

**Effects of telephonic SMS reminders influence on adherence to scheduled medication pick up appointments among adults on antiretrovirals at the Swakopmund State Hospital ART clinic Namibia.**

Emmanuel Oritseweyinmi Ugburo  
Student Number 3002334

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**SUPERVISOR: DR. GAVIN REAGON**

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## KEYWORDS

Adherence

HIV/AIDS

SMS reminder

Telephonic reminder

Pharmacy refill

Scheduled appointment

Antiretroviral Therapy

Resource limited setting

Resistance



## ABBREVIATIONS AND ACRONYMS

AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral Therapy
ARV	Antiretroviral
ANC	Antenatal care
EWI	Early Warning Indicator
HIVDR	Human Immunodeficiency Virus Drug Resistance
HIV	Human immunodeficiency virus.
MEMS	Monitoring Events Monitoring System
MoHSS	Ministry of Health and Social Services
PLHIV	People Living with HIV
PMTCT	Prevention of Mother to Child Transmission
SIM	Subscriber Identification Module
SMS	Short Message Service
UNAIDS	Joint United Nations Program on HIV/AIDS
VCT	Voluntary Counselling and Testing
WHO	World Health Organization

## DECLARATION

I declare that “**Effects of telephonic SMS reminders influence on adherence to scheduled appointments among adults on antiretrovirals at the Swakopmund State Hospital ART clinic Namibia**”, is my work and that it has not been submitted for any degree or examination in any other university and that all the sources I have used or quoted have been indicated and acknowledged by complete references.

Full Name: **EMMANUEL ORITSEWEYINMI UGBURO**

Signed: -----

Date: -----





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## ABSTRACT

**Background:** Adherence of patients on antiretroviral therapy to lifelong treatment is a major challenge within the public health system in Namibia. Missed appointments have been shown to contribute to poor clinical outcomes and treatment failure, which may necessitate switching to more expensive antiretroviral regimens. In resource limited settings monitoring of appointments for antiretroviral medication pick up is a documented and feasible method for assessing minimum levels of adherence to antiretroviral medication.

**Aim:** This study was aimed at evaluating the effects of telephonic short message service reminders influence on adherence to scheduled antiretroviral medication pick up appointments. It was also aimed at evaluating how socio-demographic parameters might moderate the effectiveness of short message service reminders.

**Study design:** A randomized double blind controlled study design was employed.

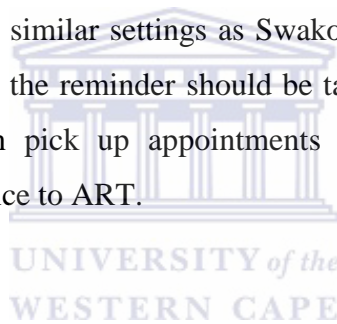
**Methodology:** Stable patients attending the ART clinic were recruited and randomly assigned to either an intervention or control group, until the sample size of 398 was reached in the two arms of the study. The study population were adult patients'  $\geq 18$  years who have been enrolled on treatment for  $\geq 3$  months. The intervention group received an unasked for single short message service reminder, sent 48 hours before their scheduled appointments and continued with standard care, while the control group received standard care without any reminder. The study participants were blinded to their study group. Also, research assistants involved in collecting baseline and outcome data were blinded to study participants study group. Baseline data was collected through a structured questionnaire. Study participants were followed up for four consecutive scheduled ARV pick up appointments. The following outcome data were collected at each follow up visit; number of days late after scheduled appointment, adherence measured by pill count and 3 days self-report recall of adherence.

**Main results:** The pre-intervention survey revealed that only 60% of the study participants were willing to be reminded of their medication pick up appointment. Overall, the SMS reminder improved adherence to medication pick up appointments by 1.6 times as compared to no reminder and also reduced the risk of missing medication pick appointments by 22% as compared to no SMS reminder. Study participants that received a reminder were also two times more likely to achieve optimal adherence to their medication, compared to those who received

no reminder. The SMS reminder improved adherence to antiretroviral medication by 11% in this study, while the mean difference in the number of days late to collect antiretroviral medication was significantly reduced by about 4 days by the intervention. Participants that are employed were more likely to adhere to antiretroviral medications as compared to the unemployed. Ironically participants that were on ART for less than one year and those that had treatment supporters reminding them of their medication appointments were significantly less likely to honour their medication pick up appointments.

**Conclusion:** Being employed was significantly associated with attaining optimal adherence to antiretroviral medication. There were no other significant associations between the patients socio-economic and demographic characteristics and adherence to scheduled medication pick up appointments, or to adherence to medication.

**Recommendations:** The Ministry of Health and Social Services should consider rolling out SMS reminders to ART sites with similar settings as Swakopmund State Hospital ART Clinic. Patients that are willing to receive the reminder should be targeted in the scaling up of the roll out. Late and missed medication pick up appointments could be used as an easy proxy measurement for assessing adherence to ART.



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# CHAPTER 1

## INTRODUCTION

### 1.1 Overview of the HIV/AIDS pandemic

There are 34 million people living with human immune deficiency virus (PLHIV) globally as at the end of 2011, with sub-Saharan Africa accounting for 68% of the global human immune deficiency virus (HIV) burden. Sub-Saharan Africa carries the greatest burden of the human immune deficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) pandemic. In 2012, 1.8 million new infections and 1.3 million AIDS-related deaths among adults and children were recorded in sub-Saharan Africa (UNAIDS, 2012). The benefit of antiretroviral therapy (ART) in the reduction of mortality and morbidity rates among PLHIV is a factor that has led to a rapid scale up of ART services globally with the number of people dying from HIV/AIDS related causes reported to have declined by 32% from 2005 to 2011. As of the end of 2011, over 8 million PLHIV were benefitting from ART, thereby enabling more PLHIV to have an improved quality of life and be productively engaged in their communities. Results achieved from the global response to the HIV/AIDS pandemic inspired the new global target of providing ART to 15 million PLHIV by 2015, an indication that HIV care and treatment has evolved from an ad hoc emergency response to the point of developing a sustainable program for the varied number of people living with HIV (Elul et al., 2011; UNAIDS 2012). As countries plan to scale up their ART programs to meet this target, retaining patients on treatment remains a cardinal challenge in sustaining the progress made thus far and successfully reaching new targets.

### 1.2 HIV/AIDS and antiretroviral therapy in Namibia

Namibia has the fourth highest HIV prevalence in Africa with the first HIV case diagnosed in 1986. Since then the prevalence of HIV has increased from 4.2% in 1992 to 19.9% of adult population in the year 2006, based on a report from the sentinel surveillance which also revealed a slight drop to 18.8% in 2010 (MoHSS 2010a). Namibia adopted a public health approach to the

HIV/AIDS epidemic by ensuring availability of high quality HIV care and treatment for all eligible patients, at no cost to patients. In addition, approximately 120,000 HIV tests are performed annually in the Voluntary Counseling and Testing (VCT) sites that are available in most health facilities and testing sites in the communities all over the country (MoHSS, 2010b; MoHSS, 2011c). However patients must meet the WHO clinical staging and social eligibility criteria before they are entered into the ART program as stipulated in the National ART Guidelines. The clinical criteria are based on the WHO clinical staging of HIV progression in patients, while the purpose of the social eligibility criteria is to maximize adherence and to reduce the risk of defaulting and ensure patients are retained on the ART program (MoHSS, 2010a). The social criteria for eligibility into the ART program include the following:

- Client must have lived at a fixed address for the past three months.
- He/she must have ready access to a designated treatment center for follow- ups.
- He/she must have a treatment supporter, preferably a close family member.
- He/she must have no underlying psychotic illness.
- He/she must not abuse alcohol or drugs.
- He/she must be committed to lifelong treatment and the practicing of safe sex.

Namibia's ART program is reputed to be one of the success stories among countries affected by the HIV pandemic in terms of the provision of ART and the coverage of the people in need of ART. There are presently 221 health facilities which includes; 1 referral hospital, 3 intermediate hospitals, 34 district hospitals, 68 health centers and clinics and 117 outreach sites that are offering ART services to approximately 84% of PLHIV in need of care and treatment.(MoHSS, 2012 a).The Ministry of Health and Social Services (MoHSS) scaled up the ART program in July 2010 by raising the eligibility criteria from less than 200 cells/cubic micro liters (<200 cells/  $\mu\text{l}^3$ ) of CD4 cells to less than 350 cells/cubic liters (<350 cells/  $\mu\text{l}^3$ ) (MoHSS, 2010a). As a result of the scale up, there was a remarkable increase in the uptake of PLHIV into the ART program. At the end of 2012, the number of PLHIV on ART increased by over 100% from 56,000 recorded in June 2010 to 107,154 at the end of March 2012. (MoHSS, 2012b). As the country strives towards achieving its target of 95% ART retention rate, it is important that PLHIV are supported in ensuring adherence to their ART regimens (MoHSS, 2012b).

### **1.3 Potential cost of non-adherence to scheduled ARV pick up appointments**

Several studies have documented different reasons reported by patients for missing clinic appointments and these include among others forgetfulness, work related issues and travelling as the major reasons why PLHIV miss their scheduled clinic appointments. Patients on ART require a lifelong commitment and missing scheduled clinic or medication refill appointments is a likely indicator for dropping out of care and patients becoming lost-to-follow-up (Horstmann et al., 2010).

The economic cost associated with missed appointments in primary care and hospital outpatients was estimated to be £360 Million by the National Health Service of England. This estimate was based on a 12% national annual rate of non-attendance, with each missed visit estimated at an average cost of £61 in 1997 (Stone et al., 1999). Direct financial cost may not be incurred at the Swakopmund ART clinic as a result of missed appointments, because the government offers care and treatment at no cost to all PLHIV. However, Murdock et al (2002) reasoned that the maximum use of resources and total time spent by patients waiting to be seen are prime considerations in missed appointments. In cases where patients do not show up, there is a reduction in waiting times, however administrative resources and equipment might be underutilized.

### **1.4 Use of mobile phones in health care delivery**

Access to mobile phones in Namibia has increased considerably from the time of the inception of the GSM technology in 1999, currently there are two mobile phone networks in Namibia. Research ICT Africa in collaboration with the Communication Regulatory Authority of Namibia (CRAN) conducted a nationally representative survey from June 2011 to August 2011. The result from the survey shows that 56.2% of Namibians owned a mobile phone and of those without mobile phones, 41% had used a mobile phone in the past 3 months, while 28% owned an active SIM (Subscriber Identification Module) card (Research ICT Africa, 2011). The report failed to differentiate between access to mobile phones in urban and rural areas, it is expected that usage of mobile phone will be much higher in urban areas than in the rural areas. The result of this survey also indicates a high rate of shared phone usage which makes privacy and confidentiality

a major concern, because of the stigma associated with HIV infection. Other studies suggests that privacy and confidentiality were not deterrents to the use of voice calls and SMSs as reminders in a rural setting in Uganda and in Durban an urban setting in South Africa (Kunutsor et al., 2010; Crankshaw et al., 2010).

Mobile phone is evolving into an integral part of the people's life, transcending socio economic and cultural groups. Business organizations are already taking advantage of the increasing access to mobile phones and have used SMS as a form of mass media to promote products and services (Cole-Lewis et al., 2010). The Ministry of Health and Social Services (MoHSS) also uses SMS to inform and educate the public on issues pertaining to public health, such as national immunization and HIV testing campaigns. SMS is also used to educate the public on other issues of public health importance. Messages are sent through this medium on designated United Nations health days such as cancer and no tobacco days. Integrating telecommunications into the health care delivery system is a priority in resource limited settings. (WHO/UNAIDS, 2006). Currently, at the Swakopmund ART clinic mobile phone is utilized as a tool to support patients on their adherence programs in both HIV and TB programs. Patients who are lost to follow up are sometimes tracked by clinic staff through the use of voice calls.

The pre-emptive use of SMS appointment reminders in reducing missed scheduled appointments and subsequent reduction in treatment interruption and lost to follow up, holds promising results. Preliminary results from the Right to Care Themba Lethu clinic shows that lost to follow up rates was reduced to less than 4% with the introduction of automated SMS appointment reminders. The system also allowed patients to reschedule their appointments at no extra cost to the patient (Maphan, 2008).

Therefore the potential of SMS appointment reminders as a health care intervention in an urban resource limited public ART program needs further investigation.

### **1.5 Adherence to scheduled medication pick up appointments at the Swakopmund ART Clinic.**

A national survey on adherence to ARV medication refills reported that 84% of patients at the Swakopmund ART clinic pick up their medications on time, as compared to the national average of which 65% of patients pick up their ARV medications on time. In this survey patients who

were late by 1-4 days were considered as being adherent to their ARV refill appointments, because it was assumed that patients are routinely given medications to last beyond their scheduled appointment dates for refill (Lates et al., 2011). Results from this survey also shows that a notable number of patients on ART miss their ARV refill appointments at the Swakopmund State Hospital ART Clinic. ARV pick up is one of the early warning indicators (EWI) recommended by the World Health Organization (WHO) for use in resource limited settings as a minimum strategy for routine monitoring of the emergence of HIV drug resistance (HIVDR). Noting that sub-optimal adherence is one of the factors associated with HIVDR, the WHO recommended a target greater than 90% for the percentage of patients picking up all ARVs on time, before the previous ARVs prescribed runs out if taken as prescribed (Hong et al., 2010). In another survey conducted at the Swakopmund ART clinic among patients who missed their scheduled appointments, Manhando et al. (2011) demonstrated that 12% of those who missed their scheduled appointments reported that they interrupted treatment. It is reasonable therefore to hypothesize that a significant proportion of the 84% of patient that were late by 1-4 days in addition to the 16 % that were non adherent to their scheduled ARV refill appointments were likely to have interrupted treatment. This evidence provides support to the argument that missed appointments is a potential risk factor for treatment interruption, which may increase the risk of more opportunistic infections, and increase the rate of treatment failure. Treatment failure consequently necessitates patients being switched to more expensive second line antiretroviral at the Swakopmund ART Clinic.

Although the impact of waiting times on non-adherence to scheduled appointments has not been fully evaluated at the Swakopmund ART clinic, one of the major complaints expressed by patients from the suggestion box in the clinic, which is reviewed bimonthly during the ART clinic meeting, was the unduly long waiting times at the pharmacy (Personal Interview, Dr. Manhando Medical Officer in charge of the clinic). Indeed waiting times have been identified and reported as a major source of demotivation for keeping scheduled ARV appointments. (Hardon et al., 2006; Nelson, 2012). When patients do not honour their scheduled appointment for ARV medication refill, the equilibrium in the number of patients expected in the different days of the month is distorted. This may be a major reason for longer waiting times on some days when many patients do arrive, whilst at other times sub-optimal use of administrative and human resources has resulted from non-adherence to scheduled appointments.

The Swakopmund ART Clinic reported a rapid remarkable increase in the number of patients on ART, with the number of patients on ART reported to have increased by over 120% from 800 patients enrolled in June 2008 to over 2,350 reported in June 2011. The staff complement in the pharmacy has not changed in the past 4 years (Niaz and Onger, 2011). Mc Coy et al. (2005) identifies weak adherence support as one of the pitfalls that is associated with the rapid scale up of ART in developing countries, with limited resources and inadequate health infrastructure. Furthermore an increase in health care provider frustration and decrease in patient-provider communication, which may complicate adherence to ART are also consequences of missed appointments (Horstmann et al., 2010).

## **1.6 Description of the study setting**

This study was conducted at the Swakopmund State Hospital ART Clinic in Swakopmund, a district in the Erongo region of Namibia. Swakopmund is an urban cosmopolitan town, its economy thrives on a booming tourism, mining and construction industries. Because of its growing economy, skilled and semi-skilled migrants from other regions are attracted to the town (Siapac & JTK, 2002). According to the 2011 census report, a population of 44,700 out of the country's estimated total population of 2.1 million resides in the Swakopmund district (National Population Commission, 2012).

Swakopmund district recorded a HIV prevalence rate of 17.7% from the 2010 ante natal clinic sentinel surveillance survey, which is slightly lower than the 18.8 % national average (MoHSS, 2010). Swakopmund ART Clinic is one of the other 34 ART sites providing full ART services to Namibians. The clinic is located within the Swakopmund State Hospital and it is the only public secondary level health facility providing preventive and curative health services to the residents of Swakopmund and surrounding settlements in addition to some private clinics also providing ART services to a limited number of paying clients or patients on medical aid (Medical Insurance) schemes.

The ART clinic provides comprehensive HIV care and treatment services, voluntary counseling and testing for HIV (VCT), nutritional assessment, alcohol screening, screening and treatment of sexually transmitted infections, family planning services, clinical investigations, voluntary medical male circumcision and linkage to social support services. The clinic also manages and



treats all HIV infected patients who have opportunistic infections and or other chronic non communicable diseases. Patients that require to be closely observed are admitted as in-patients in the hospital, while those that require more specialized management are referred to the referral hospital in Windhoek. As of December 2012, the clinic provides care and treatment to about 4,500 HIV positive patients out of which about 2,500 are on HAART (Manhando, 2010).

The Swakopmund ART clinic is staffed by three medical officers, one pharmacist and three pharmacists' assistants, five nurses, two ART data clerks and eight community counselors.

The patients' enrollment on ART program at Swakopmund ART Clinic averages 30 patients per month (MoHSS, 2008a). Enrollment of patients into the ART program in the Swakopmund ART Clinic is based on the ART national guidelines. The community counsellors routinely offer adherence counseling to all pre-ART clients before they are enrolled on ART, while patients on ART are only counselled when adherence issues are suspected or when patients are being switched to second line ARVs. In order to ensure that those in need of ART services in Swakopmund District have equitable access to ART services, a team comprising of a doctor and a pharmacy staff embarks on a monthly outreach service to Arandis and Henties Bay located 60km and 75km respectively away from Swakopmund. At the Swakopmund Hospital ART clinic, multiple appointments are scheduled over time for patients follow up, these appointments are medical, laboratory screening visits and ARV refill appointments. Medical appointments may vary from monthly to quarterly medical review visits depending on the national treatment guideline and the individual patients' clinical condition, as determined by the medical or nursing staff. However, appointments for ARV refills are more regular and are often monthly or bi monthly, moreover patients in their first 6 months on ART have up to five ARV pick up appointments. Subsequent ARV medication pick up appointments are scheduled bimonthly for stable patients reporting good adherence, according to pharmacy refill records and monthly for poorly adhering patients as indicated by their pharmacy refill records. Patients are allowed to negotiate suitable days for scheduling their ARV medication refill appointments.

The pharmacy dispensing staff sees an average of 80 patients per day; this includes patients on scheduled appointments, pre-ART patients on routine visits and walk in or sick visits. Appointments are scheduled in order to ensure a uniform spread in the number of patients attended to all through the working days of the month.

The medication refill appointment date is communicated to the patient and is recorded on the



patient's health passport. The health passport is a booklet issued to all patients, in this booklet are all of the patients medical history, interventions and prescriptions recorded.

One of the measures put in place by the MoHSS to further ensure adherence, is the concept of treatment supporters. A treatment supporter is someone who could either be a relative, friend or spouse to whom a patient voluntarily discloses his/her HIV status, for the purpose of supporting the patient with his therapy. Having a treatment supporter is one of the social eligibility criteria for initiating ART (MoHSS, 2010). One of the roles of the treatment supporter among others is in reminding the patient of their clinic and medication pick up appointments.

### **1.7 Problem statement**

A notable proportion of patients miss their scheduled ARV refill appointments at the Swakopmund Antiretroviral Clinic. Missing scheduled ARV refill appointments is a risk factor for poor clinical outcomes, treatment failure and switching to more expensive ARV regimens. Given that over 12% of patients who missed their scheduled ARV refill appointments at the clinic reported that they interrupted treatment and as the number of patients on ARV and mobile phone usage continue to increase, there is an opportunity to investigate the influence of SMS reminders on non-adherence to scheduled ARV medication pick up appointments, at the Swakopmund ART clinic.

### **1.8 Purpose of study**

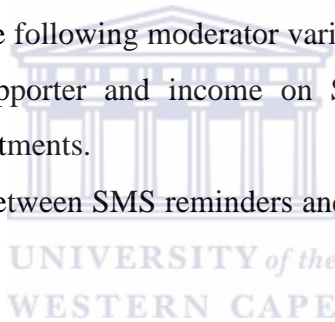
This study will add to the body of evidence on the effectiveness of the use of mobile technology as a healthcare intervention in an urban public ART care and treatment program. The results could be used to assist policy formulation around implementation of interventions to improve adherence to scheduled ARV medication refill appointments, as well as adherence to antiretroviral medication.

## 1.9 Aim

To determine the effectiveness of motivational telephonic Short Message Service (SMS) reminders in enhancing adherence to scheduled medication pick up appointments of patients on ART.

## 1.10 Objectives

- To evaluate the effectiveness of SMS reminders in improving short term adherence to scheduled medication refill appointments and adherence to taking medication.
- To assess the association between adherence to scheduled appointments and adherence to medications.
- To evaluate the influence of the following moderator variables - age, sex, marital status, type of employment, treatment supporter and income on SMS reminders and adherence to scheduled ARV pick up appointments.
- To determine the association between SMS reminders and the number of missed days before honouring appointments.



## 1.11 Hypothesis

The use of motivational (SMS) reminders will improve adherence to scheduled medication pick up appointments and adherence to the taking of medication, by patients at the Swakopmund ART Clinic.

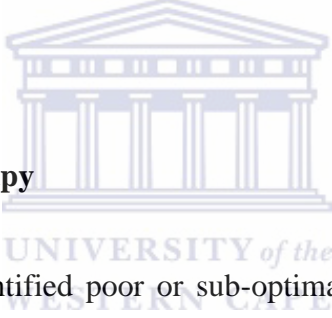
# CHAPTER 2

## LITERATURE REVIEW

### 2.1 Introduction

This chapter describes key concepts of this study, namely adherence to ART, as well as the advantages and drawbacks associated with different method of assessing and monitoring adherence. The use of clinic appointments as a means of assessing and monitoring adherence is highlighted. In this chapter, the reasons why HIV patients on ARV miss their clinic appointments are also explored. Literatures that describe the potential use of SMS as a reminder and demonstrated the effectiveness of SMS reminder in enhancing adherence to ART are presented in this chapter.

### 2.2 Adherence in antiretroviral therapy



Bangsberg and Deeks (2002) identified poor or sub-optimal adherence as a major reason for failure of potentially effective ART. It is important to note that a near perfect adherence to ART is required in order to prevent the emergence and development of viral strains that are drug resistant, which further limits the number of regimens available to patients. The HIV virus replicates at a very high rate, therefore maintenance of viral suppression requires maximum patient adherence (Chesney, 2001).

It is undoubted that poor or sub-optimal adherence to ART also leads to an increase in health cost, which is detrimental to a resource limited setting, because the second line antiretrovirals reserved for patients who fail on first lines are generally more expensive, with an additional cost of laboratory tests required to be factored in as well (Chesney et al., 2001).

Several barriers to optimal adherence to ART has been identified and reported, they are namely stigma and discrimination associated with HIV, the debilitating side effects of some HIV medicines, long waiting times at the clinic, as well as high pill burden (Potchoo et al., 2010; Elul et al., 2011; Hardon et al., 2006; Nelson, 2012).

### 2.3 Assessing and monitoring adherence

There is presently no gold standard in assessing HIV adherence with precision and accuracy, studies have reported on self-reports, pill count, pharmacy refill records, adherence to scheduled, clinic appointments and the monitoring of clinical markers as different measures of adherence with their short coming and diverse degree of accuracy(Population council, 2004).

#### *Self-report*

This is one of the routine methods of assessing and monitoring adherence in the Namibian ART program. Self-report as a measure of adherence which entails asking patients to report on how many doses they have taken or forgotten to take over a given period of time. The duration may vary from 3 days to 30 days. According to Population Council, this method is cost effective and flexible in design. Furthermore data on the reasons why doses were missed could be collected at the same time. Notable challenges associated with self-report include the tendency of patients to overestimate adherence. (APHA, 2004; Population Council, 2004).

#### *Pill counting*

At most health facilities offering ART services in Namibia, health care providers routinely conduct pill counts during scheduled clinic visits to ascertain patient adherence (APHA, 2004). Pill counts offers an estimate of the total quantity of doses consumed, usually between clinic or ARV refill scheduled appointments This method though subjective, it has been found to be cost effective and practicable in resource limited settings. In settings where mutual trust exists between health care provider and patients it offers a good measure of adherence. Pill dumping is one of the shortcomings associated with pill counting; firstly, a major drawback with pill count is that patients may manipulate their adherence score by dumping pills prior to their clinic appointments, thereby leading to an overestimate of their adherence score. Secondly, patients may intentionally leave their left over or missed pills at home making it difficult for the health care provider to assess adherence. Thirdly, pill count may deter the development of mutual trust between health care provider and the patient, because some patients may erroneously assume their health care provider do not trust them. (Population Council, 2004).

### *Electronic devices*

Medical events monitoring system (MEMS), is an electronic system connected to the caps of the medicine such that the system records every time the cap is opened, the computer chips connected to the caps records the date and time of opening and closing of medication bottle. (Population Council, 2004). The data is interpreted with the assumption that a single dose is taken each time the bottle is opened and closed. Studies have found adherence measured using MEMS correlate fairly well with medication intake.

### *Pharmacy refill monitoring*

Kunutsor et al. (2010) reported that the monitoring of scheduled clinic appointments using medication refills record is a feasible, practical and reliable method for monitoring and assessing adherence to ART in a resource limited setting. Pharmacy staff plays a key role in supporting adherence to medication by assessing and monitoring patients' adherence using pharmacy refill data (Population Council, 2004). Monitoring how patients adhere to scheduled medication refill appointments can also be used for routine adherence assessment, assuming that patients appointments are scheduled in such a manner that the patient is given just enough ARVs to last up to the next medication refill appointment, hence failure to honour an appointment could be an indication of sub-optimal medication adherence (Farley et al., 2009; Talam et al., 2008; Brenan et al., 2010). The disadvantages associated with pharmacy refill monitoring is that, it is not a measure of intake of medication, whereby patients who honour all their scheduled appointments may not necessarily take all their medicines.

### *Biological markers*

Clinical investigations such as decrease in viral load and increase in the CD4 counts of patient on ART have the potential to give an indication of possible adherence to ART (Population Council, 2004). Since the goal of ART is to lower the plasma viral load, the monitoring of viral load can therefore be used as an indicator of adherence to ART. The drawback with this method is that viral load monitoring is very expensive and may not be available in resource-constrained settings. Viral load assessment as a means of routine adherence monitoring is not sustainable in resource poor settings. In the 2003 World Health Organization (WHO) ART guidelines, the routine measurement of viral loads was not recommended in resource limited countries. However, viral load is routinely done in most high income countries. The cost of a single viral load test is estimated at \$20 - \$160 (in US dollar) and the additional constraints of inadequate

equipment and technical expertise make viral load assessment for routine adherence monitoring unsustainable in resource poor settings (Calmy et al., 2006).

#### *Therapeutic drug monitoring*

Measuring of therapeutic drug levels in the plasma could detect only recent adherence behavior, thus therapeutic drug levels were not necessarily indicative of good adherence (Desai et al., 2003). Hugen et al. (2002) also noted that low concentrations of antiretrovirals may be caused by factors other than adherence, such as mal-absorption, drug interactions, and individual metabolic differences. In clinical settings drug monitoring as a means of monitoring is expensive and it is not a cost effective and sustainable measure of adherence.

In summary, the use of more than one strategy such as self-reports, pill count and adherence to scheduled clinic appointments would enhance the accuracy of measuring ART adherence as recommended by the WHO (WHO, 2003).

## **2.4 The importance of appointment keeping and adherence assessment**

Good adherence as defined by Muyigo et al. (2008) is not limited to compliance with medication but it also includes adhering to all medical and non-medical instructions including keeping scheduled appointments. Moreover adherence to appointments has been reported as a useful proxy for medication adherence in a HIV care and treatment setting (Talam et al., 2008). In a cross sectional study embedded within a larger clinical trial, Ogedengbe et al. (2003) studied the appointment keeping behavior and adherence in hypertensive African Americans. This research concluded that appointment keeping does not have any relationship with medication adherence. This result detracts from the following studies, (Farley et al., 2003; Park et al., 2007; Fonq et al., 2008; Kunutsor et al., 2010; Talam et al., 2008), in which appointment keeping to scheduled appointments had some correlation with adherence to medication and this was associated with negative clinical outcomes such as poor virological response and immunological failure.

Farley et al. (2003), assessed the medication event monitoring system (MEMS) in measuring adherence in HIV infected children and compared this to other methods of assessing adherence. Their findings suggest that appointment keeping records which are routinely kept and pharmacy refill rates were found to be associated with virological response, although this was not statistically significant, due to the small sample size, it was clinically significant because the

highest specificity were obtained when MEMS and pharmacy refills were combined in the adherence measurement.

Park et al. (2007), reported a strong association between adherence to clinic visits after initiation of ART and later disease progression, in an observational cohort study, aimed at determining whether adherence to clinic visits after initiation of ART was predictive of long term clinical outcomes. The results indicate that adherence to clinic visits is an independent predictor of long term clinical progression to AIDS. They concluded that adherence to clinic visits may therefore be associated with adherence to ARV medicines, as taking ARVs is the only proven way to delay progression to AIDS, however, this paper did not differentiate medication refill visits from medical visits.

On their part Brennan and colleagues (2010), differentiated medication refill visits from medical visits in a retrospective cohort study at the Thembu Lethu Clinic Johannesburg in which they attempted to quantify outcomes from missing scheduled appointments in the first 6 months of initiating ART. Results from an adjusted multivariate cox proportional hazards analysis showed that generally more missed visits were associated with a higher risk of mortality and lost to follow up. They reported that missing 2 to 3 medical appointments increased the risk 2 - 4 fold while missing  $\geq 3$  ARV pick up appointments increased the risk 4 - 8 fold (HR 8.2 CI 2.0-33.7). This suggest the importance of adherence to scheduled clinic and medication refill appointments needs to be emphasized to patients very early during initiation of ART.

Fong et al. (2008), in a retrospective study by self-report among Chinese HIV infected patients demonstrated that missing clinic appointments was independently associated with partial medicine adherence. Adherence was determined by the ratio of the number of missed doses since last follow up, adherence of 100 % was defined as full adherence , while 90 -99 % was defined as partial adherence. Their definition of full adherence is high as compared to other studies which set optimal adherence at  $\geq 95\%$ .

Kunutsor et al. (2010) followed up a cohort of patients on ART in an urban hospital in central Uganda for 28 weeks. They demonstrated that 31/392 (7.9%) of clients whose clinic attendance for refills was not consistent achieved sub-optimal adherence  $< 95\%$  determined through pill count. The association between ARV refills and adherence to medication was found to be significant.

It is important to note that adherence in HIV care is more complex than the management of non-



communicable diseases such as diabetes and hypertension. It has been reported that stigmatization and discrimination of people living with HIV (PLHIV) further complicates adherence in HIV care, while hypertension and diabetes are perceived as elitist diseases in some communities (Aikins et al., 2010). PLHIV are expected to strive for 100% adherence, compared to the adherence definition of success, which is 80% for other illnesses (Murphy, 2002). The current recommendation for ART in HIV infected adults from the International AIDS Society USA Panel, recommends regular assessment of adherence with at least 95% needed for best outcomes (Murphy et al., 2002). Good adherence to ART results in undetectable viral load, while intermittent therapy and poor adherence to ARV medication causes sub-optimal drug levels, which causes natural selection of resistant mutant strains of the virus. Studies have demonstrated the inability to suppress viral replication resulting in the development of resistance which occurs at adherence levels as high as 92% (Bangsberg et al., 2003).

Adherence to clinic appointments and punctual collection of antiretroviral medication are good indicators of adherence to ART. A patient who does not keep scheduled appointments is likely to indicate poor or sub-optimal adherence because patients are generally given just enough medicines up until the next appointment date. Kunutsor et al. (2010) in a cohort study prospectively followed up 392 patients for 24 weeks and the result showed that clinic attendance for refills were statistically significantly associated with medication adherence (OR 3.89 P=0.013) .

On their part, Farley et al, (2003) assessed adherence among pediatric HIV positive patients. They compared different methods of adherence assessment namely MEMS, pharmacy refill, caregiver self-report in HIV infected children and the results correlated good appointment keeping with MEMS adherence rate  $\geq 80\%$  (65%) while 6 out of the 9 children that missed appointments had a MEMS adherence rate of  $\leq 80\%$ . The authors found this association clinically significant, even though the sample size was a limitation.

Oyugi et al. (2004) assessed and found correspondence between unannounced home pill counts, 3-day self-report, MEMS and 30 day visual analogue scale measurements. They found all measures of adherence to be closely correlated with each other and they also reported a significant association with the viral load levels. At twelve-weeks viral load was significantly associated with all adherence measures (MEMS,  $R = -0.34$ ,  $P = 0.04$ ; pill count,  $R = -0.41$ ,  $P = 0.01$ ; visual analog scale,  $R = -0.36$ ,  $P = 0.03$ ; and 3-day self-report,  $R = -0.42$ ,  $P = 0.01$ ).



Appointment keeping can therefore be used in combination with self-report and pill counts in assessing patients' adherence to antiretroviral therapy.

## **2.5 Reasons why HIV patients miss scheduled clinic appointments**

An understanding of the reasons behind non-adherence to scheduled appointments by HIV infected patients on ART will give an indication of the potential benefit of introducing SMS reminders as an intervention to improve adherence.

Indeed an unpublished self-report survey, reported on the reasons why patients on ART missed their scheduled appointment at the Swakopmund Hospital ART Clinic. The different reasons for missing appointments ranged from work related 29 (17.3%), forgetting 20 (11.9%) to transport issues, 60 (35.4%) (Manhando et al., 2011).

A similar pilot study, using self-report was carried out in Hong Kong by Park et al. (2007), in which HIV infected patients were prospectively monitored. The study indicated work issues 22 (36%) and forgetting, 13 (21%) as the major reasons for missing scheduled clinic appointments.

On the other hand Potchoo et al. (2010), in a cross sectional exploratory study conducted in Togo, West Africa, sought to identify factors related to non-adherence to HAART in 43 adult patients who missed at least one dose of their treatment. The study established forgetting 34.9%, travel 25.6%, and cost of treatment 13.9% as reasons for non-adherence.

Obviously, a significant percentage of patients in all 3 studies reviewed reported forgetfulness or forgetting and travelling issues as reasons for missing scheduled appointments. These results suggest a potential benefit from using SMS reminders in HIV infected patients on ART. The individual social demographic state of patients such as age, gender, and education might significantly affect their ability to consistently adhere to clinic appointments. Kunutsor et al. (2010) prospectively monitored a 2,267 cohort of HIV positive patients over a 28-week period in a District hospital in Uganda. They reported a significant association between patients whose adherence to clinic appointments were irregular and those with no education. In this study irregular appointment was defined as failure to achieve > 90% of total clinic appointments within a 28-week period. Also patients of 35 years and below were significantly less likely to achieve regular attendance.

## 2.6 Potential use of SMS in improving adherence to clinic appointments

Information technology has immense potential in facilitating and resolving development problems. However, the effectiveness of mobile phone technology as a health care delivery intervention has not been fully studied in resource-limited settings.

While some studies and reviews support the mobile phone intervention as a cost effective intervention to improve adherence in chronic disease conditions, other recent reviews suggest otherwise. Kaplan, (2006) systematic review shows conflicting reports both in support and in validation of the cost effectiveness of both fixed and mobile phones as devices for health care intervention, this conclusion drawn from the review may be due to the fact that the review sampled various kinds of health care interventions such as the use of communication technology in health information and in non-communicable diseases. Moreover the majority of the papers reviewed were not specifically related to adherence in HIV care. Furthermore some of the papers reviewed were pilot studies and the authors did not report on the sample sizes. The review provided weak evidence upon which a policy could be developed especially as it relates to resource limited settings, because out of 43 studies reviewed, 41 of the studies were from developed countries. The authors therefore proposed more well designed randomized trials in determining the efficacy of telephone technology as a cost effective health care intervention.

The rationale for scheduling patients' appointments is to ensure human and administrative resources are optimally utilized. Hasvold and Wooten (2011) noted that patients that fail to report for their scheduled appointments add to inefficiency in the use of resources. They conducted a systematic review of studies providing reminders as a health care intervention. The review considered manual phone calls, short message services (SMSs) and automated phone call reminders in the review. A total of 33 studies were included in the review, out of which 9 of the studies were RCTs and the other study designs were before – after interventions, non-randomized controlled trials, retrospective and prospective cohorts. The sample size of the studies reviewed ranged from 100 – 16,400, the median of the duration of the intervention was 3 months while 2.75 days was the median of the number of days between when the intervention was delivered and the scheduled appointment day. The result from this systematic review shows that there was a reduction in the rate of non-adherence to scheduled appointments in all but one of the studies. A mean relative risk reduction of non-adherence to schedule appointment of 39%

was reported in phone and SMS reminders compared to 29% of relative risk reduction among the automated reminder group, this suggests that a health worker operated reminder message might be less intrusive and therefore more effective than an automated reminder system. The dates and times the automated voice calls and SMSs were delivered are computer programmed. They found no significant effect between when the reminder was sent relative to the appointment date. It is important to note that the authors did not carry out a meta-analysis because of the heterogeneity of the studies reviewed, therefore caution should be applied in interpreting and generalizing outcomes from the study, and most importantly none of the studies reviewed were conducted in sub-Saharan Africa.

Crankshaw et al. (2008) explored the patterns of use and the feasibility of using cellular phones for clinic appointment reminders and adherence messages in an antiretroviral treatment clinic. This study was conducted in Durban, an urban setting in South Africa. Results indicate that 99% of patients were willing to receive reminder voice messages, while 98% of patients were willing to receive SMS as reminders of their appointment. Their findings confirm a higher access and use of mobile phones as expected in an urban setting.

Relatively high mobile phone access and ownership has been reported in a rural setting. Shet et al. (2010) reported a 74% ownership out of which 26% were shared ownership in rural Southern India, in an exploratory pilot study with the aim of designing mobile phone interventions that will enhance adherence to antiretroviral medication. They reported that 66% of the patients sampled were already using mobile phones to contact their health care provider and that confidentiality and privacy was not a deterrent factor in this setting. The authors concluded that mobile phones have the potential to enhance adherence in HIV care and management.

In the same vein Puccio et al. (2006) in a pilot program studied the use of cell phone reminder calls for assisting HIV infected adolescents and young adults to adhere to ART. Participants received free cell phones, with 250 free local “anytime” calls including weekends, furthermore participants received 10 USD for completing each questionnaire and the report did not indicate that the cell phones were taken back from the study participants at the conclusion of the study. In the first 4 weeks, daily calls were made to participants, after which the calls were tapered, with calls occurring from Monday through Friday from week 5- 8 and from week 9 – 12 , calls occurred on Sunday, Tuesday and Thursday. Subjects were allowed to choose their preferred time to receive calls and depending on the medication regimen, calls could either be once or

twice daily. The results from this study demonstrated that most of the participants found calls to be helpful and the intrusion into their daily lives acceptable, they also reported a significant decrease in viral load which they attributed to adherence call reminders, although the authors acknowledged the limitation of the small sample size which is expected in a pilot study.

## **2.7 Testing the effectiveness of SMS reminders in improving adherence**

In the review of literature, some studies have tested effectiveness of SMS reminders in improving adherence to clinic attendance in general outpatient departments and in primary care settings for various disease conditions.

In an observational study carried out in an ophthalmology outpatient in London, Koshy et al. (2008) reported a 38% decrease in non-attendance rate amongst patients that received SMS reminders compared to those that were not reminded. They concluded that SMS reminder is a cost effective way of improving adherence to clinic appointments. Similar results were reported by Hogan et al. (2009) in a Urology outpatient department. The high rate of non-attendance noted in the department informed the survey on the potential impact of SMS reminders on non-attendance rate. SMS reminders were sent 3 days prior to the scheduled appointment. In the two years prior to the introduction of the intervention they reported a 17.6% (4,544 patients) non-attendance rate, but after the introduction of SMS reminders the non-attendance rate declined to 12.4% (3,423 patients). The authors concluded that the SMS reminders influenced by about 50% adherence to scheduled clinic appointments. However, this result cannot be generalized because factors that lead to adherence in HIV care and management are more complex than in conditions presenting at a urology general outpatient department. In HIV care adherence is influenced by a complex interaction of patient, medicine and virus related factors, moreover PLHIV are expected to adhere to treatment throughout their life time. (Chesney, 2001; Farley et al., 2003).

Kunutsor et al. (2010) in a cross-sectional prospective study conducted in Uganda studied the use of mobile phones in improving clinic attendance in a rural setting. Study participants who owned mobile phones were immediately called or sent SMS reminders based on their preference as soon as they missed their scheduled appointments. The result indicated that 177(64%) had access to mobile phones, which is relatively high for a rural setting. A total of 176 clinic attendees for medication refills were monitored prospectively for 28 weeks. The total number of

scheduled appointments recorded was 560, out of which 477 were on scheduled visits, while 62 (11% of appointments) were missed visits. Among the group that missed their visits, 49 (79%) of those who received reminders presented for treatment within 2.2 days. Despite the mobile phone intervention, 9 scheduled appointments were still missed. Adherence levels were assessed using routine clinic based pill count before and after the mobile phone intervention. They reported adherence levels to be significantly higher during the mobile phone intervention. This sampling procedure gives room for selection bias because it is likely that a cohort of more motivated and adhering patients were enrolled into the study. The effectiveness of the reminders cannot be validly evaluated in the absence of controls and the effect of confounders was not analyzed, they could therefore not conclude that the improvement in appointment adherence could solely be attributed to the introduction of the intervention.

Appointment reminders can be delivered through different means asserts Perron et al. (2010) in a randomized control trial, designed to test the effectiveness of sequentially delivered reminders in reducing the rate of missed appointments at an urban primary health care clinic in Geneva. Study participants were randomized into two groups, the control did not receive any intervention, while the intervention arm were sent reminders sequentially, firstly by phone call, followed by a simple SMS indicating date of appointment and name of medical officer, and a postal reminder which is sent 48 hours prior to the appointment date, which is received the next day. Analysis of the results shows that the two groups were balanced and the overall intervention significantly reduced the rate of missed appointments from 11.4% in the control group to 7.8% in the intervention arm. However, in the HIV and Dietician clinic the rate of missed appointment reduction was not statistically significant  $p=0.62$  and  $0.75$  respectively, while the other clinics such as general outpatients and smoking cessation clinics reported significant reductions in missed appointments. They reported that being in the arm of the intervention decreased the odds of missing an appointment in all categories of patients (OR 0.63 95% CI 0.43- 0.89). The report also revealed that being young, male, asylum seeking and being cared for by a junior doctor rather than a senior doctor and having substance abuse problems were significantly associated with missed appointments. In a poor or resource limited setting delivering reminders sequentially as reported may not be practicable and cost effective. In resource limited settings the level of missed scheduled appointments may be higher than expected in a developed country.

Noting that sequential reminders may not be a cost effective and realistic intervention in a

resource limited setting, Chen and colleagues (2010) compared the efficacy of SMS and phone reminders in improving attendance at a health promotion centre within the university hospital in China. A total of 1,891 participants were randomly assigned into 3 groups, the first group received SMS reminders and the second group received phone reminders, while the control group did not get any intervention. The study participants were followed up for 2 months and results showed that SMS and phone reminders attendance rate 87.5% and 88.3% respectively were significantly higher than that of the controls 80.5%. The difference in attendance rate between SMS and phone reminders was not statistically significant. They found SMS to be more cost effective than phone reminders. This study was conducted in a setting of a high socio economic class, the majority of who were living within the university community, which may partly explain the high rate of adherence to appointments, reported.

The use of SMS reminders in improving adherence to scheduled appointments, because of its ability to reach large numbers of patients at a relatively lower cost and being less intrusive and more discreet, makes it a better option in an urban resource limited setting with a high mobile phone ownership rate.(Mapham, 2008)

On the other hand Pop-Ellechas et al. (2011) tested the efficacy of a SMS as a reminder in adherence to ART in a rural clinic in Kenya. They used a randomized control study design in which a total of 431 patients were randomly assigned to control and four intervention groups. The intervention groups received long daily SMS reminders, long weekly SMS reminders, short daily SMS reminders and short weekly SMS reminders. The SMS messages were chosen to address forgetfulness and lack of social support which are barriers to adherence. The short SMS messages is simply “This is your reminder”, is aimed at addressing forgetfulness. On the other hand, the long reminder which states “This is your reminder be strong and be courageous, we care about you”, was designed to address lack of social support and forgetfulness. The study participants were followed up for between 12 weeks to 48 weeks. Adherence was monitored using (MEMS). The results showed that weekly SMS reminders increased the percentage of participants achieving  $\geq 90\%$  adherence by 13-16% compared with the controls. A notable reduction in frequency of treatment interruption which is a risk factor for development of antiretroviral resistance and treatment failure was also reported. It is interesting to note that long text weekly reminders was not more effective than the short message weekly SMS. Furthermore, daily SMS did not improve attendance rate, whereas 53% of participants who received weekly



short SMS reminders achieved 90% adherence compared to 40% scored by the control  $p=0.03$ . The authors noted that daily reminders might have been too intrusive and diminishing response may be responsible for its ineffectiveness in improving adherence. With regards to message content, what best influence change in behaviour has not been fully investigated. Weekly short SMS reminders is likely to improve adherence to clinic appointments, a significant association was reported between adherence to clinic visit and adherence to medication (Talam et al., 2008). The frequency of the appointments also affects adherence to scheduled appointments. This is an ideal study design to test the efficacy of SMS reminders on adherence to antiretroviral, however the use of MEMS for routine adherence monitoring is not feasible in a resource limited setting.

## 2.8 Summary

Considering the fact that there is no gold standard for assessing HIV adherence with precision and accuracy, literature reviewed shows that self-reports, pill count, pharmacy refill records, and adherence to scheduled clinic appointments have been used with different degrees of accuracy. Noting that adherence to scheduled clinic appointments has been reported as a useful proxy for medication adherence in an HIV care and treatment setting, it is therefore a cost effective option for monitoring adherence in a resource limited setting. In addition, several studies recognized forgetting as a major reason for patients missing their scheduled clinic appointments; consequently the use of SMS reminders has the potential to enhance adherence to scheduled appointments in a resource limited setting.

# CHAPTER 3

## METHODOLOGY

### 3.1 Introduction

This chapter details the study design and sampling procedure. The study setting and the inclusion criteria as well as the exclusion criteria are also presented in this section. The data collection tools and the steps taken to improve the rigor of the study are also described in this chapter.

### 3.2 Study design

A quantitative, experimental design sometimes referred to as an interventional study design was adopted in determining effects of telephonic SMS reminders influence in enhancing adherence to scheduled medication pick up appointments. This design is analytical and is best suited to evaluate an intervention. There are different variants of intervention studies which includes randomized control trials (RCT), quasi-experimental studies, before – after studies. A before – after study requires baseline data, and in the absence of baseline data, doing a baseline will prolong the time required to conclude this study. In a quasi- experimental design one of the three essential elements is absent. The RCT study design which is considered as the gold standard of intervention studies was adopted in this study. The three essential elements of experimental design; intervention, control and randomization were employed in this study. An RCT is regarded as providing the highest proof of causality and the effect of selection bias and confounding which occurs in cross sectional designs and case control studies are largely eliminated in RCT's through experimental control measures and randomization.

This is a one centre, parallel group, double blinded and randomized controlled trial, in which study participants were randomized into 2 groups.

### 3.3 Study population

The study participants were recruited from all enrolled adult ( $\geq 18$  years) patients on ART at the Swakopmund ART Clinic, a public health facility in an urban district of Namibia.



### 3.3.1 Inclusion criteria

HIV positive patients who were 18 years and above, enrolled at the Swakopmund ART Clinic, who have been on ART for at least 3 months and were stable enough for their appointments to be scheduled at least on a monthly basis. Study participants also possessed a functional cell phone that was able to receive SMS.

### 3.3.2 Exclusion Criteria

The introduction of controls in a RCT is in order to have a control group that is similar and compares to the intervention group. This was achieved by refining the study population using exclusion criteria. The exclusion criteria were:

- Patients who are in transit
- All patients accessing care and treatment from the two outreach sites.
- All patients who were already on second line ART treatment, this entails that all adult patients on regimens containing protease inhibitors categorized as second line regimens according to the national guidelines were excluded.
- Non-ambulatory patients and those that were too ill and need to be followed up at more frequent intervals, or were stabilized on regimens other than the first line regimen as per the Namibian ART National Guidelines.

### 3.4 Sample size

In order to detect a 60% relative reduction in the rate of missed scheduled appointments and based on a 14% incidence of missed appointments, with a ratio of 1:1 in both arms at a 95% significance level and power of 80%, 190 participants per group was calculated as the required sample size needed. However, in order to accommodate transfer outs and loss to follow up, the sample size was increased to 200 in each arm of the study to enable sufficient power to detect a significant difference between the two arms. Recruitment of participants into the study commenced on 5 December 2012 until the required sample size was reached on 30 January 2013. The number of patients who declined participating in the study was recorded.

### **3.5 Sampling procedure**

Community counselors approached potential participants visiting the clinic or pharmacy. Potential subjects were invited to participate after being fully informed as to the purpose of the study and consent obtained from the patients. Consenting patients were assessed for eligibility using the inclusion and exclusion criteria.

#### **3.5.1 Randomisation**

Eligible subjects were randomly allocated into study groups by picking a marble from an opaque bag containing equal amounts of same sized and shaped red and green marbles. The colour of the marble was marked on both the patient's health passport and on the recruitment register.

#### **3.5.2 Control group (standard care plus counseling)**

All study participants received the routine standard care as prescribed by the Namibian National ART Guidelines (MoHSS, 2010). Patients routinely undergo 3 adherence counseling sessions before initiation of ART, and subsequent adherence sessions are only given to individual patients identified with adherence issues. Follow up review for medical and laboratory assessments were delivered as prescribed by the national guidelines and by physician clinical judgment. All study participants in the control group received adherence counseling at all follow-up visits by community counsellors before the outcome data was collected by the pharmacy staff. Follow up appointments for medication pick up were scheduled monthly or bimonthly based on other clinic appointments such as laboratory or clinic appointments. In order to mimic the clinic setting in this study as much as possible, participants were able to negotiate actual appointment intervals and appointment dates within a 4 – 8 weeks follow-up interval, and the actual appointment dates ranged between 24 – 66 days.

#### **3.5.3 Intervention group (standard care plus counseling plus SMS reminder)**

The intervention group received an unasked for SMS reminder with a short motivational message which read “This is your reminder for your pharmacy appointment; we care for you and the date of the appointment.” The message was sent by a designated research assistant whose responsibility was to track medication pick up appointment dates. The reminders were sent 48

hours prior to their scheduled appointment but only to participants in the intervention arm of the study. The study numbers and date of the next appointment was recorded in the appointment register with the date the SMS was sent (Appendix B). The SMSes were sent in English and Afrikaans according to the preference of the participant. The participants in the intervention group also received their usual medical care in addition to counselling at every visit. Both groups of the study continued to receive standard care as per national guidelines.

## **3.6 Data collection**

### **3.6.1 Socio- demographic and baseline data collection**

A pre-tested semi-structured questionnaire was used by trained counsellors to collect socio demographic data in a face to face interview which was held in the clinic counselling rooms. Structured questionnaires generally reduce the potential of collecting ambiguous answers, thereby strengthening the process of data collection and analysis. The interview was conducted in English, Afrikaans and Oshiwambo depending on the study participant's preference. Data on the patient's regimen, duration on ART and socio-demographic data such as age, employment status, income, marital status and the location where the patient is resident was collected. Also the unit of alcohol consumed daily and on weekend, the patient's disclosure status and the preferred form of reminder and time the patient would like to be reminded was collected (See Appendix A).

The patients' health passport was used to validate or confirm data such as respondent's regimen, date of birth, ART start date obtained from the face to face interview.

### **3.6.2 Outcome of data collection**

At every follow up visit, study participants were offered adherence counselling by community counsellors, thereafter they were referred to the pharmacy. The pharmacy staff on duty collected follow up data on appointment kept or not, pill counting, and medication adherence by 3 day self-reported adherence were also collected. (See Appendix B). The Aids Control Trials Group (ACTG) questionnaire which has been validated was adapted and incorporated into the participant information log sheet. Study participants were asked "how many doses did you miss in the last 3 days", for the collection self-reported 3 days adherence data.

Adherence data for pill count was collected at the pharmacy from left over or unused medicines,

which were counted and recorded in the participants information log sheet. (Appendix B). In cases where respondents send their treatment supporters for medication refill appointments and hence prevented the collection of adherence data by pill count and self-report, this was noted and considered in the interpretation of the results.

### **3.6.3 Outcome measurements**

The primary outcome measure is the proportion of missed visits over the total number of scheduled appointments.

Secondary outcomes that were measured include the mean number of late days, which is a count of the number of days between the scheduled appointment date and the date study participants reported for medication refills.

ARV Adherence was measured as the proportion of doses missed in the last 3 days divided by the total number of doses. Oyugi et al (2004), and the proportion of participants that did not miss any dose in the last 3 days thereby scoring 100%. Despite variability in different measures of adherence, self-reported data has been shown to correlate with other measures of adherence such as pill counts and virological suppression, therefore a 3- day self-report is a valid measure of adherence.

Pill counts is the percentage of the number of doses of medicine dispensed minus number of doses of medicine returned divided by the number of doses between medication refill visits. Unused pills were counted and recorded (Muyingo et al., 2008). We defined adherence of  $\geq 95\%$  as optimal adherence, while adherence of  $< 95\%$  was defined as sub-optimal adherence (Kunutsor et al., 2010; Mbuagbaw et al, 2011). In our research setting there is no prescribed or schedule for tracing defaulters, therefore all study participants were attempted to be traced by phone call 7 days after their scheduled appointments date for medication refills.

### **3.6.4 Blinding**

Community counselors assigned to recruit and administer a pre-tested, semi-structured questionnaire were blinded to the allocation of participants into study groups. This is an important step in reducing measurement bias as knowledge of participants grouping may influence how data is collected. Wood et al. (2008) stated that if allocation is not blinded to research staff administering allocation to groups, they are prone to influence participants into the intervention group, which in turn may bias the intervention effect by about 20-30%. The colour of marble picked determined allocation into study groups and the colour of marble which coded

for the intervention group and the colour which coded for the control group were concealed from all community counselors administering the randomization process and all pharmacy staff involved in collecting outcome data at every follow up visit. Blinding the pharmacy staff reduced the occurrence of measurement bias. Only two research assistants designated for sending the SMSs reminder and the chief researcher who supervised the research assistants, knew the allocation of participants to the study groups by the colour of the marble they picked. The chief researcher and research assistants responsible for sending the SMS reminder were not involved in data collection.

Study participants were not informed of the actual study intervention except that they would receive adherence assistance and support at every medication pick up visit. Hence, every participant probably thought they were in the intervention group as they were receiving the “intervention” of adherence assistance

This intervention then took the form of “adherence counseling” at every visit for the control group and “adherence counseling plus an SMS reminder” for the intervention group. Hence probably participants were blinded as to which group they were in. Adherence counseling covered the following themes;

- How many doses were missed from the previous visit
- Importance of taking medications as prescribed and consequences of interrupting treatment
- Side effects experienced from the medications
- Importance of keeping all clinic appointments
- Unprotected sex and HIV transmission

Blinding participants should have reduced the Hawthorne effect from occurring among subjects in the intervention group. Unblinded subjects may become more adherent by just being aware they are receiving the intervention. This usually exaggerates the difference in adherence between the two groups.

### **3.6.5 Contamination**

Contamination occurs when some study participants in the control group end up getting SMS reminders by error. The research assistant may send SMS reminder to a subject in the control

group by error. In order to be able to prevent occurrence of contamination, the research assistant recorded study numbers and names to which SMS's were sent and this register was cross checked against the questionnaire by the chief researcher. Contamination might also occur by means of participants in the intervention arm forwarding SMS reminders to their friends who were given the same appointment date. Because the outcome assessors and study participants were blinded, we were not able to access this type of contamination by self-report. However, the likelihood of this kind of contamination occurring is minimal, because all the study participants were under the impression that the monthly adherence counselling session is the intervention. In addition cell phone numbers of all study participants were collected during the interview regardless of their group.

### **3.6.6 Co-intervention**

This occurs when some other form of intervention to increase adherence is provided to study participants at the same time as the study. When study participants are exposed to other forms of intervention that encourages adherence to medication and to scheduled appointments, we cannot safely conclude that the study's SMS intervention brought about the observed difference in adherence. Co-intervention can be in the form of the clinic introducing any form of reminder system or by a support group. However throughout the duration of this study, the ART clinic or any other support group known to the ART clinic did not introduce any intervention that was aimed at increasing adherence to appointment. It is not likely that co-intervention occurred in this study.

## **3.7 Data management**

The questionnaires were numbered separately according to the colour of marble picked (blue or pink) during the randomization process. The participants study number included prefix (SN) and subjects serially generated number e.g. SN 234 –b2 or 235-p3 (Appendix A). The questionnaires were cross-checked regularly, by the chief researcher and the research assistants. Noted inconsistencies or data errors were corrected immediately and where this was not possible the error were noted and corrected at the respondents follow up visit.

Data cleaning was done manually before data was entered into Microsoft Excel 2010, also sample duplicate data entry was used to assure data quality. The data validation function of

Microsoft Excel 2010 was used to set validation criteria and data ranges thereby eliminating extraneous and ambiguous data such as three response codes in the place of two or erroneous data such as 120 years of age.

### **3.8 Data analysis**

Data was captured on Microsoft Excel 2010 and imported into Epi Info version 7. The analysis of socio-demographic and base line data was summarized using descriptive measures to compare the results of the two groups. This gives an indication as to whether potential confounding factors are evenly distributed among the two groups.

Continuous variables such as age and duration on ART were expressed as a mean with (standard deviation and inter quartile range) the data on both nominal and ordinal categorical variables was summarized as proportions. An intention to treat principle was adopted in our analysis, this entails that all participants were analyzed based on the initial arm of the study they were randomized and grouped into, irrespective of whether they dropped out or switched group.

**3.8.1 Primary analysis:** the proportion of study participants who missed appointments were determined, from which the cumulative incidence ratio (CIR) and risk difference (RD) were determined. The statistical significance was determined using the 95% confidence interval.

**3.8.2 Secondary analysis:** included the determination of percentage adherence by 3-day self-report recall and pill count. Differences in adherence between the intervention group and control group were determined. The prevalence rate will be used to compare the following variables- sex, age, location (distance from the clinic), income, treatment supporter, alcohol consumption, ART regimen and duration on ART between the 2 groups as a means to assess the success of randomization. The mean of the number of missed days was determined for the intervention and control groups of the study. The association between SMS intervention and missed appointments was tested for statistical significance. We also determined the association between missed appointments and adherence to medication by pill count and self-report. Statistical significance was determined at 95% CI.



### 3.9 Validity

Validity is defined as the capacity of a test or question to give the true result. In order to ensure rigour and validity in data collection and analysis, the following precautionary actions were undertaken.

A simple research manual outlining the purpose of the study, how to sample patients and obtain signed consent of eligible participants and how to ask questions and complete the questionnaires was produced. The research assistants who are pharmacist/pharmacy assistants and community counsellors were trained by the chief researcher before piloting.

The community counselors and pharmacy staff already have some level of competence in this regard moreover training will reduce cultural reinterpretation and contextual biases that may be associated with the use of clinic staff to interview participants.

The sampling procedure adopted in this study reduced the occurrence of systematic sampling error. Randomisation ensures that any differences between the study sample and the population are due to chance alone, it also ensures that confounding characteristics that may influence the outcome are evenly balanced among the two groups. Blinding of the outcome assessor at follow up visits reduced observer bias, for example an unblinded outcome assessor due to expectation of a higher adherence among the intervention arm, may exaggerate the adherence score. Blinding of study participants and outcome assessor until the data collection is completed also minimized the likelihood of systematic differences in ascertaining of outcomes between the study groups (Hennekens and Buring, 1987). There is currently no consensus on the standard for adherence measurement, pill count and self-report has been validated as acceptable instruments for measuring adherence in resource limited settings. (Oyugi et al., 2004; Musingo et al., 2008). The likelihood of bias in measuring other outcomes in this study is also negligible for the reason that proportion of missed appointments and the number of missed days before honouring appointments are objective measures. The effect of chance is likely to be minimal as an adequate sample size was adopted.



### **3.10 Piloting**

This study was piloted prior to commencement of the main study. In the pilot, 10 participants were randomized into study groups made up of 5 participants in the intervention and control arm of the study. All research assistants recruited to take part in the main study participated in the piloting. The participants in the pilot study were not included in the main study.

### **3.11 Reliability**

Reliability refers to the consistency, repeatability and dependability of outcome measures of the study that is the ability of a questionnaire to produce similar results in different circumstances if nothing changes (Beaglehole et al., 1997).

It describes how consistently observed outcomes are measured and interpreted on different occasions. In order to ensure data collection instrument reliability, the adherence counsellors and the pharmacy staff were trained and the questionnaire was tested during the piloting. All pharmacy staff were trained on how to fill the outcome registers. Lastly, the same trained adherence counselors and pharmacy staff were engaged throughout the study.

### **3.12 Generalisability**

Results from this study could be generalised to adult HIV infected patients on ART in other public ART clinics in urban centres in Namibia. Findings from this study would need to be generalised with caution to other public ART clinics in limited resource settings in other countries.

### **3.13 Ethical considerations**

Participation in this study was voluntary for all the eligible participants on ART. Community counsellors explained the purpose and objectives of the study and assured prospective participants of confidentiality and voluntary participation without any adverse consequences from not participating in the study. (Participants Information Sheet Appendix C). Each

participant was provided with a consent form that was signed before participating in the study. (Informed consent Appendix D). Participants were also informed of their right to withdraw at any point from the study without having to provide any reasons for their withdrawal. All participants were given adherence counselling and support routinely available at the clinic. The confidentiality of participants was guaranteed because only participant's pharmacy number was used as an identifier and research data were stored in a password controlled computer. The SMS message used was a general one so that it would not be able to deduce the participants HIV status based on viewing the message. This was important as the possibility of someone else viewing the message on participants' phones was thought to be high. Ethical approval was granted by the University of the Western Cape Senate Research Committee and from the Policy Management Development and Research Committee of the Ministry of Health and Social Services Namibia.

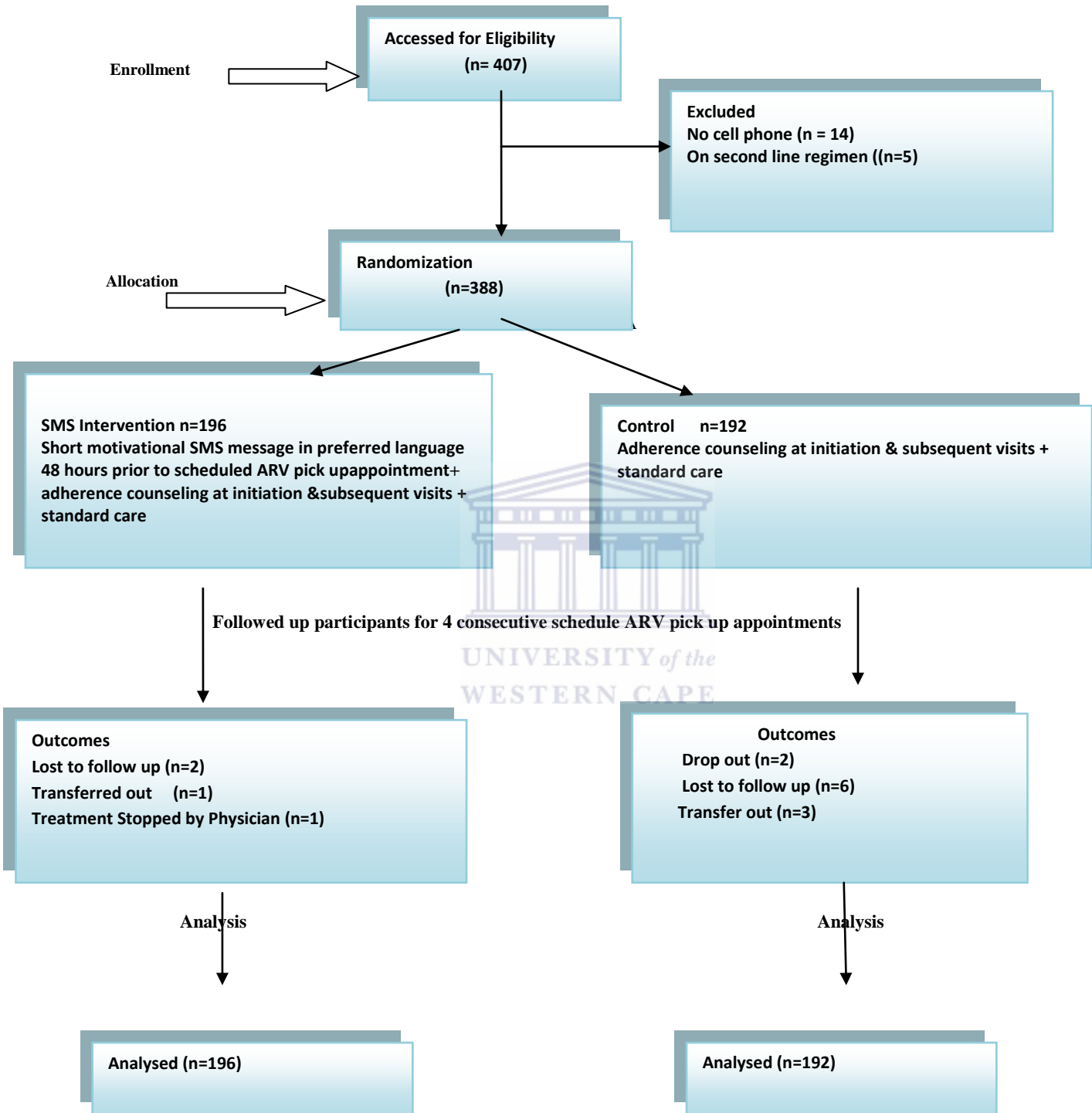


## CHAPTER 4 RESULTS

### 4.1 Sample realisation

Figure 1 shows that 407 patients on ART were approached and recruited between December 2012 and February 2013. There was no report of any patient declining to participate in the study. Of the 407 patients recruited 14 (3.9%) were not eligible because they did not have a functional cell phone (this translates into 96.6% cell phone ownership rate) and 5 patients were on second line treatment regimens (regimens containing protease inhibitors). Three hundred and eighty eight eligible clients were randomized into either the SMS intervention arm (n = 196) or the control arm (n = 192). Figure 1 shows the acquisition, follow-up and outcomes of the sample in the intervention and control groups. Two participants in the intervention group became lost to follow-up whereas 6 were lost to follow up in the control group. In addition 1 participant in the intervention group had his treatment stopped by the attending physician, while 4 participants, comprising of 1 participant from the intervention group and 3 from the control group, were transferred out of the facility and continued their treatment at another facility. Two participants dropped out from the control group without offering any reason for dropping out. An intention to treat approach was adopted in the analysis, which entailed that all participants were analyzed based on their initially allocated group.

**Figure 1: Flow diagram of the acquisition, randomisation and follow-up of the sample**



## 4.2 Socio-economic and demographic description of participants

Table 1 shows the socio-economic and demographic baseline characteristics of participants between the intervention and control groups. The groups are similar for most variables which indicates that potentially confounding factors have been balanced in both groups through the randomisation process. However, the percentage of males 114 (58.2%) in the intervention group is fairly larger than the percentage of males 89 (46.3%) in the control group, and there is a fairly large difference in the single and married categories between the intervention and control groups as well, demonstrating that the randomisation process is not infallible.



**Table 1: Patients socio-demographic characteristics, disclosure status, treatment supporter reminder and regimen characteristics at baseline in the intervention and control groups**

Variable	Intervention Group n= 196	Control Group n=192
<b>Age (Years) mean SD, IQR</b>	39.8 (8.4, 34- 45)	40.5: (8.8, 34- 45.5)
<b>Gender (%)</b>		
Male	114 (58.2%)	89 (46.3%)
<b>Marital Status (%)</b>		
Single	88 (44.9%)	104 (54.1%)
Married	61 (31.1%)	44 (22.9%)
Widowed	7 (3.6%)	4 (2%)
Divorced/Separated	4 (2%)	4 (2%)
Co-habiting	33 (16.8%)	36 (18.8%)
<b>Location (%)</b>		
Tamariskia 4km from facility	5 (2.6%)	4 (2.1%)
Mondesa 5km from facility	64 (32.7%)	70 (36.5%)
Tulinawa 8km from facility	31 (15.8%)	33 (17.2%)
DRC 15km from facility	76 (38.8%)	74 (38.5%)
Vineta 5km from facility	2 (1%)	2 (1%)
Town 3km from facility	3 (1.5%)	1 (0.5%)
Nonidas 15km from facility	2 (1%)	2 (1%)
Others	6 (3%)	1 (0.5%)
<b>Employment (%)</b>	n=193	n=191
Employed	139 (70.9%)	133 (69.3%)
<b>Type of Employment (%)</b>		
Government	2 (1.4%)	2(1.5%)
Private company	103 (72.5%)	99(74.4%)
farm	10(7%)	10 (7.5%)
Self employed	27(19%)	22 (16.5%)
<b>Monthly Income N\$ mean (SD,IQR)</b>	2,110 (1,772, 1000 – 2700)	2,161 (1,774, 900 – 3000)
<b>Alcohol consumption (%)</b>		
Yes	56 (28.9%)	55 (28.8%)
<b>Units alcohol consumed mean (SD,IQR)</b>		
Units/ weekend	2.3 (1.3, 1 – 3)	2.4 (1.5, 1- 3)
Units /per day	2 (0.4, 0 – 2)	1.3 (1.17,0.2 – 2)
<b>Treatment characteristics</b>		
<b>First line treatment regimens (%)</b>		
AZT/3TC/NVP	74 (37.9%)	63 (32.8%)
AZT/3TC/EFV	17 (8.7%)	20 (10.4%)
TDF/3TC/NVP	67 (33.9%)	86(44.8%)
TDF/3TC/EFV	34(17.4%)	22(11.5%)
D4T/3TC/NVP	3(1.5%)	1(0.5%)
D4T/3TC/EFV	1(0.5%)	0
<b>Duration on ART (Years) mean SD IQR</b>	3.54 (2.40; 2.00-5.00)	3.68 (2.39; 2.00-5.00)
<b>Treatment supporter (%)</b>		
Yes	179 (92.3%)	174 (90.6%)
<b>Treatment Supporter reminder (%)</b>	n=179	n=174
Always	107 (59.4%)	94 (51.9%)
Occasionally	40 (22.2%)	44 (24.3%)
Never	33(18.3%)	43 (23.7%)
<b>Status Disclosure (%) Yes</b>	175 (93.6%)	171 (90.9%)
<b>Type of regimens (%)</b>		
once daily	34 (17.3%)	22(11.5%)

### 4.3 Participants preferences regarding SMS telephonic reminders

Table 2 shows the proportion of study participants who wanted a telephonic appointment reminder. Among those that preferred to receive a telephonic appointment reminder, their preferred type of reminder (SMS, or call, or both), their preferred time for receipt of the reminder and whether they have shared a phone with someone or not, is described as well. Out of the 388 participants randomized into the study, 137 (35%) preferred not to be reminded of their scheduled medication pick-up appointment. In principle unsolicited SMS reminders were sent to participants who preferred not to be reminded of their medication appointment. Of the 251 study participants that preferred to be reminded of their appointments, 130 (52%) preferred to be reminded with SMS only and 136 (54%) did not object to being reminded at any time of the day. Telephonic appointment reminders may be perceived as being intrusive on patients' privacy and could result in a break in confidentiality especially if patients share their phone with others. However, in this study only 81(21.6%) of study participants shared their phone with others.

**Table 2: Proportion of patients who prefer to be reminded of their medication appointments, type of reminder, preferred timing of the reminder and shared phone usage**

Variable	Intervention	Control
<b>Would like a Reminder or not</b>	n=196	n=192
Wanted a reminder	131 (66.8%)	120 (62.5%)
<b>Type of Reminder Preference</b>	n=131	n=120
Calls only	26 (19.6)	15 (12.4)
SMS only	62 (47.3)	68 (56.2)
Calls & SMS	43 (32.8)	37 (31.4)
<b>How many days before your appointment do you prefer to receive your reminder</b>	n=129	n = 120
1	38 (29.5)	31 (25.8)
2	50(38.8)	48 (40)
3	33(25.9)	19 (15.8)
4	3 (2.3)	12(10)
5	5(3.9)	10 (8.3)
<b>Preferred time of the day</b>	n = 129	n = 120
Morning	32 (24.8)	32 (26.7)
Afternoon	20 (15.5)	15 (12.5)
Evening	5 (3.9)	9(7.5)
Anytime	72 (55.8)	64 (53.3)
<b>Phone sharing</b>	n = 185	n = 189
Yes	39 (21.1)	42 (22.2)

#### **4.4 The absolute and relative association between SMS reminders and socio demographic parameters on adherence to medication pick up appointments**

Participants who were on-time for all the four scheduled medication refill appointments were considered to have kept their appointment, whereas participants who were late for any of the scheduled medication refill appointments were considered to have missed the appointment.

In this study a 'strict definition' of on-time for a scheduled medication appointment required that participants show up for their medication refill on the scheduled appointment date. In the case of the 'loose definition' criteria, participants who showed up for medication refill appointment one to two days after the scheduled appointment date were considered to be on-time.

Table 3 demonstrates the association between the SMS reminder intervention (and other independent variables) and the outcome variable of whether the medication appointment was kept or not. The relative risk was measured as the cumulative incidence ratio (CIR) while the absolute effect was measured as the risk difference (RD). The CIR as well as the RD showed a statistically significant association between the SMS intervention and adherence to scheduled ARV pick up appointments. None of the socio-demographic characteristics of the patients evaluated in this study showed statistically significant associations with adherence to medication pick up appointments.

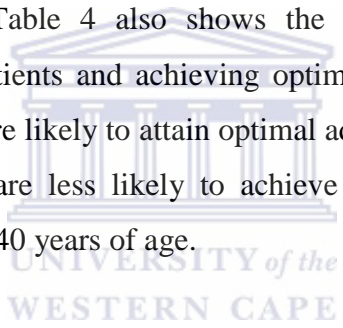


**Table 3: Bivariate analysis of the absolute and relative association between SMS reminders and socio-demographic variables on adherence to medication pick up appointments.**

Variable	Kept all medication appointments	Missed medication Appointment	CIR (95% CI)	Risk Difference (95% CI)
Received SMS reminder	112 (57.1%)	84(42.9%)	1.61 (1.29 – 2.02)	21.7 (12 – 31.4)
Control	68 (35.4%)	124 (64.6%)		
<b>Gender</b>				
Female	89 (48.1%)	96(51.9%)	1.07 (0.87-1.33)	3.3 (-6.7 – 13.2)
Male	91(44.8%)	112(55.2%)		
<b>Alcohol consumption</b>				
≤ 1 units/day & ≤ 2 units/weekend	158(47%)	178(53%)	1.09 (0.78-1.52)	3.9 (-10.7 – 18.5)
> 1 units/day & or > 2 units/weekend	22(43.1%)	29(56.9%)		
<b>Age</b>				
40 - 70 years	95(48.2%)	102(51.8%)	1.08 (0.87 - 1.34)	3.7 (-6.2 – 13.6)
18 -39 years	85(44.5%)	106(55.5%)		
<b>Disclosure status</b>				
Disclosed	160(46.2%)	186(53.8%)	1.02 (0.68 - 1.53)	1.1 (- 17.2 – 19.4)
Non-Disclosure	14(45.2%)	17(54.8%)		
<b>Duration on ART</b>				
≤ 1 year	25(35.7%)	45(64.3%)	0.73 (0.52 - 1.02)	-13.0 (- 25.5 – (- 0.53)
> 1 year	155(48.7%)	163(51.3%)		
<b>Employment</b>				
Employed	133(48.7%)	140(51.3%)	1.21 (0.94 - 1.57)	8.5 (- 2.3 – 19.4)
Unemployed	45(40.2%)	67(59.8%)		
<b>Location from facility</b>				
Live near facility	67(44.4%)	84(55.6%)	0.94 (0.75- 1.18)	- 2.9 (-13.0 – 7.3)
Live far from facility	111(47.2%)	124(52.8%)		
<b>Monthly Income</b>				
> N\$1000	90(49.2%)	93(50.8%)	1.12 (0.90 - 1.39)	5.28 (- 4.7 – 15.2)
≤ N\$ 1000	90(43.9%)	115(56.1%)		
<b>Marital status</b>				
Single/widowed/separated/divorced	96(45.7%)	114(54.3%)	0.97 (0.78 - 1.20)	-1.4 (-11.4 – 8.6)
married/cohabiting	82(47.1%)	92(52.9%)		
<b>Preference to be reminded</b>				
Needs reminder	120(47.8%)	131(52.2%)	1.11(0.88-1.42)	4.9 (-5.54 – 15.2)
Does not want to be reminded	58(43%)	77(57%)		
<b>Treatment Supporter reminder</b>				
Always/occasionally	130 (45.8%)	154 (54.2%)	0.91 (0.71–1.2)	- 4.2 (- 8.4 – 16.9)
Never	38(50.0%)	38 (50%)		
<b>Regimens</b>				
Once daily regimens	32(57.1%)	24(42.9%)	1.28(0.99 – 1.66)	12.6 (-1.46 – 26.6)
Twice daily regimens	148(44.6%)	184(55.4%)		

#### **4.5 The absolute and relative association between SMS reminders and other independent factors and adherence to antiretroviral medications.**

Table 4 shows the association between SMS intervention and adherence to medications as well as the association between keeping ARV pick up appointments and adherence to medications. Evidence from studies on adherence amongst patients with chronic disease conditions suggests that self-reported measures of adherence are often biased upward. Hence for the self-reported measure of adherence to medication, we adopted beforehand a 100% cut-off point which represents an upper bound estimate (Gilford et al., 2000). Expectedly, a significantly higher self-reported adherence was recorded as compared to pill count adherence. Participants who received the SMS reminder were slightly more likely to be adherent to their medication, while participants who kept all medication pick up appointments were two times more likely to attain optimal adherence to their medication. Table 4 also shows the association between some socio-demographic characteristics of patients and achieving optimal adherence. Our findings shows that only those employed were more likely to attain optimal adherence. On the other hand, adults who are less than 39 years old are less likely to achieve optimal medication adherence as compared to adults who are above 40 years of age.



**Table 4: Bivariate analysis of the absolute and relative association between SMS reminders, keeping appointments and patients socio-demographic characteristics and adherence to medications.**

		Adherence by pill count				Adherence by self-report			
		Optimal adherence ≥95%	Sub optimal Adherence < 95%	CIR 95% CI	RD (95% CI)	Optimal adherence 100%	Sub optimal Adherence < 100%	CIR 95% CI	RD (95% CI)
<b>Intervention</b>	SMS intervention	149	47	1.14 (1.01-1.30)	11.4 (2.4 -20.5)	171	25	1.18 (1.07 –1.31)	14.3 (6.5 – 22.2)
	Control	127	65			140	52		
<b>Kept appointments</b>	Kept all appointment	171	6	1.9(1.69- 2.24)	46.9(39.6 -54.4)	172	5	1.47 (1.33- 1.62)	29.8(22.8-36.8)
	Missed appointment	104	106			139	71		
<b>Alcohol:</b>	≤ 1 units/day & or ≤ 2 units/weekend	233	103	0.90 (0.77 1.07)	-7.1(-19.8-5.5)	266	70	0.92 (0.81 - 1.03)	-7.1(-17.5-3.3)
	> 1 units/day & or > 2 units/weekend	39	12			44	7		
<b>Age:</b>	40-70 years	127	64	0.87( 0.77-0.99)	-9.7(-18.7 –0.63)	149	42	0.94 (0.85 - 1.04)	-4.2(-12.2-3.7)
	18-39 years	149	48			162	35		
<b>Employment:</b>	Employed	207	66	1.26 (1.07 – 1.49)	14.9(4.5-25.3)	231	42	1.19 (1.05 –1.36)	13.7(4.2-23.2)
	Unemployed	67	45			79	33		
<b>Gender:</b>	Female	128	57	1.05 (0.93 – 1.20)	-4.3(-13.4-4.8)	147	38	0.98 (0.89 - 1.08)	-1.3(-9.3-6.6)
	Male	148	55			165	38		
<b>Marital status:</b> Single/widowed/separated/divorced		149	61	1.04(0.92- 1.19)	1.4(-7.8-10.6)	171	39	1.05(0.95 – 1.16)	3.3(-4.8-11.3)
	married/cohabiting	121	53			136	38		
<b>Location:</b>	Live near Facility	105	45	0.97(0.85 – 1.11)	-2.2(-11.6-7.2)	116	34	0.94(0.84 -1.04)	-4.2(-12.5-4.1)
	Live far from facility	169	66			193	42		
<b>Monthly Income:</b>	> N\$ 1000	134	49	1.07 (0.95-1.23)	-5.4(-3.6-14.5)	153	30	1.08(0.98 – 1.19)	-6.5(-14.4-1.3)
	≤ N\$ 1000	139	66			158	47		

#### **4.6 The absolute and relative association between various independent variables and adherence to antiretroviral medications**

Table 5 highlights the absolute and relative association between patients preference to be reminded or not, HIV disclosure status, receiving a reminder by a treatment supporter, type of treatment regimen and adherence to medication. The results from the bivariate model demonstrate no statistical significance between any of the variables and achieving optimal adherence as assessed by both pill count and self-report.



**Table 5: Bivariate analysis of the absolute and relative association between patients preference to be reminded or not, disclosure status, reminder by treatment supporter, type of regimen and telephonic SMS reminder on medication adherence.**

	Adherence by pill count				Adherence by self-report			
	Optimal adherence ≥95%	Sub optimal Adherence < 95%	CIR 95% CI	RD (95% CI)	Optimal adherence 100%	Sub optimal Adherence < 100%	CIR 95% CI	RD (95% CI)
<b>Reminded by treatment Supporter:</b>								
Always/occasionally	196	88	0.95(0.89-1.12)	-3.4(-14.8-8.0)	226	58	0.94 (0.84 –1.04)	-6.0(-15.1-3.3)
Never	55	21			65	11		
<b>ART Regimens:</b>								
Once daily regimens	43	13	1.02 (0.90 - 1.17)	7.5(-4.6-19.6)	46	10	1.10( 0.94- 1.30)	2.3(-8.6-13.2)
Twice daily regimens	233	99			266	66		
<b>Disclosure status:</b>								
Disclosed	243	103	0.87 (0.72 - 1.04)	-7.5(-22.9-8.0)	275	71	0.91 (0.79 –1.05)	-7.9(-20.5 – 4.7)
Non disclosed	25	6			27	4		
<b>Duration on ART:</b>								
≤ 1 year	41	26	0.83(0.68 – 1.01)	-12.6(-25.1--0.2)	54	13	0.99(0.87 – 1.13)	-0.2(10.5-10.2)
> 1 year	233	84			255	62		
<b>Preference to be reminded:</b>								
Need reminder	98	37	1.01 (0.89 - 1.16)	1.4(-8.1-10.9)	113	22	1.07 (0.87 –1.18)	5.6(-2.5-13.7)
Does not want to be reminded	176	75			197	54		

#### 4.7 Independent predictors of adherence to appointments for medication pick-up

In this study, although we found that only the SMS intervention was significantly associated with adherence to scheduled medication pick up appointments, we treated all variables with a p value  $\leq 0.1$  as potential confounders and proceeded to assess their effect via backward stepwise regression multivariate logistic model, which initially included all variables with the above criterion. Table 6 shows the initial multivariate logistic model.

**Table 6: Multivariate logistic regression analyses of potential predictors of honouring medication pick up appointments with all variables with a P value of 0.1 or lower on bivariate analysis included.**

Variable	Adjusted CIR 95%CI	p-value
<b>Group:</b> SMS Intervention	3.51(2.03-6.05)	0.00
control		
<b>Duration on ART:</b> $\leq 1$ year	0.84(0.41-1.74)	0.64
$>1$ year		
<b>Treatment supporter reminder:</b> Always/occasionally	0.79(0.40-1.57)	0.51
Never		
<b>Employment status:</b> employed	1.61(0.86-2.99)	0.14
unemployed		
<b>Regimens Type</b> Once daily regimens	1.70 (0.77-3.76)	0.19
Twice daily regimens		
<b>Reminder preference</b> willing to be reminded	0.79 (0.52-1.18)	0.24
Not willing to be reminded		

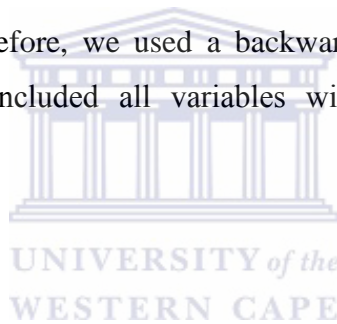
Table 7 shows the final multivariable logistic regression model using a backward stepwise approach, after all variables which after initial inclusion had a P value of greater than 0.2 were removed from the subsequent models. The final model showed an independent association of SMS intervention with adherence to appointments.

**Table 7: Final backward stepwise regression model of predictors of honouring medication appointment pick ups.**

Variable	Adjusted CIR 95%CI	p-value
<b>Group:</b> SMS Intervention	2.65(1.72-4.08)	0.00
control		
<b>Regimens Type</b> Once daily regimens	1.52 (0.84-2.73)	0.16
Twice daily regimens		

#### **4.8 Independent predictors of adherence to antiretroviral medications**

Table 8 shows the predictors of adherence to medications assessed by pill count in a multivariate logistic regression analysis. As before, we used a backward stepwise regression multivariate logistic model, which initially included all variables with a p value  $\leq 0.1$  as potential confounders.



**Table 8: Multivariate logistic regression analysis to determine predictors of medication adherence as assessed by pill count and self-report, with all variables with a P value of 0.1 or lower on bivariate analysis included.**

Variable	Pill count			3 days self-report		
	Adjusted 95%CI	CIR	P value	Adjusted 95%CI	CIR	P value
<b>Group:</b> SMS intervention	1.25(0.71-2.20)		0.43	2.31(1.23-4.36)		0.00
control						
<b>Adherence to appointments:</b> Kept all medication appointments	20.99(9.59-45.97)		0.00	9.43(4.11-21.67)		0.00
Missed medication appointment						
<b>Alcohol:</b> ≤ 1 units/day and ≤ 2 units/weekend	1.84(0.82-4.16)		0.14	1.85(0.70-4.91)		0.21
> 1 units/day and > 2 units/weekend						
<b>Employment status:</b> employed	1.91(1.06-3.42)		0.03	1.97(1.07-3.63)		0.02
unemployed						
<b>Disclosure Status:</b> Disclosed status	0.76(0.27-2.12)		0.60	0.64(0.19-2.10)		0.46
Non –Disclosed status						
<b>Treatment-Supporter Reminder:</b> Always/occasionally	1.18(0.59-2.35)		0.65	0.77(0.36-1.67)		0.51
Never						
<b>Age:</b> 40 – 70 years	0.69(0.40-1.20)		0.19	1.01(0.57-1.88)		0.91
18 – 39 years						

Table 9 shows the final model using a backward stepwise approach to determine the predictors of adherence to medications with variables having a P value > 0.2 being removed at each stage. Table 9 shows that receiving a telephonic SMS reminder and employment status are independent



predictors of adherence to antiretroviral medication

**Table 9: Final backward stepwise regression model of predictors of adherence to medication as assessed via pill count and 3 day self-report.**

Variable	Pill Count			3 Days Self-report		
	Adjusted 95%CI	CIR	P value	Adjusted 95%CI	CIR	P value
<b>Group</b>						
SMS intervention	1.15(0.68-1.95)		0.59	2.07(1.16-3.71)		0.01
control						
<b>Adherence to appointments:</b>						
Kept all medication appointments	21.61(10.00-46.68)		0.00	10.63(4.69-24.13)		0.00
Missed medication appointment						
<b>Employment status:</b>						
employed	1.97(1.13-3.42)		0.02	2.16(1.22-3.82)		0.00
unemployed						

In the final multivariate model, after removing kept medication appointments as it is likely to be an intermediate variable between receiving an SMS reminder and adherence to medication we found receiving an SMS reminder and being employed to be independently positively associated with adherence to antiretroviral medication (on both pill counts and self-report).

**Table 10: Backward stepwise regression model of predictors of adherence to ART via pill count adherence measurement and 3day self-report of adherence, with ‘adherence to appointments excluded.**

Variable	Pill Count			3 Days Self-report		
	Adjusted 95%CI	CIR	P value	Adjusted 95%CI	CIR	P value
<b>Group</b>						
SMS intervention	1.84 (1.17 – 2.88)		0.00	2.81 (1.63 – 4.04)		0.00
control						
<b>Employment status</b>						
employed	1.95 (1.21 – 3.11)		0.00	2.18 (1.28 –3.72)		0.00
unemployed						

#### **4.9 The influence of patients' preference to be reminded or not as a potential effect modifier on adherence to medication appointments for strict and loose criteria.**

Table 11 shows the sub analysis of adherence to medication appointments stratified by participants preference to receive a telephonic/SMS reminders or not. The absolute and relative effect of SMS reminders on adherence to medication appointments for both strict and loose adherence to medication appointment is also highlighted. We noted that those who 'preferred to receive a telephonic/SMS reminder' had a greater risk difference and cumulative incidence ratio than those who 'preferred not to receive a telephonic/SMS reminder' for both strict and loose adherence criteria adherence to appointments, which was statistically significant for the loose criteria but not for the strict criteria. This suggests that 'preferred to receive a telephonic/SMS reminder' is probably an effect modifier for adherence to appointments.



**Table 11: Participants preference to receive reminders and its influence as a potential effect modifier on adherence to medication appointments for strict and loose criteria**

		Strict criteria				Loose criteria			
		Kept all appointment	Missed appointment	CIR 95% CI	RD 95%CI	Kept all appointment	Missed appointment	CIR 95% CI	RD 95%CI
<b>All participants: regardless of preference</b>	SMS intervention n=196	<b>112</b>	<b>84</b>	1.61(1.29-2.02)	21.7(12.0-31.4)	144	52	1.47(1.25-1.73)	23.5(14.1-32.9)
	Control n=192	<b>68</b>	<b>124</b>			96	96		
<b>Preferred to be reminded</b>	SMS intervention n=131	80	51	1.83(1.37-2.44)	27.7(13.9-39.6)	99	32	1.71(1.59-2.14)	31.4(19.9-42.9)
	Control n=120	40	80			53	67		
<b>Preferred not to be reminded</b>	SMS intervention n=63	30	33	1.61(0.83-1.80)	8.7(-7.9-25.4)	43	20	1.14(0.89-1.47)	8.5(-7.6-24.7)
	control n=72	28	44			43	29		

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#### **4.10 The influence of patients' preference to be reminded or not as a potential effect modifier on adherence to medication.**

Table 12 shows the results from the sub-analysis of the influence of the SMS intervention on medication adherence among patients who indicated a preference on whether “to be reminded or not to be reminded” of their medication refill appointments during the pre-intervention survey. The results indicate that SMS reminders had a statistically significant positive association with adherence to medication among the cohort of patients who were willing to be reminded of their appointments, but not amongst those who were not willing to be reminded of their appointments. The actual CIR and RD differences between the two groups (prefer SMS reminder and prefer not to receive SMS reminder) were however small and were not statistically significant. This however still suggests that, although not conclusively shown by this study, willingness to receive a SMS reminder probably acts as an effect modifier on the relationship between receiving a SMS reminder and adherence to medication.



**Table 12: Participants preference to receive reminders and its influence as a potential effect modifier on medication adherence assessed pill count and 3 day self –report.**

	Intervention	Adherence by pill count				Adherence by self-report			
		Optimal adherence ≥95%	Sub optimal Adherence < 95%	CIR 95% CI	RD 95%CI	Optimal adherence 100%	Sub optimal Adherence < 100%	CIR 95% CI	RD 95%CI
<b>All participants: regardless of preference</b>	SMS intervention	149	47	1.14(1.01-1.31)	11.4(2.4-20.5)	171	25	1.18(1.07-1.31)	14.3(6.5-22.2)
	Control	127	65			140	52		
<b>Preferred to be reminded</b>	SMS intervention	102	29	1.28(1.08-1.52)	17.0(5.8-28.3)	113	18	1.25(1.08-1.43)	17.1(6.9-27.2)
	Control	73	47			83	37		
<b>Preferred not to be reminded</b>	SMS intervention	45	18	1.00(0.21-1.25)	0.6(-14.7-15.9)	56	7	1.12(0.96-1.30)	9.72(-2.5-21.9)
	Control	51	21			57	15		

#### **4.11 Number of late Days**

A Risk Difference (Attributable risk) of 22% 95% CI (12.1 – 31.5) was recorded for SMS reminders and missed appointments in this study. The mean number of days late was 3.8 and 8.3 days for the SMS and control groups respectively with a statistically significant mean difference of 4.4 days late 95% CI (2.7 – 6.2).



## **Chapter 5**

### **Discussion**

#### **5.1 Introduction**

This chapter discusses the findings from the study on the effectiveness of motivational telephonic SMS reminders influence on adherence to medication pick up appointments as well as adherence to antiretroviral medications at the Swakopmund State Hospital ART clinic. The influence of participants socio-economic and demographic characteristics on the effectiveness of SMS reminders to adherence is also discussed in this chapter. In addition the association between adherence to scheduled medication refill appointments and adherence to medications was explored.

#### **5.2 SMS reminders and adherence to scheduled medication pick up appointments**

Scheduled medication pick up appointments significantly increased the likelihood of honoring all medication appointments in an urban HIV setting in Namibia. The results shows that study participants that received the SMS reminder were 1.6 times more likely to honour all medication pick up appointments as compared to participants that did not receive the SMS reminder. Additionally, after adjusting for duration on ART, treatment supporter reminder, employment status and the patient preference of receiving reminder or not, the final multivariate model demonstrates that SMS reminder is an independent predictor of adherence to scheduled medication pick up appointments with CIR 2.65 (95% CI: 1.72-4.08).The risk difference indicates that the SMS intervention reduced the risk of missing medication pick up appointment by about 22% as compared to participants that did not receive the reminder.

In this study, a strict and a loose criterion were set beforehand for on-time medication pick up appointments. This is due to the fact that in routine clinic practice, patients are normally given extra medicines to cover for 2 days after the scheduled appointment date (MoHSS, 2014). Expectedly, more participants kept all appointments using the loose criteria as compared to the strict criteria, and it is important to note that our result shows that the SMS intervention improved the likelihood of honoring all appointments in both the strict and loose criteria for on-

time pick up for medication. Despite the positive results we found for the effect of the SMS intervention on adherence to medication appointments, we should be circumspect about this finding as evidence for the effectiveness of SMS reminders on attendance rate is sparse and has not been consistent. A study from a rural clinic in Sierra Leone showed that daily SMS reminders sent 2 days prior to clinic appointments did not improve adherence to medication appointments (Kelly et al., 2012). Even though that study was an RCT, it was limited by an inadequate sample size and short evaluation period. Likewise, a randomized control study conducted in Switzerland in which phone call, SMS reminder and postal reminders were sent sequentially to patients in a primary health clinic, reduced missed appointment from 11.4% to 7.8%, however sub analysis of the effect of the sequential intervention in the HIV outpatient department did not show significant improvement in attendance rate (Perron et al., 2010), on the contrary, the positive results from this current study are corroborated by the findings from 2 systematic reviews. In the systematic review made up of 8 RCTs and 10 observational studies reported by Rebecca et al. (2012) it was found that the SMS reminder increased the likelihood of kept appointment by 50% as compared to participants that did not receive the reminder in primary health care and hospital outpatient settings. In this review, SMS reminders were significantly associated with the likelihood of honouring clinic appointments with a RR of 1.48 (95% CI: 1.23-1.72) with no significant sub group differences by clinic type.

Likewise, in another systematic review of 8 RCTs involving 6,615 participants, Gurol-Urganci et al. (2013), reported that 7 out of the 8 RCTs showed that SMS reminders substantially improved attendance rates of clinic appointments as compared to no reminders with a RR 1.14 (95% CI: 1.03-1.26) in primary health care and hospital outpatient settings. It is important to note that the types of clinics in the hospital outpatient settings were not specified in both systematic reviews. It is also worth noting that in our current study the participants in the control arm had a higher adherence to medication pick-up appointments than that found in the 2012 Namibian National Adherence Baseline Survey (Tjijuka et al. 2013). Whether this is due to inherent higher than national average adherence at Swakopmund State Hospital, or whether the counselling at each visit resulted in an increased adherence among the patients at Swakopmund State Hospital is unclear, and since counselling at every appointment has become standard care, we could not ethically include an additional 'without counseling arm' to this study.



***Preference to receive SMS/telephonic reminders or not and adherence to medication appointment:*** The use of mobile phones has been shown to improve service utilization among population groups such as teenagers and young adults, however it has been noted that a significant proportion of older adults may be less able or willing to use mobile phones hence limiting the potential benefit in this population group (Horvart et al., 2012). The pre-survey revealed that 35% of study participants preferred not to be reminded of their medication pick up appointments. It is not unlikely that the concern of stigma and discrimination associated with HIV infection may be one of the factors responsible for unwillingness to receive reminders by some patients. Stigma and discrimination associated with HIV infection may either be perceived or real, for instance over 10% of respondents in the National adherence baseline survey of 2012 reported that employers refused to give permission to take time off for clinic visits and likewise, 10% of patients did not want it to be known that they were receiving ARVs. Sub analysis of participants preference to be reminded or not to be reminded showed a higher CIR and RD among patients who preferred to receive an SMS reminder, for honouring all medication appointments using the strict criteria. It is important that policy makers consider participants need or willingness to receive reminders in the rollout of the SMS intervention, even though an improvement was noted even among patients that did not want a reminder as we anticipate a more cost effective intervention among patients willing to receive the SMS reminder, due to the higher likelihood of it being more effective in this group.

***The timing of the reminder:*** Data from this study suggests that patients preferences for timing of the telephonic SMS reminder varied and it was evenly spread out over 1-3 days, which makes it quite difficult to choose the best time to send the SMS reminder. It is also likely that if the reminder were to be sent daily repetitively over the commonest time period chosen, of 3 days, then the problem of patients getting annoyed by the repeated SMSes which might appear as “spam”, may not be ruled out. In this same vein, Pop-Elleches et al. (2012) reported that more frequent and repeated reminders may bring about a diminishing effect in adherence and in particular he reported that daily SMS reminders were less effective compared to weekly SMS reminders, on adherence to ART. Taking this insight into consideration and noting that over 67% of study participants who indicated a need for a reminder in the pre-intervention survey, preferred to receive their reminder 2 days prior to their scheduled medication pick up appointment, we opted to deliver the intervention 2 days prior to scheduled medication pick up

appointments. Furthermore, results from a meta-analysis of 7 RCTs reported by Guy et al.,(2012) showed no significant sub group differences by message timing of reminders delivered 24, 48 and 72 hours prior to scheduled appointments.

***Message content and adherence to medication appointments:*** Telephonic / SMS preventive health programs are theoretically more likely to demonstrate greater impact potential if their content is based on evidence of effectiveness and follows the advice of behavioral change theory (Fry and Neff, 2009). We acknowledge that this intervention was not based on any specific behavioral change theory such as the health belief model or the theory of planned behavior. However, it has been proven that SMS reminders are an effective means of support, encouragement and reinforcement of positive health behaviors even when the intervention is not specifically based on any change theory (Cole-Lewis and Kershaw, 2010). It is important to note that this intervention was based on the evidence that forgetfulness is a major reason reported by patients at Swakopmund for missing or not keeping scheduled clinic or medication pick up appointments. The Namibia national adherence baseline survey of 2012 also revealed that 67% of patients reported forgetfulness as the major reason for not keeping scheduled medication refill appointments (Tjijuka et al., 2010). The impact of the message content on the outcome of the intervention cannot be fully ascertained because there is sparse evidence to suggest that the way the message is framed may influence patients response to making a behavioral change or not, however Pop-Elleches (2010) showed that the length of the message does not influence adherence. Despite the rejoinder by Pop-Elleches above, we thought it prudent to steer clear of long and potentially annoying messages, therefore in this study the message was kept short and simple: “This is your reminder; we care for you and the appointment date”. However, for an HIV setting, it is important that the message be discreet because of privacy and confidentiality concerns. Considering the fact that about 22% of the study participants reported shared phone usage, it was therefore imperative that the SMS message be communicated in such a way that patients HIV status was not inadvertently disclosed to third parties.

### **5.3 Association between adherence to scheduled medication pick up appointments and achieving optimal antiretroviral medication adherence.**

This study demonstrates that patients who kept all scheduled medication pick up appointments are two times more likely to achieve optimal adherence to ART, as compared to those who miss one or more scheduled medication appointments, with a large and significant risk difference for both adherence assessed by pill count 47% and self-reported adherence 30%. Similarly, results from the bivariate analysis indicates a statistically significant positive association (both relative and absolute) between adherence to appointments and achieving optimal adherence to medication. However, the adjusted CIR increased significantly from the bivariate level, demonstrating that keeping all medication appointments is a partial or intermediate predictor of adherence to ART, because patients who received the SMS reminder are more likely to keep all appointments and those who achieve optimal adherence to ART are also more likely to honour all medication appointments. This correlation between keeping medication appointments and adherence to ART has been described by Kunutsor and colleagues, (2010) in a rural hospital in Uganda, in which a cohort of treatment experienced patients on ART were followed up for 28 weeks. Interestingly, adherence was assessed by both clinic based pill counts and self-reported adherence, with similar definitions of optimal adherence as adopted in the current study. Their result showed that adherence to appointments is a strong predictor of adherence medications. Even though we could not correlate adherence to viral suppression or clinical outcome due to cost and logistic constraints, Park et al., (2007) in a prospective cohort study in which 387 patients were followed up for one year after initiating ART in an urban referral hospital in South Korea, found missed clinic visits to be a strong predictor of poor clinical outcome in HIV infected patients. Moreover, previous studies done in resource limited settings have also correlated pill count and self-reported adherence measures to patients viral load suppression. We therefore do not envisage that the detractive value of this study will be much affected by the non-assessment of patients' viral load and other clinical outcomes, as there is evidence for this link (Elul et al., 2011; Mugavero et al., 2010).

Regardless of documented challenges associated with pill count such as patients dumping pills, as well as patients not coming to the pharmacy with left-over pills and the social desirability and recall biases associated with self-reported measure of adherence, and while acknowledging that

both methods tend to overestimate adherence, pill count and self-report still remains the only practicable tools for the monitoring and the assessment of adherence to ART in resource-constrained settings (WHO, 2006). Despite its fallibility pill count and self-report are quite difficult to measure and require a considerable investment of resources and staff time if used as a monitoring tool of medication adherence. In the light of the above, and noting that monitoring patients adherence to medication is critical to maintaining the continuum of health care for PLHIV, using adherence to medication pick up appointments would be a useful and easy to monitor proxy measure and has the added benefit of being able to monitor the retention of patients in care (Tjijuka et al., 2012). As noted from our results discussed above, patients appointment keeping behaviour could indeed be used as a proxy marker for identifying non adherent patients to ART and would be especially useful in a resource-constrained setting. Considering the fact that at the Swakopmund State Hospital ART clinic patients visit the clinic more frequently for medication pick ups as compared to medical visits, and as such adherence issues are more likely to be identified and detected earlier during medication pick up visits from missed appointments. Furthermore, the appointment keeping data of patients could be tracked manually on the patients health passport and also electronically. In addition the use of the medication pick up appointment data is cost effective and easily retrievable by pharmacy staff and can be shared with the rest of the medical team for possible intervention, making it an ideal medication adherence measurement.

#### **5.4 The influence of duration on ART, disclosure status, treatment supporter reminder and type of regimen on the effectiveness of SMS reminders on adherence to scheduled medication pick up appointments.**

***Duration on ART:*** The mean duration of the study participants on ART was 3.6 years and this was fairly balanced for the intervention and control arm of the study. The findings from this study suggests that duration on ART is not significantly associated with adherence to medication pick up appointments. However, the bivariate model shows that 36% of the patients who have been on ART for less than 1 year kept all medication appointments as compared to 49% of patients on ART for more than 1 year. This infers that patients who have been on treatment for less than one year are less likely to honour all medication pick up appointments as

compared to patients on ART for more than one year. Similarly, Kunutsor et al.(2010) did not report any significant association between the duration on ART and adherence to appointments, however they noted that patients who are less than 2years on ART are less likely to honour all medication appointments.This indicates that being less than 1 to 2years on ART may be a risk factor for missing medication pick up appointments. Even though duration on treatment is not a predictor of adherence to appointments, it is worthy of noting that patients who miss one or two visits within the first year after initiating treatment, have an increased risk of mortality and lost to follow up (Brennan et al 2010). Furthermore non-adherence to clinic and medication pick up appointments very early after initiating ART, has been shown to reduce the overall effectiveness of treatment and result in poorer long term clinical outcomes in this group of patients (Park et al., 2006). Our results therefore suggest that in addition to SMS intervention for those patients willing to receive SMS reminders, other supportive measures such as early linkage to community or peer support groups must be considered for patients less than one year on ART.

***Treatment supporter reminder:*** A treatment supporter is anyone the patient chooses from amongst their family members, friends or workplace colleagues whose task is to accompany the patient to the clinic, provide support with daily adherence to ART, such as helping to pick up medications and reminding patients of appointments and taking medications on time. One of the social eligibility criteria for starting ART is that patients should ideally have a treatment supporter before they are initiated on ART. It is important to note that the guidelines state that patients should not be denied ART if they do not have a treatment supporter (MoHSS, 2014). It is therefore not a surprise that over 92% of the study participants reported having treatment supporters. The pre-intervention survey revealed that over 70% of study participants reported that their treatment supporter reminds them of their medication pick up appointments regularly, which is one of their roles as previously noted. Unexpectedly, the results from this study indicates that patients who were reminded of their appointment by treatment supporters were less likely to adhere to medication pick up appointment by about 11% than those who were not although this association was not statistically significant on either bivariate or multivariate analysis. Regrettably, we could not find any previous studies showing the impact of the role of treatment supporters on adherence to medication pick up or clinic appointments in a similar setting. We may however cautiously infer that the principle of habituation and diminishing response to frequent SMS reminders on adherence to medication noted above, may also apply to

repeated reminders of scheduled appointments by treatment supporters, to patients on ART. Additionally, it is likely that some HIV infected patients may find repeated reminders by supporters as overbearing and intrusive.

**Disclosure of HIV status:** The result from the pre-intervention survey revealed that over 92% of the study participants reported that they disclosed their HIV status to a friend, family member or spouse. The high level of disclosure rate is not unexpected noting the equally high proportion of study participants that reported having a treatment supporter. This study reports that patients' HIV disclosure status was not predictive of adherence to appointments based on the bivariate and multivariate regression analysis. Similarly, both the Namibian Antiretroviral Adherence Baseline Survey of 2012 and the Rwandan Antiretroviral Adherence survey of 2011 did not report a significant association between patients HIV disclosure status and adherence to medication pick up appointments. Generally, it is anticipated that patients who have disclosed their HIV status are more likely to be willing to receive SMS reminders without fear of stigmatisation. Whether perceived or actual, HIV related stigma still remains a formidable barrier to achieving optimal adherence to ART by HIV infected patients, in resource limited settings (Mills et al., 2006). Indeed previously 17% of patients on ART surveyed at the Swakopmund ART clinic reported work place related privacy issues as a reason for missing medication pick up appointments (Manhando & Uguro, 2012). It is not unlikely that some patients may miss their clinic appointments because they do not want their employers to know they are receiving ART, for fear of stigma and discrimination in the workplace. The finding from this study suggests that SMS reminders may not be effective in patients that are employed and have not disclosed their status. It is encouraging to note that throughout the duration of this study, there was no report of study participants requesting to stop receiving SMS reminders, or expressing concern that their HIV status being disclosed inadvertently, as a result of the SMS reminders.

**Type of regimens:** In general there are 6 first line regimens recommended in the Namibia ART guidelines. Of the 6 regimens only Tenofovir/Lamivudine/Efavirenz is a once daily regimen while the other 5 are twice daily regimens. It is worthy of note that before the launch of the revised guidelines in January 2014, Tenofovir/Lamivudine/Nevirapine was the preferred first line regimen. This explains the lower proportion of participants on the once daily regimen of Tenofovir/Lamivudine/Efavirenz, which at the time of our investigation, was then an alternate



first line regimen given to those who had a contraindication to Efavirenz. In this study there was no association between being on a once or twice daily regimen and adherence to medication pick up appointments. Review of the literature indicated sparse publication on the association between the frequency of dosing and adherence to appointments, rather published studies on regimens compared pill burden or frequency of dosing and adherence to medication (Elul et al., 2011;Tjituka et al., 2012; Nachege et al., 2014). It is important to note that pill burden was not considered in this current study.

### **5.5 The influence of socio-economic and demographic characteristics of patients on the effectiveness of SMS reminders on adherence to scheduled medication pick up appointments.**

Conclusions from previous studies on the influence of patients socio-economic and demographic characteristics on the effectiveness of SMS reminders on adherence to appointments are conflicting and largely inconsistent. Eventhough forgetfulness has been cited as a major reason of missed appointment among patients on ART, evidence indicates that factors such as transport and distance from clinic, work related issues, unscheduled travelling and waiting time are some of the documented barriers of adherence to medication refill appointments as well as clinic visits (Brennan et al., 2010; Tjijuka et al., 2012; Manhando and Ugburo, 2010; Cole-Lewis, 2013).

The findings from the current study indicate that the following socio-demographic and economic variables; age, gender, alcohol use, distancefrom the clinic, marital status and employment status are not significantly associated with honouring all medication pick up appointments. Likewise, the Namibian adherence baseline survey of 2012 did not report any significant association between age, gender, alcohol use, distance from the clinic, marital status, employment status and adherence to appointments. The patients socio-economic and demographic characteristics in relation to effectiveness of SMS reminders and adherence to appointments are worth noting.

**Gender:** In the overall, there were slightly more males 203(52.3%) than females recruited into the study. this is consistent with the gender distribution in our setting based on the December 2012 monthly report of the clinic, the male pateints accounted for 54% of adults on

treatment, It is worth noting that there were slightly more males (58.2%) in the intervention arm of the study.

**Marital status:** In this study, the proportion of single and married statuses constituted over 70% of the reported marital status with the proportion of married patients slightly higher in the intervention arm of the study. Vice versa the proportion of single patients was slightly higher in the control arm of the study. This indicates that randomisation is not a flawless procedure.

**Employment status:** An unemployment rate of about 30% is reported by participants in this study. Interestingly, this is consistent with the official unemployment rate of 30% reported in the Namibia Population and Housing Census Indicators report of 2011 for Erongo region (Namibia 2011 Population and Housing Census Indicators). The results from the bivariate model shows that a higher proportion of employed patients honoured all medication pick up appointment as compared to the unemployed, although we found the cumulative incidence ratio and risk difference statistically insignificant. It is probable that some of the unemployed patients may miss medication pickup appointments due to inability to afford transportation cost for those living far from the clinic.

**Alcohol use and adherence to appointments:** The result from the current study reveals that 28.6% of participants consume alcohol. Interestingly, in 2002, a study conducted by the Ministry of Health and Social Services reports that 56% of adults in Namibia consume alcohol with an average of 30 units/beer consumed in the previous week (MoHSS, 2002). Also, the level of alcohol consumption reported by patients in this study indicates that an average of 1, 7 and 2.3 units of alcohol are consumed per day and weekends respectively. This result suggests that alcohol use among patients is recreational, considering the safe limits of 21 and 14 units of alcohol consumption per week for men and women respectively which was set by the Royal College Physician (Thomas et al., 2012). It is important to note that not abusing alcohol or refraining from alcohol abuse is one of the social eligibility criteria for starting patients on ART, consequently patients are continuously screened and counseled on alcohol abuse, this may have influenced the level of alcohol consumption in the study population as compared to higher levels reported in the general population. Furthermore, there was no significant association between consuming  $\leq 1$  unit of alcohol/day and  $\leq 2$  units of alcohol/weekend or  $> 1$  unit of alcohol/day and  $> 2$  units of alcohol/weekend and honouring all medication pick up appointments.



**Age:** The findings from this study did not show any significant association between age and keeping medication appointments. Even though Kunutsor et al. (2010) and Bofilla et al. (2006) reported that younger aged patients are more likely to honour schedule clinic appointments, Brennan et al. (2010) demonstrated older patients are more likely to adhere to schedule appointments than younger patients. Naturally, we would have expected a significant influence of the reminder among younger patients because they are more technologically disposed, however, older, employed patients with busy schedules may be more inclined to forget appointments and therefore find SMS reminders more supportive.

**Distance from health facility:** In this study, we classified walk able distances between 0 – 5km as near to the clinic and 5 – 15km as far from the clinic. It is logical to expect more patients living near the health facility to adhere better to appointments as compared to living distant from the health facility. Surprisingly, the results from this study indicates otherwise, we found that 44% of patients residing near the clinic honour all medication pick up appointment as compared to 47.2% of patients residing distant from the clinic. However, this association was not statistically significant in relative and absolute terms. Interestingly, there is no data to suggest that distance to the health facility is predictive of adherence to appointments, in addition only 3% of respondents in the Namibian national adherence baseline survey of 2012 indicated difficulty in assessing health facility as a reason for missing appointment.

## **5.6 SMS reminders and adherence to medications.**

The findings from this study shows that motivational SMS reminders delivered two days prior to scheduled medication pick up appointment significantly influenced adherence to antiretroviral medication. In this study self-reporting and pill count was used to measure adherence and both results were compared. Beforehand, optimal adherence for pill count assessment was defined as  $\geq 95\%$  adherence levels, while adherence levels  $<95\%$  was defined as sub-optimal adherence. The differences noted in the results from adherence assessed by pill count and self-report was not unexpected because self-reported adherence is often exaggerated (Simoni et al., 2006). Expectedly, in this study a higher adherence levels were recorded from self report however, there is a fair correlation between the CIR recorded from pill count 1.14 (95%CI:1.01-1.30) and self-reporting 1.18 (95%CI:1.07-1.31) as well as the risk difference. However, the association was not statistically significant at the multivariate logistic regression level for pill count. On the

other hand, the adjusted CIR and RD indicates a statistically significant association between SMS reminder and adherence assessed via self-report. After removing “adherence to appointments” from the backward stepwise regression model, the result shows a change in the adjusted CIR and a significant association for both self-reported and adherence assessed via pill count. It thus appears that adherence to appointments is acting as a partial intermediate variable between SMS reminder and adherence to medications, suggesting that patients who received SMS reminder are more likely to keep appointments and in the same vein, are more likely to be adherent to medications. In spite of this encouraging result, previous studies on the effectiveness of SMS reminders on adherence to ART in Sub-Saharan Africa has been largely conflicting. Hitherto, only 2 studies both conducted in Kenya reported that SMS reminders significantly improved adherence to ART (Lester et al., 2010; Pop-Ellechas et al., 2011). On the other hand, the Cameroon Mobile Phone SMS (CAMPS) trial and a pilot study conducted in rural Sierra Leone reported that SMS reminders did not significantly improve adherence to ART (Mgbaugwu et al., 2012 ; Kelly et al., 2012). The findings from these studies should be interpreted in the context of the study setting, duration of follow up and the content of the SMS message.

The CAMPS trial was an urban, single site randomised control trial in which a one way non interactive weekly motivational SMS reminders were sent to treatment experienced patients in the intervention arm of the study and participants followed up for 3 months and 6 months. Adherence was assessed by visual analogue scale (VAS), self-report and pharmacy refill data, with > 95% adherence defined as optimal adherence. Mgbaugwu and colleagues (2012), concluded that SMS reminder did not result in significant improvement in adherence to ART. Likewise, Kelly and colleagues (2012) did not report significant improvement in adherence to ART, in a rural single site randomised control pilot trial in which a non interactive SMS reminders were sent daily from the 2nd day prior to the appointment, while the control group only received weekly SMS reminders and thrice weekly community home visits in addition to standard care available to both groups. This study is limited by the inadequate sample size and a short follow up duration of 3 months. Contrary to findings from CAMPS trial and the rural Sierra Leone pilot trial, Lester and colleagues (2010) reported that patients that received a weekly interactive SMS reminders recorded a 19% improvement in adherence as compared to standard treatment without reminders. It is important to note that this was a multi centre trial of newly

initiating patients on ART which were followed up for 1 year without masking participants and clinic staff involved in data collection. Optimal adherence was defined as > 95% adherence in the previous 30 days by self-report, interestingly SMS reminder was also associated with significant viral load suppression. Pop-Elleches and colleagues also reported that SMS reminders increased the proportion of participants achieving optimal adherence by approximately 11% as compared to no SMS reminders in a rural setting. Moreover, Horvath et al. (2012) pooled the two Kenya trials in a meta analysis and demonstrated that short SMS reminders significantly reduced missed appointment by 22% regardless of whether the reminder message was long or short at 48-52 weeks. Our result is fairly similar to the 11 – 19% improvement in adherence to ART in reported in the two SMS intervention studies conducted in Kenya (Pop-Ellechas et al., 2011; Lester et al., 2010).

Sub analysis of the patients preference or need for reminder shows that willingness to receive reminders is a potential effect modifier of SMS reminder and adherence to ART.

Lastly, the result from the current study suggests that sending motivational reminders 2 days prior to scheduled medication pick up appointments produces fairly similar improvements in adherence to ART as weekly SMS reminders. This is worth considering in a resource constrained settings where more human and material resources may be required to scale SMS reminder.

### **5.7 The influence of socio-economic and demographic characteristics of patients on the effectiveness of SMS reminders on adherence to ART.**

In order to determine socio-economic and demographic variables that are independently associated with adherence to ART, all variables that were < 0.1 in the bivariate were incorporated in our multivariate model. This current study is suggesting patients employment status is a predictor of adherence to ART. In addition, younger aged patients < 35 years are less likely to adhere to ART although this association is not statistically significant. The results from this study did not demonstrate statistically significant differences between adherence to ART and the following independent variables; gender, duration on ART, alcohol consumption, distance from the clinic and marital status. Conclusions from previous studies on the influence of patients socio-economic and demographic characteristics on adherence to ART has been conflicting.

**Age:** The results from the bivariate analysis shows that patients of younger age (less than 35 years) are less likely to attain optimal adherence as compared to older patients by about 6 – 13% with a significant risk difference. However, the adjusted CIR indicates that age is not independently associated with achieving optimal adherence at the multivariate level for both measures of adherence. Similarly, age was not reported to be independently associated with adherence to ART in the Rwandan national baseline survey of 2010 (Elul et al., 2011). On the other hand, Parietal et al. (2004), Williams et al. (2006) and Kunutsor et al. (2010) showed that younger age is independently associated with poor adherence. On the contrary Golin et al. (2002) and Mbaugbaw et al., (2012) did not find age to be predictive of medication adherence. In the light of the outcome of this study, patients who are less than 35 years of age and are willing to be reminded of their medication appointment may also be supported with other adherence improvement measures such as being linked to community support groups.

**Employment Status:** The bivariate analysis indicates that, patients who are employed are more likely to attain optimal adherence by about 19 – 26% as compared to the unemployed. In terms of risk difference, the patients who are unemployed have a 14 % risk of not achieving optimal adherence. The adjusted CIR also shows a significant association between employment status and medication adherence. This result therefore suggests that the patients employment status is an independent predictor of medication adherence. However results from the Namibia national adherence baseline survey of 2012 did not find any association between employment status and medication adherence, Tjijuka et al.,(2012), proposed that government effort to make ART available and accessible to patients without payment regardless of social status might explain the insignificant association between socio economic and demographic factors and adherence to ART. We are cautious to suggest that SMS reminders probably influenced adherence among patients that are employed in this study, even though it is also likely that patients who are employed may be more motivated to adhere to ART and less likely to forget taking their medicines as prescribed.

The conflicting conclusions from previous studies stated above may be due to the complex interplay of several factors and because behaviour change sits right in the pathway between the intervention (SMS reminder) and health outcome (adherence), a complex interaction of psychosocial and demographic variables and adherence has been proposed (WHO. 2003).

Williams et al. (2006) and Golin et al. (2002) reported substance abuse and depression to be predictors of non adherence to ART, in addition, Parietal et al., (2004). found depression to be independently associated with virological failure. Furthermore, Mills et al. (2006) and Nelson (2012) reported that high level of patient motivation and positive experiences are key facilitators of adherence to ART. These variables were not considered and tested in this study due to logistic constraints.

### **5.8 The association between SMS reminders and the number of missed days.**

The SMS reminder significantly reduced the duration of the number of missed days between scheduled medication appointment date and date of visit as compared to participants that did not receive reminders. The number of days late is a pointer to non adherence to ART because study participants were given about enough medicines to last until the next appointment date. Studies have demonstrated the association between treatment interruption of 1- 3 days and virological failure. Brennan et al. (2010) showed a significant increase in virological failure and mortality among patients who missed appointment for more than 3 days. In the same vein patients that have experienced one late pick up or  $\geq 20$  % late pick ups were found to be significantly associated with virological failure at 12 months after initiation of ART. (MoHSS 2010). The number of days that elapsed between a missed visit and the next visit is critical, for the reason that as the number of days late increased, the occurrence of new AIDs defining illnesses and death increases significantly (Park et al., 2007). The mean difference between patients that received the SMS reminders and those that did not receive the SMS reminders was 4.4 days during the four consecutive ARV refill appointments. When the number of days late is  $> 30$  days, the hazard ratio increased significantly by a factor of 5 (Park et al., 2007). In a resource limited setting, sending SMS reminders have the potential of reducing the number of late days, unlike phone calls, messages could be saved on the phone especially when phone is not shared as a continuous reminder and in situations where privacy and confidentiality of patients is compromised the message could be deleted.

## 5.9 Study limitations

Results from this study are based on the premise that patients who fail to adhere at short term are much less likely to adhere in the long term. However it is acknowledged that those who adhere in the short term might not adhere in the long term and a longer follow up period is desirable in order to assess adherence in the long term. It is anticipated that confounding variables will be balanced based on the RCT study design adopted for this investigation, however our failure to test effectiveness of SMS reminders influence on psychosocial variables such as depression, substance abuse, social support, level of education, co-morbidities, use of other reminders such as alarm devices, and community support program is acknowledged as a limitation in this study.

In this study adherence to medication by a 3- day self-report and by pill count which are both fallible methods of assessing adherence. In addition, pill count was only done for one component of the regimen in cases where we have two medicines making up the regimen. We assume patients adhere equally to both medicines noting that this may not always be the case. However, research assistants could not ascertain whether participants brought all pills for counting at the commencement of the study. As a result of logistical and cost limits we could not validate adherence by viral suppression which is a more objective measure of adherence and a superior means of assessing HIV treatment outcome.

The occurrence of contamination was not envisaged, and we could not check if any individual in the control group had a SMS reminder passed on to them by those in the intervention group. However even if this did occur it would only have influenced the results if those control subjects who received these passed on SMSs had the same appointment date as the intervention participants who passed them on. In the same vein, we did not check if participants utilized other types of reminders such as alarms, which could have influenced adherence. Also we could not ascertain whether the SMSs were either received or read by participants in the intervention group in order to evaluate to what extent the SMS reminder actually influenced any behavioral changes that brought about differences in keeping appointments and adherence between the two groups. We could only confirm to whom SMSs were sent and that they were delivered.

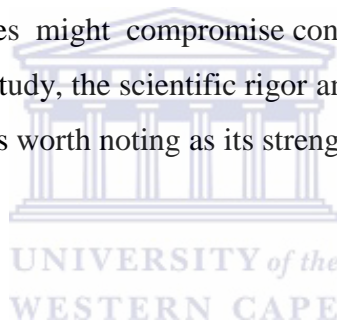
Data and analysis on cost effectiveness of the intervention could not be done due to time and logistical constraints, therefore the sustainability of this intervention could not be determined.

The monthly adherence counseling session given to all participants was likely to exaggerate adherence in both arms of the study, as compared to other patients not exposed to monthly adherence counseling therefore this need to be noted when interpreting the results from this study.

Only those participants that were willing or preferred to be reminded of their appointments should have been included in this study, in essence the result of the study would only have been generalized to only about 60% of patients who were willing to receive reminders, our result shows that the SMS reminders is more effective among patients who were willing to be reminded. In essence we were able to assess unsolicited SMS reminders and our results can be generalized to all patients in similar settings.

Short message service confidentiality was not an issue in this study, throughout the duration of the study, none of the participants in the intervention group objected to reminder messages, however shared usage of cell phones might compromise confidentiality.

Aside from the limitations of this study, the scientific rigor and the very low proportion of lost to follow up during the study period is worth noting as its strength.





# Chapter 6

## Conclusion and Recommendations

### 6.1 Conclusion

Short motivational SMS reminders sent two days before scheduled medication pick up appointments were found to be effective in improving adherence to scheduled medication refill appointments. SMS reminders increased the likelihood of keeping scheduled appointment by 22% and SMS reminders significantly reduced the number of days late for medication refill appointments, thereby reducing the risk of patients interrupting treatment which may lead to development of resistance, treatment failure and switching patients to more expensive second line antiretroviral medication. Similarly, although to lesser extent, SMS reminders improved antiretroviral adherence. The patients that received SMS reminders are more likely to attain optimal adherence by about 14 – 18%. Those who preferred to receive SMS reminders were more likely to benefit from the SMS reminder, but this result was not statistically significant. To the best of our knowledge this is the first reported trial on SMS reminders and adherence to ART medication and adherence to ART refill medication appointments in Namibia. However, more research is needed in evaluating the impact of the message content and timing of the message on the effectiveness of SMS reminders.

Since adherence to medication appointments showed a strong association with adherence to ART medication, the use of medication refill appointments monitoring, as an easy to do proxy measure of adherence to medication, it is feasible and especially useful in a resource constrained setting. Patients that have been on ART for less than one year and those whose treatment supporters reminded them of their appointments, were paradoxically significantly less likely to adhere to medication refill appointments. Being employed was significantly associated with attaining optimal adherence to antiretroviral medication. There were no other significant associations between the patients socio-economic and demographic characteristics and adherence to scheduled medication pick up appointments, or to adherence to medication.



## 6.2 Recommendations

The Namibian Ministry of Health should consider rolling out the same or a similar SMS reminder to patients on ART (and by implication any other chronic medication) and especially to patients who indicate willingness to receive a SMS reminder.

Late and missed appointments are easy to measure and therefore it can be used as a proxy measure for adherence to medication. The practice of treatment supporters reminding patients to take their medication and to keep their appointments should be thoroughly reviewed, as it appears to be unhelpful.



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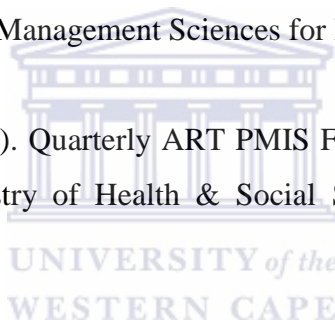
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## Appendix A

Interviewers Name \_\_\_\_\_

### SMS REMINDER AND CLINIC APPOINTMENT STUDY

STUDY NO: SN-Ib OR 2r

Coding Column

Blue Marble	1
Red Marble	2

2. DURATION ON TREATMENT: In Years and months

3. REGIMENS

NRTI

AZT based 1

TDF based 2

D4T based 3

NNRTI

NVP based 1

EFV based 2

PI's

YES 1

NO 2



4. AGE: AT LAST BIRTHDAY (YEARS)



5. SEX

MALE	1
FEMALE	2

6. MARITAL STATUS

SINGLE	1
MARRIED	2
WIDOWED	3
DIVORCED/SEPARATED	4
CO-HABITING	5

7. HAVE YOU INFORMED YOUR PARTNER/RELATIVE/ FRIEND OF YOUR HIV STATUS

YES	1
NO	2



8.LOCATION (Assessing Distance From Clinic)

WHERE DO YOU LIVE

TAMARISKIA	1
MONDESA	2
TULINAWA	3
DRC	4
VINETA	5
TOWN	6
NONIDAS	7
OTHERS..(List).....	

9. EMPLOYED

- YES 1
- NO 2

IF YES TO 8.

10. TYPE OF EMPLOYMENT

- GOVERNMENT 1
- PRIVATE COMPANY 2
- FARM 3
- SELF EMPLOYED 4

11. WHAT IS YOUR MONTHLY INCOME N\$

12. ALCOHOL

DO YOU DRINK ALCOHOL

- YES 1
- NO 2



13. IF YES TO 10.

HOW MANY UNITS OF BEER/ WINE/ SPIRIT/ LOCAL BREW  
DO YOU DRINK ON WEEKDAYS AND WEEKENDS

14. DO YOU HAVE A TREATMENT SUPPORTER

- YES 1
- NO 2

15. IF ANSWER TO 12 IS YES

HOW OFTEN DOES YOUR TREATMENT SUPPORTER REMIND YOU OF

YOUR CLINIC APPOINTMENT

- ALWAYS 1
- OCCASIONALLY 2
- NEVER 3

16. DO YOU WANT TO BE REMINDED OF YOUR CLINIC APPOINTMENT

- YES 1
- NO 2

17. HOW DO YOU PREFER TO BE REMINDED

- THROUGH CALLS 1
- SMS 2
- CALLS AND SMS 3



18. DO YOU HAVE A CELLPHONE?

- YES 1
- NO 2

19. IF YES TO 18 DO YOU SHARE YOUR PHONE WITH YOUR PARTNER/FRIENDS

- YES 1
- NO 2

20. IF NO TO 18 DO YOU HAVE DAILY ACCESS TO A CELLPHONE

21. WHAT TIME OF THE DAY WILL YOU PREFER TO RECEIVE A REMINDER

- MORNING 1
- AFTERNOON 2
- EVENING 3

ANYTIME 4

22. How long before your appointment would you like to receive your reminder

1 day 1

2 days 2

3 days 3

4 days 4

5 days 5

Signature of Interviewer \_\_\_\_\_



## APPENDIX B

### SMS REMINDERS AND CLINIC APPOINTMENT STUDY PARTICIPANTS APPOINTMENT LOG SHEET

STUDY NO: \_\_\_\_\_

Scheduled Appointment Date A	Date of Visit B	Missed=1 On time=0 C	No of Days Missed D	Pill Count 5 $\frac{\text{No of doses given- left over pill}}{\text{No of doses required to be taken in the time period}} \times 100 = \% \text{ adherence}$	How many doses did you miss in the last 3 days (Self report)
<b>Total</b>					



## Appendix C

# UNIVERSITY OF THE WESTERN CAPE

## School of Public Health

Private Bag X17 • BELLVILLE • 7535 • South Africa

Tel: 021- 959 2809, Fax: 021- 959 2872

### **Participant Information Sheet**

July 2012.

Dear Participant,

Thank you for your willingness and interest in this research. What follows is an explanation of the research project and an outline of your potential involvement.

The research is being conducted for a thesis, which is a requirement for the Masters in Public Health which I am completing at the University of the Western Cape. If there is anything you do not understand or are unclear about, please feel free to ask me. My contact details and those of my supervisor are attached.

### **Title of research**

An evaluation of adherence to scheduled appointments among adults on highly active antiretrovirals at the Swakopmund ART Clinic

### **Purpose of the study**

The purpose of the study is to improve adherence to antiretrovirals, thereby improving health outcomes. It is hoped that this research will guide policy makers in making policies that will improve adherence to scheduled ARV pick up appointments.

### **Description of the study and your involvement**

This study will require interviews which will not last more than 30 minutes. Information about your age, socioeconomic and demographic status will be asked.

### **Confidentiality**

Your name and records of your participation will be kept confidential at all times, including a

signed consent form, which we will need from you, should you agree to participate. All documents pertaining to you and the information you provide will be destroyed after the research is completed.

### **Voluntary participation and withdrawal**

Your participation in this research is entirely voluntary and there is no adverse consequence if you decide not to participate. If you choose to participate, you may stop at any time. You may also choose not to answer any questions that are asked in this study, if there is anything you may prefer not to discuss.

### **Benefits and cost**

You may not get any direct benefit from this study, however the information we get from participants in this study may help in guiding policy makers and program managers on how best to support patients in adhering to care and treatment. Other than the 30 minutes or less that you will be required to spend for the interview, there are no other costs for participating in this study.

### **Informed consent**

Your signed consent to participate in this study is required before I proceed to interview you. I have included the consent form with this information sheet so that you will be able to review the consent form and then decide whether you would like to participate in this study or not.

### **Enquiries**

Should you have further enquiries or wish to know more, I can be contacted as follows.

Emmanuel Ugburo

Student Number: 30003234

Cell Phone: 0813416274 Work Phone: 061- 2032348

e-mail :[deleman2010@gmail.com](mailto:deleman2010@gmail.com)

I am accountable to Dr. Gavin Reagon, my supervisor at UWC, his contact details are

School of Public Health

University of the Western Cape

Private Bag x17. Bellville

021-9593563

Fax: 021-9592872

Email [greagon@uwc.ac.za](mailto:greagon@uwc.ac.za)

**Appendix D**

**UNIVERSITY OF THE WESTERN CAPE**

**School of Public Health**

Private Bag X17 • **BELLVILLE** • 7535 • South Africa

Tel: 021- 959 2809, Fax: 021- 959 2872

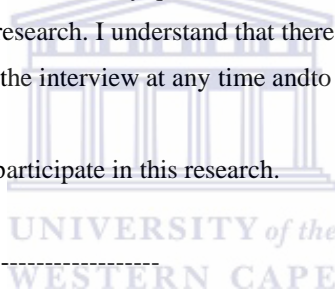
**TITLE**

**An evaluation of adherence to scheduled appointments among adults on antiretroviral at the Swakopmund State Hospital ART Clinic.**

-----  
I have read the information about this research study on the Participant Information Sheet or it has been read to me and I have had the opportunity to ask questions and my questions have been answered to my satisfaction .

I consent to voluntarily participate in this research. I understand that there are no adverse consequences if I do not participate and that I have the right to end the interview at any time and to choose not to answer particular questions I'm asked in the study.

My signature indicates my willingness to participate in this research.



-----  
Participant Name (Printed)

-----  
Participant Signature

-----  
Consent Date

-----  
Researcher Conducting Informed Consent (Printed)

-----  
Signature of Researcher

-----  
Date



## Appendix E

### Definition of Terms

#### Scheduled clinic appointment

Kunutsor (2010) defines schedule clinic appointments as regular appointments e.g monthly appointments for medication pickups. In this study, schedule appointments are defined as scheduled ARV refill appointments which are monthly. This date is communicated to the patient before leaving the pharmacy and noted legibly on the patient's health passport which is normally taken home, this is a very important step in ensuring adherence to scheduled appointments as noted by Pinsker et al (1995). The medical or physician only appointments are scheduled in line with the national ART guideline and by the clinical judgment of clinicians. It is worth noting that the two appointments may coincide, for example the physician may give a 3 – 6 months follow up date to a stable patient, while the pharmacy schedules monthly appointments, the third and the last of which coincides with the physician's appointments

#### Lost to Follow Up (LTFU)

These are patients that cannot be traced after concerted attempts to do so, however operationally in our setting for the purpose of adherence monitoring, a patient is said to be LTFU if he/she fails to turn up 90 days after the last scheduled appointment for ARV pickup and if he /she was not known to have transferred to another treatment centre, stopped therapy without restarting or died. (Hong et al., 2010; Ugburo and Ongeru, 2011)

#### Missed appointment:

In this study, two definitions for missed appointment will be adopted. A strict definition of missed appointment is failure to turn up on the day he/she is scheduled for ARV refill, without prior rebooking. While a less strict definition is where patients fail to turn up within 2 days of scheduled ARV refill appointment without prior rebooking. In the event of rebooking a new follow up date will be given to the patient. The rate of missed appointments is the ratio of the number of times a patient fails to turn up for pre-arranged ARV refills appointments over the total number of scheduled appointments (Mugavero et al., 2010). The first definition is those who failed to turn-up on scheduled day. While the second category are those who turned up within 2 days of their scheduled appointment.

**Appendix F**  
**Oshiwambo Translation**

Sepetemba 2012

Osikola Yuundjolo wele wopa shigwana

Uuyelegele wanakukutha omblinga

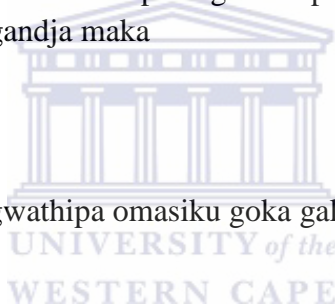
Nakukutha ombinga omusimanekwa

ndapandula uumene shiwuna Ehalo neyi tulemo Iyo kukutha ombinga mekongo iyomayu yelegele ndika. Shi shalandulago

mpaka; Ehokolo nkene tashivuliko awuka kuthe unyelegele. Ekongo iyo mauyelegele ndika olili onga oshitopolwa sheyi longo iyonzapo yo mbanda (master in Public Health), ndjoka ngame teningi ko shiputudhiyo shopombandasha Western Cape. Ngele otapukallaka ompumber yandje no yomukuluntugwa ndge yili ondeyigandja maka

Edhina Iyo Shilongwa

Eko nakono nkene aavu haya gwathipa omasiku goka galukila ko kapangelo kepango iyo mbuto kalmo Swakopmund.



Elalaka Iyo Shilongwa Shika

Ela kukano okahumitha komehonkene aavu yena kugalukila kokapangelo, no kumawa paleka undjolare waantu.

Edhina Iyanakupala\_\_\_\_\_

## SMS REMINDER AND CLINIC APPOINTMENT STUDY

STUDY NO : SN-Ib OR 2r

Coding Column

Blue Marble	1
Red Marble	2

2. ETHIMBO IYEPANGO : Liti momvula noo mwedhi

3. ONGUNDU YOMITI

NRTI

AZT based	1
TDF based	2
D4T based	3

NNRTI

NVP based	1
EFV based	2
PI's	
YES	1
NO	2



4. OOMVULA: PEVALO IYAPITI

5. SEX

MALE	1
FEMALE	2

6. MARITAL STATUS

INO HOMBOLA	1
OWAHOMBOLWA	2
OMUFIYELKADI	3
OKWAHENGANA	4

7. OWALOMBAELE OMUHOLIKE GWOYE MPA WATHINKA NOMBUTO YO

EE	1
AYE	2

8. EHALA

(OHOZI PENI)

TAMARISKIA	1
MONDESA	2
TULINAWA	3
DRC	4
VINETA	5
TOWN	6
NONIDAS	7
OTHERS..(List).....	



9. OHOLONGO

EE	1
AYE	2

IF YES TO 8.

10. OHOLONGO IILONGO YOLUDHI LUNIPO

MEPANGELO	1
EHANGANNO IYOPAWUMUWENE	2
UUNAMAPYA NUUNIIMUNA	3
HWIILONGELE	4

11. IYEMO YOYE YOKOMWEDHI N\$

12. LIKODWITHA

OHONU OMALOVU

EE	1
AYE	2

13. IF YES TO 10.

OHONU SHITHIKEPE MONASIKU GOSHIKE

MEHULILO SHIWIKE

14. OWUNA OMUKWATHI GWEPANGO

EE	1
AYE	2

15. IF ANSWER TO 14 IS YES

OMUKWATHI GWOYE OHEKUDHIMBULILUKITHA LUNGAPI

ALUHE

OKATHIMBO NOKATHIMBO	2
----------------------	---

I	HADHIMBULUKITHANDJE	3
---	---------------------	---

16. OWAPUBWA KUKALA HODHIMBALUKIFERA ESIKU NDI WUNA OKUSHUPA

EE	1
AYE	2

17. OWAHAKA KUDHIMBULUKITWA NOMAKALOGUNI

OKUDHENGELWA ONGODHI	1
----------------------	---

OKATUMWALAKA OKAHUPI	2
----------------------	---

ONGODHI NOKATUMVWALAKA OKATTIPI	3
---------------------------------	---

18. OWUNA ONGODHI YOMEKWAMO?

- EE 1
- AYE 2

19. NGELE EE KU 18, O HO GANDJA ONGODHI YOYE KAAKOLITE YEYE

- EE 1
- AYE 2

20. NGELE AAYE KU 18 , OHO MONO ONGODHI YO KU LONGIDHA

21. OTOPUMBWA OKUDHIMBULIKITWA PANGODHI ETHIMBO .....

- ONGULA 1
- OMUTENYA 2
- KONGULOHI 3
- KEHETHIMOBO 4



22. OWAHALA WUDHIMBULIKITWE KUNA OMASIKU GANGAPI, KESIKU  
IYOKUYAKO KAPANGELO

- EESIKE IIMWE 1
- OMASIKU GAALI 2
- OMASIKU GATATU 3
- OMASIKU GANE 4
- OMASIKU GATANO 5

Signature of Interviewer\_\_\_\_\_

## **Appendix G**

### **Afrikaans Translation**

Liewe deelnemer,

Dankie vir jou bereidwilligheid en belangstelling in hierdie navorsing. Wat volg is 'n verduideliking van die navorsingsprojek en 'n uiteensetting van jou moontlike betrokkenheid. Die navorsing word uitgevoer vir 'n tesis, wat 'n vereiste vir die Magister in Aneniets is wat jy nie verstaan nie of onseker is oor, voel asseblief vry om my te kontak. My kontakbesonderhede en die van my toesighouer is aangeheg.

Titel van navorsing

'N evaluering van Voldoening aan Geskeduleerde Aanstellings onder volwassenes op besonder aktiewe anti-retrovirale middels by die Swakopmund ART Clinic.

Doel van die studie

Die doel van die studie is om die nakoming van antiretrovirale middels te verbeter en sodoende die verbetering van die gesondheid uitkomst. Daar word gehoop dat hierdie navorsing beleidmakers sal lei in die maak van beleid wat sal verbeter nakoming geskeduleer ARV optel aanstellings.

Beskrywing van die studie jou betrokkenheid

Hierdie studie sal vereis onderhoude wat nie meer as 30 minute duur. Inligting oor jou ouderdom, sosio-ekonomiese en demografiese status sal gevra word.

.

Vertroulikheid

Jou naam en rekords van jou deelname vertroulik gehou sal word te alle tye, met inbegrip van 'n getekende toestemming vorm, wat ons van u nodig sal he, moet jy

saamstem om deel te neem. Alle dokumente met betrekking tot jou en die inligting wat u verskaf sal vernietig word na die navorsing voltooi is

Vrywillige deelname en onttrekking

U deelname is hierdie navorsing is heeltemal vrywillig, en daar is geen nadelige gevolge, as jy besluit om nie deel te neem. As jy kies om deel te neem, kan jy op enige tyd stop. Jy kan ook kies om nie enige vrae wat gevra word in hierdie studie te beantwoord nie, daar iets is wat jy verkies om nie te bespreek nie.

## Voordele en koste

Jy kan nie enige direkte voordeel uit hierdie studie, maar die inligting wat ons kry van die deelnemers in hierdie studie kan help in die begeleiding van beleidmakers en program bestuurders op die beste manier om pasiente te ondersteun in die voeding aan sorg en behandeling. Anders as 30 minute of minder wat jy sal verwag word om te spandeer vir die onderhoud, daar is geen ander koste vir deelname in hierdie studie.

## Ingeligte toestemming

U getekende toestemming om deel te neem in hierdie studie word vereis voordat ek voortgaan om 'n onderhoud te voer met. Ek het die toestemming van met hierdie inligtingstuk ingesluit sodat jy in staat sal wees om die toestemming vorm te hersien en besluit dan of jy wil om deel te neem in hierdie studie of nie.

## Navrae

Indien u verdere navrae of wil meer weet, kan ek gekontak word soos volg.

Emmanuel ugburo

Student nommer: 30003234

Selfoon: 0813416274

Werk foon: 061-2032348

e-pos: deleman2010@gmail.com

Ek is verantwoordig aan Dr Gavin Reagon, my toesighouer by UWC, sy kontakbesonderhede is die skool van Openbare Gesondheid.

University van Die Weste Kaap

Privaat Sak x17. Bellville

021-9593563

Fax: 021-9592872

e-pos: greagon@uwc.ac.za





ONDERHOUD'S NAAM;

BOODSKAAP ONTHOU EN KLINIEK AFSpraak STUDIE.

1. STUDIE NOMMER; SN-1B or 2P

Blue Marble	1
Pink Marble	2

2 VOORTDURING AAN BEHANDELING; in yare en maande.

3 LEEFWYSE,REGIMENT

NRTI

AZT based	1
TDF based	2
D4T based	3

NNRTI

NVP based	1
EFV based	2

PI's

Yes	1
No	2



4 OUDERDOM;

5 GESLAG;

MANSMENS	1
VROUMENS	2

6

ONGETROUD	1
GETROUD	2
WEDUWEE	3
GESKEI	4
GEWOONTE/ BEROEPSDRAG	5

7.HET JY JOU MAAT,FAMILY OF IMAAND LAAT WEET VAN DIE SIEKTE.

YA.	1
NEE.	2

8.LOCASIE?

WAAR WOON U?

Tamariskia	1
Mondesa	2
Tulinawa	3
DRC	4
Vineta	5
Town	6
Nonidas	7
Others.....	

9.WERK U?

YA	1
NEE	2
If Ya to 9.	



10.WATTER SOORT WERK DOEN U?

STAD	1
PRIVAAT	2
PLAAS.	3
EIE WERK.	4

11. WAT IS U MAANSLIKE INCOMSTE N\$?

12. DRANK.

DRINK U

YA	1
NEE	2

13. HOEVEEL MEETEENHEID VAN DRANK, WYN OF LOKAAL BEER VAT U?

A. DRINK U WEEKSDAE EN IN DIE NAWEEK.

14. HET U BEHANDELING HULP ONDERHOUD?

YA 1  
NEE 2

15. HOEVEEL KEER SE JOU ONDERHOUD VIR JOU OM KLINIEK TOE TE GAAN  
VIR AFSPRAAK?

ALTYD 1  
SOMS 2  
NOOIT 3.

16. WILL JY GE LAAT ONTHOU WORD AAN JOU AFSPRAAK OM KLINIEK TOE TE  
GAAN?

YA 1  
NEE 2

17. HOE WILL U GE LAAT ONTHOU WORD?

DEUR TETEFOON 1  
BOOBKAAP 2  
ALTWEE 3.



18. HET U 'N TETEFOON?

YA 1  
NEE 2

19. DEEL U, U FOON MET VRIENDE, MAATS OF FAMILIE?

YA 1  
NEE 2

20. IS U ALTYD BESKIKBAAR OP JOU FOON?

YA 1  
NEE 2

21.HOE LAAT WILL U GE LAAT ONTHOU WORD?

- |           |   |
|-----------|---|
| OGGEND    | 1 |
| NAMIDDAG  | 2 |
| AAND TYD  | 3 |
| ENIGE TYD | 4 |

22. HOE LANG VOOR JOU AFSPRAAK WILL U GE LAAT ONTHOU WORD?

- |          |    |
|----------|----|
| A DAG    | 1  |
| TWEE DAE | 2  |
| DRIE DAE | 3  |
| VIER DAE | 4  |
| VYF DAE  | 5. |

Signature of Interviewer \_\_\_\_\_



## Appendix H

### Consolidated Standards for Reporting Trials (CONSORT) Checklist

#### Title and Abstract

##### 1a. Title

The Title does not identify this study as a randomised trial.

##### 1b. Abstract

The abstract is presented as a structured summary consisting of trial design, methods, results, and conclusions.

#### Introduction

##### 2a. Background

Scientific background and rationale of the study covered in the introduction section.

##### 2b. Objectives

Specific objectives were clearly listed.

#### Methods

##### 3a. Trial Design

Trial design well described

##### 3b. Changes to trial design

There was no change in the trial design as approved in the protocol.

##### 4a. Participants

Eligibility and exclusion criteria for participants pre-determined.

##### 4b. Study settings

Study setting and location where the data were collected adequately described.

#### 5. Interventions

SMS reminder sent 2 days before scheduled ARV pick up appointment was the only intervention



## **6a. Outcomes**

Pre-specified primary and secondary outcome measures were defined, including how and when they were assessed

## **6b. Changes to outcomes**

No changes to trial outcomes after the trial commenced

## **7a. Sample size**

Sample size was calculated based on stated assumptions at 95% significance level and power of 80%, transfer out and lost to follow up were also considered in determining the sample size.

## **7b. Interim analyses and stopping guidelines**

Not relevant to this study

## **8a. Randomisation**

Method used to generate the random allocation sequence was explained

## **8b. Randomisation:Type**

Type of randomization covered in detail

## **9. Randomisation: allocation concealment mechanism**

Allocation and concealment mechanism was described.

## **10. Randomisation: implementation**

Randomisation implementation described in detail

## **11a. Blinding**

Study participants, baseline data collectors, care providers assessing outcomes were all blinded to allocation of participants to groups. The chief researcher and the assistants that sent the SMS reminders were unblinded.

## **11b. Similarity of interventions**

Not applicable, only one intervention

## **12a. Statistical methods**

An intention to treat principle was adopted in our analysis, this entails that all participants were analyzed based on the initial arm of the study they were randomized and grouped into,

irrespective of whether they dropped out or switched group. The proportion of study participants who missed appointments were determined, the cumulative incidence ratio (CIR) and risk difference (RD) were also determined. The statistical significance was determined using the 95% confidence interval.

### **12b. Additional analyses**

Methods for additional analyses, such as subgroup analyses and adjusted analyses was presented

## **Results**

### **13a. Participant Flow**

For each group, the numbers of participants who were randomly assigned, received intervention, and were analysed for the primary outcome

### **13b. Losses and exclusions**

Losses and exclusions covered in the sample realisation chart.

### **14a. Recruitment**

Participants were recruited until the sample size was attained, the number of follow-ups was specified in the protocol.

### **14b. Reason for stopped trial**

Not applicable

## **15. Baseline Data**

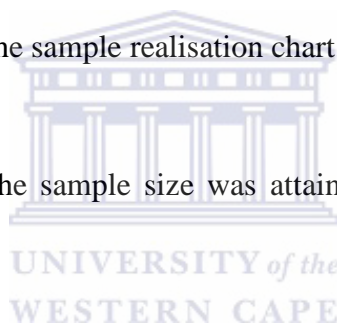
A table showing baseline demographic and clinical characteristics for each group was presented as simple proportion and for continuous variable the mean, standard deviation and interquartile range was presented.

## **16. Numbers analysed**

An intention to treat analysis approach adopted in this study and the number of participants (denominator) was included in each analysis.

## **17a. Outcomes and estimation**

For each primary and secondary outcome, results for each group, and the estimated effect size and its precision at 95% confidence interval were presented.



## **17b. Binary outcomes**

Results of binary outcomes presented in terms of both absolute (Risk difference) and relative effect (Cumulative Incidence Rate).

## **18. Ancillary analyses**

No exploratory analysis was conducted in this trial, primary and secondary analysis were as pre-specified in the protocol.

## **19. Harms**

The potential for inadvertent status disclosure of confidentiality was discussed, in addition the number of participants that dropped out and lost to follow up covered in the results section.

## **Discussion**

### **20. Limitations**

Study limitations, addressed sources of potential bias.

### **21. Generalisability**

Adequate information on the eligibility criteria, study setting, definition of outcomes, the outcomes assessed, delivery and type of intervention, in this regard the result from this study could be generalised to other ART clinics in urban centres in Namibia.

### **22. Interpretation**

The results from this study were well linked with existing literature.

### **Other information**

### **23. Registration**

Not registered, study is a mini-thesis submitted in partial fulfillment of the requirements for the degree of Master of Public Health, in the School of Public Health, University of the Western Cape

### **24. Protocol**

The full trial protocol can be assessed from the ethics committee of the School of Public Health, University of the Western Cape.

### **25. Funding**

This study was exclusively funded by the chief researcher.





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