency Virus
HPCA	Hospice and Palliative Care Association
HRSA	Health Resources and Services Administration
HSRC	Human Sciences Research Council
ICT	Information and Communication Technology
ICW	International Community of Women Living With HIV/AIDS
IDASA	Institute for Democracy in South Africa
IDV	Indinavir
IL	Interleukin
IRS	Inflammatory Reconstitution Syndrome
JAMA	Journal of American Medical Associations
LAV	Lymphadenopathy Associated Virus
IEDEA	Databases to Evaluate Aids
LOQ	Limits of Quantification
LPV	Lopinavir
LPV/r	Lopinavir/Rotinavir
MCC	Medicine Control Council
MVC	Maraviroc
MTCT	Mother-to-Child Transmission
MEDUNSA	Medical University of Southern Africa
MEMS	Medication Events Monitoring System
MMAS	Massachusetts Male Aging Study
MMWR	Morbidity and Mortality Weekly Report
MCREC	Medunsa Campus Research and Ethics Committee
MSF	Médecins Sans Frontières
E-Mum	Electronic Medication Utilization Monitoring
NAT	Nucleic Acid Amplification Testing
NFV	Nelfinavir
NGOs	Non-Governmental Organisations
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
NRTI	Nucleoside Analogue Reverse Transcriptase Inhibitor
NSP	National Strategic Plan
NVP	Nevirapine
PEPFAR	United States President's Emergency Plan for AIDS Relief

PCR	Polymerase Chain Reaction
PEP	Post-Exposure Prophylaxis
PI	Protease Inhibitor
PMTCT	Prevention of Mother-To-Child Transmission
PPIC	Plasma Protease Inhibitor Concentrations
RAL	Raltegravir
RNA	Ribonucleic Acid
RTV	Ritonavir
SAAVI	South African AIDS Vaccine Initiative
SABCOHA	South African Business Coalition on HIV & AIDS
SAMA	South African Medical Association
SAMRC	South African Medical Research Council
SANBS	South African National Blood Service
SANAC	South African National Aids Council
SAT	Self Administered Therapy
SD	Standard Deviation
SERAD	Self-Reported Adherence
SES	Socio-Economical Status
StatsSA	Statistics South Africa
STI	Sexually Transmitted Infection
TAC	Treatment Action Campaign
TB	Tuberculosis
TDF	Tenofovir
TG	Triglycerides
UN	United Nations
UNICEF	United Nations Children's Emergency Fund
UNAIDS	Joint United Nations Programme on HIV/AIDS
UNGASS	United Nations General Assembly Special Session
UNODC	United Nations Office of Drug and Crime
USD	United States Dollars
VAS	Visual Analogue Scale
VL	Viral Load
WHO	World Health Organization

CHAPTER 1

INTRODUCTION

1.1 BACKGROUND

Many African governments have been reluctant to recognise the magnitude of the continent's Human Immunodeficiency Virus (HIV) epidemic in the past (Whiteside, 2004). They have shied away from admitting that the problem existed and dismissed critics as being racist. Many governments viewed Acquired Immunodeficiency Syndrome (AIDS) as a threat to investment and tourism. Silence surrounded the HIV and AIDS epidemic in sub-Saharan Africa. The slow response to the HIV epidemic has had the effect of creating a situation where limited public discussion has led to continued stigmatisation of those who are infected (Meyer, 2008a). Cultural and religious taboos have inhibited open discussion about an epidemic that spreads primarily, but not exclusively, through sexual contact. Some faith groups in Africa believe that AIDS is a divine punishment for those who have been sexually promiscuous, fuelling the reluctance of many adults to openly admit to carrying the disease (Caldwell, 2000). The lack of political stability in some African countries has contributed to governments' failure to generate an effective public response to HIV and AIDS (Inungu & Karl, 2006).

In 1987, the apartheid Government of South Africa recognised that HIV and AIDS had the potential to become 'a major problem', even though there were few reported infections. The first antenatal survey of HIV/AIDS was conducted in 1990 in South Africa and the first public sector antiretroviral therapy (ART) was provided in Khayelitsha in the Western Cape in May 2001 (Médecins Sans Frontières` (MSF) & Infectious Disease Epidemiology Unit , 2003). An Operational Plan for antiretroviral (ARV) rollout in South Africa was only produced in 2003 (Aids Foundation South Africa (AFSA), 2005). The development of this strategic plan was initiated by the Minister of Health, Dr. Manto Tshabalala-Msimang in July 1999 in response to the President, Mr. Thabo Mbeki's, challenge to all sectors of society to become actively involved in initiatives designed to address the HIV and AIDS epidemic. The first meeting in July 1999 by a Presidential task team was held to review the then HIV and AIDS prevention, treatment and care efforts in South Africa. The South African government's first comprehensive policy document was the National Strategic Plan (NSP) of 2000-2005. This first strategic plan had not anticipated the extent of the task at hand resulting in serious capacity deficits identified at implementation level. This capacity deficit problem was caused by poor coordination at the South African National AIDS

Council (SANAC) level and a lack of clearly defined targets and a monitoring framework (DOH, 2004). This call for action did not prevent the former South African President, Mr. Thabo Mbeki, from questioning the connection between HIV and AIDS, stating instead that factors such as under-nourishment had a bigger influence on the spreading of the disease than a single virus (AFSA, 2009).

A century ago, the German bacteriologist Robert Koch, devised a test for proving that a disease is caused by a specific microbe. The test has since become a standard in medicine and is known as "Koch's postulate". Scientists agree that the evidence on the link between HIV and AIDS passes this test. Three steps are followed to prove this postulate. The microbe is isolated from an infected host and introduced into a healthy host, where it must cause the same disease. Finally, the microbe must be isolated from this last host (Joint United Nations Programme on HIV/AIDS (UNAIDS), 2004).

Critics of former President Mbeki's government such as the Treatment Action Campaign (TAC) charge that their AIDS policies were responsible for thousands of deaths. The denial that a single virus is the cause of HIV impeded the creation of effective programmes for distribution of ARV drugs (Heywood, 2004).

The lack of treatment in the Southern African region, has given rise to a situation where many patients equate infection with inevitable death. This was one of the main reasons for infected patients to keep their positive status a secret. Stigma, lack of knowledge, and lack of emotional preparedness, are still the main reasons why patients are uncomfortable about discussing HIV and its impact on their families (Meyer, 2008a). Stigma is of utmost concern because it is both the cause and effect of secrecy and denial, thus fuelling the HIV transmission flame. People who have AIDS-like symptoms often claim to suffer from a less stigma-laden disease, such as cancer or tuberculosis. Stigma delays HIV testing, an essential first step to treatment and other preventative activities. Unless the stigma associated with HIV and AIDS is acknowledged and addressed appropriately, prevention efforts to curb its spread are doomed to fail (Brown *et al.*, 2003). Convincing people to get tested is only the first step in a long chain of very difficult steps that needs to be taken in an attempt to curb the spread and ensure eventual eradication of HIV. Testing is the only way to save the productive generation of the present and the future. Africa seems to be the continent worst affected by HIV infection with the most reported cases (World Health Organization (WHO), 2008a). The meaningful involvement of infected and affected people in all aspects of living with HIV is an essential element to facilitate understanding and an effective response (Horizons/Population Council, International HIV/AIDS Alliance & Tata Institute of Social Sciences, 2001). Expansion of HIV testing and counselling will increase

the number of people with HIV who are aware of their HIV status and can benefit from HIV-related prevention, care, treatment and health promotion, and to reduce the risk of HIV transmission to others (WHO, 2008b).

Resource limitations make affordability of medication a big hurdle facing individuals and all treatment providers. Since 2001 with the advent of generic medication, a reduction of 99% in the price of some first line fixed-dose combination medication (lamivudine (3TC) / didanosine (ddl) / nevirapine (NVP) has occurred. However, the next real challenge is the affordability of newer ARV drugs. The treatment of HIV and AIDS requires lifelong adherence to drugs and side-effects as well as resistance make the future development of newer less toxic, more effective drugs imperative (Médecins Sans Frontières (MSF), 2009).

In June 2006 an expert review panel of the World Health Organization (WHO) formulated the following 13 areas of importance for people living with HIV (WHO, 2008b):

- Psychosocial counselling and support
- Disclosure, partner notification and testing and counselling
- Co - Trimoxazole prophylaxis
- Tuberculosis (TB)
- Preventing fungal infections
- Sexually transmitted and other reproductive tract infections
- Preventing malaria
- Selected vaccine preventable diseases (hepatitis-B, pneumococcal, influenza vaccine, and yellow fever vaccines)
- Nutrition
- Family planning
- Preventing mother-to-child transmission of HIV
- Needle-syringe programmes and opioid substitution therapy
- Water sanitation and hygiene

Positive prevention, as it is commonly known, includes three key components namely healthy living, prevention of HIV transmission and the involvement of people living with HIV (WHO, 2008b).

An evaluation of successful implementation strategies for HIV planning revealed the following common approaches (Horizons/Population Council, International HIV/AIDS Alliance & Tata Institute of Social Sciences, 2001):

- Combine strategies to create environments for the empowerment of people with HIV
- Protect and promote human rights and ethical principles, including the right to privacy, confidentiality, informed consent and the duty to do no harm
- Include measures to prevent the stigmatization of, and discrimination against people with HIV, while still focusing on the particular needs and rights of people with HIV
- Balance the public need for HIV prevention with the private need of people living with HIV for sexual well-being and their human rights.

Since the introduction of treatment regimens which combine antiretroviral therapy (ART) in the form of highly active antiretroviral therapy (HAART) the mortality and morbidity due to HIV have declined strongly and increased life expectancy (Horizons/Population Council, 2004; Lohse *et al.*, 2008). Clinical trials and cohort studies have shown that continuous and lifelong adherence according to very strict standards is one of the most important factors to treat and manage the disease and improve life expectancy (Horizons/Population Council, 2004), Programmes to increase adherence to ARV medication increase life expectancy and quality of life and use less funds per patient, so that more patients can be treated with anti-retroviral medication. HIV infection can now be viewed as a chronic disease (Vervoort *et al.*, 2007).

Adherence is regarded as successful when an adherence rate of at least 95% is achieved (Horizons/Population Council, 2004). Adherence levels of less than 95% or treatment interruptions may allow the virus to replicate rapidly and provide the opportunity for more resistant mutant strains to emerge which have also been linked to the development of drug resistance (Kaplin & Hsu, 2009). Similar conclusions were reached in other investigative studies (Vervoort *et al.*, 2007). The presence of drug resistance limits the future treatment options due to cross-resistance.

There is a limited choice of ARV drugs in the HIV treatment protocol of the National Department of Health (DOH) of South Africa, due to financial constraints. Every time the patient's regimen is changed (mainly due to drug intolerance or treatment failure, i.e. resistance) the available treatment options decrease (DOH, 2004).

Table 1.1: Current adult HIV treatment regimens offered by the National Department of Health, South Africa

REGIMEN	DRUGS
1a	Lamivudine (3TC) + stavudine (d4T) + efavirenz (EFZ)
1b	d4T + 3TC + nevirapine (NVP)
2	zidovudine (AZT) + didanosine (ddl) + lopinavir (LPV) and Ritonavir (RTV)

Source: DOH, 2004

Interventions to increase adherence can be divided into the following four main categories (Osterberg & Blaschke, 2005):

- Patient orientated measures which include patient and family education to understand the disease and treatment options
- Medication orientated measures which include improved dosing schedules like simplifying drug regimens, using pillboxes, and cues to remind the patient of appointments and doses (e.g. cell phones, electronic reminder devices and buddy reminder service)
- Facility orientated measures which include greater accessibility to clinics and extension of open-hours and staff
- Improved communication which includes better establishment of interpersonal relationship measures between the professional team and patient

1.2 STUDY PROBLEM

The best approach to HIV would be to prevent the infection. Once infection occurs it becomes important to

- increase the quality of life of patients;
- ensure treatment of the greatest number of patients with the limited budget; and
- extend the life expectancy of most patients.

Disease management rests on several pillars, with adherence to ART as one of the most important pillars (Horizons/Population Council, 2004). Successful adherence is regarded as the achievement of a 95% minimum rate (Horizons/Population Council, 2004). There are many approaches aimed to improve adherence. An electronic adherence monitoring (e-MuM) system was developed in South Africa to assist with adherence monitoring. The system has been tested with tuberculosis (TB) patients, but not with ARV patients.

Geo-ICT Health Pty (Ltd) approached the Department of Pharmacy at the University of Limpopo, Medunsa Campus, to be a research partner in the pilot study of the electronic adherence monitoring system. The e-MuM system consists of a container lid with an

embedded data collection microprocessor (device), a separate reminder unit (watch) and a software programme to analyse data. The monitoring device is embedded into a tablet vial lid, which fits standard medication containers. These special lids are indistinguishable to the untrained eye, from standard medication container lids. Appendix A shows an illustration of the e-MuM system.

1.3 AIM OF THE STUDY

The aim of this study was to investigate and assess whether the e-MuM system together with verbal feedback to patients would have an impact on ART adherence. Previous adherence studies on similar population groups (Mapetla, 2007; Meyer, 2008b) investigated adherence monitoring tools (questionnaires) and their effect on patient ART adherence. This study, to test an electronic system, was a natural progression of those studies.

1.4 OBJECTIVES

The objectives of the study were as follows:

- To measure the practicality of introducing the e-MuM system within the existing patient management process at the selected site;
- To compare the impact of the different components of the e-MuM system on the adherence process (electronic microprocessor, reminder unit and verbal feedback);
- To test the effectiveness of this tool in the adherence process;
- To test the ease of use for the patient and pharmacist;
- To obtain views of the patients on this tool;
- To obtain views of the clinic staff on this tool;
- To make recommendations concerning adaptations to the e-MuM product and its use and
- To make recommendations concerning the ideal use of the e-MuM system.

1.5 SUMMARY

This chapter dealt with the background against which the problem of patients' non-adherence to ARVs evolved. The study problem was formulated within the background context, followed by the aim and an outline of the objectives of the study. The literature review on the study topic is presented in Chapter 2.

CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

Navigation of the countless articles being published on a daily basis from every corner of the world emphasises the enormity of the HIV/AIDS epidemic. The worldwide internet has around 119 million sites dedicated to HIV and AIDS (accessed via the search engine Google, October 2009). The first clinical report of what would become known as AIDS, was published by the Centres for Disease Control and Prevention (CDC) in their Morbidity and Mortality Weekly Report (MMWR) Series on 5 June 1981 and announced the diseases' first victims as follows:

"In the period October 1980 - May 1981, five young men, all active homosexuals, were treated for biopsy-confirmed Pneumocystis carinii pneumonia at three different hospitals in Los Angeles, California. Two of the patients died." (CDC, 1981)

More than 25 years have elapsed since that first case report. The spread of HIV is continuing at an alarming pace. The HIV epidemic has become a pandemic of previously unknown dimensions, rooted in the complex and interrelated social, economic, cultural and medical realities of HIV and AIDS today. The spread of HIV infection is uneven and the largest number of infected people is to be found in the developing world (UNAIDS, 2008c). The first section of this chapter on the prevalence of HIV and AIDS, paints a picture of enormous proportions. This is followed by a discussion of the management of all the disease facets.

The chapter further deals with the disease description, the extent of the problem in the Sub-Saharan region (including the South African response plans), the transmission of the disease, factors which fuel the spread and lastly the disease control.

2.2 PREVALENCE OF HIV AND AIDS

2.2.1 HIV data gathering network

There are many international and national organisations which publish HIV statistical information with varying degrees of similarity. The WHO gathers international and local

information and publishes an annual global report. The report consists of 39 national level indicators to reflect three primary areas of HIV management: prevention, treatment (availability and coverage) and care. These indicators show the availability of both drugs and health care workers in local context (WHO, 1993). The selected indicators with related international monitoring processes align to monitor interventions for women, children and other categories of HIV infected people. The international organisations include the United Nations General Assembly Special Session (UNGASS), United Nations Children's Fund (UNICEF) and the Interagency Task Team on the Prevention of HIV Infection in Pregnant Women, Mothers and their Children. The National Department of Health, South African Reserve Bank, Statistics South Africa and the Council for Scientific and Industrial Research (CSIR) are some of the South African sources used to provide statistical information.

2.2.2 Global prevalence

Global prevalence is one of the reason why international organisations like UNAIDS call for contributions to combat all facets of HIV infection. Universal access is a global commitment to scale up access to HIV treatment, prevention, care and support and is enshrined in the 2006 United Nations Political Declaration (UNAIDS, 2009a). The joint declaration for action for results issued by the United Nations AIDS (UNAIDS) Outcome Framework for 2009 reads as follows:

“The achievement of universal access will remain the fundamental priority for UNAIDS. Universal access goals can become a reality. By achieving these goals, we can contribute to the broader development agenda.”

The following statistics illustrate the size of the problem (UNAIDS, 2009a):

- 7,400 people become infected with HIV every day
- Nearly 4 million people are currently receiving treatment, while 9.7 million people are still in need
- For every two people put on treatment, five more become infected
- 123 countries have held national consultations to identify obstacles to scaling up to universal access
- 111 countries have set ambitious national targets to reach universal access
- 83 countries have integrated their national universal access targets into their National Strategic plans

Countries have demonstrated their commitment to universal access through comprehensive national targets. Ninety nine countries have set targets for treatment while 98 countries have set targets for one or more prevention interventions (UNAIDS, 2009a).



Source: UNAIDS, 2008b (Darker colours reflect higher numbers)

Figure 2.1: Interactive map: Towards Universal Access

Table 2.1: Total global HIV infection numbers and funding (2008) of the thirteen countries with highest HIV infection rates

Country	Spending/million (USD)	Country	HIV infections/million
South Africa	622	South Africa	5,7(4,9-6,6)
Nigeria	19	Nigeria	2,6(2,0-3,2)
Tanzania	324	Tanzania	1,4(1,3-1,5)
Zimbabwe	130	Zimbabwe	1,3(1,2-1,4)
USA	-	USA	1,2(0,690-1,9)
Zambia	190	Zambia	1,1(1,0-1,2)
Russian Fed	305	Russian Fed	0,94(0,63-1,3)
Brazil	565	Brazil	0,73(0,6-0,89)
China	124	China	0,7(0,45-1,0)
Botswana	229	Botswana	0,3(0,28-0,31)
Namibia	131	Namibia	0,2(0,16-0,23)
Mexico	176	Mexico	0,2(0,15-0,31)
Australia	101	Australia	0,018(0,011-0,036)

Source: UNAIDS, 2008c (The ranges define boundaries within which the actual numbers lie)

UNAIDS has identified nine priority areas for its support to countries to help them to achieve their universal access targets. These areas will contribute directly to the achievement of universal access and will simultaneously enable advancement to the millennium development goals.

- To prevent sexual transmission
- To stop mothers from dying and babies from becoming infected
- To ensure that people living with HIV receive treatment
- To prevent people with HIV from dying of TB
- To protect drug users from becoming infected with HIV
- To remove punitive laws, policies, practices, stigma and discrimination that block effective responses to AIDS

- To empower young people to protect themselves from HIV
- To enhance social protection for people affected by HIV

Table 2.2: UNAIDS global numbers (estimates) of important HIV groupings in 2008

Category	Estimate/million	Range/million
People living with HIV	33.4	31.1-35.8
Adults living with HIV	31.3	29.2-33.7
Woman living with HIV	15.7	14.2-17.2
Children living with HIV	2,1	1.2-2.9
People newly infected with HIV	2.7	2.4-3.0
Adults newly infected with HIV	2.3	2.0-2.5
Children newly infected with HIV	0.43	0.24-0.61
Aids deaths	2,0	1.7-2.4
Adult Aids deaths	1.7	1.4-2.1
Children Aids deaths	0.28	0.15-0.41

Source: UNAIDS, 2009b (The ranges define the boundaries within which the actual numbers lie)

The Joint United Nation Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO), estimated that an excess of 27 million people have succumbed to AIDS since it was first recognised on December 1, 1981 (WHO, 2010).

Table 2.3: Estimated global and regional statistics (Adult HIV infections, prevalence and AIDS-related deaths)

World region	People living with HIV in 2008 (million)	Estimated adult HIV prevalence (%) in 2008	Estimated Aids-related deaths in 2008 (million)
Globally	33.4(31.1-35.8)	0.8(<0.8-0.8)	2.0(1.7-2.4)
Sub-Saharan Africa	22.4(20.8-24.1)	5.2(4.9-5.2)	1.4(1.1-1.7)
South and South-East Asia	3.8(3.4-4.3)	0.3(0.2-0.3)	0.27(0.22-0.31)
Eastern Europe and Central Asia	1.5(1.4-1.7)	0.7(0.6-0.8)	0.087(0.072-0.110)
Latin America	2.0(1.4-1.7)	0.6(0.5-0.6)	0.077(0.066-0.089)
North America	1.4(1.2-1.6)	0.4(0.3-0.5)	0.025(0.020-0.031)
Western and Central Europe	0.85(0.71-0.97)	0.3(0.2-0.3)	0.013(0.010-0.015)

Source: UNAIDS, 2009b (The ranges define the boundaries within which the actual numbers lie)

In 2008, an estimated 1.9 million people were newly infected with HIV in sub-Saharan Africa, bringing the number of people living with HIV to 22.4 million. Just over 10% of the world's population lives in sub-Saharan Africa but two thirds (67%) of the global total of 32.9 million people with HIV live in this region. A total of 75% of all HIV-related deaths

occurred in this region (UNAIDS, 2008b). The number of new infections climbed with a staggering 2.7 million people in 2008 and HIV infected people with access to ART in low- and middle income countries increased with 1.2 million to 5.2 million at the end of 2009 (UNAIDS, 2009b)

Two million of the infected people in sub-Saharan Africa are children younger than 15 years of age. More than three quarters of all women living with HIV are in Sub-Saharan Africa. South Africa had the largest HIV population in 2007 in world terms (5.7 million), followed by Nigeria with 2.6 million infected people (UNAIDS, 2008b).

2.2.3 South Africa

According to Statistics South Africa the population of South Africa was 49.3 million in the middle of 2009 (Statistics South Africa, 2009). In South Africa, adults (15 years or older) living with HIV (whether they have developed symptoms or not) have increased from 4.7 million to 5.7 million in seven years (2001 to 2007). Numbers of infected children up to 14 years old have risen from 150,000 to 280 000 (WHO, 2008b). Deaths related to HIV also increased from 180,000 to 350,000 in 2008. This increase has led to retarded economic growth and increased poverty (WHO, 2008b). A statistic with profound emotional, social and financial impact was included in the WHO (2008b) report and reflects an increase in AIDS orphans from 400,000 to 1.4 million from 2001 to 2007.

Without treatment, about nine out of every 10 persons with HIV will progress to AIDS after 10-15 years. Even after HIV has progressed to diagnosable AIDS, the average survival time with ART (as of 2005) is estimated to be more than five years. Globally, men are expected to live until 65 and women until almost 70, but in Africa, men are expected to live until 52 and women until 54. In South Africa, the life expectancy for men is 49 and for women 50 (WHO, 2008a).

Table 2.4 illustrates the difference in HIV prevalence in the nine provinces in South Africa. KwaZulu-Natal is the second smallest province in terms of land area, but comprises the second largest share of the South African population and has the highest HIV prevalence rate. Northern Cape is the province with the smallest share of the South African population while the Western Cape has the lowest HIV prevalence.

Table 2.4: Percentage distribution of provincial land, the projected provincial share of the total population, HIV prevalence and Gross Domestic Product (GDP)

Province	Provincial land area (%)	2009 Population (%)	2008 Population HIV prevalence (%)	2007 Contribution to GDP (%)
Eastern Cape	13,9	13,5	9	7,8
Free State	10,6	5,9	12,6	5,4
Gauteng	1,4	21,4	10,3	33,5
Kwazulu-Natal	7,6	21,2	15,8	16,2
Limpopo	10,2	10,6	8,8	6,9
Mpumalanga	6,5	7,3	15,4	6,9
Northern Cape	29,7	2,3	5,9	2,2
North West	9,5	7,0	11,3	6,5
Western Cape	10,6	10,9	3,8	14,5
National (Undefined)			7.1	

Source: Shisana *et al.*, 2009; Statistics South Africa, 2009

2.3 MAIN ROLE PLAYERS IN THE SOUTH AFRICAN STRATEGY TO COMBAT THE GLOBAL HIV PANDEMIC

2.3.1 South African Government

The South African Government's Department of Health, has in recent years, after a slow start and a counter-productive period under the previous Minister of Health, Manto Tshabalala-Msimang, embarked on an ambitious but achievable strategy as set out in the National Strategic Plan (NSP). The HIV and AIDS and Sexually Transmitted Infection (STI) Strategic Plan for South Africa, 2007-2011 had some key recommendations to consolidate and build existing partnerships and increase the contribution of the business sector. The NSP is the conceptual vehicle structured by the South African Government as a way forward in dealing with all aspects of the HIV and AIDS pandemic.

2.3.1.1. *The HIV and AIDS and STI strategic plan for South Africa, 2007-2011*

The HIV and AIDS and STI strategic plan for South Africa (2007-2011) identifies four priority areas to be reached by 2011 (DOH, 2007):

- **Prevention.** Included in this section is the provision of information, education and access to voluntary testing. Closely linked to this thrust is the challenge to change behaviour or attitudes. People will have to be convinced of the vested interest they have in managing their own HIV status. The target is a 50% reduction in new cases. It seems unlikely that this target will be reached. Prevention will also

include specific programmes and prevention of mother-to-child transmission. The plan states that with a properly managed programme, mother to child infections can fall below 5%.

- **Treatment, Care and Support.** Included in this section is communication about ARV programmes, education and supply of information. Nutritional intervention and choice of treatment is envisaged. The target is to reach 80% of people and their families living with HIV.
- **Research, Monitoring and Surveillance.** The goal was to allocate 4% to 7% of the HIV and AIDS budget on a sustainable basis to this sometimes neglected objective.
- **Human Rights, Access to Justice and Law Reform.** Respect for human rights will create an environment in which people will not shy away from voluntary testing and will receive follow-up treatment and support.

2.3.1.2. ARV treatment sites

The ARV roll-out programme started at 32 accredited sites in April 2004 (Hudspeth *et al.*, 2004). These treatment sites have increased from 179 in 2005 to 362 in 2007. (UNAIDS, 2008a). This increase in the number of sites (nearly 50% in two years) has not translated into the same increase in patient numbers able to access ART medication. The HIV infected people able to access ART medication has only risen to 27% (460 000) out of 1.7 million patients needing treatment. The number of pregnant women receiving antiretroviral (ARV) medication to prevent mother-to-child transmission has risen from 75 000 to 127 000 (UNAIDS, 2008a).

According to DOH statistics, more than 90% of government clinics (3382 of 3663) were providing prevention of mother-to-child transmission (PMTCT) services by 2008 (TAC, 2008)

2.3.1.3. Patient enrolment programme

Blood tests to determine HIV status and CD4 count are done before patients can even be considered for enrolment on ART. The DOH has selection criteria for eligible patients of either a CD4 count of less than 200 cells/mm³ or being in the WHO Stage 4 phase of the disease (irrespective of CD4 count) (DOH, 2004). If patients meet the criteria mentioned, psychological readiness is to be established. The readiness assessment is supposed to be conducted by trained HIV counsellors during a first of three sessions over a two to four week period before starting ARV treatment. The patients' readiness for commitment to

lifelong adherence is vital to minimise defaulting on the treatment. New patients are given a months' supply of co-trimoxazole to clear up opportunistic infections and given a return date. During this return session adherence to the co-trimoxazole should be assessed through a tablet count. Patients are re-assessed for readiness to start treatment and further education sessions are held. Thereafter, ARV treatment can then commence (DOH, 2004).

The roll-out of ART has not been without problems. A budget allocation problem faced many of the provincial Health Departments during the 2008/2009 financial year. In Limpopo this has led to huge overspending on the budget and in the Free State the department placed a moratorium on enrolment of new patients in November 2008 due to shortage of funds (Ndlovu, 2009).

2.3.1.4. Pharmacovigilance

Pharmacovigilance is linked to the monitoring of problems related to HIV drug toxicity, intolerance and drug-drug interactions which can lead to adherence being compromised and patient confidence eroded. By the end of 2008, three pharmacovigilance centres had been envisaged and establishment planned by DOH to monitor and investigate adverse reactions to antiretroviral treatment (South African Government, 2008). Reports received by the Cape Town Pharmacovigilance Centre include all monitoring information and feedback and not only information on HIV. This is reported to the Medicines Control Council (MCC) for analysis. The National Operational HIV Pharmacovigilance Centre is located at the University of Limpopo (Medunsa Campus). The third centre planned for the Free State province has not been established yet.

2.3.2 Health care workers

Over-crowded and under-resourced public sector hospitals, is a common problem faced by healthcare workers. They work under difficult circumstances to provide care for the wave of HIV infected people who make up 70% of their case load. Staff shortages are large and in Kwazulu-Natal with the highest HIV infection numbers of the nine provinces, 37% of health posts were vacant in early 2005. Work burden, excessive patient load, poor working conditions and personal stress and depression developing after dealing with terminally ill and dying HIV patients on a daily basis has been cited as reasons for resignations. Furthermore, infection rates of 11.5% were found among healthcare workers in two hospitals in Johannesburg (AIDS Foundation South Africa [AFSA], 2009).

2.3.3 Traditional healers (culture)

There are about 200 000 traditional healers in South Africa compared to 25 000 qualified doctors. Despite urbanisation and in a context of poor access to quality public health services, these traditional healers are the primary medical caregivers for 85% of the African population. Traditional healers offer diagnosis and treatment of sexually transmitted infections (STIs) and AIDS. They also claim to be able to address emotional, psychological and spiritual health and provide counselling and care for terminally ill people and their families. They treat a patient as part of a family and a community, not as an individual. It is because of exactly this involvement that they are well-placed to educate people about HIV and AIDS. They should be able to identify and advise on risky behaviour in the cultural context in which HIV is spreading.

Despite this tremendous potential to positively influence community responses to HIV and AIDS, the role of traditional healers has been controversial. AIDS Foundation South Africa (AFSA) supports HIV and AIDS education and training for traditional healers. Change in behaviour of individuals is unlikely to happen without change in cultural and social beliefs in the community, supported by traditional leaders, who are the custodians of culture. This is one of the reasons why AFSA supports interventions targeting traditional healers, traditional leaders and initiation schools.

In 1995, AFSA launched and managed a programme, in partnership with the National Traditional Healers' Association of South Africa that trained more than 6 000 traditional medical practitioners in KwaZulu-Natal over a period of six years. Subsequent programmes have been implemented by DOH. In 2005, AFSA, in partnership with traditional healer organisations, introduced a treatment literacy training course for traditional medical practitioners. The main objective was to dispel myths and inaccuracies that HIV and AIDS is curable through the use of traditional medicines and alternative therapies. The traditional healer's understanding of biomedical treatment of opportunistic infections, ART and the importance of promoting treatment compliance, and the improvement of their understanding of the relationship between HIV and AIDS, culture and gender was approached.

Cultural beliefs, traditions and practices have a direct influence on the health and wellbeing of communities. Some have the potential to strengthen or weaken the fight against HIV and AIDS. Patriarchy is entrenched in most communities and is often a factor in the increased risk of HIV infection among girls and women, due to unequal gender relationships and male decision-making power. Male circumcision, which takes place as

part of initiation into manhood in some cultures, has been shown to reduce the risk of HIV infection by 60%. Other aspects of initiation, including instruction of initiates in their traditional roles as men and sexual partners, entrench the subordinate role of women and may encourage sexually risky behaviour (AFSA, 2009).

2.3.4 Community

In the early years of the pandemic the family, friends and neighbours of people affected by HIV and AIDS were called upon to provide care for dying patients and orphaned children. The explosion of new cases witnessed in the new millennium has stretched this survival network to breaking point. In reaction to this, the South African Government has started to support home and community-based care givers as well as promoting training for councillors. The Non-Governmental Organisations (NGOs) and the Community-Based Organisations (CBOs) have been the back-bone of HIV/AIDS response (AFSA, 2009)

2.3.5 Non-Governmental Organisations (NGOs)

Many NGOs have been established in South Africa to address HIV and AIDS. Some NGOs are limited to specific towns, districts and provinces, while the bigger NGOs operate nationally and internationally. The functions offered by the NGOs are as varied as the communities they assist and may include the supply of information, legal services to restore human rights, the coalition to advocate a universal income grant, promotion of the rights and well-being of children, designing, planning and evaluating programmes towards the restructuring of the health system, as well as promoting collaboration, participation in research and involvement in policy formulation. Most notable and visible amongst NGOs have been the Treatment Action Campaign (TAC) and AIDS Law Project. These NGOs have been involved in a wide range of services ranging from programmes to support affected people and communities in practical and education programmes to the approach of donors for financial support.

NGOs were the driving force for access to HIV treatment, lower medicine prices, improved care and effective policy on HIV and AIDS during the previous government's lack of response. The relationship between NGOs and the government vary, for example, the National Association of People Living with AIDS receives government funding while the TAC has been attacked by government.

2.3.6 Professional Organisations

Some of the organisations focus on supplying information and education like the South African Medical Association (SAMA) maintaining a website to provide medical practitioners with information, news and advice necessary for meeting the challenges of health care delivery in South Africa (Richter, 2007).

The programme of the Foundation for Professional Development (FPD) supports the expansion of access to comprehensive HIV and AIDS care. The focus of the organisation is on service delivery and human capacity development with a view to increase the detection and treatment of patients with TB and HIV co-infection (Foundation for Professional development [FPD], 2009).

The mission of the 75 independent hospices brought together under the umbrella of the Hospice and Palliative Care Association (HPCA), is to provide and enhance the provision of sustainable, accessible, quality palliative care (Hospice and Palliative Care Association [HPCA], 2009).

2.3.7 Donors

Huge sums of money, as well as human and technical resources have been pouring into South Africa for the fight against HIV and AIDS since the mid-1990s. The Gates Foundation has put millions of dollars into the Global Fund for HIV/AIDS, TB and Malaria. The Global Fund (joint effort between UN agencies, governments, private and corporate donors and individuals) is focused on treatment. The effectiveness of the fund is undermined by beneficiaries not putting forward applications that meet the criteria. Donor policy usually attaches conditions to grants related to donors' domestic concerns. A demonstration of these conditions was the previous United States (US) government of George W Bush insisting on only funding abstinence and prevention programmes. It excluded projects that distributed condoms or made available information on reproductive rights.

The President of the US, Barack Obama, who was elected in 2009, promised to remove this condition. The United States President's Emergency Plan for AIDS Relief (PEPFAR) channels the US Government's financial support (nearly \$590.9 million in 2008) to organisations in countries worldwide on all levels. It partly funds the implementation of the South African Government's Strategic Plan and works with other diverse partners, academic institutions, non-governmental organisations, faith-based organisations, and

private-sector partners. Although huge sums of money have been channelled to NGOs, some donors have insisted on this money being spent on high profile projects instead of in local communities in need. The Joint Civil Society Monitoring Forum has been instrumental in bringing all role players together for a more co-ordinate forum in the fight against the pandemic (AIDS Foundation South Africa [AFSA], 2009).

Funding for South Africa was dogged by political controversy under Manto Tshabalala-Msimang, a previous Minister of Health. She delayed a grant to KwaZulu-Natal because it had not gone through her department and then in 2008 the Global Fund rejected a 'poor' proposal submitted by the South African National AIDS Council (SANAC). This resulted in a R1.1 billion loss of funding for national programmes and R600 million for the Western Cape over five years. The United Kingdom's Department for International development announced a 15 million pounds boost for the NSP (AIDS Foundation South Africa [AFSA], 2009).

2.3.8 Business (private sector)

A survey of 1000 businesses (retail, construction and manufacturing) conducted by the University of Stellenbosch in 2004, found 34% had already reported a negative effect on profitability attributed to HIV and AIDS (AIDS Foundation South Africa [AFSA], 2009). Many employers have initiated workplace awareness and education programmes. Anglo American initiated a programme of testing and free ARV medication in 2002. As a result of this foresight, and enrolling ARV positive employees in a wellness programme, 94% of 2500 employees on treatment in 2004 were able to carry out normal work.

The second South African Business Coalition on HIV & AIDS (SABCOHA) private sector conference was held by Business Unity South Africa (BUS), South African Business Coalition on HIV & AIDS (SABCOHA) and Metropolitan Life on 5-6 November 2008 in Kempton Park. The main aim was to address the lack of engagement by business in South Africa in addressing the prevention, care, support and treatment of HIV infections. The general consensus amongst the keynote speakers, including Professor Wiseman Nkuhlu, the president of the International Organisation of Employers and chairman of Metropolitan Holdings, was the possibility that South Africa would not reach the International Community's target of providing access to HIV and AIDS treatment to infected patients by 2010 unless immediate action was taken. Jay Naidoo, Chairman of the Development Bank of South Africa, put forward the objectives of SABCOHA, and pointed out the fact that as a result of an apathetic private sector, 20% of potential

customers might be dead in 5-8 years' time (South African Business Coalition on HIV and AIDS [SABCOHA], 2008).

2.3.9 Labour (trade unions)

Congress of SA Trade Unions (COSATU) has been a champion for workers' rights, demanding adequate care and treatment for HIV infected people. Together with the Treatment Action Campaign (TAC) COSATU has engaged in a campaign to ensure a universal government grant for all South Africans to meet their basic needs. COSATU has also engaged with business, pharmaceutical companies and donors to improve access to and affordable treatment. Labour unions like COSATU have put pressure on companies and bargaining councils to put in place policies to deal non-discriminately with HIV and AIDS sufferers, but cases of discrimination and dismissals based on HIV status still exist (AIDS Foundation South Africa [AFSA], 2009)

2.3.10 South African Medical Research Council (SAMRC)

The council has a mission "To Improve the Nation's Health and Quality of Life through Promoting and Conducting Relevant and Responsive Health Research" and a vision of building a healthy nation through research.

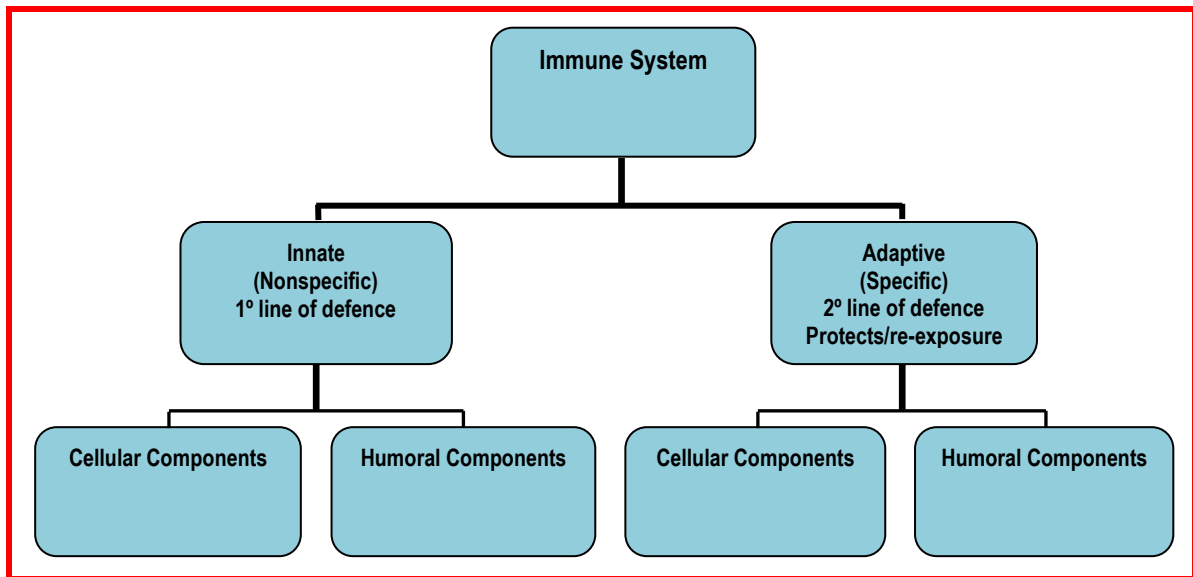
The Council was promulgated in the Government Gazette by Act 58 of 1991 and operates according to the Strategic and Research Plan 2005-2010. A period of growth and transformation has made it possible to consolidate its position as one of the leading health research institutions in Africa and the developing world. The SAMRC had a budget in 2008 of over R482 million; with a Government grant of nine, accounting for 39% of this total; and the remainder coming from other grants and contracts. A large portion of the budget is spent on research and capacity development. A sign of the continuing research is the 669 peer-reviewed publications produced by the 42 SAMRC research units – 40% of South Africa's health research output. The Council is involved in circumcision research projects and plays an important role in vaccine development (South African Medical Research Council [SAMRC], 2008).

2.4 IMMUNE RESPONSE

Pathogens may replicate intracellular (viruses and some bacteria and parasites) or extracellular (most bacteria, fungi and parasites). Different components of the immune system have evolved to protect against these different types of pathogens. In vitro,

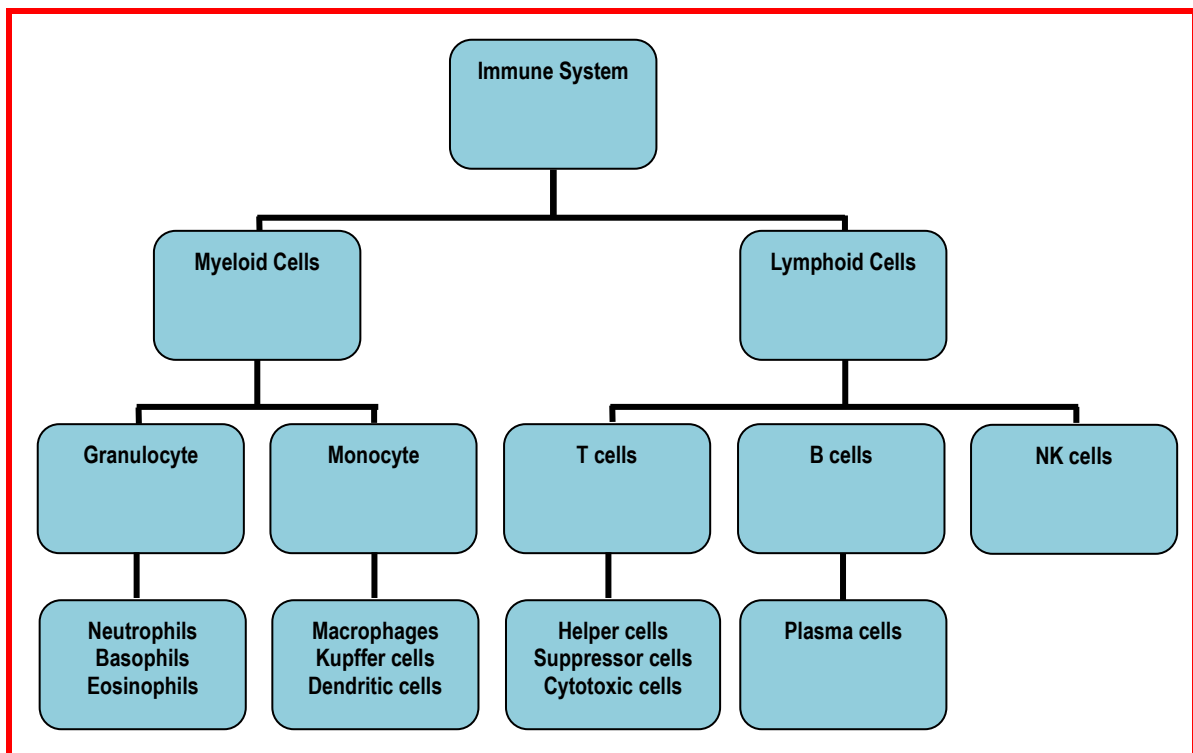
interleukin-2 can induce the proliferation and differentiation of peripheral-blood mononuclear cells from patients infected with the human immunodeficiency virus (HIV) (Kovacs *et al.*, 1995) (see Figures 2.2 and 2.3).

Innate immune response is present at birth and adaptive response develops as the body encounters and recognize pathogens from previous encounters. Illustrated below are the two divisions of immune response and cells responsible for the immune response (Dipiro *et al.*, 2002).



Source: Mayer, 2009

Figure 2.2: Overview of the immune system



Source: Mayer, 2009

Figure 2.3: Cells of the immune system

After the cell has been infected by a virus, two pathways are possible: either the virus becomes latent and the infected cell continues to function, or the virus becomes active and replicates, and can then infect other cells to kill or interrupt the normal function of the cell.

Table 2.5: Main differences of the two branches of the immune system

Non-specific (innate) immunity	Specific (adaptive) immunity
Response is antigen-independent	Response is antigen-dependent
There is immediate maximal response	There is a lag time between exposure and maximal response
Not antigen-specific (Does not have a "memory")	Antigen-specific (Remembers that an invasive organism has been encountered during subsequent exposure)

Source: Mayer, 2009

2.4.1 Cells and mediators of the immune system

All cells of the immune system have their origin in the bone marrow and differentiate along distinct pathways. For T cell development the precursor T cells must migrate to the thymus where they undergo differentiation into two distinct types of T cells, the CD4⁺ T helper cell and the CD8⁺ pre-cytotoxic T cell. Two types of T helper cells are produced in the thymus the TH1 cells, which help the CD8⁺ pre-cytotoxic cells to differentiate into cytotoxic T cells, and TH2 cells, which help B cells, differentiate into plasma cells, which secrete antibodies.

One of the functions of the CD4 cells is to produce interleukin-2 (IL-2), to stimulate other cells (T cells and B cells) in the human immune system to respond to infections. Without the IL-2, T cells do not reproduce as they normally would in response to infection, and B cells are not stimulated to respond to the infection. When CD4⁺ T cell numbers decline below a critical level, cell mediated immunity is lost, and the body becomes progressively more susceptible to opportunistic infections (including those associated with AIDS). Individuals die from malignancies or infections associated with the progressive failure of the immune system (Mayer, 2009).

2.4.2 Human Immunodeficiency Virus (HIV)

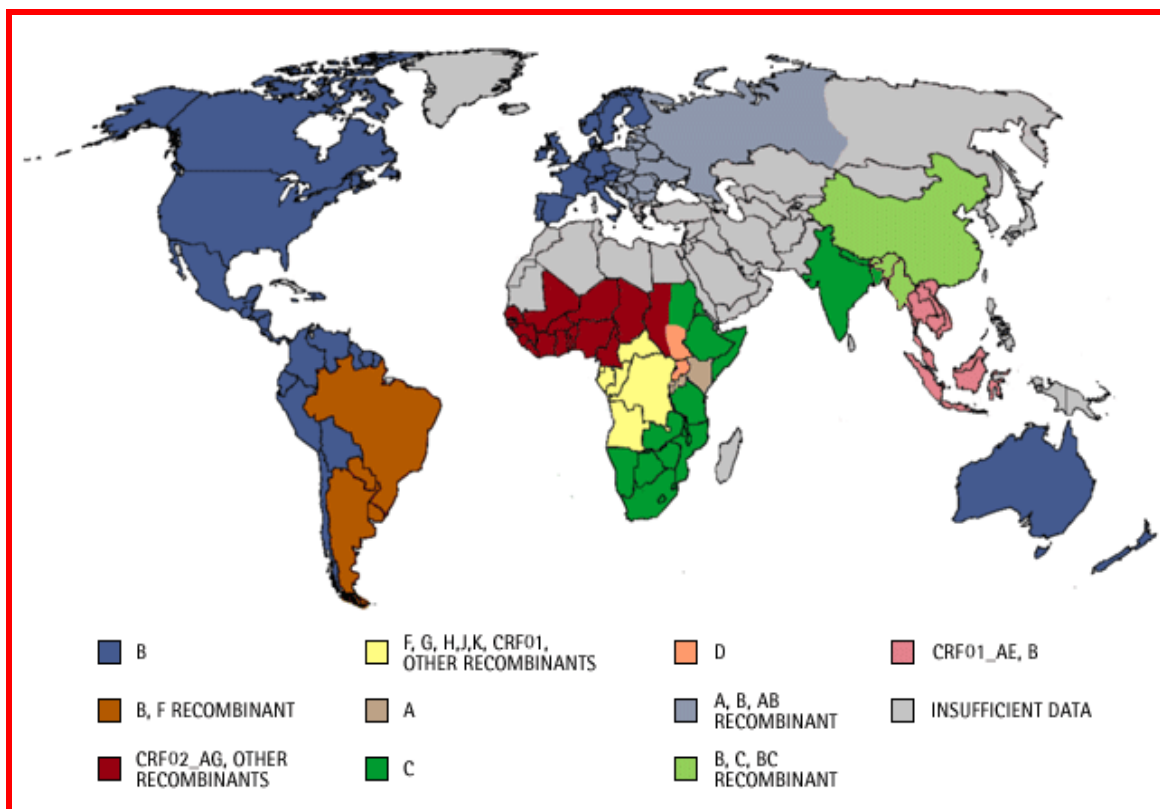
2.4.2.1. Classification

HIV is a member of the genus Lentivirus, part of the family of Retroviridae. Lentiviruses, characteristically have a long incubation period. Lentiviruses are transmitted as single-stranded, positive-sense, enveloped RNA viruses (ICTVdB, 2006).

There are two strains of HIV known to exist: HIV-1 and HIV-2. HIV-1 is the virus that was initially discovered and termed lymphadenopathy associated virus (LAV). It is more virulent, relatively easily transmitted, and is the cause of the majority of HIV infections globally. HIV-2 is less transmittable and is largely confined to West Africa (School of Pharmacy, 2005).

2.4.2.2. Prevalence of HIV strains

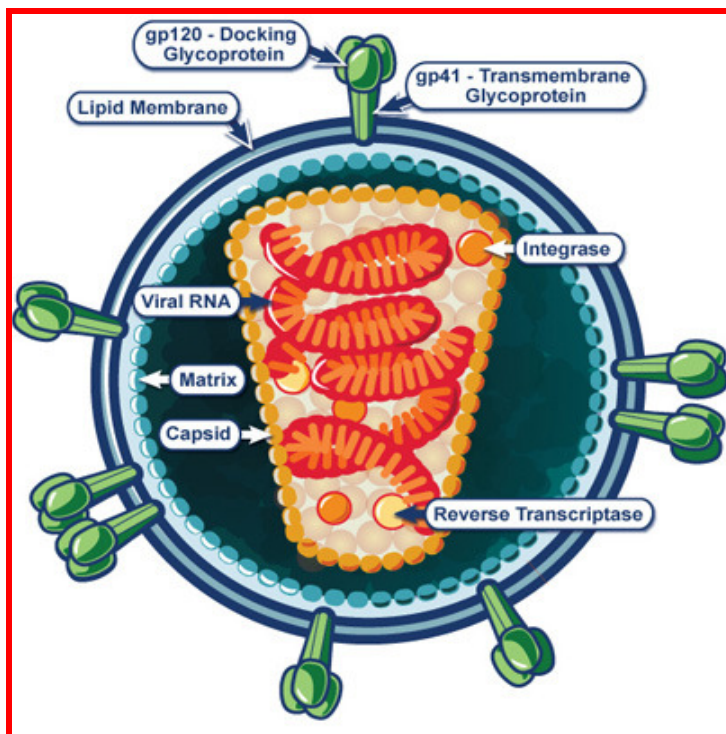
Group M is the most prevalent and is subdivided into eight subtypes (or clades), based on the whole genome, which are geographically distinct. The most prevalent are subtypes B (North America and Europe), A and D (Africa), and C (Africa and Asia); these subtypes form branches in the phylogenetic tree representing the lineage of the M group of HIV-1. In 2000, the last year in which an analysis of global subtype prevalence was made, 47.2 percent of infections worldwide were of subtype C. Most HIV-1 research is focused on subtype B; few laboratories focus on the other subtypes (Quinn, 2008).



Source: Quinn, 2008

Figure 2.4: Global prevalence of HIV sub-types and recombinants

2.4.2.3. HIV structure



Source: NIAID, 2009

Figure 2.5: Structure of HIV

HIV has a core of genetic material (Ribonucleic acid [RNA]), containing the viral replication information surrounded by a protective sheath; the capsid. Antigens on the cell surface, glycoprotein (gp) 120, gp 41, allow the virus to attach to T cells and infect them. Another HIV antigen is an antigen, gp 24, of the core of the virus that is measured to estimate the amount of active free-floating virus in the blood of HIV positive people. HIV RNA has an enzyme called "reverse transcriptase", which means "writing backwards". This protein is crucial for viral replication inside T cells (CD4 cells). The CD4 cell surface has co-receptors, either CCR5 or CXCR4 to which the HIV can also attach itself. (Clapham and McKnight, 2001; Zaitseva *et al.*, 1998).

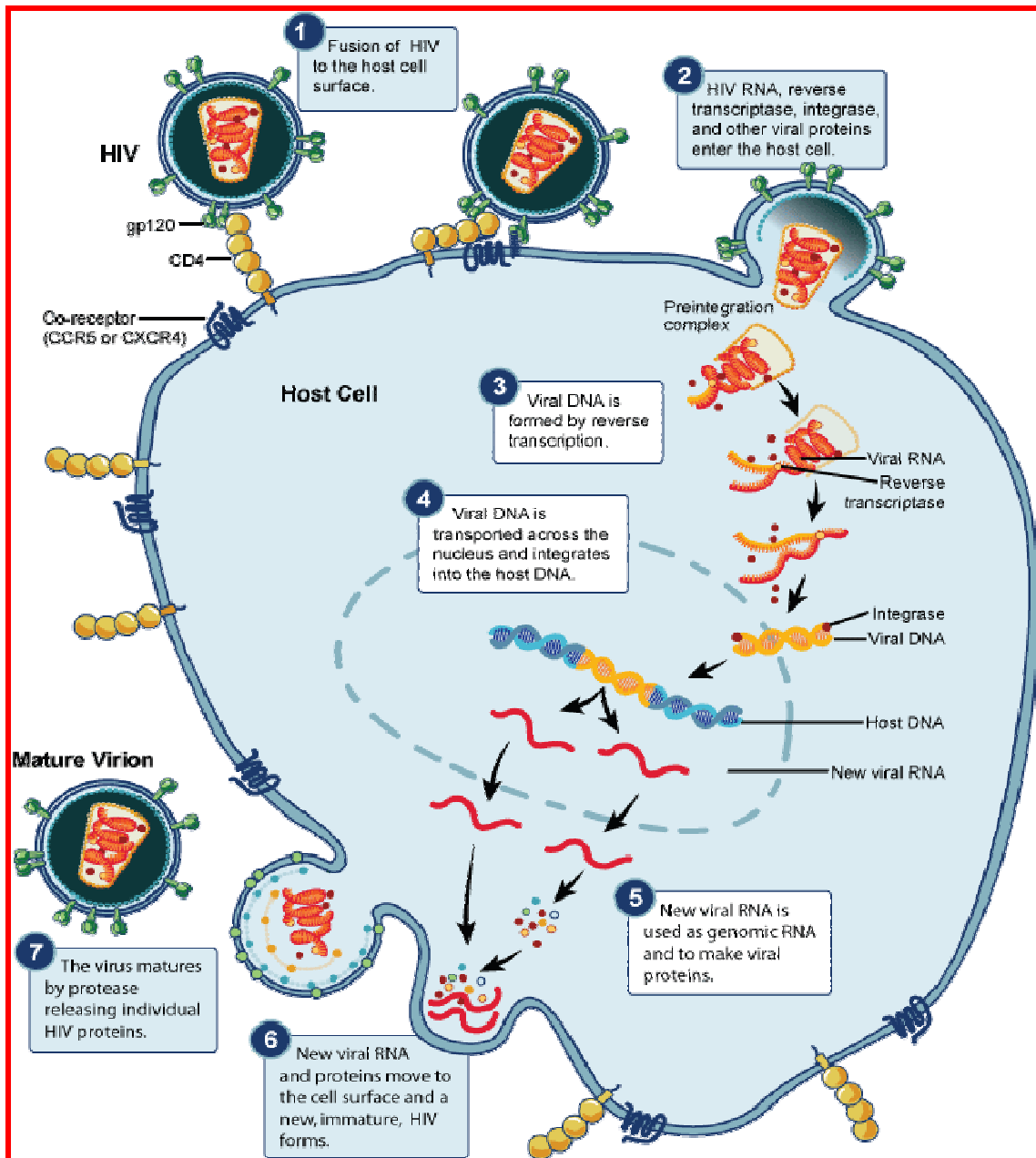
2.4.2.4. HIV replication and reconstruction

HIV differs from many viruses in that it has very high genetic variability. This diversity is a result of its fast replication cycle, with the generation of 10^9 to 10^{10} virions every day, coupled with a high mutation rate of approximately 3×10^{-5} per cycle of replication. Recombinants can only occur between viruses replicating within the same cell and result from 7-30 crossovers per genome per round (Robertson *et al.*, 1995).

HIV is considered a retrovirus because of its capacity to transform RNA into DNA, reversing the natural process that takes place in cells. This is accomplished by the reverse transcriptase.

Once transformed, the viral deoxyribonucleic acid (DNA) will travel into the T cell's nucleus and attach itself to the cell's DNA.

T cells are the main target of HIV in the blood, and act as the host that the virus needs in order to replicate. However, macrophages, B cells, monocytes, and other cells in the body can also be infected by HIV. The T cell has at its surface a CD4 receptor site. The HIV gp 120 antigen is a mirror image of the CD4 protein. HIV can therefore attach to the T cell's surface. When HIV successfully latches onto a T cell, the next step is to inject its core with the viral RNA and the reverse transcriptase. Once inside the cell, the capsid dissolves, liberating the viral RNA and the reverse transcriptase. The viral RNA travels into the T cell's nucleus. Normally the T cell's nucleus communicates with the rest of the cell by transforming DNA into RNA and sending it out of the nucleus. RNA acts as a cell messenger between the nucleus and the rest of the cell. The genetic material's passport to leave the nucleus is to be transformed into single-stranded RNA. In the same fashion, the passport to enter the nucleus is to be transformed into double-stranded DNA. T cells help keep the immune system strong, which makes HIV particularly devastating to immune health. In the process of replication, the virus destroys increasing numbers of T cells leaving the body open to opportunistic infections (Berger, 2007).



Source: NIAID, 2009

Figure 2.6: HIV replication cycle

2.4.2.5. Mutations

The process of reverse transcription is extremely error-prone and it is during this step that mutations may occur. Such mutations may cause drug resistance. The provirus can remain inactive for a long time without triggering viral replication, or it can start dividing, eventually destroying the T cell (Knipe *et al.*, 2001).

2.4.2.6. Tropism

HIV attaches to either the CCR5 or CXCR4 receptor on the CD4 cell to gain entry to the cell in order to replicate (Clapham and McKnight, 2001; Zaitseva *et al.*, 1998). Explanation of the resistance of some individuals to certain HIV strains can be made by referring to tropism. Different strains of the HIV virus use either of the co-receptors while others use both.

A new class of HIV drugs blocks the attachment of the HIV to the cell surface. CCR5 inhibitors like maraviroc are only effective in blocking the CCR5 receptor site and preventing HIV replication. However, the HIV that uses CXCR4 receptors for cell entry will be unaffected, and replication can continue. Macrophage (M-tropic) strains of HIV-1 use the β -chemokine receptor CCR5 for entry and is thus unable to replicate in macrophages and CD4+ T cells. This CCR5 co-receptor is used by almost all primary HIV-1 isolates regardless of viral genetic subtype.

The Trofile™ assay tests the ability of the virus to replicate in the presence of the CCR5 cells (CCR5 tropic). If the virus replicates in the presence of the CXCR4 cells, it is CXCR4 tropic (X4). When HIV replicates in the presence of both CXCR4 and CCR5 cells, it is said to be dual tropic (Zaitseva *et al.*, 1998). Maraviroc-containing regimens can be used for people who are R5 infected.

2.4.3 Immune activation

HIV can infect a variety of immune cells such as CD4 T cells, macrophages, and microglial cells. HIV-1 entry to macrophages and CD4 T cells is mediated through interaction of the envelope glycoprotein's (gp 120) with the CD4 molecule on the target cells and also with chemokine co receptors (Clapham and McKnight, 2001).

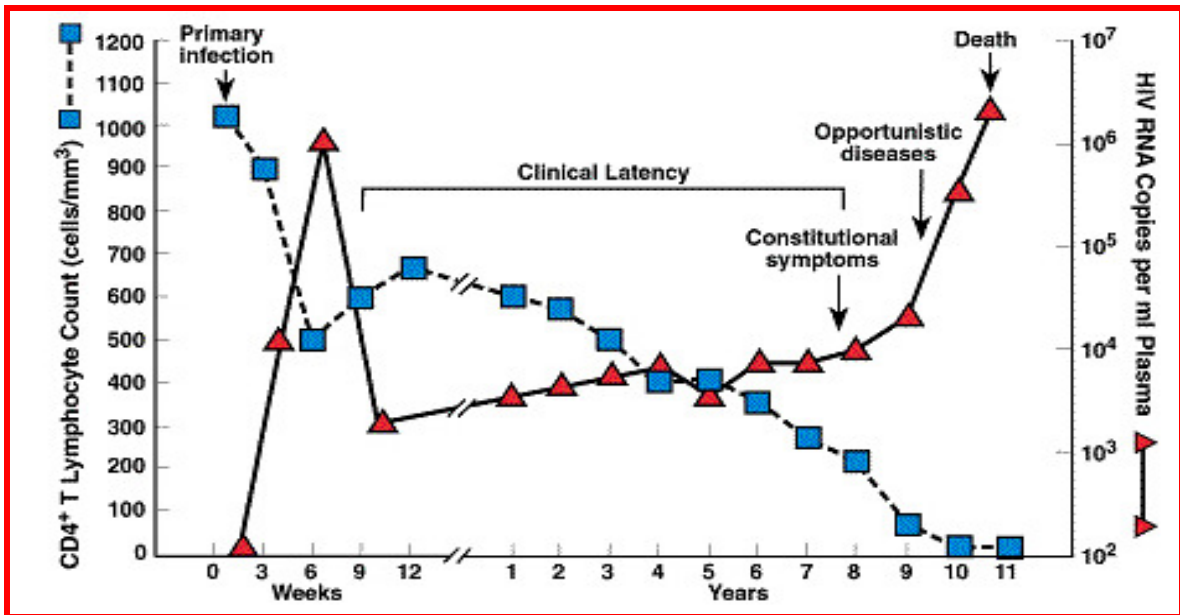
T-cell immune activation causes disease progression in HIV-infected individuals and can be grouped in three main classes:

Stimulation of naive and memory CD4 T-cell activation, proliferation and differentiation, leading to increased CCR5 expression that renders these cells more susceptible to infection.

Alterations of long-term homeostasis of the naive and memory T-cell pools that lead to their gradual depletion and that interfere with the capacity of the host to effectively mount adaptive immune responses.

The induction of inflammation and fibrosis likely destroy secondary lymphoid tissue niches required for the production and homeostasis of CD4 T cells. HIV infection is associated with a progressive decrease of the CD4 T cell count and an increase in viral load (VL). The stage of infection can be determined by measuring the patient's CD4 T cell count, and the VL in the blood (Sodora and Sylvestri, 2008).

2.4.4 The clinical course of HIV infection



Source: Fauci, 1996

Figure 2.7: The relationship between VL (Viral Load) and CD4 count

Clinical markers correlate with clinical progression of HIV disease. They can therefore be used to identify patients most at risk, determine the HIV staging, predict development of opportunistic infections associated with AIDS and monitor the therapeutic efficacy of immune-modulating or antiretroviral treatments (Gupta & Gupta, 2004).

Clinical markers should be easily quantifiable, reliable, clinically available and affordable in resource poor settings (Bentwich, 2005). The clinical markers most often used for these reasons are CD4 count, VL and body mass.

2.4.4.1. CD4 count

CD4 cells are T-helper lymphocytes with surface markers. The determination of the clinical stage of HIV infection and decision when to start antiretroviral therapy (ART); depends on the CD4 count. This marker can also be used and the determination of necessity for treatment changes (Bentwich, 2005). CD4 cell tests are normally reported as the number

of cells in a cubic millimetre of blood, or mm^3 . The number of CD4 cells is counted to assess the immune status of patients, determine the susceptibility to opportunistic infections, the need for HAART treatment or for evaluation of the efficacy defining the onset of AIDS. In normal individuals this count varies between 500 and 1500 cells/ mm^3 (Gallant, 2008).

According to Gallant (2008), the following factors can have an influence on the CD4 count:

- Seasonal and diurnal variation (lowest at 12:30 PM, highest at 8:30 PM)
- Surgery
- Fatigue
- Stress
- Viral infections
- Tuberculosis
- Medications e.g. corticosteroids and cancer chemotherapy

As with measurement of blood pressure, it is best to retest at the same time of day and to use the same laboratory.

2.4.4.2. Viral load

Viral load (VL) is a serology (plasma) test used in addition to the CD4 count to detect the amount of HIV RNA in blood. It is expressed as copies/ml of plasma. Viral load is calculated on a base 10 logarithmic scale. As with CD4 counts and other laboratory tests, the most important factor is the trend in viral load over time, and not a single test result. Measuring VL reflects the extent of the patient's loss of immune function but not the speed of HIV replication in the body. The viral load test is based on PCR (polymerase chain reaction) techniques. Factors that increase viral load are low drug concentration or resistance, non-adherence, poor pharmacokinetics or acute infections (Spacek & Nettles, 2009).

Changes in viral load tend to precede and mirror changes in the CD4 count. As the viral load increases over time, the CD4 count decreases (although ARV medication can reverse these changes). Sustained improvements in several markers (particularly HIV viral load and CD4 count) in combination appear to be the most predictive of clinical effect.

2.4.4.3. Body mass

The importance of body mass as a clinical marker was established in 1987 when the Centres for Disease Control and Prevention (CDC) in the USA included HIV-associated wasting as an AIDS defining condition. HIV-wasting is defined as an involuntary weight loss of 10% of baseline body weight plus either diarrhoea, fever, or weakness for 30 days in the absence of a concurrent illness. Weight loss was found to start early after HIV infection, before any significant compromise in immune status (Mangilli *et al.*, 2006).

“Wasting” is a less precise term that suggests weight loss due to inadequate nutrient intake. Although wasting generally refers to a loss of body mass, questions have been raised about the type of mass lost. In HIV infected individuals, most of the studies suggest that weight loss is an initial fat loss from patients with adequate fat deposits. Fat loss seem to be a sensitive marker, starting at CD4 counts of <600 cells/mm³. Opportunistic infections usually start with CD4 levels of <200 cells/mm³.

Weight loss amongst HIV-infected people is associated with lower CD4+ cell counts and is an independent predictor of mortality (Mangilli *et al.*, 2006). Based on a large longitudinal study, Mangilli and co-workers (2006) reported that for each 100-cell/mm³ decrease in CD4+ count patients' weight decreased with 1.9-kg. The relative risk of mortality increased six fold for patients with a weight loss of 10% from baseline.

HIV associated wasting can be attributed to factors divided into the following two main categories:

- Decreased nutrient intake
- Altered nutrient metabolism

Episodes of acute weight loss were associated with oral symptoms (infections) and difficulty swallowing but not with anorexia. The participants with or without diarrhoea, were not influenced by the use of HAART. HIV load and HAART have independent effects on resting energy expenditure. HAART itself increases resting energy expenditure. Higher metabolic rates may be responsible for the continued weight loss and wasting observed in HIV infection and with the body-shape abnormalities seen during the present era (Mangili *et al.*, 2006).

Treatment of wasting syndrome was studied in some HIV positive participants taking anabolic steroids alone and some with an additional strength training added to the anabolic steroid treatment. It was found that both treatment groups had positive results in

an improvement in body composition but that results did not significantly differ from those participants treated with nutrition alone (Mangilli *et al.*, 2006)

A cohort study performed in France confirmed the role of weight loss in the prediction of disease progression to AIDS, independently of powerful indicators such as low CD4 cell count. It was found that only one cross-sectional measure of body mass index (BMI) can predict the risk of disease progression as well as weight loss measured during follow-up (Malvy *et al.*, 2001).

The following factors affect caloric demands and change in intake:

- HIV disease and its complications (e.g. oral complications making swallowing difficult)
- HAART medication may make patients feel worse before they start to feel better, hence food intake may be decreased. Medication like adefovir is well known for its substantial weight loss effect
- Socio-economic factors (limited money to buy food) underlie the causes and impinge on the treatment of infections
- Medical factors (patients with other chronic diseases, including diabetes)
- Gastrointestinal tract (GIT) dysfunction which is exacerbated by HIV/AIDS (e.g. malabsorption and diarrhoea)

2.4.5 Stages of HIV

HIV infection is marked by four stages and will be discussed according to the WHO classification (WHO, 2008b). Clinical staging is intended for use where HIV infection has been confirmed by HIV antibody testing.

Table 2.6: WHO clinical staging of HIV/AIDS for adults and adolescents

Primary HIV Infection
<ul style="list-style-type: none"> ❖ Asymptomatic ❖ Acute retroviral syndrome
Clinical Stage 1
<ul style="list-style-type: none"> ❖ Asymptomatic ❖ Persistent generalized lymphadenopathy
Clinical Stage 2
<ul style="list-style-type: none"> ❖ Moderate unexplained weight loss (<10% of presumed or measured body weight) ❖ Recurrent respiratory infections (sinusitis, tonsillitis, otitis media, and pharyngitis) ❖ Herpes zoster ❖ Angular cheilitis ❖ Recurrent oral ulceration ❖ Papular pruritic eruptions ❖ Seborrheic dermatitis & Fungal nail infections
Clinical Stage 3
<ul style="list-style-type: none"> ❖ Unexplained severe weight loss (>10% of presumed or measured body weight) ❖ Unexplained chronic diarrhoea for >1 month ❖ Unexplained persistent fever for >1 month (>37.6°C, intermittent or constant) ❖ Persistent oral candidiasis (thrush) ❖ Oral hairy leukoplakia ❖ Pulmonary tuberculosis (current) ❖ Severe presumed bacterial infections (e.g. pneumonia, empyema, pyomyositis, bone or joint infection, meningitis, bacteraemia) ❖ Acute necrotizing ulcerative stomatitis, gingivitis, or periodontitis ❖ Unexplained anaemia (haemoglobin <8 g/dL) ❖ Neutropenia (neutrophils <500 cells/μL) ❖ Chronic thrombocytopenia (platelets <50,000 cells/μL)
Clinical Stage 4
<ul style="list-style-type: none"> ❖ HIV wasting syndrome, as defined by the CDC ❖ <i>Pneumocystis pneumonia</i> ❖ Recurrent severe bacterial pneumonia ❖ Chronic herpes simplex infection (orolabial, genital, or anorectal site for >1 month or visceral herpes at any site) ❖ Esophageal candidiasis (or candidiasis of trachea, bronchi, or lungs) ❖ Extra pulmonary tuberculosis ❖ Kaposi sarcoma ❖ Cytomegalovirus infection (retinitis or infection of other organs) ❖ Central nervous system toxoplasmosis ❖ HIV encephalopathy ❖ Cryptococcosis, extra pulmonary (including meningitis) ❖ Disseminated nontuberculous <i>Mycobacterium</i> infection ❖ Progressive multifocal leukoencephalopathy ❖ Candida of the trachea, bronchi, or lungs ❖ Chronic cryptosporidiosis (with diarrhoea) ❖ Chronic isosporiasis ❖ Disseminated mycosis (e.g. histoplasmosis, coccidioidomycosis, penicilliosis) ❖ Recurrent nontyphoidal <i>Salmonella</i> bacteraemia ❖ Lymphoma (cerebral or B-cell non-Hodgkin) ❖ Invasive cervical carcinoma ❖ Atypical disseminated leishmaniasis ❖ Symptomatic HIV-associated nephropathy ❖ Symptomatic HIV-associated cardiomyopathy

Source: The AIDS Education & Training Centres (AETC) National Resource Centre, 2009

Clinical stage 1 is asymptomatic, as shown in Table 2.6 above.

Clinical progression stages 2-4

- The **second stage** usually includes weight loss <10% bodyweight and can include symptoms as listed in the Table 2.6. This stage is marked by an acute viremia associated in virtually all patients with the activation of CD8⁺ T cells, which kill HIV-infected cells, and subsequently with antibody production (sero-conversion). The CD8⁺ T cell response is thought to be important in controlling virus levels, which peak and then decline, as the CD4⁺ T cell counts rebound to around 800 cells per μl (the normal blood value is 1200 cells per μl). A good CD8⁺ T cell response has been linked to slower disease progression and a better prognosis, though it does not eliminate the virus.
- The **third stage** shows weight loss > 10% body weight and more serious infections listed above. In healthy individuals a strong immune defence reduces the VL in the blood stream. When CD4⁺ T cell numbers decline below critical level, cell-mediated immunity is lost, and infections with a variety of opportunistic micro organisms appear. Common opportunistic infections and tumours, most of which are normally controlled by robust CD4⁺ T cell-mediated immunity then start to affect the patient.
- AIDS, the **fourth and final stage** of HIV infection shows as symptoms of various opportunistic infections.

The Karnofsky score is an assessment of an individual's health and well-being, based on a performance index of physical ability. It is often used in clinical research to monitor and record the health of patients (Aidsmap, 2009).The criteria and ranking are as follows:

- 100% - normal, no complaints or signs of disease
- 90% - normal activities, slight symptoms or signs of disease
- 80% - normal activity with effort, some symptoms or signs of disease
- 70% - can take care of self, but not engage in normal or work activities
- 60% - requires occasional assistance, but can take care of most needs
- 50% - requires frequent help and medical care
- 40% - disabled and needs special care and assistance
- 30% - severely disabled, hospital admission indicated, but no risk of death
- 20% - very ill, requires hospitalisation and supportive measures/ treatment urgently
- 10% - approaching death with rapidly progressive fatal disease processes
- 0% - death

2.5 FACTORS FUELING THE SPREAD OF HIV/AIDS IN AFRICA

2.5.1 HIV-associated stigma

One of the most important factors in the spread of HIV is HIV-associated stigma, which leads to ignorance of HIV status, denial, lack of disclosure and reluctance to seek help. A host of definitions have been formulated but they all conclude that the result of stigma is unfair treatment and discrimination. Descriptions range from words like tainted, discounted individuals to undesirable and ostracized stereo types. Not recognizing and hiding this problem contributes to a delay in testing and treatment or prevention of infection. HIV positive untested pregnant woman can expose their children to infection during delivery and while breastfeeding (Inungu & Karl, 2006).

2.5.2 Socio-economical status

A bidirectional link between poverty and HIV exists. Poverty leads to poor nutrition, weakening the immune system and making poor populations more susceptible to infectious diseases like TB and HIV (Canadian AIDS Society, 2004). In addition women, will, in the light of family commitments (food, clothes) succumb to risky practices like prostitution. The result of both these may inevitably lead to the infection with HIV. In a news article, published 18 August 2009, the deteriorating economic status of African countries, and in this case, Uganda, was highlighted as it influences the adherence patterns of HIV positive people (PlusNews, 2009). The Minister interviewed expressed alarm and highlighted the consequence of this abandonment as a future struggle with resistance and death.

2.5.3 Cultural and traditional practices

2.5.3.1 Married and co-habiting couples

According to Demographic and Health Surveys in five African countries (Burkina Faso, Cameroon, Ghana, Kenya, and the United Republic of Tanzania), two thirds of HIV-infected couples were sero-discordant, that is only one partner was infected. Condom use was found to be rare: in Burkina Faso, for example, almost 90% of the surveyed cohabiting couples said they did not use a condom the last time they had sex.

A separate, community-based study in Uganda has shown that, among sero-discordant heterosexual couples, the uninfected partner has an estimated 8% annual chance of contracting HIV. Strikingly, in about 30% – 40% of the sero-discordant couples surveyed,

the infected partner was female. Indeed, it appears that more than half of the surveyed HIV-infected women who were married or cohabiting had been infected by someone other than their current partner (UNAIDS, 2008a).

In a study conducted in Rwanda and Zambia the research team observed a three- to five-fold lower rate of HIV transmission in mixed-status heterosexual couples (only one partner infected) on ART compared to those not using ART. It can however not be stressed enough that being on ART medication is not be considered a primary means of HIV prevention, but can reduce the risk of infection considerably (WHO, 2008a). The reduction in risk of HIV transmission in this study falls considerably short of the efficacy assumed for antiretroviral therapy in preventing transmission projected by a World Health Organization modelling exercise in which a 99% decline in HIV transmission was envisaged with all infected people being on treatment (Sullivan *et al.*, 2009a).

2.5.3.2. Polygamy and widow inheritance

It is an African practice to ensure continued status and survival of a widow by engaging her in a polygamous union within a family structure, usually her husband's younger brother (South African History Online, 2009). The inherited widows were found to have casual sex with multiple partners (Okeyo & Allen, 1994). In urban areas where adhering to traditional practices is no longer the norm, men may include sex workers and others woman in their sexual practices. Men with three or more wives were more likely to engage in extramarital sex (Caldwell, 2000). Another misconception amongst HIV infected men is that sex with a young girl will cure them (De Bruyn, 1992).

2.5.3.3. Dry sex

This is a concept where drying and tightening of the vagina enhances a male's experience, by increased friction. The lack of lubrication results in lacerations of the epithelial lining of the vagina creating a portal for HIV entry (Runganga *et al.*, 1992). Condoms breaking during increased friction and exposure to STIs are also possible.

2.5.3.4. STIs

The presence of untreated STIs significantly increases the possibility of contracting HIV. In Southern Africa, men suffering with bleeding sores caused by STIs, seem not to be deterred from sexual intercourse with women (Holmberg *et al.*, 1988).

2.5.4 War and armed conflicts

Armed conflicts destroy economic and social infra-structures. They result in people losing their livelihood, fleeing the region, being separated from family and loved ones and being raped or turning to prostitution. A life of poverty, powerlessness and social instability increase a societies' vulnerability to HIV/AIDS. Combating HIV/AIDS will further deplete resources and increase competition, fuelling political instability and violence (Roderick, 2006). Peacekeepers and armed forces are also guilty of perpetrating sexual abuse and exploitation (Fleshman, 2004). It is therefore not surprising that countries with a history of recent civil unrest (South Africa, Rwanda, Congo, Zimbabwe and Ethiopia) have a high prevalence of HIV infection.

2.5.5 Labour and migration

HIV infection in rural areas emanates from urban areas and migration is one of the major contributing factors to this pattern (Lagarde, 2003). Spouses travel without partners, engaging in casual sex with prostitutes with a higher infection rate than the general adult population. Miners, farm workers, military personnel, transport workers and others finally return home with money and infect their wives or girl friends, and they in return transmit the virus to the children during childbirth or breastfeeding. This pattern is striking in countries with extensive mining operations (South Africa, Zimbabwe, Zambia and Congo).

2.5.6 Drug and alcohol abuse

Heterosexual transmission is by far the most common mode of HIV transmission in Africa. However, the significance of intravenous-drug use appears to be higher than commonly believed (United Nations Office of Drug and Crime [UNODC], 2009). Heroin addiction is a serious problem found primarily in Kenya and Mauritius but is now emerging in other countries in the region, including Ethiopia. In Mauritius, where HIV and AIDS prevalence rates are lower than in other Eastern and Southern African countries, a sample of HIV-infected people revealed that 21% used intravenous drugs.

Alcohol consumption reduces a person's ability to reason and make informed choices concerning safer sex and protection from HIV infection. In a study of 149 men and 78 women attending an STI clinic in Cape Town, (Simbayi *et al.*, 2004) it was found that 52% of men and 17% of women abuse alcohol. Alcohol abuse was found to be associated with greater numbers of sex partners in the month prior to the survey. Other compelling reasons included a history of condom failures, a lifetime history of sexually transmitted

infections, as well as lower rates of practicing risk-reduction skills. These findings underscore the need for comprehensive and accessible substance abuse treatment programmes.

2.5.7 Homosexual communities

Several recent studies suggest that unprotected anal sex between men is probably a more important factor in the epidemics in sub-Saharan Africa than is commonly thought. In Zambia, one in three (33%) surveyed men who have sex with men tested HIV-positive. In the Kenyan port city of Mombasa, 43% of men who said they had sex only with other men, were found to be living with HIV. A study by the WHO conducted in Dakar, Senegal found an HIV prevalence of 22% among 463 men who have sex with men (UNAIDS, 2008c).

2.6 TRANSMISSION OF INFECTION

Major transmission routes include the following:

- Blood and blood products
- Semen
- Vaginal fluid
- Pre-ejaculate
- Unprotected sexual intercourse (homo- and heterosexual)
- Breast milk
- Transmission from an infected mother to her baby at birth

HIV has been found at low concentrations in the saliva, tears and urine of infected individuals but no evidence of transmission in this fashion has been found. Facilitating factors in HIV transmission include poor hygiene and poor nutrition (WHO, 2008b).

2.6.1 Sexual route (intercourse)

The majority of HIV infections are acquired through unprotected sexual relations. Sexual transmission can occur when infected sexual secretions of one partner come into contact with the genital, oral or rectal mucous membranes of another.

Sex work is an important factor in many of West Africa's HIV epidemics. More than one third (35%) of female sex workers surveyed in 2006 in Mali were living with HIV, and infection levels exceeding 20% have been documented among sex workers in Senegal and Burkina Faso. Sex work plays an important, but less central, role in HIV transmission

in Southern Africa, where exceptionally high background prevalence results in substantial HIV transmission during sexual intercourse unrelated to sex work (UNAIDS, 2008c).

Condoms are the preferred method of the prevention of sexual spread of HIV. Some critics suggest that the increased availability of condoms will lead to promiscuity. This was refuted in a meta-analysis of 174 studies published in the March 2006 edition of the "Journal of Acquired Immune Deficiency Syndromes" where the use of condoms did not seem to lead to earlier sex, more sex, or more partners when used in HIV prevention (Smoak *et al.*, 2006)

2.6.2 Male circumcision

Three randomized trials conducted in South Africa, Kenya and Uganda over a two year period, resulted in a reduced rate of infection of between 51% and 60% of circumcised, heterosexual men. The findings have led to a recommendation by WHO to include this practice and correct condom use in a comprehensive HIV prevention package. Another study by the Medical Research Council (SAMRC) and Human Sciences Research Council (HSRC) reported in the SA Medical Journal in 2008, found no difference in HIV infection of circumcised and uncircumcised men. Circumcision is only partly protective as the female partner is still at the same risk. Women's groups, such as the International Community of Women Living with HIV/AIDS (ICW), have argued that male circumcision is being promoted as an HIV prevention strategy without taking into full account the possible impact on women's sexual and reproductive health. One concern was that if men believed circumcision eliminated the risk of HIV infection, they would continue to have multiple sexual partners and penetrative sex without a condom (Siegfried *et al.*, 2003). Circumcision with an unsterile blade can still lead to infection.

2.6.3 Blood and blood products

If infected blood comes into contact with any open wound, HIV may be transmitted. This transmission route can account for infections in intravenous drug users, haemophiliacs and recipients of blood transfusions (Kaplan, 1992). People who give and receive tattoos, piercing and scarification procedures can also be at risk of infection.

In a press release reported by Good News in July 2008, Dr Sam Gulube, Director of the South African National Blood Service (SANBS) declared that blood transfusions in South Africa are safe from HIV infection since a more advanced HIV testing method was introduced in South Africa in October 2005. SANBS uses standard HIV testing methods to

test blood for the presence of antibodies in the immune system, while the nucleic acid amplification testing (NAT) method tests the properties of nucleic acids for viruses to reduce the window period during which viruses can be detected (SANBS, 2008).

2.6.4 Mother-to-child transmission (MTCT)

The transmission of the virus from the mother to the child can occur in utero during pregnancy and intra-partum at childbirth. However, where combination antiretroviral drug treatment and Caesarean section are available, this risk can be reduced to as low as one percent (Petropoulou, 2006).

It is advised that pregnant woman to change from a regimen containing Efavirenz to Nevirapine (DOH, 2004). The percentage of HIV-infected pregnant women receiving services to prevent mother-to-child transmission increased from 15% in 2005 to 33% in 2007. There is a 30% risk of HIV transmission from a HIV-positive mother to her child during pregnancy or delivery or via breastfeeding. This risk is significantly reduced when the mother and child are given antiretroviral therapy (UNAIDS, 2008c).

2.6.5 Other routes

HIV has been found at low concentrations in the saliva, tears and urine of infected individuals, but there are no recorded cases of infection by these secretions and the potential risk of transmission is negligible (WHO, 2008b).

2.7 STEMMING THE SPREAD OF HIV

Inungu and Karl (2006) identified six essential activities when planning a comprehensive prevention programme (These activities also feature in the NSP for 2011).

Educate. The population has to know as much as possible about HIV prevention, spread (transmission) and signs and symptoms of the disease.

Promote knowledge of HIV status. This is the first step in eliminating all future risky behaviour. HIV negative people still have to employ protection. HIV positive people have to inform sex partners of their status and seek counselling and care.

Care for the marginalized and those already infected. This principle has as its goal reduction of the infectiousness of positive patients and decreasing the incidence of new

cases. Good nutrition may delay the onset of terminal phase of AIDS and also reduce costly treatment.

Train effective personnel to staff and manage HIV prevention programmes. Senegal and Uganda are two nations with strong leadership, and have shown a decline in HIV incidence.

Empower people and encourage self-efficacy. Provision of skills to become financially independent, will result in less exploitation by men. Young girls must also be encouraged to stay in school and become educated.

Banish harmful rituals and promote love and justice. Traditional practices, including widow inheritance, dry sex and polygamy must be outlawed.

2.8 HIV TESTS

It is standard practice in virology to use virus isolation or co-culturing to confirm the presence of a virus in any sample. This approach was a requirement stated by Prof Montagnier (Director of the World Foundation for AIDS Research and Prevention in Paris) and one of the Nobel laureates for 2008 credited with co-discovery of the HI virus in the 1980s (Cookson, 2008).

Most people infected with HIV will develop a detectable level of antibodies within three months of infection (UNAIDS 2008a). The condition of testing positive for HIV antibodies in the blood is called sero-conversion, and HIV negative people who have become HIV-positive are called sero-converters. The veracity and reliability of these tests are key to the validity, reliability, quality and accuracy of epidemiological data used by any country. All HIV diagnosis in South Africa is supported by laboratory tests. HIV screening is always followed by two confirmatory tests. All immunoassays in South Africa are designed, calibrated, optimised and standardised to the level of their discriminating power to discriminate between negative and positive cases. Comparison of data from three laboratories in South Africa shows a low false positive rate (DOH, 2001).

ELISA-HIV-1 testing consists of initial screening with an enzyme-linked immuno-sorbent assay (ELISA) to detect antibodies to HIV1 and confirmatory testing done with a more specific supplemental test (e.g. WESTERN BLOT TEST). The antibody ELISA test is based on the reaction between the unique viral protein (the gp24 proteins) and serum antibodies from a blood sample. An advantage of this test is its specificity and high sensitivity, making it widely acceptable since it is able to detect all the possible HIV

infections. Only specimens that are repeatedly reactive by ELISA and reactive by WESTERN BLOT TEST are considered HIV-positive and indicative of HIV infection (Essig, 2009). Possible reasons for concern from the South African Department of Health may be that gp24 proteins, the basis for the ELISA antibody test, have been found to cross react with a wide variety of uninfected human tissue and blood samples from other disease states; for example, antibodies to candida and mycobacterium infections cross react with gp 24.

As with the ELISA test, the WESTERN BLOT TEST can produce a non-specific positive reaction to a number of diseases (including tuberculosis, a variety of parasitic infections and other viral infections) in the absence of HIV infection (DOH, 2001). This might be regarded as a disadvantage of the two tests.

POLYMERASE CHAIN REACTION (PCR) TEST is a third test not very often used. This test identifies the genetic material (RNA) of HIV. This test requires technical skill and expensive equipment. The advantage of the test is its usefulness in the days or weeks after exposure when only genetic material may be found and antibody concentration cannot be detected (WebMD, 2009).

2.9 TREATMENT FOR HIV

2.9.1 Vaccine

The only way of lowering infection rates would be by uninfected people avoiding infection (achieved by abstinence from sex) or successful vaccination against the causative agent. No preventative vaccine is available, although the first vaccine tests in America began in 1987. Insufficient information on immune correlation of protection is currently available and the high immunologic variability of HIV strains makes the development difficult. Since 1987 more than 30 vaccines have been tested in over 70 phase I/II clinical trials in both industrialized and developing countries (Esparza, 2001). The advantage of an effective vaccination is its cost effectiveness.

However, the development phase of vaccines can result in added risk. A report published in the January 2008 US National Library of Medicine and National Institutes of Health magazine demonstrated a typical example of the results being observed in the development of vaccines. The first trial of a test vaccine designed to strengthen cellular immunity has shown no protection against infection and has now shown an increase in the rate of HIV infection in individuals with prior immunity against the virus vector used in the

vaccine (Sekaly, 2008). The PAVE 100 trial, based on a vaccination regimen developed at the National Institutes of Health (NIH) Vaccine Research Centre in America, was supposed to begin enrolling participants in October 2007. The presence of vector adenovirus 5's antibodies in previously circumcised men (formed after prior exposure to the vector used in both PAVE and STEP vaccine regimens) lead to both trails being placed on hold. The original design of the PAVE trial involved 8500 participants on 3 continents. PAVE was subsequently scaled back to 2400 circumcised gay men in the United States who screened negative for antibodies to adenovirus 5.

Two HIV vaccines developed by the South African AIDS Vaccine Initiative (SAAVI), a lead programme of the SAMRC, began clinical testing in the United States in December 2008 and in South Africa in January 2009. A Phase I safety trial called SAAVI 102/HVTN 073 is being conducted in the USA. It will test two vaccines developed by the University of Cape Town and based on HIV subtype C, the dominant strain in southern Africa. These are the first HIV test vaccines developed in Africa to progress into human clinical trials. A Phase I trial for an HIV vaccine generally involves volunteers who do not engage in risky sexual behaviour or intravenous drug use and are therefore at low risk for infection. This phase tests for safety, tolerability and side-effects but also starts to look at the effect of the vaccine on the human immune system. If successful, larger phase II and III trials follow which involve more volunteers and provide information on whether the product is able to protect against infection. A vaccine can only be licensed for public use after it has been tested and found successful in all three phases of clinical trials (SAMRC, 2008).

2.9.2 Post-exposure prophylaxis

A course of antiretroviral treatment administered immediately after accidental exposure to infected blood or body fluid such as rape, referred to as post-exposure prophylaxis, is believed to reduce the risk of infection. This treatment must be started as quickly as possible (within 1 to 2 hours) for 28 days. Post-exposure prophylaxis consists of Zidovudine (AZT) and Lamivudine (3TC) and in severe cases a third drug lopinavir/ritonavir is added. Psycho-social support must always accompany incidents of accidental exposure (DOH 2004).

2.9.3 HAART

Current treatment for HIV infection, referred to as Highly Active Antiretroviral Therapy or HAART, has been highly beneficial to many HIV-infected individuals since its introduction in 1996. The objective of HAART is to achieve optimal viral suppression, prevent drug

resistance and achieve the highest adherence rate possible from the patient (>95%) (School of Pharmacy, 2005). Current HAART options are combinations (or "cocktails") of at least three drugs belonging to at least two types, or "classes," of antiretroviral agents. The different classes of ARVs and examples of drugs within each class are shown in Table 2.7.

Table 2.7: HIV drug classes with examples

CLASS	DRUGS
Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI)	lamivudine (3TC), stavudine (d4T), zidovudine (AZT), didanosine (ddl), abacavir (ABC), tenofovir (TDF), emtricitabine (FCT)
Nucleoside Reverse Transcriptase Inhibitors (NRTI)	efavirenz (EFV), nevirapine (NVP)
Protease Inhibitors (PI)	indinavir (IDV), lopinavir (LPV), ritonavir (RTV), nelfinavir (NFV)
Integrase Inhibitors	raltegravir (RAL), elvitegravir (EFG)
Fusion Inhibitors	enfuvirtide (ENF)
CCR5 Inhibitors	maraviroc (MVC)

Source: WHO, 2006

When combined with another drug ritonavir is written as /r, e.g. LPV/r is the combination of lopinavir and ritonavir.

Table 2.8: Side-effects of ARVs

Drug	Side effects
Didanosine	Pancreatitis, peripheral neuropathy, GIT effects (bloating, diarrhoea, nausea) and lactic acidosis
Efavirenz	Dizziness, insomnia, impaired concentration, drowsiness, abnormal dreams, hallucinations, manic and paranoid reactions, depression, skin rash and Stevens-Johnson syndrome
Lamivudine	Diarrhoea, pancreatitis, lactic acidosis
Nevirapine	Skin rash, deadly hepatitis, nausea and vomiting
Ritonavir	Bitter taste, GIT symptoms (diarrhoea), raised cholesterol and triglyceride (TG), lipodystrophic changes
Stavudine	Peripheral neuropathy, hepatic steatosis, lactic acidosis, pancreatitis
Zidovudine	Headache, malaise, myalgia, anorexia, nausea, anaemia and neutropenia (bone marrow suppression), lactic acidosis

Source: (DOH, 2004)

Table 2.9: Combinations (regimens) most widely used in South Africa

REGIMEN	PI	NRTI	NNRTI
NNRTI BASED	=====	2	1
TRIPLE NRTI BASED	=====	3	=====
PI BASED	1 OR 2	2	=====

Source: School of Pharmacy, 2005

Table 2.10: Toxicities of first-line ARVs and recommended substitutes

ARV drug	Common associated toxicity	Suggested substitute
ABC	Hypersensitivity reaction	AZT or TDF or d4T
AZT	Severe anaemia or neutropenia Severe gastrointestinal intolerance	TDF or d4T or ABC
AZT	Lactic acidosis	TDF or ABC
d4T	Lactic acidosis Lipoatrophy / metabolic syndrome	TDF or ABC d
D4T	Peripheral neuropathy	AZT or TDF or ABC
TDF	Renal toxicity (renal tubular dysfunction)	AZT or ABC or d4T
EFV	Persistent severe central nervous system toxicity	NVP or TDF or ABC (or any PI h)
EFV	Potential teratogenicity (pregnancy first trimester or women not using adequate contraception)	NVP or ABC (or any PI h)
NVP	Hepatitis Hypersensitivity reaction	EFV or TDF or ABC (or any PI h)
NVP	Severe or life-threatening rash (Stevens- ABC Johnson syndrome)	TDF or (or any PI h)

Source: WHO, 2006

2.9.3.1. ARV combination construction

Specific guidelines apply when constructing treatment combinations and certain combinations should be avoided as they could result in toxicity, virological failure or antagonism (see Table 2.11). Mono therapy or dual therapy should not be used to treat chronic HIV infection. PMTCT and post-exposure prophylaxis (PEP) are exceptions to this rule (WHO, 2006).

Table 2.11: NRTI combinations to be avoided

Toxicity	Virological failure	Antagonism
d4T + ddl	TDF + 3TC + ABC	d4T + AZT
3TC + FTC	TDF + 3TC + ddl	
	TDF + ddl + any NNRTI	

Source: WHO, 2006

2.9.3.2. First-line therapy ARV drugs

One reason for expanding the range of drugs recommended as choices for first-line therapy is the long-term toxicity of stavudine, widely used in national programmes as the preferred NRTI. The reason for choosing this drug is based on cost and availability, but due to long-term lipoatrophy it is no longer the preferred choice. At the time of this study, two ARVs, e.g. tenofovir (relatively cheap and a once daily dose) and abacavir were previously recommended for second-line ART and emtricitabine was been added as an equivalent for lamivudine for first-line ART options. Affordability of treatment is still one of the WHO's main objectives when drug suggestions are made. Simplifying drug regimens

and managing toxicity and drug interaction of first-line drugs have been prioritised. Evidence of triple NRTI regimens being less effective (virologically) in clinical trials than other first line combinations is the reason why triple NRTI combinations should be reserved for people already taking medication for certain situations, such as tuberculosis (WHO, 2006).

2.9.3.3. *Second-line therapy drugs*

Drugs like didanosine should be reserved for second-line treatment. A combination of tenofovir and didanosine with boosted PIs can be used with caution and monitoring. Second-line therapy remains based on the PI class, ideally supported by an NRTI backbone using two new (previously unused) agents to minimize cross-resistance; ritonavir-boosted PIs are recommended in order to enhance potency. The choice of new NRTIs for use following the failure of an initial two NRTIs/NNRTI-based regimen remains a challenge. The efficacy of NRTIs in a second-line regimen can be expected to be compromised by the accumulation of NRTI mutations when switching is based on clinical or immunological failure (WHO, 2006). Table 2.12 shows some of the WHO recommendations for switching from first-line to second-line ARV drugs.

Table 2.12: Recommendations for switching from first- to second-line drugs

First-line regimen		Second-line regimen	
		NRTI component	PI component
Standard strategy	AZT or d4T + 3TC +NVP or EFV	ddl + ABC or TDF+ ABC or TDF+ 3TC (± AZT)	RI/r
Standard strategy	TDF + 3TC +NVP or EFV	ddl + ABC or ddl + 3TC (± AZT)	
Standard strategy	ABC + 3TC + NVP or EFV	ddl + 3TC (± AZT) or TDF + 3TC (± AZT)	
Alternative strategy	AZT or d4T + 3TC b + TDF or ABC	EFV or NVP ± ddl	

Source: WHO, 2006

2.9.3.4. *Starting HAART*

The first six months on ART are of utmost importance to establish a routine (Brinkhoff *et al.*, 2008). Clinical and immunological improvements are not always apparent and drug toxicities may emerge and some patients fail to respond as expected or may exhibit clinical deterioration initially. Non-adherence, in the first few weeks following the initiation of ART, is seen most commonly in patients with severe immunodeficiency. The apparent failure of a patient with advanced HIV disease to improve initially does not necessarily

reflect a poor response to ART. Reasons may be that HIV viral replication is not yet controlled by ART and that it takes time for the patient's immune system to strengthen. It also takes time for reversal of the catabolism associated with HIV infection, particularly in patients with significant HIV-associated wasting. A strengthening of the immune system may even cause exacerbation of previously subclinical infections (e.g. tuberculosis). A condition called inflammatory reconstitution syndrome (IRS) includes clinical signs and symptoms resulting from the restored ability to mount an inflammatory response associated with immune recovery (Müller *et al.*, 2010).

WHO is evaluating strategies for simplifying or enhancing long-term second-line therapy. A boosted PI mono-therapy following an initial phase of three-drug therapy is under evaluation in treatment-naïve patients with promising results by study groups. The strategy has many similarities with standard TB treatment, but unlike TB treatment, however, ART does not have an endpoint representing cure (WHO, 2006).

2.9.3.5. *Switching treatment*

Current WHO guidelines for ART in resource-limited settings suggest that if viral load (VL) testing is not available a switch to a second-line regimen should be made if an individual develops new symptoms of serious immune suppression (WHO stage 3 or 4 symptoms), or if the CD4 cell count declines by 50% from its peak or 33% within the past six months. The WHO definition of treatment failure for patients on first-line ART regimen is shown in Table 2.13.

Viral load testing may prevent the development of resistance. Switching treatment in response to viral load test results rather than CD4 cell counts or new symptoms would not result in significantly improved survival (WHO, 2006).

Table 2.13: Definition of treatment failure for patients on first-line ARV regimen

Failure	Definition
Clinical failure	New or recurrent WHO stage 4 conditions
CD4 cell failure	<ul style="list-style-type: none"> • Fall of CD4 count to pre-therapy baseline (or below); or • 50% fall from the on-treatment peak value (if known); or • persistent CD4 levels below 100 cells/mm³
Virological failure	Plasma viral load above 10 000 copies/ml

Source: WHO, 2006

2.9.3.6. Determining the optimum time to start HAART

In an attempt to avoid patients defaulting on HIV treatment, two aspects should be considered prior to medication initiation: determination of patient readiness for lifelong, 100% adherence and measurement of VL and CD4 count

The timing for HIV treatment initiation is still being debated. There is no question that treatment should be started before the patient's CD4 count falls below 200 (DOH, 2004), but there is some evidence from cohort studies that treatment should be started before the CD4 count falls below 350 or even before it falls below 500. In a nine-year study review conducted by a research team at the University of Washington, including 17000 HIV positive patients from different studies in American states (1996 to 2005), the results showed that patients with CD4 levels between 351 and 500 cells were 69% more likely to be alive at the end of the nine-year period, while those initiating drug treatment at CD4 counts of 500 or more were 94% more likely to have survived. Researchers concluded from study evidence that the survival benefit of starting treatment earlier outweighed the potential deleterious effects (Kitahata *et al.*, 2008). In patients with a CD4 cell count above 350cells/mm³, initiation of therapy should be strongly considered because of the high risk for cardiovascular disease, co-infection with hepatitis B or C (resulting in faster progression of liver disease), and the occurrence of HIV-associated nephropathy (OARAC, 2008).

In those countries where CD4 counts are not available, patients with WHO stage III or IV disease should be offered treatment (WHO, 2008b).

Research to improve current treatments includes decreasing side effects of current drugs, further simplifying drug regimens to improve adherence, and determining the best sequence of regimens to manage drug resistance.

2.10 ADHERENCE TO HAART

Adherence is a dynamic behaviour with some individuals showing differing patterns when measured at different times or intervals. The importance of adherence to ART is linked to the development and rapid replication of resistant viruses during periods of treatment interruption (Horizons/Population Council, 2004). Adherence is regarded as a therapeutic alliance or contract between the patient and the physician in which the patient is not merely following instructions (Osterberg & Blaschke, 2005).

The question of adherence is complex. A meta-regression analysis (Mills *et al.*, 2006) published in the Journal of American Medical Associations (JAMA) of 27 studies in sub-Saharan African countries and 31 North American studies indicated adequate adherence in 77% of African patients and only 55% of North American patients. There were some differences in the study populations, including duration of therapy, regimen complexity and disease stage. Some of the reasons offered for the higher level of African adherence were less complicated regimens or the fact that patients were in early treatment phase with dramatic clinical improvement and without long term side effects.

A table comparison of adherence studies conducted in developed and developing countries as well as different countries on the African continent was presented at the 2008 “Access to Health Care in Africa” conference in Cape Town and illustrated the variation in levels of adherence (Meyer, 2008a) (see Table 2.14).

Table 2.14: Comparison of studies conducted in developed and developing countries as well as different countries on the African continent

Study	Mean Adherence	Source
REACH Project (US) (n = 110)	70%	(Bangsberg, 2006)
San Francisco (US) (n = 84)	75.9-84.2%	(Giordano <i>et al.</i> , 2004)
Tanzania (n = 107)	90%	(Hardon <i>et al.</i> , 2007)
Botswana (n = 496)	93-98%	(Hardon <i>et al.</i> , 2007)
Uganda (n = 34)	91-94%	(Oyugi <i>et al.</i> , 2004)
South Africa (n = 278)	87.2%	(Orrell <i>et al.</i> , 2003)

Source: Meyer, 2008a

The most important factor to ensure adherence to HAART would be to solve and eliminate non-adherence problems and reasons. Patients adhering to HAART are being enthused by the improvement in general health they experience making it possible to continue leading a normal life. This effect was demonstrated by Swedish data collected via two cross-sectional patient surveys in 1998 and 2002, The level of adherence improved from 28% in 1998 to 57% in 2002, possibly due to simplified treatment and a new multi-professional treatment model at the clinic (Södergård *et al.*, 2006).

The possibility of developing high levels of HIV-1, (often HAART resistant), if treatment is stopped, may also act to improve adherence.

2.10.1 Optimum levels of adherence

The majority of studies published to date still regard missing “as few as possible” doses as the norm to avoid virus replication and drug-resistance. A study done on ninety nine people for six months as far back as 2000 demonstrated that adherence above 95% ensured superior virological and immunological response (Paterson *et al.*, 2000).

The results shown in Table 2.15 were obtained after three months of treatment.

Table 2.15: Association between adherence and VL

% Medication (doses) taken	% Patients with VL suppression (undetectable VL)
>95%	81
90%-95%	64
80%-90%	50
70%-80%	25
< 70%	6

Source: Patterson *et al.*, 2000

It is safe to assume, then, that treatment failure most often occurs with medication adherence levels of less than 95%, which have also been linked to the development of drug resistance (Kaplin & Hsu, 2009). An adherence rate of at least 95% is recognised as a successful level in the Horizons/Population Council study (Horizons/Population Council, 2004). To achieve 95% adherence a patient must not miss more than one dose a week for a three times daily regimen or no more than three doses per month for a twice daily regimen.

In a study report of 32 patients followed for a three year period in Canada, 44% patients with intermediate adherence levels (80-90%) developed at least one virological breakthrough (Genotype mutation). The patients with adherence levels above 90% and below 80% had 17% and 7.7% development of one virological breakthrough during the study (Raffa *et al.*, 2006)

Reported results from a group of studies with NNRTI based regimens presented at the 3rd International Conference on HIV Treatment Adherence held during March 2008 in Jersey City USA, diverge from the view that only a average adherence of 95% will ensure viral suppression (Parienti *et al.*, 2008). Different studies were presented to demonstrated different interruption patterns. Researchers suggest that virological rebound can more easily occur after certain interruption periods than with low-to-moderate overall adherence levels. The Cohen FOTO (five-days-on, two-days-off) Concept demonstrated suppression of viral replication to less than 50 copies/ml during the 48 week study (Cohen *et al.*, 2007).

Patients dealing with an already complicated treatment regimen consisting of a cocktail of medication taken at different times during the day should not be confused and expected to memorise drug holidays or periods on-and-off medication. A tablet taking routine according to a strict time table will keep adherence as close to 100% as possible to eliminate virological breakthrough. Taking medication everyday at the same time results in even lower viral loads (Liu *et al.*, 2006a)

2.10.2 Life-long adherence

A decrease in morbidity and mortality of people dying from HIV infection and AIDS can only be achieved by keeping people on HAART (Mills *et al.*, 2006). Adherence among patients on acute medication is higher than for those on chronic medication and adherence drops most dramatically after six months (Osterberg & Blaschke, 2005). Due to the fact that AIDS has to be managed as a chronic disease (with no cure or immunisation available to date), adherence to ARV therapy is a very important aspect in the treatment of the disease (Horizons/Population Council, 2004).

2.10.3 Non-adherence

Predictors of poor adherence to ART have been identified as follows (School of Pharmacy, 2005):

- Poor relationship with medical staff
- Drug and alcohol abuse
- Mental illness
- Lack of patient information about the disease
- Inability to identify different medication and medication regimens
- Unreliable access to primary healthcare
- Discrimination or stigma
- Medication side-effects
- And other social factors like homelessness or domestic violence

Non-adherence and non-persistence with antiretroviral therapy are the major reasons most individuals fail to benefit from HAART. The reasons for non-adherence are varied and overlapping. Factors contributing to non-adherence also include inadequate bioavailability of medication and emerging resistance.

2.10.4 Factors which influence (non-) adherence

2.10.4.1. Socioeconomic factors

Age, gender, race, educational and income level are inconsistent in influencing adherence. Examination of 17 studies focused on the impact of income on adherence rates, only half found any associated statistical significance. More than two thirds of the cases examined to determine a correlation between education and adherence level found no significant correlation (Falagas *et al.*, 2008).

Social support from family and friends affects adherence positively (WHO, 2008b). A Social Model to explain the level of adherence in Sub-Saharan African patients describes a core of patients recognising help by healthcare workers and then reciprocating by trying to reduce work and burden of care. This positive social loop helps patients to overcome economic barriers and strengthen relationships. Forming relationships in resource limited settings is a valuable social mechanism to cope with poverty. This means a patient is able to call on others in time of need (Ware *et al.*, 2009).

According to the meta-analysis of Mills and co-workers published in 2006, North American self-reporting adherence results were 70% compared to 82% self-reporting adherence from Africa. Studies used similar thresholds for measuring appropriate grouped adherence (e.g. 100%, >95%, >90%, >80%). Analysis indicates that African patients have significantly greater levels of adherence, 77.1% (95% confidence interval [CI], 67.3% to 85.6%), $I^2=98.5%$), than North American patients, 54.7% (95% CI, 48.0% to 61.3%, $I^2=98.6%$), comparison odds ratio 2.5, 95% CI, 2.2 to 2.8, $P<0.0001$ (Mills *et al.*, 2006).

A review of 21 articles published between 1999 and 2008 (Reisner *et al.*, 2008), raised additional factors influencing adherence amongst young people aged 13 to 24 in the USA. Being at school seemed to improve adherence in contrast to repeating a grade, which was linked to poor adherence. The likelihood of poor adherence was also higher amongst younger children who started to use marijuana. In this review, a less complex regimen increased adherence and the level of adherence decreased with the length of time on ART.

2.10.4.2. Healthcare team and system-related factors

Clear instructions, providing adequate knowledge about the relationship between adherence and resistance, and better medical follow-up lead to improved adherence

levels. Support from nurses and pharmacists positively influences adherence (McLean, 2003).

2.10.4.3. Condition-related factors

The CD4 cell count, VL and time living with HIV do not significantly correlate with non-adherence in all studies. Absence of visible signs and symptoms may lead to diminished urgency by patients to adhere 100% (Graham *et al.*, 1994). Greater outpatient appointment non-attendance was associated with less severe illness (Catz *et al.*, 1999).

2.10.4.4. Therapy-related factors

The antiretroviral regimen is complex. The number of tablets, number of daily doses, food restrictions and fitting the regimen into daily living are given as reasons for non-adherence by patients (Gifford *et al.*, 2000; Paterson *et al.*, 2000).

Side effects related to HAART are strongly associated with non-adherence, especially in persons who started treatment in an asymptomatic phase (School of Pharmacy, 2005).

2.10.4.5. Patient-related factors

Patients with psychological distress and depression have been shown to have higher non-adherence. Mixed results were found for anxiety and depressive symptoms. Forgetfulness and substance abuse (drugs and alcohol) are reasons for non-adherence (WHO, 2008b).

Providing HIV/AIDS care in a changing environment (HRSA, 2005) adds the following non-adherence reasons:

HAART can make people initially feel worse (not better).

- Co-morbid conditions such as mental illness, diabetes or tuberculosis add to patient's attitude and tablet burden.
- Patient concerns about long term side effects.

Missed doses, not observing dose intervals and not following dietary instructions are some of the forms of non-adherence that can lead to the development of resistance (Osterberg & Blaschke, 2005). Several studies show that approximately a third of patients reported missing doses of ARV medication in a two to four week period and more than 10% reported to have missed one or more doses on any given day (Horizons/Population

Council, 2004). The consequences of poor adherence include emergence of resistant viral strains, limited future treatment options and ultimately higher costs to the individual and ARV programmes (Horizons/Population Council, 2004).

2.11 IMPROVING ADHERENCE

Programmes to increase adherence to ARV medication increase life expectancy and quality of life (fewer days in hospital) and use less funds (first line drugs are cheaper than second line drugs) per patient to provide treatment (more patients can be treated within budget constraints) (Paterson *et al.*, 2000).

Systematic reviews of 38 studies to assess the effectiveness of adherence interventions published between 1990 and 2005 concluded that interventions or tools to improve adherence are of great importance and new innovations in theory and practice are crucial (Van Dolmen *et al.*, 2007). In another meta-analysis of study trials from 1996 to 2004 (Amico *et al.*, 2005) the observation was made that interventions targeted individuals with already poor adherence and therefore yielded better results. The improvements however did not seem to decay over time. The results from the two meta-analyses concurred. The findings were that the intervention effect was significantly stronger in studies enrolling mainly participants with an existing adherence problem than in those studies that did not target participants with adherence problems (Simoni *et al.*, 2006).

The Cochrane Collaboration published an analysis of nineteen studies in 2008. Studies with interventions aimed at individual patients were 67% successful (10/15) compared to 0% of four studies provided in group settings. Interventions provided over a period of 12 weeks or longer were 86% successful compared to 0% for a lesser period (Rueda *et al.*, 2008).

Tools to improve adherence can be separated into the following four major intervention categories:

2.11.1 Technical intervention (simplification of medication regimen)

Simplifying a medication regimen aims to either reduce the number of doses per day (extended release formulations), or reduce the number of different drugs (tablet burden) in the regimen (fixed dose combination tablets). A meta-analysis illustrating this effect was published in 2002 showing that the average adherence rate is significantly higher for once daily dosage than for multiple daily dosages (91.4% versus 83.2%, $p < 0.001$) (Iskedjian *et al.*, 2002). In a more recent study with antiretroviral-naive HIV-1-infected patients,

atazanavir/ritonavir once-daily demonstrated similar antiviral efficacy to lopinavir/ritonavir twice-daily, with less gastrointestinal toxicity but with a higher rate of hyperbilirubinaemia (Molina *et al.*, 2008).

Table 2.16: Currently available fixed dose combinations (co-formulations and co-blister packs) of antiretrovirals used in first line and second line regimens

Three-drug fixed-dose combinations	AZT + 3TC + ABC (co-formulation and co-blister)
	AZT + 3TC +NVP (co-formulation and co-blister)
	AZT + 3TC + EFV (co-blister)
	d4T + 3TC + NVP (co-formulation)
	TDF + FTC + EFV (co-formulation)
Two-drug fixed-dose combinations	ABC + 3TC (co-formulation)
	AZT + 3TC (co-formulation)
	d4T + 3TC (co-formulation)
	LPV/r (co-formulation)
	TDF + FTC (co-formulation)

Source: WHO, 2006

Co-formulations combine two or more active pharmacological products in the same capsule, tablet or solution.

Blister packs are defined a plastic or aluminium blisters containing two or more capsules or tablets.

2.11.2 Behavioural interventions

Patients are provided with memory aids and reminders, whether by mail, telephone, computer, or by home visits. Studies illustrated an improvement in adherence when patients made use of calendar packs, medication tablet organizers and electronic vial caps. Some electronic vial caps displaying the time when the container was last opened and beeped when a dose was due to be taken (Iskedjian *et al.*, 2002). Studies illustrated that electronic adherence declined with increase in number of doses and the use of calendars or diaries, while providing feedback, support or rewards also had limited success (Claxton *et al.*, 2001).

Implementing a home visit system proved feasible in four studies conducted in Los Angeles, Haiti, Boston and rural South Africa. The vast majority of people requiring ART live in conditions of social privation and healthcare may be fragmented and non-existent. Interventions are mostly aimed at patient motivation, knowledge and improvement in adherence. The results demonstrated an adherence greater than 90% in the intervention

group of the studies. Major limitations to this intervention are logistical demands and cost (Williams *et al.*, 2006).

Testing adherence by conducting unannounced telephone tablet counts has proved to be more cost effective and practical than making home visits. The telephone counts excluded bias due to patients not bringing all their medication to the facility or dumping the medication beforehand. In a study conducted in Atlanta, USA, 13 unannounced telephone tablet counts were immediately followed by a home visit. Eighty percent of the participants reported an accurate tablet count while 20% were discordant (Kalichman *et al.*, 2007).

2.11.3 Educational intervention

This approach includes teaching and providing information. Depending on how comfortable patients are with their medication, education can be done individually or in groups and in a direct method (face-to-face), audio-visually, by telephone, by e-mail or via home visits. The Cochrane research group conducted a systemic review of nineteen studies involving a total of 2159 participants, but due to a lack of homogeneity (populations, interventions, comparison groups, length of study and follow-up), a meta-analysis was not possible. The authors did however conclude from evidence found in the studies that the effectiveness of individual patient education interventions delivered over more than 12 weeks or more did improve adherence to antiretroviral therapy (Rueda *et al.*, 2008)

2.11.4 Social support interventions

In a meta-analysis of 122 studies, (DiMatteo *et al.*, 2000), it appeared that practical social support yielded significantly higher effects than emotional and undifferentiated support.

A large randomized clinical trial demonstrated that interpersonal structured adherence support was associated with improved long-term medication adherence and virologic and immunologic HIV outcomes. In a group of 928 participants, followed for a median of 30 months, the first virologic failure was 13% and 28% respectively lower in all interventions by a medication manager compared to intervention with a medication alarm (Mannheimer *et al.*, 2006).

2.11.5 Complex or multi-faceted interventions

A meta-analysis of 24 studies with the focus on analysis of the impact of enrolment strategies on adherence intervention outcomes was published in 2005 by Amico and co-

workers. The studies done with patients known or anticipated to have adherence problems had significantly larger effects on results, than those not targeting such patients. The adherence levels did not decay over time, suggesting that the adherence effect achieved by selection of low-adherent patients was not an artefact of the selective process (Amico, *et al.*, 2005).

Van Dolmen *et al* (2007) came to three conclusions after assessment of randomised trials that reported adherence and treatment outcomes with a follow-up period of at least six months.

- Firstly, less than half (45%) of the interventions resulted in improved adherence.
- Secondly, those interventions that were effective for long-term care were exceedingly complex and labour intensive.
- Thirdly, even the most effective interventions did not lead to large improvements in adherence and treatment outcomes.

In motives stated for a review study, the slow progress made by adherence research over three decades was key as well as the disappointing results reported in many adherence interventions. The 'review of reviews' methodology of this study indicated some findings concerning the current adherence interventions and the underlying theoretical perspectives (Van Dolmen *et al.*, 2007)

- Firstly, there are effective adherence interventions based on technical solutions such as simplifications of dosage and packaging.
- Secondly, there are effective adherence interventions, such as behavioural interventions including incentives and reminders that seem specifically worthwhile for the subgroup of non-adherent patients who regularly forget to take their medication.
- Thirdly, there is a scarcity of comparative studies explicitly contrasting biomedical, behavioural or educational models and it is therefore unclear which are more or less powerful in improving adherence.

Even though a large portion of patients from all studies referred to indicate that they “simply forgot” to take medication, application of a single intervention did not seem to increase adherence across the board. The underlining complexity of ARV adherence makes a gold standard and intervention strategy impossible and “one-size-does-not-fit-all” (Chesney, 2006).

2.12 MEASUREMENT OF ADHERENCE

2.12.1 Accuracy of adherence measures

Objective measures of adherence include pharmacy records, tablet counts, electronic drug monitoring, and biological sampling to measure drugs or metabolites in plasma or urine. Indirect or subjective measures include questionnaires, visual analogue scales (VAS) and assessment of fixed time periods for missed doses (two, three, seven or 30 days). The advantages and disadvantages of the different measures of adherence are shown in Table 2.16.

In research settings and clinics, using objective measures of adherence is neither feasible nor affordable. Important considerations related to the optimisation of self-report are the staggering variety of questions on questionnaires. The lack of standardisation reflects a limited knowledge about basic methodological issues such as time constraints applicable and the list of probable answers to every question. The second is that researchers lack consensus about how to assess the validity of adherence self-report (Wilson *et al.*, 2009).

Attempts to standardise self adherence reports within studies have been made by pairing these methods or comparing them to a central reference standard. Researchers tried to standardise patient self-reports and clinicians' collateral reports and composite adherence scores using electronic monitoring (EM) as a reference. None of the measures showed high sensitivity alongside high specificity, leading to the conclusion that combining measures might increase accuracy and sensitivity (Schafer-Keller *et al.*, 2008).

Table 2.16: Direct and indirect measures of adherence: advantages and disadvantages

Measure	Main advantage	Direct/Indirect	Main disadvantage
Directly observed ART (DAART)	Most accurate	Direct	Patients can hide and discard medication
Drug concentration or metabolites in blood or urine	Objective	Direct	Other medication can have an influence on pharmacokinetics
Biological attached drug marker in blood	Objective in clinical trials	Direct	Assays are expensive
Tablet counts	Objective and easy to perform	Indirect	Tablets may be discarded before count
Questionnaires	Simple and inexpensive	Indirect	Facts can be distorted by patient
Repeat prescriptions,	Objective-easy if patient use same pharmacy	Indirect	Repeats are not equivalent to taking medication
Patient diaries,	Assess adherence routine	Indirect	Relies on patient's memory and honesty
Visual analogue scale (VAS)	Inexpensive	Indirect	Concept not easy to explain to some illiterate patients
2/3 day adherence recall	Simple and inexpensive	Indirect	Relies patient's memory
7-day adherence recall	Simple, inexpensive	Indirect	Relies patient's memory
Electronic medication monitors	Accurate, quantified information, identify adherence problems	Indirect	Expensive

Source: Osterberg & Blanschke, 2005

2.12.2 Direct measurement

2.12.2.1. Directly observed therapy for ART (DAART)

Directly observed therapy (DOT) is known as directly administered antiretroviral therapy (DAART) in HIV therapy. The observation of patients taking their medication is one of the strategies to improve adherence in a population of poor adherence patients. Recent data from feasibility pilot studies (Mitchell *et al.*, 2007; Tyndall *et al.*, 2007), support DAART implementation.

Directly administered antiretroviral therapy (DAART) can improve health outcomes among HIV-infected drug users. In a randomised, controlled trial of DAART versus self-administered therapy (SAT) among 141 HIV-infected drug users monitored over a six month period the mean adherence for directly observed visits was 73%, and the

adherence for SAT was 79%. The mean overall adherence score for both groups was 77%. These results were seen despite the finding that 75% of participants indicated that they would prefer to take their own medications. Major causes of DAART discontinuation in this study included hospitalization, incarceration, and entry into drug-treatment programmes. The presence of depression and the unwillingness to travel to receive DAART predicted time-to-discontinuation (Smith-Rohrber-Maru *et al.*, 2008).

A study conducted in Mombasa, Kenya with a total of 234 HIV-infected but treatment-naïve patients on HAART between September 2003 and November 2004 demonstrated a higher mean adherence over 24 weeks in the DAART group compared to the non-DAART group (96% vs. 90%; $p = 0.042$) (Horizons/Population Council, 2004). According to the Mombasa study, the main reasons for patients not wanting to continue with the surveillance therapy included distance/proximity of site to work or home, quality of health care at the site, financial or confidentiality reasons and being too sick to attend clinic visits.

In a study conducted between 2001 and 2003 involving 67 patients to test the acceptability of DAART by patients, concerns were raised about stigmatisation. In exit surveys from patients a positive rapport seemed to have developed between patients and their community worker (Wohl *et al.*, 2004).

According to Wohl and colleagues (2004), restrictions to a successful DAART programme seemed to be as follows:

- The reliable contact information (changing appointment time or location) and availability of telephones.
- The community workers ability to communicate in the language that their patients speak.
- Medication dosing frequency and the number of tablets with different dose intervals
- An optimal communication between the DAART staff and the pharmacy to ensure timely delivery of medications.
- Ensure HIV medication is not discontinued after a finite period of time like with TB treatment.
- A patient does not have the luxury of being declared free from infection and has to be motivated for the lifelong adherence.
- Spread of TB is airborne, making it a much more involuntary spread compared with HIV.

Two studies (Parsons *et al.*, 2006; Glikman *et al.*, 2007) demonstrated a reduction in mean plasma RNA (VL) while improvements achieved under DAART supervision were lost when the patients left hospital or were placed back under caregiver supervision (Reisner *et al.*, 2008).

Numerous settings have been proposed for DAART, including community based outreach programmes, clinic, prisons, long-term care facilities, and resource-poor countries. A clinic-based DAART programme can only be effective if the staff can be integrated with existing clinic staff to maximize coordination and oversight of patient care and services (Wohl *et al.*, 2004).

2.12.2.2. Drug concentration or metabolites measured in blood or urine

Serum or urine drug or metabolite levels are more objective measures of adherence and persistence, but do not describe the timing of doses and can still be manipulated by patients (medication dosing can be resumed or extra doses of medication can be taken before an visit to avoid appearing non-adherent). As a result of pharmacokinetic variability in drug absorption, distribution, metabolism, and excretion, ranges that are consistent with adherence may be wide. Furthermore, accurate measurement of serum or urine drug metabolites is only available for certain drugs (e.g. prednisone and 6-mercaptopurine).

Dosing of ARV agents is very complex, requiring administration of drugs in doses at different times throughout the day. Because of this complexity, specimen collection to simultaneously monitor peak and trough concentrations of all antiretroviral drugs is difficult to accomplish. Peak concentrations of NRTIs and PIs occur at different times after dosing; therefore, a single sample does not reflect optimum timing for peak concentration for all drugs. For example, in a regimen including lamivudine, nevirapine, and zidovudine, a specimen collected just before the morning dose reflects trough concentrations for all drugs (but zidovudine should be undetectable), and a specimen collected two hours after a dose would reflect peak concentrations except for nevirapine, which reaches peak concentration more than four hours after the dose. If didanosine replaces lamivudine in the regimen, the dosing schedule would require substantial adjustment because didanosine must be administered without food - the peak concentration for zidovudine would occur two hours earlier than the peak for didanosine (Moyer *et al.*, 1999).

Spot urine samples to detect nevirapine (to monitor adherence and metabolism) in patients using nevirapine (NVP) containing regimes and in volunteers taking a single dose of NVP, were taken at 24 hour intervals. The NVP was detected up to nine days after

administration and was therefore not suitable to detect single dose ingestion (Kumar *et al.*, 2006).

To test the effectiveness of the plasma concentration as a measure of adherence, a study done in 1997 compared self reported adherence with plasma concentration for 642 patients. Patients were classified as highly, moderately and non-adherent on the evidence of medication doses missed in the period directly prior to the study. Patients with no missed doses of their ARVs were classified as highly adherent, patients were considered moderately adherent if they reported missing no more than 20% of their treatment and patients taking less than 80% of their medication were marked as non-adherent. The limits of quantification (LOQ) of PI in the plasma for indinavir, ritonavir, nelfinavir and its active metabolite M8 [nelfinavir (+M8)], and saquinavir were 5, 30, 30 (+30), and 9 ng/ml, respectively. Patients classified on the basis of questionnaire results as moderately or highly adherent were reclassified as non-adherent if their plasma protease inhibitor concentrations (PPIC) were lower than the LOQ. The results in this study reported PPIC was below the limit of quantification (LOQ) in 32% of non-adherent patients and in only 8% of adherent patients. (Patients with PPIC below LOQ were considered to be non-adherent). PPIC (combined with self-report) may therefore be considered a reliable measure to detect non-adherence although PPIC are mainly used in the detection and management of pharmacological interactions, adverse events and therapeutic drug monitoring (Duran *et al.*, 2003).

In some diseases, measuring intermediate markers of drug use are useful. For example, plasma viral load in patients with the human immunodeficiency virus (HIV) can act as a surrogate for adherence to antiviral therapy (Ruddy *et al.*, 2009).

2.12.2.3. Biological attached drug marker measurement in blood

Marker assays are based on materials that can be added to a drug and are easily detected. Kastrissios and co-workers (1998) conducted a study where participants attended routine clinic visits and provided a blood sample and dosing history. Adherence was assessed using plasma drug concentrations and defined by the presence of detectable drug in a plasma sample obtained within a specified analysis window. The analysis of 722 plasma samples revealed that approximately 75% contained detectable concentrations of the assigned drugs and 5-14.5% contained no detectable drugs. Non-adherence was moderate but uniform amongst the treatment groups and may have contributed to a marginal reduction in the power of the primary analysis to detect differences in efficacy amongst the assigned treatments (Kastrissios *et al.*, 1998).

2.12.3 Indirect adherence measurement

2.12.3.1. Tablet counts

Tablet count adherence is calculated by counting the remaining doses of medication and assuming that remaining tablets in excess of what is expected represent missed doses. The sensitivity of tablet counts for detecting non-adherence is compromised when patients remove tablets or capsules from their containers without taking them ("pill dumping" or "decanting") (US Department of Veterans Affairs, 2007).

In a Canadian study with health care workers visiting patients at home, only 64% of 319 the patients' had tablet counts available for adherence monitoring. The estimates of adherence derived from the last prescription dates found adherence were underestimated when the actual dates patients stated they started with their medication were compared (Vik *et al.*, 2005).

Studies within the Adult AIDS Clinical Trials Group (AACTG) have also not found tablet counts to be helpful in assessing patient adherence, particularly in studies of combination antiretroviral medication (American Public Health Association [APHA], 2004). A more accurate way for assessing adherence by tablet counts, would be to conduct counts during unannounced visits in patients' homes. This home visit method is costly and often impractical (time consuming) and may be met by an absent home owner. Conducting unannounced tablet counts by telephone may be a viable alternative for objectively assessing medication adherence. Unannounced home-based tablet counts correlated with electronic medication monitoring (Kalichman *et al.*, 2007). The correlation between phone and home-based number of tablets counted (correlation = .997, 95% correlation .995 – .998, $P < .001$) and percent of tablets taken (correlation = .990, 95% correlation .986 – .992, $P < .001$), was found to be high.

$$\% \text{ Adherence} = \frac{\text{Quantity dispensed} - \text{quantity returned}}{\text{Quantity expected to be taken}} \times 100$$

Figure 2.8: Formula to Calculate Percentage Adherence

2.12.3.2. Questionnaires

❖ Design of questionnaires

Questionnaires can be designed to incorporate both qualitative and quantitative research questions. Quantitative studies include large representative samples in a fairly structured

data collection procedure (Struwig & Stead, 2001) while qualitative methods include participant observation and interviews.

Key factors in questionnaire design are as follows (Patten, 2004):

- a. Sensitive information is often divulged during the study. Examples of “sensitive” subjects are mental illness, STIs, alcohol or drug use, criminal record, sexual practices. Participants must be assured of anonymity and sensitive wording must be used.
- b. The co-operation of the participants in the study is essential to ensure dependable results:
 - Keep questionnaire short
 - Make it convenient for respondents
 - Reward for completing the questionnaire
- c. Researchers must be able and willing to answer the same questions as those put to the participants in their study. This process might include sharing personal and intimate information.

Objectives in question design will include the following (Morisky *et al.*, 1986):

- a. Valid measurements of study variables must be used.
- b. Ease of completion by both the interviewer and interviewee.
- c. Ease of data entry and processing (simplicity of questions and answers and speed of completion of questionnaire).

Questions must be well planned to be relevant, in the correct sequence, non-ambiguous and phrased in such a way as to elicit the correct response. Limitations to be considered are time constraints from both parties and a limited study budget.

During the design of questionnaires for drug studies, existing validated scales may be employed to measure veracity of patients’ self-reported adherence. The Morisky Adherence Scale was developed in an attempt to identify patients with poor adherence rates due to lack of observable characteristics distinguishing these patients. The Morisky Adherence Scale developed in a study with patients suffering from hypertension, measured the concurrent or predictive validity of patients’ self-reported adherence. Items on the scale addressed barriers to medication taking and provided feedback for personnel to reinforce positive adherence behaviours.

Morisky and co-workers (1986) chose the following four self-reported medication-taking scale questions:

- a. Do you ever **forget** to take your medicine?
- b. Are you **careless** at times about taking your medicine?
- c. When you **feel better** do you sometimes stop taking your medicine?
- d. Sometimes when you **feel worse** when you take the medicine do you sometimes stop taking it?

The underlying theory for the above questions was that they cover the four major reasons for patients' non-adherence to their medication (Morisky *et al.*, 1986). Values of 1 and 0 were awarded for no and yes respectively.

❖ Use of questionnaires in adherence studies

The reliability of the Morisky Adherence Scale was reflected in the relatively high (0.61) measure of consistency among the study participants. An item-to-total correlation coefficient for each question was done. The patients with a low score had a disease control rate of 42% compared to those with higher score having a control rate of 57% (Morisky *et al.*, 1986).

Comparison of two adherence assessment questionnaires (the AACTG and the MMAS) showed results of 35% patients with incomplete data on the AACTG questionnaire in comparison to only 2% of the MMAS questionnaires with incomplete data. The reason for this might be that the AACTG questionnaire is too complicated and therefore lack power. MMAS may be superior to AACTG due to less internal attrition (Sodergard *et al.*, 2006).

Monitoring adherence in the clinic environment can be difficult and a discrepancy may exist between what a patient discloses in independent interviews and what a doctor believes about a patient's adherence. Patients with suboptimal adherence may have reduced or undetectable viral loads. On the other hand, viral load may not decrease in patients with perfect adherence because of pre-treatment resistance, poor drug metabolism, or other factors. It is therefore important for a multidisciplinary approach involving patients, health care professionals, family, and friends to exist to optimize adherence (Miller & Hays, 2000).

In a study done in France, the relationship between the non-adherence and detectable viral load was demonstrated by 32% of non-adherent patients and 8% of adherent patients having PI concentration below limit of quantification (Duran *et al.*, 2003).

Four methods were used in a multi-centre study involving 464 HIV outpatients, generating results with high levels of correlation in adherence measures and with significant validity. The methods were: Self-reported Adherence (SERAD) questionnaire, tablet count, electronic monitoring, and plasma drug monitoring). Agreement between methods was observed when adherence was high, but fell as adherence decreased. The questionnaire was completed correctly, the interviewers did not report uncovered aspects, and the information was collected easily (Munoz-Moreno *et al.*, 2007).

❖ Questionnaires in a multilingual environment

Section 6 of the Constitution of the Republic of South Africa, 1996, recognizes the principle of multilingualism by providing for eleven official languages of South Africa to be treated equitably. This Act which entrenches the eleven languages is called the South African Languages Act, 2000. The country's Constitution guarantees equal status to the 11 official languages (Afrikaans, English, IsiNdebele, IsiXhosa, IsiZulu, Sepedi, Sesotho, Setswana, SiSwati, Tshivenda, Xitsonga).

The implication of this language parity is that all questionnaires have to be translated into the language spoken by the participants (see Chapter 3, Section 3.3.5.2).

English is the country's *lingua franca*, and the primary language of government, business, and commerce. It is a compulsory subject in all schools, and the medium of instruction in most schools and tertiary institutions. Hence most questionnaires are also compiled in English.

❖ Use of questionnaires by interpreters and data collectors

The role of the data collector or interpreter in face-to-face interviews or completing of questionnaires is of utmost importance. Conducting interviews and completing questionnaires especially in languages other than that of the research team might lead to mistakes and lead to errors rendering a whole research project futile (Babbie & Mouton, 2001).

The low level of literacy of the South African society has made interviews essential to gather information in the research environment (Babbie & Mouton, 2001). Special care must be taken to employ acceptable interview and questionnaire techniques with ethical aspects kept in mind at all times.

One of the most important aspects is to keep the role of the interviewer as neutral as possible to have the least possible influence on the outcome of the answers to the questions and to yield information more or less “as it is” (Henning *et al.*, 2004). To do this it is important not ask leading questions or force the interviewee to confess facts for which he/she is not ready.

The appearance and demeanour of the interviewers are very important and according to Babbie and Mouton (2001) the most acceptable demeanour to test participants is one of middle-class neatness and cleanliness. In the modern setting this might not be possible and a quick assessment of the community the participants come from might lead to a more appropriate contact.

When dealing with strangers it is very important to win the confidence of the person and keep societal differences in mind (Babbie & Mouton, 2001).

2.12.3.3. Monitoring of repeat prescription frequency

If a prescription is not collected, it is a sign that the patient is not taking his/her medication. The following are practical problems in the implementation of repeat prescription monitoring as an adherence measure (American Public Health Association [APHA], 2004):

- Patients may get their prescriptions at different pharmacies.
- Prescriptions monitored on Medical Aid level are lost when patients move to new Medical Aid.
- Gaining access to pharmacy records remains difficult.
- Relationship between repeats and actual ingestion of medications is difficult to ascertain.

A study of pharmacy ‘refill’ (repeat prescription) adherence assessments showed that they were as accurate as CD4 counts for detecting virological failure in patients and had the potential to predict virological failure before it occurred (Bisson *et al.*, 2008). On the other hand, a retrospective study with 58 treatment-experienced HIV positive adults in North Carolina America found in a six month period of pharmacy refills, adherence rates above 70% did not show an improvement in CD4 count when adherence rates increased. Adherence rates falling lower than 70% did however correlate with a progressive decline in CD4 count (Townsend *et al.*, 2007).

2.12.3.4. Patient diaries

This method is easy to use and an inexpensive instrument but data from several studies suggest that the tendency to overestimate actual adherence is common. A study to explore adherence rates in hypertensive patients found that 67% overestimated their adherence when self-reports from diaries were compared with data from the MEMS caps (Straka *et al.*, 1997). Researchers have on a regular basis demonstrated that paper diaries make it difficult for study patients to comply with the protocol. In the table highlighting fake entries, approximately 25% of paper data was invented. The 25% did not include data made unreliable by temporal uncertainty or error.

Table 2.17: Table of HIV studies using paper diaries to measure ART adherence.

Study reference	Measures counted (as % of expected)	Measures reported (as % percent of expected)	Faked (as % of reported)	Number of subjects
Jonasson G <i>et al.</i> , Eur. Respir J 14, 1999	77%	93%	17%	163
Milgrom H <i>et al.</i> , J of Allergy & Immunol 98, 1996	58%	95%	39%	24
Spector S <i>et al.</i> , J Allergy Clin. Immunol 7, 1986	47%	90%	48%	19
Straka RJ <i>et al.</i> , Pharmacotherapy 17, 1997	55%	71%	23%	68
Verschelden P <i>et al.</i> , Eur Respir J 9, 1996	44%	55%	20%	20
Chemelik F <i>et al.</i> , Annals of Allergy 73, 1994	85%	100%	15%	20
Simmons M <i>et al.</i> , Chest 118, 2000	Not reported	Not reported	30%	101
Mazze R <i>et al.</i> , American J of Medicine 77, 1984	Not reported	Not reported	40%	14
Weighted avg.(% Faked x N)/N			24.4%	

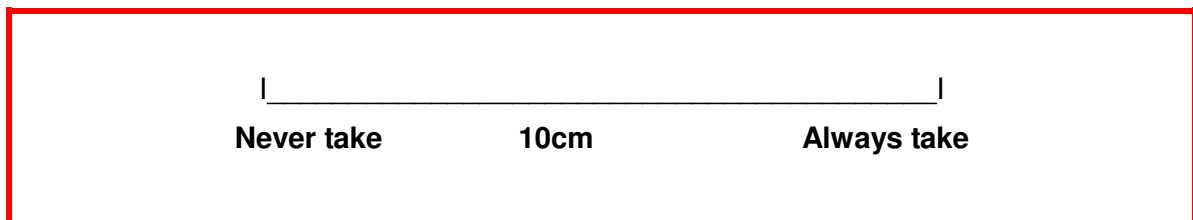
Source: PHT Corporation, 2010

Researchers found that the diary entries differed from the MEMS recordings in 30% of the studies (Galetkko *et al.*, 1996).

2.12.3.5. *Visual analogue scale (VAS)*

This assessment instrument was first used to judge pain relief in pain management. The assessment is clearly highly subjective, and of most value when looking at change within individuals over time. The scale is of less value for comparing across a group of individuals at one time point (Gould *et al.*, 1992)

This is an ordinal scale anchored at 0% and 100%. The scale is often labelled 0 to 10 or descriptively, e.g. 'Never' to 'Always'. The line linking the two extremes represents the percentage of medication taken relative to the prescribed doses for a specific medication during a particular period, e.g. four weeks. Patients are shown where 50% adherence is located on the line and asked to assess their own medication adherence.



Source: Gould, 1992

Figure 2.9: Example of VAS Scale

The VAS instrument to assess adherence was used in California (USA) to evaluate 87 patients over a four month study period. In the study it was combined with a more complicated 3-day recall and unannounced tablet counts. Results reported an 82.5%, mean adherence measured by VAS, 84.2%, mean adherence measured by 3-day recall and 75.9%, mean adherence measured by unannounced tablet counts respectively. The three methods correlated well and stayed the same over time. The measures used also inversely correlated with HIV viral load. Given its simplicity, the visual analogue scale adherence instrument should be useful in research and may be useful in routine patient care (Giordano *et al.*, 2004).

Another study involving two adherence instruments was conducted in a large clinic setting in America. In a study comparing an AACTG (Adult Aids Clinical Trial Group) questionnaire (3 day recall) and a VAS scale (30 day recall), both scales produced comparable adherence rates of (81%) and (87%) respectively. Results correlated significantly ($r = 0.585$). In the study 61 participants (42%) reported higher adherence rates on the VAS, and 36 participants (24%) reported higher adherence rates on the AACTG. Two reasons have been suggested to explain this tendency. The VAS (30-days) may be more prone to favourable estimation of adherence than reports of adherence that are anchored in recall of very recent adherence events. Secondly the coarseness of the

VAS scale (see illustration in Figure 2.9 above) in comparison to the AACTG specific questions may have resulted in higher VAS estimates of adherence (Amico *et al.*, 2006).

2.12.3.6. Other adherence recall scales

A 2-day adherence recall was used in a previous study by Mapetla (2007) to determine the self-perceived adherence (see Figure 2.10). Patients were asked to recall how much of their medication they had missed in the last two days. A sun and moon chart was used to facilitate patients understanding of the 2-day recall. The same method of recall will also be employed in this study.

Figure 2.10: Two (2)-day adherence recall

The patients are first asked to try and recall the previous seven days, followed by questions.

Did you miss any tablets in that time? If yes, How many?

Drug A _____ Drug B _____ Drug C _____ Drug D _____

Figure 2.11: Seven (7)-day adherence recall

In a study comparing data from an electronic monitoring system to a 3-, 7- and 1-month recall self-report in 643 visits made by 156 patients and found that over-reporting increased with a decrease in time considered (Lu *et al.*, 2008).

2.12.3.7. Electronic medication monitors

The main reason for the development of this method of adherence assessment was the subjective nature of most indirect measures used. Questioning a patient can be susceptible to misinterpretation of information by the interviewer and might tend to overestimate medication use by the patient (Osterberg & Blaschke, 2005). Electronic devices are thought by some to provide a valid and reliable measure of medication adherence.

These devices contain computer microprocessors that fit on standard medication containers or into the lids of specially constructed bins in multiple medication dispensers. The microprocessor stores the date and time that the container is opened. This approach assumes that the opening coincides with taking of the medicine. A long-life battery that cannot be switched off is included. Data are retrieved by downloading the information from the cap device to a computer. A spreadsheet displays an overview of individual adherence by calculating the number of time-appropriate bottle openings compared to the number of expected doses over the study period. Adherence may also be shown as a graph of time of container opening over a given period (Geo-ICT Health (Pty) Ltd, 2009).

Electronic monitoring devices (Med^oic, Certiscan, eCAP, MEMS cap) (IMC, 2010) are used in the United States. Some electronic vial caps display the time of the container's last opening and beep when a dose is due to be taken (Iskedjian *et al.*, 2002).

Devices have been tested with mixed results in the United States. A study done with schizophrenic patients using an electronic device found that a significant number of patients dropped out of the study. Some study patients lost the container containing the microprocessor. The study found that some patients may also sabotage the accuracy of records by opening the container but not ingesting the medication. A comparison of tablet counts and drug serum concentrations with electronic device data were conducted. The authors concluded that neither intermittent drug serum concentrations, nor tablet counts, would have identified the frequency of missed doses for newly diagnosed and long-term epilepsy patients that were revealed with electronic device data (Cramer *et al.*, 1995).

The strategy of combining two methods like tablet counting with an electronic Medication Event Monitoring System (MEMS) may be employed to identify different patient groups with differing adherence patterns (APHA, 2004). In a study of zidovudine adherence in an HIV clinic, researchers found that adherence rates varied significantly by data source. MEMS data provided ranges for adherence rates of 9-100%, tablet counts from 50-100%, self-report rates of 80-100% and physician assessments of 30-100% (Geletkko *et al.*, 1996).

Researchers set the acceptable adherence target at 80% of medication taken in a study of scheduled monthly visits in a study with 91 hypertension patients. Acceptable adherence by tablet count was observed at 68% of the follow-up visits, while non adherence was measured at 47% of those visits with MEMS. Blood pressure was within goal in 50% of the participants who were adherent by both tablet count and MEMS throughout their follow-up visits, and only 14% of the participants were identified as non-adherent by one or both methods. From the results the conclusion was reached that electronic monitoring and tablet counts are successful in assessing adherence. Feedback of electronically collected information on dosing intervals to participants and staff may enhance adherence (Rudd *et al.*, 1993)

A disadvantage of electronic monitoring devices is that patients cannot use pillboxes because every dose must be taken from the original container. Another disadvantage is that only one medication can be assessed with one electronic device. Pillboxes are widely used because of their convenience and inconspicuous nature. Electronic monitoring is a very expensive intervention and although it can be very accurate in recording container activity, mechanical or technical problems can render the device useless. The use of an electronic device requires prior education for the patient and the health team and repetitive reminding to use the device (AlignMap, 2006). A big advantage of electronic monitoring devices is the recorded adherence pattern to identify specific periods of non-adherence.

❖ **Adjusting or censoring data**

Electronic monitoring differs from other adherence methods because it can identify periods of non-adherence much more accurately. It is therefore important to eliminate periods in which the patient did not use the container, which can then be labelled as a temporary discontinuation of treatment before data analysis starts. Adjusting data for periods when patients are not in control of their medication for various reasons including hospitalisation has been suggested to achieve maximum analyzing accuracy. Differences

in interpretation of these “selected” periods occur when adjustments have to be made. Identifying anomalous periods on a selective basis might lead to bias and lead to a loss of immeasurable study credibility. Suggestions have been made to identify these periods by using questionnaires, interviews or personal diaries. The problem with most instruments is that they may be very vague. Data adjustment may be dangerous and may lead to incorrect adherence rates if periods of no cap activity are automatically censored without information to substantiate this review.

Proposals to use nonparametric methods have been suggested to identify medication taking behaviour over time and group adherence patterns like strong sustained, strong but unsustained, steady poor, steady very poor and progressive decay. (Dunsiger *et al.*, 2006). When using uncensored data the only aspect being assessed is the opening of the container and not necessarily the taking of the medication (adherence). There is currently no standardization when adjusting data and no consensus on the protocol for adjusting electronic monitoring device data (Fennie *et al.*, 2006).

One of the companies in South Africa testing an electronic monitoring system is Geo-ICT Health Pty (Ltd). The e-MuM system consists of a software programme, lid with microprocessor (device), and reminder unit (watch). Research to test the e-MuM system to increase and monitor adherence to medication was done in 2007 and the 200 TB HAART patients demonstrated a 10% increase in overall adherence.

2.13 SUMMARY

In this chapter the literature within the context of the study was discussed. The origin of HIV, the methods of contracting the disease, complications that may develop if the infection remains untreated and factors fuelling the spread of the disease were described. The distribution of HIV positive patients globally and in South Africa, as well as organisations involved in the HIV/AIDS pandemic, were outlined.

Antiretroviral medicines and current treatment regimes available for the treatment of HIV were discussed. The importance of adherence, reasons for non-adherence and methods to improve adherence were outlined. The chapter ended with a discussion of various measures which can be used to measure adherence and to assist patients in improving adherence.

In the next chapter, the methods used in this study are described in detail.

CHAPTER 3

METHOD

3.1 INTRODUCTION

This chapter describes the methods used to investigate the impact of an electronic monitoring system on the adherence of patients to antiretroviral medication at the Tshepang Clinic at Dr George Mukhari Hospital. In the first section background to research methodology as guidelines for information gathering is discussed. This is followed by aspects pertaining to the study which includes the site, research staff, patient sampling, data collection instruments, study period and phases with work flow logistics. Planning of the methodology is important to ensure validity and reliability and to conduct the study according to morals and rules to prevent unethical behaviour and misconduct (Struwig & Stead, 2001).

3.2 BACKGROUND TO RESEARCH METHODOLOGY

3.2.1 Research

One description of research is that it is the selective, systematic gathering of information without prejudice before critical evaluation of the resulting data (Struwig & Stead, 2001).

3.2.2 Characteristics of research

Research is marked by three main differentiating characteristics. The three characteristics considered during the planning and reporting of this study were as follows (Struwig & Stead, 2001):

3.2.2.1. *Open system of thought*

The study had to be designed to test whether the system was effective, without having to prove the effectiveness (Struwig & Stead, 2001).

3.2.2.2. *Critical examination of research data*

The data had to be obtained systematically, be valid and be reliable. Collected data had to be interpreted and the meaning understood (Struwig & Stead, 2001).

3.2.2.3. Generalisation of the results and specification of limits

This point refers to critical sample selection and the context in which the results could be deemed applicable. It is important to establish whether findings can be generalised legitimately to the wider population (Struwig & Stead, 2001).

3.2.3 Study design

The design of studies will vary in different facilities, depending on the following factors (WHO, 2008b):

- Information needs of the managers/administrators/researchers
- Types of record-keeping in the facility
- Types of patient accommodated in the facility
- Resources available to carry out the study

An appropriate study design provides the researcher with a structured plan to ensure control of the study areas, keeping within set boundaries, and making sure that each facet of the research is systematically dealt with. The study should be designed to answer the research question, when extraneous factors are controlled, and to make generalisations that are valid (Jang, 1980).

In the collection of data, four information gathering determinants have to be specified. These determinants are the nature of data, the type of data, the sources of data and the form of data (Struwig & Stead, 2001).

3.2.4 Information (data) gathering methods

There are two main types of data – qualitative and quantitative. Quantitative data can be described as being hard, rigorous, credible and scientific while qualitative data is more frequently describe as sensitive, nuanced, detailed and contextual. In social research, there is an awareness of the fact that qualitative and quantitative data are intimately related to each other. All quantitative data is based upon qualitative judgments; and all qualitative data can be described and manipulated numerically (Trochim, 2006).

These data can be gathered in a range of ways, which is briefly described in the following section.

3.2.5 Study types

3.2.5.1. Exploratory studies

An exploratory study is undertaken when not much is known about the situation at hand or no information is available on how similar problems or research issues have been solved in the past. When some facts are known but more information is needed for developing a viable theoretical framework, insight into a problem can be acquired by investigating different interpretations of a specific problem and how they solve the problem. The researcher has to do fieldwork and observe and ask about the individual's interpretation of the problem and how they apply solutions. Every observation, captured by with all the senses (seen, heard and smelled), has to be captured (Hardon *et al.*, 2001).

In such cases, extensive preliminary work needs to be done to gain familiarity with the situation and understand what is occurring before a model is developed and rigorous design for comprehensive investigation is set up. In essence, exploratory studies are undertaken to better comprehend the nature of the problem. Extensive interviews with many people might have to be undertaken. More rigorous research could then proceed. Some qualitative studies where data are collected through observation or interviews are exploratory in nature (Sekaran, 2003).

3.2.5.2. Descriptive studies

These investigations describe the characteristics of the subject under study. They enquire into aspects that try to describe the phenomenon for example they try to answer questions like who, what, where, when and how of the research. The purpose of this type of research is to find out the cause behind the events under study. Generally the descriptive research begins with a problem statement, identifies the information needed to solve the problem and establishes the procedures needed to carry out the research. The purpose of descriptive research is just to describe and not to establish any relationships. The advantages of descriptive research are that it can provide a lot of information. It is useful in identifying further areas of research. The main disadvantage of this type of research is that the cause behind a phenomenon cannot be identified, described and reported (Sekaran, 2003).

Systematic collection and presentation of data are required to give a clear picture of a specific situation. Data include the views and needs of people and the comparison of the description of problems and causes (Hardon *et al.*, 2001).

3.2.5.3. Comparative studies

Comparing two or more groups; with or without problems, or the problems of varying in degree in different groups, present the researcher with a way of resolving the research problem. Various study designs which are appropriate for the research question include the following (Hardon *et al.*, 2001):

- **Studies comparing cross-sections of a population**

In this approach communities at high risk are compared with those at low risk. The aim is to try to identify factors from the compared communities that could explain the discrepancy (Hardon *et al.*, 2001).

- **Case-control studies**

In epidemiological studies a group might be divided into individuals experiencing all symptoms, another group experiencing some symptoms and individuals with unique symptoms. The researcher starts with the result and then extrapolates back to determine the presence or absence of certain factors associated with the problem (Hardon *et al.*, 2001).

- **Cohort studies**

This type of study compares reactions from a group of individuals (study), after exposure to a risk factor with individuals not at risk (control). The researcher prospectively follows both groups over time and compares the occurrence of the problem that is expected to be related to the risk factor in both groups (Hardon *et al.*, 2001).

3.2.5.4. Intervention studies

The researcher intervenes in a situation and evaluates or measures the effects of this intervention. Two approaches are commonly used namely quasi-experimental study and before-after study (Hardon *et al.*, 2001).

- **Quasi-experimental studies**

Here, two or more groups are studied, one of which serves as the control group (in which no intervention is done). Groups are observed prospectively, before and after the intervention. This is to test whether the intervention has made any difference (Hardon *et al.*, 2001).

- **Before-after studies**

Analyses of the situation to observe differences, before and after intervention, is done to determine the effect (if any) of the intervention in a single group (Hardon *et al.*, 2001).

3.2.5.5. Experimental design studies

In a study with an experimental design, the purpose is to observe the influence an independent variable has on a dependent variable, in a comparison of the experimental and control groups (Fisher & Foreit, 2002).

There are certain characteristics to consider when developing the method of experimental studies:

- a. One or more hypotheses are developed to predict the effects of independent variables on the dependent variables
- b. An independent variable has two or more levels (e.g. gender, age group)
- c. The participants are randomly assigned
- d. Controls are put in place to protect validity
- e. Results can be generalised to the larger population (Struwig & Stead, 2001)

3.2.6 Information gathering determinants

3.2.6.1. Nature of data

A research project can focus on a single point or event in time, or include events happening over a period of time (Struwig & Stead, 2001). Data can be retrospective, concurrent or prospective in nature.

3.2.6.2. Type of data

Four types of data can be distinguished. These include numeric, non-numeric, verbal and non-verbal (Struwig & Stead, 2001).

3.2.6.3. Source of data

Data can be obtained from primary sources, secondary sources or a combination of the two (Struwig & Stead, 2001). Primary sources involve personal information collection by the research team, while in secondary data sources the data collectors might use

available data gathered previously. Combining primary and secondary sources will involve expansion of already existing data, or re-interviewing the subjects of a previous study.

3.2.6.4. Form of data

Data collection during interviews or focus groups is verbal or overt data collection. Exit interviews (structured and semi-structured) and focus groups are two of the most widely used tools in research to obtain participants and administrators evaluation of study aspects, e.g. study design, study personnel, study period and to allow suggestions for change or improvement. Sending out questionnaires by mail or taking photos are examples of non-verbal or non-overt methods (McNamara, 2006).

3.2.7 Focus group discussions (FGD)

Focus group discussions are a qualitative research technique used to gain an in-depth, but not necessarily representative, understanding of the attitudes, beliefs and perceptions of a specific group of people in their own language. A focus group is a facilitated, open conversation, recorded and/or observed by a transcriber. A focus group moderator or facilitator asks questions that stimulate interaction among participants on subjects relevant to the evaluation. Each participant should have the opportunity to speak, ask questions of other participants and respond to the comments of others, including the moderator or facilitator (McNamara, 2006).

The focus group as evaluation tool can gather a great deal of information, discuss issues and explore subjective matters, including expectations resulting from study results, attitudes both before during and after the study, feelings and experiences in its multiple interview format. The information can be used to shed light on study problems, and interpreting the data received on specific items (McNamara, 2006). Validity, feasibility, and costs of these tools are key considerations.

There are several advantages and disadvantages of focus group discussions as an indirect evaluation or data collection method, of which some are listed below (Dixon, 2005).

3.2.7.1. Advantages

- Useful to gather ideas, details, new insights and to improve questionnaire design
- Can be used to get more in-depth information on specific issues
- Can clarify issues not completely understood from another instrument.

- A moderator can ask follow up questions when necessary.
- Can be used in conjunction with a quantitative study to confirm or broaden one's understanding of an issue.

3.2.7.2. Disadvantages

- Sample may be biased
- Moderators require training
- Differences in the responses between groups can be troublesome
- Groups can be difficult to assemble
- Moderator has less control than in individual interviews

3.2.8 Dependent and independent variables

A variable is a phenomenon measurable in two or more categories. An independent variable's presence determines or changes the dependent variable. Independent variables usually stay the same throughout the study, while dependent variables will change.

The measurement of the dependent variables must be reliable and the independent variable is introduced as a test of the theory that it will improve the dependent factors (Struwig & Stead, 2001).

By using a technique called multiple-regression, the relationship between one dependent variable and a variation of independent variables can be determined (Chapter 4). The extent to which the independent variables influence the outcome of the dependant variable can also be predicted (Struwig & Stead, 2001).

3.2.9 Multiple-regression

Multiple-regression is a mathematical technique used to model the relationship between independent predictor variables and a single outcome variable. It is used in research and diagnostic studies where the outcome is dependent on more than one factor (Marill, 2004).

3.2.10 p-Value

The p-value is based on the assumption that the probability exists of obtaining a test statistic at least as extreme as the one that was actually observed, assuming that the null hypothesis is true (Trochim, 2006). A p-value of significance is usually $p < 0.05$ and no significance $p > 0.05$ (Vowler, 2007).

3.2.11 Standard deviation (SD)

The standard deviation is the square root of the variance of a probable population or probable distribution and an indication of how reliable the data is and how close to the mean the data is (Trochim, 2006).

3.2.12 Mean, median and mode

Averages can be divided into mean, median and mode. Mean is the result of an addition of the number (N) of values in a data set and then dividing the result by N . Most people equate the arithmetic mean to their understanding of the term “average”. The mean of five and 10 is 7.5 (Trochim, 2006).

A median is described as the number separating the higher half of a sample from the lower half of a population, or a probability distribution. The median of a data set is the middle number when the set is sorted in numerical order (Trochim, 2006).

The value that occurs the most frequently in a data set or a probability distribution is also called the population mode (Trochim, 2006).

3.2.13 Hypothesis, null hypothesis and statistical hypothesis

A hypothesis is an assumption. No decisions or conclusion can be drawn from it. It cannot be used to prove something but only as a measure to accept or reject (Trochim, 2006).

The null hypothesis is an assumption that data acquired (result) is valid and a true measured of the predicted outcome or behaviour. In the rejection of the hypothesis, data can be added to test the hypothesis again (Trochim, 2006).

Statistical hypothesis testing is used to test the null hypothesis and accept or reject it (Fisher, 1966).

3.2.14 External validity

External validity refers to the approximate truth of conclusions and involves generalizations. Three major threats to external validity are people, places or times and these constitute the three ways the researcher can be wrong. External objections to discredit the results of the study might be the unusual type of sample of the population, the unusual place the study was done or that the study was done at a peculiar time.

Criticisms of generalizations can be eliminated by showing that the study could be done in a variety of places, with different people and at different times and with similar results. External validity (ability to generalize) will be stronger the more a study is replicated (Trochim, 2006).

3.2.15 Independent *t*-test

An independent sample *t*-test is used when two separate independent but identically distributed samples are obtained, one from each of the two populations being compared.

Independent *t*-test for means follows a probable distribution of the ratio after repeated measurements performed on a single sample of the population or two related sample population. The measurement (data) is compared at selected intervals. It is usually employed when the underlying *t*-test cannot be satisfied.

An independent *t*-test for means is used to calculate the difference between two sample (population) means, and for confidence intervals for the difference between the two sample (population) means. It is used when the population is small and to estimate a probability distribution that arises from the estimation of the mean using a normally distributed population.

The overall shape of the probability density function of the *t*-distribution resembles the bell shape of a normally distributed variable with mean 0 and variance 1, except that it is a bit lower and wider. As the number of degrees of freedom grows, the *t*-distribution approaches the normal distribution with mean 0 and variance 1 (Statistics Solutions, 2009).

3.2.16 Wilcoxon two-sample test for medians

Wilcoxon two-sample test for medians is performed when the study performed on the chosen population sample does not result in a probable (preconceived) distribution of results. Wilcoxon test is a non parametric test that is used for two dependent samples. Dependent sample: Two correlated samples, or a before and after study of a sample, are examples of the dependent sample. There are two types of dependency:

- Before and after sample with the same people at different points of time and
- Matched paired study with the same people at different points of time (Statistics Solutions, 2009).

3.2.17 Pearson's correlation

Pearson's correlation reflects the degree of linear relationship between two variables. It ranges from +1 to -1. A correlation of +1 reflects a perfect positive linear relationship between variables. When computed in a sample, it is designated by the letter "r" (Statistics Solutions, 2009).

3.2.18 Sampling methods and sample size

Stratified random sampling, also sometimes called proportional or quota random sampling, involves dividing the population into homogeneous subgroups and then taking a simple random sample in each subgroup. When the same sampling fraction within strata is used, it is termed proportionate stratified random sampling (Trochim, 2006).

The following factors can influence the determination of a sample size (Struwig & Stead, 2001):

- The basic characteristics of the population.
- A sample as small as one (in a homogeneous population) may suffice but larger samples may be necessary for a more heterogeneous population.
- The objectives of the research.
- The significant characteristics of a population should be represented in the various strata of a sample in quantities large enough to allow for appropriate statistical analysis and valid interpretation.
- Data analysis, credibility and financial constraints.
- Larger samples tend to increase the likelihood of precision (reliability) but they also inevitably increase the cost of the research. The taking of bigger samples is not a replacement for accurate sampling.
- Non-response factor.
- A number of test subjects do not always complete the questionnaire satisfactorily.
- Statistical precision.
- In random sampling it is possible to calculate a sample size to give a desired degree of precision.
- Sample sizes of research in previous studies can be used to judge the sample size.

Different methods may be employed to calculate the sample size. Computer programs with integrated formulas are readily available (Statistic solutions, 2009). The following formula is an example of how the sample size may be determined (Zikmund, 1994):

$$n = Zq^2S^2/H^2$$

n= sample size

Z= value of Z for given confidence level

S= standard deviation of population

H= desired precision level

q= desired confidence level

3.2.19 Ethical considerations

The “Guidelines for Good Practice in the Conduct of Clinical trials in Human Participants in South Africa” were published by the Department of Health in 2000 (DOH, 2000) and should be used as basis for the conduct of an ethically sound study that involves patient participation. This document deals with guidelines of professional conduct during data collection, data analysis and publication of results.

In addition, all research projects should undergo scrutiny from a recognised ethical review committee, e.g. a university research and ethics committee.

3.2.20 Pilot study

A pilot study is usually conducted to try and minimise and solve problems before full scale data collection starts. The pilot study tests a small sample under similar conditions to those planned in the main study. It uses the same instruments as intended to be used in the main study. The problems revealed in this way can then be rectified and loss of resources (e.g. time and money) is kept to a minimum. Testing of questionnaires and logistics can then be altered before the main study starts (Cozby, 1981).

3.2.21 Hawthorne effect

This phrase was first used in a series of productivity studies at the Hawthorne plant of the Western Electric Company in Chicago, USA. The researchers in this study found that their presence affected the behaviour being studied (Babbie & Mouton, 2001). This presence

leads to a distortion of results, due to people's behavioural pattern changing from their normal ("usual") behaviour when they know that they are being observed. Studies should be conducted in such a way as to minimize the impact that the experiment will have on people's behaviour.

3.3 RESEARCH METHODOLOGY AND PROCESS

The study arose when Geo-ICT Health Pty (Ltd) approached the Department of Pharmacy at the University of Limpopo, Medunsa Campus to be a research partner in a study on an electronic monitoring system (e-MuM) (see Chapter 1, Section 1.2). This section describes the methodology followed in this study.

3.3.1 Study design

The study design was a four phase, prospective, randomised experimental, longitudinal study. The study was designed to introduce the different aspects of the e-MuM system plus verbal feedback over time in a test group and to compare the data with a control group which had no intervention other than discreet monitoring.

The study design included a comparison of patients' adherence behaviour with a starting point at the enrolment when the study started (baseline). The adherence behaviour of the test and control groups before and after the introduction of each of the new elements was compared. To test each element of the e-MuM system independently and give patient feedback, the study comprised four phases, outlined in Table 3.1. The introduction of a new element in an already existing system made it necessary to employ a primary (direct contact to explain the use of system) and not secondary (file data) approach (Struwig & Stead, 2001). The longitudinal aspect of the study focussed on the behaviour of patients over an eight month period and data were collected at different points in time during that period.

As can be seen from Table 3.1, all patients were treated identically up to the end of Month 4 of the study.

Table 3.1: Study phases

Phases	Study period: months	Procedures for test and control groups	
Baseline	1 and 2	Study population enrolment: n=210 (target n=300) Monitor (Adherence: VAS, 2- and 7-day recalls; Clinical data: CD4 count, viral load) Ensure accurate contact details of patients for device retrieval in case of default.	
1	3 and 4	Start Phase 1: Issue e-MuM container Monitor (Adherence: VAS, 2- and 7-day recalls) Stratification and randomisation of patients into two balanced groups according to time on ARVs, gender and age	
		Control Group: n=105 (target n=150)	Test Group: n=105 (target n=150)
2	5 and 6	Monitor (Adherence: VAS, 7-day recall and electronic monitoring system). Start using new shortened questionnaire	Start Phase 2: Issue reminder unit and give training. Monitor (Adherence: VAS, 7-day recall and electronic monitoring system). Start using new shortened questionnaire
3	7	Monitor (Adherence: VAS, 7-day recalls and electronic monitoring system)	Start Phase 3: Do counselling, give Feedback I Monitor (Adherence: VAS, 7-day recalls and electronic monitoring system)
4	8	Monitor (Adherence: VAS, 7-day recalls and electronic monitoring system; Clinical data: CD4 count, viral load)	Start Phase 4: Do counselling, give Feedback II Monitor (Adherence: VAS, 7-day recalls and electronic monitoring system; Clinical data: CD4 count, viral load)
		End Phase 4: Do counselling and give Feedback III Monitor (Adherence: VAS, 7-day recall and electronic monitoring system)	

Phase 1: After issuing the e-MuM unit until issuing the reminder unit

Phase 2: After issuing the reminder unit (test group only) until before Feedback I

Phase 3: After Feedback I until Feedback II (Feedback was given to test group only)

Phase 4: After Feedback II, until Feedback III (Feedback given to both groups at Feedback III)

At the end of the study, two focus group discussions (one with staff and one with study group patients) were held to explore the effectiveness of the e-MuM system as a tool to monitor and improve the adherence process and the ease of use for the patient and pharmacist.

3.3.2 Study planning

3.3.2.1. Role players in Tshepang Clinic ARV e-MuM adherence study

- a. Tshepang Clinic (study site)
- b. Research staff from the Department of Pharmacy at the Medunsa Campus of the University of Limpopo (two data collectors, the post graduate student, the supervisor and co-supervisor)
- c. Geo-ICT Health Pty (Ltd) and staff members. This Information and Communication Technology (ICT) Company is a South African, Black Economic Empowerment (BEE) female-owned entity, formed in February 2000 to provide Information and Communication Technology (ICT) services, solutions and products locally and internationally. Geo-ICT Health Pty (Ltd) focuses on the development and supply of medical related technology and information systems for the public and private health care industry, enabling them to develop solutions that are scalable and sustainable (Geo-ICT Health Pty(Ltd), 2009).
- d. Patients on ARVs (matching study criteria in study population)
- e. Staff members of Tshepang Clinic (doctors, pharmacists, nurses, counsellors, welfare officers, and data capturers)
- f. Statisticians

3.3.2.2. Study site

In this study, access to numbers of patients using the same regimen and returning to the same site was important for monitoring purposes. A DOH designated ARV roll-out site to conduct the study was therefore essential. Visits to ARV treatment sites to observe workflow and logistics were conducted to plan the study around a certain work pattern, causing minimal disruption to normal workflow.

Due to large numbers of patients at the ARV site, not all patients at the clinic could be provided with the electronic monitoring device as part of this study. Retrieval of the devices throughout the study was critical to data collection. It was therefore decided to run the study at a known site where the staff were motivated and keen to co-operate, and where the administrative systems are known to work.

Due to reasons given above, the Tshepang Clinic at Dr George Mukhari Hospital was finally chosen as a study site (see Chapter 3, Section 3.4.1).

3.3.2.3. Research staff (study personnel)

- **Selection and training of data collectors**

Two data collectors with experience in previous projects, which involved interviews and administration of questionnaires, were identified. A week of training sessions was held collaboratively by Geo-ICT Health Pty (Ltd) and the research staff prior to the pilot study, with the purpose of training the data collectors in the technique of interviewing. Confidentiality, consistency and use of the software programme were covered. The schedule for selection and training of data collectors is shown in Appendix B.

- **Supervision of data collectors**

During the first weeks of each study phase, daily visits were made by the researcher or supervisors to assist the data collectors and to attend to any logistical problems. Regular weekly and sometimes daily visits were maintained through-out the study period by one of the research team members.

3.3.3 Study population and sample

3.3.3.1. Sampling methods and sample size

A statistician was consulted with regard to the calculation of the sample size. An enrolment target of 300 was set to make provision for drop-out. The statistician utilised nQuery Advisor® Release 6.0 (Statistical Solutions) software and a 'Two group test of equivalence in proportions' (large equal numbers), for the power and sample size calculation.

The initial sample size was calculated based on a minimum projected adherence difference of 5% between the test and control groups. As 95% adherence was the target value, a sample of 143 patients per group was required to detect the difference between 95% and 90% adherence. The expected difference in adherence between the test and control group was greater than 5%. A sample size of 150 patients per group would allow for some loss to follow-up.

❖ **Inclusion criteria**

- Adults > 18 years
- ARV users willing to provide informed consent (see Appendices C1 and C2).
- Patients who obtained their ARVs at the study site for the full duration of the study period
- All patients having had clinical markers measured within a month of the start of the study, and again within a month of the end of the study.
- Patients on either Regimen 1a or Regimen 1b of the National Department of Health Guidelines (patients taking lamivudine)

Note: It was decided to use lamivudine for the e-MuM container as the tablets are not packed in blister packs, most patients are on lamivudine and it is a twice daily regimen.

❖ **Exclusion criteria**

- Children younger than 18 years
- Adults not able to get their medication on a monthly basis from the chosen site
- Patients in the middle of their clinical marker cycle
- Patients using pillboxes as an adherence tool

3.3.3.2. Patient enrolment programme

The Tshepang clinic data capturers were consulted to clarify the patient enrolment process.

New patients are enrolled in groups on Tuesdays and Fridays. Each group is given a sequential number and generally the groups remain together, with common appointment dates. Files for these groups are kept together in bundles, rather than being re-filed under the record number. A database for cross-reference of file numbers and group numbers is maintained at the clinic. One hundred and ninety six groups were already enrolled at Tshepang clinic when the study started.

A list of patients expected on any given day is generated in advance. These lists were used to identify the group file bundles for patients potentially eligible for inclusion.

The group file bundles in the filing room were then examined by data collectors to identify potentially eligible patients. A patient identified as being eligible (receiving one or two months ART supply at each visit and being on Regimen 1a or 1b) for the study was marked with a purple sticker on the outside of the file.

The data collectors approached patients the next day. A pre-qualifying questionnaire (see Appendix D) was administered before the patients were enrolled in the study and consisted of three questions about the patient's ability to attend clinic visits. It also excluded patients already using other adherence tools. These questions were chosen to try to minimise the drop-out rate and to ensure that the outcome achieved could be ascribed to the e-MuM system tested. Patient files for those who indicated willingness to be included in the study were marked with a pink sticker.

A control sheet (see Appendix E) was stapled on the inside of the file and was ticked when patients were interviewed by the data collectors. Patients who went to the pharmacy for medicine without having first seen the data collectors, could then be identified and sent back to the data collectors by pharmacy staff.

3.3.3.3. Test and control groups

The study design made patient enrolment from a single site possible. During Phase 1 (see Table 3.1), participants were stratified by the project co-ordinator from Geo-ICT Health Pty (Ltd) and randomised into the test group and the control group.

3.3.3.4. Stratification and randomisation procedure

Step 1: The patients were sorted based on the ARV treatment period (from earliest enrolment to most recent).

Step 2: Patients were allocated to one of two groups alternately, until all patients had been allocated.

Step 3: One group was called test and the other group control.

Step 4: Averages of age, gender and period on ARV treatment were calculated for each group, to verify balance between the groups.

3.3.3.5. Final sample

The final sample size of the test- and control groups, after the stratification and randomisation process, is shown in Figure 3.1. Initially, 211 patients were enrolled into the study. The stratification and randomisation resulted in 105 patients allocated to the test group and 106 patients to the control group. Two patients (one from the test group and one from the control group) were excluded from the groups because of incomplete data

(Register numbers 0 and “invalid”). Two replacement patients were recruited and enrolled (Register numbers 31 and 38). Of these two patients, one (Register number 31, a control group patient) was transferred to another facility soon after enrolment. This left a total of 210 patients enrolled for the study (105 test group patients and 105 control group patients).

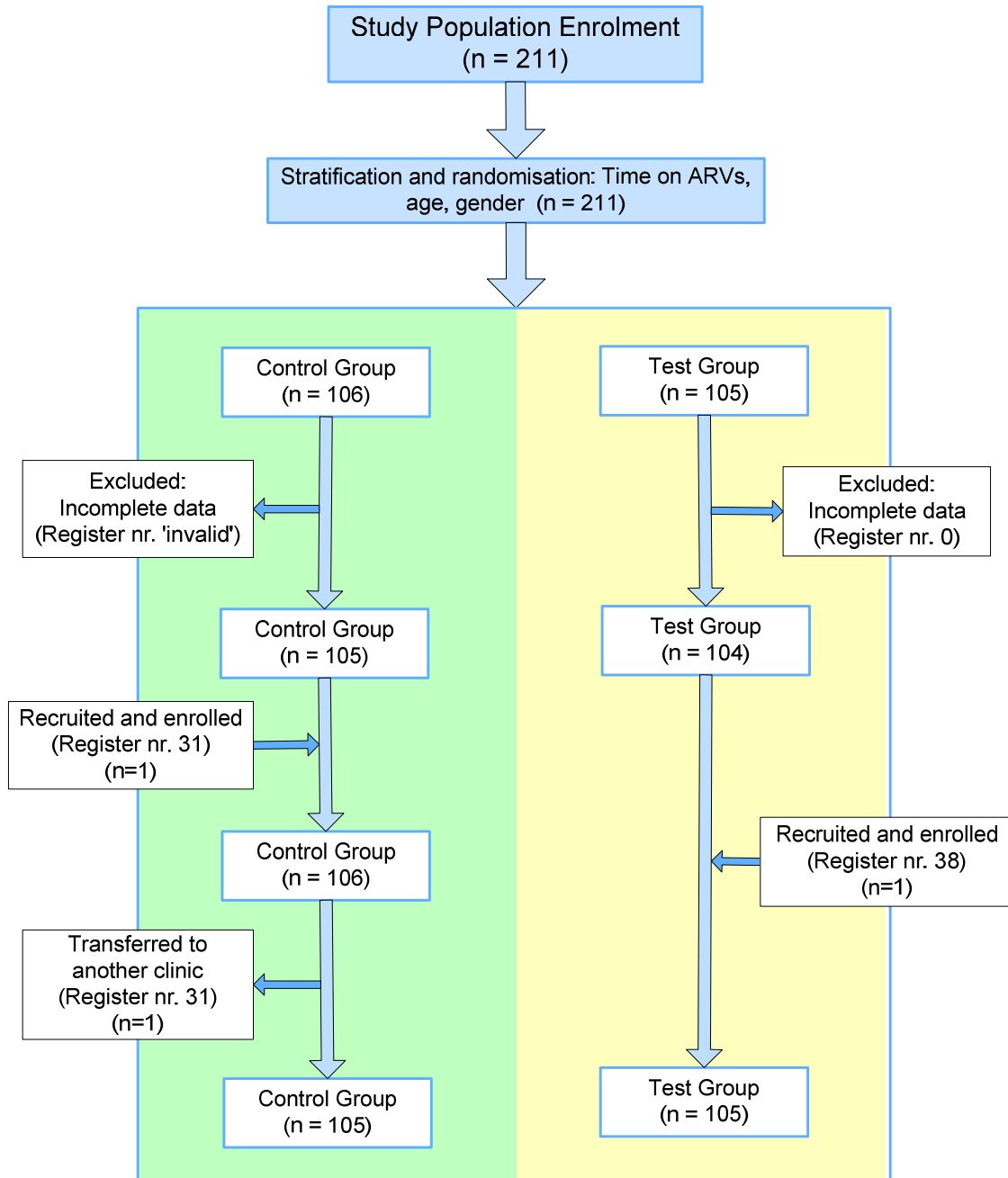


Figure 3.1: Final sample: Stratification and randomisation process

3.3.4 Study process

3.3.4.1. Pilot study

A pilot study is usually conducted at a separate site but in this case the pilot study was performed as part of the phased introduction of patients to the study, as the logistics of the study could only be tested at the proposed site.

Patient enrolment during Week 1 of the study was regarded as a pilot study to determine the logistics of patient flow, ease of putting translated questions to patients and time needed to complete all steps necessary in the process. Editing of the questionnaires was performed on site.

3.3.4.2. Flow charts

The patient flow process was complex, due to the number of items that had to be covered at any given visit. Hence, flow charts were generated at the start of each phase to standardise the procedures and to stipulate the activities and responsibilities within that particular phase. The flow charts for the different phases of the study are available in Appendix F.

3.3.4.3. Study phases

The phases of the study are illustrated in Figure 3.2 and described in more detail in the sections thereafter.

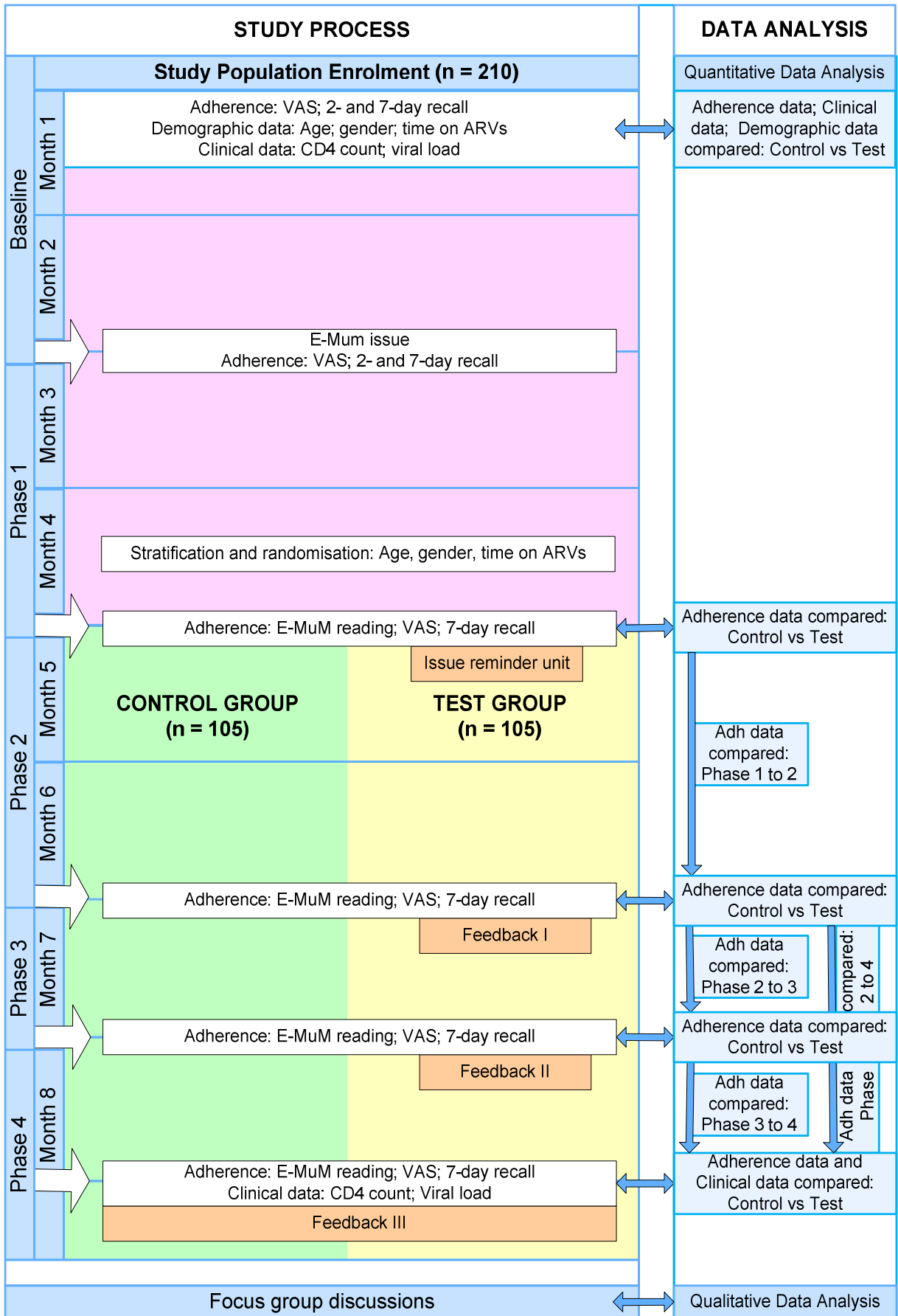


Figure 3.2: e-MuM study diagram

❖ **Baseline**

At baseline all participants completed the same demographic and adherence questionnaires (see Appendices G1 and G2). Participants were also asked to return with their regular tablet containers.

❖ **Phase 1**

The electronic monitoring device was issued as part of the lamivudine container lid at the end of 2nd month. Patients were requested to return with that container, but not told its purpose. Patients were stratified and randomised into a test group and control group. Electronic monitoring of both groups started at the end of the 2nd month of the study. Patients returned the e-MuM device and data were downloaded discreetly, out of patient view, at each return visit. Adherence monitoring with the VAS and two- and seven-day recall, in the form of questionnaires continued (see Appendix F for workflow). During this phase the patients were not aware that they were being monitored electronically. No interventions were scheduled during the first phase.

❖ **Phase 2**

At the start of Phase 2 (end of Month 4), the test group was issued with an electronic dosage reminder unit in the form of a watch with alarms. The test group patients were asked not to discuss the watch issue with anyone outside the immediate study staff (see Appendix H for wording used at issuing of reminder unit). They were also informed that the unit was a loan unit only and would have to be returned at the end of the study. During this second phase (months five and six), the effect of the reminder unit on the adherence of the test group was monitored. Monitoring with e-MuM continued discreetly for both groups and the shortened questionnaire (2-day recall omitted) was also completed (see Appendix F for workflow and Appendices I1 and I2 for shortened questionnaire).

❖ **Phase 3**

At the start of Phase 3 (end of Month 6), the patients in the test group were informed that their medication consumption was being monitored electronically. The first of two intervention phases started when test group patients were given feedback (Feedback I) on their adherence levels as obtained from the electronic monitoring in the study so far (end of Month 2 to end of Month 6). An example of an ART Adherence Report generated by the e-MuM system, is shown in Appendix J. During the verbal discussion, a

questionnaire/report was completed to identify reasons for and/or times the patient was non-adherent (see Appendix K). This verbal feedback to the test group was monitored for the effect on adherence (see Appendix F for workflow).

❖ **Phase 4**

At the start of Phase 4 (end of Month 7), the patients in the test group were given the second feedback intervention (Feedback II) obtained from the electronic monitoring for the period of Month 7 (see Appendix J for an example report). During the verbal discussion, a questionnaire/report was completed to identify reasons for and/or times the patient was non-adherent (see Appendix K). This verbal feedback to the test group was monitored for the effect on adherence (see Appendix F for workflow).

At the end of Phase 4 (end of Month 8), the patients in the test group were given feedback (Feedback III) obtained from the electronic monitoring for the period of Month 8 (see Appendix J for an example report). Patient adherence progress or deterioration over the study period was discussed. During the verbal discussion, a questionnaire/report was completed to identify reasons for and/or times the patient was non-adherent (see Appendix K). This verbal feedback to the test group was not monitored for its effect on adherence, as Month 8 was the last month of the study.

At the end of Month 8, because it was the end of the study, control group patients were informed that their medication consumption had been monitored electronically for the duration of the study. Contrary to the previous months where the control group patients were not given feedback on their adherence monitoring, they were then also given feedback obtained from the electronic monitoring for the entire monitoring period (end of Month 2 to end of Month 8) (see Appendix J for an example report).

3.3.4.4. Focus group discussions

Two focus group discussions, which were audio recorded for later transcription, were held at Tshepang clinic on 2 December 2008. Eight randomly chosen patients with diverse adherence patterns participated in the voluntary focus group discussion. The duration of both focus group discussions (FGDs) was one-and-a-half hours. Some questions about problems already identified in the questionnaires were included for discussion. The focus group guides and the topics included are shown in Appendix L.

The basic rules pertaining to multiple interviews were kept in mind in the focus group planning (McNamara, 2006):

- Relevant information about time, duration, recording and scope of session were conveyed to participants a few days before the meeting.
- The language of the patients was predominantly Setswana. An experienced Setswana- and English- speaking person was employed to conduct the Focus group.
- The clinic staff was interviewed by the postgraduate student in English
- Participants were seated, put at ease and able to observe all the other participants.
- Refreshments were served while the moderator introduced the group and thanked them for their time and participation.
- The need to respect confidentiality and anonymity was stressed and the consent form was signed by all study participants(See Appendices C2)
- The moderator (after giving participants a few minutes to reflect on one question at a time) kept focus on questions, maintained momentum, ensured even participation and ensured closure on questions (summarising).
- The session was tape-recorded with the knowledge and consent of participants to avoid relying on memory only.
- Shortly after thanking the participants for their time and participation, notes about the meeting were updated by listening to the recording.

3.3.5 Study data collection instruments (DCIs)

Different methods of data collection are available. Discussion of these methods was covered in Chapter 2 under Measurement of adherence (see Section 2.12). In this study three self-reporting measures were combined with measuring of clinical data and tablet counts. Self-reported adherence may be an accurate predictor of virological response to HAART (Mannheimer *et al.*, 2006).

3.3.5.1. Language considerations

Most patients spoke little or no English. Questionnaires were translated beforehand into Setswana by a registered translator (see Appendices G1, G2, I1 and I2). They were administered by the Setswana and English-speaking data collectors. The Setswana questionnaires were used by the data collectors as a basis during interviews and responses were recorded on the questionnaires in English.

3.3.5.2. Questionnaires

- a. Appendices C1 and C2 show the English and Setswana consent form, signed by every study participant, to ensure their full co-operation and understanding of the study goal and period.
- b. The questionnaire completed during the interview (Appendices G1 and G2) consisted of the following:
 - Basic demographic data collected at baseline
 - A section to test drug knowledge
 - An adherence section, including a 2-and 7-day recall and VAS
 - Details of the patient's normal tablet-taking routine and factors that may influence this routine
 - A tablet count
- c. The questionnaire shown in Appendices I1 and I2 was a shortened version of the baseline questionnaire (Appendices G1 and G2) with only a 7-day recall on adherence and a tablet count. This was a logistical measure for the last phases of the study when the data collectors were performing time-consuming additional functions (downloading e-MuM, programming, explaining the reminder unit and giving feedback).
- d. An ART Adherence Report of adherence behaviour during the previous period was generated from computer data by the data collector (see Appendix J). An Adherence Feedback Form (see Appendix K) compiled by study personnel to obtain patient explanations about the reasons for missing doses (non-adherence) was completed based on this adherence report. The feedback allowed questions to be put to patients in order to obtain information about the previous period of treatment. Feedback is only appropriate as part of a planned phase of study, with appropriate controls. Discussion of problem areas occurred and controlled improvement measures were implemented. A copy of the feedback form was inserted as additional information in the patient file before sending the patient for his/her doctor's appointment. Doctors were asked during the focus group session if this had any impact on what they focussed on and the way they spoke to the patient.

3.3.5.3. Review of clinical records

The official patient medical records served as an information base to gather additional demographic data needed on the baseline questionnaire. Clinical data (CD4 count and viral load) were obtained from the patient files and entered into the database at the start and end of the study.

3.3.5.4. Tablet counts

The questionnaire (see Appendices G1, G2, I1 and I2) made provision for monthly tablet counts and to observe whether the patient kept the different medication in the prescribed containers or carried all their medication in one container.

3.3.5.5. e-MuM system

A detailed description of the e-MuM system as well as its operation is attached as Appendix A. The system consists of a lid with embedded micro processor chip, a reminder unit (watch) able to be programmed to emit a signal at pre-determined times and the back-up (backbone) software programme. Every time the lid of the medication container is opened, the time is recorded on a micro processor embedded in the lid of the e-MuM container. Hence, the activities related to opening and closing the container, were monitored routinely for all patients in the test and control group for all phases.

Each e-MuM device has a unique number. The number of the device issued to every patient was entered on a data sheet against the patient's name and telephone number. Data were downloaded by the trained data collectors, from the microchip embedded in the medication container lid to the personal computer at the monthly prescription repeat visits. This operation was performed out of patient sight. Data from the e-MuM were downloaded automatically and adherence information was summarised by an automated programme into spreadsheet format.

3.3.5.6. Focus group guides

Focus group guides with a set of pre-determined open-ended questions were used to steer the focus group discussions. Refer to focus group guides in Appendix L for the topics included in the focus group discussions.

The descriptive reporting during the focus group discussions was guided by the following:

- Open ended questions were used to place less constraint on answers supplied by participants Participant's words but not names were used in the transcription
- Descriptive phrases or words used by participants in discussions were noted
- Themes in the responses to the key questions were identified
- A description of participant enthusiasm was included
- Any inconsistencies between participant comments were reported
- The overall mood of discussion was summarised
- The bias of the moderator was taken into consideration in interpretation

The following short introductory remarks were used for both focus group discussions:

- a. Introduction of study personnel and participants
- b. Thank participants for agreeing to participate, all share a common feature – they are on ARV treatment, are here to share their thoughts about taking ARVs, we want to learn from participants
- c. Explain purpose of study, purpose of this discussion, reassurance about confidentiality, agree on rules:
 - The identity of every patient will remain confidential and responses given will only be used by the study personnel
 - The proceedings will be recorded for use by the study personnel only
- d. Participants sign consent forms

3.3.6 Study period and schedule

Patients remained in the study for a period of eight months with the first-recruited patients enrolled in January and the last patients recruited in March, 2008. Hence patients completed the study from August to early November, 2008

Information sessions were held with counsellors, data capturers and filing personnel. During the first month the researcher and data collectors were at the early morning prayer meetings (07H00). The request for volunteers for the project was made to the patients at this early morning meeting by clinic staff. Patients were asked for their co-operation.

A study register for participating patients was set up. This register contained the name, hospital file number and quantity of medication issued (one or two months) for each patient. A study number was assigned to the patient and the date of enrolment in the study was stipulated.

3.3.7 Workflow logistics

Data were collected by the data collectors in a face-to-face interview (questionnaire) with each patient on a monthly basis. Data collection and file identification were done full time on Mondays, Wednesdays and Thursdays (regular clinic days for existing patients) and patient file identification on Tuesdays and Fridays.

Three cubicles in front of the pharmacy, but away from normal patient traffic areas, were utilised as semi-private areas to interview patients. Files were placed in a wire basket in the reception area of the pharmacy by the patients after visiting the doctor, social worker

or serologist from where they were taken by the data collector. The patient returned to the waiting area after the interview and the file immediately given to the pharmacy.

3.3.8 Data entry and analysis

3.3.8.1. Data entry

Data from the e-MuM were downloaded automatically and adherence information was summarised by an automated programme into spreadsheet format.

The Visual Analogue Scale (VAS) for each of the questionnaires was measured by the data collector and the distance recorded on the questionnaire. Data from the questionnaires (Appendices G1, G2, I1 and I2) were then captured on a MS Excel™ spreadsheet by the full time data collector and were proof-read by the researcher.

The two audio-taped focus group discussions were transcribed and translated into English where applicable, with the aim to capture as much as possible of the original meaning. Focus group data were typed and saved as MS Word™ documents.

3.3.8.2. Data analysis

The data analysis process which was carried out according to the phases of the study is illustrated in Figure 3.2 (see Chapter 3, Section 3.3.1). Data were extracted from the system by Geo-ICT Health Pty (Ltd), initial data analysis was performed and the data were made available to the researcher for further analysis (see Appendix M).

Demographic, adherence and clinical data obtained at the start of the study formed the baseline. Descriptive demographic comparisons of total enrolees, study and control groups were then made for the different phases of the study.

Independent variables (with sub-groups) included age, gender, marital status, educational level, employment status and time on ARVs. Due to the large quantity of data collected, and based on review of similar studies, only the key variables of age, gender and time on ARV medication were selected for analysis.

Comparisons were made of adherence data obtained from the different adherence assessment methods. These adherence assessment methods included questionnaires (recall, VAS, tablet counts and tablet-taking habits), e-MuM data, and biological markers (CD4 count and VL). Two of these methods (tablet counts and 2-day-recall) did not yield

results that could be used in the analysis as i) a large number of patients did not return with their medication as requested (see limitations in Chapter 6, Section 6.3.2) and ii) the 2-day recall was omitted from the questionnaires at the end of Phase 2, due to time constraints encountered by the data collectors as the phases became more complex and time consuming.

Data from the focus group discussions were read and re-read to explore and obtain an understanding of the data. Categories were developed into a framework of key themes. An overall interpretation of the themes was made to support the quantitative findings obtained from the e-MuM and the adherence questionnaires.

3.3.9 Ethical considerations

Ethical approval to conduct the study was obtained from the University of Limpopo, Medunsa Campus, Research and Ethics Committee (MREC) prior to the commencement of the study. Refer to Appendix N for a copy of the clearance certificate.

Permission to conduct the study at Tshepang Clinic was obtained from the Chief Executive Officer of Dr George Mukhari Hospital, the Clinical Head and Clinic Manager of Tshepang Clinic.

A semi-private interview area was set-up in the clinic to ensure adequate privacy during interviews. Delays for patients were minimised by interviewing them as they were waiting for their ARVs to be dispensed. Participants were assured of confidentiality and that all data collected will remain anonymous. All participants signed an informed consent form, which was available in English and Setswana (see Appendices A1 and A2). Each study patient was assigned a study number, which was kept in a data base. Confidentiality of all patient-related data will be maintained according to the Guidelines for Good Practice in the Conduct of Clinical Trials in Human Participants in South Africa (DOH, 2000).

A particular dilemma needed to be addressed in fulfilment of the study aim. The study aim was to assess the effect (if any) of the e-MuM unit on the adherence of patients to their ARV medication. The implication was that the initial goal of the system was monitoring and not to improve adherence. The information given to participants was that their medication use would be evaluated, but the way in which it would be done was omitted as this did not pose any threat or physical danger to the patients.

3.3.10 Validity and reliability of the data

Validity is the trustworthiness of a data collection method, including the compilation of questionnaires and the use of statistics which emanate from the data collection method. Validity would then as a matter of fact exclude all bias from obtaining and processing data (Struwig & Stead, 2001).

Reliability is the extent of accuracy, consistency and stability of results. The reliability of the results is linked to the probability of reproducing the results (Struwig & Stead, 2001).

The data collection instruments for adherence measurement have already been used in previous studies (Mapetla, 2007).

The following measures were taken during the course of the study, data entry and data analysis to ensure the validity and reliability of the data and study results:

- Training of the data collectors to ensure reliability and validity and avoid bias
- The pilot study, which was carried out during the first week of the study period (see Chapter 3, Section 3.2.20)
- Workflow charts
- Non-discriminate and random selection of a sample
- Treating both groups identically in Phases 1 and 2
- Scheduling the participants of the control and study groups to attend the clinic on different days to minimise inter-group contact. This proved impossible, hence contributed to limitations of the study
- Patient files had coloured stickers specific to the study so as to avoid missing patients.
- Staff at the clinic were briefed beforehand about the use of the stickers.
- Availability of an informed consent form in the local language to ensure that sample selection would be on a voluntary and informed basis
- Availability of an appropriate questionnaire in the local language
- Patients on disability grants are at high risk of defaulting once treatment success is achieved. However, these patients were not excluded from the study, as it could have compromised study validity. Patients on disability grants were identified at the initial contact and those who dropped-out of the study will be followed-up in a future study
- Automated data collection from the e-MuM system
- Downloading of e-MuM data out of sight of the study participants

- Checking e-MuM units when they were not functioning properly
- Requesting the participants not to discuss their participation in the study with other patients
- Minimisation of the influence of knowledge of participation in the study (Hawthorne effect)
- Interviews were used to identify possible decanting habits of study participants. These decanting habits were considered in the interpretation of the data
- Checking of questionnaires for completeness and follow-up if necessary
- Data cross checks
- Interpretation of feedback forms
- 'Lenient' and 'strict' definition of adherence
- Focus group discussions in the participants' language of preference

3.4 STUDY CHALLENGES

Throughout this study, major logistical challenges were faced, which necessitated on-going adaptation to the planned approach. Due to the impact of the challenges on the conduct of the study, this method chapter diverts from the norm, in that it includes descriptions of those challenges and explanations as to how they were overcome.

3.4.1 Change of study site

Rustenburg Hospital was initially considered to be the most suitable study site for the study. The Wellness Clinic at Rustenburg Hospital was a designated ARV roll-out site and had been used successfully in previous studies (Mapetla, 2007; Meyer, 2008b). The personnel were both reliable and helpful.

After several visits made to Rustenburg for consultation, the logistics were planned in detail. The study protocol scheduled the study to start in July 2007 after a pilot study in June 2007.

The protocol which named Wellness Clinic as the study site was submitted to MCREC in April 2007 and required several resubmissions to clarify sections of the study protocol. Random sample selection, the role of the post graduate student in the study, translation of questionnaires into Setswana, focus group selection and questions about awareness by study participants of the study goal had to be clarified before permission was granted on 22 August 2007.

Due to staff shortages (non-replacement of pharmacists at Rustenburg Hospital) and budget constraints, the satellite pharmacy serving Wellness Clinic closed in October 2007 with no prospect of re-opening in the immediate future. Hence, the study had to be moved to another site. A decision to change the study site from Rustenburg was made late in 2007.

Fortunately, a newly expanded clinic site, Tshepang Clinic at Dr George Mukhari Hospital, was finished and opened in early December 2007. In addition, a preliminary visit showed that the study could be conducted with the minimum of alteration to the patient handling process, thus minimising the Hawthorne effect. The choice of the study site was thus convenience-based, but this approach was deemed justifiable, as the objective of the study was to test the system with the minimum of confounding variables.

This move resulted in the additional benefit of having the study site adjacent to Medunsa Campus of the University of Limpopo, making quick and easy access possible.

The personnel at Tshepang Clinic were keen to participate in the study. After visits and discussion with management, an amendment to the research protocol was made to reflect Tshepang Clinic as the new study site and submitted to the Medunsa Campus Research and Ethics Committee (MCREC) in January 2008 (see Appendix N2). The protocol amendment was accepted and the study started on the 22nd January 2008.

3.4.2 Speed of recruitment and loss of patients

The following problems encountered during Phases 1 and 2 of the study resulted in a slow recruitment and loss of some patients enrolled in the study:

- a. In an effort to reduce workload at the clinic, the clinic staff started issuing trustworthy and adherent patients with two months' supply of ARV medication. This meant that patients who received two months' medication before the start of the study on the 22nd January only returned in March.
- b. All patients with appointments on the 29th January were given three months' supply of medication as their two month return date fell on Easter Monday.
- c. Although patients and staff agreed not to have test patients down referred, three enrolled patients were lost as a result of down-referral (due to a misunderstanding by a filing clerk)
- d. Bad weather (rain) lead to some patient visits missed during February and they subsequently only returned in March.

- e. Illness and absence of a data collector on two occasions during the enrolment period meant a much slower enrolment pace during these days.
- f. Lack of patient remuneration, embarrassment and patients wanting to attend clinics located more conveniently to their homes (down referral) were reasons for unwillingness to participate in the study.

The slow recruitment had an on-going major logistical impact on the study, as it resulted in two phases of the study running concurrently. The latter approach was not planned and hence put major logistical pressure on the data collectors. The slow recruitment also had an impact on the recruitment number (sample size). The target sample of 300 patients could not be reached within the budgeted time frame of the study.

3.4.3 Group visits on same day

Random stratification of daily enrolled patients into the control and test groups on the day of enrolment was the ideal. Due to the uneven enrolment of patients (stratification criteria for age, gender and time on ARVs) this could not be done until all the enrolees were recruited. The result of stratifying patients into the control and test group after enrolment of all 210 patients resulted in some patients from the control and test group returning on the same day. The fear was that this could lead to bias through discussions of differences in study procedures between the test group and the control group patients.

3.4.4 Hawthorne effect

Minimising and limiting an unwelcome external influence to extract information from patients acting naturally was essential. Uploading of e-MuM microprocessor was done out of sight and test group patients were only informed about being monitored during Phase 4. The result was that too much emphasis could not be placed on patients to divert from their usual tablet taking routine. This led to patients not taking their medication from the container, until given specific instructions to do so.

3.4.5 Overcrowding

Due to the increased rate of enrolment of patients on ARVs at Tshepang, the clinic rapidly became very overcrowded. This was partly due to the attempts to reach targets set out in priority area 2 of the HIV & AIDS and STI Strategic Plan for South Africa 2007-2011 (DOH, 2007). This target aimed to provide treatment, care and support services to 80% of HIV

positive people and their families by 2011. Pressure by NGOs and the business sector also placed the burden for faster enrolment on clinics.

The pharmacy waiting area was completely inadequate in size and was moved to the outside of the clinic in May, leading to patient flow being severely interrupted and data collectors having to search for patients.

3.4.6 Patient enrolment programme

Overcrowding became a problem at Tshepang Clinic and was addressed in different ways by the staff. Some of the measures taken impacted negatively on the study and remedial action was taken swiftly by members of the research team. As mentioned above, an administrative official was found referring willing adherent patients to smaller clinics to continue treatment. As a result, three of the study patients were lost. This practice was brought to the attention of the management and discontinued for study participants.

3.4.7 Renovations at the clinic

Following the overcrowding problem the clinic, rebuilding and renovation work was carried out at the clinic. This work aggravated the overcrowding problem for an even longer period. The data collectors lost their work space for several weeks and had to work next to the medication issue area, in an already crowded space.

3.4.8 Filing re-organisation

An external management decision was taken in early August to change the filing system from the group system to the individual numbering system, used in the rest of the hospital. The files for patients enrolled on any specific day were not kept together anymore. Filing according to file number was conducted. This approach resulted in major disruption over a period of two weeks in August 2008. Patients enrolled on the same day usually returned on the same day every month. File reorganisation made a rapid location of files impossible. Many patients were seen without files during these two weeks. The study database and data collectors proved highly helpful to clinic staff during this period. The old system was re-introduced and matters returned to normal.

3.4.9 Software changes

Geo-ICT Health Pty (Ltd) was very consistent in their willingness to update programmes to suit the requirements of the study. However, as in many new studies several programming

problems as well as printing anomalies had to be addressed during the study period. Due to logistics of dealing with an external company, a waiting period before changes were made slowed the rate of data entry at crucial periods during the study. The data collectors also had to enter some of the data more than once. Another problem occurred when the computer did not generate graphs after data download from the e-MuM or displayed no time frame with only the dots of the graph on the screen. Usually this problem could be corrected by resetting and restarting the computer programme. This happened often and time would elapse from when the problem is reported to when a response is received from the company. Having no back-up programme during Phase 1 and 2 meant all data collected in the two questionnaires had to be re-entered.

The software programme (backbone) of the e-MuM system contained a summary programme suitable for incorporation into a Microsoft Excel™ spreadsheet used in data analysis. This programme was only used as a starting point, and these automated report formats for strict and lenient adherence needed cleaning and was exported to the spreadsheet for data analysis by a local university statistician.

3.4.10 e-MuM monitoring unit

A lack of container sturdiness was encountered and during the first weeks of the study more than 20 patients returned their containers with no data being recorded. After consultation with Geo-ICT Health Pty (Ltd), it was clear that this had happened because of malfunctioning of certain electronic parts inside the lid. Similar problems have been encountered where the same units have been used in previous studies.

3.4.11 Time constraints

- Measures were taken to shorten the time devoted to every patient. This included shortening the questionnaire towards the end of Phase 2 and eliminating the 2-day recall from the questionnaire.
- The time spent on recording the adherence of the instruments (VAS and 7-day recall) was still substantial.
- The e-MuM unit data had to be downloaded out of the sight of the patient. As the project progressed the setting (or resetting) of the reminder unit (watch) by data collectors took time.
- A substantial number of patients required explanations on the different adherence questionnaire instruments at every visit.

- The time taken to deal with a patient ranged from 20 to 45 minutes. The average time required was 25 minutes per patient.

3.4.12 Limited funding

The budget constraints for the study was a challenging factor, with no additional funding available for the engagement of additional staff during periods when the data collectors needed time to implement new phases and explain the instruments to the study patients.

3.5 SUMMARY

The 8-month study to evaluate the e-MuM device was conducted at the Tshepang Clinic situated at the Dr George Mukhari Hospital. Enrolment of patients started on 22 January 2008 and the study was finalised in November 2008. Data collector training and clinic staff information sessions were held before the study commenced. Data were collected from 210 volunteer patients meeting sampling criteria and allocated at random to a test and control group at the end of Phase 1 of the study. Data collection took place according to a workflow schedule. The data collection instruments included questionnaires, 2-day recall (omitted at the end of Phase 2), 7-day recall, tablet counts, VAS and e-MuM system. The VL and CD4 count results for study patients were obtained from the clinic files and computer system. Separate focus group discussions for patients and clinic staff were held after conclusion of the study. The results on the adherence data are presented in Chapter 4 and the focus group findings in Chapter 5.

CHAPTER 4

RESULTS AND DISCUSSION - QUANTITATIVE DATA

4.1 INTRODUCTION

In this chapter the demographics of the test and control groups, followed by the adherence data from the study, are presented. The data were gathered during the monthly routine visits by enrolled study patients, using the e-MuM system and questionnaires. Biological markers at the start and end of the study are reported.

4.2 PATIENT POPULATION AND STUDY GROUPS

After enrolment, stratification and randomisation, the study population consisted of 210 patients with 105 patients in the test group and 105 patients in the control group (see Chapter 3, Figure 3.1).

4.2.1 Patient demographics

4.2.1.1 *Age*

The distribution of test and control group patients according to age for each phase of the study is shown in Table 4.1 below. Three patients from the test group and one patient from the control group had birth date data missing and could not be included in the age demographic comparison. This factor resulted in enrolment numbers of 105 in both test and control groups being adjusted to 102 in the test and 104 in the control group for the age group comparison.

Table 4.1: Age at enrolment for Control and Test group at each phase

Composition of group at each study phase*	Age (years) at enrolment: test group			Age (years) at enrolment: control group			P**
	N	Median Mean±SD	Range	N	Median Mean±SD	Range	
At enrolment	102	35 37.6±9.5	19 - 59	104	35 36.7±9.6	20 - 62	0.566 0.457
At issue of e-MuM unit	71	35 37.7±9.9	19 - 59	64	35 36.2±9.9	20 - 62	0.475 0.367
Phase 1	69	34 37.4±9.8	19 - 59	57	35 35.8±9.7	20 - 60	0.531 0.373
Phase 2	66	34.5 37.7±9.6	19 - 59	50	35 36.4±9.2	20 - 60	0.760 0.436
Phase 3	57	34 37.6±9.8	19 - 59	45	36 36.0±8.9	20 - 55	0.759 0.416
Phase 4	44	34 38.0±10.6	19 - 59	42	36 36.4±9.3	20 - 60	0.743 0.440

* Phase 1: After issuing the e-MuM unit until issuing the reminder unit

Phase 2: After issuing the reminder unit (test group only) until before Feedback I

Phase 3: After Feedback I until Feedback II (Feedback was given to test group only)

Phase 4: After Feedback II, until Feedback III (Feedback given to both groups at Feedback III)

**Wilcoxon two-sample test for medians, independent t-test for means

As can be seen from Table 4.1, there was no statistically significant difference between the age distribution of the control and test groups at any point in the study.

The study excluded patients younger than 18 years. Most of the study participants were aged from 30 to 50 years (see Figure 4.1).

4.2.1.2. Gender

Figure 4.1 below shows the age and gender distribution of the total group (n=210) at the start of the study.

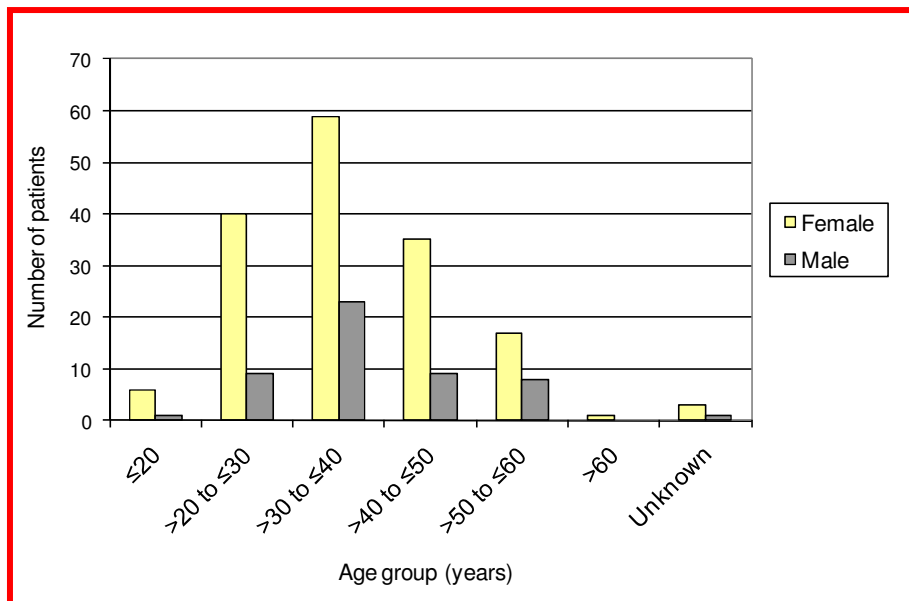


Figure 4.1: Study population at enrolment according to age and gender

The gender composition of the test and control groups at each phase of the study is shown in Table 4.2. There was no statistically significant difference in the gender balance of the test and control groups at the start of the study. Towards the end of the study the groups were still not statistically different in terms of gender balance, despite there being a relatively higher percentage of females than males in the control group compared to the test group. Figure 4.2 illustrates that relatively more males than females had been lost from the control group.

Table 4.2: Gender composition of control and test group at each study phase

Composition of group at each study phase*	Test group				Control group				P (Chi square test)		
	N	Female n	%	Male n	%	N	Female n	%		Male n	%
At enrolment	105	81	(77%)	24	(23%)	105	79	(75%)	26	(25%)	0.746
At issue of e-MuM unit	73	53	(73%)	20	(27%)	65	54	(83%)	11	(17%)	0.141
Phase 1	70	50	(71%)	20	(29%)	58	48	(83%)	10	(17%)	0.132
Phase 2	68	49	(72%)	19	(28%)	51	44	(86%)	7	(14%)	0.063
Phase 3	58	43	(74%)	15	(26%)	46	40	(87%)	6	(13%)	0.106
Phase 4	45	32	(71%)	13	(29%)	43	37	(86%)	6	(14%)	0.089

* Phase 1: After issuing the e-MuM unit until issuing the reminder unit

Phase 2: After issuing the reminder unit (test group only) until before Feedback I

Phase 3: After Feedback I until Feedback II (Feedback was given to test group only)

Phase 4: After Feedback II, until Feedback III (Feedback given to both groups at Feedback III)

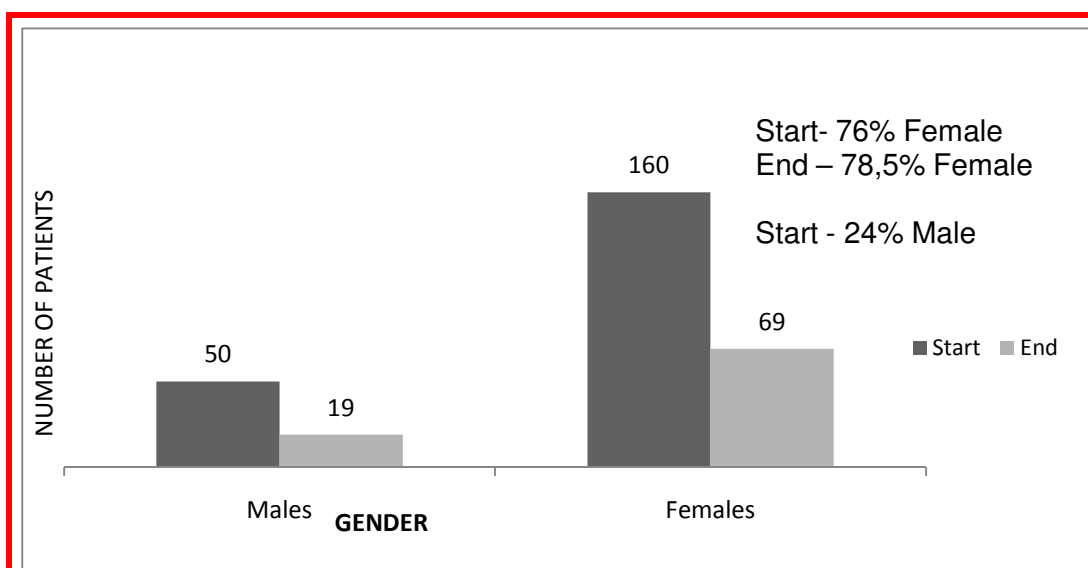


Figure 4.2: Number of males and females in total group at start and end of study

The HIV positive population in South Africa makes up 18.1% of the total population. Among females, HIV prevalence is highest in patients between 25 and 29 years old. Among males, the peak is in the group aged 30-34 years (UNAIDS, 2008 c). Women older than 15 years made up 60% of the HIV infected population in South Africa in 2007 (UNAIDS, 2008 c). Gender inequalities continue to increase the vulnerability of women and girls to HIV infection. In sub-Saharan Africa, 14 women are infected for every 10 males (UNAIDS, 2008c).

The study population was recruited on a voluntary basis. After enrolment, at the start of the study period 76% were women; at the end of the study it included 78% women.

The most recent gender data from Tshepang clinic (2010) of patients currently on ART show that females predominate (67% females vs. 33% males). Other studies conducted in similar settings in South Africa also reflected these gender proportions (Mapetla, 2007; Meyer, 2008b). Hence, it appears that relatively fewer males than females seek treatment at Tshepang, when compared to those infected.

In a large Kenyan study, men were more likely to be lost to follow-up than women (Wools-Kaloustian *et al.*, 2006). Some evidence of men being less likely to return to clinics than women emerged in retrospective data from 15 treatment programmes in the network of HIV/AIDS treatment programmes in Africa, Asia and South America (The Antiretroviral Therapy in Lower-Income Countries [ART-LINC] in collaboration with the International Epidemiological Databases to Evaluate AIDS [IEDEA]) (Brinkhof *et al.*, 2008).

4.2.1.3. Time on treatment (months)

Tshepang clinic opened in 2004. The patients enrolled into the study all had treatment periods at Tshepang of less than 48 months when the study commenced.

At the stage of data analysis, the dates of starting treatment (as shown in the e-MuM database and subsequently used in the randomisation plan, n=210) were verified against those indicated in a handwritten list of patients referred to Tshepang clinic. The dates differed for 51 patients. An interpretation error by datacollectors of confusing first visit and treatment start dates and used by Geo (ITC) when randomisation was done could explain the huge discrepancies. Some of the patients had received pre-counselling without immediate treatment initialization which resulted in a considerable difference in time from first visit to start of treatment.

The date discrepancies ranged from -539 days to +535 days and were greater than 30 days for 29 patients. This finding prompted further verification of the date of treatment initiation, using two further sources: Dates of pre-treatment session 3, as entered into e-MuM system (n=173), and beginning of treatment as stated by patients and entered into the e-MuM system (n=199).

As explained in Chapter 3 (see Section 3.3.3.2), patients starting at the clinic on the same day are given the same group number and kept in these groups for future appointment dates and identification purposes. Hence, if a date and group did not correspond in the data, the information was checked and edited. A total of 45 dates in the randomisation plan were corrected.

Based on the corrected data, the groups still did not differ significantly in terms of their mean or median duration on treatment at any phase of the study (see Table 4.3 below).

Table 4.3: Duration on treatment: Control and Test group

Composition of group at each study phase*	Duration on treatment (months): test group			Duration on treatment (months): control group			P (Chi square test)
	N	Median Mean±SD	Range	N	Median Mean±SD	Range	
At enrolment	105	7.3 12.5±11.4	0.6 - 44.1	105	8.5 13.6±12.1	0.5 - 43.4	0.466 0.495
At issue of e-MuM unit	73	6.4 12.5±11.7	0.6 - 44.1	65	6.9 11.9±12.1	0.5 - 43.4	0.771 0.771
Phase 1	70	6.4 11.8±11.0	0.6 - 42.4	58	7.0 11.6±11.8	1.5 - 43.4	0.939 0.904
Phase 2	68	6.4 12.6±12.0	0.6 - 44.1	51	7.6 12.0±11.5	0.5 - 43.4	0.970 0.798
Phase 3	58	7.3 12.9±11.5	0.6 - 42.4	46	8.0 12.4±11.9	0.5 - 43.4	0.829 0.830
Phase 4	45	12.3 14.7±12.5	0.6 - 44.1	43	8.3 11.9±10.7	1.5 - 43.4	0.392 0.252

* Phase 1: After issuing the e-MuM unit until issuing the reminder unit
 Phase 2: After issuing the reminder unit (test group only) until before Feedback I
 Phase 3: After Feedback I until Feedback II (Feedback was given to test group only)
 Phase 4: After Feedback II, until Feedback III (Feedback given to both groups at Feedback III)

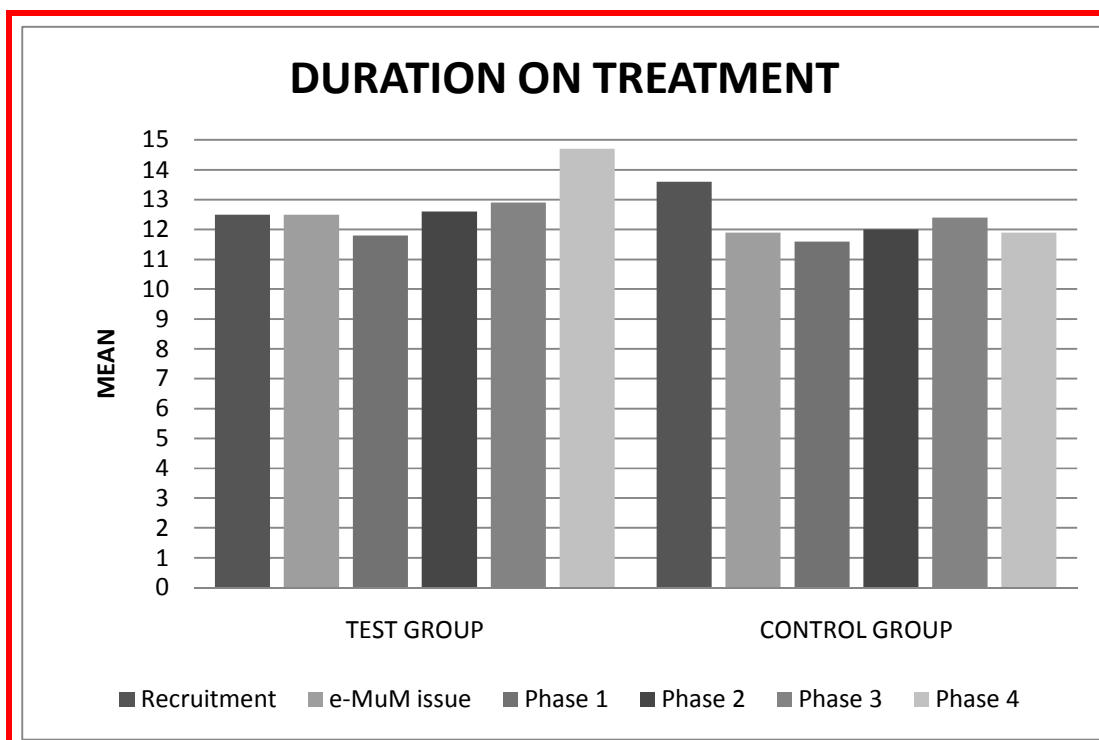


Figure 4.3: Mean duration on treatment: Control and Test group

There is a higher mean (and median) duration on treatment for the test group by Phase 4. This finding follows a general trend that patients who have been on treatment for longer, tend to remain in studies. A tendency by patients to leave a study is more likely during the first six months on treatment than any other study period (Brinkhof *et al.*, 2008).

In Phases 3 and 4 the test group patients were shown their adherence results from the e-MuM printout and asked questions about non-adherence periods. It is possible that some non-adherent patients did not return for the second feedback as a result of this.

4.2.1.4. Additional socio-demographic information

The patients enrolled in the study had an unemployment rate of 75%. The educational level of 82% of patients enrolled in the study was an incomplete secondary level or lower.

The marital status of 87% of the study patients was single, divorced, widowed or separated.

In a systematic review of 116 articles and 17 original studies (Falagas *et al.*, 2008) the authors evaluated the association between some socio-economical status (SES) factors and adherence to ARV treatment. They found no conclusive support for a clear association between income, education and occupation of patients and their adherence to ARV medication. The studies did demonstrate a positive trend, but did not establish statistical significant association between the three SES determinants and adherence.

In this study, 59 (28%) of the 210 study patients received social grants. Of these 59 patients, only 12 (20%) completed the study with e-MuM data, clinical data and attendance at all visits. On the other hand, 76 (50%) of the 151 study patients who did not receive social grants, completed the study with e-MuM data, clinical data and attendance at all visits. These figures show that more patients who were not receiving social grants, compared to those who were receiving social grants, completed the study. Based on the information available in the study, no specific reasons could be identified why more patients who were receiving social grants dropped out of the study. Nine of 12 patients receiving social grants recorded an increase in CD4 count at the end of the study period. Social grant money might indirectly strengthen adherence, as it could be used for travelling expenses to attend appointments and collect medication. To the contrary, patients may also interrupt medication schedules to keep their CD4 count below the required 200 cell/mm³ and hence not lose the grant (TAC, 2009).

4.3 ADHERENCE MEASUREMENT

4.3.1 Adherence measured with e-MuM device

The e-MuM software was programmed to calculate average adherence for each patient at each phase of the study as well as overall adherence. Two different time windows were used to define whether a dose was taken as prescribed.

- In the ‘**lenient**’ definition, the time window allowed for taking the required doses was the **correct day**;
- In the “**strict**” definition, it was within **an hour before or after** the prescribed time.

Adherence was calculated as the percentage of required events (opening the container) that occurred within the required time frame.

4.3.2 Adherence overviews

The frequency distributions for percentage adherence are illustrated in histograms for the two groups at each study phase. The data are presented as the percentage of patients in 10% adherence blocks from 0 to 100% adherence.

The histograms show adherence levels without any clear pattern for groups and phases. The exceptions are histograms for Phases 3 (see Figure 4.4d) and 4 (see Figure 4.4e). Phase 3 histograms show an improvement in the number of test group patients with 80%, 90% and 100% adherence. This trend is also repeated in Phase 4 histograms for test group patients with 80%, 90% and 100% adherence.

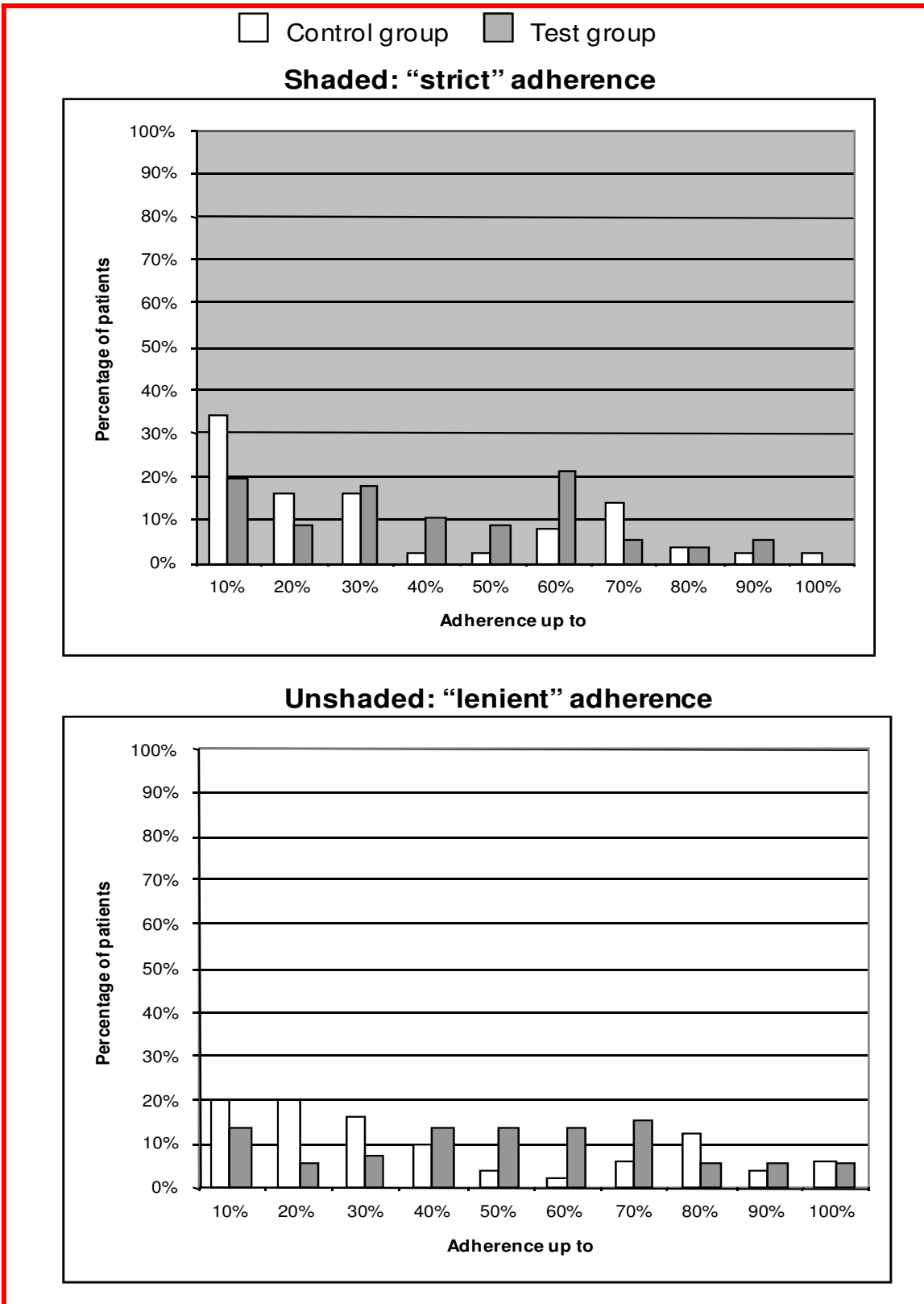


Figure 4.4a: Adherence overview: Full period (Phase 1-4)

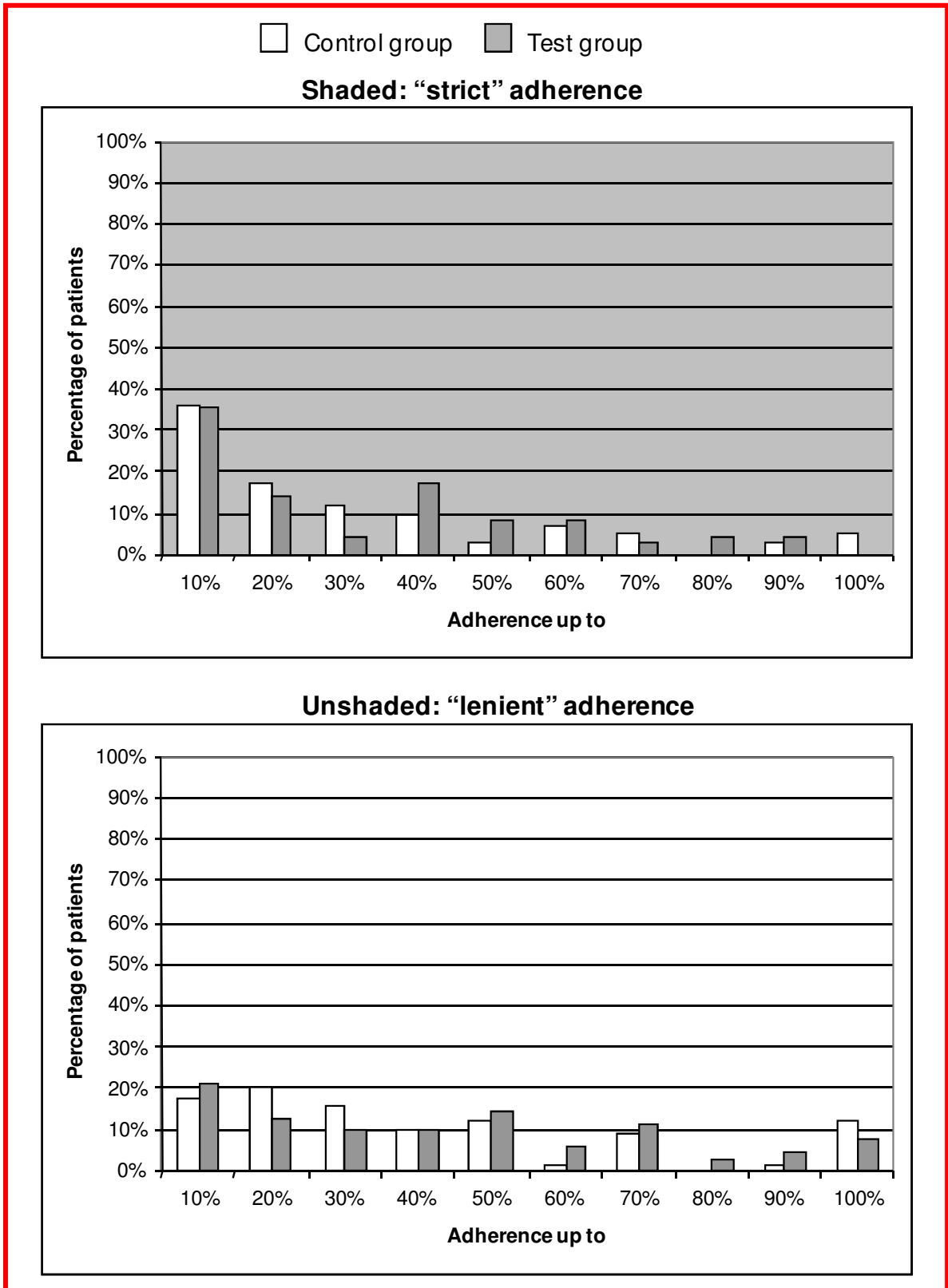


Figure 4.4b: Adherence overview: Phase 1 (from issue of e-MuM to issue of reminder unit)

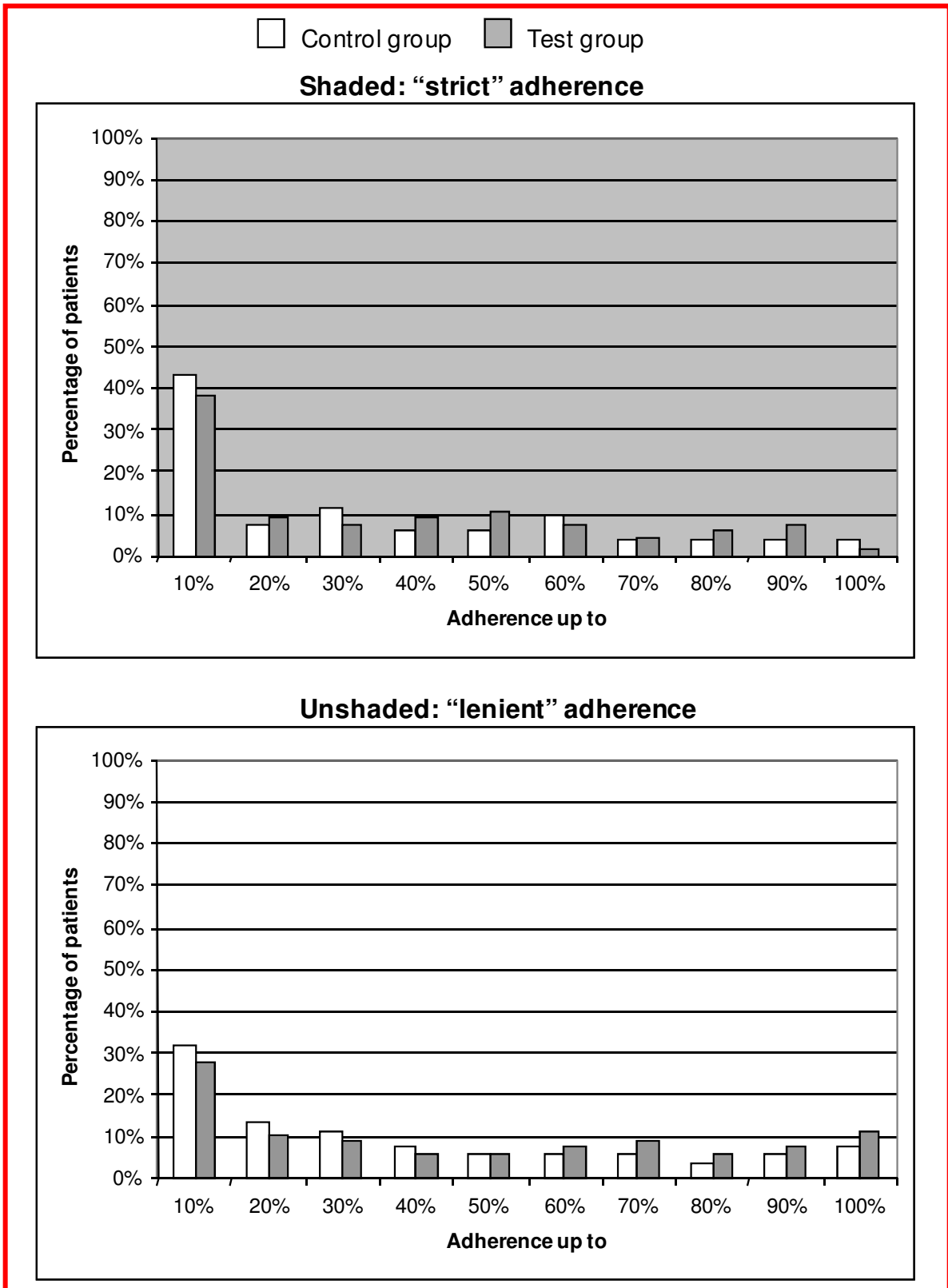


Figure 4.4c: Adherence overview: Phase 2 (from issue of reminder unit to just before Feedback I)

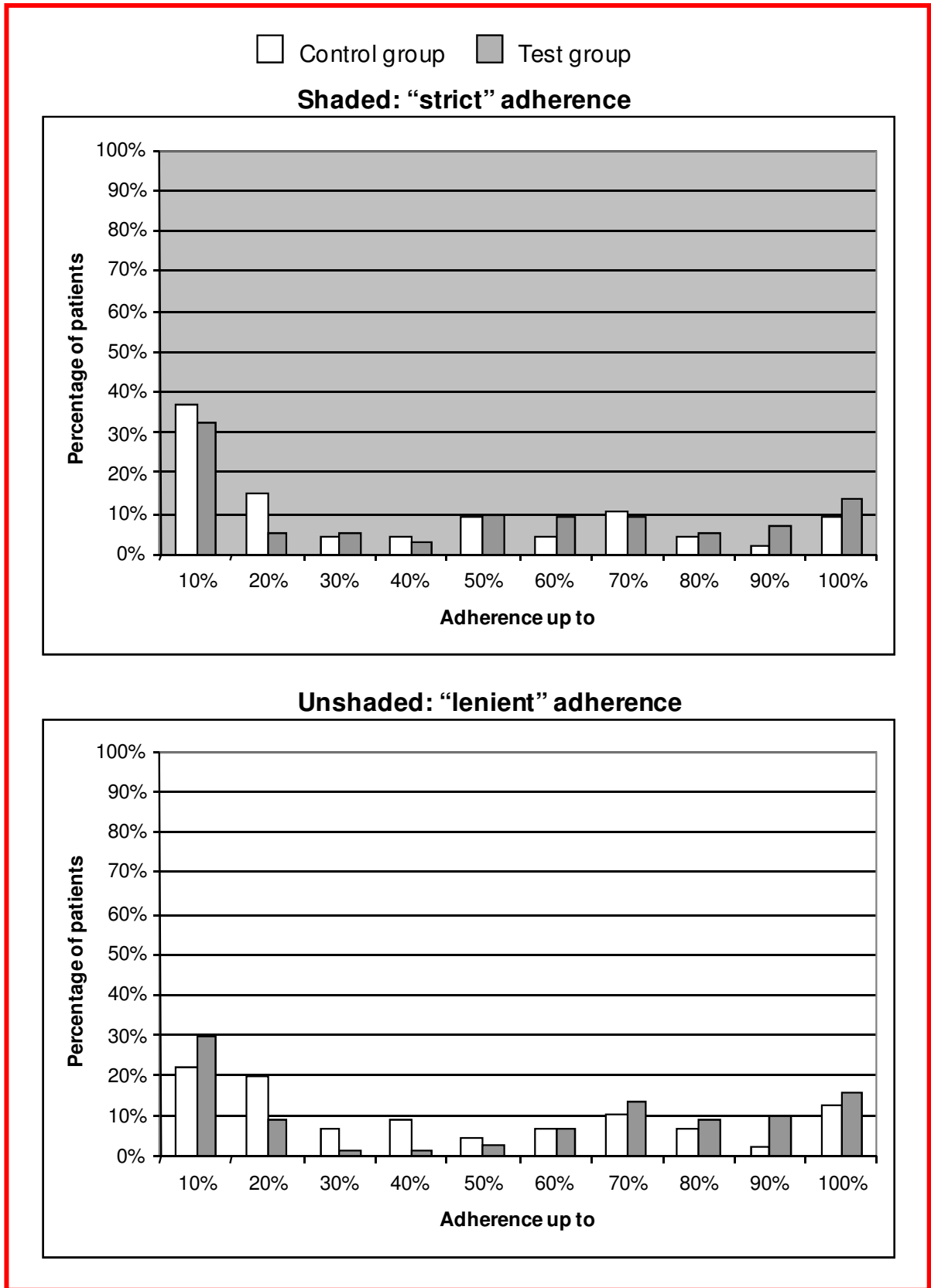


Figure 4.4d: Adherence overview: Phase 3 (from Feedback I to just before Feedback II)

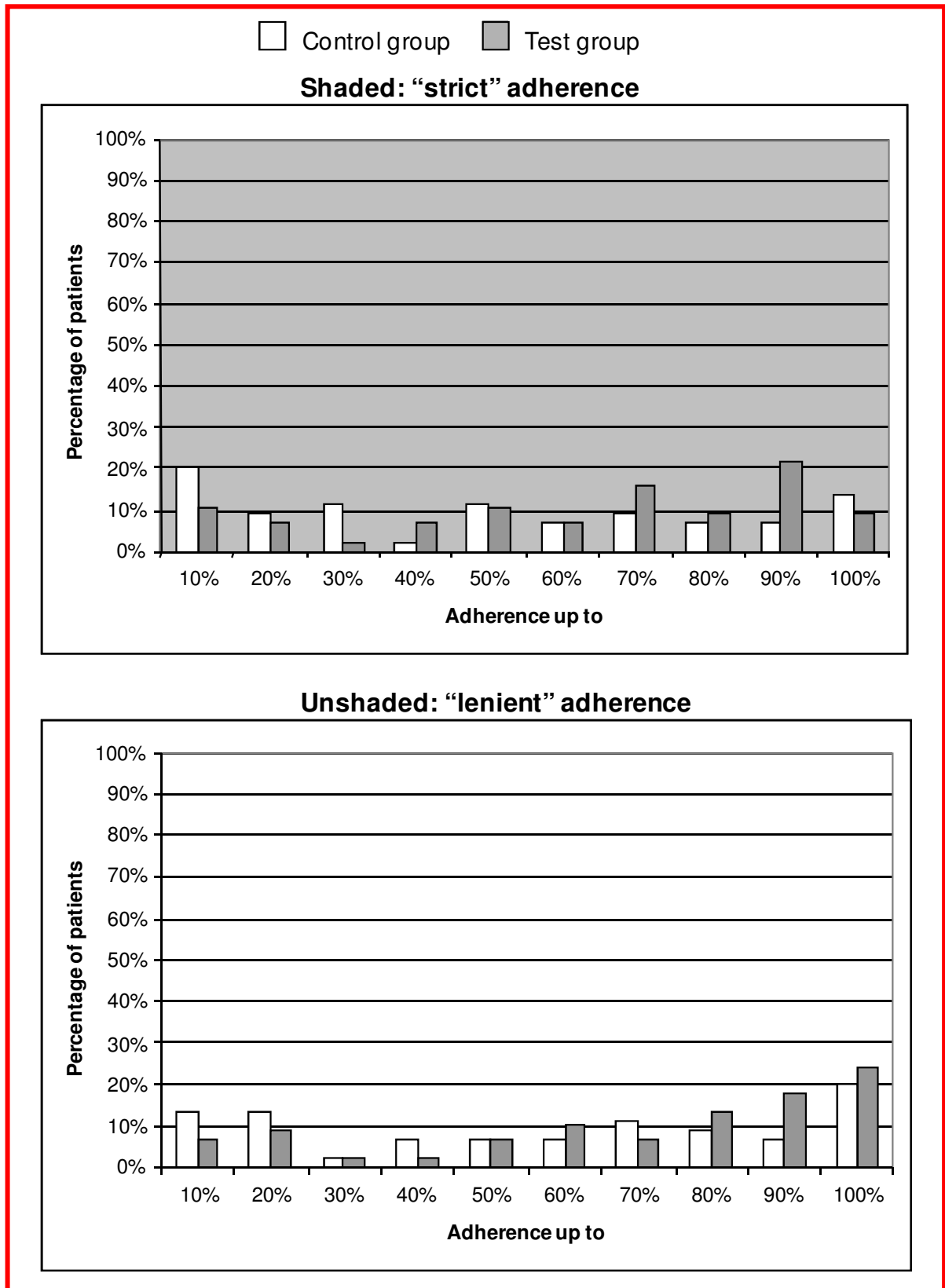


Figure 4.4e: Adherence overview: Phase 4 (from Feedback II to just before Feedback III)

4.3.3 Mean and median adherence (e-MuM)

Overall, the data reports generated by the e-MuM system indicated that on average 33% of doses were removed from the container within an hour before or after the prescribed time (“strict” definition), and 41% were removed on the correct day (“lenient” definition). The individual percentages were widely scattered, with large standard deviations of 26% and 28% respectively (see Table 4.4 below). Individually-recorded adherence for the different patients ranged from 0% to 100%.

Table 4.4: Comparison of percentage adherence according to e-MuM data: Test group vs. Control group

Study phase*	Test group		Control group		P**
	N	Median (%) <i>Mean ± SD</i>	N	Median (%) <i>Mean ± SD</i>	
Phase 1 (strict)	70	20.8 <i>27.8±24.6</i>	58	17.4 <i>27.7±27.3</i>	0.979 <i>0.982</i>
Phase 1 (lenient)	70	35.1 <i>38.9±28.5</i>	58	27.2 <i>36.5±29.2</i>	0.601 <i>0.651</i>
Phase 2 (strict)	68	22.5 <i>31.0±29.0</i>	51	17.9 <i>28.2±28.7</i>	0.647 <i>0.592</i>
Phase 2 (lenient)	68	31.7 <i>41.1±32.9</i>	51	26.8 <i>34.9±31.1</i>	0.472 <i>0.299</i>
Phase 3 (strict)	58	43.8 <i>41.8±34.5</i>	46	18.8 <i>32.9±31.9</i>	0.264 <i>0.180</i>
Phase 3 (lenient)	58	58.0 <i>48.6±35.9</i>	46	35.7 <i>40.4±33.2</i>	0.325 <i>0.237</i>
Phase 4 (strict)	45	64.3 <i>57.5±30.2</i>	43	44.6 <i>45.4±33.6</i>	0.095 <i>0.079</i>
Phase 4 (lenient)	45	75.0 <i>65.6±30.3</i>	43	55.4 <i>53.8±33.5</i>	0.118 <i>0.085</i>
Full Period (strict)	57	35.4 <i>36.1±23.7</i>	50	20.8 <i>29.8±27.4</i>	0.143 <i>0.201</i>
Full Period (lenient)	57	45.6 <i>45.5±26.1</i>	50	26.0 <i>36.6±29.4</i>	0.087 <i>0.100</i>

**“Strict”: doses taken within an hour of the prescribed time (shaded)

“Lenient”: doses taken on correct day (unshaded)

Phase 1: After issuing the e-MuM unit until issuing the reminder unit

Phase 2: After issuing the reminder unit (test group only) until before Feedback I

Phase 3: After Feedback I until Feedback II (Feedback was given to test group only)

Phase 4: After Feedback II, until Feedback III (Feedback given to both groups at Feedback III)

** Wilcoxon two-sample test for medians, independent t-test for means

Adherence percentages as calculated by the e-MuM software at each study phase were compared between the test group and the control group. Where the calculated results were 0% due to missing data for the calculation for both strict and lenient adherence, patients were excluded for that particular phase. The comparisons are shown in Table 4.5 and Figure 4.5 below. The differences between adherence levels in the two groups shown

in Table 4.4 approached statistical significance over time, with the test group having higher average rates of adherence as judged by recorded events, although they did not reach the significance level of $p < 0.05$.

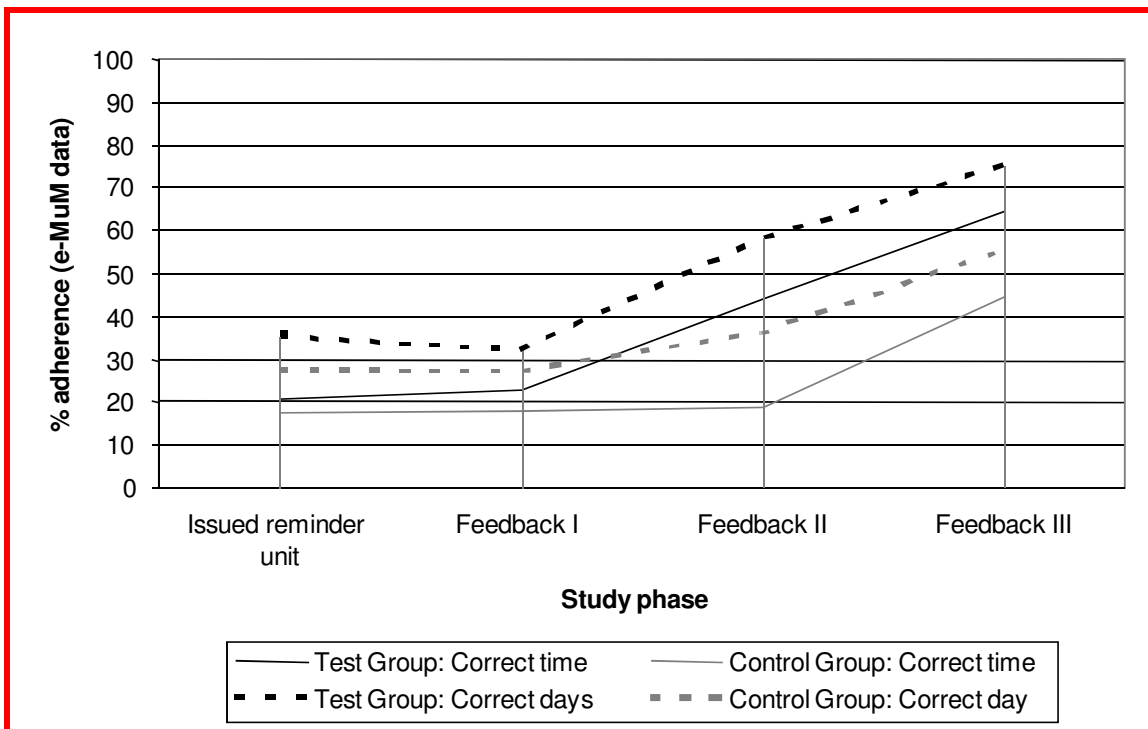


Figure 4.5: Median adherence levels: Overview

From Figure 4.5 above, the following key points can be observed:

- Test group: An increase in strict adherence levels from 27.8% in Phase 1 to 57.5% in Phase 4 was observed. For the full period, the mean strict adherence level was 36.1%. Adherence based on the lenient measure increased from 38.9% in Phase 1 to 65.6% in Phase 4 with a mean lenient adherence of 45.5% for the full period.
- Control group: The adherence based on the strict measure increased from 27.7% in Phase 1 to 45.4% in Phase 4 with the mean strict adherence for the full period at 29.8%. The mean lenient adherence measure increased from 36.5% in Phase 1 to 53.8% in Phase 4. For the full period the mean lenient adherence was 36.6%.
- For the control group, the increase in adherence from Phase 3 to 4 of 12.5% (strict) and 13.4% (lenient) was unexpected and the question was raised that the control patients might have received counselling. No confirmation of this fact could be obtained from the data collectors or doctors.

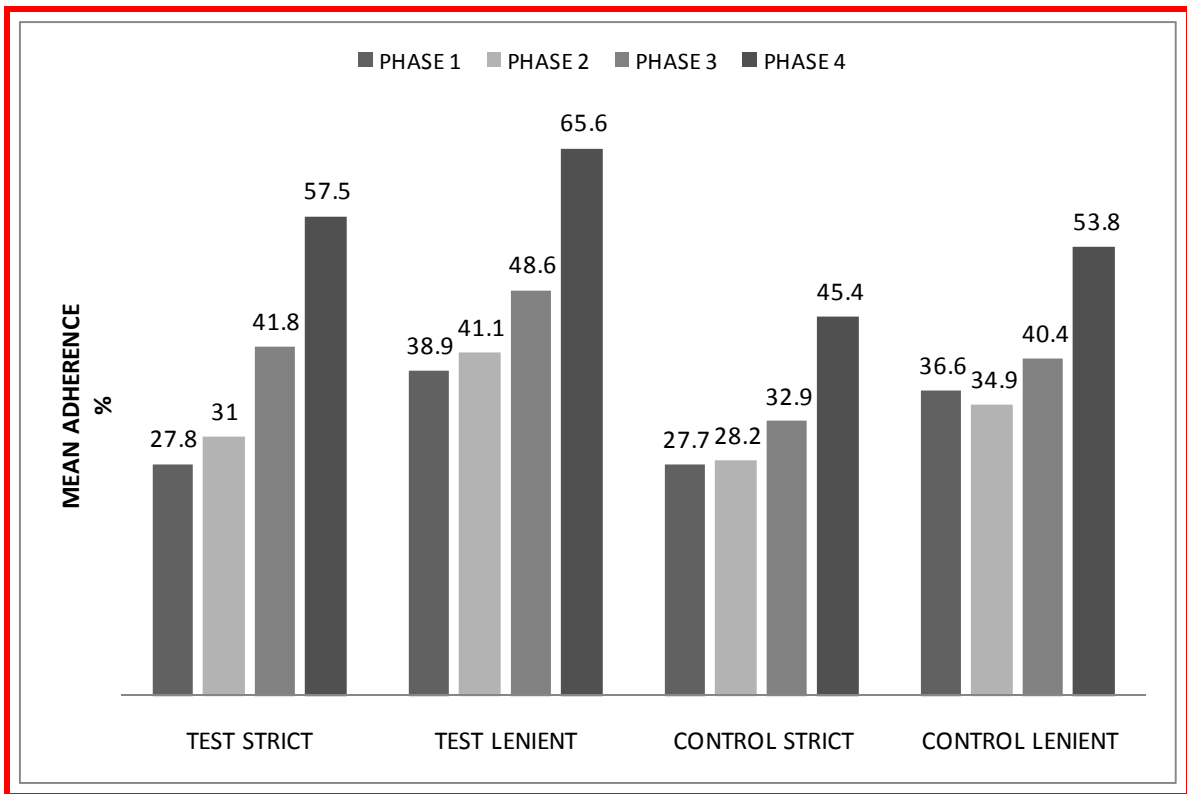


Figure 4.6: Comparison of mean adherence according to e-MuM data: Test group vs. Control group

4.3.4 Comparison of adherence changes (eMuM) between study phases

The changes in adherence between consecutive study phases are given in Table 4.5 below for the test group and Table 4.6 for the control group. The terms “Start” and “End” used in Tables 4.5 and 4.6 refer to the start of the period being compared, e.g. in Table 4.5 Phase 1 to 2 would be measured from the start of Phase 1 to the end of Phase 2.

Small changes occurred between the different phases for both the test and the control groups. The percentage increase in mean strict adherence of the test group at the end of Phase 2 (used reminder unit) was 3.8% (SD=25.3) and the control group without intervention, exhibited a decline in adherence of -1.4% (SD=22.4). The mean strict adherence increased after Phase 3 (received Feedback 1) for the test group with 9.5% (SD=29.1) and the control group (no intervention) 6.4% (SD=22.7). The percentage increase in the final phase for the test group strict adherence was 6.6% (SD=30.6) while the 11.4% (SD=18.0) increase for the control group was unexpectedly high (see Section 4.3.5).

Table 4.5: Changes of adherence (e-MuM data) over time: Test group

Test group		Start		End		Change		P**
Study phase*		N	Median (Mean \pm SD)	N	Median (Mean \pm SD)	N	Median Mean \pm SD	
Phase 1 to Phase 2 (received reminder unit)	Strict	70	20.8 27.8 \pm 24.6	68	22.5 31.0 \pm 29.0	65	0.4 3.8 \pm 25.3	0.615 0.224
	Lenient	70	35.1 38.9 \pm 28.5	68	31.7 41.1 \pm 32.9	65	1.5 2.4 \pm 30.4	0.901 0.520
Phase 2 to Phase 3 (received one feedback)	Strict	68	22.5 31.0 \pm 29.0	58	43.8 41.8 \pm 34.5	57	8.6 9.5 \pm 29.1	0.002 0.017
	Lenient	68	31.7 41.1 \pm 32.9	58	58.0 48.6 \pm 35.9	57	3.0 5.7 \pm 32.9	0.105 0.017
Phase 2 to Phase 4 (received two feedbacks)	Strict	68	22.5 31.0 \pm 29.0	45	64.3 57.5 \pm 30.2	45	22.6 18.8 \pm 33.2	<0.001 <0.001
	Lenient	68	31.7 41.1 \pm 32.9	45	75.0 65.6 \pm 30.3	45	10.7 15.0 \pm 35.4	<0.001 <0.001
Phase 3 to Phase 4 (received second feedback)	Strict	58	43.8 41.8 \pm 34.5	45	64.3 57.5 \pm 30.2	43	3.5 6.6 \pm 30.6	0.280 0.161
	Lenient	58	58.0 48.6 \pm 35.9	45	75.0 65.6 \pm 30.3	43	5.4 6.6 \pm 32.7	0.164 0.195

*"Strict": doses taken within an hour of the prescribed time (shaded)

"Lenient": doses taken on correct day (unshaded)

Phase 1: After issuing the e-MuM unit until issuing the reminder unit

Phase 2: After issuing the reminder unit (test group only) until before Feedback I

Phase 3: After Feedback I until Feedback II (Feedback was given to test group only)

Phase 4: After Feedback II, until Feedback III (Feedback given to both groups at Feedback III)

** Sign test for medians; paired t-test for means

Table 4.6: Changes of adherence (e-MuM data) over time: Control group

Control group		Start		End		Change		P**
Phases*		N	Median (Mean \pm SD)	N	Median (Mean \pm SD)	N	Median Mean \pm SD	
Phase 1 to Phase 2 (no intervention)	Strict	58	17.4 27.7 \pm 27.3	51	17.9 28.2 \pm 28.7	47	-4.1 -1.4 \pm 22.4	0.054 0.670
	Lenient	58	27.2 36.5 \pm 29.2	51	26.8 34.9 \pm 31.1	47	-6.4 -3.7 \pm 25.8	0.019 0.336
Phase 2 to Phase 3 (no intervention)	Strict	51	17.9 28.2 \pm 28.7	46	18.8 32.9 \pm 31.9	43	2.9 6.4 \pm 22.7	0.117 0.073
	Lenient	51	26.8 34.9 \pm 31.1	46	35.7 40.4 \pm 33.2	43	3.8 7.5 \pm 22.8	0.088 0.037
Phase 2 to Phase 4 (no intervention)	Strict	51	17.9 28.2 \pm 28.7	43	44.6 45.4 \pm 33.6	40	9.8 14.3 \pm 23.3	0.010 <0.001
	Lenient	51	26.8 34.9 \pm 31.1	43	55.4 53.8 \pm 33.5	40	12.5 16.0 \pm 24.5	0.014 <0.001
Phase 3 to Phase 4 (no intervention)	Strict	46	18.8 32.9 \pm 31.9	43	44.6 45.4 \pm 33.6	38	7.1 11.4 \pm 18.0	0.020 <0.001
	Lenient	46	35.7 40.4 \pm 33.2	43	55.4 53.8 \pm 33.5	38	5.4 12.3 \pm 19.4	0.011 <0.001

* "Strict": doses taken within an hour of the prescribed time (shaded)

"Lenient": doses taken on correct day (unshaded)

Phase 1: After issuing the e-MuM unit until issuing the reminder unit

Phase 2: After issuing the reminder unit (test group only) until before Feedback I

Phase 3: After Feedback I until Feedback II (Feedback was given to test group only)

Phase 4: After Feedback II, until Feedback III (Feedback given to both groups at Feedback III)

** Sign test for medians; paired t-test for means

The changes reflected in the last columns of Tables 4.5 and 4.6 are combined in Table 4.7. The results in Table 4.7 show that adherence levels, as measured by the e-MuM system, increased over time in both groups, but the increase in adherence was not statistically significantly different *between* the groups.

Table 4.7: Comparison of changes in percentage adherence (e-MuM data) over time: Test group vs. Control group

Study phase*		Changes: Test group (TG)		Changes: Control group (CG)		P**
		N	Median Mean ± SD	N	Median Mean ± SD	
Phase 1 to Phase 2 (TG received reminder unit)	Strict	65	0.4 3.8% ± 25.3	47	-4.1 -1.4% ± 22.4	0.069 0.258
	lenient	65	1.5 2.4% ± 30.4	47	-6.4 -3.7% ± 25.8	0.091 0.268
Phase 2 to Phase 3 (TG received one Feedback)	Strict	57	8.6 9.5% ± 29.1	43	2.9 6.4% ± 22.7	0.288 0.565
	lenient	57	3.0 5.7% ± 32.9	43	3.8 7.5% ± 22.8	0.890 0.747
Phase 2 to Phase 4 (TG received two feedbacks)	Strict	45	22.6 18.8% ± 33.2	40	9.8 14.3% ± 23.3	0.211 0.475
	lenient	45	10.7 15.0% ± 35.4	40	12.5 16.0% ± 24.5	0.722 0.873
Phase 3 to Phase 4 (TG received second feedback)	Strict	43	3.5 6.6% ± 30.6	38	7.1 11.4% ± 18.0	0.328 0.387
	lenient	43	5.4 6.6% ± 32.7	38	5.4 12.3% ± 19.4	0.349 0.339

* "Strict": doses taken within an hour of the prescribed time (shaded)

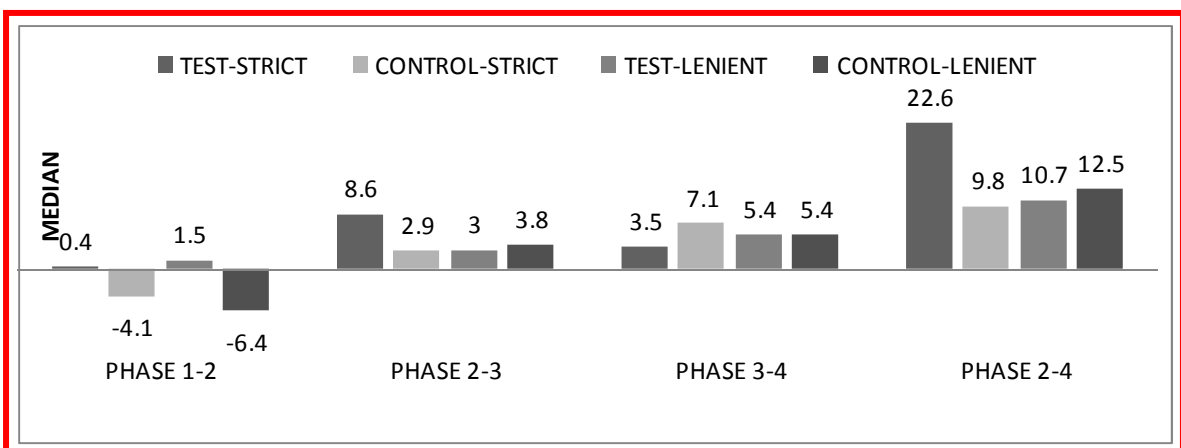
"Lenient": doses taken on correct day (unshaded)

Phase 1: After issuing the e-MuM unit until issuing the reminder unit

Phase 2: After issuing the reminder unit (test group only) until before Feedback I

Phase 3: After Feedback I until Feedback II (Feedback was given to test group only)

Phase 4: After Feedback II, until Feedback III (Feedback given to both groups at Feedback III)



** Sign test for medians; paired t-test for means

Figure 4.7: Comparison of changes (Median) of adherence (e-MuM data) over time: Test group vs Control group

Changes in mean adherence (strict) across the different study phases for the test group and the control group are summarised below:

Test group (strict) mean adherence:

- From Phase 1 to 2 (with reminder unit) increased by 3.8%
- From Phase 2 to 3 (after first feedback) increased by 9.5%
- From Phase 3 to 4 (after second feedback) increased by 6.6%
- The most significant increase occurred between Phases 2 and 4 (after both feedbacks) by **18.8%**

Control group (strict) mean adherence (no interventions):

- From Phase 1 to 2 decreased by -1.4%
- From Phase 2 to 3 increased by 6.4%
- From Phase 3 to 4 increased by **11.4%**
- The most significant increase occurred between Phases 2 and 4 by **14.4%**

4.3.5 Comparison of test and control groups

According to the e-MuM data the test group had 43 cases and the control group 41 cases of 0% adherence for Phases 3 and 4. These cases of 0% adherence were excluded from the analysis. This did not constitute any difference in analysing adherence results from control and test groups and was of similar magnitude.

The most significant difference in adherence data collected was mainly due to the increase in adherence of 13 control group patients whose data are shown in Table 4.8 below.

Table 4.8: Control group patents with most improved adherence during Phases 3 and 4

N	Patient registration number	Phase 3 strict	Phase 4 strict	Difference	Phase 3 lenient	Phase 4 lenient	Difference
1	26	7.14	28.57	31.43	12.50	42.86	30.36
2	33	10.34	41.84	31.50	15.52	51.02	35.5
3	68	67.86	94.29	26.43	75.0	94.29	19.29
4	58	0	96.43	96.43	0	100	100
5	73	46.43	71.43	25.00	50.0	76.79	26.79
6	76	46.55	66.67	20.12	63.79	79.63	15.84
7	98	63.39	87.04	23.65	68.75	90.74	21.99
8	107	42.59	68.97	26.38	51.85	72.41	20.56
9	108	8.04	44.64	36.6	14.29	55.36	41.07
10	128	55.36	88.69	33.33	69.64	93.45	23.81
11	156	0	82.14	82.14	3.57	85.71	82.14
12	163	19.64	44.64	25.00	39.29	69.64	30.35
13	179	17.86	50.00	32.14	37.50	82.14	44.64

The reason for the unexpectedly large increase in control group mean adherence (11.4%) from Phase 3 to 4 could not be determined with certainty but a telephonic interview with a doctor from Tshepang clinic shed some light on this phenomenon. According to her, clinic staff routinely counsel all patients and focus in particular on those showing reduced levels of adherence (missing visits, decrease in CD4 count).

A second possible explanation for this increase might be that due to same day visits, overcrowding and long waiting periods for data collectors to be available. It is possible that some control group patients observed the blue sheets containing feedback graphs in test group patients' files, as test group patients were looking at the sheets while waiting in the queue to see the doctor. It might be possible that control group patients increased e-MuM use (adherence) to avoid any e-MuM download reflecting a non-adherent pattern. They were unaware that they would not have feedback. A small number of these patients might have erroneously been given feedback by the data collectors.

The print-out graphs presented concrete evidence to the test group patients of their lamivudine taking routine. This meant that patients were not only asked to apply self-assessment methods, but were presented with pre-recorded adherence evidence during Phase 4 and then asked to explain non-adherent periods.

4.3.6 Decanting habits

On the questionnaires, patients were asked to state whether, and if so how often, they transferred any of their medication from the original container into any other containers or places at any time, to facilitate easier access to their tablets. This behaviour, called

“decanting”, may be used for the sake of convenience or to avoid being seen with a container of tablets labelled as ARVs. Patients answered positively to this question at anything between one to nine visits (see Table 4.9).

Table 4.9: Number of visits at which patients reported decanting tablets in the preceding month

Number of visits when decanting habits were stated	Number of test group patients	Number of control group patients	Total patients	Total visits
1 visit	14	16	30	30
2 visits	4	3	7	14
3 visits	7	7	14	42
4 visits	6	9	15	60
5 visits	7	9	16	80
6 visits	17	13	30	180
7 visits	23	17	40	280
8 visits	17	20	37	296
9 visits	10	10	20	180
Total	105	104	*209	1162

* No decanting data were available for one of the control group patients

Decanting behaviours changed over time for most of the patients. From a total of 209 patients with decanting information, 145 reported at least two different types of decanting habits over the study period; five patients reported all four of the behaviours shown in Table 4.9 and Figure 4.7. Decanting directly affected the results recorded by the e-MuM system. It also greatly complicated data interpretation.

Table 4.10: Self-stated medicine decanting habits: Control group vs. Test group

Self-stated decanting behaviour	Times stated (Test group)		Times stated (Control group)		Total
No decanting	370	63%	352	62%	722
Once daily	162	27%	180	32%	342
Weekly	16	3%	13	2%	29
Unspecified frequency	43	7%	26	5%	70
Total	591	100%	571	100%	1162

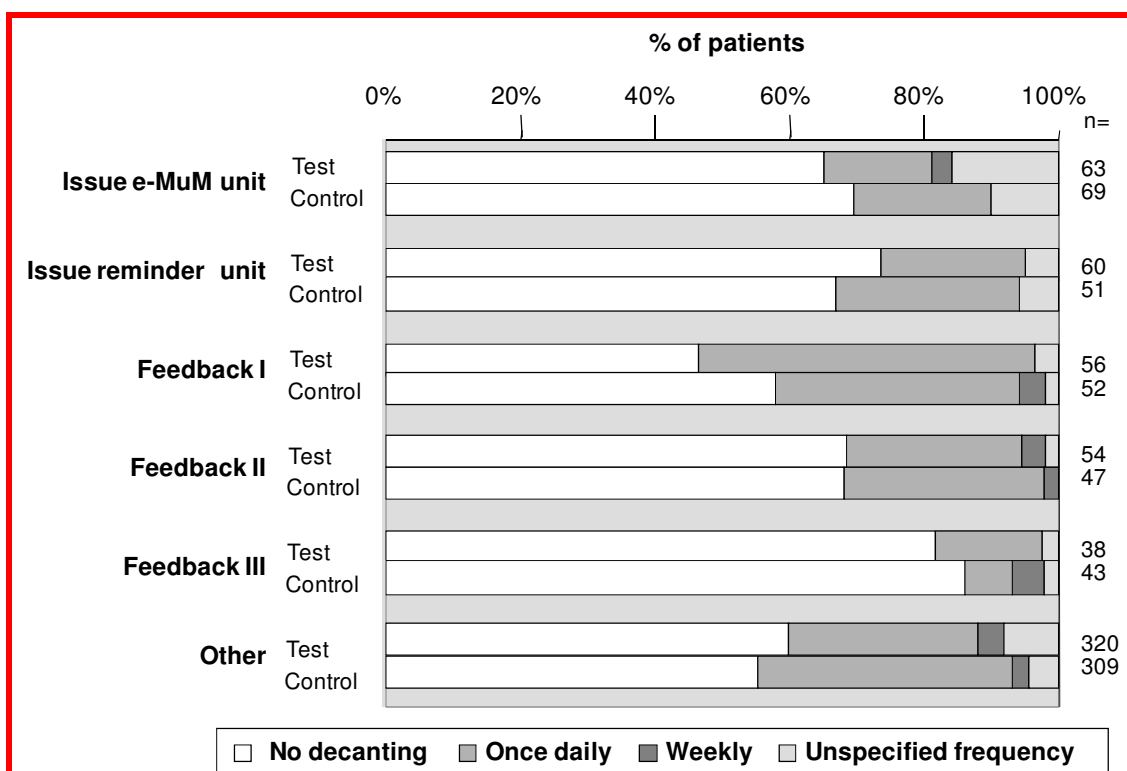


Figure 4.8: Self-stated medicine decanting habits: Control group vs. Test group according to study phases

Patients' statements on their decanting habits were compared with the data recorded by the e-MuM system, to see whether it was possible to adjust calculated adherence levels accordingly. It was found that the two sets of data did not always correlate at the individual level, and that adjustments would require making assumptions for each individual patient. Some case studies and data from focus group discussions are presented in Chapter 5.

A collective adjustment can be made in each of the groups based on e-MuM data and patients' statements about decanting (see Table 4.10). The calculation is based on the assumption that the decanting practices shown in Figure 4.8 were applied consistently by the respective proportions of patients. Average adherence levels recorded by the e-MuM software are adjusted proportionately within each group, i.e. doubled for the proportion decanting daily, multiplied by 14 for the proportion decanting weekly, and multiplied by six (assuming that three days' supply were removed from the containers) for the proportion who did not specify a frequency.

The calculated adjusted adherence levels shown in Table 4.11 suggest two points: Firstly, patient-reported decanting practices do not appear to explain the low adherence levels calculated by the e-MuM system. Other factors must have played a role, since most adjusted averages are well below adherence levels as reported in some other studies. Studies done in African and American settings have however also reported lower than

expected adherence amongst low-income HIV patients. In a systematic review of 116 potentially relevant literature studies and 17 original studies, a positive trend among components of socio-economic status and adherence to ARV medication was found. This trend was only statistically significant in less than half the studies for income and less than a third for education (Falagas *et al.*, 2008).

Table 4.11: Adjusted estimates of percentage adherence based on patient-reported decanting habits

Patient-reported decanting frequency	Doses de-canted ('factor')	Calculation	Phase 1	Phase 2	Phase 3	Phase 4	Full period
Study Group		x: Average % of doses removed from container on correct day (e-MuM data)	39%	41%	49%	66%	46%
a) None	1	a1) Proportion of patients	65%	73%	46%	69%	82%
		a2) % Doses taken (x * a1 * factor)	25%	30%	23%	45%	37%
b) Once daily	2	b1) Proportion of patients	16%	22%	50%	26%	16%
		b2) % Doses taken (x * b1 * factor)	12%	18%	49%	34%	14%
c) Weekly	14	c1) Proportion of patients	3%	0%	0%	4%	0%
		c2) % Doses taken (x * c1 * factor)	17%	0%	0%	34%	0%
d) Unspecified	6	d1) Proportion of patients	16%	5%	4%	2%	3%
		d2) % Doses taken (x * d1 * factor)	37%	12%	10%	7%	7%
		Adjusted average % of doses taken on correct day (a2 + b2 + c2 + d2)	92%	60%	82%	120%	59%
Control Group		x: Average % of doses removed from container on correct day (e-MuM data)	37%	35%	40%	54%	37%
a) None	1	a1) Proportion of patients	70%	67%	58%	68%	86%
		a2) % Doses taken (x * a1 * factor)	25%	23%	23%	37%	32%
b) Once daily	2	b1) Proportion of patients	20%	27%	37%	30%	7%
		b2) % Doses taken (x * b1 * factor)	15%	19%	30%	32%	5%
c) Weekly	14	c1) Proportion of patients	0%	0%	4%	2%	5%
		c2) % Doses taken (x * c1 * factor)	0%	0%	22%	16%	24%
d) Unspecified	6	d1) Proportion of patients	10%	6%	2%	0%	2%
		d2) % Doses taken (x * d1 * factor)	22%	12%	5%	0%	5%
		Adjusted average % of doses taken on correct day (a2 + b2 + c2 + d2)	63%	55%	79%	85%	66%

Patients' statements about decanting were not always accurate, as shown in the wide variations between calculated adherence rates. If the patients had decanted and taken their doses as stated, the percentage of prescribed doses taken on the correct day would have ranged between 55% in Phase 2 by control group patients and 120% in Phase 4 by test group patients, which is quite unlikely. In this study, the records on decanting behaviour were not reliable enough to allow adjusting adherence levels calculated by the e-MuM system.

In an interview with the data collectors a vague and non-specific answer was identified as follows: Some patients might have indicated that they took medication from the bulk container, and meant exactly that. Other patients answered the question as follows:” I take my medicine from the bulks”. This answer is non-specific about the number of times they opened the container daily. In addition, the words could also be interpreted to mean that “I take (i.e. decant) my medicine from the bulk”. There is also some potential confusion in the word “take” – in South African English, patients often refer to “drinking” tablets, whereas the word “take” denotes taking something away. These question interpretation differences may account for the lack of correlation with downloaded e-MuM openings.

4.3.7 Adherence: Visual analogue scale (VAS)

Patients rated their self-perceived adherence on a 10 cm Visual Analogue Scale (VAS) a total of 885 times during the study. Despite repeated explanations by data collectors, 100 (11%) of the patients’ marks were made out of the scale bounds. The results of the remaining 785 marks are summarised in Table 4.11 below.

Table 4.12: Patient-reported adherence (VAS)

Purpose of visit	Test group (TG)			Control group (CG)		
	N	Median Mean	±SD	N	Median Mean	±SD
Issue e-MuM unit	46	9.0 9.01	±0.57	42	9.1 9.18	±0.55
Issue reminder unit (TG only)	47	9.0 8.94	±0.67	8	8.8 8.66	±0.57
Feedback I (TG only)	56	8.8 8.61	±0.56	51	9.0 8.81	±0.54
Feedback II (TG only)	53	8.8 8.74	±0.54	48	9.0 8.93	±0.70
Feedback III (TG only)	48	8.6 8.65	±0.47	46	8.9 8.77	±0.50
Unspecified visits (other)	167	8.8 8.76	±0.86	173	9.0 8.77	±1.04
Total	417	9.0 8.77	±0.71	368	9.0 8.84	±0.84

Data collectors stated that they observed a lack of understanding of the VAS from certain patients. These patients had difficulty interpreting the abstract nature of the VAS scale. The education level of 82% of patients enrolled in the study was an incomplete secondary level education or lower. The data collectors confirmed that some patients needed an explanation every time.

A second explanation is that patients did not want to admit to less than perfect (expected) adherence levels. Support can be found in comments by the head clinician (herself an ethnic African) at Tshepang during the focus group discussion that “...black people will tell you what you want to hear...to please you...” (see Chapter 5, Section 5.4.7) as well as from the 7-day recall results.

Because there was a large proportion of visits which did not fall on one of the events which delimited the study phases, the results for the test and control groups are shown in Figure 4.9 by date sequence as weekly average scores. Both Table 4.11 and Figure 4.9 indicate that there was little difference between the groups, and that perceived adherence did not change greatly over time. Average and median values at each phase, and changes between phases, were compared statistically and no significant differences were found.

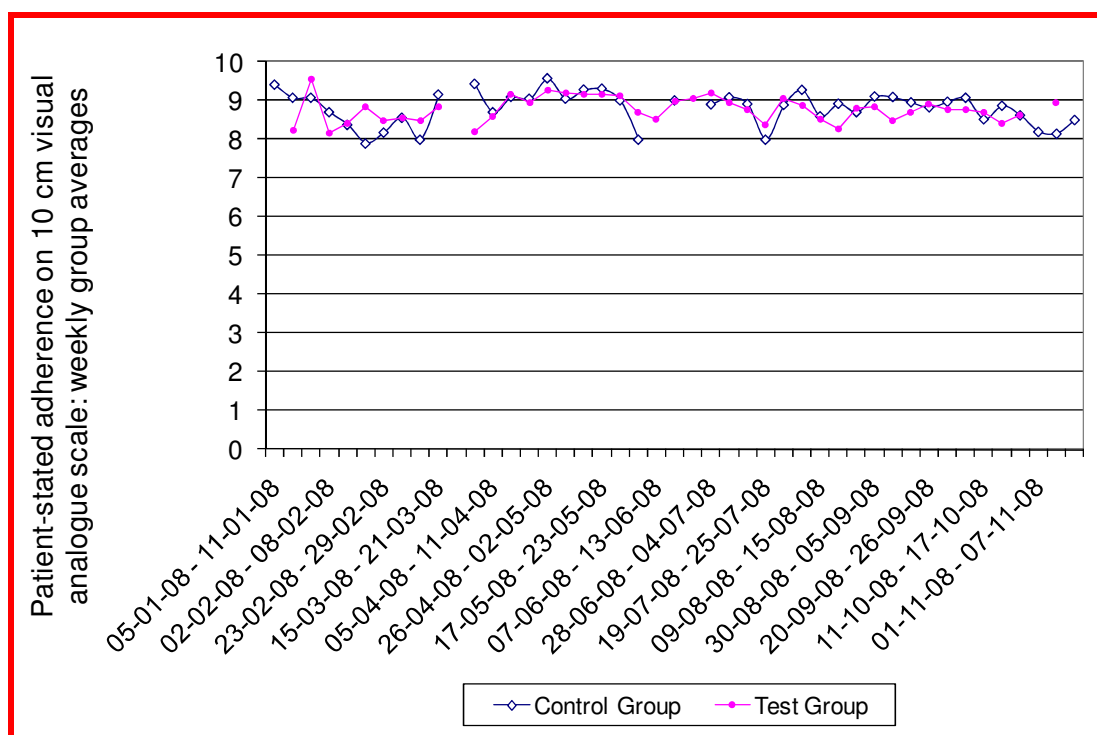


Figure 4.9: Patient-reported adherence (VAS) over time

4.3.8 7-day recall of doses missed

A total of 1243 visits were registered on the software programme for all patients enrolled in the study over the study period of eight months. The 7-day recall was one of the adherence measures in which the patients rated themselves as being adherent (taking all their medication doses) for the week leading up to the visits to the clinic in 93.6% of the test group and 92.8% of the control group visits. This data are in stark contrast with the data obtained by the e-MuM, but correspond with the other self-assessment tool (VAS).

According to the literature, patients are known to overestimate their adherence when using self assessment methods (Berg & Arnsten, 2006; Gill *et al.*, 2005; Liu *et al.*, 2006 b).

None of the proportions shown in Table 4.13 differed significantly between the groups.

Table 4.13: Recall of doses missed in the seven days preceding each visit

	Visits at which no missed doses were reported		Visits at which one or more missed doses were reported		Total
	No of visits	%	No of visits	%	
Control group	569	93.6%	39	6.4%	608
Test group	589	92.8%	46	7.2%	635
Total	1158	93.2%	85	6.8%	1243

4.3.9 Tablet counts

Tablet counts were planned for all patients, but many patients did not bring their medication to the clinic, although they had been requested to do so repeatedly. Reasons varied from the patient not wanting the people at work to see them having medication in their bags, to the bulkiness of the container making carrying it around difficult.

Tablets were only brought back on 60% of visits by test group patients and 64% of control group patients. Reasons for this phenomenon are discussed in Chapter 6 under Limitations of the study (see Section 6.3).

Counting tablets would not confirm if the patient had indeed taken the medication, only that the medication had been removed from the container.

Observation and discussions with patients and clinic staff at Tshepang and Rustenburg Wellness Clinics before the study commenced, revealed that some patients carry all their different medication together in one container. This is done, due to practical considerations and for convenience sake.

As previously stated (see Chapter 2, Section 2.12.3.7), one of the disadvantages of the e-MuM is the inability to monitor more than one drug per container. As explained previously (see Chapter 3, Section 3.3.3.1), lamivudine was the single drug chosen to be monitored in this study. The number of lamivudine tablets brought back at different visits could not be converted into adherence rates, because the visits were unevenly spaced, and it could not be confirmed whether patients received the same number of tablets at every visit. Sometimes the pharmacy only supplied enough medication to bridge periods until they knew enough stock would arrive. The result of this conservation measure was that some

patients received less than a 30 day supply, e.g. if they brought back 10 tablets, they would only be supplied with 50 lamivudine tablets, so that they have enough tablets for the following month. Stock shortages occurred during the study period, as a result of Government budget constraints (see Chapter 2, Section 2.3.1.3).

Table 4.14: Percentage of visits at which tablet counts were performed

	Visits at which tablet counts were performed		Total
	Count	Percentage	
Control group	392	64%	608
Test group	385	60%	638
Total	777	62%	1246

4.4 CLINICAL DATA

As shown in Table 4.3 (see Section 4.2.1), the test group and the control group were composed similarly in terms of patients' duration on treatment at each of the study phases. The CD4 counts and viral loads were recorded at the beginning and at the end of the study (see Tables 4.15 and 4.16).

Table 4.15: Average and median CD4 counts at the beginning and at the end of the study: Test group vs. Control group

Result	Study group			Control group			P*, Test group vs. control group
	N	CD4 (cells/mm ³)		n	CD4 (cells/mm ³)		
		Mean ± SD Median	Range		Mean ± SD Median	Range	
Beginning of study	58	219.6±121.7 213	10-533	48	213.0±149.0 193	4-640	0.802 0.497
End of study	55	291.6±129.8 290	57-641	38	284.9±169.8 277	2-803	0.831 0.667
Change	50	76.2±106.9 54.5	-94-481	33	72.2±91.2 69	-121-287	0.861 0.775
P **, change		<0.001 <0.001			<0.001 0.014		

* Independent t-test (parametric), Wilcoxon two-sample test (non-parametric)

** Paired t-test (parametric), Sign test (non-parametric)

Table 4.15 shows that the CD4 counts increased significantly in both groups during the study period, but there was no significant difference between the groups at the beginning, at the end or in terms of increase.

Table 4.16: Average and median log viral loads at the beginning and at the end of the study period: Test group vs. Control group

Result	Test group			Control group			<i>P</i> [*] , Test group vs. control group
	N	Log viral load (copies/ml)		n	Log viral load (copies/ml)		
		Mean ± SD Median	Range		Mean ± SD Median	Range	
Beginning of study	57	1.19±1.97 0	0-5.89	49	1.76±2.21 0	0-5.70	0.166 0.128
End of study	55	0.48±1.23 0	0-4.52	37	1.05±1.71 0	0-4.97	0.085 0.079
Change	49	-0.81±1.99 0	-5.89-3.11	33	-0.56±2.20 -0.56	-5.58-3.15	0.598 0.973
<i>P</i> ^{**} , change		0.006 0.021			0.153 0.332		

* Independent t-test (parametric), Wilcoxon two-sample test (non-parametric)

** Paired t-test (parametric), Sign test (non-parametric)

Table 4.16 shows that the viral load (VL) counts decreased in both groups during the study period, but there was no significant difference between the groups at the beginning, at the end or in terms of decrease.

Table 4.17: Number of patients who achieved VL suppression during the study

Patients with viral load suppression (<400 copies/ml)	Test group n=105	Control group n=105	<i>P</i> (Chi square test)
Beginning of study	41/57*	32/49*	0.463
End of study	49/55*	28/37*	0.088
Achieved during study period	11/49*	6/33*	0.986

* Laboratory results were not available for all patients in either patient files or on the computer system at Tshepang clinic, therefore only patients with available data were included in the calculation

Eleven patients from the test group achieved VL suppression during the study and six control group patients (see Table 4.17 and Figure 4.10). However, there was no significant difference between the two groups in terms of mean viral loads at the beginning or at the end of the study, or the decrease during the study period. However, the proportion of patients who achieved viral load suppression during the study period was higher for the test group. The test group patients with VL suppression increased from 72% to 89% (17%) and the control group patients increased from 65% to 75% (10%).

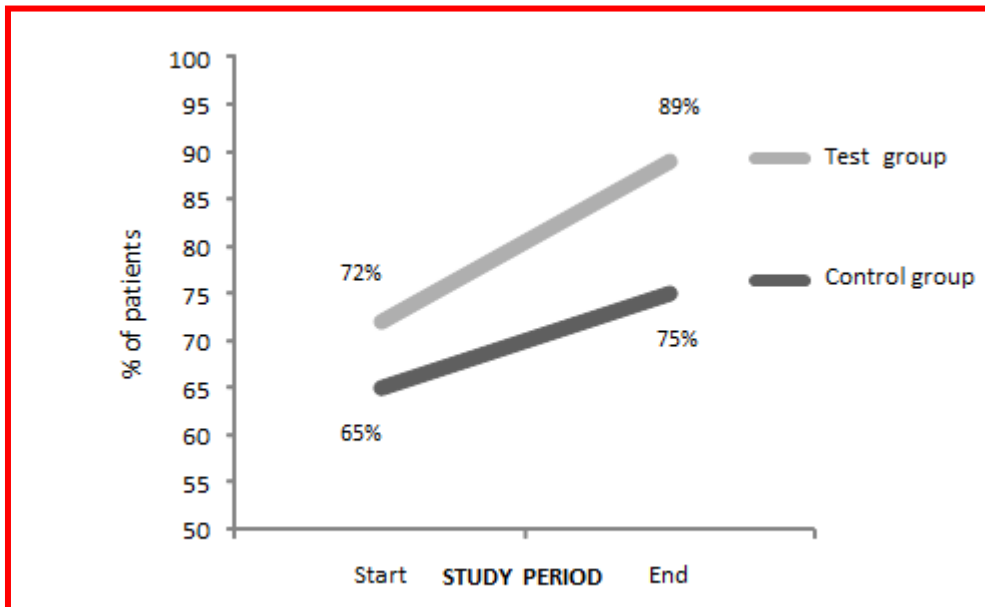


Figure 4.10: Percentage of patients with viral load <400 copies/ml

4.5 SUMMARY

In this chapter the results of the study were presented and discussed. No statistically significant difference existed between the demographic data of the test group and the control group at any point in the study.

Adherence measured with the e-MuM system was regarded as “strict” adherence for medication taken within an hour of the correct time and as “lenient” adherence for that taken at any time on the correct day. The results showed a large scattering of adherence for both groups. The most significant increase in mean strict adherence was from Phase 2 to Phase 4 (after two verbal and visual feedback sessions). Adherence increased with 18.8% for the test group and with 14.3% for the control group. The test group showed a mean strict adherence level of 36.1% for the full study period, compared to 29.8% for the control group. Mean lenient adherence for the full period was higher for both groups, namely 45.5% in the case of the test group and 36.6% for the control group. Although adherence increased over time for both groups, the difference between the groups was not statistically significant at $P < 0.05$.

Data interpretation was made difficult due to patients’ decanting habits. Decanting habits were compared with the data recorded by the e-MuM system, but did not correlate at an individual level and were found not reliable enough to allow adjusting adherence levels calculated by the e-MuM system.

Self-reported adherence was in stark contrast with the data obtained from the e-MuM system. The mean adherence according to the VAS was 87.7% and 88.4% respectively for the test group and the control group. With the 7-day recall self-reported adherence was 93.6% for the test group and 92.8% for the control group patients. The 2-day recall was omitted at the end of Phase 2.

Tablet counts were available in only 60% of visits by test group patients and 64% of control group patients and could not be used as a result. Biological markers (CD4 and VL) showed a positive tendency towards the end of the study, although differences between the test and control groups were not statistically significant.

In the next chapter, the findings of two focus group discussions and selected patient cases are presented and discussed.

CHAPTER 5

RESULTS AND DISCUSSION - QUALITATIVE DATA AND CASE STUDIES

5.1 INTRODUCTION

The first section of this chapter presents the findings of two focus group discussions (FGDs) conducted at the end of the study. The purpose of the focus groups was to shed additional light on study findings. The focus groups were not intended for in-depth analysis but merely to complement the main quantitative study. The first FGD was held for patients and the second for clinic staff.

In the second section of this chapter, selected patient cases are presented to illustrate some of the adherence issues that were uncovered with the feedback graphs that were generated as part of the e-MuM software.

5.2 FOCUS GROUP PARTICIPANTS

5.2.1 Patient group

A combination of patients with diverse adherence patterns was targeted for the patient focus group discussion. Table 5.1 shows the eight patients, who were included and attended in the focus group discussion. These patients had average e-MuM adherence levels covering the whole spectrum. Due to the anonymity of the patient discussion group, participating patients were allocated a number from 1 to 8 at the start of the session, and asked to use the allocated numbers when participating in the discussion. The numbers were used to group contributions from different participants together.

The patient group discussion was guided by pre-set questions covering all the elements of the study.

Table 5.1: Focus group participants (patients)

Patient	Overall adherence	
	Strict adherence	Lenient adherence
Patient 1	42.1%	58.1%
Patient 2	88.2%	92.3%
Patient 3	66.2%	84.7%
Patient 4	0%	0.50%
Patient 5	82.0%	91.7%
Patient 6	29.6%	49.7%
Patient 7	53.0%	57.1%
Patient 8	1.60%	3.8%

5.2.2 Clinic staff group

The following nine clinic staff members participated in the staff focus group discussion:

- Clinic manager
- Chief physician (clinical head)
- Medical officer
- Clinic sister
- ARV pharmacist
- Counsellor and data capturer
- Counsellor
- Default tracer
- Project data capturer

5.3 FINDINGS OF THE FOCUS GROUP DISCUSSIONS

Careful and systematic analysis of the focus group discussions provided valuable information that can be used for improvement of further studies. The findings of the FGDs also explain some of the problems and unexpected results from the study.

5.3.1 Recruitment for the study and informed consent

At recruitment, one of the patients was worried that her inclusion in the group rested on the desperation of her situation (low CD4 count), but this fear was dispelled by the clinic staff and she made herself available.

5.3.2 e-MuM system

5.3.2.1. Size of the container

Concerns about the size of the container were discussed with Geo- ICT Health Pty (Ltd) during the planning stage of the study, but size reduction was deemed impractical at that stage. The microprocessor available determined the size of the container to be used.

The focus group participants unanimously condemned the size of the container as too bulky and remarked that it was unsuitable for carrying medication to work on a daily basis. The size of the container, lead to patients taking out more than one tablet at a time and the majority of the patients in the focus group discussion confessed to decanting for a couple of days into small plastic containers. Most of them requested to have a smaller container in future, as a male patient who decants his tablets when attending a funeral said:

“I also second the fact if it came back it must please come with smaller container that’s portable.” (Patient)

5.3.2.2. Lid of the container

The lack of lid sturdiness was highlighted by one of the participants who explained how he tried to repair the lid after the “electronics” fell out. He was then questioned by the data collector about the 10 times he opened his container in an attempt to replace and refasten the “electronics” to the lid. Another participant also commented on the lid breaking and that he had reported this matter to the data collectors.

From the participants’ discussion, it was clear that the lid had to be replaced firmly to register an event.

Some patients commented that they placed the container in a bag and travelled in overcrowded taxis leading to additional (unwanted) events being registered by the lid due to the rigorous bumping inside the bag. Others did not replace the lid properly whilst the medication was stored on a shelf. Hence, no events were recorded, despite medication being taken.

The sister in charge commented on what she observed as lack of transparency in staff not telling patients that the container lid would monitor their medication adherence at the beginning of the project and cautioned about patients being suspicious of being spied

upon. This concern, although valid, was dealt with under ethics (see Chapter 3, Section 3.3.9). The test group patients were only informed about the monitoring function of the lid before the feedback phase and the control group after completion of the study.

5.3.2.3. Disclosure and stigma

It was clear from answers supplied by all the participants that for them, the most important aspect of treatment was to keep their status secret and only after that to improve their health, hence the size of the e-MuM container made it impractical for regular use.

One of the patients said that because of her undisclosed status to members of her sports team, she could not use the container for a month while on a sports tour. She explained as follows:

“... sometimes I go away for a month or so, I can’t take the container with because the people I work with do not know my status. So that forced me to decant into small containers that do not state the names of what’s inside. ... what could they do to accommodate us by making smaller containers, so I can take along because in sports we sometimes leave things lying around so I won’t have to worry about who sees it.” (Patient)

Some of the staff members questioned the sustainability of any such an adherence improvement instrument, because patients were being identified in church and in taxis by cell phone reminder ringtones. They commented on black people’s close proximity in everything they do and suggested a vibrating reminder.

Staff also referred to the change in patients’ behaviour when money becomes available. According to them, patients would then buy small pillboxes but not tell anybody.

5.3.2.4. Usefulness of e-MuM for regular monitoring

During the staff focus group discussion, participants did not reach consensus about the usefulness of the e-MuM for regular use in the clinic setting.

Staff members agreed that if it was economically possible, the e-MuM system should be implemented for specific individual patients, specific categories of patients and also extended to TB patients. The sister in charge suggested that the e-MuM system be used for new patients for the first six months on treatment, as she said the following:

“... I would suggest maybe we use the container for six months so that we can make sure that they did understand what we said initially...because we sometimes find that they defaulted and that they had information.” (Sister)

This type of monitoring would verify that patients know how to use their medication and that they are adherent. It is well documented that the first six months on ART are critical (Brinkhof *et al.*, 2008). During this period, clinical and immunological improvement should manifest but are not always apparent and drug toxicities may emerge.

5.3.3 Reminder unit

All the patients in the focus group discussion found the reminder watch very helpful, as one of them explained:

“... it helped a lot because even in the morning and evening and when I was supposed to come for visits.” (Patient)

They also seemed to prefer the reminder watch to cell phones. The following reasons were provided:

- Watches needed no resetting.
- Watches were not affected by load shedding.
- No electricity was needed.
- No expensive radio or cell phone batteries were required.

5.3.4 Feedback to patients on adherence

According to the focus group participants, most of the patients were very positive about the visual effect of the feedback and the fact that clinic staff (data collectors) would notice if they defaulted. Patients had the following views:

“I would say it has made a positive impact in such a way that my CD4 count was fluctuating (maybe I was not taking my medication well, actually I was not taking it well). After getting the feedback I changed because I realise that they were helping me.” (Patient)

“The feedback shows clearly how well you progress because before I used to default and no one would notice.” (Patient)

Patients attributed improvement in their health to them taking their ARVs regularly, when they saw the feedback graphs:

“I would say yes because every time I went to see the doctor there would be a problem that my Viral Load was decreasing slowly but since on the programme it improved.” (Patient)

Staff members were divided about the usefulness of the feedback graphs from the e-MuM data in the patient files. One of the doctors alluded to the fact that they counselled all patients irrespective of whether they were test group participants or not. This prompted a telephonic interview with her after a larger than expected improvement in control group patients' adherence was observed. She confirmed that the patients with any sign of becoming non-adherent (e.g. cancelling visits, worsening clinical data) would routinely be counselled. This was also done during the study period without regard and might be a reason for the control group patients' adherence improvement during the last phase of the study.

Another doctor felt differently and related a case she was involved with when a patient insisted that she was adherent, despite her VL dropping. She admitted being non-adherent only after being confronted with the feedback graph. Patients might have tried to convince the attending doctor of their adherence but had no defence when confronted by the graph printout. One staff member remarked that with the e-MuM equipment being defective, the resulting graphs were not always trusted. It was clear that patients appreciated the help from the study, but they were not always in agreement with the results.

The sister in charge though stressed the fact that the tone of information sessions for patients should never be accusative. She was reassured that the data collectors were trained on those aspects before the study started.

5.3.5 Benefit of the study for participants

A female patient with high overall adherence levels (88.2% lenient; 92.3% strict) remarked that being part of the study kept them conscious of their treatment:

“... it helped us a lot and it should be brought back. Because there would be times when you don't feel like taking your pills but that gave us courage knowing that I was being watched... Yes, because sometimes we default but since the container it is not easy to do so.” (Patient)

Some focus group members were dissatisfied about not having been informed about the fact that they have not been informed the function of the e-MuM lid to their twice daily tablet taking routine. According to them, they would have liked to deliver better results if they had known they were being monitored.

5.3.6 Logistics and length of the study

The logistics of the study was frustrating to some of the participants in the beginning, as was the additional time it took to complete the questionnaire at each visit. Impatience with the queuing and length of time spent at the clinic during the second half of the study was addressed in the shortening of the questionnaire.

Some patients wanted to be down referred and transferred to a local clinic, but because of their inclusion in the study, they had to wait until the end of the study to do so.

On the other hand, some patients were glad to stay on at Tshepang Clinic, as one of the doctors explained:

“I got two patients who were in the study and very positive. One came with the watch - I did not have a reminder-now I have a reminder! Another patient that was positive said I wish this could continue because I know I will remain a patient of Tshepang and do not want to be transferred.” (Doctor)

Patients were recruited and enrolled in the study voluntarily and three prequalifying questions were used. Willingness of patients to stay in the study for eight months was one of these questions. Study challenges have been discussed in more detail in Chapter 3, Section 3.4.

5.3.7 Non-adherence and non-attendance

Not all the study participants attended all their appointments. A very interesting comment about patient behaviour was made by the head clinician, herself an ethnic African:

“... they usually don't tell you what they want to tell you - they tell you what will make you happy”. (Doctor)

According to her, black people do not always tell the truth if they feel it will offend or disappoint the recipient. They would therefore not complain to the study staff about any problems (lack of travel money, being sick and going to hospital or having problems at

work and not being able to keep appointments) and sometimes stay away until they could come again. This might “explain” the time periods during which patients did not visit the clinic.

5.3.8 Feeling better and adherence

The clinical head of the clinic remarked that patients sometimes do not persist with ARV treatment as they do not always see a quick improvement. It is apparent that not all patients “feel better” straight away after starting ARV medication. Some patients fail to respond as expected or may even exhibit clinical deterioration initially. These issues combine to present specific challenges for simplified clinical management.

Complications in the first few weeks following the initiation of ART are seen most commonly when therapy is started in patients with severe immunodeficiency. The apparent failure of a patient with advanced HIV disease to improve initially does not necessarily reflect a poor response to ART. It takes time for HIV viral replication to be controlled by ART and for the patient’s immune system to strengthen. It also takes time for reversal of the catabolism associated with HIV infection, particularly in patients with significant HIV-associated wasting. Additionally, as a patient with advanced disease recovers immune function, exacerbation of previously subclinical coexisting infections (e.g. tuberculosis) may occur, resulting in an apparent worsening of disease. This is not attributable to failure of the therapy but to its success and the resulting immune reconstitution. Such symptoms might be interpreted as an initially poor response to ART. It is important to allow sufficient time on therapy before judging effectiveness and to consider the possibility of the inflammatory reconstitution syndrome (IRS) in patients with worsening disease in the first few months of ART. In such cases, the switching of ART would be inappropriate (WHO, 2006).

The visible illness aspect was also mentioned by one of the doctors in the focus group discussion. She mentioned that many of the HIV positive patients only present at the clinic when they are at death’s door, showing many of the WHO stage 3 signs.

5.4 CASE STUDIES

Graphs compiled from the available data and generated electronically by the e-MuM microprocessor during the 8-month study period were valuable for the added visual insight they brought to the study. The visualization of adherence problems was presented to the test group patients during the feedback sessions and was also included in test patient files

to assist the study personnel and other clinic staff to establish non-adherence patterns at a glance.

The case studies below illustrate and highlight different adherence patterns, e-MuM related problems such as hardware problems, winter of 2008 and dose time shifts. Cases have been included to show improvement in time of taking medication. Some cases in which adjustment and censoring of adherence data might have resulted in higher adherence rates are highlighted. Correlation of adherence and clinical data are discussed.

5.4.1 Near-perfect adherence with increased CD4 count

Figure 5.1 illustrates a good or near perfect adherence pattern. The graph of Patient 122 exhibits a near-flawless adherence pattern (99.5%) to medication from the start to the end of the study. The patient's CD4 count also increased from 330 to 469 cells/mm³ during the study period. The patient's self-reported adherence for the VAS and 7-day recall were 89% and 100% respectively. The VL increased from undetectable to 2.64 and could allude to viral resistance developing and should be addressed by the physician.

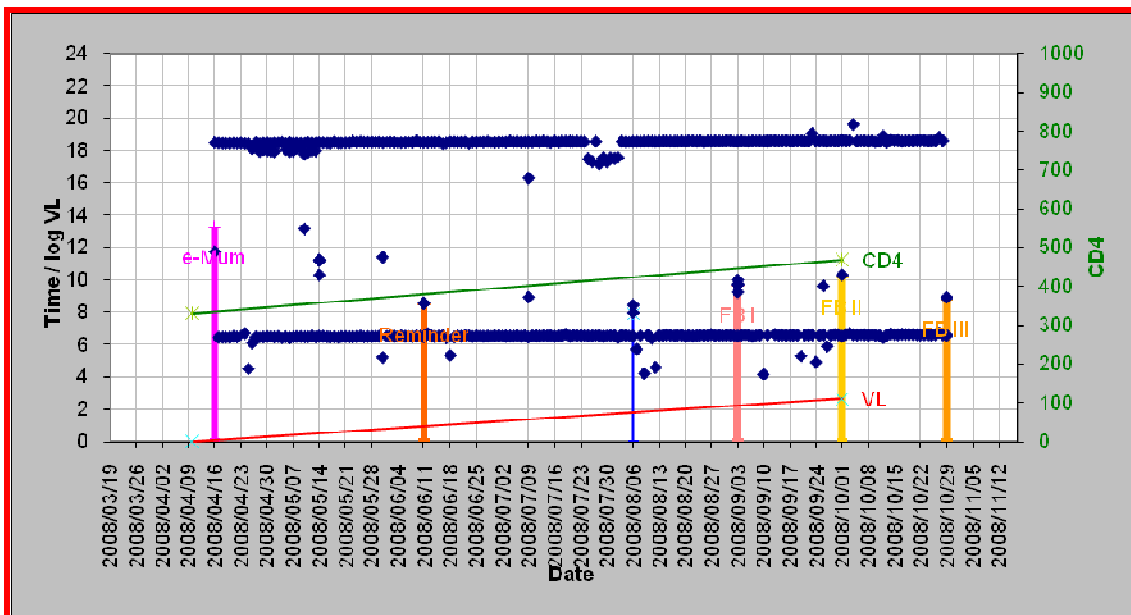


Figure 5.1: e-MuM data for Patient 122 (Control group)

5.4.2 Different adherence patterns (but same overall adherence rate)

The next group of graphs show different adherence patterns, but similar overall adherence rates. The percentage of doses taken within a specific time window of electronic monitoring as the only information to determine adherence rates will also include the non-adherence patterns for specific patients. Successfully addressing non-adherence periods and the associated problems, could lead to an improvement in overall adherence rates for

these patients. However, the adherence pattern for each patient is very different, as can be seen in the three graphs below. These patients each had an overall adherence rate of $\pm 70\%$.

Study Patient 185 from the test group had a 70.5% overall adherence of doses taken within the time window. This patient did not use the e-MuM container after the second feedback phases (0% adherence from Feedback II to Feedback III). The CD4 count increased from 340 to 375 cells/mm³ with VL staying undetectable. The VAS and 7-day recall were 90% and 100% respectively.

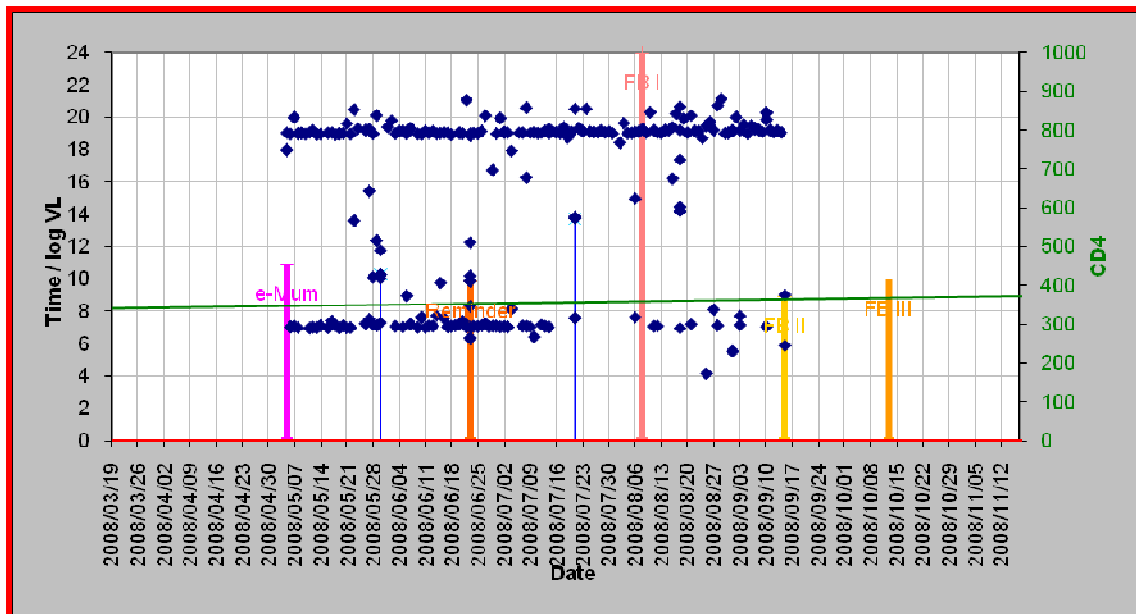


Figure 5.2: e-MuM data for Patient 185 (Test group)

Patient 195 had an overall adherence of 69.3%. A different scenario compared to Patient 185 existed for this patient. This patient had two periods of one and three weeks respectively of apparent non-adherence in June and July, while using the e-MuM very diligently for the rest of the study period. The CD4 count increased from 105 to 217 cells/mm³ while the VL remained undetectable. The VAS and 7-day recall were 95% and 100% respectively.

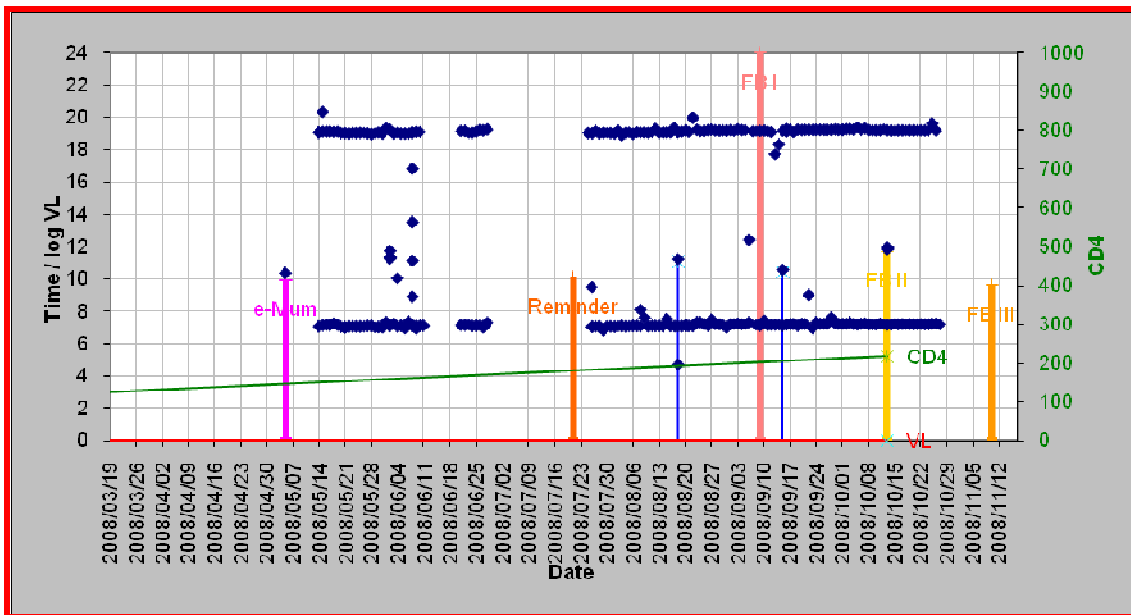


Figure 5.3: e-MuM data for Patient 195 (Test group)

Patient 34 had an overall adherence rate of 69.9%. This patient had a near perfect morning adherence rate, with evening openings of the container happening only on occasion. The influence of adherence patterns on electronic monitoring is discussed in Chapter 2, Section 2.12.3.7. The CD4 count fell from 533 to 439 cells/mm³ and the VL remained undetectable. The VAS and 7-day recall were 90% and 100% respectively.

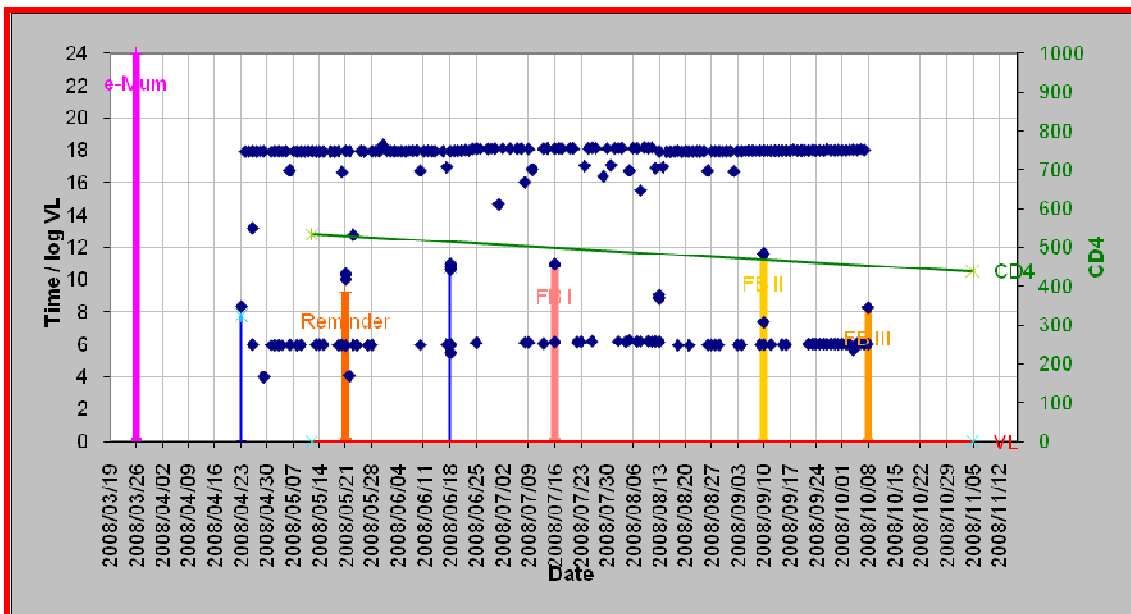


Figure 5.4: e-MuM data for Patient 34 (Test group)

5.4.3 Hardware problems

With some patients (e.g. Patient 15; see Figure 5.5) the lid of the e-MuM unit was tested by the data collector on several occasions and seemed functional on clinic visits. The patient was adamant that she was adherent, although data suggested otherwise. On 6

August 2008 a new lid was issued. Data collected for the period following the issue of the new lid, showed that the patient was indeed adherent. The CD4 count increased from 342 to 392 cells/mm³ with VL staying undetectable. The VAS and 7-day recall were 89% and 100% respectively.

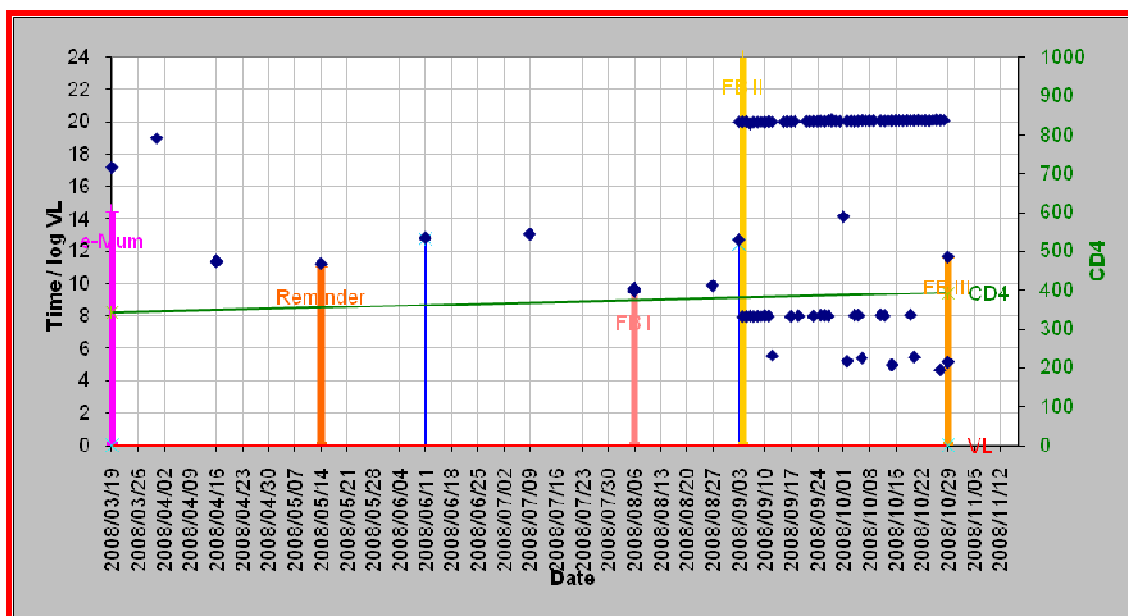


Figure 5.5: e-MuM data for Patient 15 (Test group)

Patient 44 (see Figure 5.6). This patient showed a very unusual e-MuM opening pattern. The e-MuM was opened many times on the day she received it. She did report a broken lid and was given a new container lid but no data were recorded until August, when it seems she opened the contained multiple times in one week. One of the other patients (Patient 37) reported that he had to open his container multiple times on certain days to replace the microprocessor when it fell out and felt bad when questioned by data collectors about it. Keeping the comment from one of the staff members in mind that Africans would not want to offend you and want to please you (see Chapter 5, Section 5.4.7), another unreported hardware malfunction might have taken place. Confirmation of that can be found in self-assessing data and biological markers. The CD4 count increased from 161 to 312 cells/mm³ and VL remained undetectable. The VAS and 7-day recall were 91% and 100% respectively.

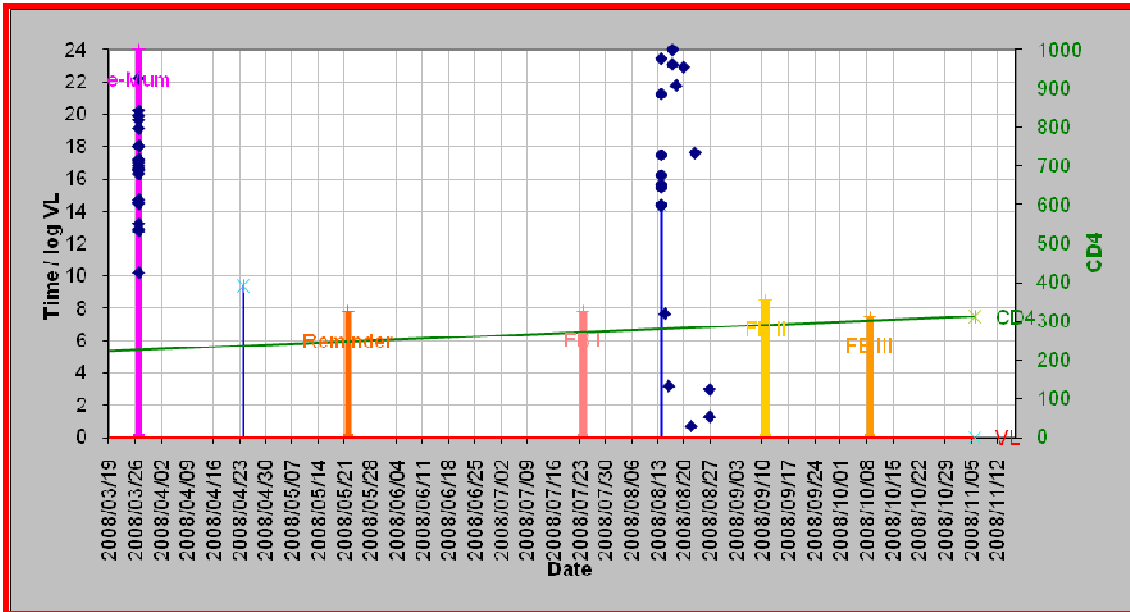


Figure 5.6: e-MuM data for Patient 44 (Test group)

No hardware problems can be blamed for the adherence pattern resulting in an adherence rate of 64.3% for doses taken within the time window indicated. Patient 62 (see Figure 5.7) indicated on his questionnaire that medication was taken directly from the container without any decanting. Looking at the graph in Figure 5.6 it was evident that the adherence pattern comprised a combination of once daily and “no decanting” events at random. The patient’s CD4 count decreased from 297 to 263 cells/mm³ with VL remaining undetectable. Die VAS and 7-day recall were 81% and 90% respectively.

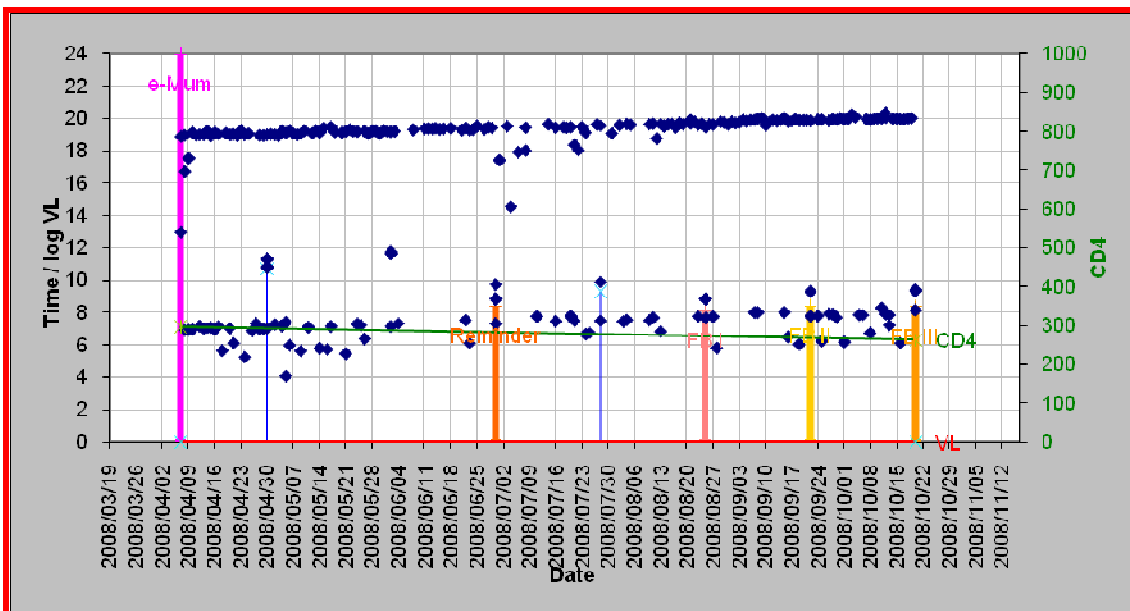


Figure 5.7: e-MuM data for Patient 62 (Test group)

5.4.4 “Time drift”

A “time drift” problem was identified on the graphs generated for patients and was at first attributed to a software problem. The drift for the evening dose is clearly visible in the graph for Patient 62 (see Figure 5.7 above). It was concluded at a later stage that the problem occurred as a result of an error in the pre-programming of the e-MuM unit microprocessor. This could not be solved and had to be kept in mind when evaluating patients’ medication taking at the pre-set time.

5.4.5 Winter of 2008

A very interesting clinic attendance pattern emerged in the analysis of non-adherent periods compared to the months of the year. Some of the patients presented with a very low overall adherence rate due to defaulting for a couple of weeks and sometimes months during the winter. The e-MuM was functioning and recorded events before and after these periods. Patients gave no reason for their absence during these periods.

The CD4 count of Patient 29 from the control group (see Figure 5.8) increased from 222 to 291 cells/mm³ with the VL remaining undetectable. The VAS and 7-day recall were 74% and 100% respectively.

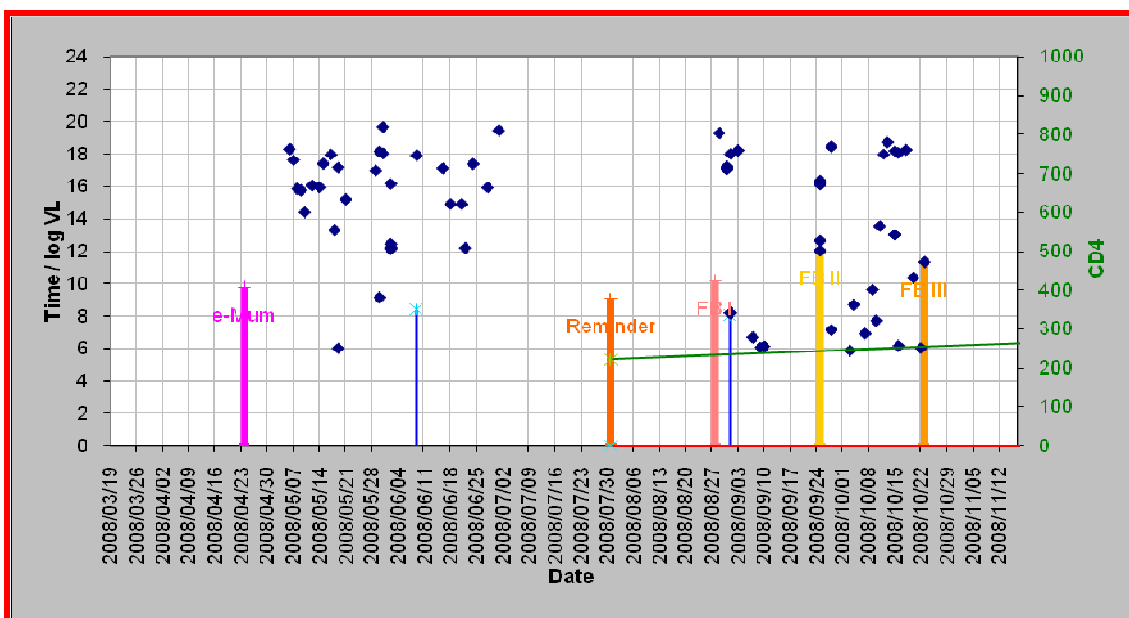


Figure 5.8: e-MuM data for Patient 29 (Control group)

The CD4 count of another patient from the control group (Patient 101; see Figure 5.9) increased from 148 to 150 cells/mm³ and her VL increased from 0 to 3.15. VAS and 7-day recall were 81% and 90% respectively. The increase in VL indicated that the VL test probably needs to be repeated for this patient.

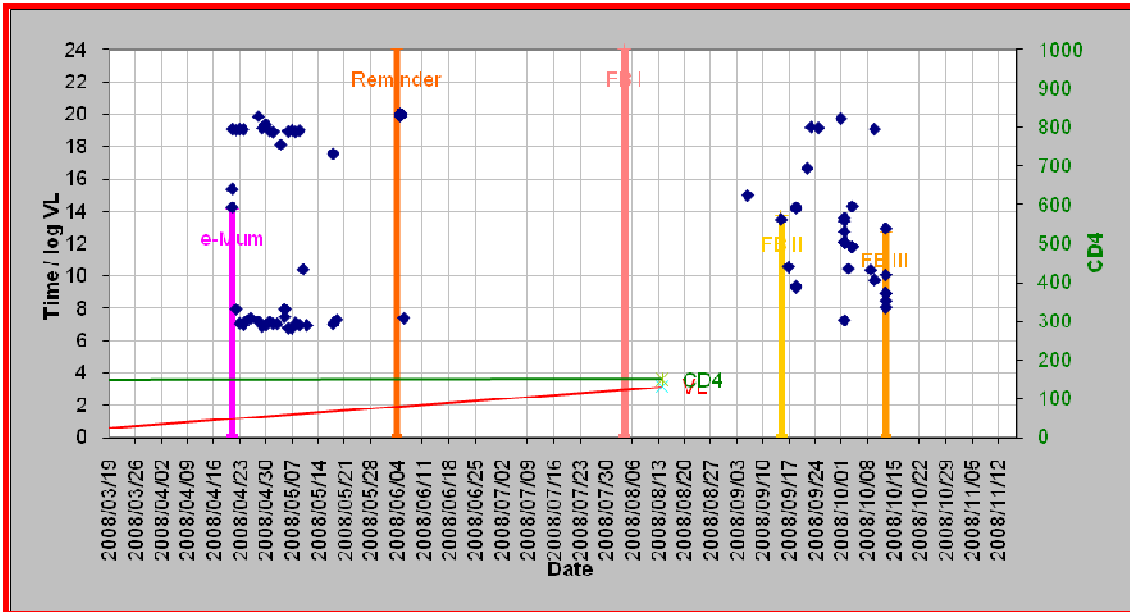


Figure 5.9: e-MuM data for Patient 101 (Control group)

For Patient 152 from the test group (see Figure 5.10), the CD4 count decreased from 119 to 64 cells/mm³ as did the VL from 4.08 to 3.98. The VAS and 7-day recall were 86% and 100% respectively.

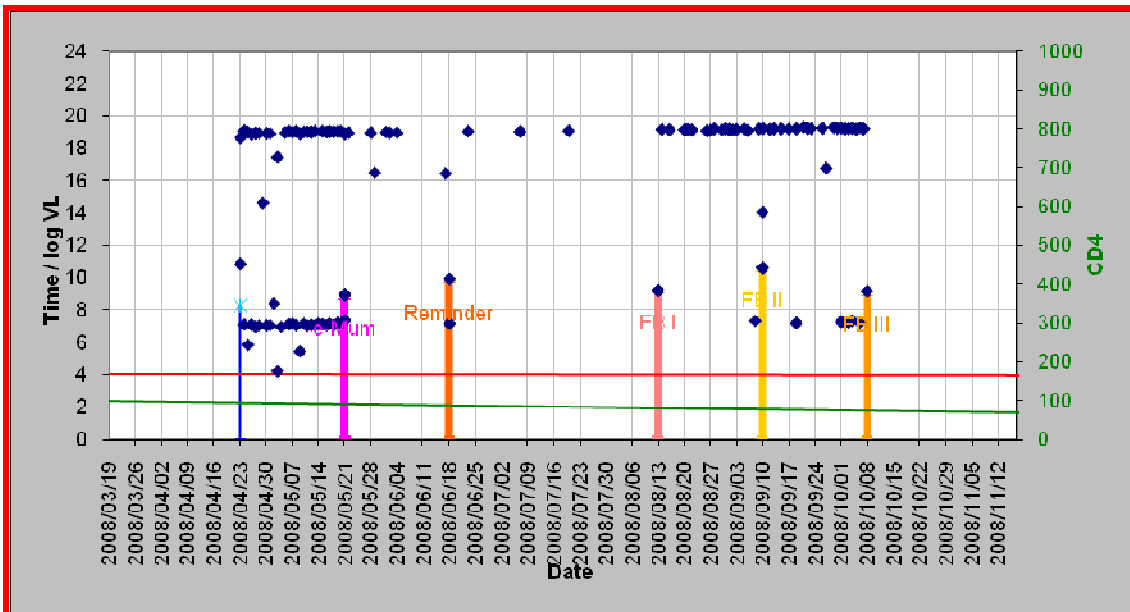


Figure 5.10: e-MuM data for Patient 152 (Test group)

5.4.6 Dose time shift

A strict tablet-taking routine is very important to keep the adherence rate above 95%. To achieve this, patients are encouraged to establish a routine and take medication everyday at the same time. Patient 92 (see Figure 5.11) was part of the test group and even after the reminder unit was issued, most of the doses were not taken at a specific time, but within a two hour band twice daily. The CD4 count increased from 364 to 384 cells/mm³

and the VL remained undetectable. The VAS and 7-day recall were 90% and 100% respectively.

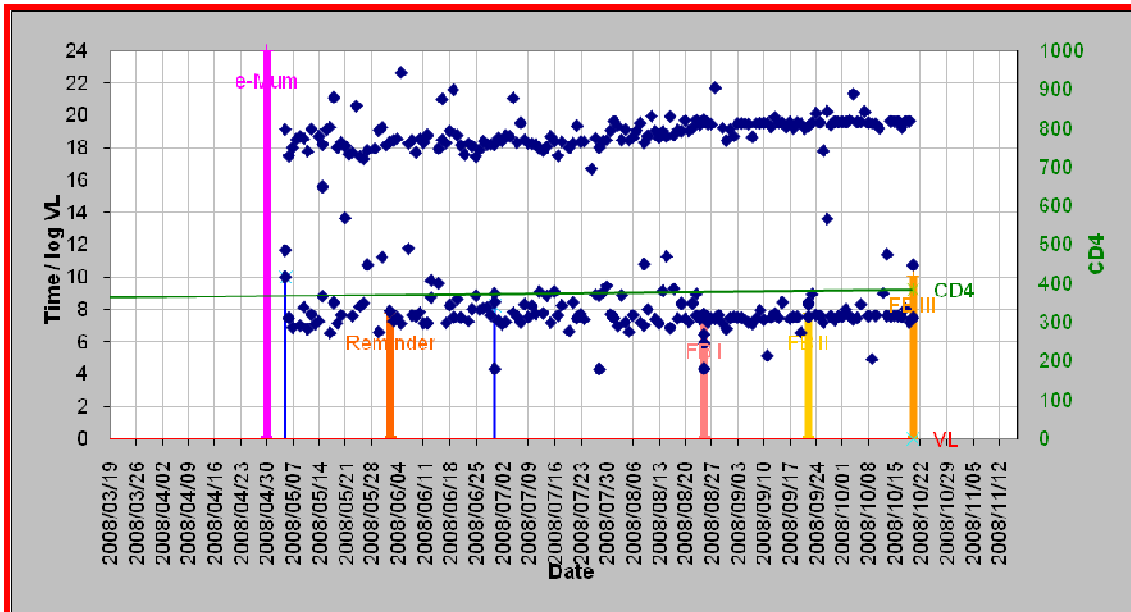


Figure 5.11: e-MuM data for Patient 92 (Test group)

5.4.7 Improvement in medication-taking over time

Patient 7 (see Figure 5.12) presented with an improved adherence pattern from July 2008. His CD4 count increased from 211 to 329 cells/mm³ and his VL remained undetectable. The VAS and 7-day recall were 85% and 100% respectively.

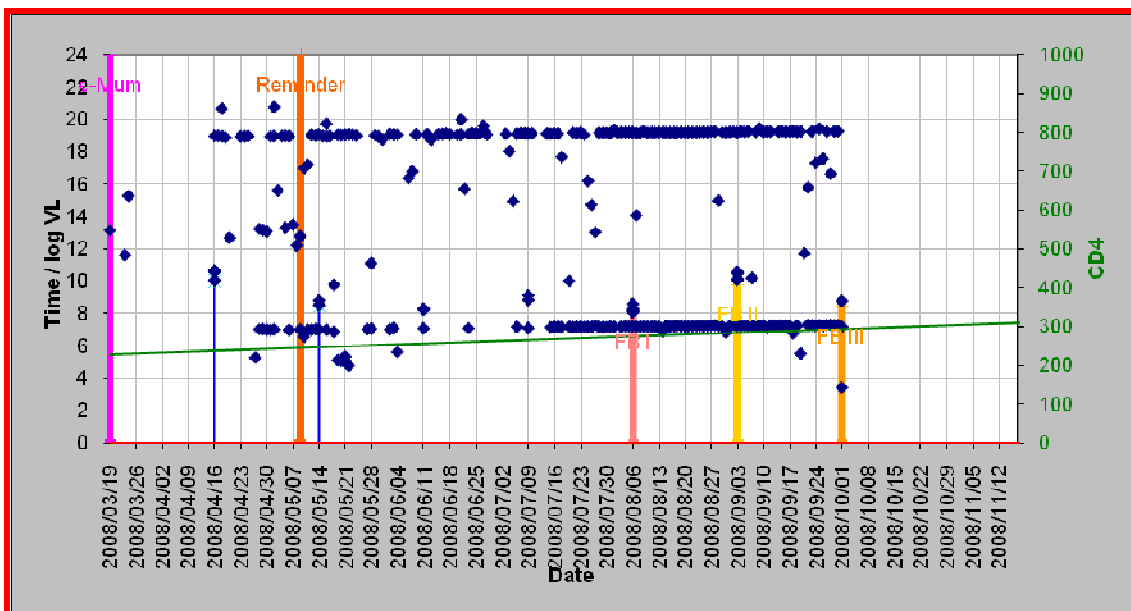


Figure 5.12: e-MuM data for Patient 7 (Test group)

Figure 5.13 shows the adherence pattern of Patient 134 with an improved adherence schedule from July 2008. Her CD4 count increased from 10 to 260 cells/mm³ and her VL remained undetectable. The VAS and 7-day recall were 91.5% and 100% respectively.

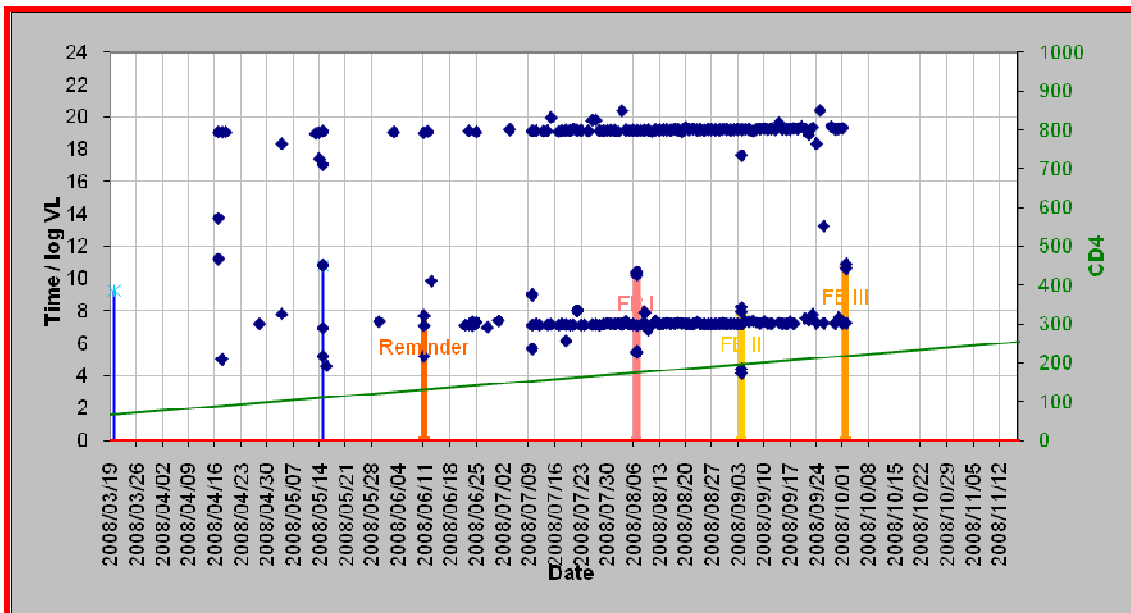


Figure 5.13: e-MuM data for Patient 134 (Test group)

Patient 166 (see Figure 5.14) from the test group demonstrated an improvement in adherence after Feedback II. Her CD4 count increased from 81 to 210 cells/mm³ and the VL decreased from 4.94 to undetectable levels. The VAS and 7-day recall were 86% and 80% respectively.

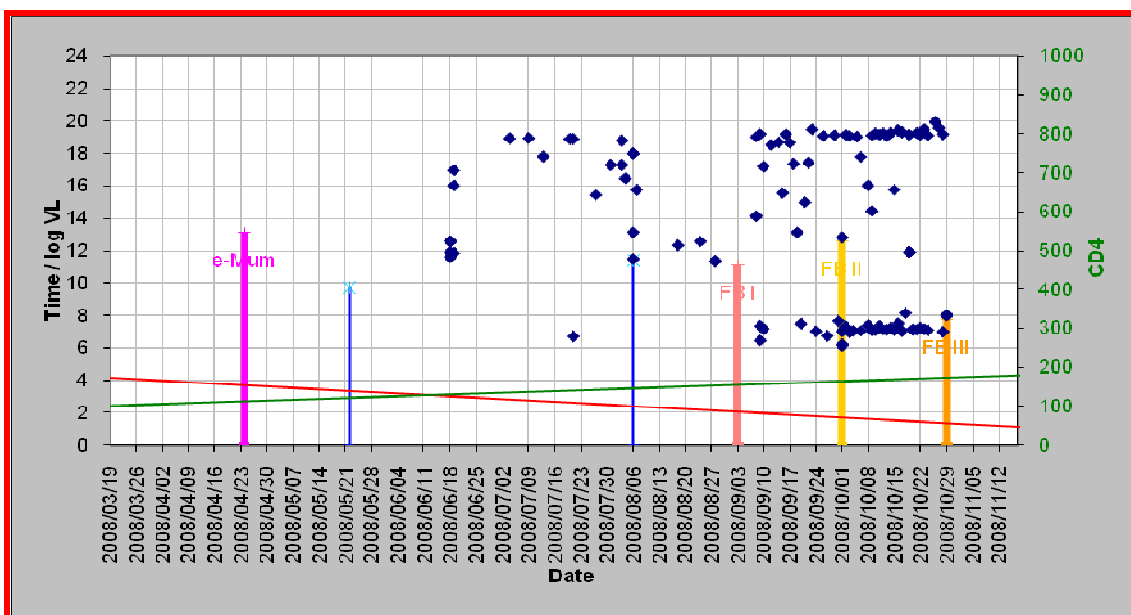


Figure 5.14: e-MuM data for Patient 166 (Test group)

On the other hand, Patient 107 (see Figure 5.15) from the test group also demonstrated an improvement in adherence after Feedback II. The CD4 count fell from 33 to 12

cells/mm³ and her VL increased from 3.2 to 3.92. The VAS and 7-day recall were 91% and 100% respectively. The reason for this could not be determined as part of this study. Possible explanations could be resistance, non-adherence to other ARVs in the regimen or other secondary infections.

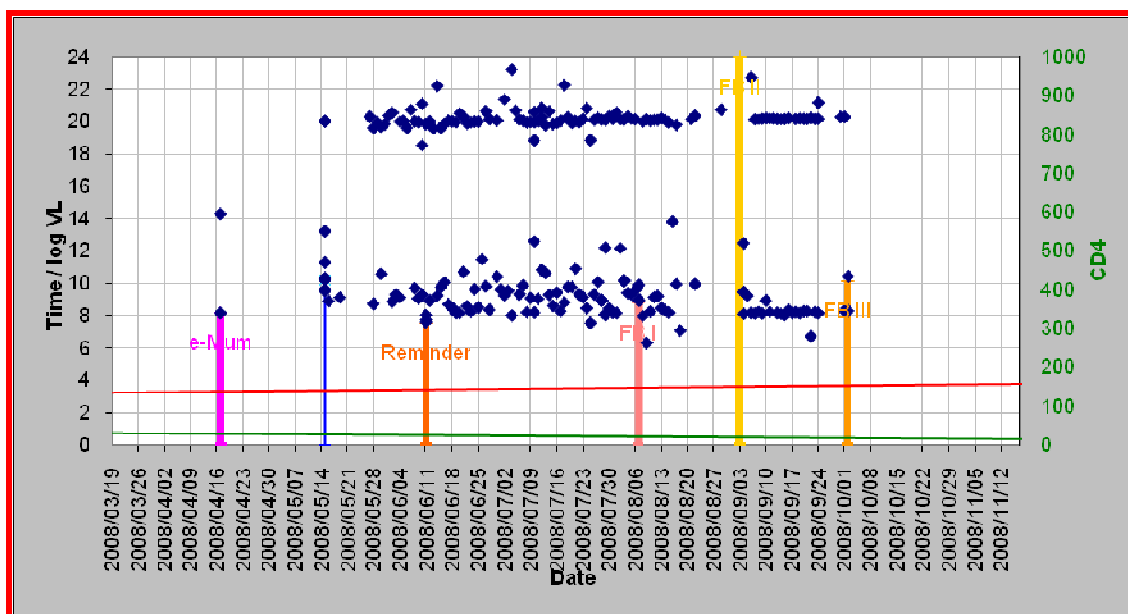


Figure 5.15: e-MuM data for Patient 107 (Test group)

5.4.8 Adjusting and censoring adherence data

The e-MuM container was issued to patients with the instruction by the data collectors not to change their tablet taking routine. The data collectors observed that some patients were still using medication from the previous month at the next visit and requested them to start using only from the e-MuM container. To screen the patients for adjustment of data was complicated by the absence of daily diaries to evaluate the reasons for non-adherence. Another factor in data adjustment is that no universal boundaries have been set in research for specific adjustments (Fennie *et al.*, 2006).

Results obtained from Patient 149 (see Figure 5.16) can be used to illustrate the problem of deciding whether adherence data had to be adjusted or not. Without direct proof, it is possible that this patient was one of the patients using tablets from her ordinary container. After switching to the e-MuM container (three weeks after receipt), adherence was near perfect. The three weeks at the start of the study resulted in a lower overall adherence rate. The patient's CD4 count increased from 199 to 280 cells/mm³ and her VL decreased from 3.15 to undetectable levels. The VAS and 7-day recall were 90% and 100% respectively.

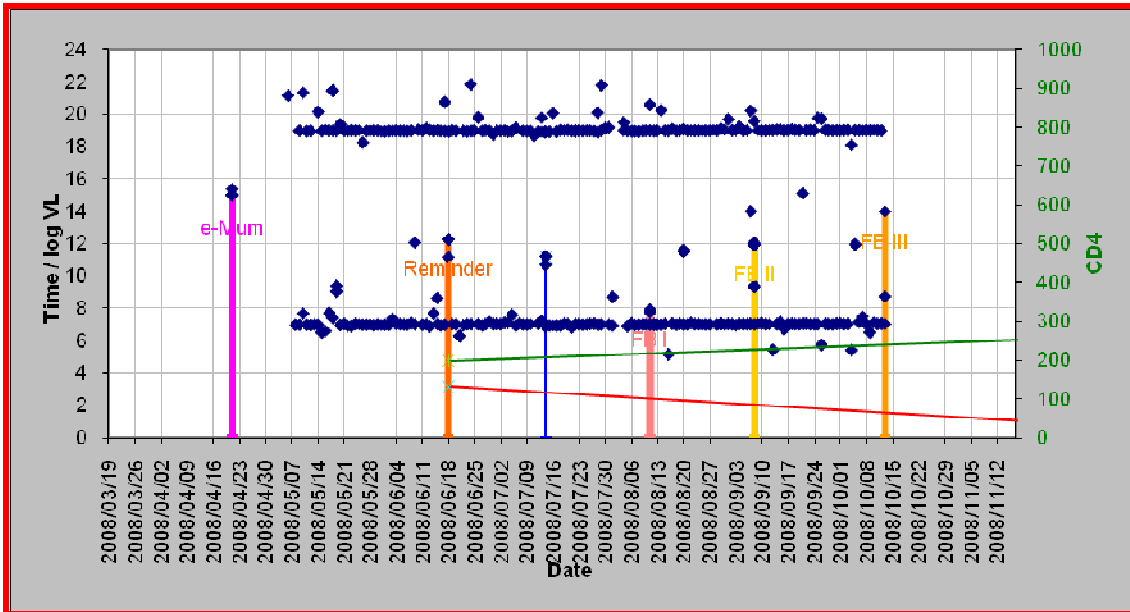


Figure 5.16: e-MuM data for Patient 149 (Test group)

Another possible case for adjustment could have been made when data were not recorded by the e-MuM units for the periods before malfunctioning container lids were replaced (20 patients) or when the computer data cable malfunctioned (see study limitations in Chapter 6, Section 6.3.4). Data on the microprocessor could not be read (see Patient 138; Figure 5.17). The problem was reported at the start of October 2008 and had to be solved by Geo-ICT Health Pty (Ltd). Instructions were supposed to be sent to the study personnel for lost data recovery, but nothing was received. The patient's CD4 count increased from 208 to 420 cells/mm³ and the VL decreased from 4.91 to undetectable. The VAS and 7-day recall was 80% and 80% respectively.

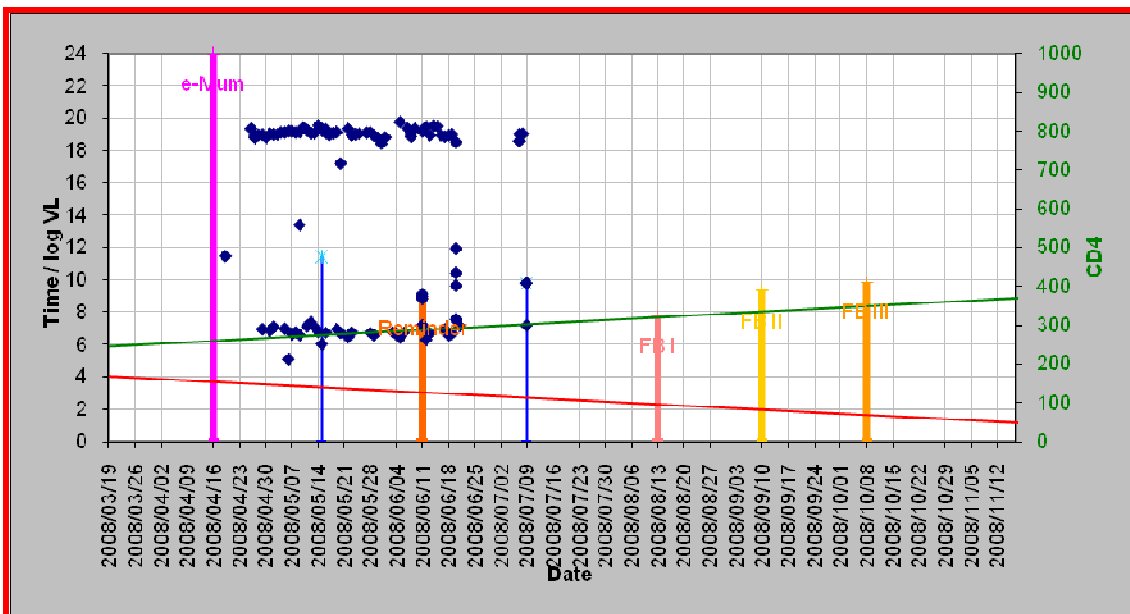


Figure 5.17: e-MuM data for Patient 138 (Test group)

5.4.9 The impact of adherence on CD4 count responses

For some patients an improvement in tablet taking routine during the course of the study resulted in an improvement in the overall adherence rate and an improvement in CD4 count. A substantial gain in CD4 count from 10 to 260 cell/mm³ was observed in Patient 134 (see Figure 5.13 above) from the baseline biological markers taken at the start of the enrollment until the end of the study (11 months). After using the e-MuM container only occasionally, this patient's adherence pattern changed in July 2008 for the last three months, to a near flawless adherence pattern, as measured by the e-MuM microprocessor. The self-reported adherence routine recorded for the last three months of the study in the questionnaire was also “no decanting”. Subsequently the patient's CD4 count increased, which could be attributed to the improved adherence. A Canadian study demonstrated that adherence to HAART can be the predictor of an increase in CD4 count even for patients with a CD4 count below 200 cell/mm³ (Wood *et al.*, 2006).

Patient 78 (see Figure 5.18) indicated the frequency at which his medication was taken from the container as once daily. The adherence reported on the questionnaire was similar to the adherence data from the microprocessor in the e-MuM lid. The overall adherence for this patient, downloaded from the e-MuM was 60.5%. However, the 7-day recall (self-report) was 100% and the VAS was 9.1 (91%). The CD4 count declined from 275 to 243 cells/mm³ and the VL remained undetectable.

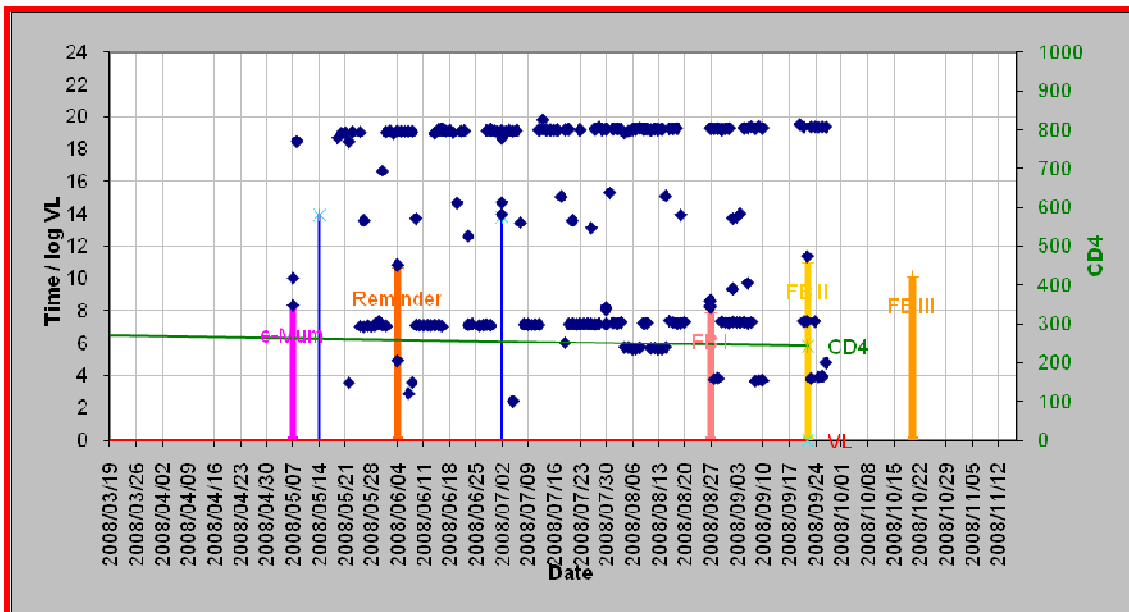


Figure 5.18: e-MuM data for Patient 78 (Test group)

5.5 SUMMARY

In this chapter, the results from the two focus group discussions (patients and clinic staff), were presented. The patient focus group discussion highlighted problem areas like the size of the e-MuM container, hiding of medication to avoid being stigmatised, problems experienced at clinic visits and decanting habits. It also highlighted differences about the reminder unit, as some regarded it as a welcome tool while others were still afraid it might identify their HIV status. The staff members at the clinic were also divided about the usefulness of the e-MuM system. Their duty as care givers was to counsel all the patients on adherence, while some thought it might be useful to establish adherence patterns for new and non-adherent patients.

This section was followed by a discussion of a selection of patient cases with the aim to illustrate certain adherence patterns, as determined with the e-MuM system, the relationship between adherence and clinical markers as well as the influence of the device itself on patients' adherence behaviour. Hardware problems and changed adherence patterns during a specific period (winter of 2008) were highlighted. Certain cases which showed improved adherence over the study period were discussed. Cases with specific non-adherence periods and the effect censoring would have had to increase adherence rates, were outlined. A summary discussion, the conclusion of the study and recommendations are presented in Chapter 6.

CHAPTER 6

SUMMARY DISCUSSION, CONCLUSION AND RECOMMENDATIONS

6.1 INTRODUCTION

In HIV treatment, as in many other chronic or long term treatments, adherence to medication is important to manage the disease and ensure long-term health. Non-adherence to ART leads to viral replication, development of viral resistance and secondary co-morbid diseases. Antiretroviral treatment adherence of 95% has to be sustained to achieve viral suppression, ensure minimal HIV related effects, cut down on unnecessary spending and lessen the economic burden on South Africa, Africa as a whole and globally (UNAIDS, 2005). Measures to enhance and monitor adherence assist patients to manage their treatment better. Electronic monitoring systems can be applied in a dual role, as drug monitors and dose reminders. The e-MuM system tested in this study at an HIV clinic was used to monitor one of the ARV drugs (lamivudine) in an attempt to increase adherence. This chapter presents a summary discussion and the conclusion according to the objectives of the study as set out in the first chapter. The chapter ends with recommendations which are offered and based on the results of the study.

6.2 SUMMARY DISCUSSION

6.2.1 Background

The aim of the study was to measure the adherence of 210 patients on ART in this eight-month, four phase, prospective, randomised experimental, longitudinal study. Respondents were allocated to either the test or control group which were balanced in terms of gender, age and length of time on ARV treatment. After randomised stratification the control group and the test group's adherence were electronically monitored by the e-MuM. Only the test group received further interventions i.e. a dosage reminder device and adherence feedback on electronic monitoring of Lamivudine use.

The study was structured to employ an inter-group and inter-phase comparison of four different ARV adherence assessment methods as well as biological markers.

6.2.1.1. Phases of the study

The results are presented and discussed according to the following four phases (Section 3.3.4.3, Fig 3.2):

- Phase 1: From issue of the e-MuM unit until issue of the reminder unit (watch)
- Phase 2: From issue of the reminder unit (test group only) until before Feedback I
- Phase 3: After Feedback I until Feedback II (Feedback given to test group only)
- Phase 4: After Feedback II, until Feedback III (Feedback given to test group only).

6.2.1.2. Adherence assessment methods

The following adherence assessment methods were used:

- Patient self-assessment (questionnaires) monthly: decanting habits, 7-day recall and VAS.
- e-MuM electronic recorded adherence downloaded monthly to a specially designed software programme.
- Biological markers (VL and CD4 count) measured at the start and at the end of the study period.
- Results from limited tablet counts performed monthly and a 2-day recall omitted at the end of Phase 2, which were subsequently not used in the analysis due to incompleteness of data.

6.2.2 Demography

Most of the participants in the study were in the age group 30-50 years. The age distribution and gender balance in the test and control groups at the start of the study were maintained until study conclusion, with no statistical difference between the groups. This was accomplished despite there being a relatively higher percentage of females than males in the control group compared to the test group (see Figure 4.2). Relatively more males than females had been lost from the control group by the end of the study.

The study population was recruited on a voluntary basis and 78% of the study population at the conclusion was women compared to 76% at the start of the study.

The gender data from Tshepang clinic (2010) of patients on ART show that females predominate (67% females vs. 33% males). Data from other South African studies (Mapetla, 2007; Meyer, 2008b) also reflected these gender proportions. Hence, it appears

that relatively fewer males than females seek treatment at Tshepang Clinic, when compared to those infected with HIV.

A similar pattern was seen in a large Kenyan study (The Academic Model for the Prevention and Treatment of HIV/AIDS [AMPATH]). It was found that women stayed in the study longer than men, who were more likely to be lost to follow-up (Wools-Kaloustian *et al.*, 2006).

The majority of enrolled patients were unemployed (75%). The educational level of most patients was incomplete with 82% not even in possession of a secondary education certificate.

The marital status of 87% of the study patients was single, divorced, widowed or separated. Studies which investigated the influence of socio-economic factors on ARV adherence rate found that no clear influence of marital status on ARV adherence could be established (Talam *et al.*, 2008).

In a systematic review of 116 articles and 17 original studies Falagas and colleagues (2008) evaluated the association between some socio-economic status (SES) factors and adherence to ARV treatment. They could not find conclusive support for a clear association between income, education and occupation of patients and their adherence to ARV medication. Adherence to ARV medication was only statistically influenced by components of socio-economic status in less than half the studies for income and less than a third for education, but no statistically significant association between the three SES determinants and adherence was established (Falagas *et al.*, 2008).

In this study, 59 (28%) of the 210 study patients received social grants. Of these 59 patients, 47 (80%) did not complete the study and presented incomplete e-MuM data, clinical data and attendance at some or all visits. In contrast, 76 (50%) of the 151 study patients not receiving social grants completed the study with e-MuM data, clinical data and attendance at some or all visits. Only one fifth of “social grant” patients completed the study compared to half of the patient’s not receiving a social grant.

6.2.3 Duration on treatment

There was no statistically significant difference in either the test or the control group’s mean or median duration on treatment during any of the study phases. At enrolment, the test group had a mean duration on treatment of 12.5 months, which increased to 14.7 months at the end of the study. The control group had a mean duration on treatment of

13.6 months at the start and this decreased to 11.9 months at the conclusion of the study (see Section 4.2.1, Table 4.3).

The higher mean (and median) duration on treatment for the test group by Phase 4 followed a general trend that patients who had been on treatment for longer, and received an intervention tend to remain in studies (Brinkhof *et al.*, 2008). A tendency by patients to leave a study is more likely during the first six months on treatment than any other study period (Brinkhof *et al.*, 2008).

6.2.4 Adherence

6.2.4.1. Visual analogue scale (VAS)

Patients rated their self-perceived adherence on a 10 cm Visual Analogue Scale (VAS) a total of 885 times during the study. Despite repeated explanations by data collectors, 100 (11%) of the marks were made out of the scale bounds

The explanation from data collectors was that they observed a lack of understanding of the VAS from certain patients. These patients had difficulty interpreting the abstract nature of the VAS scale. The demographic data showed that the education level of 82% of patients enrolled in the study was an incomplete secondary level education or lower, which may have influenced these results. The data collectors confirmed that some patients needed an explanation at every visit. According to one of the clinicians at the clinic, another possible reason for high self reported adherence is that patients did not want to admit to less than perfect (expected) adherence levels (see Chapter 5, Section 5.3.7).

The data showed that there was little difference between the test and the control groups, and that there was little difference between the Phases, and that perceived/reported adherence did not change greatly over time (see Section 4.3.7, Table 4.12 and Figure 4.9). Average and median values at each phase, and changes between phases, were compared statistically and no significant differences were found.

6.2.4.2. Seven-day recall

The 7-day recall (medication taken correctly in the week before the clinic visit) was one of the adherence measures in which the patients rated themselves as being adherent (93.6% for the test group and 92.8% for the control group). These results are in stark contrast with the data obtained by the e-MuM unit. The 7-day recall results were similar to

the VAS self-assessment results done by the patients, i.e. remained high throughout the study with very little change from month to month. According to the literature, patients are known to overestimate their adherence when using self-assessment methods (Berg & Arnsten, 2006; Gill *et al.*, 2005; Liu *et al.*, 2006b).

6.2.4.3. Tablet counts

The patients were asked at every visit to bring back their left-over medication when they came for the next visit. Medication was only brought back on 60% of visits by test group patients and 64% of visits by control group patients. In addition it was difficult to establish whether returned tablets included only those dispensed at the previous visit or also patients' previous stocks. The varying interval between visits and mixed tablets in boxes made the tablet counts unreliable; hence data could not be used for analysis.

Observation and discussions with patients and clinic staff at Tshepang and Rustenburg Wellness Clinics before the study commenced, revealed that some patients carry all their different medication together in one container or decanted their medication in a plastic bag. This is done due to practical considerations, for convenience sake, as well as to avoid rigid ARV labelled tablet containers giving away their HIV status.

6.2.4.4. e-MuM adherence patterns

Two different time windows were used for adherence measurement with e-MuM. "Lenient" adherence referred to taking the required doses on the correct day and "strict" adherence referred to taking the dose within an hour before or after the prescribed time. Frequency distributions (histograms) from the individual percentages of e-MuM adherence were widely scattered. The histograms for Phase 3 and Phase 4 showed an improvement in the number of test group patients with 80%, 90% and 100% mean adherence compared to earlier phases of the study.

An unexpected increase in control group mean adherence from the end of Phase 2 to Phase 4 was noted. This increase could possibly be explained by doctors' counselling of all patients as per their usual routine and cross contamination by the test group patients who had the blue feedback sheets containing graphs of their adherence patterns included in their files.

The results showed that e-MuM data underestimated adherence due to various factors, as summarised below:

- Different decanting habits (reported by patients and registered by e-MuM).
- Malfunctioning of e-MuM equipment.
- Data were not adjusted to accommodate patients' decanting patterns. Adjustment of e-MuM data was not possible because insufficient and inconsistent records were available from patient decanting patterns reported in questionnaires for this purpose.

From Table 4.4 (see Section 4.3.3) it can be seen that there was a trend towards a greater improvement in the adherence in the test group than in the control group. The SD was so great in each group/phase (25-34%) that these trends did not show statistical significance at a 95% level. At a 90% significance level Phase 4 data showed statistical significance between the two groups based on mean and median adherence, as did the adherence data for the full period. The change in the median for the test group strict adherence from Phase 2 to 4 was 22.6 and the change in the test group mean adherence of 18.8, with a large standard deviation of 33.2 (see Section 4.3.4, Table 4.7). This finding could be due to various reasons, including but not limited to the following points:

- Positive patient selection over the study period. More adherent patients were likely to remain in the study.
- Better understanding of study conditions by patients lead to increased proportion of patients apparently practicing “no decanting” after Feedback I, although communication was a problem.
- There were more malfunctioning units at the beginning than at the end of the study.

The difference between the test and control groups in terms of changes in adherence over time did not reach the significance level of $p < 0.05$.

6.2.5 Biological markers

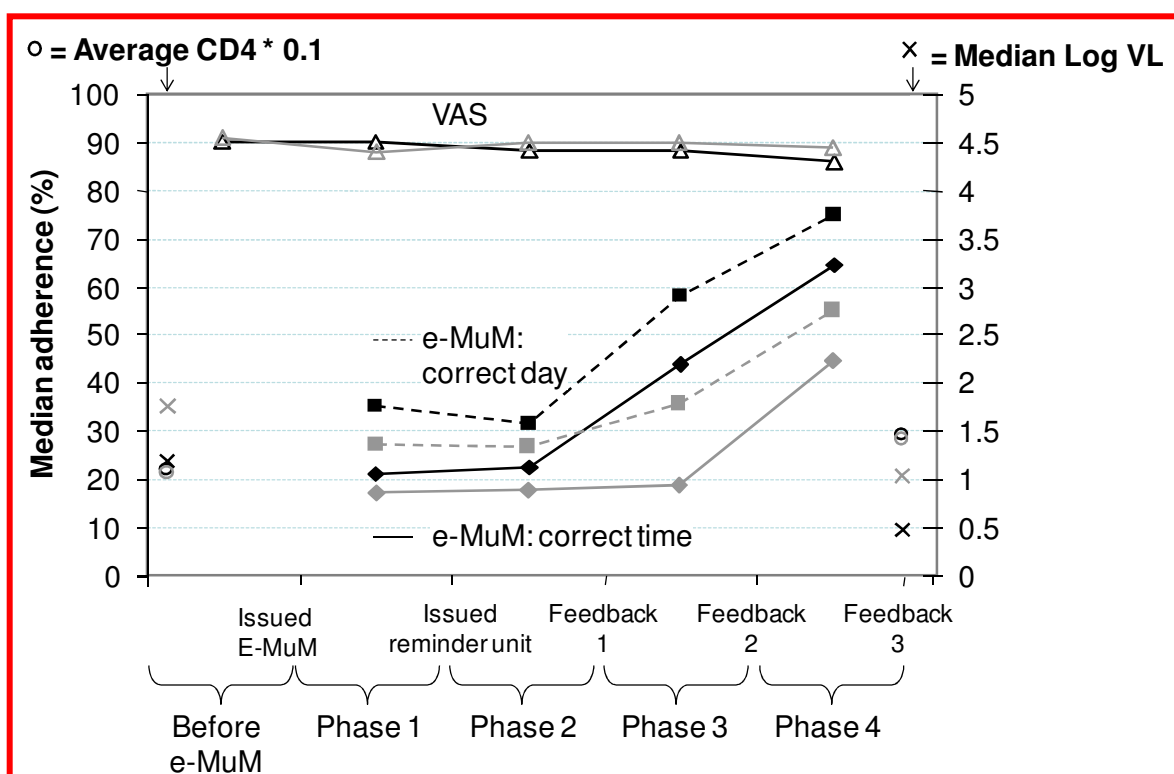
The mean CD4 counts increased statistically significant over the study period for both the test and the control groups, although there was no significant difference between the two groups. The mean increase in CD4 count in the test group over the period was 76.2 and the control group 72.2 ($p < 0.001$).

The number of patients with VL < 400 copies/ml increased from 72% to 89% (19%) in the test group and from 65% to 75% (13%) in the control group over the study period.

The biological markers indicated that antiretroviral treatment was effective in both groups (control and test). The following points were noted:

- Statistically significant increase in CD4 counts for both groups
- Viral loads decreased in both groups; significantly so in the test group

6.2.6 Adherence: self-report vs. e-MuM



Test group (black); Control group (grey)

Figure 6.1: Adherence (e-MuM and VAS), CD4 and VL:

An overestimation of adherence compared to e-MuM was observed when patients had to self-assess their adherence. The average adherence measured with the VAS for both the test and control group was 90% over the study period. The average adherence measured with the 7-day recall was 93.6% for the test group and 92.8% for the control group.

Comparison of the different adherence measures produced the following results:

- Self-assessment methods (VAS and 7-day recall) correlated and patients assessed themselves as being highly adherent (80% to 100%).
- The e-MuM adherence did not correlate with any other adherence measure.
- When individual cases were considered, the clinical data (CD4 and VL) did not correlate with any adherence measure. A higher adherence (using any of the

methods) did not always result in an improvement in clinical data for specific patients (see Chapter 5, Section 5.4.9).

Munoz-Moreno and colleagues (2007) measured adherence using the SERAD (Self-Reported Adherence) questionnaire, which is a qualitative and quantitative self-reported instrument. In addition, they also used tablet counts, electronic monitoring and plasma drug monitoring. Adequate levels of agreement between methods were observed, particularly when adherence was high. Differences between methods of measuring adherence increased as adherence decreased (Munoz-Moreno *et al.*, 2007). Correlation between this e-MuM study's methods was highest for patients with high e-MuM adherence data because most of the patients from this study regarded themselves as being adherent when asked to self-assess their adherence,

6.2.7 Effect of interventions

Van Dolmen *et al.* (2007) came to three conclusions after assessment of randomised trials that reported adherence and treatment outcomes with a follow-up period of at least six months.

- Firstly, less than half (45%) of the interventions resulted in improved adherence. In this study the intervention did result in an improved adherence, although this was not statistically significant.
- Secondly, those interventions that were effective for long-term care were exceedingly complex and labour intensive. The e-MuM system is expensive and would require dedicated, trained staff to manage the program and it is difficult to anticipate the DOH being able to afford this adherence monitor and reminder for routine use by patients at clinics coping with financial constraints.
- Thirdly, even the most effective interventions did not lead to large improvements in adherence and treatment outcomes. The results from this study showed an increase in mean strict adherence of the test group registered by the e-MuM system of 22.6 % with large SD ranging from 25.3 to 33.2 (see Table 4.5).

In addition in this study even the control group patients showed increased adherence (see Section 4.3.4, Table 4.6). The added contact/interest could have played a role (see Hawthorne effect, Chapter 3, Section 3.2.21).

6.3 LIMITATIONS OF THE STUDY

Limitations are often imposed on a study by budget and time constraints (Walonick, 2005)

- Limitation refers to reasons that make the research impossible and difficult to extrapolate results to another population.
- Limitation may also refer to the introduction of bias to the study.
- Reliability and validity problems are regarded as limitations.

The following limitations pertaining to elements of the study were experienced during the study period.

6.3.1 Enrolment problems

Plans for multiple site enrolment of patients had to be cancelled due to logistical problems, thus patients were enrolled at a single site. The use of a single public sector site could be regarded as a limitation as this population would not necessarily be representative of patients spread over the entire country. Due to fact that only willing patients were enrolled, this could be regarded as bias in the enrolment procedure.

6.3.2 Tablet counts

The patients were requested and instructed to bring their left-over medication with them, every time they come for a return visit, but unfortunately this did not always happen. Most patients blamed a “bad memory” and simply said they “forgot”. Although this might be true for some patients, it is possible that many did not want their tablets to be counted for various reasons. The main reason being that the tablets left probably did not correspond with the expected quantity. They might have been afraid that as a result no medication would be issued. This resulted in the tablet counts as an adherence measure being abandoned due to too few patients with sufficient and consecutive tablet counts able to be compared as an adherence tool.

6.3.3 Loss of patients (defaulters)

A system to trace patients not keeping appointments was theoretically part of the standard operational procedures of the clinic. When a patient did not keep the appointment, a social worker should have phoned to enquire about reasons for defaulting. The patient should be persuaded and encouraged to continue with the treatment. This unfortunately did not

happen because no telephone was available for this purpose and no budget had been allocated to follow-up on patients.

In Phase 3 and 4 of the study, test group patients were confronted with evidence of their adherence and asked questions about non-adherence periods. Some patients may not have returned for the second feedback as a result.

6.3.4 e-MuM broken lids

More than 20 patients came back with either a broken e-MuM lid or the microprocessor having recorded no events at all from the date of issue until their return visit. This was due to the malfunctioning microprocessor and meant that the lids had to be replaced.

6.3.5 Adjusting or censoring data

A decision not to censor data was taken during the data analysis phase. In this study the patients were not asked to keep a daily diary, and it was therefore impossible to determine the reason for non-adherence on any specific day or week.

The only documentation available for potentially censoring data was the monthly feedback questionnaire (reports) completed after interviewing patients at the end of last three months. Adjustments of e-MuM data might have been appropriate for specific patients. For example, Patient 24 in this study admitted not taking her e-MuM container on a long sports camp. She was afraid that her undisclosed HIV status would be discovered. She divulged this during the focus group discussion. This meant that periods existed in which the patients were not using the container (like at the start of the study when patients were still finishing medication issued before they joined the study). Another problem was the 20 plus patients who had broken e-MuM lids and no recorded data for periods during which they might have been adherent. These periods would now be regarded as “non-adherent” periods.

6.3.6 Decanting

One of the problems identified by both e-MuM and self-reported questionnaires, was a very varied and inconsistent pattern of decanting. Some patients reported up to four different decanting habits over the study period. Hence the self-reported decanting could not be used to verify any problems that might have occurred while using the e-MuM container.

6.3.7 Time constraints

The process of data collection during patients' monthly return visits was lengthy (as much as 20-45 minutes per patient). The result of this lengthy process was that patients had to wait, which was not acceptable to them. This waiting time was especially problematic when patients did not return on the scheduled days.

6.4 CONCLUSION

This section will address each of the objectives as set out in Chapter 1.

A total of 1243 visits were registered on the software programme for all patients enrolled in the study over the study period of eight months.

Objective 1: To measure the practicality of introducing the e-MuM system within the existing patient management process at the selected site.

Study process

- The study process was cumbersome due to the multifaceted study design and it was difficult to manage the logistics. In a conversation with data collectors the most troublesome and time consuming aspect seemed to be the completion of the questionnaire.
- Study patients became agitated when they had to wait longer than other patients. This aspect would not be present in a normal clinic situation with downloading of data being part of patients' morning registration for the day's clinic visit.

e-MuM System

- Management of the e-MuM system consisted of a very quick downloading of data. The issuing of the reminder unit was a once off occurrence and in an existing clinic system, only non-adherent patients would need to be counselled.
- One of the disadvantages of the e-MuM is the inability to monitor more than one drug per container. Due to the nature of ARV treatment, a cocktail of drugs is necessary (see Chapter 2, Section 2.9.3). The eMuM could therefore be used to monitor one of the drugs patients have difficulty in adhering to because of side effects or similar problems. Some fixed dose combinations in a single tablet have become more readily available (see Chapter 2, Section 2.11.1).

Objective 2: To compare the impact of the different components of the e-MuM system on the adherence process (electronic microprocessor embedded in container lid, reminder unit and verbal feedback)

Impact of data obtained from the electronic microprocessor embedded in container lid on the adherence process

- The downloaded data were made available to the doctors at the clinic but only a few of the doctors found any value in the data. One of the doctors said that they were duty bound to counsel all patients irrespective of adherence (see Chapter 5, Section 5.3.4). Education of the staff about the advantages of the kind of information might change this.

Impact of the reminder unit and feedback

- The increase in adherence for test group patients after the reminder units were issued was smaller than expected (see Table 4.5). The mean adherence (strict) increased by only 3.8%. The most significant mean adherence increase of 18.8% occurred from the start of the feedback phases till the end of the study (Phase 2 to 4).
- The study group was very positive about the function of the reminder unit but did not like the feedback they received. This was due to some of them only finding out about the monitoring function of the container lid during the feedback phases. Some of them also maintained that they were adherent even though computer generated graphs demonstrated a different picture. Due to the large number of broken lids, the study staff could not be sure of where the fault lay.

Objective 3: To test the effectiveness of this tool in the adherence process.

Statistical significance over the full study period

Table 6.1: Comparison of percentage adherence (full period) according to e-MuM data: test group vs. control group

Study Phase*	Test group		Control group		P**
	N	Median (%) Mean ± SD	N	Median (%) Mean ± SD	
Full Period (strict)	57	35.4 36.1±23.7	50	20.8 29.8±27.4	0.143 0.201
Full Period (lenient)	57	45.6 45.5±26.1	50	26.0 36.6±29.4	0.087 0.100

- In Table 6.1 the percentage adherence over the full study period of the test and control groups as measured by the e-MuM are shown to highlight the approach of statistical significance. The test group have higher average rates of adherence as judged by recorded events, For the full period, the test group mean strict adherence level was 36.1%, with lenient mean measure of 45.5%. The control group mean strict adherence for the full period was 29.8% and mean lenient adherence was 36.6%. The difference of the mean strict adherence between the test and control group over the full study period was 6.3% and difference in lenient adherence over the full was 8.9%. However due to large SD of between 20 and 30 the p-value for the full period mean strict adherence was 0.201 and for the lenient adherence increased to 0.100.

e-MuM system

- Some of the e-MuM data from adherent patients showed multiple openings on the same day, with twice daily opening before and after these incidents. These data entries might be due to excessive movement of the container, e.g. travelling in a bumpy, overcrowded taxi which might increase the registrations recorded by the microprocessor.
- The data generated by the e-MuM software do not reflect adherence as such. Data merely reflect container opening patterns. The data must be seen in the context of other findings, such as those collected by the questionnaires (see Appendices G and I), and of various constraints which were inherent to the use of this electronic adherence monitoring system at the specific study clinic. Some examples of these constraints are illustrated in Chapter 3, Section 3.4.

Objective 4: To test the ease of use for the patient and pharmacist.

e-MuM system

- The patients did not find the container difficult to open and the reminder unit was pre-programmed for them. Some of them did have to ask the staff to change the reminder alarm time for them. The patients from the focus group alluded to the fact that no “click” was heard to be certain the container closed properly.
- The e-MuM device did not present any problems for the pharmacist in the replacement of the normal lid with the special lid.
- Patients were asked to state whether, and if so, how often, they transferred any of their medication from the original container into any other containers or places, at any time, to facilitate easier access to their tablets. This behaviour, called “decanting”, may be used for the sake of convenience or to avoid being seen with

a container of tablets labelled as ARVs. (see Chapter 4, Section 4.3.6 and Table 4.9).

- The effectiveness of any electronic monitoring system depends on the users' taking of medication directly from the container and registering an "opening" or taking of medicine at the correct time.
- Variations of decanting behaviours emerged and changed over time for most of the patients. From decanting data available for a total of 209 patients, 145 reported at least two different types of decanting habits over the study period, with five patients who reported all four of the behaviours shown in Table 4.9 and Figure 4.8. This constant changing in decanting behaviour greatly complicated data interpretation.
- Self reported decanting habits and with the data recorded by the e-MuM system, were compared to see whether it was possible to adjust calculated adherence levels accordingly. It was found that the two sets of data did not always correlate at the individual level, and that adjustments would require making assumptions for each individual patient.
- Patients' self-reported decanting habits adherence levels were adjusted. Decanting practices do not appear to explain the low adherence levels calculated by the e-MuM system.

Study process

- Some strain was placed on the pharmacy staff to shorten the waiting period for, or give preferential treatment to study patients having already waited longer for data collectors to complete all the study instruments, compared to others not enrolled in the study.

<p>Objective 5: To make recommendations concerning adaptations to the e-MuM product and its use</p>
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- It was unanimous from all patients and staff that the size of the container was the biggest obstacle to the 'no decanting' requirement for optimum use of this adherence intervention tool. Patients removed medication doses when going to work and to maintain the secrecy of their status for fear of stigmatization.
- The sturdiness of the e-MuM lid with the microprocessor used for the study was questionable as can be seen in Table 6.2

Table 6.2: Reported e-MuM problems and errors

Equipment malfunction	Logistical /procedural problems			Patient loss		
e-MuM lid/device broken	Forgot e-MuM unit at home	Patient defaulted (longer than 3 months)	Family or friend collected medicine	Patient transfer out	Regimen change	Patient moved to ante-natal clinic
N=20	N=23	N=9	N=3	N=3	N=4	N=1

Objective 6: To make recommendations concerning the ideal use of the e-MuM system

- Some of the patients mentioned their willingness to use the e-MuM routinely because it kept them conscious of their medication regimen.
- The staff suggested that the e-MuM could be used during the initiation phase to ensure new patients are adhering to their ARVs as they should and then to reserve it for problem groups of non-adherent patients.
- See Recommendations below in Section 6.5.

Objective 7: To obtain views of the patients on this tool.

- Views of patients were gathered during the study and focus group discussion as reflected in Chapter 5.
- The two most important issues that bothered the patients was keeping their status secret and the size of the container being too big to hide and fit into handbags. The second issue was the dispute by patients from the test group about the accuracy of information used in feedback sessions (see Section 5.3.4).
- The test group patients did express a positive attitude towards using of the reminder unit.

Objective 8: To obtain views of the staff on this tool.

- Views from staff were gathered during the study and focus group discussion as reflected in Chapter 5.
- The head clinician remarked that African patients are not always truthful about problems, due to the fact that they did not want to offend the benefactors.
- One of the other doctors was sceptical about the routine use of the e-MuM because it was their duty to council all patients.

6.5 RECOMMENDATIONS

Based on the results of this study, suggestions from this researcher to increase adherence and utilize the e-MuM system include the following:

6.5.1 Medication regimen

- The ideal medication dose for patients would be once daily and to be electronically monitored a single tablet (fixed dose combination) would be the most advantageous. Change the dose intervals to a once daily regime and/or a fixed dose combination single drug.

6.5.2 e-MuM device

- For the e-MuM system to work effectively, the device (container with embedded micro chip) has to be small, portable and sturdy.

6.5.3 Patients

- Patients will have to be educated to take every dose from the e-MuM container (no decanting).
- Follow-up on all patients not keeping their appointments should be done by the social worker.
- When electronic monitoring is used to measure or monitor adherence, patients should be requested to keep a daily diary of their medication taking behaviour, including decanting of tablets.

6.5.4 Education

- Patients using e-MuM data need to understand the system and the importance of registration of all medication doses.
- For accurate and betimes data interpretation, a trained, dedicated person will be needed and this person has to be very sensitive about the HIV treatment and how to address non adherent patients.

6.5.5 Strategic role in NSP for e-MuM device

- The e-MuM could be made a strategic partner of the National Department of Health to improve management of HIV treatment. An allocation of 4% to 7% of the HIV and AIDS budget was earmarked (on a sustainable basis) for the Research, Monitoring and Surveillance (see Section 2.3.1).
- Data obtained could be used for individual patient's adherence monitoring in the clinics.

- The data obtained by the e-MyM system could also be supplied to improve pharmacovigilance information plan by the National Department of Health (see Section 2.3.1). A study published earlier this year involved three focus group discussions conducted with clinic staff in two towns in the Eastern Cape Province of South Africa. Some of the reasons for underreporting of adverse drug effects and patient non-adherence were high workload, lack of feedback and fears by staff of not being taken seriously (Ruud *et al.*, 2010). Some of these problems could be addressed by the e-MuM device. Adequate and continuous training in pharmacovigilance will lead to the subsequent increase in confidence among healthcare professionals managing patients in primary health care facilities on ARVs.

6.6 CLOSURE: PAINTING THE HIV AND ARV PICTURE

Patients receiving HAART from public health facilities (government hospitals, clinics and NGOs) find it increasingly difficult to afford basic necessities including food and transport fare. This has led to people not keeping appointments to renew prescriptions and not being able to afford food. A news article in Plus News on 18 August 2009 paints a picture of desperation in Uganda (PlusNews, 2009). A spokesperson from the TAC said in an interview with Mail and Guardian (Mail & Guardian, 2006) that people are not taking medicine to get better. He claimed that the reason for this is the way government structures the social grant at present. The TAC has proposed that all unemployed people be given a basic income grant (TAC, 2009). This would prevent HIV positive people being fearful of losing their grant when they got better.

The National Strategic Plan (NSP), which aims to give 80% of HIV-positive people access to ART by 2011, was allocated 11.4 billion rand in the HIV budget for 2009/10. The Institute for Democracy in South Africa (IDASA) reports that an affordability problem would make sustainable supply problematic, particularly in view of the recent recession and budget deficits (Mukotsanjera *et al.*, 2009).

Having knowledge and opportunity, but not applying it, is equal to flushing money down the drain. In a policy document, 'AIDS in Africa: Three scenarios to 2025', the WHO commented on the fact that by 2025 nobody under the age of 50 will know what a world without AIDS looked like. The legacy of a future generation will depend on how well this generation deals with this problem. Three different scenarios can emerge to cover different behaviour, conduct and outcomes.

The first scenario 'Tough choices: Africa takes a stand', discussed in this document from the WHO, paints a picture in which African leaders choose to take tough measures that reduce the spread of HIV in the long term, even if it means difficulties in the short term. Total HIV and AIDS spending grow rapidly until the year 2013, with a levelling off towards 2025. The biggest chunk of the HIV budget from 2014 will be spent on prevention, which should scale up rapidly.

A second scenario 'Traps and legacies: The whirlpool' followed on the first and could involve a picture of Africa failing to escape from its more negative inheritance and history with AIDS deepening and poverty, underdevelopment and marginalization.

The last scenario 'Times of transition: Africa overcomes' paints an African continent on which all of today's good intentions are translated into coherent and integrated development response necessary to tackle HIV and AIDS. The worst of the Pandemic's impact is still to come, but a great deal can be done to change the longer-term prospects of Africa and to soften the HIV impact on the medical and financial sectors. Immediate priority should be to reduce the overall numbers of people whom the pandemic will affect. Optimising antiretroviral therapy to stave off the development of resistance and to minimise side-effects will affect and curb HIV overspending and might just make the difference between poverty and prosperity for Africa (UNAIDS, 2005).

The first scenario described above is starting to materialise in the South African context – leaders are beginning to act positively in the fight against HIV/AIDS. It would be wonderful to hope that the first scenario could be translated into the third scenario, 'Africa overcomes – but it could equally slide into the second scenario, 'The whirlpool'.

This present study has emphasised the constraints which face the South African public sector health service. There was difficulty in introducing a technologically-based adherence tool as part of the ARV scale-up process in an already over-stretched clinic. The logistics of any new process are likely to be problematic in a situation where both staff levels and facilities are already overloaded.

Whilst the adherence tool mainly worked well, it would be unlikely to find general acceptance in the public sector. The eMuM system could be used beneficially for new or problem patients in the public sector. It could certainly play a strong role, in individualised patient care, in both public and private sector settings where the computer and counselling support systems are in place.

For the system to function optimally, it requires proper staff training regarding its use and interpretation of the data. It is also important to educate patients on how to read the adherence graphs.

Above all, the data interpretation needs to be coupled with a validated method for adjustment of data to compensate for varied decanting practices

An aspect that was not examined in this study was the compatibility of the eMuM software with other patient databases. This would have to be ensured to gain the maximum benefit from the system.

It must also be noted that over the study, both test and control groups improved in adherence. The role of added personal contact (through the study process) in the reinforcement of better adherence, cannot be ruled out and should not be under-estimated. This finding of the study serves to emphasise yet again the importance of proper patient counselling and support throughout treatment

The research done in this study contributes to a better understanding of the complex and dynamic nature of adherence.

Adherence is influenced by a cluster of inter-linked factors that can best be managed by a team of multidisciplinary professionals including doctors, pharmacists, nurses, social workers and various other care groups. Not least in this whole scenario is the role of the patient. Commitment by government and other role players can only succeed if individuals take responsibility to adhere to their own medication and healthy lifestyle routines.

Adherence has to be a way of life.

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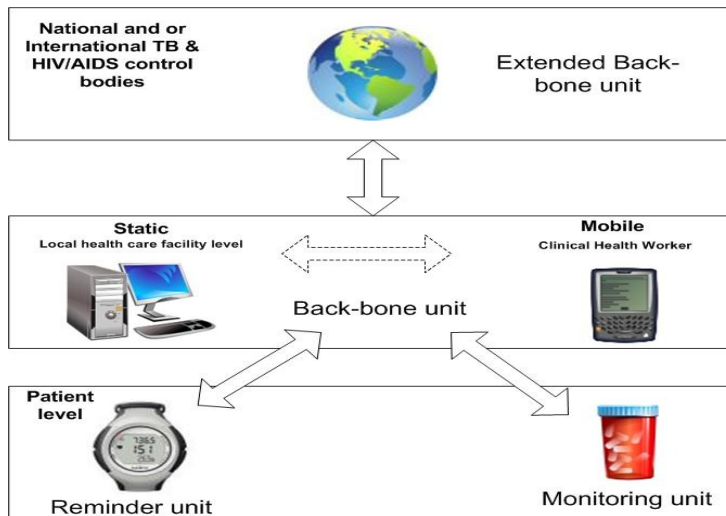
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Appendix A: An illustration of the e-MuM Device

An illustration of the e-MuM device:



<p>e-MuM Monitoring Unit</p> <ul style="list-style-type: none"> • Log usage of medicine content on rule set of uploaded prescription algorithm. • Non-volatile memory to log 8 months of usage data. • Battery powered. • Store patient's medical records and history on the unit. • Small enough to fit inside pill container's lid. • Robust – shock and water resistant. • Cost effective solution. • Mechanism to remind patient of next clinic appointment. • Assist in the monitoring of patient visiting and checking by field workers. 	<p>e-MuM Reminder Unit</p> <ul style="list-style-type: none"> • Mechanism to remind a patient when to take medication on rule set of prescription algorithm. • Mechanism to remind patient of next clinic appointment. • Battery powered - runs 5 years form single battery. • Non-volatile memory to store patient's medical records and history and the prescription algorithm on the unit. • Small enough to fit inside a watch, jewellery or an item that will not distinguish the patient from normal society. • Robust – shock and water resistant. • Cost effective solution. 	<p>e-MuM Backbone</p> <ul style="list-style-type: none"> • Hardware unit capable of processing, displaying and communicating. • Functions required by any TB and HIV/AIDS controlling body. • GUI interface to enter patient prescription algorithm. • Input and output facility to download and upload data from the monitoring and reminder system in remote locations. • Database capabilities of storing backup of patient data and history and prescription history. • Resource inventory software capable of predicting chemotherapy drug availability and prescribed programs. • Electronic booking system for patient visits. • Statistical analysis capabilities to process all relevant data to interpretable information. • All the above requirements must be able to be integrated with the already existing hardware in the public health care facilities.
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Appendix B: Data collector selection and training

Conducting Interviews, Recording Data and Transcribing of Recorded Data

1. Two data collectors (Lebogang Kgatuke and Xoliswa Mpofu) were identified to help with interviews, data collection, and capturing in this project. Their selection was based on the following: a. Involvement in previous projects (knowledge of research environment); b Knowledge of the local language and ability to speak English; c Ability to interact with people from different genders and ages
2. The role of the data collector in face-to-face interviews is of utmost importance because mistakes in this first phase of research may lead to errors rendering the whole research project futile (Babbie & Mouton, 2001:249).
3. An information week was held before the start of data collecting to familiarize everyone involved with the computer program developed by GEO (ICT) for data capturing in this project as well as to standardize the filling in of the questioners and clear up all questions regarding the procedures to be followed in the recruitment of test subjects at the pharmacy. The two data collectors were given the research proposal as well as relevant, additional material to study and were tested at the end of the information week, because familiarity with the questioner prevented stumbling over words and not knowing the intention of asking specific questions.
4. The low level of literacy of the South African society has made interviews essential to gather information in the research environment (Babbie & Mouton, 2001:249) Special care was taken to employ acceptable interview techniques but ethical aspects were kept in mind at all times.
5. One of the most important aspects is to keep the role of the interviewer as neutral as possible to have the least possible influence on the outcome of the answers to the questions and to yield information more or less "as it is" (Henning *et al.*, 2004:52) To do this it is important not ask leading questions or force the interviewee to confess facts for which they are not ready .
6. The interviewers were given detailed explanations on how to approach subjects, introduce themselves and close interviews. The appearance and demeanor of the interviewers are very important and according to Babbie & Mouton the most acceptable demeanor to most test participants is one of middle-class neatness and cleanliness.
7. Dealing with strangers it is very important to win the confidence of the person and keep societal differences in mind. Being friendly but not too casual will be strived for in establishing good rapport.
8. Allaying any notion that the information will be used in any way detrimental to the individual should be done during the first interview
9. Following the exact wording and refraining from interpretation as well as recording exact answers was stressed.

The data collectors were given time to ask questions and a trial session involving staff members of the Department of Pharmacy speaking the local language were envisaged but could be held due to campus unrest and lack of time. Questionnaires would have been completed during this trial session to test for standardization and consistency.

Data collector training for adherence interpretation (with and without reminder unit)

Phase 4

1. Equate the e-MuM container data with the data given on the Questionnaire.
2. If specific times seems to be a problem >>>suggestions
3. Enhance with patient the benefit of taking medication at the right time.
4. Reminder of drug failure consequences.

Appendix C1: Consent form (English)

University Of Limpopo (Medunsa Campus) Patient Consent Form

Statement concerning participation in a Research Project

Project*: THE ADHERENCE OF PATIENTS TO ARV MEDICINE AT THE TSHEPANG CLINIC, DR GEORGE MUKHARI HOSPITAL

I have been provided with information on 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 pressurized to participate in any way. I also agree to participate in one group discussion if needed.

I understand that participation in this project is completely voluntary and that I may withdraw from it at any time and without supplying reasons. This will have no influence on the regular treatment that holds for my condition neither will it influence the care that I receive from my regular doctor. I understand that the information provided will remain confidential.

I know that this Project has been approved by the Research, Ethics and Publications Committee of Faculty of Medicine, University of Limpopo (Medunsa Campus). 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 patient/volunteer Signature of patient/volunteer	
..... 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
-----------------------------	--------------------	---------------	----------------

** **Note:** The words "electronic monitoring device" has been deliberately omitted from the project title in the consent form, so as not to influence the patient's adherence behaviour.*

Appendix C2: Consent form (Setswana)

Yunibesith Ya Limpopo (Medunsa Campus) Foromo Ya Tetla Ya Molwetse

**Porojeke*: TIRISO YA BOIKANYEGO YA BALWETSE YA MOLEMO WA ARV KWA
TSHEPANG CLINIC, KWA SEPETLELENG SA DR GEORGE MUKHARI.**

Ke filwe tshedimisetso ka ga thuto e e tshitshintsweng, ka fiwa gape tshono ya go botsa dipotso, ka ba ka fiwa nako e e lekaneng ya akanya kgang e. Ke thlaloganya maikemisetso le maikaelelo a thuto e ka bophepa. Ke dumela gape gore ke tseye karolo mo puisanong ya sethlopha.

Ga ke a pateletsiwa le fa e le go patikiwa ka tsela e pe go tsaya karolo. Ke thlaloganya gore botsayakarolo mo porojekeng a ke jwa boithaupo ka bothlalo le gore ke ka nna ka intsha mo go yona ka nako nngwe le nngwe ntle le go fa mabaka. Go dira jalo ga go kitla go thlotheletsa thlokomelo e ke amogelang mo ngakeng ya me ya gale.

Ke thlaloganya gore botsayakarolo mo puisanong ya sethlopa le tshedimisetso e e filweng e tla nna khupamarama, gape ke thlaloganya le gore puisano e tla go kgatesiwa gomme dikgatiso le tsone di tla nna khupamarama.

Ke itse gore Porojeke e e rebotswe ke Komiti ya Dipatlisiso, Boitshwaro le Phasalatso (Research, Ethnic and Publications Committee) ya Lephata la Bongaka kwa Unibesithi ya Limpopo(Medunsa Campus). Ke itse ka botlalo gore dipholo tsa Porojeke e di tla diriswa mo mererong ya saense le gore di ka nna phasaladiwa. Ke dumelana le se, fa fela bosephiri jwa me bo ka thlomamisiwa.

Ke dumela go tsaya karolo mo Porojekeng ya Puisano e.

.....
Lena la molwetse/moithaopi

.....
Tshaeno ya molwetse/moithaopi

.....
Lefelo

.....
Lethla

.....
Mosupi

Polelo ka Mmatlisisi

Ke file tshedimisetso e e builweng ka molomo tebang le Porojeke e
Ke dumela go araba dipotso dipe tsa nako e e tlang tebang le Porojeke ka bojothle jwa
me
Ke tla tshegetsatsamaiso e e rebotsweng

.....
Leina la Mmatlisisi

.....
Tshaeno

.....
Lethla

.....
Lefelo

Appendix D: Pre-qualifying questions for patients before joining the study

Patients must be on Lamivudine and have had Cd4 count and viral load done in the last 30 days or be due in the next 30 days

Name of interviewer: _____
Name of facility: _____
File number _____
Study number: _____
Date: _____

} Complete before the interview

1. Do you use multiple pill boxes (weekly) to help you in remembering to take all your ARV medicines on time and every day?

Yes No

2. Will you be able to attend this clinic (Tshepang) at Dr George Mukhari hospital for the next 8 months, without being down referred to another clinic?

Yes No

3. Will you be able to attend this clinic (Tshepang) EVERY month for the next 8 months?

Yes No

Appendix E: Control sheet

MONTH	VISIT DATE
January	
February	
March	
April	
May	
June	
July	
August	
September	
October	
November	
December	

Appendix F: Flow chart e-MuM**Baseline (Months 1 and 2)**

	Activity period	Site	Staff	Activity
1	Friday/Monday/Tuesday	Computer room	L&X	Collect patient list from Thabiso for next day
2	Friday/Monday/Tuesday	Filing room	L&X&C	Identify eligible patients according to protocol criteria and mark files with pink sticker
3	Monday/Wednesday/Thursday	Receiving area for pharmacy	L&X	Take identified files from wire basket and call patient for interview
4	Monday/Wednesday/Thursday	Interview cubicle	L&X	Interview patients and fill in Appendix G1 or G2 (tablet count)
5	Monday/Wednesday/Thursday	Pharmacy	L&X	Give interviewed patient file to pharmacist for dispensing of prescription
6	Monday/Wednesday/Thursday	Interview cubicle	L&X	Enter patient name in register
7		Interview cubicle/home	C	Fill in Cii as identified to be done by pharmacist (Appendix G1)
8	Friday/Tuesday	Filing room	L&X	Collect files of already interviewed patients
9	Friday/Tuesday	Computer room	L&X	Enter patient details into Geo(ICT)software program

Phase 1 (Months 3 and 4)

Flow order	Activity period	Site	Staff	Activity
1	Once weekly(Wednesday)	Interview cubicle	C	Identify the number of patients due back for phase 1 in the next week
2	Once weekly(Wednesday)	Interview cubicle	C	Decant Lamivudine into e-MuM container
3	Once weekly(Wednesday)	Interview cubicle	C	Label Lamivudine into e-MuM container
4	Once weekly(Wednesday)	Interview cubicle	C	Place e-MuM container(Lamivudine) into plastic bag and staple unique given number to top of bag
5	Once weekly(Wednesday)	Interview cubicle	C	Place ready prepared containers in plastic bags into box and take to pharmacy storeroom.
6	Monday/Wednesday/Thursday	Interview cubicle	L&X	Take box with pre-prepared eMuM containers to 2 nd cubicle
7	Monday/Wednesday/Thursday	Receiving area for pharmacy	L&X	Take identified files from wire basket and call patient for interview
8	Monday/Wednesday/Thursday	Interview cubicle	L or X	Interview patients in 1 st cubicle and fill in Appendix G1 (tablet count)
9	Monday/Wednesday/Thursday	Interview cubicle	L or X	Take patient file to 2 nd cubicle (out of site) and enter patient details on eMuM control sheet and assign a e-MuM container to a patient
10	Monday/Wednesday/Thursday	Pharmacy	L&X	Give patient file with e-MuM container to pharmacist to be filled

Phase 2 (Months 5 and 6)

Flow order	Activity period	Site	Staff	Activity
1	Thursday 08 May 2008	Geo ICT	J	Identify whether the patient is in control or test group (Use computer printout of names.
2	Friday 09 May 2008	Patient register	H	Mark the names of the test and control groups with different colour markers
3	Monday 12 May 2008	Conference/Tea room Tsepang clinic	B&H	Meet with doctors and nurses to explain the issuing of reminder units to certain patients and reminder mechanism.
4a	Monday/Wednesday/ Thursday	Receiving area for pharmacy	L&X	Take identified files from wire basket and call patient for interview
4b	Monday/Wednesday/ Thursday	Receiving area for pharmacy	L&X	Pull previous questionnaires to ensure all questions have been answered
5a	Monday/Wednesday/ Thursday	Interview cubicle	L or X	Interview patients in 1 st cubicle and fill in Appendix G1 (tablet count)
5b	Monday/Wednesday/ Thursday	Interview cubicle	L or X	Check old outstanding questions for answers and compare recent answers with time in study
6 (test group)	Monday/Wednesday/ Thursday	Interview cubicle	L or X	Take patient e-MuM container to 2 nd cubicle (out of site) and download e-MuM information into the computer. Enter test patient details on eMuM control sheet and collect watch reminder from box. Program watch with patient's specific tablet taking schedule and next appointment date. Issue watch reminder to patient with detailed explanation on how to use the reminder
6a (test group) MONTH 5	Monday/Wednesday/ Thursday	Interview cubicle	L or X	Print adherence report on blue sheet after e-MuM information has been downloaded. Record patient's normal tablet removal from the container on the report at the bottom of the page and place in the patient's file, ready for Dr feedback at Month 6.
7 (control group)	Monday/Wednesday/ Thursday	Pharmacy	L&X	Give patient file with e-MuM container to pharmacist to be filled
8 (test group)	Monday/Wednesday/ Thursday	Pharmacy	L&X	Give patient file with e-MuM container to pharmacist to be filled.

Appendices

Phase 3 (Months 7 and 8)

Flow order	Activity period	Site	Staff	Activity
1	Tuesday, 3 June 2008	Tsepang Clinic	BS	Give information to the doctors and other staff involved on how patients will receive feedback
2	Date to be decided (before 14 July 2008)	Tsepang Clinic	H&B-L&X	Give training to the data collectors on feedback (test group and control group)
3	Monday/Wednesday/Thursday	Receiving area for pharmacy	L&X	Take identified files from wire basket and call patient for interview
4	Monday/Wednesday/Thursday	Receiving area for pharmacy	L&X	Pull previous sets of questionnaires to ensure that all questions have been completed
5a	Monday/Wednesday/Thursday	Interview cubicle	L or X	Interview patients in 1 st cubicle and fill in Appendix G1 (tablet count)
5b	Monday/Wednesday/Thursday MONTH 8	Interview cubicle	L or X	Record recent CD4 count and viral load from the patient's file. If lab results do not appear in the file, keep the file aside for follow-up later (see point 10)
5c	Monday/Wednesday/Thursday	Interview cubicle	L or X	Check old outstanding questions for answers and compare recent answers with time in study
6	Monday/Wednesday/Thursday	Laptop/Interview cubicle	L or X	Take patient e-MuM container to 2 nd cubicle (out of site) and download patient results collected during the previous time period into computer
7 (test group)	Monday/Wednesday/Thursday	Interview cubicle	L or X	Give feedback to patient about data collected in 4 month period. Test group briefed about influence of reminder unit on adherence rate.
8	Monday/Wednesday/Thursday MONTH 8	Interview cubicle	L or X	Collect the reminder units from test group. Collect e-MuM containers from test and control group
9	Monday/Wednesday/Thursday	Interview cubicle	L or X	Thank everybody for their participation in study.
10	Monday/Wednesday/Thursday FOR FILES WITH NO LAB RESULTS	Interview cubicle	L or X	Collect blood results from the data capturer for those patients whose results do not appear in their files.
11	Monday/Wednesday/Thursday	Pharmacy	L&X	Give patient file to pharmacist to be filled

Appendix G1: Interview with ARV users – baseline (English)

Name of interviewer: _____	} Complete before the interview
Name of facility: _____	
Group number _____	
File number _____	
Study number: _____	
Date: _____	

- Greet the patient and introduce yourself
- (Explain the purpose of the interview) You have come here today to get your ARV medication. We are doing some research to help patients to have better treatment. Would you have about half an hour to answer some questions, now, whilst you wait? This information would not go to anyone here at the clinic. We would also need about 5 minutes of your time at each of your next visits over the next six months
- (Consent form) If you are interested to help; we need you to sign a consent form. Would you mind signing this form to show that you agree to participate?
- Thank you very much. Because you are prepared to spend time with us, it will help to improve treatment and service.

1. Socio-demographic information on patient

a) Sex:

b) Age:

c) Highest level of education:

None / primary not completed	
Primary completed	
Secondary(Incomplete)	
Grade twelve	
Tertiary or vocational	

d) Marital status:

Single	
Married	
Divorced	
Separated	
Widowed	

Appendices

e) Do you have any children? Yes No

If yes, how many are still living with you? _____

f) Who do you live with?

Spouse	
Children	
Friends	
Parents	
Other.	

g) Do you own the house you stay in? Yes No

How long have you been staying there? _____

h) Are you employed? Yes No

i) If yes, where do work?

j) Do you receive a government pension or disability grant of any kind? Details

k) How do you get to the facility?

Taxi	
Bus	
Own car	
Walk	
Other	

l) How long do you take to get to the facility?

m) How much do you spend to get to the facility (including petrol for own car)?

n) And your lifestyle - are you a smoker?

o) Do you take alcohol? (If no – add “Not even occasionally?”)

2. Medical history of patient

a) When were you first tested HIV+?

b) When did you start treatment for HIV (HAART)?

c) Since you started treatment, are you feeling?

Better	
Same	
Worse	

Explanation

3. Assessment of adherence and non-adherence

We are trying to find out how patients manage to take their medicines – for some people it's not a problem, but we also know that others don't always find it easy. Please feel free to be open about the problems you face with this. Everything you say here will remain confidential, and will not be shared with anyone at the clinic.

a) Do you have your medicines with you? May I see them? Please can you tell me when you take each of the medicines?

Drug A: _____

How is it taken? _____

Drug B: _____

How is it taken? _____

Drug C: _____

How is it taken? _____

Drug D: _____

How is it taken? _____

Appendices

b) Are there any other medications you are taking? (e.g. cotrimoxazole, herbs, immune boosters, chronic medication for example hypertension, diabetes, etc)

Yes No

Specify _____

c) i) Now remember the last seven days. Did you miss any pills in that time? If yes, how many?

Drug A _____ Drug B _____ Drug C _____ Drug D _____

d) ii) Now try and remember the last two days. When did you take each medicine, and when did you have meals? Mark with crosses below:

Yesterday

	am					1 pm														
	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Please mark with crosses on each line when you took:																				
- Drug A																				
- Drug B																				
- Drug C																				
- Drug D																				
Meals																				

Day before yesterday

	am					1 pm														
	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Please mark with crosses on each line when you took:																				
- Drug A																				
- Drug B																				
- Drug C																				
- Drug D																				
Meals																				

Postgrad to complete:

	Yesterday:			Day before yesterday:		
	Pills taken	Pills on time	Pills according to food requirements	Pills taken	Pills on time	Pills according to food requirements
Drug A				A		
Drug B				B		
Drug C				C		
Drug D				D		

e) iii) The line below is a scale of how well people manage to take their ARVs. It goes from “never take any of the ARVs” to “always take all the ARVs”. Where would you make your own mark on this line for taking ARV's the past month?

Never take take	Always
10cm	

f) i) We understand how difficult it can be to take pills on a daily basis. If you sometimes miss a dose, please can you tell me what causes this to happen? Can you give an example or two? (Include even if ‘simply forgot’.)

ii) If the answer to question i) does not correlate with the mark on the line then proceed to ask if the answer for i) was for the last month.

Give the patient a second chance to make a mark (2 marks on the line). **Mark which answer was first.**

g) On the other hand, what is it that *helps* you to take your pills regularly and on time? (e.g. organizations, individuals, clock etc)

h) Please describe your daily tablet-taking routine to me (try to identify if patient decants the day's supply of tablets from the bulk container)

i) Have you disclosed your status to any one? If so, who? Do they help you to take your pills? [If not covered in (e)]

j) *Have you had your treatment changed at any moment since you started on ART? If yes, why? (e.g. treatment failure, side effects)

k) Have you ever missed an appointment at your ART clinic? (Reasons and details on type of consultation: review/refill etc.)

l) Have you ever thought about stopping ART? If yes, details.

4. Do you have any questions for me?

Thank you for your time and co-operation!

Tablet Count

DRUG A Name:	
DRUG B Name:	
DRUG C Name:	
DRUG D Name:	

Appendix G2: Interview with ARV users - baseline (Setswana)

POTSOLOTSO LE BADIRISI BA ARV (ntlha ya tshimologo)

Leina la mmotsolosi: _____
 Leina la lefelo: _____
 Nomoro ya faele: _____
 Nomoro ya thuto: _____
 Letlha: _____

} Tlatsa pele ga potsolotso

- Dumedisa molwetse o be o ikitsise
- (Tlhalosa lebaka la potsolotso) O tlile fa gompieno go tsaya molemo wa ARV wa gago. Re dira patlisiso go thusa balwetse go tokafatsa kalafi ya bona. A o ka nna le seripa sa ura go araba dipotso dingwe, jaanong, o sa ntse o letile? Tshedimoseto e ga e ka ke ya isiwa go ope mo tliniking. Re tla tlhoka metsotso e le metlhano ya gago ka nako tsotlhe fa o etela tliniki mo dikgweding tse thataro tse di latelang tsa go etela tliniki.
- (Foromo ya tetla) Fa o kgatlhegela go thusa, re go tlhoka gore o saene foromo e. A o ka nna le mathata go ka saena foromo e go bontsha fa o dumela go tsaya karolo?
- Re go leboga thata. Gonne o iketleeditse go tsaya lobaka le rona, go tla thusa go tokafatsa kalafi le tirelo.

1. Tshedimosetso ya loago le dintlha tsa botshelo jwa molwetse

a) Bong:

b) Dingwaga:

c) Thuto e o e fitlheletseng:

Ga go epe / ga a wetsa poraemari	
O weditse poraemari	
Sekontari (ga a e wetsa)	
Setlhopla sa bolesomepedi	
Thuto tse dikgolwane kgotsa thuto ya ditiro tsa diatla	

d) Kemo ya nyalo:

Ga a nyala/nyalwa	
Nyetse/nyetswe	
Tlhalane	
Kgaogane	
Swetswe	

e) A o na le bana? Ee Nnyaa

Fa e le Ee, ke ba ba kae ba ba santseng ba nna le wena? _____

f) O nna le mang?

Monna/mosadi wa me	
Bana	
Ditsala	
Batsadi	
Ba bangwe	

g) A ntlo e o nnang mo go yona ke ya gago? Ee Nnyaa

Ke nako e kae O nna mo go yona? _____

h) A o thapilwe? Ee Nnyaa

i) Fa e le Ee, o thapilwe kwa kae?

j) A o amogela phenšene ya puso kgotsa kabelo ya bogole bongwe? Dintlha

k) O tsamaya jang go fitlha mo lefelong la botihatlhobelo?

Tekesi	
Bese	
Koloi ya me	
Dinao	
Tsa dingwe	

l) O tsaya lobaka lo lo kae go fitlha kwa o tthatlhobelwang teng?

m) O dirisa madi a makae gore o fitlhe mo lefelong la botlhatlhobelo?

n) Mokgwa wa botshelo jwa gago – A o goga motsokwe?

o) A o nwa bojalwa? (Ga ele nnyaa – tlatsa.”Le e seng ka sewelo”)

2. Hisetori ya bongaka ya molwetse

a) O tlhatlhobilwe lwa ntlha leng gore o HIV+?

b) O simolotse kalafi ya HIV(HAART) leng?

c) Fa e sale o simolotse kalafi, a o ikutlwa o le?

Botoka	
Tshwana	
Ekegetse	

Tlhaloso

3. Tlhatlhobo ya kobamelo ditaelo le botlhoka-kobamelo jwa ditaelo

Re leka go batlisisa gore balwetse ba kgona jang go nwa melemo ya bona – mo batong bangwe ga go na bothata, mme re itse gape gore ba bangwe ga ba bone go le botlhofo ka metlha yotlhe. Tsweetswee gololosega go mpolelela mathata a o lebaganang le ona ka seno. Sengwe le sengwe se o tla se buang fa se tla bolokwa se le sephiri, e bile ga se ka ke sa abelanwa le ope mo tliniking.

a) A o tshotse melemo ya gago? A nka e bona? Tsweetswee mpolelela gore o nwa epe ya melemo e leng?

Molemo A: _____

O nowa jang? _____

Molemo B: _____

O nowa jang? _____

Molemo C: _____

O nowa jang? _____

Molemo D: _____

O nowa jang? _____

b) A go na le molemo mengwe gape e o e nwang ? (seka. cotrimoxazole, ditlhatshana, molemo wa madi a a kwa godimo, bolwetse ba sukiri, jalo jalo)

Ee Nnyaa

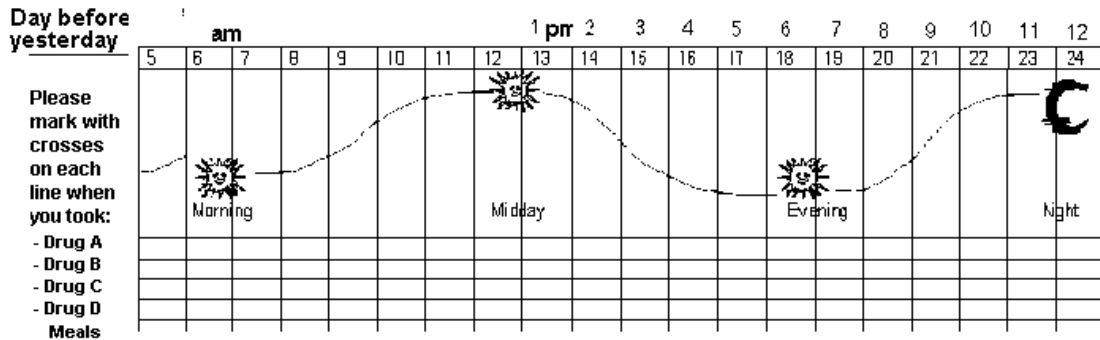
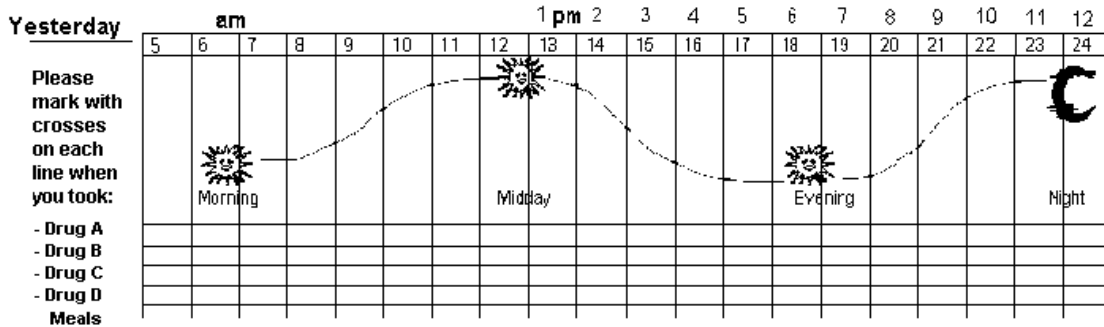
Totobatsa _____

c) I) Jaanong gopola malatsi a a supa a a fetileng. A o kile wa tlodisa go nwa pilisi nngwe nako nngwe? Fa e le Ee, tse kae?

Molemo A _____ Molemo B _____ Molemo C _____ Molemo D _____

d) ii) Jaanong leka go gopola malatsi a mabedi aa fetileng. O nwele molemo morgwe le mongwe leng, gape o jele leng? Tshwaya ka difapaano fa tlase:

Appendices



Data collector to complete:	Yesterday:			Day before yesterday:		
	Pills taken	Pills on time	Pills according to food requirements	Pills taken	Pills on time	Pills according to food requirements
	Drug A			A		
	Drug B			B		
	Drug C			C		
Drug D			D			

e) iii) Mola o o fa tlase o ke sekala sa gore batho ba kgona jang go nwa di ART tsa bona. Se simolola ka “Ga a nke a nwa” se feleetse ka “Nwa ka metlha yotlhe”. O tla baya lotshwao lwa gago fa kae mo moleng o la go nwa melemo ya ARV hgwedi e e fetileng?

Ga a nke a nwa	10cm	Nwa ka metlha yotlhe

f) i) Re tlhaloganya gore go ka nna boima jang go nwa melemo ka letsatsi lengwe le lengwe, ga ele gore nako nngwe o tlovisa go nwa pilisi tswetswee, a o ka mpolelela gore ke eng se se bakang tiragalo e? A o ka naya sekao kgotsa tse pedi? (Akaretsa: le fa e le “ke ne ke lebetse”)

ii) Fa karabo ya potso, ga e tshwane le karabo ya mo laeneng. E fa molwetsi monyetla/tshone ya go kgetha gape. (Kgetha ga bedi mo laeneng). Jaanong tswela pele o botsa ka karabo ya ya kgwedi e e fetileng.

g) Ka fa letlhakoreng le lengwe, ke eng se se go *thusang* go nwa dipilisi tsa gago ka metlha le metlha e bile ka nako? (sekai, mekgatlho, batho tshupanako, jalo jalo)

h) Tsweetswee ntlhalosetse mokgwa wa letsatsi le letsatsi wa go nwa pilisi. (leka go bona gore a molwetse o tshela dipilisi tse a di nwang letsatsi le letstsi go tswa mo setshelong se segolo go ya mo go se sennye)

i) A o boleetse mongwe boemo ja gago? Ga go le jalo, mang? A ba go thusa go nwa dipilisi tsa gago? [fa e sa akarediwa mo go (e)]

j) *A o kile wa fetola kalafi ya gago ka motsi mongwe fa e sale o simolola go nwa ART? Fa go le jalo, goreng? (sekai. Go tlholega ga kalafi, ditlamorago)

k) A o kile wa tlodisa go tla kwa tlilining ya gago ya ART? (Mabaka le dintlha ka mokgwa wa therisano: thadiso/tlatso-gape jalo jalo)

l) A o kile wa nagana go tlogela ART? Fa gole jalo, neela dintlha.

m) A o na le dipotso tse o ka mpotsang tsona?

Ke lebogela nako ya gago le tirisano mogo ya gago

Appendix H: Wording for issue of reminder unit

Wording for issue of Reminder Unit (Watch)

To help you remember to take your medicines, we would like you to use this watch until the end of the study. Not all the people in the study will be getting the watch to use, so please do not discuss it with other patients.

The watch has two alarms that we will set for you. One alarm will remind you to take your medicines in the morning and the evening. There is another alarm that we will set to remind you to come to come for your next clinic visit.

Demonstrate how to use watch.

Appendix I1: Interview with ARV users – final (English)

Name of interviewer: _____	} Complete before the interview
Name of facility: _____	
File number _____	
Study number: _____	
Date: _____	

We are trying to find out how patients manage to take their medicines – for some people it’s not a problem, but we also know that others don’t always find it easy. Please feel free to be open about the problems you face with this. Everything you say here will remain confidential, and will not be shared with anyone at the clinic.

a) Now remember the last seven days. Did you miss any pills in that time?

Yes No

If yes, how many?

Drug A _____ Drug B _____ Drug C _____ Drug D _____

b) The line below is a scale of how well people manage to take their ARVs. It goes from “never take any of the ARVs” to “always take all the ARVs”. Where would you make your own mark on this line for taking ARV’s the past month?

Never take take		Always	
10cm			

c) i) We understand how difficult it can be to take pills on a daily basis. If you sometimes miss a dose, please can you tell me what causes this to happen? Can you give an example or two? (Include even if ‘simply forgot’.)

ii) If the answer to question i) does not correlate with the mark on the line then proceed to ask if the answer for question i) was for the last month.

Give the patient a second chance to make a mark (2 marks on the line).

Mark which answer was first.

d) On the other hand, what is it that helps you to take your pills regularly and on time? (e.g. organizations, individuals, clock etc)

Appendices

e) Please describe your daily tablet-taking routine to me. (Patient normal tablet removal from main container):

Twice daily
Daily
Weekly
Other

f) Medication brought back by patient? Yes No

Tablet Count

NAME	CORRECT(ORIGIN AL)CONTAINER	OWN CONTAINER	SEPARATE/ TOGETHER	QUANTITY
DRUG A Name:				
DRUG B Name:				
DRUG C Name:				
DRUG D Name;				

Remind patient to bring medication back on every visit.

Thank you for your time and co-operation!

Appendix I2: Interview with ARV users – final (Setswana)
MAMETLELELO YA C1

POTSOLOTSO LE BADIRISI BA ARV (morago ga ntlha ya tshimologo)

Leina la Mmotsolotsi: _____
 Leina la lefelo: _____
 Nomoro ya faele: _____
 Nomoro ya thuto: _____
 Letlha: _____

} Tlatsa pele ga potsolotso

- Dumedisa molwetse o be o ikitsise.
- (Tlhalosa maikaelelo a potsolotso) O tsile fano gompieno go tsaya moriana wa ARV Re dira dipatlisiso go thusa balwetse go amogela kalafi e e botoka. A o ka nna le seripa sa ura go araba dipotso dingwe, jaanong, fa o sa ntse o letile? Tshedimosetso e ga e ka ke ya ya go ope mo tliniking. Re tla tlhoka gape metsotso eka nna tlhano(5) ya nako ya gago ka nako nngwe ya go etela tliniki mo dikgweding tse thataro tse di tlang.
- (Foromo ya tetla) Fa o na le kgatlhego go ka thusa, re go tlhoka gore o saene foromo e. A o tla belaela go ka saena foromo e go bontsha fa o dumela go tsaya karolo?
- Ke go leboga thata. Ka gonne o iketleeditse go tsaya lobaka le rona, e tla thusa go tokafatsa kalafi le tirelo.

1. Thatlhubo ya kobamelo ditaello le botlhoka-kobamelo jwa ditaello

Re leka go batlisisa gore balwetse ba kgona jang go nwa melemo ya bona – mo batong bangwe ga go na bothata, mme re itse gape gore bangwe ga ba bone go le botlhofo ka metlha yotlhe. Tsweetswee gololosega go mpoletlela mathata a o lebaganang le ona ka seno Sengwe le sengwe se o tla se buang fa se tla bolokwa se le sephiri, e bile ga se ka ke sa abelanwa le ope mo tliniking.

a) A o tshotse melemo ya gago? A nka e bona? Tsweetswee mpoletlela gore o nwa epe ya melemo e leng?

Molemo A: _____

O nowa jang? _____

Molemo B: _____

O nowa jang? _____

Molemo C: _____

O nowa jang? _____

Molemo D: _____

O nowa jang? _____

b) A go na le melemo mengwe gape e o e nwang? (seka. cotrimoxazole, ditlhatshana, molemo wa madi a a kwa godimo, bolwetse ba sukiri, jalo jalo)

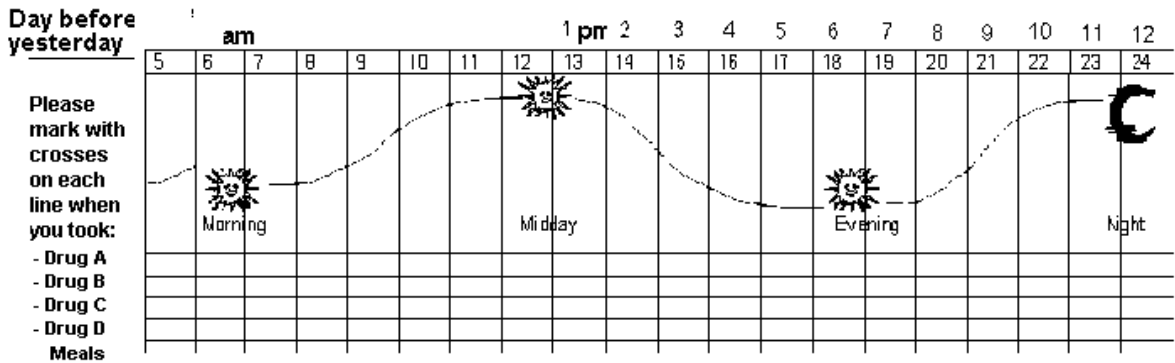
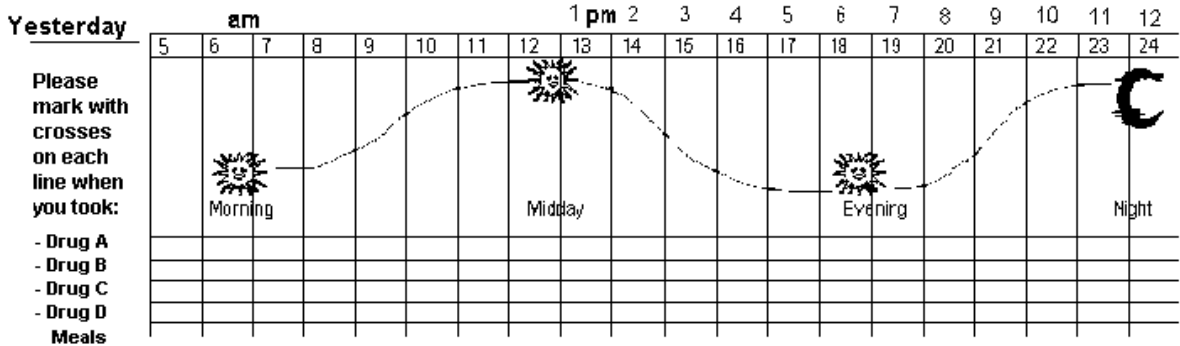
Ee Nnyaa

Totobatsa _____

c) i) Jaanong gopola ka malatsi a a supa a a fetileng. A o kile wa tlovisa go nwa pilisi nngwe nako nngwe? Fa e le Ee, tse kae?

Molemo A _____ Molemo B _____ Molemo C _____ Molemo D _____

d) ii) Jaanong leka go gopola malatsi a mabedi a a fetileng. O nwele molemo morgwe le mongwe leng, gape o jele neng? Tshwaya ka difapano fa tlase:



Data collector to complete:

	Yesterday:			Day before yesterday:		
	Pills taken	Pills on time	Pills according to food requirements	Pills taken	Pills on time	Pills according to food requirements
Drug A				A		
Drug B				B		
Drug C				C		
Drug D				D		

e) iii) Mola o o fa tlase o ke sekala sa gore batho ba kgona jang go nwa di ART tsa bona. Se simolola ka “Ga a nke a nwa” se feleletse ka “Nwa ka metlha yotlhe”. O tla baya lotshwao lwa gago fa kae mo moleng o la go nwa melemo ya ARV kgwedi e e fetileng?

|-----|

Ga a nke a nwa **10cm** **Nwa ka metlha yotlhe**

f) i) Re tlhaloganya gore go ka nna boima jang go nwa melemo ka letsatsi lengwe le lengwe, ga ele gore nako nngwe o tlovisa go nwa pilisi tsweetswee, a o ka mpoletlela gore ke eng se se bakang tiragalo e? A o ka naya sekao kgotsa tse pedi? (Akaretsa: le fa e le “ke ne ke lebetse”)

ii) Fa karabo ya potso, ga e tshwane le karabo ya mo laeneng. E fa molwetsi monyetla/tshone ya go kgetha gape. (Kgetha ga bedi mo laeneng). Jaanong tswela pele o botsa ka karabo ya kgwedi e e fetileng.

Appendices

g) Ka fa letlhakoreng le lengwe, ke eng se se go *thusang* go nwa dipilisi tsa gago ka metlha le metlha e bile ka nako? (sekai, mekgatlho, batho tshupanako, jalo jalo)

h) Tsweetswee ntlhalosetse mokgwa wa letsatsi le letsatsi wa go nwa pilisi. (leka go bona gore a molwetse o tshela dipilisi tse a di nwang letsatsi le letstsi go tswa mo setshelong se segolo go ya mo go se sennye)

i) A o boleetse mongwe boemo ja gago ga e sale re bolela nako e efitileng? Ga go le jalo, mang? A ba go thusa go nwa dipilisi tsa gago? [fa e sa akarediwa mo go (e)]

j) *A o kile wa fetola kalafi ya gago ka motsi mongwe fa e sale o simolola go nwa ART re bolela kgwedi e e fetileng? Fa go le jalo, goreng? (sekai. Go tlolega ga kalafi, ditlamorago)

k) A o kile wa tlovisa go tla kwa tiliniking ya gago ya ART? (Mabaka le dintlha ka mokgwa wa therisano: thadiso/tlatso-gape jalo jalo)

l) A o kile wa nagana go tlogela ART? Fa gole jalo, neela dintlha.

m) Molwetse o tlile le melemo ? Ee Nnyaa

Tablet Count

LEINA	SETSHELO NTHLA	SA	SETSHELO SA GAGO	AROGANA/KOPANYA	BOLENG
Molemo A Leina:					
Molemo B Leina					
Molemo C Leina:					
Molemo D Leina;					

A o na le dipotso dingwe tse ka di mpotsang?

Ke lebogela nako ya gago le tirisano mmogo ya gago

Appendix J: ART Adherence Report

ART Adherence Report

Adherence: 91.4%

June 8, 2008

The patient's current regimen (Other) started on 25 January 2008:

Drug:	Strength:	Interval:	Time:	Dosage Form:	Monitored:
Stavudine	40mg	12 hourly	08:00:00	Capsules	No
Lamivudine	150mg	12 hourly	07:00:00	Tablets	Yes
Efavirenz	600mg	At night	20:00:00	Tablets	No

Since adherence monitoring started on 17 April 2008, the patient recorded 69 events. A total of 58 events were required and 53 events were in the correct time windows. 3 dosages were skipped. The overall adherence percentage is 97.6%.

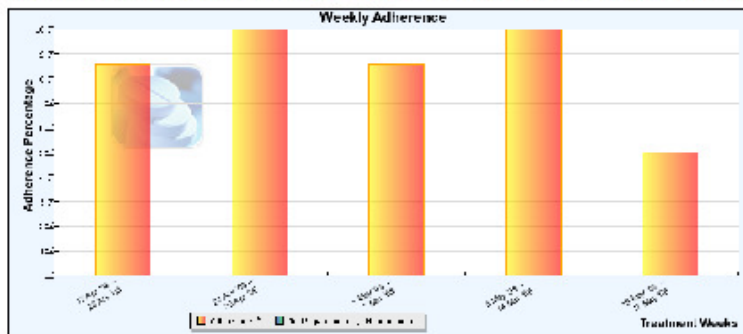


Figure 1: Weekly Adherence Graph

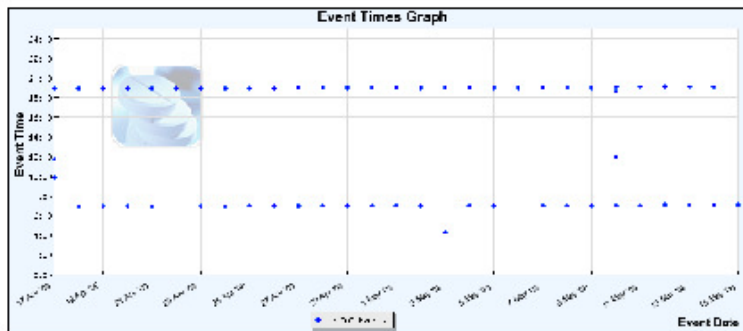


Figure 2: Event Times Graph

Note: The above adherence data has been calculated up to the date of 15 May 2008.

Patient normal tablet removal from main container: Twice daily; Daily; Weekly; _____

Signature of GP giving feedback _____ Date _____

Signature of Data Capturer _____ Date _____

CONFIDENTIAL

Page 1 of 1

Appendix K: Adherence feedback report form

Patient #:

Date of report:

Notes: Good (**green** highlighter)
Could do better (**pink** highlighter)
Needs explanation (**yellow** highlighter)

1. Good week (**green** highlighter)-well done
2. Not such a good week according to record (**pink** highlighter) - what happened?

a. Do you open your container according to a routine?	Y/N
b. Do you take your medication at the same time every day?	Y/N
c. Do you take your medicine every day?	Y/N

3. Information missing (**yellow** highlighter) - what happened on these days (period)?
(Please ask patient).

4. Missed visits. This form shows that you missed some visits. Did you collect medicine on all your appointment dates?

5. The record shows you only opened your container once after you received your medicine. Where do you store your medicine for daily use?

Comments from patient (Please ask patient)

Report prepared by:

1. Dr Beverley Summers
2. Dr Hannelie Meyer

Department of Pharmacy University of Limpopo Tel: 0125214673

Appendix L: Focus group guides

A. PATIENT GROUP TOPICS (QUESTIONS)

Question 1 - e-MuM Monitoring Unit (tablet container)

- What did you think about the container in which you received your Lamivudine the past 9 months?
- Probe for ease of use (opening and closing)
- Probe for size and portability
- Did knowing the opening and closing of the container are being monitored, make you feel any different about remembering to take your ARVs? Prompt
- Do you have any other comments about the container?

Question 2 – Reminder Unit

- What did you think about the reminder unit (watch) that was given to you?
- Probe for ease of use
- Did it affect your tablet taking routine? How?
- Did you use any other method / device to remind you to take your ARVs together with the reminder unit? Specify
- Do you have any other comments or suggestions about the reminder unit?

Question 3 – Feedback

- Did the feedback on how you were taking your ARVs affect your tablet taking routine in any way? How?

Question 4

- How do you think you will be affected now that you do not have the e-MuM device/container anymore?

Question 5

- Was the period during which you knew you were monitored and receiving feedback, long enough to change your tablet taking behaviour?

B. STAFF GROUP TOPICS (QUESTIONS)

Question 1 - e-MuM Monitoring Unit (tablet container)

- Before the study started, did you have any specific expectations of the study?
- How did you think using the e-MuM container would influence the patients' adherence?
- Did you pick up any comments – positive or negative from patients about being in the study?
- Did you pick up any comments – positive or negative from patients about not being in the study?
- Did patients' make any comments about the container?
 - Ease of use
 - Size and portability

Question 2 - Reminder Unit

- How did you think using the reminder unit would influence the patients' adherence?
- Did you pick up any comments – positive or negative from patients about being issued/not issued with the reminder unit?
- Did patients' make any comments about the reminder unit?
 - Ease of use

Question 3 - Feedback

- Did the availability of feedback and graphs affect your interaction with the patient?
- What is your opinion about providing objective feedback to patients on their tablet taking routine?
- Did you experience any difference in adherence from the patients during (beginning to end) the study?

Question 5 - Adherence

- What do you think is the role of electronic monitoring units (monitoring unit and software) and objective feedback in a clinic like this?
- What is your opinion on using the e-MuM container for all patients or specific groups of patients on ART?

Question 6 - Having dealt with patients using the e-MuM unit and feedback, how did you feel about dealing with patients not using the unit (not in study)?

Appendix M: Data analysis request for Geo-ICT

Data analysis

Part 1

Descriptive demographics

**Phase 1 - Total enrollees and then when divided (done before phase 2 started) into test and control group (comparison with start group is retrospectively).

Phase 2 - Test and control group

Phase 3 - Test and control group

***Phase 4 – Test and control group and total enrollees left in study

The following independent variables to be used

- a. Age
- b. Gender
- c. Marital status (can change during study)
- d. Education level (can change during study)
- e. Employment status (can change during study)
- f. Time on ARV's

The following groups (sub groups) were identified.

a. Age: 18-29

30-39

40-49

50+

* Another consideration is to compare young and old (cut-off 35 years)

b. Gender: Male/female

c. Marital status: Single (divorced/widowed)

Married (partner)

d. Education level: Primary level up to and including grade 7

Secondary level from grade 8 upwards

e. Employed/unemployed

f. Less or more than 12 months on ARV's

**The control and test groups for the baseline phase (done before e-MuM was issued) will have to be compared for Descriptive data, self reporting and clinical data to show that both groups were equal at the start of the study

***The number of patients left in phase 4 will determine the number of patients that can be

compared per phase (eg. 25 compared with 25)

Part 2

Could change though the course of the study

Control vs study group by phase for strict and lenient adherence criteria for above demographics and independent variables.

Measure the **change** in adherence by phase (over the whole period of the phase) and get an average or take a single point in time.

This would mean that the adherence for a patient compared with a dependent variable in every phase would have to be looked at and then compared to the average adherence during the whole study period.

e-MuM baseline vs reminder

e-MuM baseline vs Feedback I & II

Reminder vs Feedback I & II

The following dependent variables were identified:

- a. % of doses taken correctly according to either strict or lenient adherence criteria (within 1 hour of dose time vs during the day-any time) within phases
- b. Phases
 - i With e-MuM container (Months 2-4)(e-MuM baseline)
 - ii. Reminder unit Phase (Months 4-6)
 - iii. Feedback Phase (Months 6-8)

Table 3.1: Study phases

Phases	Study period: months	Procedures for test and control groups	
Baseline	1 and 2	Study population enrolment: n=210 (target n=300) Monitor (Adherence: VAS, 2- and 7-day recalls; Clinical data: CD4 count, viral load) Ensure accurate contact details of patients for device retrieval in case of default.	
1	3 and 4	Start Phase 1: Issue e-MuM container Monitor (Adherence: VAS, 2- and 7-day recalls)	
		Control Group: n=105 (target n=150)	Test Group: n=105 (target n=150)
2	5 and 6	Monitor (Adherence: VAS, 7-day recall and electronic monitoring system). Start using new shortened questionnaire	Start Phase 2: Issue reminder unit and give training. Monitor (Adherence: VAS, 7-day recall and electronic monitoring system). Start using new shortened questionnaire
3	7	Monitor (Adherence: VAS, 7-day recalls and electronic monitoring system)	Start Phase 3: Do counselling, give Feedback I Monitor (Adherence: VAS, 7-day recalls and electronic monitoring system)
4	8	Monitor (Adherence: VAS, 7-day recalls and electronic monitoring system; Clinical data: CD4 count, viral load)	Start Phase 4: Do counselling, give Feedback II Monitor (Adherence: VAS, 7-day recalls and electronic monitoring system; Clinical data: CD4 count, viral load)
		End Phase 4: Do counselling and give Feedback III Monitor (Adherence: VAS, 7-day recall and electronic monitoring system)	

Phase 1: After issuing the e-MuM unit until issuing the reminder unit

Phase 2: After issuing the reminder unit (test group only) until before Feedback I

Phase 3: After Feedback I until Feedback II (Feedback was given to Test Group only)

Phase 4: After Feedback II, until Feedback III (Feedback given to both groups at Feedback III)

Part 3

Correlation between e-MuM end adherence vs change in CD4, viral load and weight

Comparison of independent and dependent variable to

a. Clinical markers (comparison between start and finish of study)

i. CD4 ii. Viral load iii. Weight

Adherence (e-MuM) vs CD4 (should ideally increase)

Adherence (e-MuM) vs viral load (should ideally decrease)

Adherence (e-MuM) vs weight (should ideally increase)

Part 4

Adherence recall

Correlation between self reported adherence and e-MuM evidence for each phase

b. Adherence recall

i. 2 day recall (2 days only) – Do only one month to show uselessness!!

ii. 7 day recall (7 days only)

iii. VAS (is the perception 24 hours or adherence as a whole?)

Appendix N1: MREC Clearance Certificate


Spare copy

UNIVERSITY OF LIMPOPO
Medunsa Campus

MEDUNSA CAMPUS RESEARCH & ETHICS COMMITTEE

FACULTY OF HEALTH SCIENCES

CLEARANCE CERTIFICATE


P O Medunsa
Medunsa
0204
SOUTH AFRICA
Tel: 012 - 521 4000
Fax: 012 - 560 0086

MEETING: 03/2007 **PROJECT NUMBER:** MCREC/H/62/2007: PG

PROJECT Title: The impact of an electronic medication monitoring device on the adherence of patients to anti retroviral medication at the Wellness Clinic, Rustenburg hospital

Researcher: Ms CJ Engelbrecht

Supervisor: Dr B Summers, Dept. of Pharmacy

Co-supervisor: Mrs JC Meyer, Dept. of Pharmacy

Hospital Superintendent: Dr Sein (Rustenburg Hospital Rustenburg)

Department: Pharmacy


School: School of Health Care Sciences


Degree: MSc (Med) Pharmacy

DATE CONSIDERED: August 08, 2007

DECISION OF THE COMMITTEE:
REPC approved the project.

DATE: August 22, 2007

PG 
PROF GA OGUNBANJO
DIRECTOR: RESEARCH & CHAIRPERSON



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 N2: Change of study venue

UNIVERSITY OF LIMPOPO

Medunsa Campus

Prof GA Ogunbanjo
Director: Research & Chairperson
P.O.Box 210
University of Limpopo
Medunsa Campus, 0204

☎: (012) 521-4307
Fax: (012) 521-5811
E-mail: repcmed@ul.ac.za

Dr B. Summers
Department of Pharmacy
School of Health Care Sciences
Medunsa Campus
0204

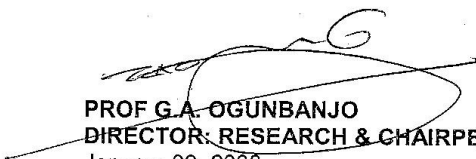
Dear Dr Summers

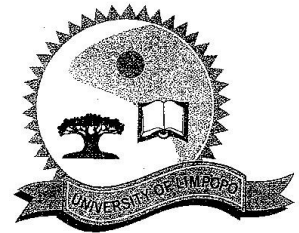
**RE: CHANGE OF STUDY VENUE - IMPACT OF AN ELECTRONIC
MEDICATION MONITORING DEVICE ON THE ADHERENCE OF
PATIENTS TO ANTI RETROVIRAL MEDICATION AT THE WELLNESS
CLINIC, RUSTENBURG HOSPITAL**

Your letter dated December 05, 2007 has reference.

The committee **APPROVED** your request for change of study venue from ARV pharmacy at Wellness clinic, Rustenburg Hospital to Tshepang clinic at Dr George Mukhari Hospital.

Yours Sincerely,


PROF G.A. OGUNBANJO
DIRECTOR: RESEARCH & CHAIRPERSON
January 09, 2008



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